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Risk of Bleeding Following Non–Vitamin K Antagonist Oral Anticoagulant Use in Patients With Acute Ischemic Stroke Treated With Alteplase

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IMPORTANCE Current guidelines advise against intravenous alteplase therapy for treatment of acute ischemic stroke in patients previously treated with non–vitamin K antagonist oral anticoagulants (NOACs).

OBJECTIVE To evaluate the risk of bleeding and mortality after alteplase treatment for acute ischemic stroke among patients treated with NOACs compared to those not treated with NOACs.

DESIGN, SETTING, AND PARTICIPANTS This nationwide, population-based cohort study was conducted in Taiwan using data from Taiwan's National Health Insurance Research Database from January 2011 through November 2020 and included 7483 patients treated with alteplase for acute ischemic stroke. A meta-analysis incorporating the results of the study with those of previous studies was performed, and the review protocol was prospectively registered with PROSPERO.

EXPOSURES NOAC treatment within 2 days prior to stroke, compared to either no anticoagulant treatment or warfarin treatment.

MAIN OUTCOMES AND MEASURES The primary outcome was intracranial hemorrhage after intravenous alteplase during the index hospitalization (the hospitalization subsequent to alteplase administration). Secondary outcomes were major bleeding events and mortality during the index hospitalization. Propensity score matching was used to control potential confounders. Logistic regression was used to estimate the odds ratio (OR) of outcome events. Meta-analysis was performed using a random-effects model.

RESULTS Of the 7483 included patients (mean [SD] age, 67.4 [12.7] years; 2908 [38.9%] female individuals and 4575 [61.1%] male individuals), 91 (1.2%), 182 (2.4%), and 7210 (96.4%) received NOACs, warfarin, and no anticoagulants prior to their stroke, respectively. Compared to patients who were not treated with anticoagulants, those treated with NOACs did not have significantly higher risks of intracranial hemorrhage (risk difference [RD], 2.47% [95% CI, −4.23% to 9.17%]; OR, 1.37 [95% CI, 0.62-3.03]), major bleeding (RD, 4.95% [95% CI, −2.56% to 12.45%]; OR, 1.69 [95% CI, 0.83-3.45]), or in-hospital mortality (RD, −4.95% [95% CI, −10.11% to 0.22%]; OR, 0.45 [95% CI, 0.15-1.29]) in the propensity score–matched analyses. Furthermore, the risks of bleeding and mortality were not significantly different between patients treated with NOACs and those treated with warfarin. Similar results were obtained in the meta-analysis.

CONCLUSIONS AND RELEVANCE In this cohort study with meta-analysis, compared to no treatment with anticoagulants, treatment with NOACs prior to stroke was not associated with a higher risk of intracranial hemorrhage, major bleeding, or mortality in patients receiving intravenous alteplase for acute ischemic stroke.

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Supplemental content

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Intravenous alteplase is a first-line therapy aimed at improving clinical outcomes in acute ischemic stroke.[1-3] Non-vitamin K antagonist oral anticoagulants (NOACs) have become a common treatment for the prevention of ischemic stroke in the past decade.[4-8] However, in patients with acute ischemic stroke, oral anticoagulant treatment is a contraindication for intravenous alteplase therapy unless patients meet the appropriate criteria. Current guidelines recommend their consideration when coagulation test results are normal or if the patient has not taken NOACs for more than 48 hours and has normal kidney function.[3,9] However, the recommendation is based on the consensus of expert opinion, and concrete clinical evidence has not been firmly established.

Two recent clinical studies demonstrated that in patients with acute ischemic stroke treated with intravenous thrombolysis, those with NOAC pretreatment had no significantly higher risk of intracranial hemorrhage (ICH) compared to those without anticoagulants.[10,11] However, limited evidence exists specifically for the Asian population, although Asian individuals are thought to have higher hemorrhagic risks during thrombolytic therapy.[12] We conducted a cohort study in an Asian population to investigate bleeding and mortality risks in patients with acute ischemic stroke pretreated with NOACs and receiving alteplase. We further performed a meta-analysis summarizing the current evidence on the safety of intravenous thrombolysis in patients taking NOACs before stroke.

Key Points

Question Is treatment with non–vitamin K antagonist oral anticoagulants (NOACs) associated with a higher risk of bleeding in patients with acute ischemic stroke receiving intravenous alteplase?

Findings This Taiwanese nationwide cohort study including 7483 patients and meta-analysis including 257 389 patients showed that among patients with acute ischemic stroke receiving intravenous alteplase, treatment with NOACs before stroke was not significantly associated with a higher risk of intracranial hemorrhage or major bleeding events compared to no treatment with NOACs.

