Use of Oral Anticoagulants for Stroke Prevention in Patients With Atrial Fibrillation Who Have a History of Intracranial Hemorrhage

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Background—The risk of further intracranial hemorrhage (ICH) and the benefit of stroke risk reduction with the use of oral anticoagulants for patients who have atrial fibrillation with a history of ICH remain unclear. We aimed to investigate the risks and benefits in patients who have atrial fibrillation with a previous ICH treated with warfarin or antiplatelet drugs in comparison with no antithrombotic therapies.

Methods and Results—This study used the National Health Insurance Research Database in Taiwan. Among 307 640 patients who have atrial fibrillation with a CHA_2DS_2-VASc score ≧2, 12 917 patients with a history of ICH were identified and were assigned to 1 of 3 groups, that is, no treatment, antiplatelet therapy, and warfarin. Among patients with previous ICH, the rate of ICH and ischemic stroke in untreated patients was 4.2 and 5.8 per 100 person-years, respectively. The annual ICH and ischemic stroke rates in warfarin users were 5.9% and 3.4%, respectively. Among users of antiplatelet agents, the rates were 5.3% per year and 5.2% per year, respectively. The number needed to treat for preventing 1 ischemic stroke was lower than the number needed to harm for producing 1 ICH with warfarin use for patients with a CHA_2DS_2-VASc score ≧6 (37 versus 56). The number needed to treat was higher than the number needed to harm for patients with a CHA_2DS_2-VASc score <6 (63 versus 53).

Conclusions—Warfarin use may be beneficial for patients who have atrial fibrillation with a previous ICH having a CHA_2DS_2-VASc score ≧6. Whether the use of non–vitamin K antagonist oral anticoagulants could lower the threshold for treatment deserves further study. **(*Circulation*. 2016;133:1540-1547. DOI: 10.1161/CIRCULATIONAHA.115.019794.)**

Key Words: atrial fibrillation ■ CHA_2DS_2-VASc score ■ intracranial hemorrhages ■ stroke

Atrial fibrillation (AF) represents an important risk factor of ischemic stroke,[1,2] and stroke prevention with oral anticoagulants (OACs) is the cornerstone for the management of AF. Treatment with vitamin K antagonists (eg, warfarin) effectively reduces the risk of stroke by 64% in comparison with placebo/control.[3] However, warfarin-related bleeding is the leading cause of emergent hospitalizations for adverse drug events in the elderly.[4] Among warfarin-related bleeding events, intracranial hemorrhage (ICH) is the most devastating complication, with an in-hospital mortality rate as high as 22%.[5,6] The efficacy and safety of warfarin is closely related to the quality of anticoagulation control, as reflected by the time in therapeutic range (TTR) with a TTR>70% being recommended.[7,8] Concerns about ICH could lead physicians to withhold OACs for some AF patients despite a high stroke risk, especially in Asian patients where the prevalence of ICH is much higher than in non-Asians, and the quality of anticoagulation control (ie, TTR) may be suboptimal.[9]

Clinical Perspective on p 1547

In recent years, several non–vitamin K antagonist OACs (NOACs) have been demonstrated to be at least as effective

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as warfarin in stroke prevention, but were much safer in relation to the risk of ICH.[10] Improvements in the efficacy, convenience, and safety of NOACs in comparison with warfarin may potentially lower the threshold for initiating OACs for AF patients; however, patients with a history of ICH were excluded from the recent trials of NOACs in comparison with warfarin.[11,12] Therefore, the risk of further ICH and the benefit of stroke risk reduction by the use of OACs remains unclear for AF patients with a history of ICH, and the appropriate strategy about stroke prevention by using OACs for these patients remains unknown.

Our objective is to investigate the risks and benefits in AF patients with previous ICH treated with warfarin, in comparison with antiplatelet or no antithrombotic therapies, in a large nationwide cohort study.

