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ORIGINAL RESEARCH

Changing or Retaining Direct Oral Anticoagulant After Ischemic Stroke Despite Direct Oral Anticoagulant Treatment

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BACKGROUND: The optimal antithrombotic strategies for patients with atrial fibrillation who experience ischemic stroke (IS) despite direct oral anticoagulant (DOAC) therapy remain inconclusive. This study compared outcomes for patients with DOAC treatment failure who changed or retained their prestroke DOAC.

METHODS AND RESULTS: This retrospective cohort study analyzed data from the National Health Insurance Research Database from 2012 to 2020. Patients with atrial fibrillation who experienced IS during DOAC therapy were assigned to either (1) the DOAC-change group: changing prestroke DOAC or (2) the DOAC-retain group: retaining prestroke DOAC. The primary outcome was a composite of recurrent IS and transient ischemic attack. The secondary outcomes included intracranial hemorrhage, major bleeding, systemic thromboembolism, and all-cause death. Propensity score–based inverse probability of treatment weighting was applied to balance the baseline characteristics between the DOAC-change and DOAC-retain groups. The Cox proportional hazards model compared the risk of outcomes between the 2 groups. In total, 1979 patients were enrolled (609 DOAC-change patients and 1370 DOAC-retain patients). The incidence rates of recurrent IS or transient ischemic attack were 7.20 and 6.56 per 100 person-years in the DOAC-change and DOAC-retain groups, respectively (hazard ratio [HR], 1.07 [95% CI, 0.87–1.30]). A nonsignificantly higher incidence rate of intracranial hemorrhage was observed in the DOAC-change group compared with the DOAC-retain group (0.75 versus 0.53 per 100-person-years; HR, 1.49 [95% CI, 0.78–2.83]). The systemic thromboembolism, major bleeding, and death rates were comparable between the DOAC-change and DOAC-retain groups.

CONCLUSIONS: Changing prestroke DOAC does not reduce the risk of recurrent cerebral ischemia in patients with atrial fibrillation who develop IS during DOAC therapy. However, future studies should continue to observe the potential trends of increased intracranial hemorrhage risk.

Key Words: atrial fibrillation ■ changing DOAC ■ direct oral anticoagulant ■ ischemic stroke

Direct oral anticoagulant (DOAC) therapy is the first-line oral anticoagulant therapy for patients with atrial fibrillation (AF).[1–3] Nevertheless, despite receiving DOAC therapy, ≈1% to 2% of patients with AF still experience stroke.[4] The causes are multifactorial, including off-label drug dose,[5] poor drug adherence,[6] insufficient drug level,[7] malignancy,[8] and competing stroke pathogenesis.[9]

DOACs remain effective and safe in patients with a history of ischemic stroke (IS). They are associated with a lower risk of systemic thromboembolism (STE) and major bleeding than warfarin.[10–13] Therefore, DOACs are recommended as the first-line therapy for secondary prevention.[3] However, the most appropriate preventive strategy for patients with AF who develop IS despite receiving oral anticoagulant treatment

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CLINICAL PERSPECTIVE

What Is New?

- Changing a prestroke direct oral anticoagulant (DOAC) does not reduce the risk of recurrent cerebral ischemia in patients with atrial fibrillation who develop ischemic stroke during DOAC therapy.
- Instead, a potential trend of increased intracranial hemorrhage risk was observed among patients whose prestroke DOAC was changed.

What Are the Clinical Implications?

- The type of DOAC might not be the underlying cause of treatment failure. Prescribing an on-label DOAC regimen or improving DOAC adherence is more important.
- Monitoring of the potential risk of intracranial hemorrhage is crucial when considering a change of prestroke DOAC.

Nonstandard Abbreviations and Acronyms

DOAC	direct oral anticoagulant
ICH	intracranial hemorrhage
IPTW	inverse probability of treatment weighting
IS	ischemic stroke
NHIRD	National Health Insurance Research Database
STE	systemic thromboembolism

remains unclear. Common practices include changing the anticoagulant type, changing the anticoagulant regimen, and adding antiplatelet therapies. Previous investigations comparing strategies for changing or retaining prestroke oral anticoagulant therapy were mostly conducted with a sample of ≈50% DOAC users and 50% warfarin users.[9,14,15] Therefore, their results may not be generalizable to a broader population of DOAC users. In addition, some studies only recorded outcomes 90 days after stroke.[9,15] However, the long-term outcomes of these secondary prevention strategies remain unclear. This study aimed to compare the long-term outcomes of patients with AF who changed and retained their prestroke DOAC after IS.