Meaning Treatment with NOACs may be considered safe in patients with acute ischemic stroke receiving intravenous alteplase.

Methods

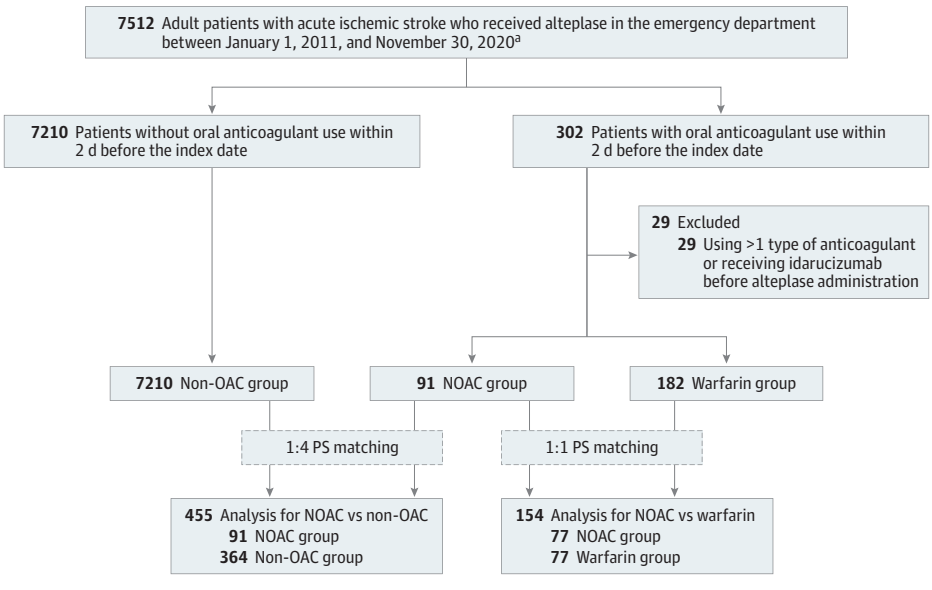
Data Source

This nationwide cohort was conducted using Taiwan's National Health Insurance Research Database (NHIRD), which contained health care information from approximately 23.6 million individuals, covering more than 99% of Taiwan's population.[13,14] The details of NHIRD are summarized in eMethods in Supplement 1. This study was approved by the Research Ethics Committee of Hualien Tzu Chi Hospital (REC No.: IRB110-170-C). Because NHIRD data have been deidentified, the need for written informed consent was waived. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Study Population

We identified all adult patients 20 years or older diagnosed with acute ischemic stroke treated with intravenous alteplase in the emergency department from January 2011 through November 2020 from the NHIRD. **Figure 1** shows the patient selection process. Intravenous alteplase treatment for acute ischemic stroke is indicated strictly according to current Taiwan acute ischemic stroke guidelines and payment regulation of thrombolytic agents for ischemic stroke in National Health

Figure 1. Patient Selection Flowchart



NOAC indicates non–vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; PS, propensity score.

[a] There were 28 individuals with missing data for age, sex, or income information, accounting for 0.37% of the initial eligible study population; these individuals were excluded from subsequent data extraction and analyses.

Insurance.[15,16] The diagnostic codes used for identifying acute ischemic stroke included the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes 433 and 434 and *International Statistical Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)* codes I63 and I64. The diagnostic accuracy of acute ischemic stroke using these codes in the NHIRD has been validated previously.[14,17-19] The index date was defined as the date that patients were diagnosed with ischemic stroke in the emergency department. Index hospitalization was defined as the corresponding hospitalization with the date of admission within 3 days after the index date.

Patients were categorized into 3 mutually exclusive groups based on their treatment status prior to their acute ischemic stroke event: the NOAC, warfarin, and no oral anticoagulant (non-OAC) groups. The NOAC group included patients who had prescriptions for dabigatran, rivaroxaban, apixaban, or edoxaban within 2 days before the index date. The warfarin group, serving as the active comparator, included those who received warfarin prescriptions within the same 2-day time frame before the index date. The non-OAC group, referred to as the control group, included patients who had not used any anticoagulant medications within 2 days before the index date.