Methods

This study used the National Health Insurance Research Database (NHIRD) released by the Taiwan National Health Research Institutes. The National Health Insurance system is a mandatory universal health insurance program that offers comprehensive medical care coverage to all Taiwanese residents. NHIRD consists of detailed healthcare data from >25 million enrollees, representing >99% of Taiwan's population. In this cohort data set, the patients' original identification numbers have been encrypted to protect their privacy, but the encrypting procedure was consistent, so that a linkage of the claims belonging to the same patient is feasible within the National Health Insurance database and can be followed continuously. The large sample size of this database provided a good opportunity to study the risk of increased ICH and benefits of stroke risk reduction with warfarin use in AF patients with a history of ICH.

Study Population

The study protocol of the present study was similar to our previous studies.[13–15] From January 1, 1996, to December 31, 2011, a total of 307 640 newly diagnosed AF patients aged ≥20 years with a CHA_2DS_2-VASc score ≥2 were identified from the NHIRD as the study population. AF was diagnosed by using the *International Classification of Diseases, Ninth Revision, Clinical Modification* codes (427.31) registered by the physicians responsible for the treatment of patients. To ensure the accuracy of diagnosis, we defined patients with AF only when it was a hospital discharge diagnosis or confirmed for at least 2 times in the outpatient department.[13,14] The diagnostic accuracy of AF using this definition in NHIRD has been validated previously.[16,17] Among the study population, there was a total of 12 917 (4.2%) patients who had a history of ICH (subarachnoid hemorrhage in 12.3%, intracerebral hemorrhage in 68.6%, epidural hemorrhage in 2.5%, subdural hemorrhage in 12.6%, and nonspecified type in 4.0%), and they were assigned to 1 of 3 groups based on the principal antithrombotic therapy used for stroke prevention (Figure). At the time when the previous ICH event happened, 636 (4.9%) had concurrent head injury, 883 (6.8%) were taking antiplatelet agents, and 64 (0.5%) were treated with warfarin. The mean duration between the previous ICH event and the diagnosis of AF was 3.3±3.6 years.

Calculation of Score and Definitions of Clinical End Points

The CHA_2DS_2-VASc score was calculated for each patient by assigning 1 point each for age between 65 and 74 years, history of hypertension, diabetes mellitus, recent cardiac failure, vascular disease (myocardial infarction or peripheral artery disease), and female sex, and 2 points each for a history of a stroke, transient ischemic attack, or age≥75 years.[18]

The clinical end point was the occurrence of ischemic stroke, with concomitant imaging studies of the brain, including computed tomography or MRI. The accuracy of diagnosis of ischemic stroke in Taiwan's NHIRD has been reported to be ≈94%.[19] Another validation study also demonstrated that the diagnostic accuracy of ischemic stroke in NHIRD was high, with the positive predictive value and sensitivity of 88.4% and 97.3%, respectively.[20] The safety end point was the occurrence of ICH necessitating admissions to intensive care units.

Propensity Match Analysis

We performed propensity score–matched analyses for 2 kinds of comparisons among patients with previous ICH: antiplatelet agents