METHODS

Study Design and Data Source

This study analyzed the National Health Insurance Research Database (NHIRD) using a retrospective cohort study design. The Taiwan National Health Insurance covers >99% of the population, and the NHIRD contains claims data for all beneficiaries who incurred any service use during a specific year. The NHIRD contains information regarding patient demographics, encounters, diagnoses, procedures, and pharmacy claims. To calculate mortality rates, the NHIRD was linked to the National Death Index. Data between June 1, 2012 and December 31, 2020, were used for this study. This study was reviewed and approved by the National Taiwan University Hospital International Ethics Committee (REC No. 202206102W). Informed consent was waived since the NHIRD contains only deidentified information. The data that support the findings of this study are not available; access may be obtained upon reasonable request and application to the Health and Welfare Data Science Center, Ministry of Health and Welfare of Taiwan.

Inclusion and Exclusion Criteria

Adult patients (aged >20 years) with IS were identified between January 1, 2013 and December 31, 2019. Patients were included if they had at least 1 inpatient or 2 outpatient diagnoses of AF within 180 days before admission. To ensure that IS developed during DOAC therapy, patients were required to be on DOAC therapy for at least 7 consecutive days within the 180 days before IS admission, and the therapy needed to continue until 3 days before the admission.

Patients were excluded if they had valvular AF, artificial heart valve replacement, or mitral stenosis or used >1 anticoagulant agent concomitantly 180 days before IS admission. Patients who had a missing discharge date or died before discharge were also excluded. Medical conditions were identified using the *International Classification of Diseases*, *Ninth* and *Tenth Revisions*, *Clinical Modification* (*ICD-9-CM* and *ICD-10-CM*) codes. Medications were identified using the World Health Organization's Anatomical Therapeutic Chemical (ATC) codes. The diagnostic codes for inclusion and exclusion criteria are listed in Table S1, and the ATC codes for medications are listed in Table S2.

Exposure

The major exposure was whether the patients received different types of DOAC therapy after stroke than before stroke. Four DOACs were evaluated: dabigatran, rivaroxaban, apixaban, and edoxaban. The patients were assigned to the DOAC-retain group if they received the same DOAC before and after the stroke, and the patients were assigned to the DOAC-change group if they switched to a different DOAC after the stroke. Group assignment was based on the consistency between the last DOAC prescription before

admission and the last DOAC prescription that lasted for >7 days within 28 days after discharge. The DOAC-retain group was used as the reference group for all comparisons.

Antithrombotic Treatment Pattern Before and After IS

In Taiwan, 4 DOACs were approved in different years: rivaroxaban in 2009, dabigatran in 2011, apixaban in 2013, and edoxaban in 2015. To assess the potential impact of DOACs launched during the study period on our findings, we first documented the treatment pattern before and after stroke to see whether there was significant shift in the prescription rates of DOACs over time.

Study Outcomes

The primary outcome was a composite of an IS and a transient ischemic attack (TIA). The secondary outcomes were STE, intracranial hemorrhage (ICH), major bleeding, and all-cause death. The outcomes of STE included IS, TIA, myocardial infarction, coronary artery disease, peripheral artery disease, and venous thromboembolism. The major bleeding events included ICH, gastrointestinal bleeding, and other major bleeding. The diagnostic codes for all clinical outcomes are listed in Table S1.

Follow-Up Duration

The date of the last DOAC prescription that met the following 2 criteria was set as the index date: (1) the DOAC prescription lasted for >7 days, and (2) the DOAC prescription was prescribed within 28 days after discharge. The follow-up duration started from the index date and ended with discontinuation of the index DOAC therapy (ie, stopped DOAC therapy or changed to a different DOAC), occurrence of any of the outcome events, death of the patient, or the end of the study period (ie, December 31, 2020), whichever came first. Discontinuation of DOAC therapy was defined as a gap of >30 days between the 2 DOAC refills.

Covariates

The covariates adjusted for in this study included patient baseline characteristics that may affect the use of DOACs, and comorbidities and comedications that may be risk factors of the outcomes or may be the confounders that may affect both the use of DOACs and the outcomes. Specifically, we included age at the IS admission, sex, comorbidities, and comedications recorded within 180 days before the IS admission. We calculated the CHA_2DS_2-VASc score for baseline thrombosis risk evaluation and the HAS-BLED score for baseline bleeding risk evaluation. We also used a claims database validated using the Stroke Severity Index to assess patients' IS severity. Based on the Stroke Severity Index, IS severity was classified as mild (≤5 points), moderate (>5 to ≤12 points), and severe (>12 points).[16] In addition to the previously mentioned risk factors, we adjusted diseases listed in the CHA_2DS_2-VASc and HAS-BLED score, as well as diseases known to affect the study outcomes. The comorbidities encompassed congestive heart failure, myocardial infarction, coronary artery disease, IS, TIA, hypertension, type 2 diabetes, renal disease, liver disease, peripheral artery disease, venous thromboembolism, ICH, gastrointestinal bleeding, and other bleeding events. Medications adjusted in this study included those commonly prescribed treatments for cardiovascular diseases or those with known drug interaction with DOACs. These medications encompassed agents acting on the renin–angiotensin system, antiarrhythmics (amiodarone, diltiazem, dronedarone, quinidine, verapamil), β blockers, calcium channel blockers, digitalis glycosides, antiepileptics (phenytoin, phenobarbital, carbamazepine, oxcarbazepine, levetiracetam, valproic acid, topiramate), statins, nonsteroidal anti-inflammatory drugs, and proton pump inhibitors. The *ICD* and ATC codes used for comorbidities, comedications, CHA_2DS_2-VASc scores, HAS-BLED scores, and Stroke Severity Index scores are listed in Tables S1 through S5.

