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ORIGINAL RESEARCH

Comparison of Different Dosages of Alteplase in Atrial Fibrillation–Related Acute Ischemic Stroke After Intravenous Thrombolysis: A Nationwide, Multicenter, Prospective Cohort Study in Taiwan

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BACKGROUND: Insufficient evidence is available for patients with acute ischemic stroke with atrial fibrillation (AF) to determine the efficacy and safety of different dosages of intravenous thrombolysis treatment. This study examined clinical outcomes in Chinese patients with stroke with and without AF after intravenous thrombolysis treatment with different intravenous thrombolysis doses.

METHODS AND RESULTS: This multicenter, prospective cohort study recruited 2351 patients with acute ischemic stroke (1371 with AF and 980 without AF) treated with intravenous thrombolysis using alteplase. The Totaled Health Risks in Vascular Events score is a validated risk-scoring tool used for assessing patients with acute ischemic stroke with and without AF. We evaluated favorable functional outcome at day 90 and symptomatic intracranial hemorrhage within 24 to 36 hours and outcomes of the patients receiving different doses of alteplase. Compared with the non-AF group, the AF group exhibited a 2- to 3-fold increased risk of symptomatic intracranial hemorrhage according to the National Institute of Neurological Disorders and Stroke standard (relative risk [RR], 2.10 [95% CI, 1.35–3.26]). Favorable functional outcome at 90 days and symptomatic intracranial hemorrhage rates according to the European Cooperative Acute Stroke Study II and the Safe Implementation of Thrombolysis in Stroke-Monitoring Study standards did not significantly differ between the AF and non-AF groups. In addition, the low-dose alteplase subgroup exhibited an increased risk of symptomatic intracranial hemorrhage according to the National Institute of Neurological Disorders and Stroke standard (RR, 2.84 [95% CI, 1.63–4.96]). A validation study confirmed these findings after adjustment for scores determined using different stroke risk-scoring tools.

CONCLUSIONS: Different alteplase dosages did not affect functional status at 90 days in the AF and non-AF groups. Thus, the adoption of low-dose alteplase simply because of AF is not recommended.

Key Words: acute stroke ■ atrial fibrillation ■ functional outcome ■ intravenous thrombolysis ■ symptomatic intracranial hemorrhage

The prevalence of atrial fibrillation (AF) increases with age.[1–3] AF causes one-fourth of acute ischemic stroke cases worldwide.[4–6] In Taiwan, AF is the most common arrhythmia and accounts for 20% to 25% of acute ischemic stroke.[7,8] Studies have reported that AF-related stroke causes more disabilities

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CLINICAL PERSPECTIVE

What Is New

- After adjustment for the Totaled Health Risks in Vascular Events and other prognostic risk scores, clinical outcomes were comparable between stroke patients with and without atrial fibrillation treated with intravenous thrombolysis.
- Increased symptomatic intracranial hemorrhage was only observed in patients treated with a lower dose of alteplase according to the National Institute of Neurological Disorders and Stroke standard (any point decline in National Institutes of Health Stroke Scale score) but not for ECASS II (European Cooperative Acute Stroke Study II) and SITS-MOST (Safe Implementation of Thrombolysis in Stroke-Monitoring Study) standards (National Institutes of Health Stroke Scale of ≥4 points).

What Are the Clinical Implications?

- This study determined 90-day clinical outcomes between the AF and non-AF groups.
- In our cohort of Asian patients, AF was not the reason indicated for prescribing low-dose alteplase.

Nonstandard Abbreviations and Acronyms

FFO	favorable functional outcome
FI	functional independence
IPTW	inverse probability of treatment weighting
IVT	intravenous thrombolysis
SICH	symptomatic intracranial hemorrhage

compared with stroke not related to AF.[9,10] Despite receiving intravenous thrombolysis (IVT) treatment, patients with AF-related acute ischemic stroke had poorer functional outcomes and higher hemorrhagic transformation risk.[11,12] In addition, compared with White patients with AF, Asian patients with AF had a higher incidence of stroke[13,14] and up to 2- to 4-fold higher risk of intracranial bleeding.[15–18]

Few risk-scoring tools are available to predict clinical outcomes in acute ischemic stroke with AF. The THRIVE (Totaled Health Risks in Vascular Events) score[19] assesses age, and the National Institutes of Health Stroke Scale (NIHSS) score assesses at the time of hospital admission and evaluates the presence of hypertension, diabetes, and AF. Studies have reported the broad utility of the THRIVE score[19] to predict clinical outcomes, namely functional status, mortality, and hemorrhagic transformation after IVT.[20,21] In addition, the applicability of the THRIVE score in Chinese patients with acute ischemic stroke treated with IVT was validated.[22,23]

Since the earlier J-ACT (Japan Alteplase Clinical Trial)[24] in 2006 advocated using a lower dose of alteplase (0.6 mg/kg) to achieve equivalent efficacy and ensure safety of IVT in patients with acute ischemic stroke, the debate on the different dosages of IVT for Asian patients with stroke has been ongoing. Our previous studies, the TTT-AIS (Taiwan Thrombolytic Therapy for Acute Ischemic Stroke) study I and II,[25,26] and a 2019 octogenarian study,[27] have reported an association of a lower dose with decreased mortality and increased favorable functional outcomes (FFOs) for mild stroke. This study evaluated clinical outcomes after IVT treatment between stroke patients with AF and those without AF by adjusting the THRIVE score and determined outcomes in patients with AF-related stroke treated with different IVT doses.

METHODS

The data that support the findings of this study are available from the corresponding author (A.-C.C. [achch@cc.kmu.edu.tw]) upon reasonable request.

Study Design and Participants

The TTT-AIS study included a nationwide Chinese stroke cohort with longitudinal follow-up data for 90 days.[25,26] This multicenter, prospective cohort study included patients from 30 hospitals throughout all regions in Taiwan from December 1, 2004 to December 31, 2016. On arrival at the hospital within 3 hours of stroke onset, patients with acute ischemic stroke were treated with IVT, with alteplase as the thrombolytic agent. The inclusion criteria were the following: (1) receiving IVT treatment adhering to the National Institute of Neurological Disorders and Stroke (NINDS) criteria,[28] (2) undergoing brain computed tomography (CT) before IVT and another CT scan within 24 to 36 hours after IVT, and (3) having complete data of the IVT dose using alteplase. According to the ECASS (European Cooperative Acute Stroke Study), early ischemic changes on brain CT were defined as subtle gray matter hypodensity, subtle cortical hypodensity, loss of the insular ribbon, sulcal effacement attributable to early edema, and the hyperdense middle cerebral artery sign.[29–31] A dose of 0.9 mg/kg (0.86–0.95 mg/kg) of alteplase for IVT was defined as the standard-dose subgroup, whereas 0.6 mg/kg (0.55–0.65 mg/kg), 0.7 mg/kg (0.66–0.75 mg/kg), and 0.8 mg/kg (0.76–0.85 mg/kg) were defined as low-dose subgroups.[25,32–34] The exclusion criteria for IVT were based on the SITS-MOST (Safe Implementation of Thrombolysis in Stroke-Monitoring Study) criteria.[35] The following data

for each enrolled patient with stroke were prospectively retrieved and registered: age; sex; history of hypertension, diabetes, and coronary artery disease; alcohol use; presence of AF; the baseline NIHSS score; laboratory testing data; and antithrombotic medications. Written informed consent was obtained from patients who were mentally competent or from patients' legal surrogates when they could not provide the consent. This study was approved by the institutional review board of Kaohsiung Medical University Hospital (reference number: KMUH-IRB-20140305).

Measurement of Risk Scores in Patients With Stroke

To evaluate each patient's THRIVE score,[20] 1 point each was assigned for the age of 60 to 79 years, AF, hypertension, and diabetes; 2 points each for the age ≥80 years and an NIHSS score of 11 to 20 at baseline, and 4 points for an NIHSS score of ≥21 at baseline. In addition, we used additional validated risk-scoring tools for Chinese patients with stroke treated after IVT[36] despite no inclusion of AF in these scoring tools to estimate hemorrhagic transformation risk and clinical response. The following risk-scoring tools were used to examine the baseline severity of the enrolled patients with stroke: the HAT (Hemorrhage After Thrombolysis) score[37]; the SITS-SICH (Safe Implementation of Thrombolysis in Stroke-Symptomatic Intracranial Hemorrhage) score[38]; the Cucchiara score[39]; SEDAN (Blood Sugar, Early Infarct Signs and Hyperdense Cerebral Artery Sign, Age, and NIHSS) score[40]; SPAN-100 Index (Stroke Prognostication Using Age and National Institutes of Health Stroke Scale-100 Index)[41]; and GRASPS (Glucose, Race, Age, Sex, Pressure, Stroke Severity) score[42] (see Table 1 for details).