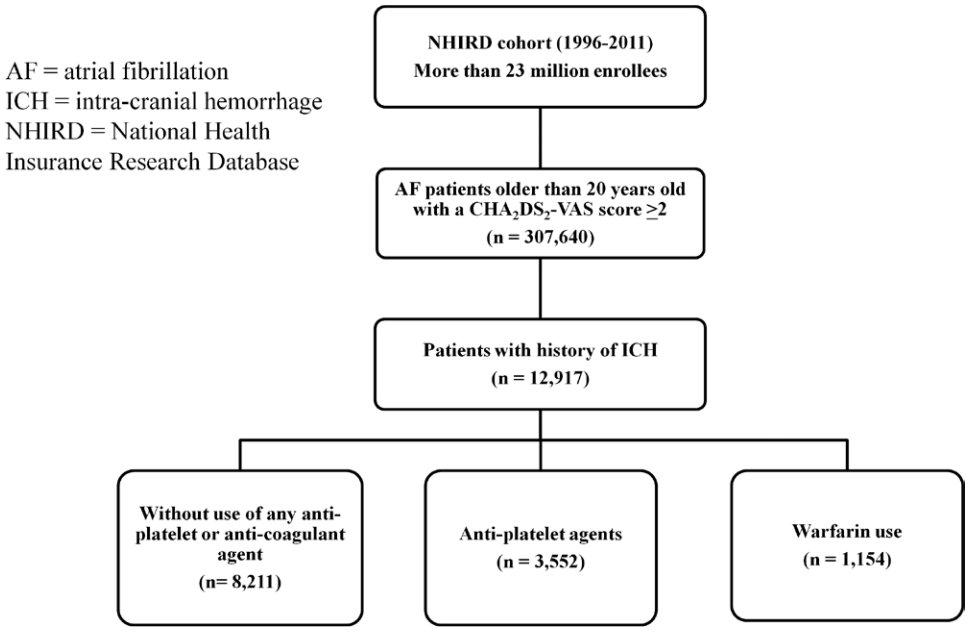

Figure. Flowchart of the enrollment of the study cohort. From January 1, 1996, to December 31, 2011, a total of 307 640 AF patients aged ≥20 years with a CHA_2DS_2-VASc score ≥2 were identified from the NHIRD as the study population. A total of 12 917 patients with a history of ICH were enrolled into the study cohort. The risk of ICH and benefit of stroke risk reduction were analyzed between patients without the use of any antithrombotic agent and those with warfarin use. AF indicates atrial fibrillation; ICH, intracranial hemorrhage; and NHIRD, National Health Insurance Research Database.

versus no antithrombotic therapy and warfarin versus no antithrombotic therapy. We calculated propensity scores for the likelihoods of receiving antiplatelet agents and warfarin in comparison with no antithrombotic therapy by multivariate logistic regression analyses, conditional on all baseline covariates listed in Table 1. After that, we matched patients in the antiplatelet agent group to those in the no antithrombotic therapy group with a 1:1 ratio on the basis of age, sex, and the closest propensity score for the use of antiplatelet agents within a threshold of ±0.01. If >1 patient in the no antithrombotic therapy group could be matched to the corresponding subject in the antiplatelet agent group, 1 patient from the no antithrombotic therapy group was selected randomly without repeat sampling. Similar matching processes were performed for the comparisons of warfarin versus no antithrombotic therapy based on the propensity scores for the use of warfarin.

Statistical Analysis

Data were presented as mean (standard deviation) for normally distributed continuous variables, and median (25th, 75th percentiles) for skewed data, and proportions for categorical variables. Differences between continuous values were assessed by using an unpaired 2-tailed *t* test for normally distributed variables and Mann-Whitney rank sum test for skewed variables. Differences between nominal variables were compared by the χ^2 test. The risks of ischemic stroke and ICH were assessed by using the Cox regression analysis. The incidences of ischemic stroke and ICH were calculated from dividing the number of events by person-time at risk, and the number needed to treat (NNT) for preventing 1 ischemic stroke and number needed to harm (NNH) for producing 1 ICH with warfarin use were derived accordingly. All statistical significances were set at a $P<0.05$.

The present study was approved by the institutional review board at Taipei Veterans General Hospital, Taipei, Taiwan.

Results

The baseline characteristics of patients with and without a history of ICH are shown in Table 1. Patients with a history of ICH had a higher CHA_2DS_2-VASc score and more comorbidities, with the exception of end-stage renal disease, in comparison with patients without a history of ICH.

Ischemic Stroke and ICH on No Antithrombotic Therapy

Among the whole study population (n=307 640), 157 829 patients (8211 with a history of ICH; 149 618 without a history of ICH) did not receive any antithrombotic therapy. During the follow-up of 3.3±3.6 years, there were 3857 (2.4%) ICH events and 21 017 (13.3%) ischemic stroke events.

The incidence rate of ICH was higher in patients with ICH history than those without it (4.2 versus 0.6 per 100 person-years of follow-up; Table 2). After adjusting for age, sex, CHA_2DS_2-VASc score, and comorbidities other than the components of the CHA_2DS_2-VASc score (hyperlipidemia, chronic obstructive pulmonary disease, malignancy, and end-stage renal disease), a history of ICH was still an independent risk factor of further ICH with an adjusted hazard ratio (HR) of 5.27 (95% confidence interval [CI], 4.83–5.75, $P<0.001$), even without any antithrombotic therapies. In the AF patients with previous ICH, clinical risk factors predictive of recurrent ICH were diabetes mellitus (HR, 1.41; 95% CI, 1.09–1.81; $P=0.008$) and vascular disease (HR, 1.38; 95% CI, 1.09–1.74; $P=0.007$).