Notably, patients in the warfarin group were theoretically taking subtherapeutic warfarin (an international normalized ratio ≤1.7) according to the Taiwan Stroke Society guideline for intravenous thrombolysis.[15,16,20] Before 2019, there were no explicit restrictions in Taiwan regarding the administration of alteplase to patients previously treated with NOACs. During our primary study period, such patients were considered eligible for intravenous alteplase administration.[15,16] Even in the 2019 guidelines in Taiwan, the caution against such administration within 48 hours was primarily based on expert opinion.[16] In addition, hospitals in Taiwan were unable to measure NOAC plasma levels in clinical practice during the study period. If a patient had several episodes of acute ischemic stroke and was treated with intravenous alteplase during the study period, we only analyzed the data of the first episode. Patients who received multiple types of anticoagulants or any anticoagulant other than NOACs and warfarin were excluded. Patients who had received idarucizumab were excluded.

Outcome Measures

The primary outcome was the development of ICH after intravenous alteplase administration during the index hospitalization. The secondary outcomes included all major bleeding events during the index hospitalization, all-cause 30-day mortality, and all-cause in-hospital mortality. The major bleeding events included (1) ICH, (2) gastrointestinal tract bleeding, and (3) bleeding in other critical sites, such as intraorbital bleeding or retroperitoneal bleeding. These outcomes were identified using the *ICD-9-CM* and *ICD-10-CM* diagnostic codes summarized in eTable 1 in Supplement 1. These outcomes have been validated and widely used in previous studies.[21-23] Patients' vital statuses were sourced from Taiwan's National Register of Deaths. In-hospital mortality referred to deaths during the index hospitalization, while 30-day mortality indicated deaths within 30 days after the index date.

Covariates

Baseline characteristics, including age, sex, income level, index year, health care utility, estimated National Institutes of Health Stroke Scale (NIHSS) score, Charlson Comorbidity Index, comorbidities, and baseline medications, were collected.[24,25] Notably, the NIHSS score was not directly collected but was estimated using the claims-based Stroke Severity Index.[26-28] Details of covariates are presented in eMethods in Supplement 1.

Statistical Analyses

We used propensity score matching to balance baseline differences and eliminate potential confounding effects. To estimate the probability of receiving NOACs for each patient, a propensity score was calculated using multivariable logistic regression models based on all covariates listed in **Table 1**, including age, sex, income, index year, health care utility, estimated NIHSS score, Charlson Comorbidity Index, several comorbidities, and baseline medications. Propensity score matching was conducted using nearest-neighbor matching algorithms without replacements. A caliper width equal to 0.2 of the SD of the logit of the propensity score was adopted.[29] We adopted a 1:4 matching ratio for comparing the NOAC and non-OAC groups and a 1:1 ratio for comparing the NOAC and warfarin groups. Each head-to-head comparison, regardless of the overall, subgroup, stratified, or sensitivity analysis, was conducted after performing propensity score matching. The standardized mean difference was used to compare baseline characteristics between groups; a value less than 0.1 indicated a negligible difference.[30,31] The absolute risk difference (RD) between groups and odds ratios (ORs) with their corresponding 95% CIs were calculated. Univariable logistic regression models were used to estimate ORs. All statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc), and Stata, version 17.0 (Stata Corporation LLC). A 2-tailed $P < .05$ was considered statistically significant.

Sensitivity Analyses

In Taiwan, atrial fibrillation (AF) is the primary indication for oral anticoagulant therapy. To determine whether the presence of AF influenced our findings, we conducted a sensitivity analysis focusing on patients with a current or past history of AF, defined as any diagnosis of AF either before or on the index date. Additionally, recognizing that residual imbalances may persist even after matching, we conducted another sensitivity analysis using multivariable logistic regression models to adjust for potential covariates with a standardized mean difference greater than 0.1 after matching.[32] Furthermore, we performed sensitivity analyses by redefining the NOAC and warfarin groups, including patients with NOAC and warfarin prescriptions within 1 or 7 days before the index date.

Meta-Analysis

To contextualize our results with those from previous studies, we conducted a meta-analysis to investigate the risk of ICH, major bleeding events, and mortality. This review adhered to a preregistered protocol (PROSPERO: CRD42023392402) in accordance with the Preferred Reporting Items for System-

Table 1. Baseline Characteristics of Patients With Non–Vitamin K Antagonist Oral Anticoagulant (NOAC) Use or Without Any Oral Anticoagulant (OAC) Use Prior to Acute Ischemic Stroke Before and After Propensity Score (PS) Matching