Measurement of Clinical Outcomes

The primary objective was to determine differences in FFO rates at 90 days and symptomatic intracranial hemorrhage (SICH) after IVT within 24 to 36 hours between the AF and non-AF groups. Two standards of favorable functional status[43] were applied: (1) FFO was defined as a modified Rankin Scale (mRS) score of 0 to 1, and (2) functional independence (FI) was defined as an mRS score of 0 to 2. Three standards of SICH within 24 to 36 hours were used: (1) the NINDS standard,[28] in which any intracranial hemorrhage occurred with the deterioration of the NIHSS score to ≥1 or death; (2) the ECASS II standard,[44] in which any intracranial hemorrhage occurred with the deterioration of the NIHSS score to ≥4 or death; and (3) the SITS-MOST standard,[35] in which a type 2 parenchymal hemorrhage occurred (a local or remote parenchymal intracranial hemorrhage exceeding 30% of the infarct) with the deterioration of the NIHSS score to ≥4 or death

Table 1. Risk-Scoring Models Used in the Validation Study

Stroke risk-scoring tools	Variables required	Cutoff values (points obtained for each item)
THRIVE score[20]	Age, y	60–79 (1), ≥80 (2)
	NIHSS	11–20 (2), ≥21 (4)
	Hypertension	Yes (1)
	Diabetes	Yes (1)
	Atrial fibrillation	Yes (1)
HAT score[37]	NIHSS	15–20 (1), >20 (2)
	Glucose >200 mg/dL or diabetes	Yes (1)
	Hypodensity on CT	<1/3 of the MCA territory (1), ≥1/3 of the MCA territory (2)
SITS-SICH score[38]	Age, y	≥72 (1)
	NIHSS	7–12 (1), ≥13 (2)
	Glucose	≥180 mg/dL (2)
	Systolic blood pressure	≥146 mm Hg (1)
	Weight	≥95 kg (1)
	Onset to thrombolytic time	≥180 min (1)
	Aspirin monotherapy	Yes (2)
	Aspirin+clopidogrel	Yes (3)
	Hypertension	Yes (1)
Cucchiara score[39]	Age	>60 (1)
	NIHSS	>10 (1)
	Glucose	>150 mg/dL (1)
	Platelet count	<150 000/mm^3 (1)
SEDAN score[40]	Glucose	145–216 mg/dL (1), >216 mg/dL (2)
	Early infarct on CT	Yes (1)
	Dense cerebral artery sign on CT	Yes (1)
	Age, y	>75 (1)
	NIHSS	≥10 (1)
SPAN-100 Index[41]	Age+NIHSS	≥100 (1)
GRASPS score[42]	Age, y	≤60 (8), 61–70 (11), 71–80 (15), >80 (17)
	NIHSS	0–5 (20), 6–10 (27), 11–15 (34), 16–20 (40), >20 (42)
	Glucose	<100 (2), 100–149 (6), ≥150 (8)
	Systolic blood pressure	<120 (10), 120–149 (14), 150–179 (18), ≥180 (21)
	Race	Asian (9), non-Asian (0)
	Sex	Male (4), female (0)

CT indicates computed tomography; GRASPS, Glucose, Race, Age, Sex, Pressure, Stroke Severity; HAT, Hemorrhage After Thrombolysis; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; SEDAN, Blood Sugar, Early Infarct Signs, and Hyperdense Cerebral Artery Sign, Age, and National Institutes of Health Stroke Scale; SITS-SICH, Safe Implementation of Treatment in Stroke-Symptomatic Intracerebral Hemorrhage; SPAN-100, Stroke Prognostication Using Age and National Institutes of Health Stroke Scale-100 Index; and THRIVE, the Totaled Health Risks in Vascular Events.

Table 2. Baseline Characteristics of Patients With and Without AF (N=2351)

Characteristics	Non-AF, n=1371	AF, n=980	*P* value
Age, y	66.4±13.0	71.7±11.9	<0.0001
Age groups, %			<0.0001
<60 y	29.7% (407/1371)	17.0% (167/980)	
60–79 y	54.9% (752/1371)	54.8% (537/980)	
≥80 y	15.5% (212/1371)	28.2% (276/980)	
Female sex, %	33.2% (456/1371)	41.8% (410/980)	<0.0001†
Medical history, %			
Hypertension	69.3% (946/1365)	74.8% (733/980)	0.0036
Diabetes	33.5% (457/1365)	30.4% (298/980)	0.1164
Hyperlipidemia	37.9% (520/1371)	31.5% (309/980)	0.0014†
Coronary artery disease	11.4% (156/1365)	17.0% (167/980)	0.0001†
Alcoholism	8.1% (110/1365)	6.9% (68/980)	0.3126
Prestroke mRS			0.6285
mRS of 0–2	56.8% (779/1371)	55.8% (547/980)	
mRS of 3–5	43.2% (592/1371)	44.2% (433/980)	
CT scan of brain at baseline			0.0062†
Normal	88.5% (1214/1371)	84.7% (830/980)	
Early ischemic changes	11.5% (157/1371)	15.3% (150/980)	
Stroke severity, %*			<0.0001†
Mild, NIHSS of ≤10	45.2% (620/1371)	28.8% (282/980)	
Moderate, NIHSS of 11–20	39.5% (542/1371)	45.8% (449/980)	
High, NIHSS of ≥21	15.2% (209/1371)	25.4% (249/980)	
Alteplase dose, mg/kg	0.81±0.13	0.78±0.14	<0.0001†
Groups of alteplase dosage, %			<0.0001†
Standard dose, 0.9 mg/kg	32.7% (448/1371)	23.9% (234/980)	
Low dose, 0.6–0.8 mg/kg	67.3% (923/1371)	76.1% (746/980)	
MAP on arrival, mm Hg	114.0±21.2	113.6±20.6	0.5843
Time to treatment, min	116.8±60.0	135.1±45.0	<0.0001
Fasting glucose, mg/dL	155.0±81.5	145.4±86.3	0.0038†
THRIVE score	3.3±1.8	4.1±1.8	<0.0001†
Groups of THRIVE score, %			<0.0001†
0–2	38.0% (521/1371)	20.8% (204/980)	
3–5	48.4% (663/1371)	55.9% (548/980)	
6–9	13.6% (187/1371)	23.3% (228/980)	
Pre-stroke antithrombotic medications			
Aspirin	10.9% (149/1371)	11.0% (108/980)	0.9070
P2Y12 inhibitors	1.8% (25/1371)	1.9% (19/980)	0.8388
Dual antiplatelet	1.3% (18/1371)	1.8% (17/980)	0.4051
Warfarin	0.8% (11/1371)	4.4% (43/980)	<0.0001†

Continuous variables are expressed as mean±standard deviation. AF indicates atrial fibrillation; CT, computed tomography; mRS, modified Rankin scale; and NIHSS, National Institutes of Health Stroke Scale.

Statistically significant at $P<0.05$.

†The cutoff interval for the baseline NIHSS score was in accordance with the THRIVE (Totaled Health Risks in Vascular Events) score classification.

within 36 hours. The secondary objective was to examine clinical outcomes in the subgroups of patients with stroke treated with IVT using low- and standard-dose alteplase.

Statistical Analysis

The Student *t* test and Pearson χ^2 test were performed to examine differences in continuous and categorical variables, respectively, between the AF and non-AF groups. Univariate multiple Poisson regression models were used to determine the relative risks (RRs) and their 95% CIs. In these models, the study outcomes of interest were considered as dependent variables. AF versus non-AF was included as the independent variable, and the THRIVE score[20] or other stroke risk-scoring tools, prestroke mRS, early ischemic changes on brain CT, and use of antithrombotic medications were included as fixed-effects covariates. Thirty hospitals were included as a random-effects factor. The heterogeneity of the association between the different doses of IVT was estimated by adding an interaction term to the model. We performed a separate validation study to confirm the primary and secondary objectives by using stroke risk-scoring tools, namely the HAT score,[37] SITS-SICH score,[38] the Cucchiara score,[39] the SEDAN score,[40] the SPAN-100 Index,[41] and the GRASPS score.[42] Statistical significance was defined as $P<0.05$. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Sensitivity Analysis

We performed data imputation for the baseline and outcome variables with loss to follow-up at 90 days and used the inverse probability of treatment weighting (IPTW) to reduce selection bias in observational studies.[45,46] For data imputation, we used fully conditional specification multiple imputation that is performed on a variable-by-variable basis by using a set of conditional densities (with linear regression for continuous variables and logistic regression for categorical variables). The number of multiple imputations was determined using the quadratic rule with the formula $M=1+df\times\gamma^2$,[47,48] where M was the number of imputations, *df* was the desired degrees of freedom, and γ was the fraction of missing information. The standardized mean difference was determined to investigate