Table 1. Baseline Characteristics of AF Patients With and Without History of ICH

Variables	With ICH (n=12 917)				*P* Value*	Without ICH No Antithrombotic Therapy (n=149 618)	*P* Value†
	All	No Antithrombotic Therapy (n=8211)	Antiplatelet Agents (n=3552)	Warfarin (n=1154)			
Age, y	74.7±11.2	75.5±11.3	74.6±10.1	69.4±12.5	<0.001	75.5±11.0	0.97
Age 65–74 y, n (%)	3342 (26)	1963 (24)	1027 (29)	352 (31)	<0.001	39 945 (27)	<0.001
Age ≥75 y, n (%)	7397 (57)	4973 (61)	1978 (56)	446 (39)	<0.001	89 007 (60)	0.053
Sex (male), n (%)	7397 (57)	4729 (58)	2043 (58)	625 (54)	0.082	73 628 (49)	<0.001
CHA_2DS_2-VASc score, median value (25^{th}, 75^{th} percentiles)	6 (5–7)	6 (5–7)	6 (5–7)	6 (4–7)	<0.001	4 (3–5)	<0.001
Medical history (components of the CHA_2DS_2-VASc score), n (%)							
Hypertension	11 146 (86)	6959 (85)	3249 (92)	938 (81)	0.007	106 251 (71)	<0.001
Diabetes mellitus	4800 (37)	2943 (36)	1428 (40)	429 (37)	0.003	46 140 (31)	<0.001
Congestive heart failure	5412 (42)	3175 (39)	1695 (48)	542 (47)	<0.001	67 029 (45)	<0.001
Previous stroke/TIA	7429 (58)	4374 (53)	2290 (65)	765 (66)	<0.001	56 849 (38)	<0.001
Previous vascular disease	2727 (21)	1245 (15)	1125 (32)	357 (31)	<0.001	33 849 (23)	<0.001
Medical history (other than the components of the CHA_2DS_2-VASc score), n (%)							
COPD	5747 (45)	3845 (47)	1517 (43)	385 (33)	<0.001	62 253 (42)	<0.001
Hyperlipidemia	3545 (27)	1900 (23)	1258 (35)	387 (34)	<0.001	32 195 (22)	0.001
Malignancy	690 (5)	479 (6)	175 (5)	36 (3)	<0.001	10 052 (7)	0.002
End-stage renal disease	367 (3)	250 (3)	103 (3)	14 (1)	0.004	4419 (3)	0.64

AF indicates atrial fibrillation; COPD, chronic obstructive pulmonary disease; ICH, intracranial hemorrhage; and TIA, transient ischemic attack.

**P* value between groups with different strategies for stroke prevention (no antithrombotic therapy, antiplatelet agents, and warfarin).

†*P* value for the comparisons between patients with or without ICH who did not receive antithrombotic therapies.

Table 2. Incidence (per 100 Person-Years) of ICH in Patients With or Without History of ICH and Did Not Receive Antithrombotic Therapies

Groups	Number of Events (ICH)	Number of Patients	Person-Years	Incidence*
With ICH	730	8211	17 472	4.2
Without ICH	3127	149 618	501 242	0.6

ICH indicates intracranial hemorrhage.
*Number of ICH per 100 person-years of follow-up.

Among 8211 (63.6%) patients with a history of ICH who did not receive any antithrombotic drug, the annual risk of ischemic stroke during the follow-up was 5.8%, which was higher than that of patients without history of ICH (4.4% per year; Table 3). After adjusting for age, sex, CHA_2DS_2-VASc score, and comorbidities other than the components of CHA_2DS_2-VASc score, patients with a history of ICH were associated with a higher risk of ischemic stroke than those without ICH (adjusted HR, 1.10; 95% CI, 1.02–1.19; P=0.015). When stratified by the CHA_2DS_2-VASc score, the risk of ischemic stroke increased from 3.2% per year for patients with a CHA_2DS_2-VASc score of 2 to 11.3% per year for those having a CHA_2DS_2-VASc score of 9 (Table 4).

