

Resuming anticoagulation in patients with atrial fibrillation experiencing intracranial hemorrhage

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Abstract

Globally, 32% to 70% patients with atrial fibrillation (AF) are prescribed oral anticoagulants (OACs) with warfarin for stroke prevention. However, patients with AF on OACs may experience intracranial hemorrhage (ICH), which presents a treatment dilemma. We therefore investigated whether resuming OACs in these patients is beneficial. Electronic medical records of patients with AF on OACs discharged with ICH between 2001 and 2013 were retrieved from the Taiwan National Health Insurance Research Database for analysis. We excluded patients who were <20 years old, who were not using OACs 6 months prior to ICH, or who had a CHA2DS2-VASc score of ≤ 1 . We also excluded patients who died during admission for ICH, with follow-up for <6 weeks after discharge, or who started OAC >6 weeks after ICH diagnosis. The remaining patients were categorized into those who resumed OAC and those who discontinued OAC. Propensity score matching was performed between the 2 groups. Primary outcomes were mortality/ischemic stroke (IS)/systemic embolism (SE), IS/SE, and recurrent ICH at 6 months and 1 year. After the exclusion criteria were applied, 604 eligible patients (408 discontinued OAC and 196 resumed OAC within 6 weeks) were included in this study, and 186 patients in each group were 1:1 matched. Patients who resumed OAC had significantly lower mortality/IS/SE (hazard ratio [HR] = 0.39, 95% confidence interval [CI] = 0.20–0.76) and IS/SE (HR = 0.12, 95% CI = 0.03–0.53) at 6-month follow-up than patients who discontinued OAC. In addition, patients who resumed OAC had significantly lower mortality/IS/SE (HR = 0.56, 95% CI = 0.34–0.93) and IS/SE (HR = 0.26, 95% CI = 0.09–0.75) at 1-year follow-up. No difference in recurrent ICH was noted between the 2 groups. In conclusion, in patients with AF on OACs with ICH, resuming anticoagulant use was associated with significantly lower risks of composite outcomes of mortality/IS/SE and IS/SE than patients who discontinued OACs. No difference in recurrent ICH was observed between the 2 groups.

Abbreviations: AF = atrial fibrillation, ICH = intracranial hemorrhage, IS = ischemic stroke, NHI = National Health Institute, NHIRD = National Health Institute Research Database, NIHSS = National Institute of Health Stroke Scale, OAC = oral anticoagulation, SE = systemic embolism, VKA = vitamin antagonist.

Keywords: anticoagulation, atrial fibrillation, intracranial hemorrhage

Editor: Ardavan Khoshnood.

VC-CW and Y-CH contributed equally to this work.

No financial support was received for this study.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Wu VC, Huang YC, Chen SW, Liu CH, Chang CW, Chen CC, Chang SH, Lin MS, Lee TH, Chen MC, Hsieh IC, Chu PH, Lin YS. Resuming anticoagulation in patients with atrial fibrillation experiencing intracranial hemorrhage. *Medicine* 2021;100:32(e26945).

Received: 16 November 2020 / Received in final form: 29 June 2021 / Accepted: 15 July 2021

<http://dx.doi.org/10.1097/MD.00000000000026945>

1. Introduction

Anticoagulation is an indicated treatment in patients with atrial fibrillation (AF) and CHA₂DS₂-VASc score ≥ 1 in men and ≥ 2 in women.^[1] Treatment with oral anticoagulants (OACs), especially vitamin K antagonists (VKAs), is the standard management strategy in these patients to reduce the incidence of stroke, even though it is often difficult to keep the international normalized ratio (INR) within therapeutic limits and the time in therapeutic range has been consistently disappointing.^[2] Intracranial hemorrhage (ICH) is believed to be a severe complication in patients on VKAs. Landmark trials of novel oral anticoagulants (NOACs) have reported the reduced incidence of AF-related stroke with the benefits of the lowered risk of ICH compared with VKA.^[3–6] However, the global registry program GLORIA-AF revealed that 79.9% of the 15,641 patients with AF received OACs with warfarin, of whom 47.6% received NOACs and 32.3% still received VKAs.^[7] In addition, in a Danish nationwide cohort study comprising 55,644 patients with AF, up to 38,893 patients (70%) were still on VKAs.