Statistical Analysis

Baseline characteristics were presented using descriptive statistics, with mean and SD for continuous variables and frequency and percentage for categorical variables. We used inverse probability of treatment weighting (IPTW) to balance the baseline characteristics between the DOAC-change and DOAC-retain groups. We used logistic regressions to estimate the probability of changing DOACs after IS (ie, propensity score), and calculated the weights as the inverse of the propensity scores. There is sufficient overlap of the propensity scores between the 2 groups (Figure S1). No trimming or stabilization was applied to the weights, as there were no extreme weights in our study (Table S6). A standardized mean difference <0.1 indicated no meaningful difference between the 2 groups. Cox proportional hazards regression models were used to estimate event risk, and the results are presented as adjusted hazard ratios (aHRs), which is the hazard ratio weighted with IPTW. With IPTW, we estimated the average treatment effect in the overall population in this study. All the confidences were calculated by bootstrap. All analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC).

Sensitivity Analysis

We performed 3 sensitivity analyses to test the robustness of the results. We excluded patients with poststroke DOAC prescriptions for <90 days (sensitivity analysis 1) or 180 days (sensitivity analysis 2). A duration of 90 days was selected because it is the longest duration allowed for a long-term prescription under the National Health Insurance in Taiwan. A duration of 180 days was selected to reflect stable poststroke DOAC treatment. In sensitivity analysis 3, we considered death as a competing risk for study outcomes and calculated 95% CIs with bootstrapping.

RESULTS

Basic Characteristics

During the study period, 2853 patients with AF on DOAC therapy who subsequently developed IS were identified. After applying the exclusion criteria, a total of 2567 patients were included for the antithrombotic treatment pattern analysis. Before IS, rivaroxaban was the most commonly prescribed DOAC (44.4%), followed by dabigatran (33.2%), apixaban (12.2%), and edoxaban (10.1%). After stroke, 1979 patients (77.1%) resumed DOAC therapy. Rivaroxaban remained the most commonly prescribed DOAC (28.3%), but the proportion reduced in comparison with that before stroke. Despite the fact that edoxaban was approved during the middle of the study period, we did not find an increase in edoxaban prescriptions after stroke (8.2%). For the 588 patients (22.9%) who did not receive DOAC therapy after stroke, most of them did not initiate antithrombotic therapy (290 patients), followed by single antiplatelet therapy (216 patients), and then warfarin (60 patients).

For clinical outcome analysis comparing patients who changed or retained prestroke DOACs, we excluded patients who did not initiate any antithrombotic therapy within 28 days after discharge, those who received >1 anticoagulant therapy, and those who received poststroke DOAC prescription for <7 days. The final analytical sample consisted of 1979 patients, with 1370 and 609 patients in the DOAC-change and DOAC-retain groups, respectively. The process of study enrollment is depicted in Figure 1, and the antithrombotic treatment pattern before and after IS is depicted in Figure S2.

The demographic characteristics of the 2 groups are presented in Table 1. The mean age of the patients in both groups was 77 years, with 53% being men. Most of the baseline characteristics were similar between the 2 groups before IPTW, except for stroke severity and the use of β blockers. A higher proportion of patients in the DOAC-change group had a higher stroke severity (44% versus 26%) and received β blockers (67% versus 62%) than those in the DOAC-retain group. After IPTW, stroke severity and all other characteristics were comparable between the 2 groups.

The median follow-up durations were 1.09 and 1.12 years for the DOAC-change and DOAC-retain groups, respectively. The incidence rates of IS and TIA were 7.20 and 6.56 per 100 person-years in the DOAC-change and DOAC-retain groups, respectively. The adjusted risks of IS and TIA were comparable between the 2 groups (aHR, 1.07 [95% CI, 0.87–1.30]).