Ischemic Stroke and ICH on Warfarin or Antiplatelet Therapy in Comparison With No Antithrombotic Therapy

The risks of ischemic stroke and ICH in patients on warfarin and antiplatelet agents in comparison with no antithrombotic therapy among patients with a history of ICH are shown in Table 5. Among the 1599 ICH events, 7.9% were subarachnoid hemorrhage, 77.3% were intracerebral hemorrhage, 0.6% were epidural hemorrhage, 9.8% were subdural hemorrhage, and 4.4% were a nonspecified type. The status about the use of antithrombotic therapies within 30 days before the events of ischemic stroke and ICH are shown in Table I in the online-only Data Supplement and Table II in the online-only Data Supplement, respectively. The pattern of antithrombotic treatments preceding ischemic stroke and ICH were broadly consistent with that used for our study categorization for >90% of the patients. In comparison with patients without antithrombotic therapy, the use of antiplatelet agents was not associated with a lower risk of ischemic stroke, but did increase the risk of ICH with an adjusted HR of 0.90 (95% CI, 0.81–1.01; P=0.060) and 1.35 (95% CI, 1.21–1.51; P<0.001), respectively.

For patients receiving warfarin, the risk of ischemic stroke was lower than for patients without antithrombotic therapy with an adjusted HR of 0.66 (95% CI, 0.55–0.79; P<0.001). The risk of ICH was also higher among warfarin users with an adjusted HR of 1.60 (95% CI, 1.38–1.86; P<0.001).

Table 3. Incidence (per 100 Person-Years) of Ischemic Stroke in Patients With or Without History of ICH and Did Not Receive Antithrombotic Therapies

Groups	Number of Events (Ischemic Stroke)	Number of Patients	Person-Years	Incidence*
With ICH	964	8211	16 748	5.8
Without ICH	20 053	149 618	451 883	4.4

ICH indicates intracranial hemorrhage.
*Number of ischemic strokes per 100 person-years of follow-up.

Table 4. Incidence (per 100 Person-Years) of Ischemic Stroke Stratified by CHA_2DS_2-VASc Score in Patients With History of ICH and Without Antithrombotic Therapies (n=8211)

CHA_2DS_2-VASc Score	Number of Events	Number of Patients	Person-Years	Incidence*
2	18	125	568	3.2
3	68	535	1732	3.9
4	156	1205	3200	4.9
5	223	1879	4035	5.5
6	240	2105	3697	6.5
7	168	1596	2465	6.8
8	70	631	865	8.0
9	21	135	186	11.3
Total	964	8211	16 748	5.8

ICH indicates intracranial hemorrhage.
*Number of ischemic strokes per 100 person-years of follow-up.

NNT and NNH With Warfarin in Comparison With No Antithrombotic Treatment

Among 1154 patients who received warfarin treatment, 241 (20.9%) patients experienced ICH during the follow-up of 4092 person-years with an annual rate of 5.9%.

Table 6 shows the NNT for preventing 1 ischemic stroke and NNH for producing 1 ICH with warfarin based on the adjusted incidence of ischemic stroke and ICH for patients with a CHA_2DS_2-VASc score ≥6. The NNT was 37, which was lower than the NNH (56), suggesting that warfarin may provide net benefits for patients with a CHA_2DS_2-VASc score ≧6 balancing the risk/benefit ratio. When examining the crude annual risk of ICH with warfarin use (5.9%) versus the risk of ischemic stroke if left untreated, the risk of ischemic stroke outweighs the risk of ICH with warfarin for patients with a CHA_2DS_2-VASc score ≧6 (annual stroke rate=6.5%; Figure I in the online-only Data Supplement).

The risk of combined end point (either ischemic stroke or ICH) was lower in patients receiving warfarin than in nontreated subjects with an adjusted HR of 0.73 (95% CI, 0.60–0.89; P=0.002) after adjusting for age, sex, CHA_2DS_2-VASc score, and comorbidities other than the components of the CHA_2DS_2-VASc score, including hyperlipidemia, chronic obstructive pulmonary disease, malignancy, and end-stage renal disease.

