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Atrial Fibrillation is Associated With Poor Outcomes in Thrombolyzed Patients With Acute Ischemic Stroke

A Systematic Review and Meta-Analysis

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Abstract: The influence of atrial fibrillation (AF) on the clinical outcomes of patients with ischemic stroke (IS) has not been completely determined. We aimed to perform a systematic review and meta-analysis to assess the relationship between AF and adverse events in patients with acute IS treated with thrombolysis.

PubMed, EMBASE, and the Cochrane Library were searched for relevant studies regarding the association between AF and the outcomes of patients with IS treated with thrombolysis. Random and fixed effect models were used for pooling data.

Twelve cohort studies involving 14,801 patients with acute IS were included. Meta-analysis revealed that patients with AF were more likely to die within 90 days after thrombolysis (odds ratio [OR], 2.13; 95% confidence interval [CI]: 1.68–2.70, $P < 0.001$), whereas this association was not observed in hospitalized patients (OR, 1.50; 95% CI, 0.86–2.60; $P = 0.150$). AF was associated with a reduced incidence of favorable outcomes (modified Rankin Scale $\leq$ 2) (OR, 1.95; 95% CI: 1.33–2.85, $P = 0.001$) and an increased risk of symptomatic intracerebral hemorrhage (OR, 1.28; 95% CI: 1.08–1.52, $P = 0.006$). No evident publication bias was found by Begg's test or Egger's test.

Comorbidity of AF may increase the risk of adverse outcomes for patients with IS undergoing thrombolysis. Further well-designed trials are warranted to confirm this association.

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Abbreviations: AF = atrial fibrillation, CI = confidence interval, FO = favorable outcome, IS = ischemic stroke, mRS = modified Rankin Scale, NIHSS = National Institute of Health stroke scale, NOS = Newcastle–Ottawa Scale, OR = odds ratio, rt-PA = recombinant tissue-type plasminogen activator, SICH = symptomatic intracerebral hemorrhage, VISTA = Virtual International Stroke Trials Archive.

INTRODUCTION

Atrial fibrillation (AF) has been considered the most frequent persistent arrhythmia clinically, and patients with AF have been associated with a 4- to 5-fold increased risk of ischemic stroke (IS).[1] The attributable risk of stroke in patients with AF increases with age, from 1.5% for those aged 50 to 59 years to nearly 25% for those $\geq$80 years of age.[1] Approximately, 50% to 60% of IS in patients with AF are definitely or probably cardioembolic in origin.[2] As the risk of both stroke and AF increases with age, it is anticipated that the number of patients presenting with an acute stroke and concomitant AF will increase. A prior study indicated that AF was a predictive factor for severe stroke and early death.[3] Therefore, attention needs to be paid to the treatment of acute stroke patients with AF in order to improve their clinical outcomes.

One in 3 patients with IS treated with early thrombolysis within 3 hours after IS onset achieves a significant benefit.[4] Alexandrov et al[5] reported that recanalization was completed in 30% and partially completed in 40% of IS patients during recombinant tissue-type plasminogen activator (rt-PA) infusion, and early arterial recanalization has been demonstrated as a predictor of favorable outcomes after rt-PA infusion.[6] AF was independently associated with hypoperfusion, infarct growth, and hemorrhagic transformation after t-PA administration.[7] The impact of AF on the outcomes of thrombolyzed patients with IS was conflicting. Although some studies showed that patients with IS and AF had better 90-day functional outcomes following rt-PA than those without AF,[8,9] other studies indicated that comorbidity of AF was associated with poor clinical outcomes.[7,10,11] It is unclear whether patients with IS and AF respond differently to thrombolysis therapy and whether the burden of AF has any consequence on stroke outcomes. Previous evidence indicated that among patients with acute myocardial infarction, those with chronic AF had a higher in-hospital mortality rate than those with newly diagnosed AF or no AF.[12] Therefore, we carried out a systematic review and meta-analysis to investigate the effect of AF on clinical outcomes in patients with IS undergoing thrombolysis.

METHODS

This systematic review and meta-analysis was performed according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Guidelines.[13] Ethical approval was not required considering the nature of the study.

Search Strategy and Selection Criteria

A systematic search of the Cochrane Library, EMBASE, and PubMed was conducted for relevant prospective and retrospective cohort studies published before September 1, 2015. We also conducted manual searching of the reference lists of all the relevant original and review articles to identify additional eligible studies. The following keywords were used to search the English digital databases: *atrial fibrillation, stroke, cerebrovascular disorder, brain infarction, brain ischemia, tissue plasminogen activator, thrombolytic therapy,* and *fibrinolytic agent.* Studies were included if they met all of the following inclusion criteria: (1) cohort study design; (2) the study population consisted of patients with acute IS undergoing thrombolysis; (3) AF was defined as an exposure factor, and clinical outcomes were compared between patients with IS with and without AF after thrombolysis; and (4) the study included an available clinical database. Exclusion criteria were (any single one was enough for exclusion): (1) study designs of reviews, letters, comments, editorials, case reports, proceedings, personal communications, or non-English publications; (2) duplicate reporting with the same study; and (3) a lack of follow-up outcome data.