The risk of STE between the DOAC-change and DOAC-retain groups was also similar (aHR, 1.13 [95% CI, 0.95–1.33]). For the safety outcomes, the risk of major bleeding was slightly lower for the DOAC-change group (aHR, 0.95 [95% CI, 0.70–1.29]) than for the DOAC-retain group, but the risk of ICH was higher for the DOAC-change group (aHR, 1.49 [95% CI, 0.78–2.83]) than for the DOAC-retain group, although these 2 aHRs were not statistically significant. The incidence rates of the study outcomes are listed in Table 2. The comparative risks are shown in Figure 2, and the Kaplan–Meier survival curves for each outcome are shown in Figures S3 and S4.

Sensitivity Analyses

The results of the 3 sensitivity analyses were consistent with those of the main analyses. Figure 3 and Table S7 present the results for the first 2 sensitivity analyses. In total, 1536 patients received DOAC prescriptions that lasted >90 days after stroke, including 466 and 1070 DOAC-change and DOAC-retain patients, respectively. Comparable risk rates of recurrent IS and TIA were observed between the DOAC-change and DOAC-retain groups, and a nonsignificantly increased risk rate of ICH was observed in the DOAC-change patients (aHR, 1.57 [0.81–3.04]).

In total, 1315 patients received DOAC prescriptions that lasted >180 days after stroke (403 DOAC-change patients and 912 DOAC-retain patients). Similar to the main analysis, the risks of recurrent IS/TIA, STE, major bleeding, and death were all similar between the DOAC-change and DOAC-retain patients, with a nonsignificant increasing risk of ICH (aHR, 1.92 [95% CI, 0.92–3.99]).

In the third sensitivity analysis, we considered death as a competing risk and calculated CI with bootstrapping. The results were presented in Table S8, and the findings remained consistent with the main analysis. The risk of recurrent IS/TIA, STE, and all-cause death were comparable between DOAC-change and DOAC-retain groups. The risk of ICH remained higher in the DOAC-change group than that in the DOAC-retain group, but the difference was not statistically significant. Of note, the slightly lower risk of major bleeding in the DOAC-change group was not observed in the sensitivity analysis.