Table 7 shows the NNT for preventing 1 ischemic stroke and NNH for producing 1 ICH with warfarin based on the adjusted incidence of ischemic stroke and ICH for patients with a CHA_2DS_2-VASc score <6. The NNT was higher than NNH (63 versus 53) for these patients. The risk of combined end point (either ischemic stroke or ICH) did not differ significantly between patients receiving warfarin or nontreated with an adjusted HR of 0.93 (95% CI, 0.75–1.15; P=0.49) after adjusting for age, sex, CHA_2DS_2-VASc score, and comorbidities other than the components of CHA_2DS_2-VASc score.

Table 5. Risk of Ischemic Stroke and ICH in Patients With History of ICH (n=12 917) Stratified Based on the Strategies for Stroke Prevention

Stroke Prevention Strategy	n	Ischemic Stroke					ICH				
		No. of Events	Crude Incidence*	Adjusted Incidence†	Adjusted HR† (95% CI)	*P* Value	No. of Events	Crude Incidence*	Adjusted Incidence†	Adjusted HR† (95% CI)	*P* Value
No antithrombotic therapy (reference group)	8211	964	5.8	5.7	Reference	–	730	4.2	4.2	Reference	–
Antiplatelet agents	3552	581	5.2	5.1	0.90 (0.81–1.01)	0.060	628	5.3	5.2	1.35 (1.21–1.51)	<0.001
Warfarin	1154	130	3.4	3.6	0.66 (0.55–0.79)	<0.001	241	5.9	6.2	1.60 (1.38–1.86)	<0.001

CI indicates confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; and ICH, intracranial hemorrhage.

*Per 100 person-years of follow-up

†Adjusted for age, sex, CHA_2DS_2-VASc score, COPD, hyperlipidemia, malignancy, and end-stage renal disease

Propensity Matched Analyses

Baseline characteristics after propensity matching for 2 kinds of comparisons (antiplatelet agents versus no antithrombotic therapy and warfarin versus no antithrombotic therapy) are shown in Table III in the online-only Data Supplement. Propensity scores between 2 groups in each comparison were similar. Age, sex and comorbidities were not significantly different between the groups for each comparison.

Similar to the results derived from the nonmatched cohort, the use of antiplatelet agents was not associated with a lower risk of ischemic stroke but did increase the risk of ICH in comparison with patients without antithrombotic therapy with an adjusted HR of 0.89 (95% CI, 0.78–1.01; *P*=0.060) and 1.36 (95% CI, 1.19–1.57; *P*<0.001), respectively (Table IV in the online-only Data Supplement). For patients receiving warfarin, the risk of ischemic stroke was significantly lower than for patients without antithrombotic therapy, with an adjusted HR of 0.58 (95% CI, 0.46–0.73; *P*<0.001). The risk of ICH was also higher among warfarin users with an adjusted HR of 1.58 (95% CI, 1.27–1.98; *P*<0.001; Table IV in the online-only Data Supplement).

Table VA in the online-only Data Supplement shows the NNT for preventing 1 ischemic stroke and NNH for producing 1 ICH with warfarin for patients with a CHA_2DS_2-VASc score ≥6. The NNT was 27, which was lower than the NNH (ie, 91), suggesting that warfarin may provide net benefits for patients with a CHA_2DS_2-VASc score ≥6 when balancing the risk/benefit ratio. The NNT was higher than NNH (53 versus 42) for patients with a CHA_2DS_2-VASc score <6 (Table VB in the online-only Data Supplement).

Discussion

This study is the largest investigation of the risk of ICH and ischemic stroke with warfarin use for patients with history of ICH in comparison with those without, among East Asian patients. Our principal findings were as follows. (1) Even without the use of antithrombotic agents, AF patients with a history of ICH were associated with a 5-fold risk of further ICH in comparison with patients without ICH history. The risk of ischemic stroke was also higher for patients with previous ICH. (2) The use of antiplatelet agents did not significantly reduce the risk of ischemic stroke, but did increase the risk of ICH for patients with previous ICH; thus, antiplatelet therapy should not be used in AF patients with a history of ICH for stroke prevention. (3) The use of warfarin was associated

Table 6. NNT for Preventing 1 Stroke and NNH for Producing 1 ICH With Warfarin for Patients With a CHA_2DS_2-VASc Score ≥6

Groups	Number of Events	Number of Patients	Person-Years	Crude Incidence*	Adjusted Incidence†
Ischemic stroke					
Without antithrombotic agents	499	4467	7213	6.9	6.8
With warfarin	59	604	1515	3.9	4.1
NNT=37					
Intracranial hemorrhage					
Without antithrombotic agents	316	4467	7369	4.3	4.3
With warfarin	97	604	1600	6.1	6.1
NNH=56					

COPD indicates chronic obstructive pulmonary disease; ICH, intracranial hemorrhage; NNH, number needed to harm; and NNT, number needed to treat.