Study Selection and Quality Assessment

The literature search and inclusion or exclusion was independently undertaken by 2 investigators (DZL and RZY) using a standardized approach. Any inconsistencies between these 2 investigators were settled by discussion with the third investigator (JY) until a consensus was reached. A quality assessment of each selected study was conducted by 2 investigators (DZL and RZY) using the Newcastle–Ottawa Scale (NOS) for cohort studies.[14] The third reviewer was consulted for any uncertainties. Using the NOS tool, which consists of 3 quality parameters (selection, comparability, and outcome assessment), a "star system" (range, 0–9) was used to rate a maximum of 8 items. A total score of 7 or greater indicated a high-quality study, and a total score of 6 or lower indicated a low-quality study.

Data Extraction and Outcome Measures

The following information/data were extracted from studies that met the inclusion criteria: the name of the first author, year of publication, study design, number of participants, participants' age, proportion of male patients, thrombolytic therapy, follow-up time, outcome assessment, number of events, adjusted odds ratio (OR), and 95% confidence interval (CI). The primary outcome was all-cause mortality. Secondary outcomes were: (1) incidence of a favorable outcome (FO), modified Rankin Scale (mRS) score 0 to 2 or nearest equivalent at 90 days, (2) occurrence of symptomatic intracerebral hemorrhage (SICH) after thrombolysis.

Statistical Analysis

The meta-analysis and statistical analyses were performed by using Stata software 12.0 (Stata Corporation, College Station, TX). The effect of AF on the occurrence of clinical outcomes was presented as OR with 95% CI. Hedges Q statistic and Higgins I^2 statistic were calculated for heterogeneity detection. $P < 0.1$[15] and an $I^2 < 50\%$[16] were considered to be of no significant heterogeneity, and a fixed effect model was used. Otherwise, random-effect meta-analyses were performed. We regarded I^2 of <25%, 25% to 50%, and >50% as low, moderate, and high amounts of heterogeneity, respectively. Sensitivity analysis was used to investigate the influence of a single study on the overall risk estimate and was carried out by sequentially omitting 1 study at a time. Publication bias was detected with Egger's and Begg's regression intercept test. All hypothesis tests were 2-sided. $P < 0.10$ was considered indicative of statistically significant heterogeneity, and all other P-values were considered statistically significant at < 0.05, 2-sided.

RESULTS

Characteristics of Selected Studies

The selection of studies is shown in Figure 1. The initial literature search identified 568 relevant articles. After reading the titles and abstracts, we retained 19 studies for further assessment. Of these, we further excluded 7 studies. Ultimately, 12 studies, including 11,588 patients with acute IS, were included in this systematic review.

The basic characteristics of the studies are shown in Table 1, and clinical outcomes of the included studies are summarized in Table 2. Six of the included studies were prospective cohort studies,[10,17–21] whereas the others were retrospective cohort studies.[8,11,22–25] The total number of patients with AF was 3432 (range, 22–1489), and the number of patients without AF was 11,369 (range, 31–5704). The mean ages and percentage of male AF patients with acute IS were higher than those without AF, respectively. The National Institute of Health Stroke Scale (NIHSS) in AF patients with acute IS ranged from 8 to 15, whereas the scores of patients without AF were lower (4–14.5). The mean follow-up time ranged from in-hospital to 12 months. The NOS star rating of all studies was >7, demonstrating relatively high-quality studies.

Meta-Analysis

Primary Outcomes

Nine studies[8,10,18–21,23–25] reported all-cause mortality in hospital[8,20,21,23] and at the end of the follow-up period[10,18,19,24,25] for the IS patients in each group (Figure 2). Pooled data using the random-effect model showed that patients with acute IS and AF were more likely to die following intravenous thrombolysis in the short term compared to those without AF (OR, 1.88; 95% CI: 1.43–2.48, $P < 0.001$, $I^2 = 70\%$). Further, the OR for 90-day mortality was 2.13 (95% CI: 1.68–2.70, $P < 0.001$, $I^2 = 37.9\%$), and this association was not observed in in-hospital mortality (OR, 1.50; 95% CI, 0.86–2.60; $P = 0.150$). Significant heterogeneity was detected for studies reporting the data of in-hospital mortality ($I^2 = 69.8\%$, $P_{\text{heterogeneity}} = 0.019$). After excluding the study by Sanak et al,[23] meta-analysis consistently showed that AF was associated with an increased risk of all-cause death in hospital (OR, 1.76; 95% CI: 1.02–3.03, $P = 0.044$) with significant heterogeneity ($I^2 = 71.8\%$, $P_{\text{heterogeneity}} = 0.029$). Visual inspection of Begg's funnel plot did not show significant asymmetry (Figure 3A). Neither Begg's test nor Egger's test suggested publication bias (Begg $P = 0.655$; Egger $P = 0.381$).