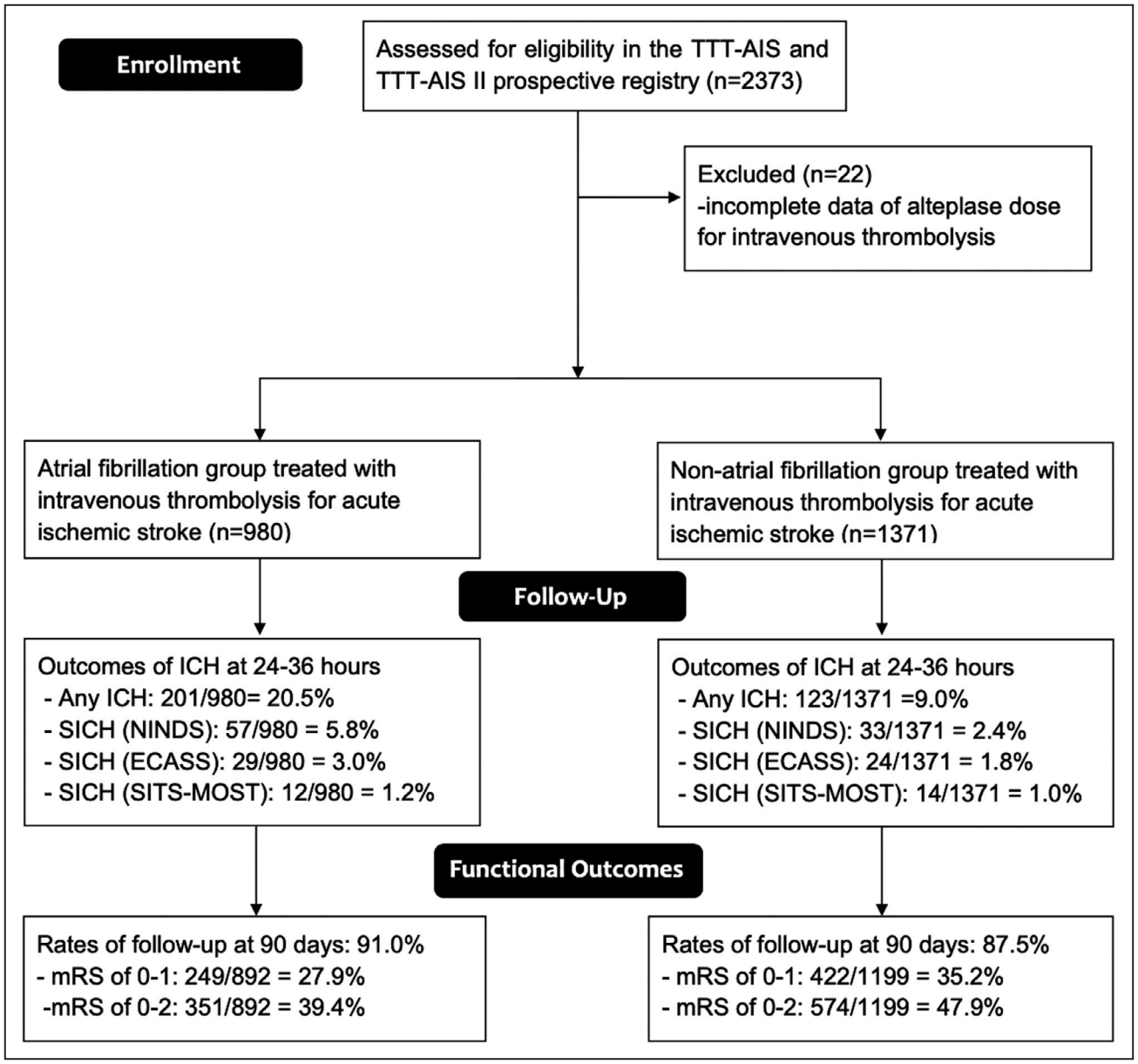

Figure 1. Flow diagram of the study.
ECASS indicates European Cooperative Acute Stroke Study; ICH, intracranial hemorrhage; mRS, modified Rankin Scale; NINDS, National Institute of Neurological Disorders and Stroke; SICH, symptomatic intracranial hemorrhage; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study; and TTT-AIS, Taiwan Thrombolytic Therapy for Acute Ischemic Stroke.

whether characteristics were balanced between AF and non-AF groups, and an absolute difference of a standardized mean difference of <0.1 was defined as a balanced status.[45,46] Three sensitivity analyses were conducted: (1) primary objectives were determined between the AF and non-AF groups, (2) a subgroup analysis of different alteplase doses (0.6 versus 0.9 mg/kg) was performed between the AF and non-AF groups, and (3) a subgroup analysis for different alteplase doses (0.6 versus 0.9 mg/kg) was performed after adjustment for scores determined using different risk-scoring tools. Patients who received alteplase doses of 0.7 and 0.8 mg/kg were excluded from the subgroup analysis. Multiple imputation and IPTW were performed using SAS 9.4 (SAS Institute).

RESULTS

Baseline Demographic Characteristics

From December 1, 2004 to December 31, 2016, there were 2351 patients with acute ischemic stroke (1371 without AF and 980 with AF) who completed IVT treatment and were enrolled in this study (Table 2). The study flowchart is presented in Figure 1. The mean ages, proportions of female patients, and mean

Table 3. Analysis of the Risk of Unfavorable Functional Outcomes and SICH With AF

Characteristics	AF	Non-AF	RR (95% CI)	*P* value	Adjusted RR (95% CI)†	*P* value
Functional outcome of mRS on day 90						
0: No symptoms	13.3% (119/892)	17.9% (215/1199)				
1: No substantive disability	14.6% (130/892)	17.3% (207/1199)				
2: Slight disability	11.4% (102/892)	12.7% (152/1199)				
3: Moderate disability	11.8% (105/892)	15.5% (186/1199)				
4: Moderate to severe disability	18.4% (164/892)	16.4% (196/1199)				
5: Severe disability	20.1% (179/892)	11.4% (137/1199)				
6: Death	10.4% (93/892)	8.8% (106/1199)	1.18 (0.89–1.56)	0.2457	0.99 (0.73–1.33)	0.9258
Favorable outcomes at 90 d						
mRS of 0–1, FFO	27.9% (249/892)	35.2% (422/1199)	0.90 (0.81–0.99)	0.0458*	0.99 (0.89–1.11)	0.8645
mRS of 0–2, FI	39.4% (351/892)	47.9% (574/1199)	0.86 (0.77–0.96)	0.0099*	1.01 (0.89–1.13)	0.9164
SICH at 24–36 h						
By NINDS standard	5.8% (57/980)	2.4% (33/1371)	2.41 (1.57–3.71)	<0.0001*	2.14 (1.36–3.37)	0.0010*
By ECASS II standard	3.0% (29/980)	1.8% (24/1371)	1.69 (0.98–2.90)	0.0571	1.43 (0.81–2.54)	0.2145
By SITS-MOST standard	1.2% (12/980)	1.0% (14/1371)	1.19 (0.55–2.59)	0.6444	0.99 (0.44–2.20)	0.9726

AF indicates atrial fibrillation; ECASS II, European Cooperative Acute Stroke Study II; FFO, favorable functional outcome; FI, functional independence; mRS, modified Rankin Scale; NINDS, National Institute of Neurological Disorders and Stroke; RR, relative risk; SICH, symptomatic intracranial hemorrhage; and SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study.

*Multivariable Poisson regression was adjusted for fixed effects of the THRIVE (Totaled Health Risks in Vascular Events) score, prestroke mRS, early ischemic changes, and prestroke antithrombotic medications, and random effects for 30 hospitals.

†Statistically significant at $P<0.05$.

dosages of alteplase were 71.7±11.9 and 66.4±13.0 years ($P<0.0001$), 41.8% and 33.2% ($P<0.0001$), and 0.78±0.14 and 0.81±0.13 mg/kg ($P<0.0001$) in the AF and non-AF groups, respectively. No significant difference in the mean arterial pressure was observed between the AF and non-AF groups. The proportions of prestroke mRS of 0 to 2 was similar in the AF and non-AF groups (56.8% and 55.8%, $P=0.6285$), and a higher proportion of the patients in the non-AF group than in the AF group had mild stroke (NIHSS score ≤10). The AF group had higher THRIVE scores than the non-AF group (4.1±1.8 versus 3.3±1.8, $P<0.0001$). Moreover, a higher proportion of the patients in the AF group than in the non-AF group exhibited early

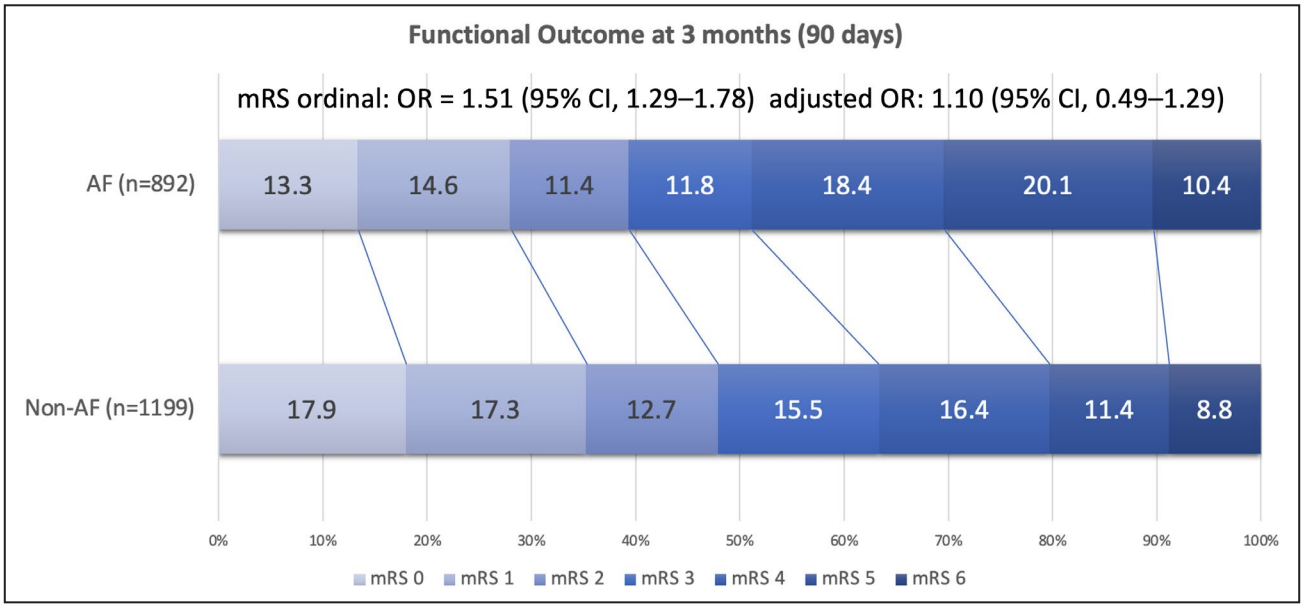

Figure 2. Distribution of functional outcomes at 90 days.
The data set shows no differences in functional outcomes between the atrial fibrillation (AF) and non-AF groups after adjustment for the THRIVE (Totaled Health Risks in Vascular Events) score (adjusted odds ratio [OR], 1.10 [95% CI, 0.49–1.29]). mRS indicates modified Rankin Scale.