In the patients with AF taking VKAs with incident ICH, increased ischemic stroke (IS) was observed if an anticoagulant was not prescribed after stabilization.^[7] In addition, a Swedish Registry study evidenced that the risk of IS without an OAC is higher than the risk of ICH with an OAC.^[8] However, no clinical trial has evaluated the efficacy and safety of OACs in such populations or the optimal time to resume OAC use in these patients. Recently, 2 European observational studies attempted to address the challenges in the treatment of patients with AF experiencing ICH. A population-based study from Denmark reported that restarting aspirin was similar in efficacy to no treatment, whereas restarting an anticoagulant with warfarin was associated with significantly decreased risks of recurrent stroke.^[9] Another Danish nationwide cohort study on the outcomes associated with resuming warfarin treatment after hemorrhagic stroke or traumatic ICH in patients with AF found that resuming warfarin therapy was associated with a lower rate of ischemic events among all patients.^[10] Accordingly, these lines of evidence provide the rationale for physicians to consider resuming OACs after patients with AF experienced ICH. However, because the incidence and characteristics of ICH differ among ethnicities, the recommendations for Asian populations may be different from those for European populations.^[11] Therefore, in this study, we evaluated the outcome of resuming OAC therapy in Asian patients with AF after ICH.

2. Materials and methods

2.1. Data source

Taiwan's National Health Institute (NHI) Program was established in 1995 and has since provided coverage for over 99.5% of the 23 million residents in Taiwan. The NHI Research Database (NHIRD) contains records of inpatient and outpatient services, diagnoses, emergency room visits, prescriptions, examinations, operations, and expenditures, with the data updated biannually. Because more than 95% of the population in Taiwan belong to the Han Chinese ethnicity, our study population is considered to be of uniform ethnic background. The Institutional Review Board of Chang Gung Memorial Hospital Linkou Branch approved this study (IRB No. 201700421B1).

2.2. Study patients

By searching electronic medical records from the NHIRD between January 1, 2001, and December 31, 2013, we retrieved the data of patients with a discharge diagnosis of AF on OACs with ICH (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] codes: 430–432). Patients aged < 20 years with no OAC use 6 months before index admission, with a CHA₂DS₂-VASc score ≤ 1 , who died during index admission, with IS, with systemic embolism, and with recurrent ICH within 6 weeks of index admission were excluded. We set a 6-week quarantine period after hospital discharge to ascertain that the events that occurred after resuming OACs could be rationally ascribed to the reinstitution of anticoagulation therapy rather than the extension of the initial ICH. Patients who either resumed or discontinued OACs within 6 weeks of hospital discharge were enrolled; those who started OAC treatment 6 weeks after index admission were excluded (Fig. 1). According to the expert consensus in clinical guidelines, resuming anticoagulation agents within 4 to 8 weeks is the appropriate management strategy;^[1] therefore, we evaluated whether resuming anticoagulation treatment within 6 weeks (middle of the period between 4 and 8 weeks) was beneficial in these patients.

2.3. Study outcomes and follow-up

We selected recurrent ICH and major bleeding as the safety outcomes and composite mortality/IS/systemic embolism (SE), all-cause mortality, and IS/SE as the efficacy outcomes. Recurrent ICH and IS/SE were defined according to the principal diagnosis at admission or an emergency visit during which IS was previously validated.^[12] ICH was validated previously with a positive predictive value (PPV) of approximately 79% to 97%,^[13] and the first ever episode of ICH was validated in our multicenter stroke registry. A total of 2153 cases were linked using the entries of date of birth, sex, admission date, discharge date, and primary diagnosis at discharge in the NHIRD and The Stroke Registry in Chang Gung Healthcare System,^[14] and the PPV of first-ever ICH was 93% (2006/2153). Major bleeding was defined according to the principal or secondary diagnosis during hospitalization and emergency visits and based on blood transfusion orders, including admission for any bleeding, requirement of blood transfusion of > 2 U, and life-threatening bleeding or vital organ hemorrhage including ICH. All-cause mortality was defined based on patient withdrawal from the NHI program.^[15] Although strong evidence suggests the benefit of OACs in the prevention of long-term thromboembolic events and mortality, recurrent ICH over the short term is a major concern.^[9] Therefore, our primary endpoints were mortality/IS/SE, IS/SE, and recurrent ICH at 6-month and 1-year follow-ups.

Diseases were diagnosed using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes. Covariates included sex; age; hospital level; ICH etiology; medical history of diabetes mellitus, hypertension, hyperlipidemia, heart failure, renal insufficiency, peptic ulcer disease, malignancy, abnormal liver function, and peripheral arterial disease; prior IS or systemic thromboembolism; prior hemorrhagic stroke; old myocardial infarction; bleeding history; alcohol consumption history; HAS-BLED predisposing drug use (antiplatelet agents and NSAIDs); Charlson comorbidity score (CCS); medication use; CHA₂DS₂-VASc score; HAS-BLED score; and follow-up years. Comorbidity was defined as having received 2 outpatient diagnoses or 1 inpatient diagnosis in the previous year. Similarly, data on medication use were retrieved