Characteristic	Before PS matching			After 1:4 PS matching[a]		
	NOAC group (n = 91)	Non-OAC group (n = 7210)	SMD[b]	NOAC group (n = 91)	Non-OAC group (n = 364)	SMD[b]
Age, mean (SD), y	74.1 (8.9)	67.2 (12.8)	0.621	74.1 (8.9)	73.9 (11.6)	0.015
Sex, No. (%)						
Female	51 (56.0)	2762 (38.3)	0.361	51 (56.0)	208 (57.1)	0.022
Male	40 (44.0)	4448 (61.7)	0.361	40 (44.0)	156 (42.9)	0.022
Income level, No. (%)						
Financially dependent	24 (26.4)	1720 (23.9)	0.058	24 (26.4)	95 (26.1)	0.006
15 840-24 999 NTD (US $490-$774)	44 (48.4)	3495 (48.5)	0.002	44 (48.4)	164 (45.1)	0.066
25 000-39 999 NTD (US $774-$1238)	13 (14.3)	1119 (15.5)	0.035	13 (14.3)	62 (17.0)	0.075
≥40 000 NTD (US ≥$1239)	10 (11.0)	876 (12.2)	0.036	10 (11.0)	43 (11.8)	0.026
Index year, No. (%)						
2011-2014	14 (15.4)	2120 (29.4)	0.341	14 (15.4)	66 (18.1)	0.074
2015-2017	26 (28.6)	2042 (28.3)	0.006	26 (28.6)	109 (30.0)	0.030
2018-2020	51 (56.0)	3048 (42.3)	0.278	51 (56.0)	189 (51.9)	0.083
Health care utilization, mean (SD)[c]						
Outpatient visits	26.4 (17.2)	20.5 (17.4)	0.343	26.4 (17.2)	27.2 (19.3)	0.039
Emergency visits	2.1 (1.4)	1.6 (1.8)	0.300	2.1 (1.4)	2.3 (3.5)	0.090
Hospitalization	1.5 (1.0)	1.2 (1.0)	0.332	1.5 (1.0)	1.7 (2.3)	0.099
eNIHSS score, mean (SD)[d]	14.2 (4.7)	13.0 (4.6)	0.265	14.2 (4.7)	14.2 (4.6)	0.000
Charlson Comorbidity Index, mean (SD)	3.1 (2.2)	2.6 (1.9)	0.241	3.1 (2.2)	3.3 (2.2)	0.092
Comorbidities, No. (%)						
Prior ischemic stroke	18 (19.8)	602 (8.3)	0.333	18 (19.8)	70 (19.2)	0.014
Prior TIA	5 (5.5)	240 (3.3)	0.106	5 (5.5)	20 (5.5)	0.000
Heart failure	28 (30.8)	506 (7.0)	0.637	28 (30.8)	112 (30.8)	0.000
Coronary artery disease	37 (40.7)	1239 (17.2)	0.536	37 (40.7)	145 (39.8)	0.017
Peripheral vascular disease	5 (5.5)	126 (1.7)	0.202	5 (5.5)	27 (7.4)	0.079
Chronic kidney disease	9 (9.9)	446 (6.2)	0.137	9 (9.9)	38 (10.4)	0.018
Malignant neoplasm	3 (3.3)	396 (5.5)	0.107	3 (3.3)	14 (3.9)	0.030
COPD	8 (8.8)	472 (6.5)	0.084	8 (8.8)	37 (10.2)	0.047
Cirrhosis	NA[e]	NA[f]	0.064	NA[e]	NA[f]	0.029
Baseline medication history, No. (%)						
Antiplatelets	13 (14.3)	2094 (29.0)	0.364	13 (14.3)	57 (15.7)	0.038
Antihypertensives	78 (85.7)	3623 (50.2)	0.822	78 (85.7)	318 (87.4)	0.048
Cholesterol reducers	38 (41.8)	1585 (22.0)	0.434	38 (41.8)	147 (40.4)	0.028
Diabetes medication	25 (27.5)	1569 (21.8)	0.133	25 (27.5)	106 (29.1)	0.037

Abbreviations: COPD, chronic obstructive pulmonary disease; eNIHSS, estimated National Institutes of Health Stroke Scale; NA, not available; NTD, New Taiwan dollar; SMD, standardized mean difference; SSI, Stroke Severity Index; TIA, transient ischemic attack.

[a] All covariates in the table were used to calculate the PS for matching. The test for goodness-of-fit yielded $P < .001$, and the *c* statistic for the PS estimation model was 0.86.

[b] An SMD less than 0.1 indicates a negligible difference.

[c] The number of outpatient visits, emergency visits, and hospitalizations in the past year.

[d] The eNIHSS score was calculated for each patient using the claims-based SSI with the following equation: eNIHSS = 1.1722 × SSI − 0.75337.

[e] According to the data privacy protection regulation of the Ministry of Health and Welfare's Statistics Department, the exact number cannot be available if there are fewer than 3 events.