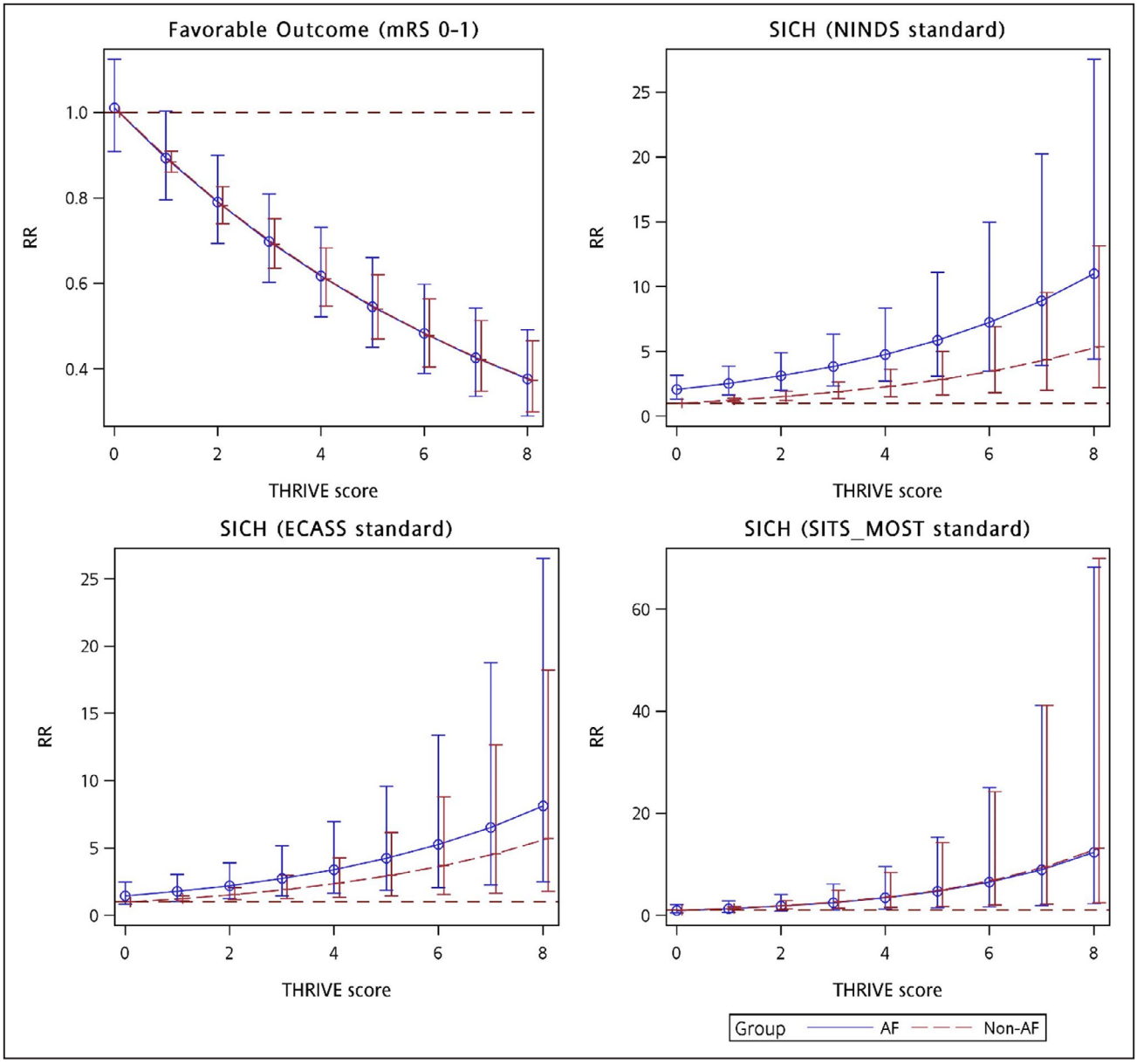

Figure 3. The relationship between the THRIVE (Totaled Health Risks in Vascular Events) score and clinical outcomes.
AF indicates atrial fibrillation; ECASS, European Cooperative Acute Stroke Study; mRS, modified Rankin Scale; NINDS, National Institute of Neurological Disorders and Stroke; SICH, symptomatic intracranial hemorrhage; RR, relative risk; and SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study.

ischemic changes (15.3% versus 11.5%, *P*=0.0062), and received warfarin before stroke (4.4% versus 0.8%, *P*<0.0001). Furthermore, 682 (29.0%), 738 (31.4%), 550 (23.3%), and 381 (16.2%) patients received 0.9, 0.8, 0.7, and 0.6 mg/kg of alteplase, respectively.

Primary Objectives (AF Versus Non-AF Group)

The primary objectives are listed in Table 3, and the functional outcome distribution in terms the mRS score at 90 days is illustrated in Figure 2. The AF group exhibited decreased FFO (RR, 0.90 [95% CI, 0.81–0.99]; *P*=0.0458) and FI (RR, 0.86 [95% CI, 0.77–0.96]; *P*=0.0099). After adjustment for the THRIVE score, no significant differences in both FFO (adjusted RR, 0.99 [95% CI, 0.89–1.11]; *P*=0.8645) and FI (adjusted RR, 1.01 [95% CI, 0.89–1.13]; *P*=0.9164) were observed between the AF and non-AF groups. The 90-day mortality rate did not significantly differ between the 2 groups. In addition, the AF group had a 2-fold increased SICH rate determined according to the NINDS standard than did the non-AF group (RR, 2.41 [95% CI, 1.57–3.71]; *P*<0.0001; adjusted

Table 4. Subgroup Analysis by Different Doses of Tissue Plasminogen Activator

Characteristics	AF	Non-AF	RR (95% CI)	*P* value	Adjusted RR (95% CI)†	*P* value	*P* value (interaction)‡
Low-dose subgroup, n=1669							
Favorable outcomes at 90 d							
mRS of 0–1	26.0% (177/680)	34.1% (274/804)	0.89 (0.79–1.01)	0.0642	0.97 (0.86–1.10)	0.6436	0.3445
mRS of 0–2	37.1% (252/680)	47.6% (383/804)	0.83 (0.73–0.95)	0.0074*	0.95 (0.83–1.09)	0.4827	0.7323
SICH at 24–36 h							
By NINDS standard	6.2% (46/746)	2.0% (18/923)	3.17 (1.83–5.45)	<0.0001	2.87 (1.63–5.04)	0.0003*	0.0047*
By ECASS II standard	3.1% (23/746)	1.7% (16/923)	1.78 (0.94–3.37)	0.0769	1.61 (0.83–3.12)	0.1618	0.3625
By SITS-MOST standard	1.2% (9/746)	0.9% (9/923)	1.24 (0.49–3.12)	0.6515	1.05 (0.40–2.75)	0.9140	0.6415
Standard-dose subgroup, n=682							
Favorable outcomes at 90 d							
mRS of 0–1	34.0% (72/212)	37.4% (148/395)	0.95 (0.77–1.17)	0.6061	1.05 (0.85–1.30)	0.6467	
mRS of 0–2	46.7% (99/212)	48.4% (191/395)	0.97 (0.77–1.22)	0.7878	1.15 (0.91–1.46)	0.2469	
SICH at 24–36 h							
By NINDS standard	4.7% (11/234)	3.3% (15/448)	1.40 (0.64–3.06)	0.3927	1.26 (0.54–2.93)	0.5956	
By ECASS II standard	2.6% (6/234)	1.8% (8/448)	1.44 (0.50–4.13)	0.5029	1.16 (0.37–3.65)	0.8005	
By SITS-MOST standard	1.3% (3/234)	1.1% (5/448)	1.15 (0.27–4.81)	0.8494	0.90 (0.19–4.32)	0.8938	

AF indicates atrial fibrillation; ECASS II, European Cooperative Acute Stroke Study II; mRS, modified Rankin Scale; NINDS, National Institute of Neurological Disorders and Stroke; RR, relative risk; SICH, symptomatic intracranial hemorrhage; and SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study.

*Multivariable Poisson regression was adjusted for fixed effects of the Totaled Health Risks in Vascular Events score, prestroke mRS, early ischemic changes, and prestroke antithrombotic medications, and random effects for 30 hospitals.

†The interaction term was between AF status and alteplase dose.

‡$P<0.05$.

RR, 2.14 [95% CI, 1.36–3.37]; *P*=0.0010). However, SICH rates determined according to ECASS II and SITS-MOST standards did not significantly differ between the 2 groups. The relationship between the THRIVE score and clinical outcomes is presented in Figure 3.