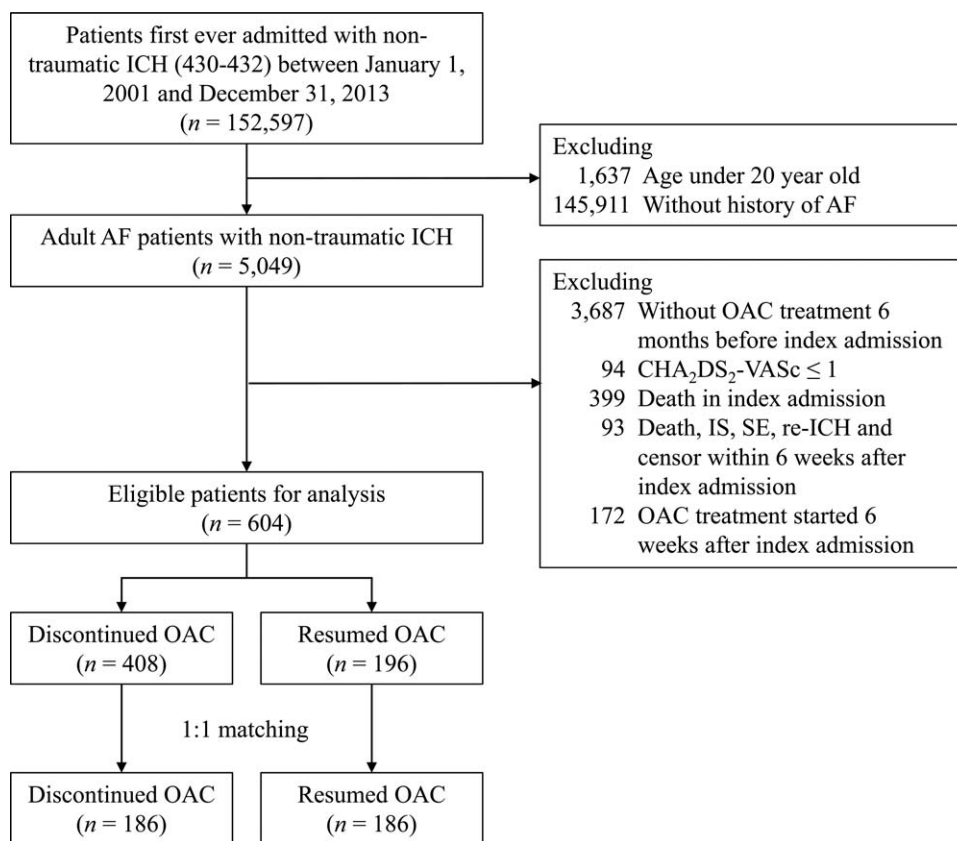


Figure 1. Flowchart of study design and screening criteria for the inclusion of patients with atrial fibrillation (AF) on oral anticoagulations (OACs) experiencing intracranial hemorrhage (ICH).

based on claims data within 6 months before and after the index date.

2.4. Ascertainment of AF and comorbidities

AF (ICD-9-CM code 427.31) was ascertained based on hospital discharge diagnosis or at least 2 consecutive outpatient clinic diagnoses (Supplemental Table 1, <http://links.lww.com/MD2/A318>). The accuracy of the diagnosis of AF based on ICD-9-CM coding in the NHIRD has been confirmed in previous studies.^[16,17] Other comorbidities included diabetes mellitus, hypertension, hyperlipidemia, heart failure, renal insufficiency, peptic ulcer disease, malignancy, abnormal liver function, peripheral arterial disease, prior IS or systemic thromboembolism, prior hemorrhagic stroke, old myocardial infarction, bleeding history, and alcohol consumption history. Most of these comorbidities have also been validated in previous studies, of which hypertension, diabetes, and dyslipidemia were diagnosed according to both the ICD-9-CM code and the use of related medications to increase diagnostic accuracy (Supplemental Table 2, <http://links.lww.com/MD2/A319>). In addition, risk score systems were used for our population, including CCS,^[18] CHA₂DS₂-VASc for IS/SE,^[19] HAS-BLED for bleeding,^[20] and estimated National Institute of Health Stroke Scale (NIHSS) score for severity of ICH.^[21]

2.5. Statistical analysis

Each patient in the resumed OAC group was matched to a patient in the discontinued OAC group according to age (± 1.5 years) and

index date (± 180 days). We compared the baseline characteristics, comorbidities, medication use, hospital level, CHA₂DS₂-VASc score, and HAS-BLED score between the study groups (discontinued OAC vs. resumed OAC) by using a *t* test for continuous variables and the chi-squared test for categorical variables. We compared the risk of all-cause mortality between the groups by using a Cox proportional-hazards model. The risk of other time-to-event outcomes (those not directly related to death) between the groups was compared using a subdistribution hazard model that considered death during follow-up as a competing risk factor.^[21] To reduce residual confounding, both the Cox models and subdistribution hazard models were additionally adjusted for CHA₂DS₂-VASc, HASBLED, and NIHSS scores.^[22] We generated a plot of the cumulative incidence rate by using the subdistribution hazard function for time-to-event outcomes. A *P* value of $< .05$ was considered statistically significant. Multiple testing (multiplicity) was not adjusted for in this study. All statistical analyses were performed using commercial software (SAS 9.4, SAS Institute, Cary, NC).