Secondary Outcomes

Eight studies[8,10,11,17–19,23,24] reported the occurrence of FO (Figure 4). Meta-analysis using the random effect model showed that patients without AF were more likely to achieve FO (OR, 1.95; 95% CI: 1.33–2.85, $P = 0.001$). Significant heterogeneity was found among the studies reporting data on FO ($I^2 = 79.1\%$, $P_{\text{heterogeneity}} < 0.001$). A sensitivity analysis further
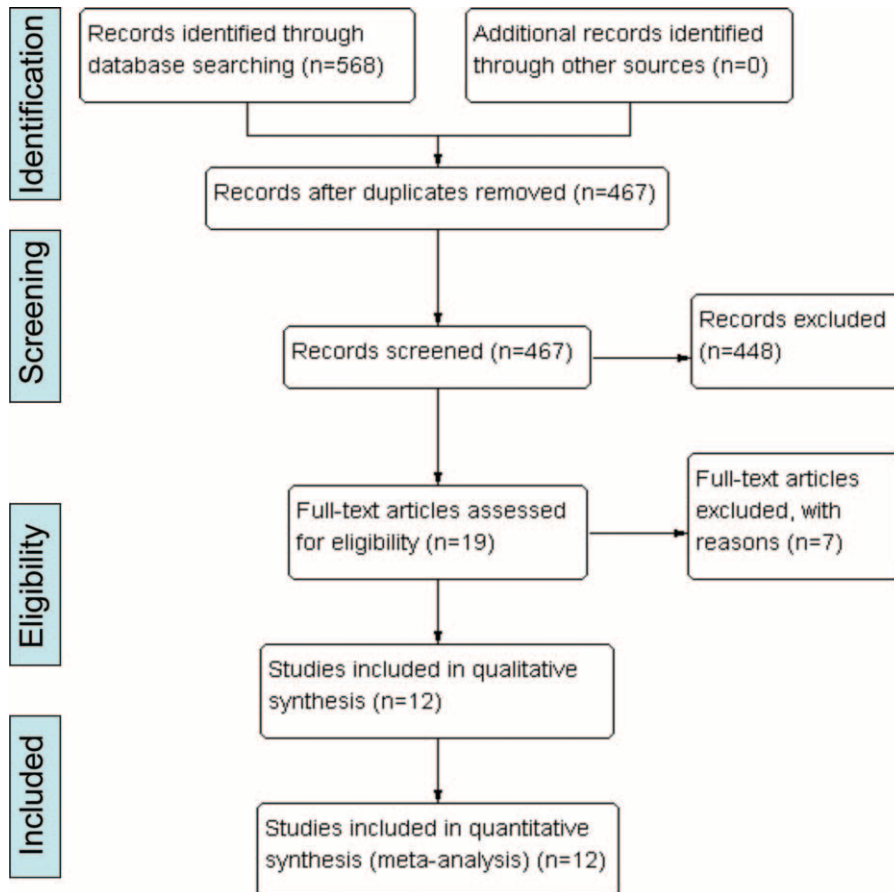
FIGURE 1. Flow diagram for study identification and inclusion.

showed that no significant change could be observed in FO after removing any included study (results not shown). Visual inspection of Begg's funnel plot did not show significant asymmetry (Figure 3B). Neither Begg's test nor Egger's test suggested publication bias (Begg $P = 0.621$; Egger $P = 0.369$).

Twelve studies[8,10,11,17–25] presented data regarding the influence of AF on the occurrence of SICH in patients with IS after thrombolysis (Figure 5). Pooled data with the fixed effect model indicated that AF was associated with an increased risk of SICH (OR, 1.28; 95% CI: 1.08–1.52, $P = 0.006$) without

