JACC: ASIA VOL. 5, NO. 3, 2025

ORIGINAL RESEARCH

Outcomes of Reinitiating Direct Oral Anticoagulants After Intracranial Hemorrhage

A Sequential Target Trial Emulation Study

Yu-Han Wu, MS, PharmD,[a,*] Shin-Yi Lin, MS,[b,c,*] Fang-Ju Lin, PhD,[a,b,c] Sung-Chun Tang, MD, PhD,[d] Chi-Chuan Wang, PhD[a,b,c]

ABSTRACT

BACKGROUND Whether or not to reinitiate direct oral anticoagulants (DOACs) in atrial fibrillation patients who survived an antithrombotic agent-associated intracranial hemorrhage (ICH) event remains inconclusive.

OBJECTIVES The primary purpose of this study was to investigate the effectiveness and safety of DOACs after ICH, with the secondary objective to explore the optimal timing of DOAC reinitiation.

METHODS A sequential target trial emulation study was conducted using the National Health Insurance claims data in Taiwan. We included AF patients receiving antithrombotic therapy who later developed an ICH event between June 2012 and December 2018. Post-ICH DOAC reinitiation status was assessed at 6 consecutive 14-day intervals after discharge. We further stratified our analysis using the stroke severity index to explore the optimal timing of DOAC reinitiation. Study outcomes were all-cause mortality, ICH, and ischemic stroke. Adjusted HRs (aHRs) were estimated using Cox proportional hazards models.

RESULTS DOAC reinitiation was associated with lower risks of all-cause mortality (aHR: 0.73; 95% CI: 0.61-0.88) without increased ICH risk (aHR: 1.21; 95% CI: 0.81-1.80) compared with no antithrombotic therapy after ICH. The ischemic stroke risk after reinitiating DOAC was similar to that with no antithrombotic therapy (aHR: 0.73; 95% CI: 0.47-1.14). Reinitiating DOACs within 14 and 28 days after discharge most benefited patients with low and high ICH severity, respectively.

CONCLUSIONS DOAC is associated with lower risk of all-cause mortality. The optimal timing of DOAC reinitiation varies by ICH severity, with later reinitiation recommended for patients with higher ICH severity. (JACC Asia. 2025;5:361-370) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Oral anticoagulant (OAC) therapy is effective for stroke prevention and reducing all-cause mortality in patients with atrial fibrillation (AF).[1] However, the benefits of direct oral anticoagulants (DOACs) must be carefully weighed against the increased risk of bleeding, especially in patients with prior intracranial hemorrhage (ICH). Few studies have explored the effects of DOACs on

From the [a]Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan; [b]Department of Pharmacy, National Taiwan University Hospital, Taipei, Taiwan; [c]School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan; and the [d]Stroke Center and Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan. *These authors contributed equally to this work as first authors.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received October 1, 2024; revised manuscript received October 23, 2024, accepted November 8, 2024.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2024.11.008

JACC: ASIA, VOL. 5, NO. 3, 2025
MARCH 2025:361–370

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

aHR = adjusted HR

DOACs = direct oral anticoagulants

ICH = intracranial hemorrhage

IS = ischemic stroke

OAC = oral anticoagulant

AF patients who survived an ICH event, which leads to uncertainty in DOAC treatment after ICH. A meta-analysis comparing OAC with antiplatelets or no antithrombotic therapy after ICH suggested that OAC is associated with lower risks of ischemic events and does not increase the risk of ICH.[2] Studies specifically addressing the timing of OAC reinitiation after ICH have reported a broad range of optimal time windows, from 72 hours to 10 to 30 weeks.[3,4] A larger Swedish registry study suggested reinitiating DOACs at 7 to 8 weeks after ICH to balance ischemic and hemorrhagic complication risks.[5] Nevertheless, the OAC included in previous studies has mainly been warfarin; thus, it is unclear if the results can be extrapolated to DOACs. In addition, previous studies have assessed exposure at a specific time point, which may not appropriately reflect the dynamics of post-ICH therapy. Therefore, a more rigorous study design that appropriately reflects the dynamics of DOAC exposure after ICH is needed.

As DOACs have become widely used in clinical practice and because of the lack of recent studies exploring the effect of post-ICH DOAC treatment on AF patients, we conducted a study with more sophisticated study design with the primary objective to investigate the effectiveness and safety of DOAC reinitiation in AF patients with ICH, and to further explore the optimal timing of post-ICH DOAC reinitiation as a secondary objective.

METHODS

DATA SOURCE. This study was conducted using the full population data provided by the Health and Welfare Data Science Center, Ministry of Health and Welfare of Taiwan. The full population data contains detailed health care data generated from the National Health Insurance system in Taiwan. Because the National Health Insurance is a mandatory health insurance program that offers comprehensive medical coverage to more than 23 million enrollees in Taiwan,[6] the full population data represent more than 99% of Taiwan's population. Data between January 1, 2011, and December 31, 2019, were used for this study.

STUDY DESIGN AND SAMPLE. This retrospective cohort study was guided by the target trial emulation framework, which applies randomized control trial principles to observational studies to mitigate common flaws, such as selection, confounding, and time-related biases. By clearly defining treatment strategies, timing, and eligibility criteria, this framework aims to improve comparability between groups. However, target trial emulation does not inherently resolve all limitations associated with observational studies. For example, issues such as residual confounding and selection biases may remain if the data are incomplete or inaccurately captured, and inaccuracies in the sequencing of events can introduce reverse causality.