3. Results

3.1. Study population

A total of 152,597 patients admitted with a principal diagnosis of ICH during 2001 to 2013 were identified from the NHIRD. We excluded patients aged < 20 years old and those without a history of AF; ultimately, 5049 adult patients with AF who had ICH were included. After further excluding patients who did not take OAC

Table 1
Primary outcome during follow-up.

Outcome	Number of event (%)		Resumed OAC vs. Discontinued OAC	
	Resumed OAC (n=186)	Discontinued OAC (n=186)	HR (95% CI)*	P value
6 mo follow-up				
Mortality/IS/SE	13 (7.0)	38 (20.4)	0.39 (0.20, 0.76)	.006
All-cause mortality	11 (5.9)	25 (13.4)	0.59 (0.28, 1.26)	.172
IS/SE	2 (1.1)	14 (7.5)	0.12 (0.03, 0.53)	.006
Recurrent ICH	2 (1.1)	6 (3.2)	0.35 (0.07, 1.85)	.219
Major bleeding†	19 (10.2)	23 (12.4)	1.92 (0.64, 5.76)	.248
1 yr follow-up				
Mortality/IS/SE	26 (14.0)	49 (26.3)	0.56 (0.34, 0.93)	.025
All-cause mortality	21 (11.3)	37 (19.9)	0.71 (0.40, 1.25)	.235
IS/SE	5 (2.7)	15 (8.1)	0.26 (0.09, 0.75)	.013
Recurrent ICH	3 (1.6)	7 (3.8)	0.46 (0.11, 1.88)	.282
Major bleeding†	21 (11.3)	29 (15.6)	1.72 (0.66, 4.47)	.267

CI=confidence interval, HR=hazard ratio, ICH=intracerebral hemorrhage, IS= ischemic stroke, OAC=oral anticoagulant, SE=systemic embolism.

* Adjusted for CHA₂DS₂-VASc, HAS-BLED, and estimated NIHSS scores.

† Including ICH.

treatment within 6 months prior to ICH, with a CHA₂DS₂-VASc score of ≤ 1 , who died during ICH admission, with a follow-up duration of < 6 weeks, and who resumed OAC treatment 6 weeks after ICH, 604 eligible patients with AF and ICH remained for analysis. We categorized these patients into 2 groups: 408 patients who discontinued OAC and 196 patients who resumed OAC (Fig. 1). After propensity score matching for age and the index date, 186 patients were included in each group. Compared with those who discontinued OACs, patients who resumed OACs were more likely to be admitted to the medical center, were more likely to be diagnosed as having subdural bleeding (ICD-9 CM: 432.xx), had a higher prevalence of heart failure, were more likely to be prescribed digoxin and diuretics, and had lower estimated NIHSS scores (right panel in Table 1).

3.2. Resuming OACs versus discontinuing OACs

During 6-month follow-up, patients who resumed OACs had significantly lower risks of composite outcomes of mortality/IS/SE (hazard ratio [HR] = 0.39, 95% confidence interval [CI] = 0.20–0.76, $P = .006$) and IS/SE (HR = 0.12, 95% CI = 0.03–0.53, $P = .006$) than patients who discontinued OACs, after adjustment for CHA₂DS₂-VASc, HAS-BLED, and NIHSS scores. In addition, no difference was noted in the risk of recurrent ICH between the 2 groups at 6-month follow-up.

During 1-year follow-up, patients who resumed OACs had significantly lower risks of mortality/IS/SE (HR = 0.56, 95% CI = 0.34–0.93, $P = .025$) and IS/SE (HR = 0.26, 95% CI = 0.09–0.75, $P = .013$) than those who discontinued OACs, after adjustment for CHA₂DS₂-VASc, HAS-BLED, and NIHSS scores (Table 2, Fig. 2). In addition, no difference in the risk of recurrent ICH was noted between the 2 groups at 1-year follow-up.

3.3. Subgroup analysis of resuming OACs

In terms of the effects of resuming OACs on risks of mortality/IS/SE, no significant differences were noted in age groups (< 75 years, ≥ 75 years) and in subgroups stratified by histology of ICH (subarachnoid hemorrhage, intracerebral hemorrhage, and subdural bleeding), CHA₂DS₂-VASc score (2–3, 4–5, ≥ 3), and

HAS-BLED score (0–2, ≥ 3). Subgroup analysis of IS/SE and recurrent ICH also revealed no significant differences among the subgroups (Fig. 3).