Secondary Objectives (AF Versus Non-AF Group With Different Doses of IVT)

Among the enrolled patients, 1669 and 682 patients with acute ischemic stroke were treated with low- and standard-dose alteplase, respectively (Table 4). The functional outcome distribution at 90 days for the different doses of alteplase subgroups is presented in Figure 4. For the patients receiving the standard dose, the good outcome status at 90 days and SICH rates did not significantly differ between the AF and non-AF groups. For the patients receiving a low dose, the AF group exhibited a >2-fold increased risk of SICH according to the NINDS standard (adjusted RR, 2.87 [95% CI, 1.63–5.04]; *P*=0.0003) compared with the non-AF group. The interaction terms between different doses of alteplase were significant for SICH according to the NINDS standard (*P*=0.0047). However, no significant differences in the good outcome status at 90 days and SICH rates according to ECASS II and SITS-MOST standards were observed between the AF and non-AF groups. The relationship between the THRIVE score and clinical outcomes for the AF group receiving different doses of alteplase is presented in Figure 5.

Validation Study (Adjustment for Different Risk-Scoring Tools)

To substantiate our findings, we verified the primary and secondary objectives by using different stroke risk-scoring tools (Table 5). Similar to the findings based on the THRIVE score, the low-dose subgroup exhibited an increased risk of SICH according to the NINDS standard after adjustment for the HAT score (adjusted RR, 2.92 [95% CI, 1.66–5.13]; *P*=0.0001), SITS-SICH score (adjusted RR, 2.83 [95% CI, 1.62–4.95]; *P*=0.0002), Cucchiara score (adjusted RR, 2.86 [95% CI, 1.63–5.04]; *P*=0.0001), SEDAN score (adjusted RR, 2.94 [95% CI, 1.68–5.16]; *P*=0.0001), SPAN-100 Index (adjusted RR, 2.90 [95% CI, 1.64–5.11]; *P*=0.0001), and GRASPS score (adjusted RR, 2.56 [95% CI, 1.46–4.49]; *P*=0.0010). However, the standard-dose subgroup demonstrated no difference in all clinical outcomes after adjustment for scores determined using any risk-scoring tools. In addition, characteristics between the low-dose and standard-dose subgroups were analyzed for age (69.1±12.6 versus 67.4±13.2 years, *P*=0.0030), proportion of the female patients (37.3% versus 35.8%, *P*=0.4964), and baseline NIHSS scores (13.9±6.7 versus 13.8±7.9, *P*=0.6721), and indicated high similarity between the low-dose and standard-dose subgroups. The distribution of each risk-scoring system for the AF and non-AF groups is presented in Figure 6.

Sensitivity Analysis

The number of imputations was 30 after applying the quadratic rule. Before imputation and IPTW, the

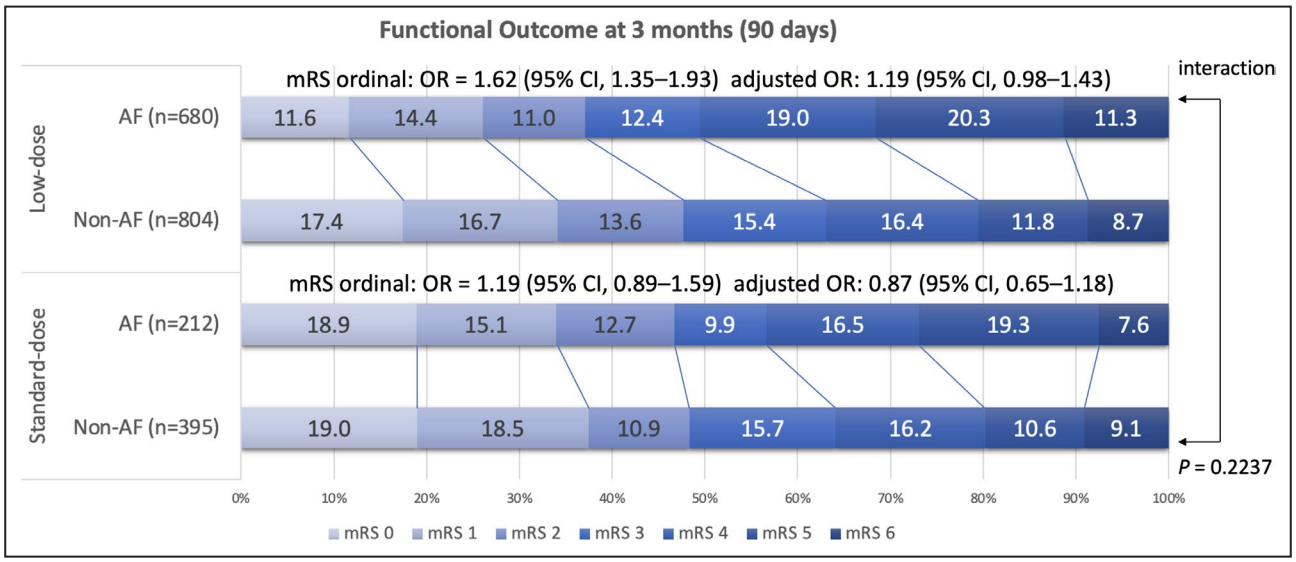

Figure 4. The distribution of functional outcomes at 90 days for subgroups receiving different doses of alteplase subgroups. The data set shows no significant differences in functional outcomes between the atrial fibrillation (AF) and non-AF groups after adjustment for the THRIVE (Totaled Health Risks in Vascular Events) score in the low-dose subgroup (adjusted odds ratio [OR], 1.19 [95% CI, 0.98–1.43]) and standard-dose subgroup (adjusted OR, 0.87 [95% CI, 0.65–1.18]), and no interaction was observed between different doses of alteplase (*P*=0.2237). mRS indicates modified Rankin Scale.

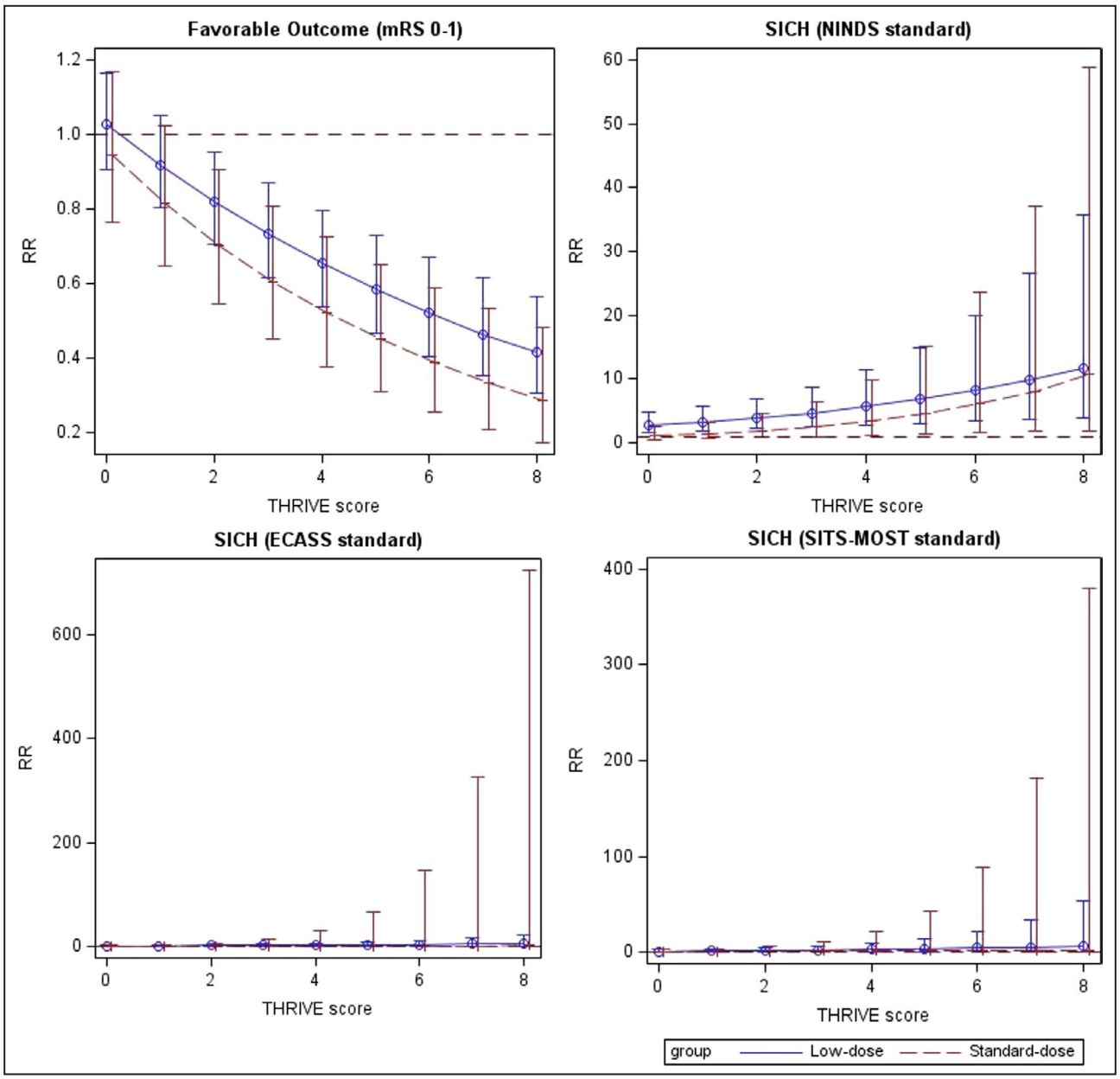

Figure 5. The relationship between the THRIVEs (Totaled Health Risks in Vascular Event) score and clinical outcomes for the atrial fibrillation group treated with different doses of alteplase.
The zero-inflated Poisson regression models were used to plot the relationship between the THRIVE score and symptomatic intracranial hemorrhage (SICH) by the ECASS II (European Cooperative Acute Stroke Study II) and the SITS-MOST (Safe Implementation of Thrombolysis in Stroke-Monitoring Study) standards. mRS indicates modified Rankin Scale; NINDS, National Institute of Neurological Disorders and Stroke; and RR, relative risk.