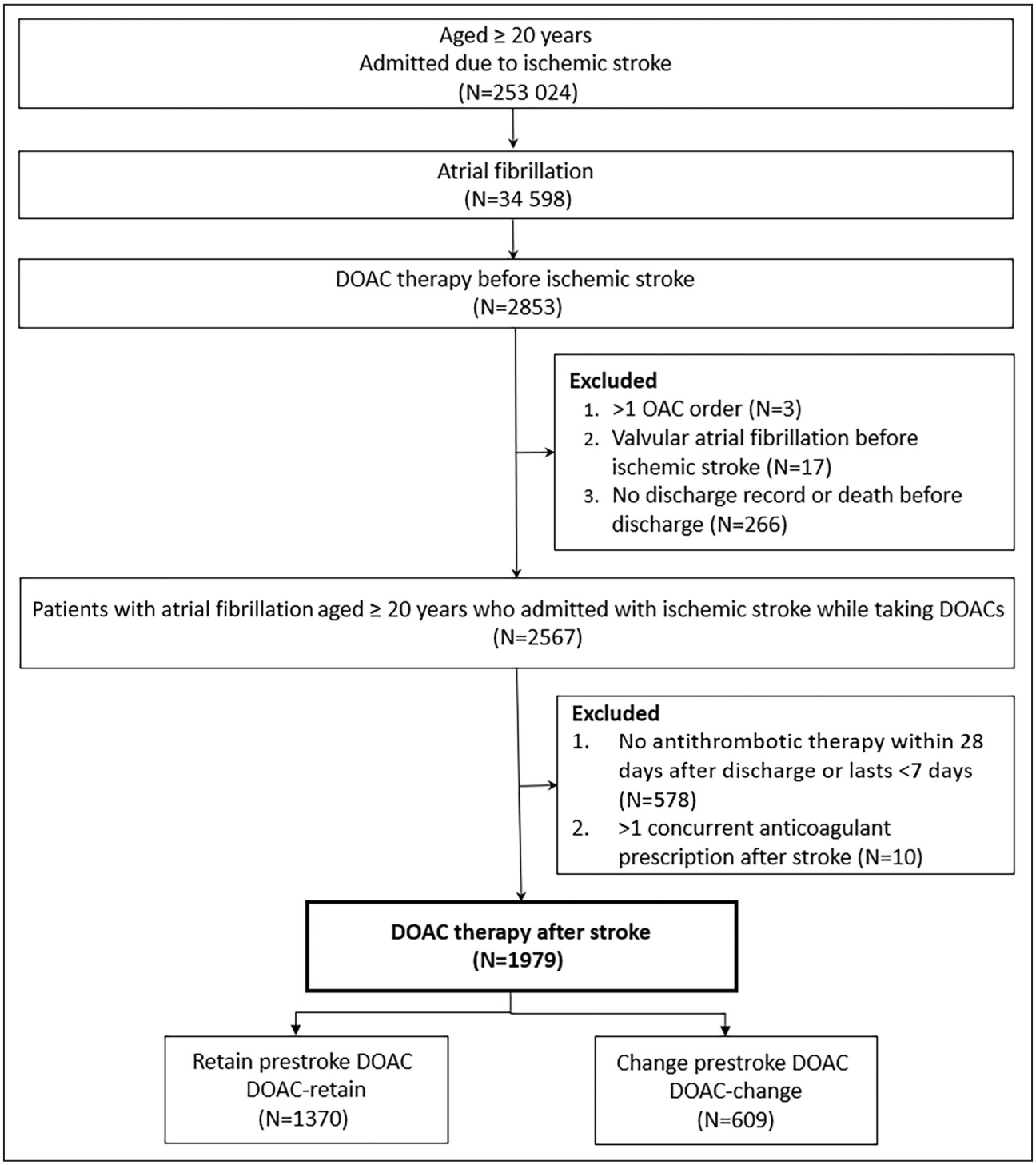

Figure 1. The process of study sample selection.
DOAC indicates direct oral anticoagulant; and OAC, oral anticoagulant.

DISCUSSION

This study investigated the effects of changing or retaining prestroke DOAC on recurrent IS/TIA in patients with AF who experienced IS despite receiving DOAC treatment. Our results showed that changing the prestroke DOAC did not reduce the risk of recurrent IS/TIA but displayed a nonsignificantly increased risk of ICH.

Previous investigations of optimal preventive strategies in patients with anticoagulant therapy failure have provided inconclusive results. One European study

Table 1. Baseline Characteristics of Patients with Changed and Retained Pre-stroke DOAC

Characteristics	Before IPTW			After IPTW		
	Change prestroke DOAC (N=609)	Retain prestroke DOAC (N=1370)	SMD	Change prestroke DOAC (N=1980.01)	Retain prestroke DOAC (N=1978.69)	SMD
Age (years), mean (SD)	77.15 (9.47)	77.47 (9.26)		77.00 (17.08)	77.57 (11.12)	
≥65	558 (91.63%)	1,252 (91.39%)	0.009	1,822 (92.01%)	1,811 (91.54%)	0.017
Sex, male	314 (51.56%)	726 (52.99%)	0.029	1,047 (52.89%)	1,040 (52.56%)	0.007
CHA_2DS_2-VASc score, mean (SD)	3.86 (1.44)	3.85 (1.46)		3.82 (2.64)	3.86 (1.74)	
≥3	514 (84.40%)	1,130 (82.48%)	0.052	1,637 (82.65%)	1,643 (83.04%)	0.011
HAS-BLED score, mean (SD)	2.64 (1.07)	2.66 (1.03)		2.64 (1.91)	2.65 (1.23)	
≥3	331 (54.35%)	763 (55.69%)	0.027	1,081 (54.60%)	1,090 (55.10%)	0.010
Stroke severity index, mean (SD)	10.76 (6.42)	8.23 (5.61)		9.09 (10.97)	8.94 (7.10)	
≤5	222 (36.45%)	733 (53.50%)	**0.348**	957 (48.31%)	955 (48.27%)	0.001
>5 to ≤12	119 (19.54%)	287 (20.95%)	0.035	406 (20.48%)	406 (20.52)	0.001
>12	268 (44.01%)	350 (25.55%)	**0.395**	618 (31.21%)	618 (31.21%)	0.000
Comorbidities						
Congestive heart failure	190 (31.20%)	419 (30.58%)	0.013	596 (30.08%)	607 (30.66%)	0.013
Coronary artery disease	171 (28.08%)	391 (28.54)	0.010	581 (29.33%)	566 (28.60%)	0.016
Ischemic stroke	98 (16.09%)	243 (17.74%)	0.044	341 (17.22%)	342 (17.27%)	0.001
Hypertension	409 (67.16%)	908 (66.28%)	0.019	1,303 (65.79%)	1,314 (66.40%)	0.013
Diabetes mellitus	192 (31.53%)	428 (31.24%)	0.006	613 (30.97%)	620 (31.35%)	0.008
Renal disease	55 (9.03%)	125 (9.12%)	0.003	183 (9.22%)	181 (9.13%)	0.003
Venous thromboembolism	13 (2.13%)	19 (1.39%)	0.057	31 (1.58%)	32 (1.60%)	0.001
Intracranial hemorrhage	7 (1.15%)	17 (1.24%)	0.008	28 (1.41%)	25 (1.24%)	0.015
Gastrointestinal bleeding	35 (5.75%)	78 (5.69%)	0.002	112 (5.66%)	112 (5.68%)	0.001
Baseline medication history						
Agents acting on the renin-angiotensin system	397 (65.19%)	882 (64.38%)	0.017	1,282 (64.75%)	1,278 (64.56%)	0.004
Antiarrhythmics	187 (30.71%)	464 (33.87%)	0.068	649 (32.75%)	651 (32.88%)	0.003
Beta blockers	408 (67.00%)	845 (61.68%)	**0.111**	1,251 (63.17%)	1,253 (63.30%)	0.003
Calcium channel blockers	280 (45.98%)	630 (45.99%)	0.000	905 (45.69%)	909 (45.93%)	0.005
Digitalis glycosides	119 (19.54%)	258 (18.83%)	0.018	370 (18.67%)	376 (19.00%)	0.008
Antiepileptic drugs	18 (2.96%)	56 (4.09%)	0.061	74 (3.72%)	74 (3.72%)	0.000
HMG-CoA reductase inhibitors	214 (35.14%)	471 (34.38%)	0.016	685 (34.59%)	686 (34.66%)	0.001
NSAIDs	319 (52.38%)	716 (52.26%)	0.002	1,025 (51.76%)	1,031 (52.11%)	0.007
Proton pump inhibitors	80 (13.14%)	176 (12.85%)	0.009	263 (13.27%)	257 (12.99%)	0.008