TABLE 1. Characteristics of Studies Included in Meta-Analysis

Author, y	Design	Country	Comparison	No.	Age, y	Male (%)	NIHSS (median)	Intervention	Time window (mean)
Kimura, 2009[17]	PC	Japan	AF/non-AF	44/41	77/69	61/70	NA	rt-PA	148.3/147.6, min
Awadh, 2010[2]	RC	UK	AF/non-AF	74/154	76/66	40/59	14/14.5	rt-PA	163/173, min
Sanak, 2010[23]	RC	Czech	AF/non-AF	66/91	68/67	58/66	13/10	rt-PA	146.3/145.5, min
Zhang, 2010[18]	PC	China	AF/non-AF	22/31	68/61	41/74	12/9	rt-PA	204/197, min
Seet, 2011[11]	RC	Singapore	AF/non-AF	76/138	79/72	42/54	13/12	rt-PA	138/144,min
Frank, 2012[24]	RC	UK	AF/non-AF	639/2388	74/66	47/58	15/13	Alteplase	NA
Sung, 2013[8]	RC	China	AF/non-AF	72/71	68/65	58/65	NA	rt-PA	NA
Saposnik, 2013[10]	PC	Canada	AF/non-AF	316/1373	NA	NA	NA	rt-PA	NA
Padjen, 2013[19]	PC	Serbia	AF/non-AF	155/579	76/64	42/56	14/10	rt-PA	148/153,min
Tong, 2013[21]	PC	USA	AF/non-AF	1489/5704	NA	NA	NA	rt-PA	NA
Saarinen, 2014[25]	PC	Finland	AF/non-AF	102/209	77/69	47/53	8/4	NA	NA
Al-Khaled, 2014[20]	PC	German	AF/non-AF	387/620	NA	NA	NA	rt-PA	NA (<4.5 h)

AF = atrial fibrillation, NA = not available, NIHSS = National Institute of Health stroke scale, PC = prospective cohort, RC = retrospective cohort, rt-PA = recombinant tissue-type plasminogen activator.

**TABLE 2.** Clinical Outcomes of the Included Studies

Author, y	Follow-Up	Comparison	Mortality, %	FO, %	SICH, %	Quality Score
Kimura, 2009[17]	90 d	AF/non-AF	NA	15.9/46.3	51.8/48.2	7
Awadh, 2010[22]	90 d	AF/non-AF	NA	NA	4/4.5	8
Sanak, 2010[23]	90 d	AF/non-AF	18.2/3.3, 7d	50/72.6	27.3/5.5	8
Zhang, 2010[18]	90 d	AF/non-AF	18.2/9.7, 90d	36.4/51.6	NA	7
Seet, 2011[11]	90 d	AF/non-AF	NA	42/56	13/5	8
Frank, 2012[24]	90 d	AF/non-AF	21.8/13.6, 30d	33.0/49.4	8.5/7.3	7
Sung, 2013[8]	90 d	AF/non-AF	5.6/11.3, 90d	38.9/23.9	8.3/9.9	8
Saposnik, 2013[10]	1 y	AF/non-AF	26.3/14.2, 30d	16.1/33.2	16.5/11.6	7
Padjen, 2013[19]	90 d	AF/non-AF	21.9/ 9.0, 90d	48/65	5.8/5.5	7
Tong, 2013[21]	In hospital	AF/non-AF	12.6/5.8	NA	6.6/3.9	7
Saarinen, 2014[25]	90 d	AF/non-AF	20/6, 90d	NA	NA	7
Al-Khaled, 2014[20]	In hospital	AF/non-AF	10.9/6.6	NA	7.5/4.7	7

AF = atrial fibrillation, FO = favorable outcome, NA = not available, SICH = symptomatic intracerebral hemorrhage.

significant heterogeneity ($I^2 = 0.0\%$, $P_{\text{heterogeneity}} = 0.508$). A further sensitivity analysis showed that no significant change could be observed in SICH after removing any included study (results not shown). Visual inspection of the Begg funnel plot did not show significant asymmetry (Figure 3C). No evident publication bias was found by Begg's test ($P = 0.681$) or Egger's test ($P = 0.531$).