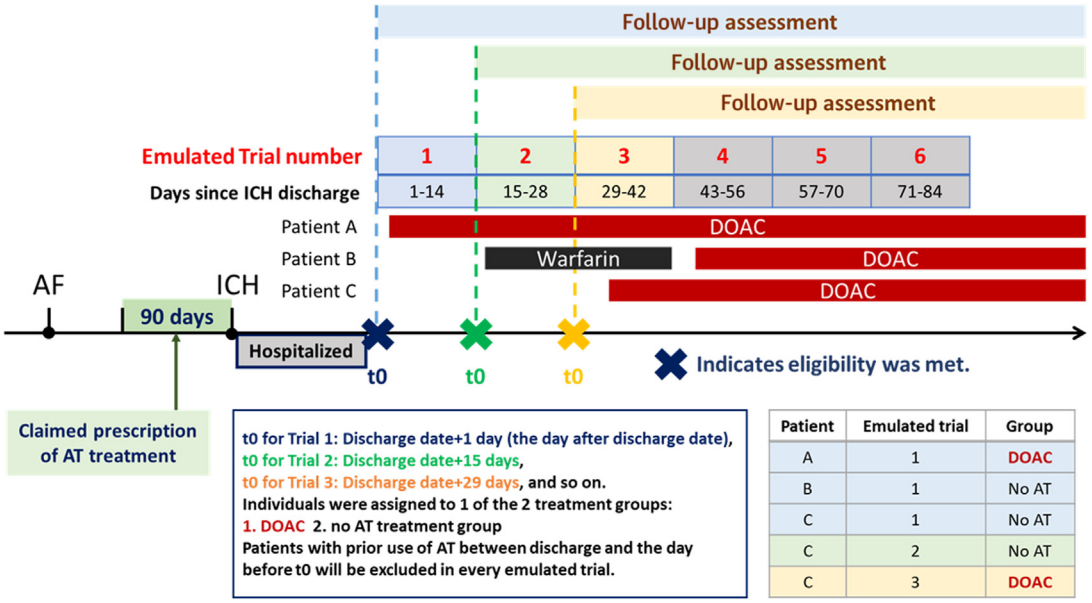
To address the effect of varied DOAC initiation timing on treatment outcomes, we conducted 6 sequential target trial emulations at 6 different time points. Subsequently, we pooled the results from these 6 emulated trials to estimate the overall effect of post-ICH DOAC therapy on treatment outcomes.

We included patients age ≥20 years at their index ICH between June 1, 2012, and December 31, 2018. We defined the index ICH as the first observed ICH event with no prior ICH for at least 365 days before the observed event. Patients were required to have a diagnosis of AF and received antithrombotic agents within 90 days before the index ICH. Antithrombotic agents included DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban), warfarin, and antiplatelet agents (aspirin, clopidogrel, prasugrel, and ticagrelor). We considered the day after discharge of the index ICH event to be the index date (i.e., time zero, t_0), and subsequently created additional 5 t_0s, each at a 14-day interval. For example, the t_0 of emulated trial 2 will be day 15 after discharge, the t_0 of emulated trial 3 will be day 29 after discharge, and so on. A total of 6 t_0s were created for 6 sequential emulated trials, which assessed the time of DOAC reinitiation from days 1 to 84 after ICH discharge (**Figure 1**).

We excluded patients who were discharged caused by terminal illness and those who had one of the following conditions within 180 days before each t_0: valvular AF, brain vascular malformation or aneurysm, end-stage renal disease, and pregnancy. Valvular AF was defined as mitral stenosis or prosthetic mechanical heart valves. Vascular malformation or aneurysm included malformation of cerebral vessels, dissection of cerebral arteries, cerebral aneurysm, and moyamoya disease. Patients who received antithrombotic agents between ICH discharge and the day before t_0 were also excluded in each emulated trial.

Patients' eligibility was evaluated at each t_0, and patients can be included in more than 1 emulated trial if they met the inclusion and exclusion criteria. Supplemental Tables 1 to 3 provide the International Classification of Diseases-9th/10th Revision-Clinical Modification (ICD-9/-10-CM) codes and the Anatomical Therapeutic Chemical codes for the enrollment

FIGURE 1 Graphical Illustration of the Sequential Emulated Trials



Patient	Emulated trial	Group
A	1	DOAC
B	1	No AT
C	1	No AT
C	2	No AT
C	3	DOAC

A total of 6 emulated trials were created in this study. The group assignment of emulated trials 1 to 3 was shown in the bottom right of the figure as an example. AF = atrial fibrillation; AT = antithrombotics; DOAC = direct oral anticoagulant; ICH = intracranial hemorrhage.

assessment. The key elements of the hypothetical target randomized controlled trial are presented in Supplemental Table 4.

EXPOSURE ASSESSMENT. We used pharmacy claims to identify patients' DOAC exposure status, which was assessed at each t_0 and classified into 2 groups in each emulated trial: DOAC reinitiation group, and no antithrombotic treatment group. Patients who had a prescription of DOAC that covered or on t_0 were assigned to the DOAC exposure group, whereas those who did not receive any antithrombotic treatment at t0 were assigned to the no-exposed group. Neither anticoagulant or antiplatelet use was allowed in the no treatment group.

COVARIATES. Baseline characteristics adjusted in this study were age at index ICH, sex, CHA_2DS_2-VASc score, HAS-BLED score, severity of the index ICH, calendar year of the ICH event, length of the index ICH stay, comorbidities, and concomitant medications. We selected these covariates because they were risk factors or confounders for the outcomes. For example, age, HAS-BLED score, ICH severity, and the duration of the initial ICH stay were linked to the risk of future ICH. The calendar year of the ICH event indicates the evolution of ICH care, influencing both post-ICH management and the likelihood of recurrent ICH. The CHA_2DS_2-VASc score, which represented the thrombosis risk in AF patients, was associated with the occurrence of stroke and systemic thromboembolism, with higher scores indicating higher risk. We collected updated covariate data available before each t_0 in every sequential emulated trial. This enabled adjustment for time-varying covariates at each time point, ensuring that our model accurately reflects changes in patient status over time. This approach minimizes bias from covariate shifts and ensures that the analysis remains consistent with the evolving health status of patients.

Comorbidities were measured with all available observation periods before each t_0, including congestive heart failure, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, myocardial infarction, peripheral artery disease, peripheral arterial thrombosis, ischemic stroke (IS), transient ischemic attack, venous thromboembolism, pulmonary embolism, bleeding events, renal disease, liver disease, chronic obstructive pulmonary disease, and cancer. Concomitant medications were identified within 180 days before t_0, including antihypertensive drugs, antidiabetic drugs, antiarrhythmic agents, rate control drugs, statins/fibrates, H_2 receptor antagonists/proton pump inhibitors, nonsteroidal anti-inflammatory drugs, strong P-glycoprotein/cytochrome P450 3A4 inhibitors, and strong P-glycoprotein/cytochrome P450 3A4 inducers. See

Supplemental Table 5 for the ICD-9/-10-CM codes for the covariates.