[f] Data are not provided to prevent the possibility of inferring fewer than 3 events in other cells.

atic Reviews and Meta-analyses (PRISMA) reporting guideline.[33] We systematically searched the Cochrane Library, Embase, MEDLINE, and Scopus databases for articles published from inception to February 2023. The search strategy details are provided in eTable 2 in Supplement 1.

We included original studies that aligned with our predefined PECO (population, exposure, comparator, and outcomes) framework. The population consisted of patients with acute ischemic stroke treated with intravenous thrombolysis; the exposure was the use of NOACs prior to stroke; the com-

Table 2. Comparison of Bleeding and Mortality Risks Between Groups After Propensity Score Matching

	NOAC vs non-OAC[a]				NOAC vs warfarin[b]			
	No. (%)				No. (%)			
Outcome	NOAC	Non-OAC	RD, % (95% CI)[c]	OR (95% CI)[c]	NOAC	Warfarin	RD, % (95% CI)[c]	OR (95% CI)[c]
Primary outcome								
Intracranial hemorrhage	9 (9.9)	27 (7.4)	2.47 (−4.23 to 9.17)	1.37 (0.62 to 3.03)	8 (10.4)	9 (11.7)	−1.30 (−11.2 to 8.60)	0.88 (0.32 to 2.40)
Secondary outcomes								
All major bleeding[d]	12 (13.2)	30 (8.2)	4.95 (−2.56 to 12.45)	1.69 (0.83 to 3.45)	11 (14.3)	13 (16.9)	−2.60 (−14.05 to 8.85)	0.82 (0.34 to 1.97)
Other critical bleeding[e]	3 (3.3)	3 (0.8)	2.47 (−1.31 to 6.26)	4.10 (0.81 to 20.67)	3 (3.9)	4 (5.2)	−1.30 (−7.88 to 5.28)	0.74 (0.16 to 3.42)
30-d Mortality	8 (8.8)	40 (11.0)	−2.2 (−8.84 to 4.45)	0.78 (0.35 to 1.73)	6 (7.8)	9 (11.7)	−3.90 (−13.24 to 5.45)	0.64 (0.22 to 1.89)
In-hospital mortality	4 (4.4)	34 (9.3)	−4.95 (−10.11 to 0.22)	0.45 (0.15 to 1.29)	3 (3.9)	9 (11.7)	−7.79 (−16.17 to 0.59)	0.31 (0.08 to 1.18)

Abbreviations: NOAC, non–vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; OR, odds ratio; RD, risk difference.

[a] There were 91 patients in the NOAC group and 364 patients in the non-OAC group after propensity score matching.

[b] There were 77 patients each in the NOAC and warfarin groups after propensity score matching.

[c] The OR and RD were calculated using the population after propensity score matching.

[d] All major bleeding was defined as any event of intracranial hemorrhage, gastrointestinal tract bleeding, or bleeding at any other critical site.

[e] Other critical bleeding was defined as all major bleeding events excluding instances of intracranial hemorrhage.

parator was the use of warfarin or no anticoagulant prior to stroke; and the outcomes focused on bleeding events and mortality. No restrictions were applied to language. Data extraction was performed independently by 4 reviewers (T.-Y.T., Y.-C.L., S.-Q.Q., and S.N.) and encompassed study characteristics, sample size, intravenous thrombolysis dosage, and outcome definitions. The main outcome measure was ICH, and the RDs and ORs were obtained. Two independent investigators (T.-Y.T. and S.-Q.Q.) assessed the quality of the included studies using the Newcastle-Ottawa Scale,[34] with interreviewer disagreements resolved through consensus and consultation with a third reviewer (H.-K.H.) if necessary.

In the random-effects meta-analysis, we calculated pooled RDs, pooled ORs, and their respective 95% CIs for the outcomes. Between-study heterogeneity was evaluated using I^2 statistics. All analyses were performed using Stata, version 17.0. The details regarding the systemic review and meta-analysis methods are described in eMethods in Supplement 1.