Subgroup Analysis

The detailed results stratified by region, design, sample size, and covariate adjustment are shown in Table 3. Subgroup analyses of in-hospital mortality showed that patients with AF had a higher risk of in-hospital mortality in the subgroup of non-Asia, prospective cohort study, sample size > 500, and adjusted confounding factors group. Heterogeneity was not
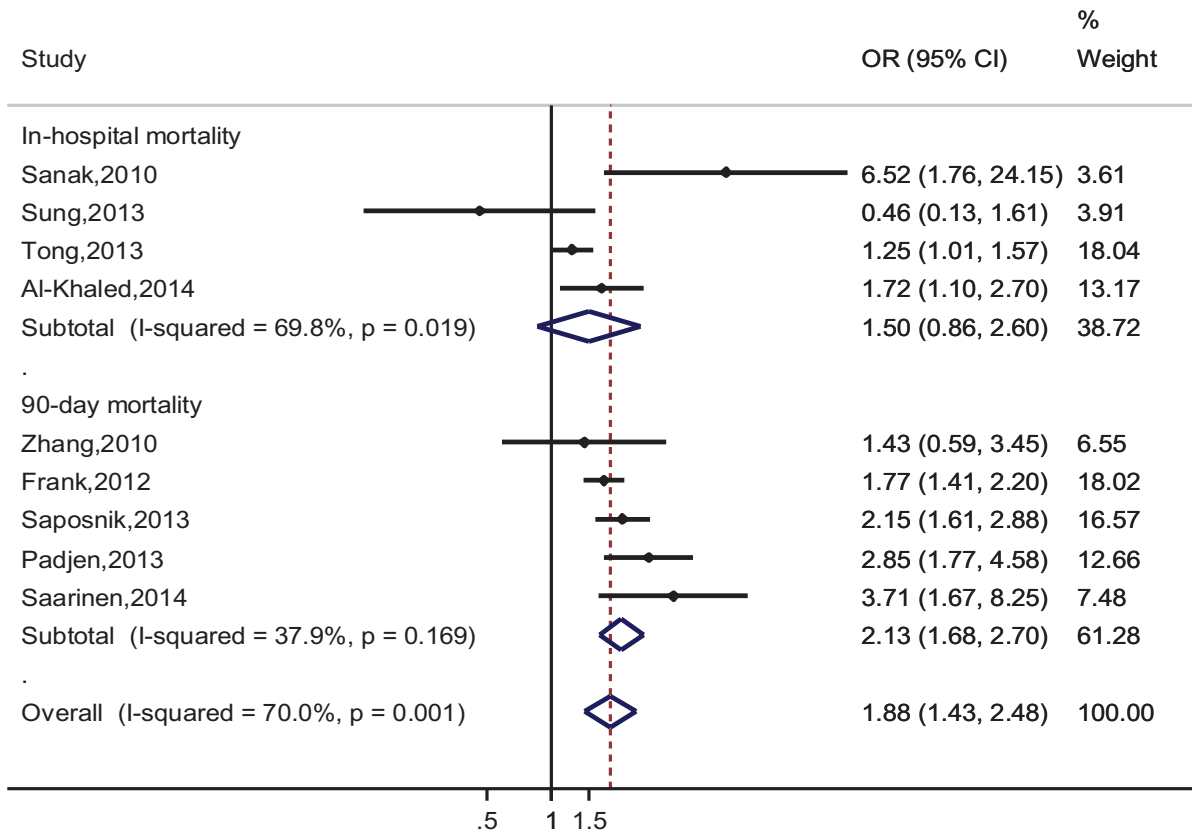
FIGURE 2. Odds ratio for in-hospital and 90-day mortality of thrombosis-treated patients with atrial fibrillation compared with those without atrial fibrillation.
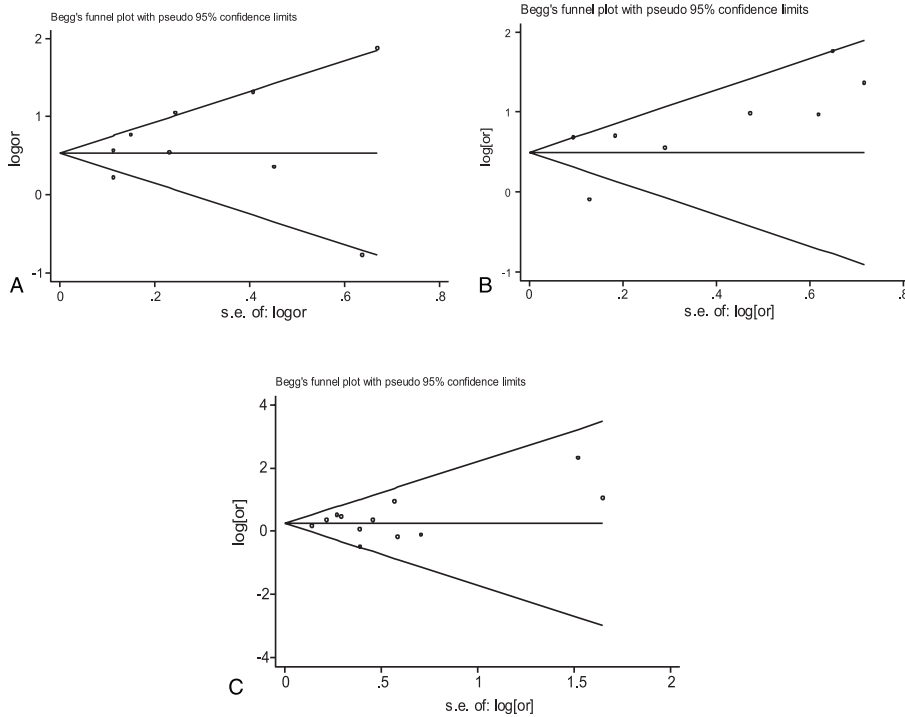
FIGURE 3. Begg's funnel plot based on the result of atrial fibrillation and risk of all-cause mortality (Panel A), favorable outcome (Panel B), and symptomatic intracerebral hemorrhage (Panel C).

observed in the subgroups listed above, except for the non-Asian studies.