4. Discussion

Our study provided several findings. This is the first study to investigate the effects of resuming OACs with warfarin in Asian patients with AF after an incident ICH. In addition to adjusting for CHA₂DS₂-VASc and HAS-BLED scores, we further adjusted for NIHSS scores in the study to account for the differences in severity of ICH in the evaluation of the time-to-resume anticoagulation. A subgroup analysis of resuming OACs revealed no difference among the subgroups in terms of the benefits from restarting anticoagulation therapy.

Traditionally, patients with AF are treated with anticoagulating agents when the CHA₂DS₂-VASc score is ≥ 1 in men and ≥ 2 in women.^[1] These patients are given VKAs as the principal OAC, with NOACs becoming available only recently.^[2,3] However, once a patient experiences ICH after receiving an OAC, another episode of ICH remains a possibility. Therefore, deciding whether to restart anticoagulation becomes difficult for the physician.^[2,4] A Danish nationwide cohort study showed that restarting OAC use was associated with a significant reduction in IS and all-cause mortality in patients with AF experiencing ICH.^[9] Recently, a meta-analysis in the United States that included 8 observational studies demonstrated that restarting OAC use was associated with a lower risk of thromboembolic complication and a similar risk of ICH recurrence in adults using anticoagulants with ICH.^[2,5] In addition, a study in Sweden investigated the optimal timing of restarting anticoagulation treatment and suggested that it may be initiated 7 to 8 weeks after ICH in patients with AF to optimize benefits from treatment while minimizing risks.^[2,6]

In this study, we followed the treatment recommendation in the guideline that suggested restarting anticoagulation 4 to 8 weeks after ICH,^[1] and we considered resuming OACs within 6 weeks as the study enrollment criteria. Similar to the Danish study,^[9] we excluded patients with events within the quarantine observation period. Our results revealed that during the follow-up of 6

Table 2**Clinical characteristics of the study patients.**

Variable	Before matching			After matching		P value
	Resumed OAC (n=196)	Discontinued OAC (n=408)	P value	Resumed OAC (n=186)	Discontinued OAC (n=186)	
Characteristic						
Gender (male)	89 (45.4)	202 (49.5)	.345	83 (44.6)	95 (51.1)	.213
Mean age	69.7 ± 11.2	75.6 ± 9.6	<.001	71.0 ± 9.7	71.6 ± 9.5	.512
Age group			<.001			.551
18–64 yrs	54 (27.6)	54 (13.2)		44 (23.7)	42 (22.6)	
65–74 yrs	75 (38.3)	111 (27.2)		75 (40.3)	67 (36.0)	
≥ 75 yrs	67 (34.2)	243 (59.6)		67 (36.0)	77 (41.4)	
Hospital level			.003			.005