Severity of the index ICH was assessed using the claims-based stroke severity index as a proxy for the National Institutes of Health Stroke Score. The stroke severity index was estimated using a multiple linear regression model and was valid for stroke severity assessment. It demonstrated a significant correlation with the National Institutes of Health Stroke Score (r = 0.731; 95% CI: 0.705-0.755) in a Taiwanese cohort.[7] The items, the corresponding National Health Insurance codes, and the coefficients used to calculate the stroke severity index score are listed in Supplemental Table 6. A higher stroke severity index score indicates higher stroke severity.

OUTCOME MEASURES AND FOLLOW-UP ASSESSMENT. The primary outcomes in this study were recurrent ICH, IS, and all-cause mortality; 2 composite secondary outcomes were major bleeding (safety) and thromboembolism (effectiveness). Major bleeding included recurrent ICH, gastrointestinal bleeding, and other bleeding, either fatal or nonfatal. Thromboembolism included IS, myocardial infarction, peripheral artery disease, peripheral arterial thrombosis, transient ischemic attack, venous thromboembolism, and pulmonary embolism, either fatal or nonfatal.

Follow-up assessment began from t_0 of each emulated trial. We used the "as-started" approach for follow-up, which ignored exposure status changes during follow-up. This approach is analogous to the intention-to-treat approach used in clinical trials. Patients were followed until the outcome of interest occurred, death, or the end date of the observation period (December 31, 2019), whichever occurred first. The outcomes of interest were determined by the primary diagnosis on an inpatient claim. See Supplemental Table 7 for the ICD-9/-10-CM codes for the outcome assessment.

STATISTICAL ANALYSES. In the main analysis, we assessed the effectiveness and safety of post-ICH DOAC therapy. To account for the potential bias caused by different timing of DOAC initiation, we pooled data from all 6 emulated trials and adjusted for both the baseline covariates and the sequential of the emulated trial. We adjusted the baseline covariates and estimated HRs using multivariable Cox proportional hazards models. As the patients might be included in more than 1 emulated trial, we used the sandwich estimator to estimate the robust variance and to compute 95% CIs. All statistical analyses were performed with SAS version 9.4 (SAS Institute). This research was reviewed and approved by the Research Ethics Committee of the National Taiwan University Hospital (NTUH-REC No: 202201070W).

EXPLORATORY ANALYSES: TIME TO REINITIATE DOAC. To explore the optimal timing of DOAC reinitiation, we stratified our analysis based on the median stroke severity index observed in the study cohort, because the severity of ICH is expected to affect patients' prognosis. Patients with stroke severity index ≤16 were classified in the low ICH severity group, and patients with stroke severity index >16 were classified in the high ICH severity group. The risk of recurrent ICH, IS, and all-cause mortality were assessed in each emulated trial.

We first calculated the event rate ratios (RRs) in each emulated trial. RRs were defined as the event rate of the DOAC group divided by the event rate of the no antithrombotic treatment group. Based on the findings from the RRs, we identified the potential optimal timing of DOAC reinitiation and further analyzed the risks and benefits of DOAC reinitiation based on this time point by adding an interaction term of DOAC reinitiation and the time of reinitiation in the Cox model.

SENSITIVITY ANALYSES. Several sensitivity analyses were conducted to ensure the robustness of our results. First, instead of using regression to adjust for potential confounders, we used stabilized inverse probability of treatment weighting to balance patients' baseline characteristics between the 2 treatment groups. Because the treatment weights were calculated as the inverse of the probability of receiving treatment (ie, the propensity scores), patients with very high or low probabilities would have extreme weights. To reduce the impact of the extreme weights, we stabilized the weights by replacing the numerator of the weights with the proportion of exposed patients in the exposure group and the proportion of unexposed patients in the unexposed group.[8] We regarded the baseline characteristics as well-balanced if the standardized mean differences after weighting between the 2 groups was <0.1. Factors remained unbalanced after weighting were further adjusted in the Cox regression model. Second, we conducted "on-treatment" analyses, where patients' follow-up was censored when treatment change was identified. This approach is analogous to the per-protocol analysis in clinical trials. Treatment change was defined as the following: patients in the no antithrombotic treatment group started antithrombotic treatment, or patients in the DOAC group changed to warfarin or antiplatelets or discontinued their DOAC treatment. DOAC discontinuation was defined as a 14-day gap between the

end of a DOAC prescription to the next refill. Third, we excluded patients with an ICH or IS event between ICH discharge and the day before t_0. Fourth, we restricted the follow-up duration to a maximum of 1 year. Fifth, we excluded patients with a long length of stay (>28 and >56 days), respectively. Sixth, instead of comparing with nonantithrombotic users, antiplatelet users served as the control group (i.e., active comparator).