In the subgroup analyses of FO, a reduced incidence of FO was observed in the group of Asian population, retrospective cohort study, sample size < 500, and adjusted and unadjusted confounding factors groups, respectively. The pooled OR of studies with adjusted confounding factors was higher compared to those without adjustment.

In the subgroup analyses of SICH, AF was a risk factor in the group of non-Asia, prospective cohort study,

FIGURE 4. Odds ratio for favorable outcome of thrombosis-treated patients with atrial fibrillation compared with those without atrial fibrillation.

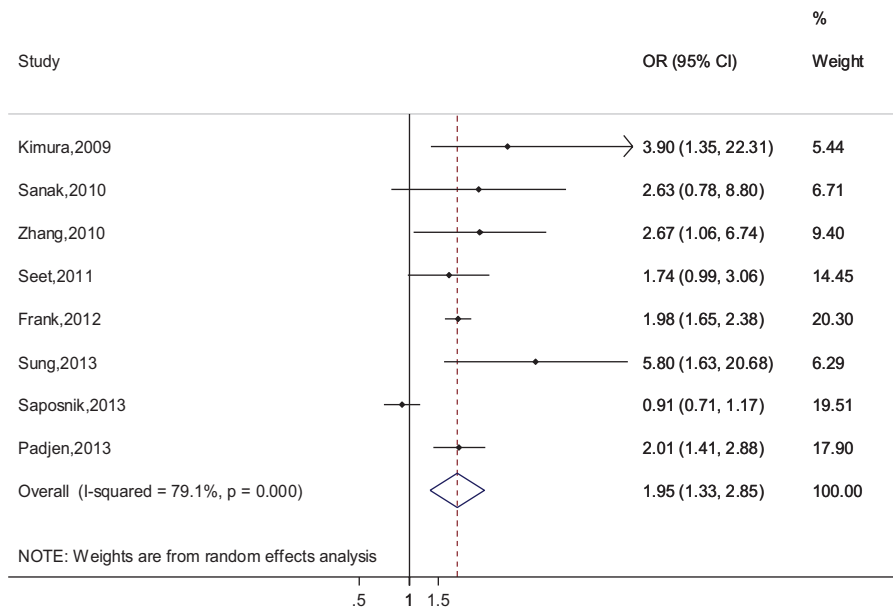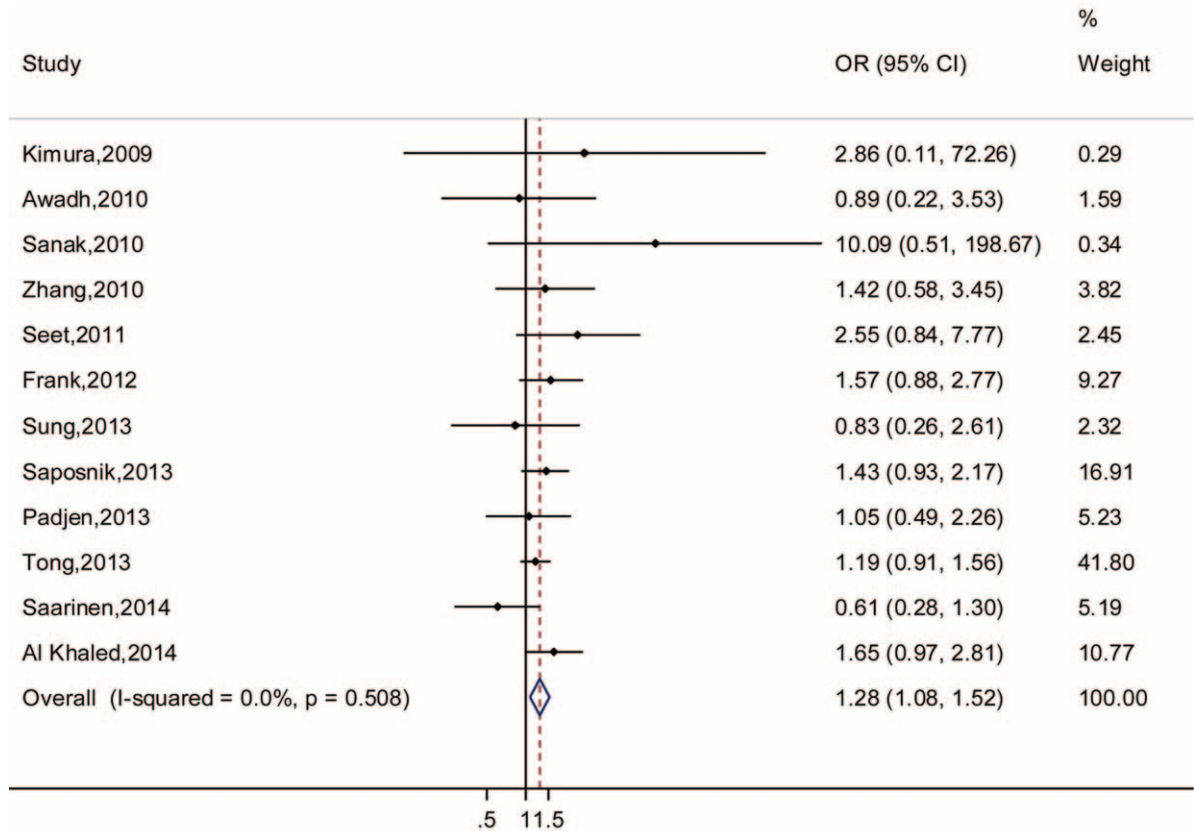**FIGURE 5.** Odds ratio for symptomatic intracerebral hemorrhage of thrombosis-treated patients with atrial fibrillation compared with those without atrial fibrillation.