Results

Patient Characteristics

Of the 7483 patients with ischemic stroke treated with alteplase (mean [SD] age, 67.4 [12.7] years; 2908 [38.9%] female individuals and 4575 [61.1%] male individuals), 91 (1.2%), 182 (2.4%), and 7210 patients (96.4%) received NOACs, warfarin, and no anticoagulants prior to stroke, respectively. Their baseline characteristics are shown in eTable 3 in Supplement 1. Compared to the non-OAC group, the NOAC group exhibited a higher mean age, a greater proportion of female individuals, and a higher prevalence of medical conditions, such as prior stroke and coronary artery disease. After propensity score matching in a 1:4 ratio, 455 patients were evaluated in the analysis comparing NOACs and non-OAC: 91 in the NOAC group and 364 in the non-OAC group. The baseline characteristics were well balanced postmatching, with all standardized mean differences less than 0.1 (Table 1). For the analysis comparing NOACs to warfarin, 154 patients were evaluated after 1:1 propensity score matching, with 77 patients each in the NOAC and warfarin groups. Most baseline characteristics were well balanced postmatching, except for a few with a standardized mean difference between 0.1 and 0.2 (eTable 4 in Supplement 1). The distribution of propensity scores after matching is shown in eFigure 1 in Supplement 1.

Comparison Between NOAC and Non-OAC Groups

For the primary outcome measure, the risk of ICH following intravenous alteplase administration was 9.9% (9 of 91 patients) and 7.4% (27 of 364 patients) in the NOAC and non-OAC groups, respectively (**Table 2**). The NOAC group did not have significantly higher risk/odds of ICH compared to the non-OAC group (RD, 2.47% [95% CI, −4.23% to 9.17%]; OR, 1.37 [95% CI, 0.62-3.03]).

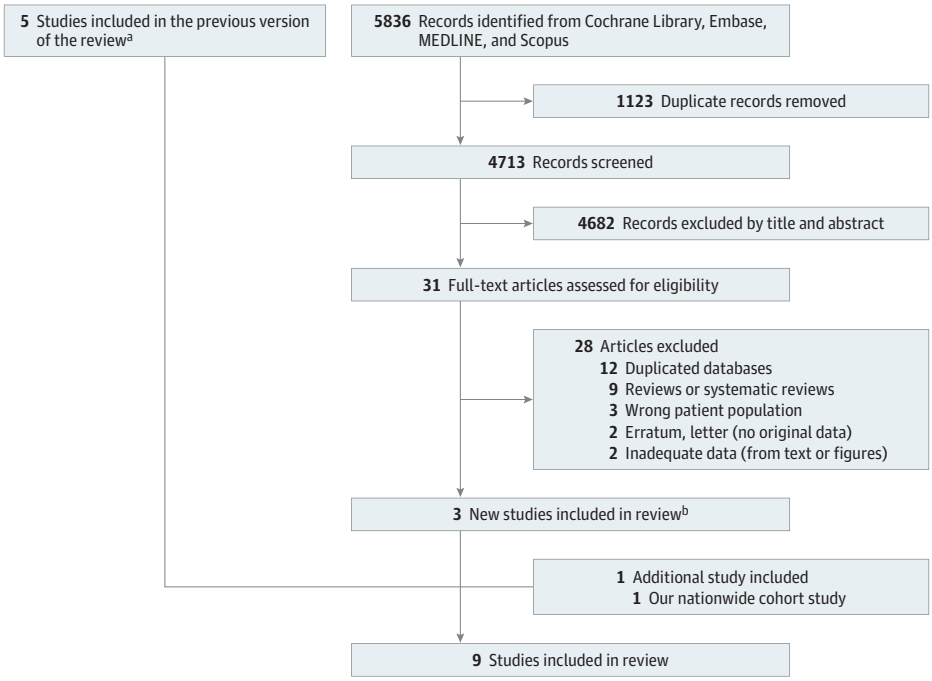
For the secondary outcome measures, compared to the non-OAC group, the NOAC group did not show a significantly higher risk/odds of major bleeding and bleeding in other critical sites. The in-hospital mortality and 30-day mortality risk/odds were also not significantly different between the NOAC and non-OAC groups (Table 2).

In the stratified analyses, the odds of ICH, all major bleeding, and other critical bleeding were not statistically different between the NOAC and non-OAC groups, regardless of age, sex, or stroke severity (eTable 5 in Supplement 1).

Comparison Between NOAC and Warfarin Groups

For the primary outcome measure, the risk/odds of ICH were not significantly different between the NOAC and warfarin groups (RD, −1.30% [95% CI, −11.2% to 8.60%]; OR, 0.88 [95% CI, 0.32-2.40]). The risk/odds of secondary outcomes, includ-

Figure 2. Literature Search and Article Selection Flowchart

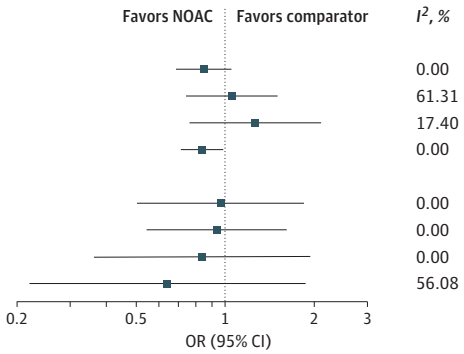


[a] The following 5 studies were included in the previous systematic review conducted by Shahjouei et al[35] in 2020: Shahjouei et al,[36] 2015; Seiffge et al,[37] 2017; Suzuki et al,[38] 2017; Xian et al,[24] 2017; and Mowla et al,[39] 2018.