RESULTS

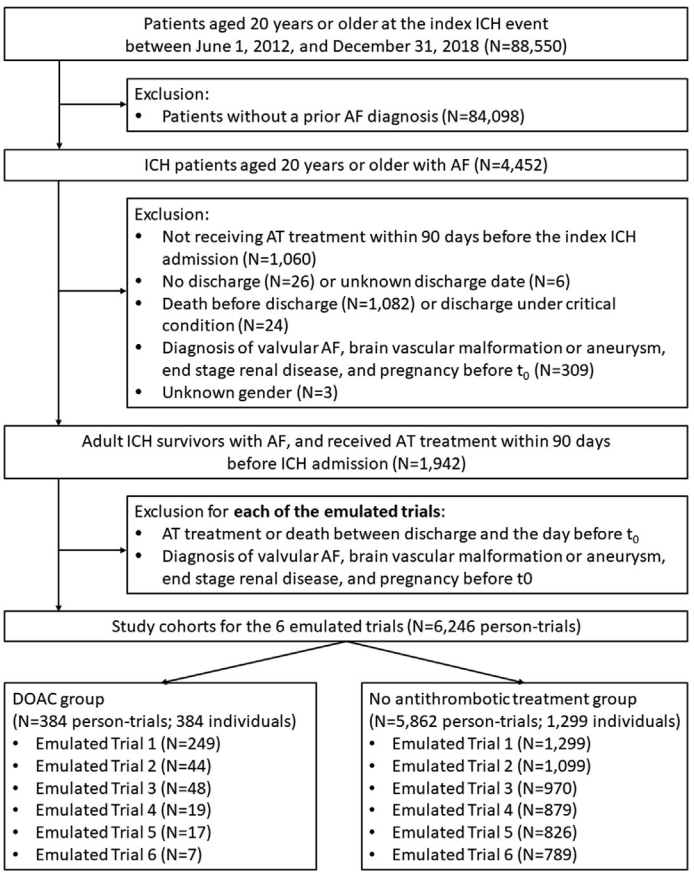
BASELINE CHARACTERISTICS OF THE STUDY SAMPLE. The sample selection flowchart is shown in Figure 2. A total of 4,452 patients with a prior diagnosis of AF had the index ICH event between June 1, 2012, and December 31, 2018, of whom, 1,942 patients received antithrombotic treatment before the index ICH admission and survived to hospital discharge. These patients contributed a total of 6,246 person-emulated trials, with 384 person-emulated trials in the DOAC group and 5,862 person-emulated trials in the no antithrombotic treatment group.

The baseline characteristics are shown in Supplemental Table 8. The characteristics between post-ICH DOAC treatment and nonuser groups were different. DOAC reinitiators had more comorbid diseases, higher CHA_2DS_2-VASc score, and lower stroke severity, and the antithrombotic agent before ICH was more likely to be DOAC. The 2 groups had similar stroke severity, with the median stroke severity index 15.01 (Q1-Q3: 9.94-19.39) in the DOAC group and 16.37 (Q1-Q3: 11.79-19.39) in the no antithrombotic treatment group. The median follow-up duration was 2.16 years (Q1-Q3: 1.18-3.23 years) in the DOAC group and 2.03 years (Q1-Q3: 0.98-3.64 years) in the no antithrombotic treatment group.

EFFECTIVENESS AND SAFETY OF POST-ICH DOAC TREATMENT. The incidence rates of the outcomes are shown in Table 1. Patients with post-ICH DOAC treatment had higher incidence rates of recurrent ICH compared with those without post-ICH antithrombotic treatment (3.73 vs 2.54 per 100 person-years) but lower incidence rates of all-cause mortality (15.13 vs 20.43 per 100 person-years) and IS (3.08 vs 4.04 per 100 person-years).

The adjusted results are shown in Figure 3. We found that post-ICH DOAC treatment was associated with significantly lower risks of all-cause mortality (adjusted HR [aHR]: 0.73; 95% CI: 0.61-0.88) compared with no antithrombotic treatment. We observed nonsignificant increases in the risk of ICH (aHR: 1.21; 95% CI: 0.81-1.80) and major bleeding (aHR: 1.27; 95% CI: 0.91-1.78), and nonsignificant decreases in the risk of IS (aHR: 0.73; 95% CI: 0.47-1.14) and thromboembolism (aHR: 0.82; 95% CI: 0.57-1.19) (Figure 3). The results of the composite of ICH and IS were nonsignificant (aHR: 0.96; 95% CI: 0.72-1.30).

FIGURE 2 Sample Selection Flowchart



A total of 4,452 patients had the index ICH event between June 1, 2012, and December 31, 2018, with a prior diagnosis of AF, of whom, 1,942 patients received antithrombotic treatment before the index ICH admission and survived to hospital discharge. These patients contributed a total of 6,246 person-emulated trials, with 384 person-emulated trials in the DOAC group and 5,862 person-emulated trials in the no antithrombotic treatment group. t0: time zero; other abbreviations as in Figure 1.

EXPLORATORY ANALYSES: TIME TO REINITIATE DOAC. Table 2 presents the event number and incidence rates between patients with post-ICH DOAC treatment and patients with no antithrombotic treatment, stratified by ICH severity. The incidence rates of all outcomes were generally higher for patients with high ICH severity than those with low ICH severity. Figure 4 presents the event RRs and aHRs of the outcomes between patients with post-ICH DOAC treatment vs those without post-ICH antithrombotic treatment by ICH severity. For patients with low ICH

TABLE 1 Incidence Rates of Clinical Outcomes in Patients With or Without Post-ICH DOAC Treatment

	Number of Events (per 100 Person-Years)	
	DOAC (n^a = 384)	No AT Treatment (n^a = 5,862)
All-cause mortality	139 (15.13)	2,941 (20.43)
ICH	33 (3.73)	350 (2.54)
IS	27 (3.08)	541 (4.04)
Composite outcome of ICH + IS	59 (7.01)	845 (6.57)
Major bleeding	48 (5.57)	584 (4.36)
Thromboembolism	39 (4.52)	742 (5.66)

[a]N indicates the number of person-emulated trials as patients can be included in more than 1 emulated trial.
AT = antithrombotic; DOAC = direct oral anticoagulant; ICH = intracranial hemorrhage; IS = ischemic stroke.

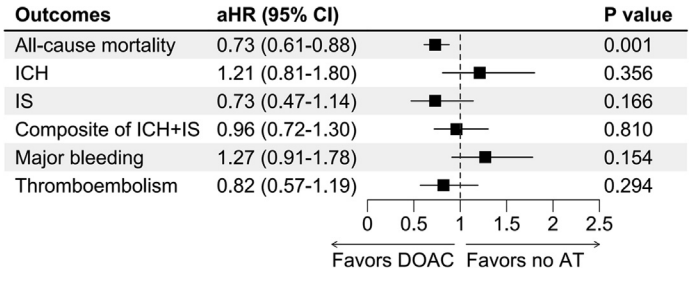
severity (Figure 4A), the RRs of the composite of ICH and IS increased with a delay in DOAC reinitiation time. The lowest RRs of both ICH and IS were found when reinitiating DOAC within 14 days after discharge (i.e., emulated trial 1). For patients with high ICH severity (Figure 4B), the RRs for the composite of ICH and IS remained constant across the emulated trials. However, it is worth noting that an intersection of RR trend lines of ICH and IS was found when reinitiating DOAC 29 to 42 days after discharge (i.e., emulated trial 3). Because of the small sample size in emulated trials 5 and 6 (n = ≤5 in those subgroups), only results from emulated trials 1 to 4 are presented in Figure 4.