Bold value indicates significant difference between the DOAC-change and DOAC-retain groups.

DOAC, direct oral anticoagulant; IPTW, inverse probability of treatment weighting; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; and SMD, standardized mean difference.

reported that changing prestroke oral anticoagulants did not decrease the IS risk.[14] Another study in the United States demonstrated that switching anticoagulation classes did not reduce recurrent IS within 3 months after stroke.[15] In contrast, one study recruited participants from both Europe and the United States and showed that changing warfarin to DOAC reduced recurrent IS in 3 months, but switching to another DOAC did not yield a similar effect.[9] The main difference between these investigations and ours is that they included patients with IS either during warfarin or DOAC treatment rather than specifically focusing on DOAC users.

Only a few retrospective cohort studies have investigated preventive strategies for patients with DOAC treatment failure. A Hong Kong study demonstrated that changing the prestroke DOAC to a different DOAC or warfarin increased the risk of recurrent IS.[17] Results from another Taiwanese study showed comparable recurrent stroke risk in patients who changed from a

Table 2. Number of Events and Incidence Rates of Outcomes in Patients With Changed and Retained Prestroke DOAC (As-Treated Analysis)

	Number of events		Person-years		Follow-up years, median (IQR)		Incidence rates (per 100 person-years)			
							Before IPTW		After IPTW	
	DOAC-change	DOAC-retain	DOAC-change	DOAC-retain	DOAC-change	DOAC-retain	DOAC-change	DOAC-retain	DOAC-change	DOAC-retain
Primary outcome										
Recurrent IS and TIA	60	131	839.25	2072.01	1.09 (0.28–1.98)	1.12 (0.35–2.24)	7.15	6.32	7.20	6.56
Secondary outcome										
Effectiveness										
STE	82	175	828.35	2022.78	1.08 (0.28–1.97)	1.07 (0.32–2.18)	9.90	8.65	10.20	8.84
Safety										
ICH	6	10	883.89	2185.58	1.13 (0.33–2.07)	1.19 (0.39–2.33)	0.68	0.46	0.75	0.53
Major bleeding	28	62	867.36	2133.76	1.11 (0.32–2.04)	1.16 (0.38–2.27)	3.23	2.91	2.82	2.93
All-cause death	87	158	886.51	2190.95	1.13 (0.39–2.33)	1.19 (0.33–2.07)	9.81	7.21	8.57	7.76

DOAC indicates direct oral anticoagulant; ICH, intracranial hemorrhage; IPTW, inverse probability of treatment weighting; IQR, interquartile range; IS, ischemic stroke; STE, systemic thromboembolism; and TIA, transient ischemic attack.

prestroke DOAC to another DOAC but increased IS risk in patients who changed from DOAC to warfarin.[18] Regarding safety, all investigations showed that changing or retaining prestroke DOAC resulted in a comparable ICH risk. However, our study reported a relatively higher hazard ratio for ICH than the other 2 studies (ie, 1.49 versus 1.06 for Hong Kong and 1.03 for Taiwanese studies),[17,18] implying that a large-scale investigation will be required for validation.