Medical center	115 (58.7)	196 (48.0)		110 (59.1)	87 (46.8)	
Regional hospital	74 (37.8)	167 (40.9)		70 (37.6)	79 (42.5)	
District hospital	7 (3.6)	45 (11.0)		6 (3.2)	20 (10.8)	
Histology of intracerebral hemorrhage			.002			.001
Subarachnoid hemorrhage (430.xx)	13 (6.6)	22 (5.4)		13 (7.0)	10 (5.4)	
Intracerebral hemorrhage (431.xx)	108 (55.1)	283 (69.4)		103 (55.4)	137 (73.7)	
Subdural bleeding (432.xx)	75 (38.3)	103 (25.2)		70 (37.6)	39 (21.0)	
Medical history						
Diabetes mellitus	43 (21.9)	93 (22.8)	.814	41 (22.0)	41 (22.0)	1.000
Hypertension	152 (77.6)	326 (79.9)	.506	145 (78.0)	150 (80.6)	.522
Hyperlipidemia	22 (11.2)	67 (16.4)	.092	20 (10.8)	26 (14.0)	.345
Heart failure	103 (52.6)	153 (37.5)	<.001	96 (51.6)	74 (39.8)	.022
Renal insufficiency	8 (4.1)	24 (5.9)	.355	8 (4.3)	9 (4.8)	.804
Peptic ulcer disease	34 (17.3)	69 (16.9)	.894	33 (17.7)	26 (14.0)	.320
Malignancy	12 (6.1)	28 (6.9)	.732	12 (6.5)	16 (8.6)	.432
Abnormal liver function	18 (9.2)	49 (12.0)	.300	17 (9.1)	23 (12.4)	.315
Peripheral artery disease	3 (1.5)	27 (6.6)	.007	3 (1.6)	9 (4.8)	.078
Prior ischemic stroke or systemic thromboembolism	55 (28.1)	123 (30.1)	.599	52 (28.0)	63 (33.9)	.217
Old myocardial infarction	12 (6.1)	23 (5.6)	.811	12 (6.5)	11 (5.9)	.830
Bleeding history	2 (1.0)	4 (1.0)	.963	2 (1.1)	2 (1.1)	1.000
Alcoholic history	0 (0.0)	1 (0.2)	.488	0 (0.0)	1 (0.5)	.317
Drug of HAS-BLED	100 (51.0)	179 (43.9)	.099	96 (51.6)	86 (46.2)	.300
Charlson Comorbidity Score	3.0 ± 1.8	3.2 ± 1.9	.427	3.0 ± 1.8	3.2 ± 1.9	.270
Medication						
Antiplatelets	24 (12.2)	49 (12.0)	.934	24 (12.9)	20 (10.8)	.521
ACEI/ARB	105 (53.6)	180 (44.1)	.029	102 (54.8)	90 (48.4)	.213
Amiodarone/dronedaron	32 (16.3)	56 (13.7)	.396	30 (16.1)	27 (14.5)	.666
Beta blockers	86 (43.9)	122 (29.9)	.001	82 (44.1)	64 (34.4)	.056
Calcium channel blockers	62 (31.6)	148 (36.3)	.262	61 (32.8)	71 (38.2)	.279
Digoxin	112 (57.1)	139 (34.1)	<.001	104 (55.9)	68 (36.6)	<.001
Diuretics	115 (58.7)	131 (32.1)	<.001	109 (58.6)	57 (30.6)	<.001
NSAIDs	85 (43.4)	130 (31.9)	.006	81 (43.5)	63 (33.9)	.055
Oral hypoglycemic agents	50 (25.5)	87 (21.3)	.250	48 (25.8)	42 (22.6)	.468
CHA ₂ DS ₂ -VAsC score	4.0 ± 1.5	4.4 ± 1.5	.001	4.1 ± 1.5	4.2 ± 1.5	.322
CHA ₂ DS ₂ -VAsC score group			.006			.568
2–3 (Moderate)	83 (42.3)	123 (30.1)		75 (40.3)	66 (35.5)	
4–5 (High)	80 (40.8)	184 (45.1)		78 (41.9)	81 (43.5)	
≥ 6 (Very high)	33 (16.8)	101 (24.8)		33 (17.7)	39 (21.0)	
HAS-BLED score	2.4 ± 0.9	2.5 ± 0.9	.040	2.4 ± 0.9	2.5 ± 1.0	.501
HAS-BLED score group			.469			.917
0–2 (Low)	108 (55.1)	212 (52.0)		100 (53.8)	101 (54.3)	
≥ 3 (High)	88 (44.9)	196 (48.0)		86 (46.2)	85 (45.7)	
Estimated NIHSS	13.4 ± 7.1	18.0 ± 7.2	<.001	13.3 ± 7.1	18.0 ± 7.2	<.001