Based on the findings from the event RRs, we further analyzed the risks and benefits associated with the possible optimal timing for DOAC reinitiation by Cox models. Among patients with low ICH severity (Figure 4A), post-ICH DOAC treatment was associated with a significantly lower risk of all-cause mortality when it was reinitiated within 14 days after discharge (aHR: 0.57; 95% CI: 0.38-0.84) but not after 14 days after discharge (aHR: 0.88; 95% CI: 0.55-1.40) compared with no antithrombotic treatment. In addition, post-ICH DOAC treatment was associated with a significantly higher risk of ICH (aHR: 3.61; 95% CI: 1.85-7.05) and the composite of ICH and IS (aHR: 1.83; 95% CI: 1.01-3.32) when it was reinitiated after 14 days after discharge. We also observed a trend toward reduced ICH, IS, and composite ICH and IS risk for reinitiating DOAC within 14 days after discharge compared with nonusers.

Among patients with high ICH severity (Figure 4B), post-ICH DOAC treatment was significantly associated with lower risks of all-cause mortality when reinitiating DOAC within 28 days after discharge (aHR: 0.74; 95% CI: 0.56-0.98) but not after 28 days after discharge (aHR: 0.83; 95% CI: 0.53-1.29) compared with no antithrombotic treatment. In addition, a trend of lower IS and composite of ICH and IS risk were observed for reinitiating DOAC in 28 days after discharge than nonusers. Nevertheless, the risk of ICH was higher in DOAC reinitiators regardless of the reinitiation time in the high ICH severity group. Together, these results suggest that reinitiating DOAC within 28 days after discharge may benefit patients overall by reducing the risk of IS.

SENSITIVITY ANALYSES. Results from the sensitivity analyses were consistent with the main analysis, which suggested the robustness of our study findings. All of the sensitivity analyses yielded similar results as the main analysis, including applying stabilized inverse probability of treatment weighting, using the on-treatment analytical approach, excluding patients with ICH or IS event between ICH discharge and the day before t_0, restricting follow-up duration to a maximum of 1 year, excluding patients with a long length of stay, and using post-ICH antiplatelet treatment as an active comparator. Results of the sensitivity analysis are presented in Supplemental Figures 1 to 6 and Supplemental Tables 9 to 11.

FIGURE 3 Clinical Outcomes in Patients With or Without Post-ICH DOAC Treatment



Post-ICH DOAC treatment was associated with significantly lower risks of all-cause mortality compared with no antithrombotic treatment. aHR = adjusted HR; IS = ischemic stroke; other abbreviations as in Figure 1.

DISCUSSION

In this sequential target trial emulation study targeting AF patients with ICH, we demonstrated that DOAC reinitiation was associated with lower risks of all-cause mortality compared with no antithrombotic treatment, and did not increase the risk of ICH. Regarding the timing of DOAC reinitiation, in patients with low ICH severity, reinitiating DOAC within 14 days after discharge is recommended; in those with high ICH severity, DOAC therapy may be delayed until 1 month after discharge (Central Illustration).

Our results are consistent with the results from the SoSTART trial (Start or STop Anticoagulants Randomised Trial), which showed that reinitiating post-ICH

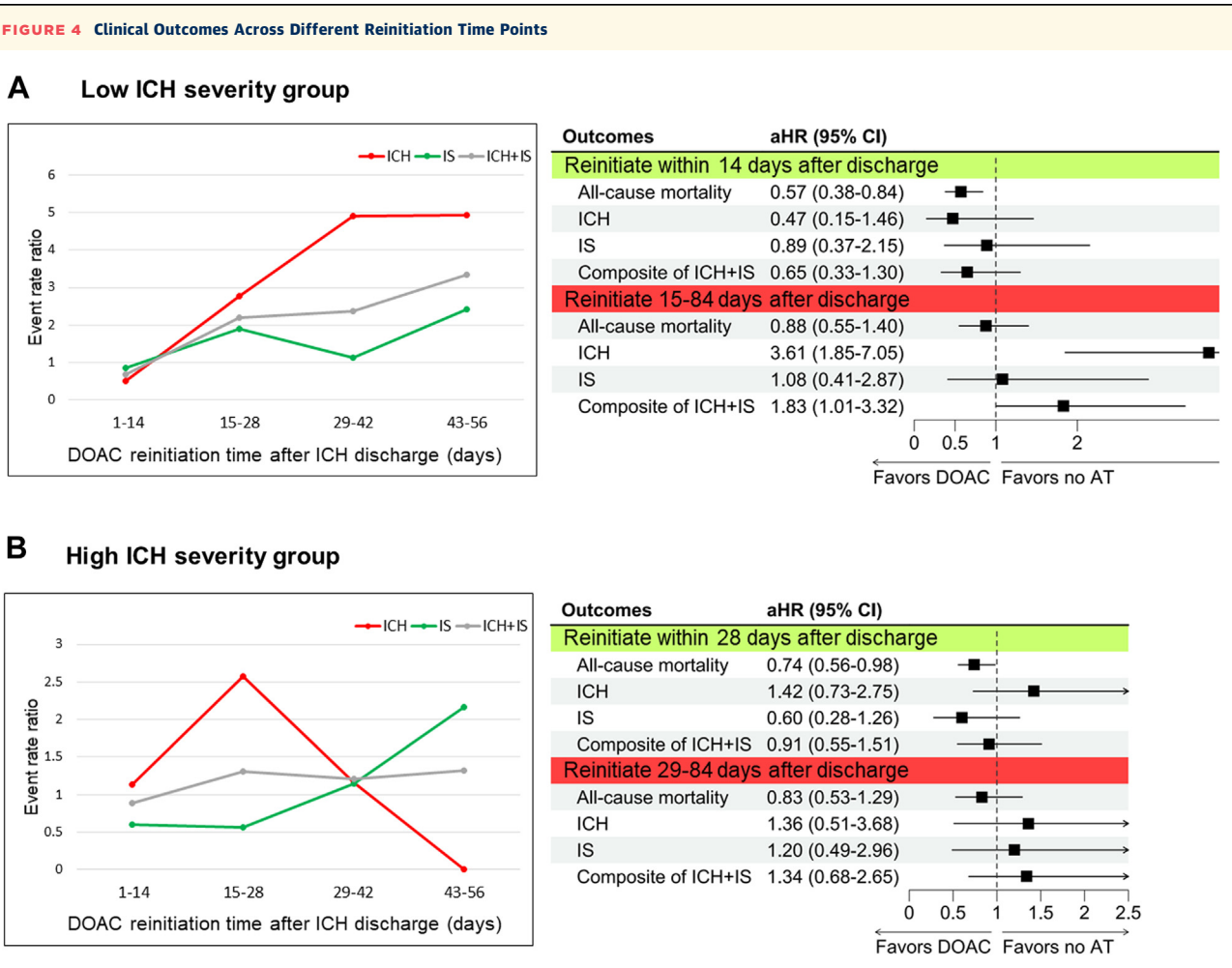
TABLE 2 Incidence Rates of Clinical Outcomes in Patients With Different ICH Severity