characteristics at baseline between the AF and non-AF groups were nearly the same as those of the original data set (Table 6). After IPTW, age, sex, medical comorbidities (ie, hypertension, diabetes, hyperlipidemia, coronary artery disease, and alcoholism), prestroke mRS score, brain CT findings at baseline, NIHSS score on arrival, alteplase dose, mean arterial pressure, time to treatment, THRIVE score, and use of antithrombotic medications were balanced between the AF and non-AF groups (standardized mean difference <0.1). After imputation and IPTW (Table 7), the primary objectives were comparable between the AF and non-AF groups except for SICH according to the NINDS standard, which exhibited twice the risk in the AF group. In subgroup analysis, the patients with AF who received 0.6 mg/kg of alteplase exhibited a 2-fold increased risk of SICH according to the NINDS standard after adjustment for the THRIVE score (Table 8) and scores obtained using other stroke risk-scoring tools (Table 9). However, in both AF and non-AF groups,

Table 5. Validation Study With the Different Risk-Scoring Models

Adjustment model	HAT score	Adjusted RR‡ (95% CI) for AF vs non-AF Groups				
		SITS-SICH score	Cucchiara score	SEDAN score	SPAN-100	GRASPS score
Low-dose subgroup, n=1669						
Favorable outcomes at 90 d						
mRS of 0–1	0.94 (0.83–1.07)	0.95 (0.84–1.07)	0.95 (0.84–1.08)	0.94 (0.83–1.07)	0.96 (0.84–1.08)	0.99 (0.87–1.12)
mRS of 0–2	0.91 (0.79–1.04)	0.91 (0.80–1.05)	0.93 (0.81–1.07)	0.90 (0.79–1.04)	0.92 (0.80–1.06)	0.98 (0.86–1.13)
SICH at 24–36 h						
By NINDS standard	2.92 (1.66–5.13)*	2.83 (1.62–4.95)*	2.86 (1.63–5.04)*	2.94 (1.68–5.16)*	2.90 (1.64–5.11)*	2.56 (1.46–4.49)†
By ECASS II standard	1.55 (0.80–3.00)	1.49 (0.77–2.86)	1.50 (0.77–2.91)	1.54 (0.80–2.96)	1.54 (0.79–3.01)	1.35 (0.70–2.61)
By SITS-MOST standard	1.08 (0.41–2.80)	1.08 (0.42–2.79)	1.08 (0.41–2.81)	1.13 (0.44–2.93)	1.05 (0.40–2.74)	0.91 (0.35–2.34)
Standard-dose subgroup, n=682						
Favorable outcomes at 90 d						
mRS of 0–1	0.98 (0.79–1.21)	1.00 (0.81–1.23)	0.99 (0.80–1.23)	0.99 (0.80–1.22)	0.98 (0.79–1.21)	1.04 (0.84–1.29)
mRS of 0–2	1.04 (0.82–1.32)	1.06 (0.84–1.35)	1.06 (0.84–1.34)	1.05 (0.83–1.32)	1.03 (0.81–1.30)	1.14 (0.90–1.44)
SICH at 24–36 h						
By NINDS standard	1.38 (0.61–3.16)	1.42 (0.62–3.22)	1.37 (0.59–3.16)	1.46 (0.63–3.34)	1.49 (0.65–3.41)	1.23 (0.55–2.75)
By ECASS II standard	1.32 (0.43–4.01)	1.33 (0.44–4.03)	1.39 (0.45–4.29)	1.28 (0.42–3.91)	1.52 (0.50–4.58)	1.18 (0.39–3.51)
By SITS-MOST standard	1.04 (0.22–4.88)	1.07 (0.23–5.01)	0.96 (0.20–4.64)	1.06 (0.23–4.93)	1.33 (0.30–5.86)	0.89 (0.21–3.87)

AF indicates atrial fibrillation; ECASS II, European Cooperative Acute Stroke Study II; GRASPS, Glucose, Race, Age, Sex, Pressure, Stroke Severity; HAT, Hemorrhage After Thrombolysis; mRS, modified Rankin Scale; NINDS, National Institute of Neurological Disorders and Stroke; RR, relative risk; SEDAN, Blood Sugar, Early Infarct Signs and Hyperdense Cerebral Artery Sign, Age, and the National Institutes of Health Stroke Scale; SICH, symptomatic intracranial hemorrhage; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study; SITS-SICH, Safe Implementation of Treatment in Stroke-Symptomatic Intracerebral Hemorrhage; and SPAN-100, Stroke Prognostication Using Age and National Institutes of Health Stroke Scale-100 Index.

*Statistically significant at $P<0.001$.

†Statistically significant at $P<0.05$.

‡Models were adjusted for fixed effects of each scoring tools, prestroke mRS, early ischemic changes, and prestroke antithrombotic medications, and random effects for 30 hospitals.

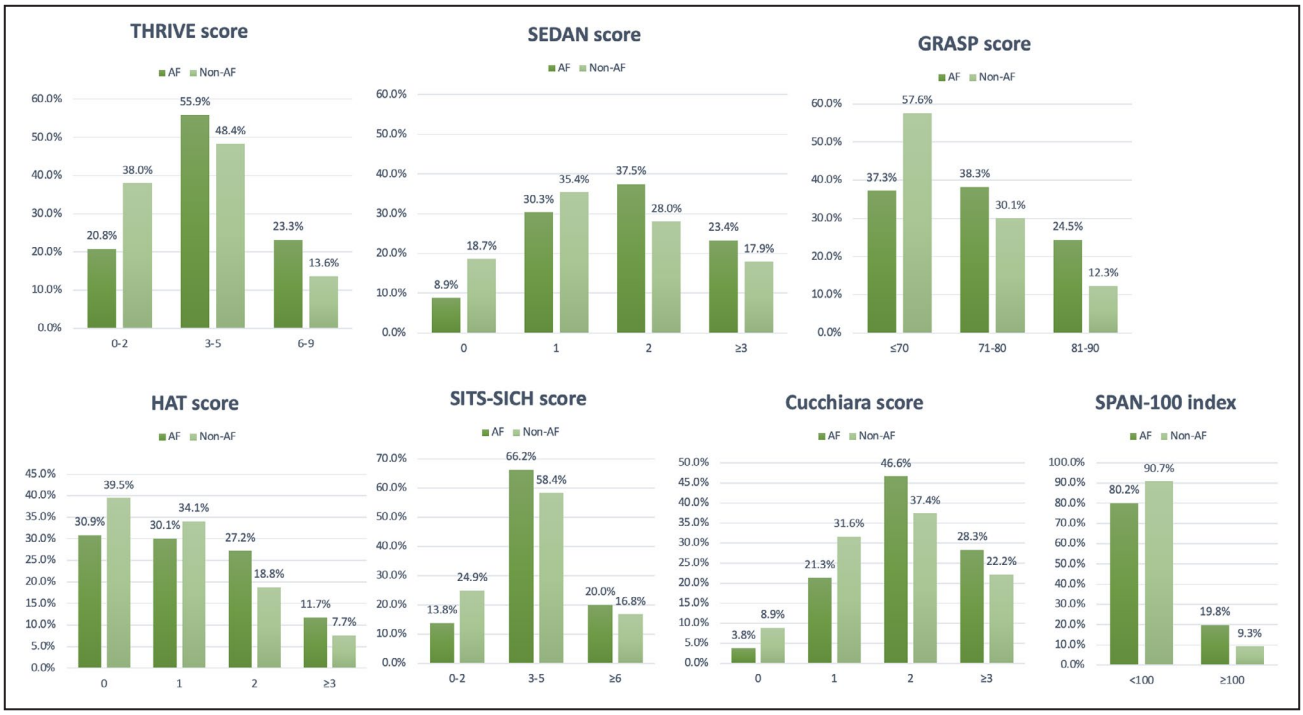

Figure 6. The distribution of each risk-scoring system for atrial fibrillation (AF) and non-AF groups.
ECASS II indicates European Cooperative Acute Stroke Study II; GRASP, Glucose, Race, Age, Sex, Pressure, Stroke Severity; HAT, Hemorrhage After Thrombolysis; SEDAN, the Blood Sugar, Early Infarct Signs and Hyperdense Cerebral Artery Sign, Age, and National Institutes of Health Stroke Scale; SITS-SICH, the Safe Implementation of Treatment in Stroke-Symptomatic Intracerebral Hemorrhage; SPAN-100, Stroke Prognostication Using Age and National Institutes of Health Stroke Scale-100 Index; and THRIVE, Totaled Health Risks in Vascular Events.

comparable outcomes were observed between the low-dose (0.6 mg/kg) and standard-dose (0.9 mg/kg) subgroups.