ACEI=angiotensin-converting enzyme inhibitor, ARB=angiotensin receptor blocker, COPD=chronic obstructive pulmonary disease, NIHSS=National Institutes of Health Stroke Scale, NSAID=nonsteroidal anti-inflammatory drug, OAC=oral anticoagulant.

months or 1 year, patients who resumed OACs had significantly lower risks of the predefined outcomes of IS/SE and mortality/IS/SE than patients who discontinued OACs.

A study showed that patients with Asian ethnicities had increased risks of ICH when they were given warfarin for AF treatment compared with White patients (HR = 4.06, 95% CI =

2.47–6.65).^[11] However, our results showed that resuming anticoagulation therapy prior to 6 weeks was not associated with increased risks of recurrent ICH and major bleeding, after adjustment for CHA₂DS₂-VAsC, HAS-BLED, and NIHSS scores. We performed a subgroup analysis of age, histology of ICH, CHA₂DS₂-VAsC score, and HAS-BLED score and found

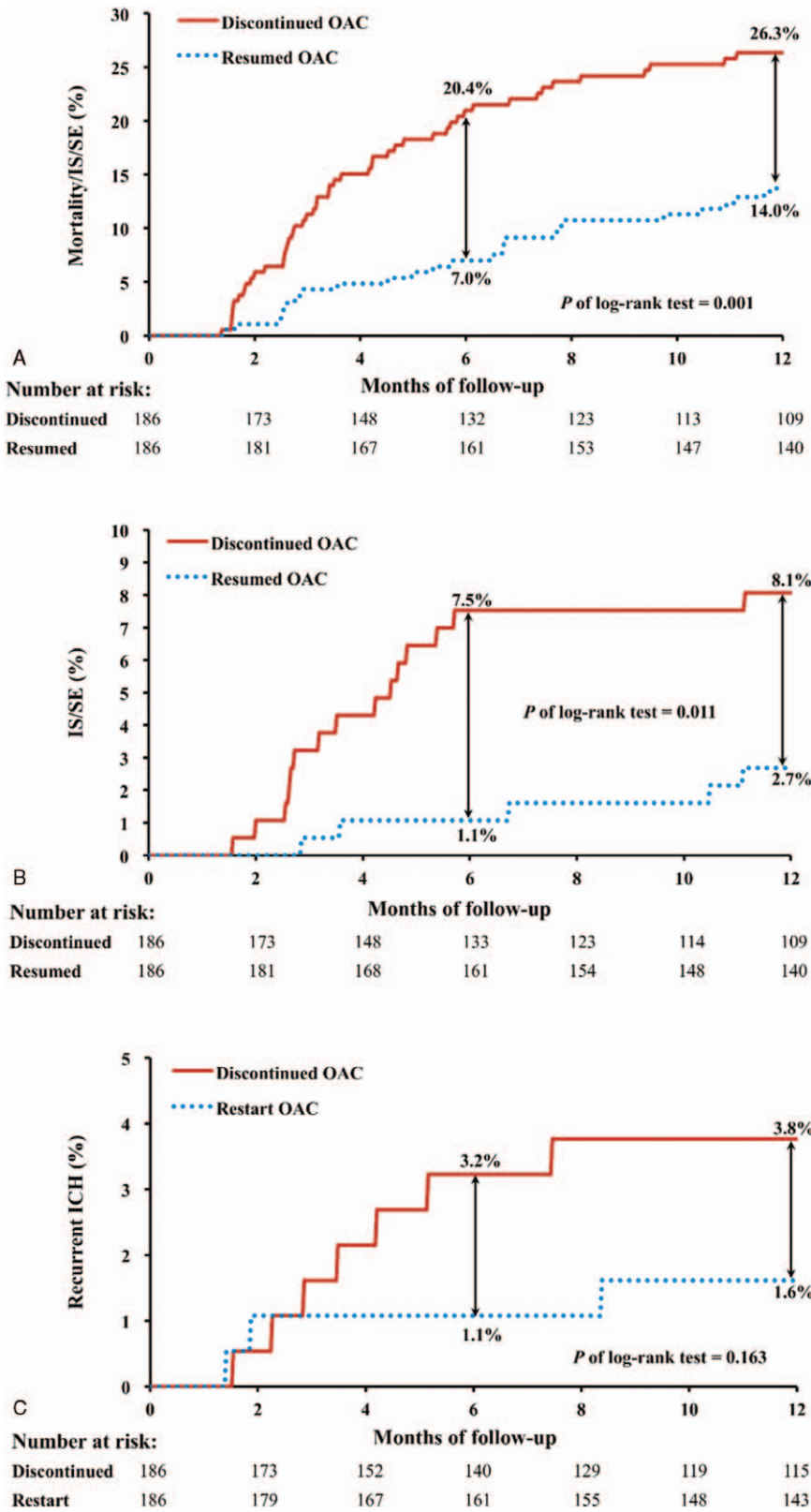


Figure 2. Event rate of mortality/ischemic stroke (IS)/systemic embolism (SE) (A), IS/SE (B), and recurrent intracranial hemorrhage (ICH) (C) during the 1-year follow-up by using the log-rank test. The resumed OAC use group was associated with significantly lower risks of mortality/IS/SE and IS/SE without increased risks of recurrent ICH.