[b] The following 3 studies were published after the last systematic review[35]: Kam et al,[10] 2022; Okada et al,[40] 2022; and Meinel et al,[11] 2023.

Figure 3. Forest Plot of the Risk of Intracranial Hemorrhage (ICH) and Other Events According to Anticoagulation Therapy Before Stroke

Outcome	No. of studies	Events, No./total No. NOAC	Events, No./total No. Comparator	Pooled OR (95% CI)	I^2, %
NOAC vs non-OAC					
Symptomatic ICH	4	105/2847	6475/193 864	0.85 (0.69-1.04)	0.00
Any ICH	5	186/2938	10 867/194 228	1.06 (0.74-1.50)	61.31
Major bleeding	4	30/2583	937/162 193	1.26 (0.76-2.08)	17.40
In-hospital mortality	3	166/2543	7983/161 440	0.83 (0.70-1.00)	0.00
NOAC vs warfarin					
Symptomatic ICH	5	15/360	49/878	0.97 (0.51-1.83)	0.00
Any ICH	6	23/437	58/955	0.94 (0.55-1.61)	0.00
Major bleeding	2	12/322	14/322	0.84 (0.36-1.92)	0.00
In-hospital mortality	2	26/322	33/322	0.64 (0.22-1.85)	56.08



NOAC indicates non–vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; OR, odds ratio.

ing major bleeding, other critical bleeding, and mortality, were also similar between the NOAC and warfarin groups (Table 2).

Sensitivity Analyses

Among the non-OAC, NOAC, and warfarin groups, 2230 of 7210 (30.9%), 80 of 91 (87.9%), and 155 of 182 patients (85.2%), respectively, were diagnosed with AF. The sensitivity analysis for patients with AF yielded results consistent with our primary analysis (eTable 6 in Supplement 1). Another sensitivity analysis, which used multivariable regressions to adjust for covariates with a standardized mean difference greater than 0.1 (applied exclusively to the NOACs vs warfarin analysis), also corroborated our primary findings (eTable 7 in Supplement 1). Additionally, the sensitivity analyses using different time frames to redefine the NOAC and warfarin groups consistently supported our primary results (eTable 8 in Supplement 1).

Meta-Analysis

Figure 2 outlines the study selection flowchart.[10,11,24,35-40] A total of 9 studies including 257 389 patients were identified.[10,11,24,36-40] The characteristics of each study are shown in eTable 9 in Supplement 1, and the risk-of-bias assessments are presented in eFigure 2 in Supplement 1. **Figure 3** summarizes the results. Comparison between the NOAC and the non-OAC groups showed that the risk/odds of symptomatic ICH were not significantly higher in the NOAC group (pooled RD, −0.60% [95% CI, −1.35% to 0.14%]; I^2 = 0%; eFig-

ure 3 in Supplement 1; pooled OR, 0.85 [95% CI, 0.69-1.04]; I^2 = 0%; eFigure 4 in Supplement 1). Moreover, the risk/odds of any ICH, major bleeding, and in-hospital mortality were not significantly higher in the NOAC group (eFigures 3 and 4 in Supplement 1).

In the comparison between the NOAC and the warfarin groups, the NOAC group showed a trend toward a lower risk of symptomatic ICH (pooled RD −3.30% [95% CI, −6.21% to −0.40%]; I^2 = 43.59%; eFigure 5 in Supplement 1). However, the pooled OR did not reach statistical significance (pooled OR, 0.97 [95% CI, 0.51-1.83]; I^2 = 0%; eFigure 6 in Supplement 1). Similar trends were observed for any ICH, major bleeding, and in-hospital mortality outcomes (eFigures 5 and 6 in Supplement 1).

Discussion

This nationwide, population-based cohort study among Asian individuals in Taiwan found that compared to no treatment with NOACs, treatment with NOACs before stroke was not associated with a higher risk of ICH, major bleeding events, or mortality in patients receiving intravenous alteplase for acute ischemic stroke. Additionally, the results of the meta-analysis were consistent with those of the cohort study, addressing a knowledge gap in the use of intravenous alteplase for acute ischemic stroke.