DISCUSSION

To our knowledge, this is the first study to analyze clinical outcomes in patients with acute ischemic stroke with and without AF by using different SICH definitions, and evaluate the effects of different dosages of alteplase with respect to FFO at 90 days and SICH within 24 to 36 hours after IVT. The results revealed that the AF group had a higher risk of intracranial hemorrhage. However, clinical outcomes, FFO at 90 days, FI, and mortality were unaffected by AF. Compared with the non-AF group, the AF group exhibited increased SICH rates only according to the NINDS standard[28] (with the deterioration of the NIHSS score to ≥1) and not ECASS II and SITS-MOST standards (with the deterioration of NIHSS scores to ≥4). We observed an increased risk of SICH in the patients with stroke treated with low-dose alteplase.

Our measurements for functional status are consistent with most studies,[49–55] reporting that patients with AF tended to have unfavorable functional outcomes at 90 days before adjustment for any covariates. Consistent with previous studies,[51–54] our results revealed that the trend of unfavorable outcomes in patients with AF was eliminated after adjustment for the baseline NIHSS scores and other demographic characteristics. By contrast, a recent meta-analysis in 2021[12] reported that patients with AF had poorer functional outcomes at 90 days and higher SICH rates than patients without AF. However, this meta-analysis[12] was limited by the statistical methods because the pooled odds ratios of each study in this meta-analysis were obtained simply by calculating the binary outcome number between patients with and without AF (the event and nonevent number in a 2×2 table). Hence, the pooled odds ratios were unadjusted for baseline stroke severity and other characteristic differences between AF and non-AF groups.

AF-related thrombi are larger and more resistant to IVT as reported in previous studies,[56,57] and more than half of the patients with AF had failed recanalization. In the current study, only the low-dose subgroup exhibited higher SICH rates according to the NINDS standard. Low-dose alteplase might lead to the incomplete resolution of AF-related thrombi, thus resulting in secondary hemorrhagic transformation; however, the secondary hemorrhagic transformation was not too

Table 6. Characteristics of the Data Set After Data Imputation and IPTW (N=2351)

Characteristics	Before IPTW			After IPTW		
	Non-AF, N=1371	AF, N=980	SMD	Non-AF, N=1371	AF, N=980	SMD
Age, y	66.4±13.0	71.7±11.9	0.4263	68.7±12.9	68.8±12.4	0.0067
Female sex, %	33.2% (456/1371)	41.8% (410/980)	0.1778	36.4% (499/1371)	35.9% (352/980)	−0.0100
Medical history, %						
Hypertension	69.3% (950/1371)	74.8% (733/980)	−0.1229	71.8% (984/1371)	73.0% (715/980)	−0.0270
Diabetes	33.5% (459/1371)	30.4% (298/980)	0.0659	31.9% (437/1371)	32.3% (317/980)	−0.0075
Hyperlipidemia	37.9% (520/1371)	31.5% (309/980)	0.1347	35.0% (480/1371)	36.0% (353/980)	−0.0209
Coronary artery disease	11.5% (157/1365)	17.0% (167/980)	−0.1582	14.1% (193/1371)	14.0% (137/980)	0.0012
Alcoholism	8.1% (111/1371)	6.9% (68/980)	0.0439	7.9% (108/1371)	7.8% (76/980)	−0.0035
Prestroke mRS			0.0202			−0.0251
mRS of 0–2	56.6% (776/1371)	55.4% (543/980)		51.7% (709/1371)	52.9% (518/980)	
mRS of 3–5	43.2% (592/1371)	44.2% (433/980)		48.3% (662/1371)	47.1% (462/980)	
CT scan of brain at baseline			0.1134			−0.0002
Normal	88.5% (1214/1371)	84.7% (830/980)		86.3% (1183/1371)	86.4% (847/980)	
Early ischemic changes	11.5% (157/1371)	15.3% (150/980)		13.7% (188/1371)	13.6% (133/980)	
Stroke severity, %			0.3468			0.0622
Mild, NIHSS of ≤10	45.2% (620/1371)	28.8% (282/980)		26.7% (366/1371)	25.2% (247/980)	
Moderate, NIHSS of 11–20	39.5% (542/1371)	45.8% (449/980)		29.2% (400/1371)	27.8% (272/980)	
High, NIHSS of ≥21	15.2% (209/1371)	25.4% (249/980)		44.1% (605/1371)	47.0% (461/980)	
Alteplase dose, mg/kg	0.81±0.13	0.78±0.14	−0.2295	0.80±0.14	0.80±0.14	−0.0003
Groups of alteplase dosage, %		0.1963			0.0018	
Standard dose, 0.9 mg/kg	32.7% (448/1371)	23.9% (234/980)		29.0% (398/1371)	28.9% (283/980)	
Low dose, 0.6–0.8 mg/kg	67.3% (923/1371)	76.1% (746/980)		71.0% (973/1371)	71.1% (697/980)	
MAP on arrival, mm Hg	113.4±21.4	113.7±20.7	0.0167	112.9±21.5	113.6±20.5	0.0346
Time to treatment, min	116.8±60.0	135.1±45.0	0.3439	125.5±59.2	126.4±47.0	0.0177
Fasting glucose, mg/dL	150.9±81.2	144.2±67.6	−0.0908	148.2±75.3	151.5±95.2	0.0440
THRIVE score	3.3±1.8	4.1±1.8	0.4446	3.6±1.9	3.6±1.8	0.0001
Prestroke antithrombotic medications						
Aspirin	10.9% (149/1371)	11.0% (108/980)	−0.0049	10.9% (149/1371)	10.4% (102/980)	0.0155
P2Y12 inhibitors	1.8% (25/1371)	1.9% (19/980)	−0.0085	1.8% (25/1371)	1.9% (19/980)	0.0032
Dual antiplatelet	1.3% (18/1371)	1.8% (17/980)	−0.0344	1.4% (19/1371)	1.4% (14/980)	−0.0002
Warfarin	0.8% (11/1371)	4.4% (43/980)	−0.2270	2.5% (34/1371)	2.3% (23/980)	0.0110

Continuous variables are expressed as mean±standard deviation. AF indicates atrial fibrillation; CT, computed tomography; IPTW, inverse probability of treatment weighting; MAP, mean arterial pressure; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SMD, standardized mean difference; and THRIVE, Totaled Health Risks in Vascular Events.

The number of imputations was 30.

severe to affect the FFO and FI at 90 days. SICH rates determined according to ECASS II and SITS-MOST standards did not significantly differ between the AF and non-AF groups. These data highlight the rationality of using standard-dose alteplase for patients with AF and support the safety of standard-dose alteplase in Asian patients with AF.

This study has many strengths. First, this study included a larger prospective cohort of patients with and without AF ever treated with IVT than that in previous studies.[49–55] Second, a solid definition for hemorrhagic transformation was adopted based on NINDS, ECASS II, and SITS-MOST standards to differentiate between varying severity levels of SICH. Third, by replacing the THRIVE score with the HAT score, SITS-SICH score, SEDAN score, Cucchiara score, SPAN-100 Index, and GRASPS score, our study validated the robustness of the primary and secondary objectives. Fourth, we

Table 7. Sensitivity Analysis I: The Risk of Unfavorable Functional Outcomes and SICH With AF

Characteristics	AF	Non-AF	After IPTW			
			RR (95% CI)	*P* value	Adjusted RR (95% CI)*	*P* value
Functional outcome of mRS at 90 d						
0: No symptoms	13.1% (128/980)	17.9% (245/1371)				
1: No substantive disability	14.0% (137/980)	16.8% (230/1371)				
2: Slight disability	11.5% (113/980)	12.0% (165/1371)				
3: Moderate disability	11.4% (112/980)	15.7% (215/1371)				
4: Moderate to severe disability	19.5% (191/980)	17.7% (243/1371)				
5: Severe disability	20.7% (203/980)	11.9% (163/1371)				
6: Death	9.8% (96/980)	8.0% (110/1371)	1.12 (0.92–1.37)	0.2618	0.99 (0.73–1.33)	0.9258
Favorable outcomes at 90 d						
mRS of 0–1, FFO	27.4% (268/980)	34.9% (479/1371)	1.03 (0.96–1.10)	0.4244	0.97 (0.87–1.07)	0.5077
mRS of 0–2, FI	38.5% (377/980)	47.0% (644/1371)	1.04 (0.96–1.12)	0.3046	0.97 (0.87–1.09)	0.6430
SICH at 24–36 h						
By NINDS standard	5.8% (57/980)	2.4% (33/1371)	2.00 (1.47–2.74)	<0.0001†	2.14 (1.36–3.37)	0.0010†
By ECASS II standard	3.0% (29/980)	1.8% (24/1371)	1.32 (0.89–1.95)	0.1680	1.43 (0.81–2.54)	0.2145
By SITS-MOST standard	1.2% (12/980)	1.0% (14/1371)	0.90 (0.51–1.61)	0.7331	0.99 (0.44–2.20)	0.9726

AF indicates atrial fibrillation; ECASS II, European Cooperative Acute Stroke Study II; FFO, favorable functional outcome; FI, functional independence; IPTW, inverse probability of treatment weighting; mRS, modified Rankin Scale; NINDS, National Institute of Neurological Disorders and Stroke; RR, relative risk; SICH, symptomatic intracranial hemorrhage; and SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study.

*Multivariable Poisson regression was adjusted for fixed effects of the THRIVE (Totaled Health Risks in Vascular Events) score, prestroke mRS, early ischemic changes, and use of antithrombotic medications, and random effects for 30 hospitals.