sample size > 500, and adjustment without significant heterogeneity.

DISCUSSION

The present systematic review and meta-analysis demonstrated that comorbidity of AF may worsen clinical outcomes in patients with acute IS after thrombolytic therapy. Specifically, AF may increase the risk of death and SICH and decrease the achievement of FO after stroke thrombolysis. Therefore, AF is probably a risk factor of poor clinical outcomes for patients with acute IS after thrombolysis.

Prior studies regarding the impact of AF on the outcomes of thrombolyzed patients with acute IS revealed inconsistent results. Zhang et al[18] found that patients with acute IS and AF benefit from thrombotic therapy in terms of 90-day FO. In Sung et al's study,[8] the presence of AF was associated with favorable 90-day outcomes following thrombolysis in patients with severe stroke at baseline (NIHSS > 10). In the Virtual International Stroke Trials Archive (VISTA) trial,[24] no significant association between AF and overall stroke outcome could be found in 7091 patients (OR, 0.93; 95% CI, 0.84–1.03; $P = 0.409$). However, some studies indicated that stroke patients with AF might have a higher mortality rate, greater risk of intracerebral hemorrhage, and a similar response trend to thrombolysis compared with non-AF patients.[7,10,23] In the present study, by pooling the results of all cohort studies, we found that patients with acute IS and AF are likely to have a higher

mortality rate, greater risk of SICH, and less FO compared to those without AF. After ECASS III, the European Stroke Organization and the American Heart Association/American Stroke Association recommended thrombolysis as a first-line treatment for eligible patients when administered within 3 to 4.5 hours after the onset of stroke. Stroke with AF was not a contraindication in these guidelines. Because we found that presence of AF might worsen the clinical outcomes for patients with IS undergoing thrombolysis, further studies are needed to determine whether specific treatment strategies against AF may improve patients' clinical outcomes.

The exact mechanisms of AF on the outcomes of stroke patients were not clear. First, the establishment of collateral circulation of cerebral infarction may reduce the area of infarction after thrombolysis, maintain cerebral perfusion in the setting of arterial occlusion, protect brain tissue, and reduce the volume and intensity of hypoperfusion.[26,27] However, with respect to large artery atherothrombotic stroke, the ability was limited to establish collateral circulation for stroke patients with AF or arterial embolism.[23] Second, stroke patients with AF may have large and old thrombi, which are not sensitive to the treatment of thrombolytic therapy.[17,28] Third, although early arterial recanalization has been considered as a predictor of improved outcomes after thrombolytic therapy,[9] the influence of AF on the incidence of early arterial recanalization in patients with IS after thrombolysis was not consistent. An early study showed that AF was associated with a lower rate of recanalization after thrombolysis.[6] However, other studies showed that

TABLE 3. Subgroup Analyses of Atrial Fibrillation and Risk of in-Hospital Mortality, Favorable Outcome and Symptomatic Intracerebral Hemorrhage