A 2022 retrospective cohort study of the US-based Get With the Guidelines-Stroke registry demonstrated that NOAC pretreatment was not associated with a higher risk of ICH after intravenous alteplase treatment for acute ischemic stroke.[10] A 2023 international collaboration retrospective study conducted by Meinel et al[11] reported a similar result. However, the 2 aforementioned studies mainly involved non-Asian patients, with only 3.4% and 20.2% of their populations being individuals of Asian descent. Given that the Asian population exhibits higher hemorrhagic risks during thrombolytic therapy,[12] the current evidence specific to Asian individuals remains limited. Furthermore, both studies extracted data from voluntary registries of enrolled hospitals rather than encompassing patients from an entire country.[10,11]

The current cohort study used nationwide, population-based data from Taiwan, with a specific focus on the Asian population. The findings offer valuable insights, addressing the existing gaps in evidence for Asian individuals. Unlike previous studies that only compared the NOAC group with the non-OAC group,[10,11] we introduced the warfarin group as an active comparator. Moreover, instead of adjusting covariates through regressions, as conducted in the previous study,[11] we adopted propensity score matching to ensure well-balanced groups for comparison, enhancing the exchangeability between the exposed and unexposed groups. We also attempted to resample comparison sets by conducting additional rounds of propensity score matching, consistently yielding results in close alignment, supporting the internal validity of our approach. Furthermore, our study specifically involved patients who neither had their NOAC plasma levels measured nor received any antidote. While European guidelines recommend the measurement of NOAC plasma levels before administering intravenous alteplase,[9] practical limitations in performing these measurements are a reality faced by many hospitals worldwide, including those in Taiwan. Consequently, the clinical scenarios explored in our study may diverge from those in previous studies,[10,11] each offering its unique value.

Beyond the cohort study, our research encompassed a meta-analysis. Since the publication of the last guidelines,[3,9] several cohort studies on this topic have emerged.[10,11,40] Our meta-analysis synthesized the latest evidence, consistently demonstrating that pretreatment with NOACs was not associated with excess harm in patients receiving intravenous thrombolysis for acute ischemic stroke. These findings provide robust evidence with potential implications for future research and guideline updates.

NOACs were first introduced and approved in Taiwan in December 2009, and their use steadily increased both in Taiwan and globally over the subsequent decade.[41,42] NHIRD data indicate that approximately 0.5% of Taiwan's population was prescribed NOACs in 2020. Considering that most NOAC users inherently belong to a high-risk group for ischemic stroke, this issue will inevitably gain increasing clinical significance. Our study offers clinicians a pivotal reference for evidence-based decision-making in clinical settings.

Strengths and Limitations

The main strength of this study is the nationwide, population-based analysis using clinical data, accompanied by a meta-analysis to integrate existing evidence. However, this study has some limitations. First, it is retrospective in nature and relies on a claims-based database, which lacks certain detailed clinical information (eg, stroke mechanism or subtype). The claims database cannot ascertain whether the treating physician considered potential bleeding risks, whether patients received alteplase against clinical guidelines, or the exact reasons behind administering alteplase to patients previously treated with NOACs. There are also no data on the day-to-day implementation of alteplase contraindications and warnings. Although we have accounted for the measured confounders by propensity score matching, residual confounders or potential selection bias may still exist. Second, as with challenges faced in previous studies, we could only determine the prescription's expiration date from the drug dispensing record, which might not accurately reflect the precise timing of the patient's last NOAC intake. Third, laboratory data on international normalized ratio were not available; thus, we could not evaluate the actual coagulation status before stroke in patients pretreated with warfarin. Fourth, although many studies use *ICD* codes from the NHIRD for ICH research, information on the severity of ICH and whether the hemorrhage occurred within 36 hours is not sufficiently provided in NHIRD-based studies.[22,23] Fifth, our cohort study used data from the NHIRD in Taiwan. Hence, the results may not be generalizable to populations from other nations or regions. However, we also conducted an updated meta-analysis to consolidate studies from various regions. Further large-scale prospective studies with a sufficient sample size are warranted to confirm our findings.

Conclusions

This cohort study and meta-analysis found no compelling evidence of higher risks of ICH, major bleeding events, and mortality following alteplase treatment for acute ischemic stroke in patients receiving NOACs compared to those not receiving any anticoagulants or those receiving warfarin prior to their stroke event. However, given that these findings were not based on randomized clinical trials, they should be interpreted with caution. Physicians should not lower their guard on the cotreatment of alteplase and NOACs, as this practice is not recommended by current guidelines. Further large-scale prospective studies are warranted to corroborate our findings.

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