†Statistically significant at $P<0.05$.

used a Poisson regression model instead of a logistic regression model because our primary analysis fulfilled the assumption of Poisson distribution[58,59] (counting of the rare event of SICH in a large cohort). Finally, this study provides real-world data for patients with stroke treated with IVT using different dosages of alteplase. In

Table 8. Sensitivity Analysis II: Subgroup Analysis by Different Doses of Alteplase

Characteristics	AF	Non-AF	After IPTW				Interaction†
			RR (95% CI)	*P* value	Adjusted RR‡ (95% CI)	*P* value	
Low dose of 0.6 mg/kg subgroup, N=381							
mRS of 0–1	23.4% (44/188)	34.2% (66/193)	0.98 (0.83–1.16)	0.8194	0.96 (0.81–1.14)	0.6473	0.1829
mRS of 0–2	33.5% (63/188)	47.7% (92/193)	0.91 (0.75–1.09)	0.2954	0.91 (0.75–1.10)	0.3359	0.1620
SICH at 24–36 h							
By NINDS standard	5.9% (11/188)	2.1% (4/193)	2.36 (1.04–5.34)	0.0400†	2.63 (1.10–6.32)	0.0302†	0.0009†
By ECASS II standard	3.7% (7/188)	1.6% (3/193)	2.04 (0.76–5.47)	0.1560	2.52 (0.86–7.43)	0.0927	0.3505
By SITS-MOST standard	1.6% (3/188)	0.5% (1/193)	4.37 (0.64–29.84)	0.1323	4.49 (0.64–31.58)	0.1313	0.8338
Standard dose of 0.9 mg/kg subgroup, N=682							
mRS of 0–1	33.8% (79/234)	37.1% (166/448)	0.91 (0.79–1.04)	0.1619	1.05 (0.91–1.20)	0.5198	
mRS of 0–2	46.2% (108/234)	52.5% (213/448)	0.85 (0.73–0.96)	0.0315†	1.09 (0.94–1.27)	0.2353	
SICH at 24–36 h							
By NINDS standard	4.7% (11/234)	3.3% (15/448)	1.23 (0.71–2.11)	0.4587	1.66 (0.92–3.01)	0.0917	
By ECASS II standard	2.6% (6/234)	1.8% (8/448)	1.21 (0.57–2.58)	0.6190	1.32 (0.57–3.05)	0.5149	
By SITS-MOST standard	1.3% (3/234)	1.1% (5/448)	1.07 (0.39–2.96)	0.8892	1.42 (0.47–4.34)	0.5359	

AF indicates atrial fibrillation; ECASS II, European Cooperative Acute Stroke Study II; IPTW, inverse probability of treatment weighting; mRS, modified Rankin Scale; NINDS, National Institute of Neurological Disorders and Stroke; RR, relative risk; SICH, symptomatic intracranial hemorrhage; and SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study.

*The interaction term was between AF status and alteplase dose.

†Statistically significant at $P<0.05$.

‡Multivariable Poisson regression was adjusted for fixed effects of the THRIVE (Totaled Health Risks in Vascular Events) score, prestroke mRS, early ischemic changes, and use of antithrombotic medications, and random effects for 30 hospitals.

Table 9. Sensitivity Analysis III: Different Risk-Scoring Models

Adjustment model	Adjusted RR (95% CI) for AF vs non-AF groups after IPTW					
	HAT score	SITS-SICH score	Cucchiara score	SEDAN score	SPAN-100	GRASPS score
Low dose of 0.6 mg/kg subgroup, N=381						
Favorable outcomes at 90 d						
mRS of 0–1	0.96 (0.81–1.15)	0.94 (0.79–1.11)	0.94 (0.79–1.11)	0.94 (0.80–1.12)	0.93 (0.79–1.11)	0.95 (0.80–1.13)
mRS of 0–2	0.93 (0.77–1.12)	0.88 (0.72–1.06)	0.88 (0.72–1.06)	0.89 (0.73–1.07)	0.88 (0.72–1.06)	0.90 (0.74–1.08)
SICH at 24–36 h						
By NINDS standard	2.48 (1.03–5.95)*	2.42 (1.01–5.79)*	2.82 (1.15–6.90)*	2.60 (1.08–6.25)*	2.52 (1.06–5.98)*	2.33 (0.97–5.63)
By ECASS II standard	2.31 (0.78–6.83)	2.10 (0.71–6.24)	2.60 (0.86–7.84)	2.35 (0.80–6.94)	2.51 (0.86–7.33)	2.18 (0.73–6.55)
By SITS-MOST standard	3.44 (0.46–25.90)	4.04 (0.56–29.16)	4.04 (0.56–29.16)	4.27 (0.61–29.70)	5.13 (0.74–35.72)	4.13 (0.58–29.48)
Standard dose of 0.9 mg/kg subgroup, N=682						
Favorable outcomes at 90 d						
mRS of 0–1	1.03 (0.90–1.18)	1.06 (0.92–1.21)	1.06 (0.92–1.21)	1.06 (0.93–1.21)	1.03 (0.90–1.18)	1.06 (0.92–1.21)
mRS of 0–2	1.07 (0.93–1.25)	1.15 (0.99–1.34)	1.15 (0.99–1.34)	1.12 (0.96–1.30)	1.12 (0.95–1.30)	1.15 (0.98–1.34)
SICH at 24–36 h						
By NINDS standard	1.25 (0.73–2.16)	1.70 (0.94–3.07)	1.65 (0.91–2.99)	1.63 (0.90–2.95)	1.78 (0.98–3.22)	1.68 (0.93–3.01)
By ECASS II standard	1.24 (0.58–2.64)	1.24 (0.54–2.85)	1.34 (0.58–3.10)	1.17 (0.51–2.68)	1.42 (0.62–3.28)	1.38 (0.61–3.16)
By SITS-MOST standard	1.11 (0.40–3.09)	1.13 (0.38–3.38)	1.22 (0.39–3.84)	1.15 (0.38–3.48)	1.39 (0.46–4.20)	1.47 (0.50–4.37)

Models were adjusted for fixed effects of each scoring tools, prestroke mRS, early ischemic changes, and prestroke antithrombotic medications, and random effects for 30 hospitals. AF indicates atrial fibrillation; ECASS II, European Cooperative Acute Stroke Study II; GRASPS, Glucose, Race, Age, Sex, Pressure, Stroke Severity; HAT, Hemorrhage After Thrombolysis; IPTW, inverse probability of treatment weighting; mRS, modified Rankin Scale; NINDS, National Institute of Neurological Disorders and Stroke; RR, relative risk; SEDAN, the Blood Sugar, Early Infarct Signs and Hyperdense Cerebral Artery Sign, Age, and National Institutes of Health Stroke Scale; SICH, symptomatic intracranial hemorrhage; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study; SITS-SICH, the Safe Implementation of Treatment in Stroke-Symptomatic Intracerebral Hemorrhage; and SPAN-100, Stroke Prognostication Using Age and National Institutes of Health Stroke Scale-100 Index.

*$P<0.05$.

Taiwan, most physicians prefer a low or standard dose of alteplase, and the ratio is ≈2.4:1 (sample size of low dose/standard dose=1669/682). Because we included enough patients in both the low- and standard-dose subgroups, our results were stable and can be generalized to other Asian populations.

In the sensitivity analysis, we performed data imputation and IPTW to determine the robustness of our findings. The rates of follow-up at 90 days were 91.0% and 87.5% in the AF and non-AF groups, respectively. The statistical findings suggested that ≈10% of missing at random can be replaced with substituted values.[60,61] In our study, the probability of a missing value was supposed to be dependent on observed quantities (such as age, medical comorbidities, and stroke severity) but to be independent of unobserved data, which fulfilled the condition for missing at random. In general, the results of our sensitivity analysis were the same as those obtained before multiple imputation and IPTW. The patients in the AF group who received 0.6 mg/kg (N=381) exhibited a 2-fold of significantly increased risk of SICH according to the NINDS standard after adjustment for the THRIVE score, SITS-SICH score, Cucchiara score, SEDAN score, and SPAN-100 Index but at borderline significance for the HAT and GRASPS scores. This borderline significance can be attributed to the inclusion of an insufficient sample size in the subgroup receiving 0.6 mg/kg of alteplase (N=381) compared with the low-dose subgroup receiving 0.6 to 0.8 mg/kg of alteplase (N=1669).

Our study has some limitations. Because our study ended in 2016, additional analysis of clinical outcomes before treatment and after the addition of new oral anticoagulants could not be performed. In Taiwan, new oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban) were approved between 2013 and 2016[62]; therefore, most enrolled patients were not yet being treated with them. In addition, before 2016, second-generation thrombectomy technique was not a standard treatment in Taiwan and was not covered by the national insurance programs. Finally, our results did not include the factor of thrombectomy. The ASPECTS (Alberta Stroke Programme Early CT Score) was not determined in our TTT-AIS study; therefore, we did not adjust for it. However, our results were determined to be robust after adjustment for subtle early ischemic changes; this finding is consistent with that of an earlier study indicating the lack of clinical significance of subtle early ischemic changes for patients with stroke treated with alteplase.[31]

In conclusion, this study examined the 90-day clinical outcomes in patients having acute ischemic stroke with and without AF. Although the patients with AF receiving low-dose alteplase had higher SICH rates according to the NINDS standard, the different dosages of alteplase exerted no overt effect on the functional status at 90 days in the AF and non-AF groups. Thus, the adoption of a low-dose alteplase simply because of AF is not recommended.

APPENDIX

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Disclosures

None.

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