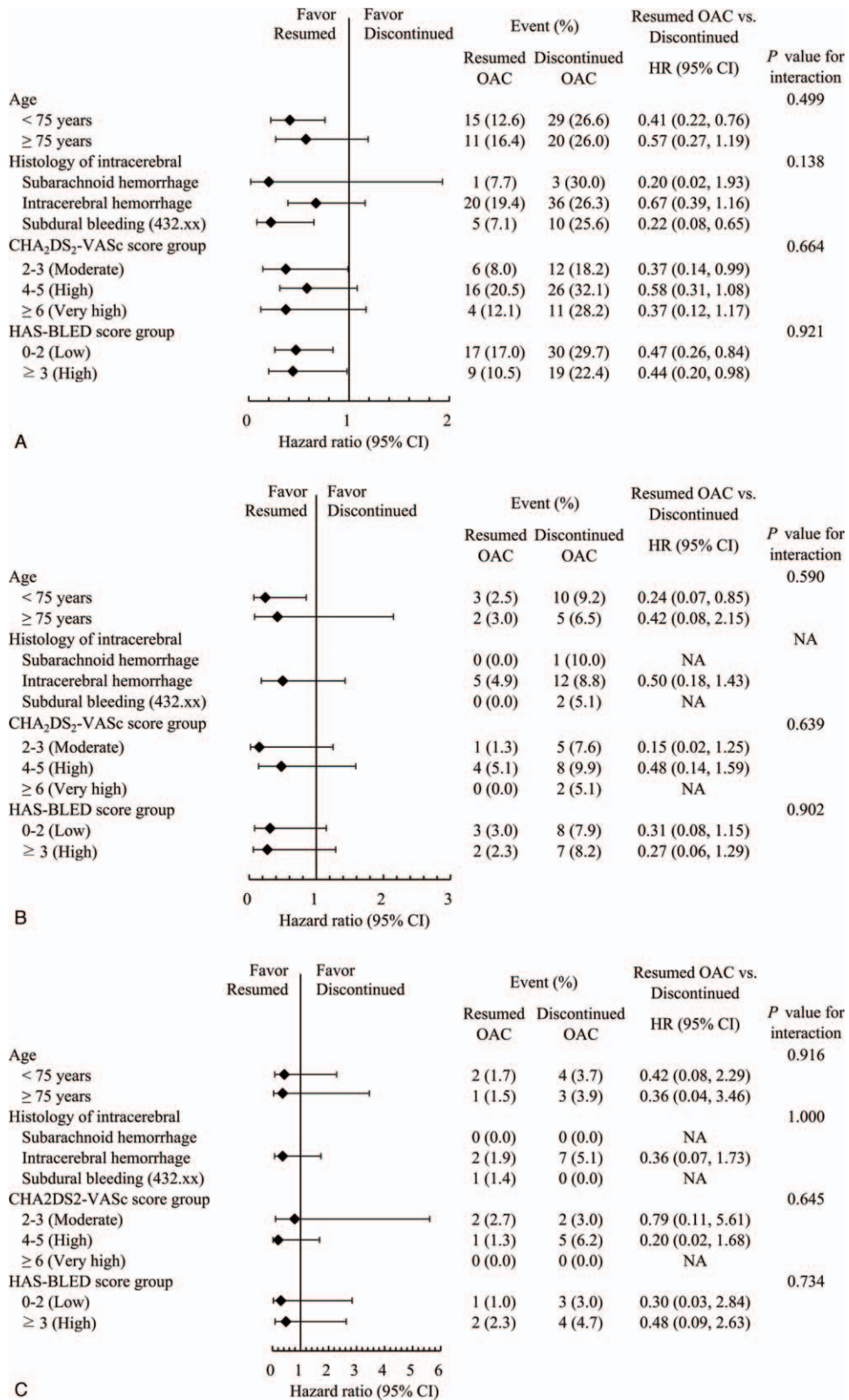


Figure 3. Subgroup analyses of mortality/IS/SE (A), IS/SE (B), and recurrent ICH (C). The analyses were stratified by age, histology of intracranial hemorrhage, CHA₂DS₂-VAsC score, and HAS-BLED score. No difference was observed among subgroup analyses in each outcome measure. This suggests that resuming OACs was associated with significantly lower risks in terms of composite endpoints of mortality/IS/SE, IS/SE, with no difference in recurrent ICH found across these variable groups.

no significant differences among these subgroups, therefore confirming our results in this selected study population. In summary, this is the first study to demonstrate that in Asian patients with AF on OACs with subsequent ICH, resuming OACs within 6 week is beneficial, with significantly lower risks of mortality/IS/SE and IS/SE without concomitant increased recurrent ICH.

5. Limitations

There are several limitations to using epidemiologic data from the NHIRD. First, the use of ICD-9-CM codes for patient screening may result in the omission of some cases due to conditions not coded correctly. This study was based on ICD-9-CM codes; only 1 ICD-9-CM code exists for the diagnosis of AF (427.31), with no distinction between paroxysmal, persistent, or chronic AF as in ICD-10. Second, the NHIRD does not contain a detailed report of imaging studies on IS and ICH; therefore, the extent of tissue damage could not be quantified. However, we could still obtain the data on incidence based on the diagnosis of ischemia or hemorrhage. Third, the NHIRD is a claims-based database; therefore, only reimbursement data are recorded. Consequently, anthropometric data such as BMI, classification such as NYHA class, and laboratory data such as eGFR and INR are not available. However, despite the lack of these data, clinical diagnoses based on ICD codes were used as surrogate clinical information. Physicians check INRs at least once every 2 to 3 months; therefore, the warfarin doses are adjusted according to the INR level and patient tolerance (bleeding condition). Fourth, the study was retrospective in nature, but in patients with AF and ICH, database-based studies remain the only pertinent method of determining whether to resume anticoagulation treatment in this high-risk clinical scenario. Fifth, the difficulty in assessing the severity of ICH is commonly seen in database-based studies; thus, the recommendation to resume OACs could not be adequately evaluated. However, in our study, we used a validated model of stroke severity index with NIHSS and functional outcomes using the modified Rankin Scale to refine the definition of stroke severity.^[21]

6. Conclusions

In patients with AF undergoing anticoagulation treatment who experienced ICH, resuming OACs was associated with significantly lower risks of composite outcomes of mortality/IS/SE and IS/SE, without increased risks of recurrent ICH at 6 months and 1 year.

Acknowledgments

The authors thank Alfred Hsing-Fen Lin and Zoe Ya-Jhu Syu for their statistical assistance during the completion of this manuscript

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Corrections

When originally published, Dr. Yi-Chun Huang's name was spelled incorrectly as Yi-Chun Hung. This has been corrected.

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