	Number of Events (per 100 Person-Years)			
	Low ICH Severity (N[a] = 3,118) SSI ≤16		High ICH Severity (N[a] = 3,128) SSI >16	
	DOAC (n[a] = 220)	No AT Treatment (n[a] = 2,898)	DOAC (n[a] = 164)	No AT Treatment (n[a] = 2,964)
All-cause mortality	51 (9.01)	962 (12.69)	88 (24.96)	1,979 (29.04)
ICH	12 (2.16)	98 (1.33)	21 (6.37)	252 (3.92)
IS	12 (2.20)	167 (2.29)	15 (4.53)	374 (6.13)
Composite outcome of ICH + IS	24 (4.50)	265 (3.76)	35 (11.35)	580 (10.00)
Major bleeding	15 (2.73)	158 (2.18)	33 (10.57)	426 (6.94)
Thromboembolism	21 (3.92)	262 (3.68)	18 (5.51)	480 (8.01)

[a]N indicates the number of person-emulated trials as patients can be included in more than 1 emulated trial.
SSI = stroke severity index; other abbreviations as in Table 1.

OAC, compared with avoiding post-ICH OAC, was associated with nonsignificantly higher risks of ICH and nonsignificantly lower risks of any major vascular event.[9] In the SoSTART trial, 95% of the patients in the OAC group received DOACs. The similarity in study groups and results between our study and the trial further supports the validity of our findings.

FIGURE 4 Clinical Outcomes Across Different Reinitiation Time Points

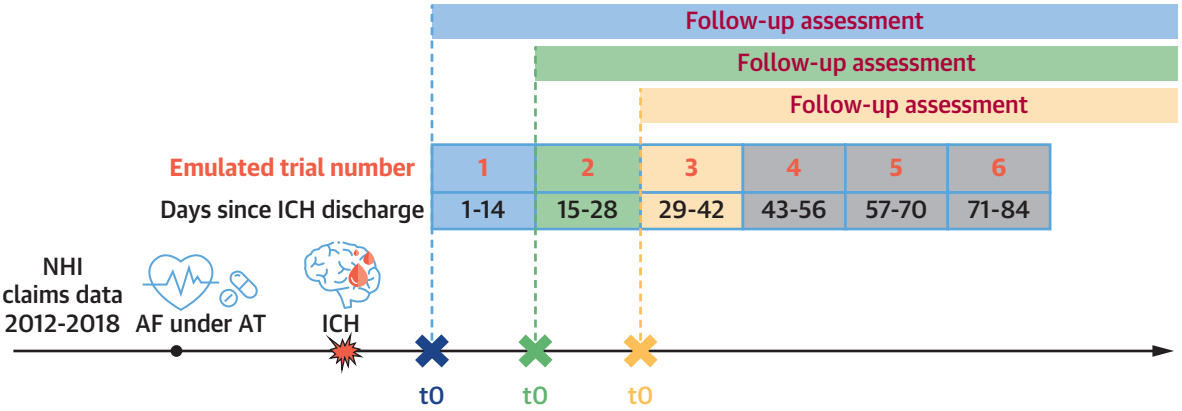


The cutpoints used in the Cox were obtained from the findings of rate ratios (14 days for patients with low ICH severity and 28 days for patients with high ICH). Abbreviations as in Figures 1 and 3.