Among patients with oral anticoagulant treatment failure, ≈30% have insufficient anticoagulation treatment,[9] highlighting the importance of evaluating the appropriateness of the dose regimen and drug adherence.[19] Prior studies have established an association between off-label underdose regimens or suboptimal drug adherence and IS risk during DOAC therapy.[5,6] Optimizing DOAC therapy is an essential aspect of managing patients with IS despite treatment.[4] Another important factor in anticoagulant treatment failure is the competing stroke mechanism (ie, ≥2 mechanisms according to the Trial of Org 10 172 in Acute Stroke Treatment classification criteria),

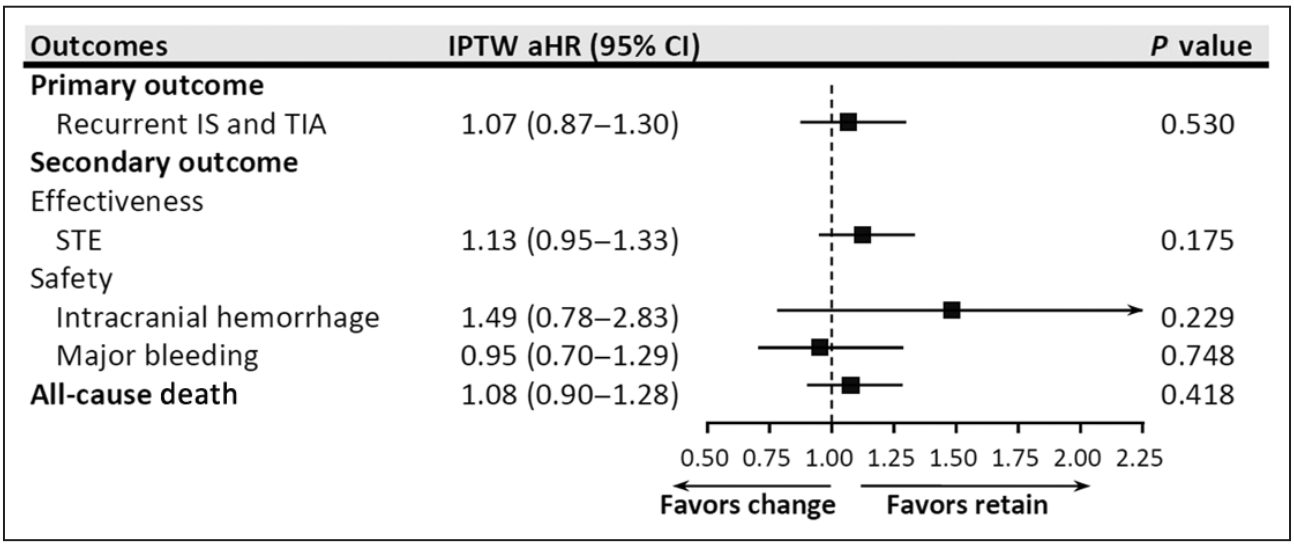

Figure 2. Hazard ratio for outcomes of patients with changed and retained prestroke direct oral anticoagulant prescription.
aHR indicates adjusted hazard ratio; DOAC, direct oral anticoagulant; IPTW, inverse probability of treatment weighting; IS, ischemic stroke; STE, systemic thromboembolism; and TIA, transient ischemic attack.