Factors	No. of Studies	Meta-Analysis Pooled OR (95% CI)	*P*	Heterogeneity I^2	*P*
In-hospital mortality					
Region					
Asia	1	1.50 (0.86–2.60)	0.227	–	–
Non-Asia	3	1.76 (1.02–3.03)	0.044	71.8	0.029
Design					
Prospective	2	1.38 (1.03–1.83)	0.029	35.5	0.213
Retrospective	2	1.72 (0.13–23.02)	0.680	87.8	0.004
Sample size					
More than 500	2	1.38 (1.03–1.83)	0.029	35.5	0.213
Less than 500	2	1.72 (0.13–23.02)	0.68	87.8	0.004
Covariate adjustment					
Adjusted	1	1.25 (1.01–1.57)	0.047	–	–
Unadjusted	3	1.25 (1.00–1.56)	0.365	75.7	0.016
Favorable outcome					
Region					
Asia	4	2.51 (1.518–4.16)	<0.001	17.0	0.306
Non-Asia	4	1.62 (0.99–2.66)	0.054	88.8	<0.001
Design					
Prospective	4	1.78 (0.93–3.89)	0.08	83.4	<0.001
Retrospective	4	2.02 (1.64–2.48)	<0.001	4.8	0.369
Sample size					
More than 500	3	1.53 (0.90- 2.60)	0.118	92.4	<0.001
Less than 500	5	2.39 (1.59–3.58)	<0.001	0.0	0.457
Covariate adjustment					
Adjusted	5	2.40 (1.03–5.58)	0.042	77.0	0.002
Unadjusted	3	1.96 (1.68–2.30)	<0.001	0.0	0.904
Symptomatic intracerebral hemorrhage					
Region					
Asia	4	1.49 (0.83–2.66)	0.185	0.0	0.559
Non-Asia	8	1.26 (1.05–1.51)	0.013	11.6	0.340
Design					
Prospective	5	1.29 (1.06–1.58)	0.012	0.0	0.753
Retrospective	7	1.24 (0.87–1.76)	0.228	27.8	0.217
Sample size					
More than 500	5	1.32 (1.09–1.59)	0.004	0.0	0.266
Less than 500	7	1.10 (0.71–1.70)	0.671	21.4	0.724
Covariate adjustment					
Adjusted	4	1.30 (1.05–1.61)	0.018	0.0	0.561
Unadjusted	8	1.25 (0.93–1.67)	0.143	14.1	0.320

CI = confidence interval, OR = odds ratio.

strokes caused by cardiac thrombus or AF have a higher rate of recanalization after thrombolysis.[29] Interestingly, a study by Frank et al did not even indicate a difference in the recanalization rate between the AF and non-AF groups.[24] Therefore, there is a controversy over whether or not there is better arterial recanalization in stroke patients with AF.

Our meta-analysis showed that AF was associated with worse outcomes in thrombolyzed patients with acute IS. The quality of included studies was high with an NOS score of >7, and no significant publication bias was found. However, in the included studies, patients with acute IS and AF were generally with older with a higher NIHSS, and we did not adjust for age or NIHSS in the meta-analysis. The high heterogeneity of studies

with regard to in-hospital mortality and FO was associated with the confounding factors between IS patients with and without AF. In the VISTA trial,[24] 29% of the variability could be explained by differences of combining age with baseline NIHSS in the population with acute IS; thus, AF was not independently associated with the 90-day outcomes, with a lower percentages of FO for IS patients with AF, compared to patients without AF. In Saposnik et al's studies,[3,10] although patients with IS and AF were older, more likely to have severe stroke, higher mortality rate, and risk of intracerebral hemorrhage, AF appeared to be a marker of high age and baseline NIHSS rather than an independent risk factor for poor stroke outcomes and it had no discernible impact on the effect of thrombolysis for patients

with acute IS. AF may have an increasingly deleterious effect in elderly patients, or maybe elderly patients with AF had a more hypercoagulable or prothrombotic state. The interaction between age and AF could worsen the clinical outcomes of thrombolyzed patients with acute IS. In addition, subgroup analysis in our meta-analysis revealed that AF was associated with a reduced incidence of FO, and an increased risk of in-hospital mortality and SICH using pooled adjusted ORs, whereas the pooled unadjusted data did not suggest an association between AF and worse outcomes. Thus, the confounding factors may have influenced the actual outcomes. Finally, there were some differences in the definitions of FO and SICH among the studies. The outcome measures in our study were not clearly defined, and this may introduce potential bias. Therefore, the pooled data for AF and worse outcomes after stroke thrombosis should be interpreted with caution, and further large studies are needed to evaluate these associations.

Our analysis has several limitations that should be considered when interpreting our findings. First, although we conducted subgroup analysis stratified by covariate adjustment, limited studies were adjusted for baseline difference, and the statistical power was not strong. Second, the included studies did not provide enough information about the types of AF and the severity of stroke; therefore, we could not investigate the association between different types of AF on the clinical outcomes of patients with AF with different levels of stroke after thrombosis. Third, the follow-up duration of the included studies was short; the longest was 90 days. We could not investigate the association between AF and the long-term prognosis of patients with acute IS undergoing thrombolytic therapy.

In conclusion, AF may worsen the clinical outcomes for patients with acute IS after thrombolysis. Patients with acute IS and AF have increased risk of mortality and SICH and less FO compared to patients without AF. Further studies with larger sample sizes using rigorous study designs and well-matched patient characteristics (especially in risk factors) are needed to confirm the findings of our study.

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