JACC: ASIA, VOL. 5, NO. 3, 2025
MARCH 2025:361-370

CENTRAL ILLUSTRATION The Study Design and Main Findings

Design: Sequential Target Emulated Trials



Treatment Groups

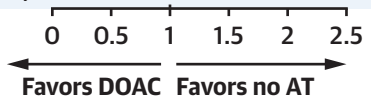
Restart DOAC

vs

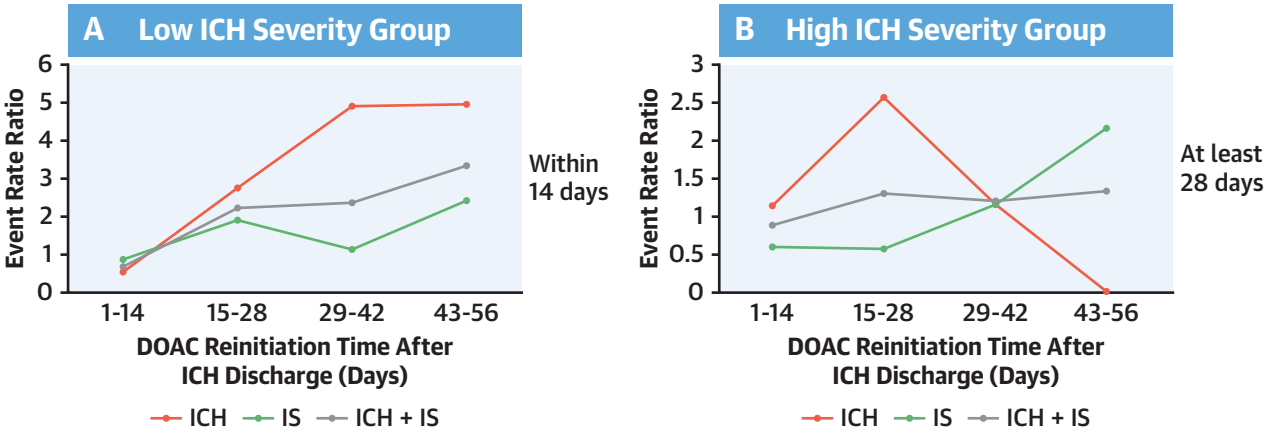
No AT

Reinitiate DOAC or no AT

Outcomes	aHR (95% CI)	*P* Value
All-cause mortality	0.73 (0.61-0.88)	0.001
ICH	1.21 (0.81-1.80)	0.356
IS	0.73 (0.47-1.14)	0.166
Composite of ICH + IS	0.96 (0.72-1.30)	0.810
Major bleeding	1.27 (0.91-1.78)	0.154
Thromboembolism	0.82 (0.57-1.19)	0.294



Time to Reinitiate DOAC



Wu Y-H, et al. JACC Asia. 2025;5(3):361-370.

A total of 6 emulated trials were created in this study. The group assignment of emulated trials 1 to 3 was shown in the figure as an example. Patients were classified to direct oral anticoagulant (DOAC) or nonantithrombotic therapy (AT) group based on the treatment after intracranial hemorrhage (ICH). Post-ICH DOAC treatment was associated with significantly lower risks of all-cause mortality compared with no antithrombotic treatment. IS = ischemic stroke; NHI = National Health Insurance.

Although our results are consistent with results from the SoSTART trial, our findings are not fully consistent with the findings from previous observational studies, which mostly showed a significant reduction in the risk of thromboembolic events. A Taiwanese study showed that post-ICH OAC significantly reduced the risk of IS and thromboembolism and did not increase the risk of ICH compared with no antithrombotic treatment.[10] Additionally, a Korean study found that post-ICH OAC significantly reduced the risk of severe thrombotic events and severe hemorrhage events compared with no antithrombotic treatment.[11] Two reasons may explain the discrepancy between the findings of this study and others. First, previous studies analyzed DOAC and warfarin together as OAC, whereas we investigated DOAC solely. Therefore, our findings specifically reflect the effect of DOACs. Second, previous studies assessed OAC exposure at a specific time point (eg, discharge, first OAC prescription, or 90 days after discharge). Nevertheless, the timing of DOAC reinitiation can be influenced by the patients' baseline condition such as bleeding or thromboembolic risk, and ICH severity and should be considered to reduce time-related bias. In our study, we anchored a series of time points to repeatedly assess patients' DOAC exposure, which could more appropriately reflect the dynamics of post-ICH therapy.

No randomized controlled trials have addressed the optimal timing of reinitiating post-ICH OACs. Some retrospective cohort studies have addressed this issue. A Korean study found that reinitiating OAC at 6 to 8 weeks after ICH onset showed a tendency of a lower risk of all-cause mortality.[11] In a Swedish registry study, patients were classified into low or high thromboembolic risk based on age, length of stay for the ICH event, prior risk other than AF, and prior antithrombotic treatment.[5] The results showed that starting OAC at 7 to 8 weeks after ICH onset lowered the risk of thromboembolism and the composite of vascular death and nonfatal stroke, while not increasing the risk of major bleeding. Unlike previous studies, our study defined the index date as the discharge date rather than the ICH onset to ensure stabilized OAC treatment. Furthermore, this approach aimed to reduce bias caused by events that occurred during hospital stay and could not be clearly attributed to DOAC therapy or rebleeding of ICH. After adding the median length of hospitalization (52 days [Q1-Q3: 24-132 days]) of our cohort, our proposed timing of DOAC reinitiation is quite similar to previous investigations and complies with guideline recommendations (i.e., 4-8 weeks after the ICH event).[12]

To the best of our knowledge, this is the first study to address the effectiveness and safety between post-ICH DOAC reinitiation and no antithrombotic treatment among ICH survivors with AF, specifically exploring the optimal timing of DOAC reinitiation after ICH in AF patients. As DOACs have become widely used in clinical practice, related real-world evidence is important for clinical decision making. We provided further evidence of optimal timing of DOAC reinitiation by stratifying patients with ICH severity. ICH severity has not been taken into consideration in previous studies; however, it might directly affect the decision of the timing of post-ICH DOAC reinitiation given that ICH severity is positively associated with the incidence of major bleeding and mortality. Therefore, patients with severe ICH may delay their post-ICH DOAC therapy because of concerns about the bleeding risk. We tried to eliminate this confounding by disease severity issue by stratifying our analyses based on stroke severity index and using a series of different time points for fair comparisons. We applied design principles from randomized controlled trials to this observational study using the sequential target trial emulation design. This design helps to eliminate potential time-related bias and provides information on the effectiveness and safety of DOAC reinitiation at different time points. Separate recommendations for patients with different characteristics may be more useful for clinical application.