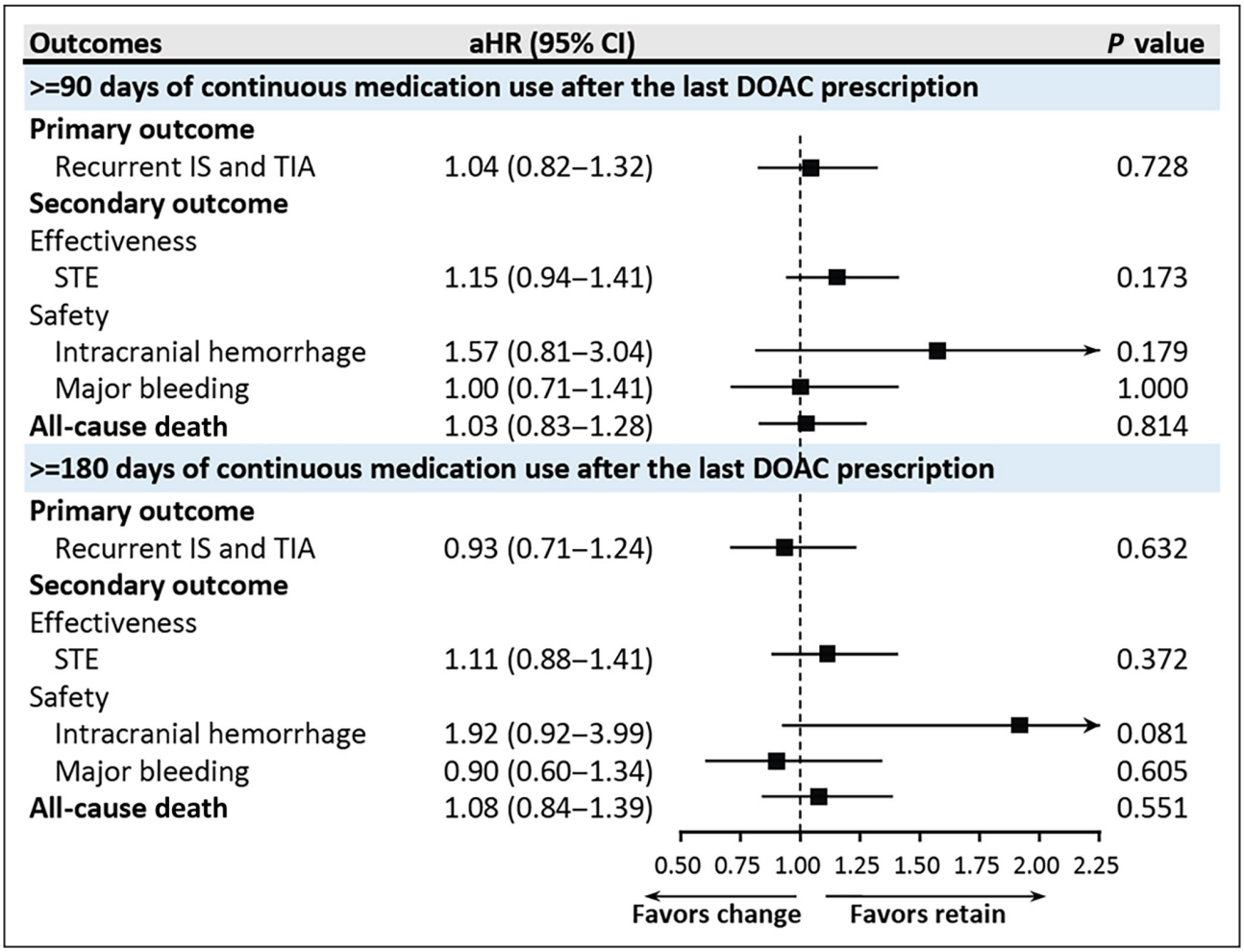

Figure 3. Hazard ratios for outcomes in patients with changed and retained prestroke DOAC (≥90 and ≥180 days of continuous medication use after the last DOAC prescription).
aHR, adjusted hazard ratio; DOAC, direct oral anticoagulant; IPTW, inverse probability of treatment weighting; IS, ischemic stroke; STE, systemic thromboembolism; and TIA, transient ischemic attack.

particularly large-vessel occlusion.[9,17] Therefore, strategies for stroke prevention, including blood pressure, sugar, and lipid control, cigarette cessation, and regular exercise, should also be strictly followed.[3] Finally, concurrent medications that affect DOAC concentrations, such as cytochrome P or P-glycoprotein modulators, are also important issue.[8,17] For these patients, the DOAC dose should be properly adjusted according to the label, and monitoring of the DOAC level should be considered.[4]

Physicians might have frequently changed the antithrombotic treatment during the first 3 to 6 months after a stroke. To measure the effectiveness and safety of stable DOAC treatment after the index IS, we excluded patients with DOAC prescriptions for <90 and 180 days. The results were all similar to those from the main analysis. Compared with retaining prestroke DOAC, changing prestroke DOAC imposed a similar risk of recurrent IS. Because a nonsignificant increase in ICH risk was still observed in the DOAC-change group, a change in DOAC is deemed necessary, and a comprehensive DOAC treatment plan is strongly recommended, including on-label dose prescription, regular renal or liver function monitoring, pharmacist counseling, and drug-level monitoring.[4,19] In addition, vascular risk factors, such as hypertension, should be properly treated.[3]

The strength of this study was the use of a nationwide database to inform potential treatment strategies for patients with DOAC treatment failure. However, this study has the following limitations. First, some clinical data, such as creatinine clearance and body weight, were not available in the NHIRD. Therefore, we were unable to determine whether the DOAC regimen was on- or off-label. It is possible that some of the DOAC switching was an adjustment from off-label to on-label use (or vice versa), but this study was neither able to identify those cases nor investigate the effect of such

switching on risk of recurrent IS. Second, our study focused on a specific population with a relatively small sample size, making it challenging to detect the differences in various outcomes by DOACs. Further analysis that investigates whether bleeding risk vary by DOAC subgroups is necessary. In addition, owing to the small number of patients who used warfarin-containing antithrombotic treatment (72 patients), we were not able to compare the effectiveness and safely of changing from DOAC to warfarin after stroke. Finally, the different antithrombotic treatment groups were not randomly selected and may not be comparable, even with IPTW. Specifically, there is a potential for reverse causality by which people who changed their treatment may have different baseline stroke risk of severity and therefore have a higher risk of further stroke. To further investigate this important question, future large-scale studies with randomized controlled designs are recommended.

In conclusion, among patients with AF who experience IS during DOAC therapy, changing prestroke DOAC does not reduce the risk of recurrent IS but seems to increase ICH risk. Vigilant monitoring of the potential risk of ICH is crucial when considering a change of prestroke DOAC.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S8
Figures S1–S4

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