STUDY LIMITATIONS. First, it was conducted using nationwide claim data where the detailed information of index ICH, such as neuroimaging results and detailed clinical presentation of the ICH was not available. We could not access the subtypes of the ICH event, but lobar ICH may have higher risks of recurrent ICH compared with nonlobar ICH.[13] Although with limited information, we used a previously validated claim-based algorithm, stroke severity index, as a proxy of ICH severity in our study.[7] Second, we defined the index date for clinical outcome observations as the date of discharge rather than the date of ICH onset. This decision was made because of the lack of precise timing of ICH onset and DOAC initiation in the inpatient records. Additionally, we considered that DOAC treatment during admission is often interrupted for procedures, operations, and hemorrhage, which may result in a short follow-up duration. Nevertheless, our results provide further insight on the effectiveness and safety of post-ICH DOAC treatment among patients with stabilized treatment. Third, we were unable to measure patients' socioeconomic status using the claims database. However, given Taiwan's comprehensive, accessible,

and affordable universal health care coverage, we believe that patients' socioeconomic status should have a minimal effect on patients' access to health care services, including DOAC treatment and care for ICH. As a result, the residual confounding from unmeasured socioeconomic status should be minimal. Fourth, despite being a nationwide, population-based study, the statistical power may still be limited. This was anticipated because our study focused on a unique population (i.e., AF patients who underwent treatment and subsequently had an ICH event) with rare occurrences. Moreover, statistical power is partially influenced by effect size. The comparable event incidence rates between the 2 groups under comparison (refer to **Tables 1 and 2**) suggest that a much larger sample size would be needed to identify significant differences, which may not be feasible. Despite the limited evidence on this particular issue, our research remains one of the few studies providing population-level data on this specific group and offers valuable insights to the current body of literature. Finally, even though we tried our best to balance the baseline risk of bleeding and thromboembolism, it is possible that physicians tend to reinitiate DOAC therapy earlier in patients with better conditions and delay DOAC therapy in those with worse conditions. Future randomized controlled trials are still necessary to determine the optimal timing of post-ICH DOAC therapy. Instead of using sequential emulated trials, future studies could verify our results with alternative analytical approaches, such as recurrent event analysis with time-dependent treatment assignment.

CONCLUSIONS

Among AF patients with ICH, DOAC reinitiation is recommended because it is associated with lower risks of all-cause mortality. The optimal timing of DOAC reinitiation may vary by patients' ICH severity. DOAC reinitiation within 14 days after discharge is recommended for patients with low ICH severity, and delaying DOAC reinitiation to 28 days after discharge is suggested for patients with high ICH severity.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by the Ministry of Science and Technology in Taiwan (MOST 111-2636-B-002-019 and NSTC 113-2320-B-002-054). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Prof Chi-Chuan Wang, School of Pharmacy, National Taiwan University, Room 202, No.33, Linsen S. Road, Zhongzheng District, Taipei City 100, Taiwan. E-mail: chicwang@ntu.edu.tw.

REFERENCES

1. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the Diagnosis and Management of Atrial Fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42(5):373-498. https://doi.org/10.1093/eurheartj/ehaa612

2. Murthy SB, Gupta A, Merkler AE, et al. Restarting anticoagulant therapy after intracranial hemorrhage: a systematic review and meta-analysis. *Stroke*. 2017;48(6):1594-1600. https://doi.org/10.1161/strokeaha.116.016327

3. Majeed A, Kim YK, Roberts RS, Holmström M, Schulman S. Optimal timing of resumption of warfarin after intracranial hemorrhage. *Stroke*. 2010;41(12):2860-2866. https://doi.org/10.1161/strokeaha.110.593087

4. Hawryluk GW, Austin JW, Furlan JC, Lee JB, O'Kelly C, Fehlings MG. Management of anticoagulation following central nervous system hemorrhage in patients with high thromboembolic risk. *J Thromb Haemost*. 2010;8(7):1500-1508. https://doi.org/10.1111/j.1538-7836.2010.03882.x

5. Pennlert J, Overholser R, Asplund K, et al. Optimal timing of anticoagulant treatment after intracerebral hemorrhage in patients with atrial fibrillation. *Stroke*. 2017;48(2):314-320. https://doi.org/10.1161/strokeaha.116.014643

6. National Health Insurance Administration. National Health Insurance Annual Statistical Report 2020 (2021). Accessed October 1, 2024. https://www.nhi.gov.tw/en/cp-1216-01a1a-90-2.html

7. Hung LC, Sung SF, Hsieh CY, et al. Validation of a novel claims-based stroke severity index in patients with intracerebral hemorrhage. *J Epidemiol*. 2017;27(1):24-29. https://doi.org/10.1016/j.je.2016.08.003

8. Chesnaye NC, Stel VS, Tripepi G, et al. An introduction to inverse probability of treatment weighting in observational research. *Clin Kidney J*. 2022;15(1):14-20. https://doi.org/10.1093/ckj/sfab158

9. Effects of oral anticoagulation for atrial fibrillation after spontaneous intracranial haemorrhage in the UK: a randomised, open-label, assessor-masked, pilot-phase, non-inferiority trial. *Lancet Neurol*. 2021;20(10):842-853. https://doi.org/10.1016/s1474-4422(21)00264-7

10. Lin SY, Chang YC, Lin FJ, Tang SC, Dong YH, Wang CC. Post-intracranial hemorrhage antithrombotic therapy in patients with atrial fibrillation. *J Am Heart Assoc*. 2022;11(6):e022849. https://doi.org/10.1161/jaha.121.022849

11. Moon JY, Bae GH, Jung J, Shin DH. Restarting anticoagulant therapy after intracranial hemorrhage in patients with atrial fibrillation: a nationwide retrospective cohort study. *Int J Cardiol Heart Vasc*. 2022;40:101037. https://doi.org/10.1016/j.ijcha.2022.101037

12. Chiang CE, Wu TJ, Ueng KC, et al. 2016 guidelines of the Taiwan Heart Rhythm Society and the Taiwan Society of Cardiology for the management of atrial fibrillation. *J Formos Med Assoc*. 2016;115(11):893-952. https://doi.org/10.1016/j.jfma.2016.10.005

13. Biffi A, Anderson CD, Battey TW, et al. association between blood pressure control and risk of recurrent intracerebral hemorrhage. *JAMA*. 2015;314(9):904-912. https://doi.org/10.1001/jama.2015.10082

KEY WORDS atrial fibrillation, direct oral anticoagulants, intracranial hemorrhage, target trial emulation

APPENDIX For supplemental tables and figures, please see the online version of this paper.

Go to http://www.acc.org/jacc-journals-cme to take the CME/MOC/ECME quiz for this article.