*Number of events per 100 person-years of follow-up.

†Adjusted for age, sex, CHA_2DS_2-VASc score, COPD, hyperlipidemia, malignancy and end-stage renal disease.

Table 7. NNT for Preventing 1 Stroke and NNH for Producing 1 ICH With Warfarin for Patients With a CHA_2DS_2-VASc Score <6

Groups	Number of Events	Number of Patients	Person-Years	Crude incidence*	Adjusted incidence†
Ischemic stroke					
Without antithrombotic agents	465	3744	9535	4.9	4.8
With warfarin	71	550	2316	3.1	3.2
NNT=63					
Intracranial hemorrhage					
Without antithrombotic agents	414	3744	10103	4.1	4.1
With warfarin	144	550	2492	5.8	6.0
NNH=53					

COPD indicates chronic obstructive pulmonary disease; ICH, intracranial hemorrhage; NNH, number needed to harm; and NNT, number needed to treat.

*Number of events per 100 person-years of follow-up.

†Adjusted for age, sex, CHA_2DS_2-VASc score, COPD, hyperlipidemia, malignancy, and end-stage renal disease.

with a lower risk of ischemic stroke, but also a higher risk of ICH in comparison with AF patients without antithrombotic therapy. (4) The NNT was lower than NNH for patients with a CHA_2DS_2-VASc score ≥6 receiving warfarin treatment (37 versus 56), but the NNT was higher than NNH for patients with a CHA_2DS_2-VASc score <6 (63 versus 53), suggesting that warfarin use should perhaps be reserved for Chinese AF patients with previous ICH with a CHA_2DS_2-VASc score ≧6.

Stroke Prevention in AF Patients With History of ICH

Although warfarin use can substantially decrease the risk of ischemic stroke and mortality in AF patients, its underuse is a worldwide problem.[21] In addition to the inconvenience of warfarin usage, including multiple drug-food interactions and a narrow therapeutic range necessitating frequent monitoring, fear of catastrophic bleeding (especially ICH) also might contribute to the underuse of OACs for AF, particularly among Asians. Indeed, Asians had a 4-fold increased risk of ICH in comparison with whites when treated with warfarin.[22] Because patients with a history of ICH have been excluded from previous randomized clinical trials for stroke prevention in AF, whether OACs should be used for these AF patients is unclear and remains as a big challenge.

In the present study, we demonstrate that the risk of further ICH was 5-fold higher in nontreated AF patients with a history of ICH than in those without ICH (4.2% versus 0.6% per year). Among patients with a history of ICH, the annual risk of recurrent ICH increased from 4.2% for patients left untreated to 5.9% when treated with warfarin. We also show that aspirin increased the risk of recurrent ICH but did not reduce the risk of ischemic stroke in comparison with untreated patients. Because the risk of further ICH is high, the risk/benefit ratio with warfarin use for stroke prevention should be carefully weighed for this special AF population.

Given the high risk of recurrent ICH for patients with a history of ICH, the threshold for initiating warfarin for these patients may be different from the general AF population. On inspection of the NNT and NNH, our results suggest that warfarin may be considered for patients with a CHA_2DS_2-VASc score ≥6 balancing the increased risk of ICH and benefits of stroke risk reduction. Also, the data we provided here can be useful for sharing decision making with patients to discuss the absolute risk and benefit, which is an important point emphasized by the current guideline.[23] In the era of NOACs, the threshold for initiating OACs for stroke prevention in AF has been lowered given their relative efficacy, safety, and convenience, and their markedly lower risk of ICH in comparison with warfarin. During the present study, NOACs were not yet available in Taiwan; therefore, we did not have data on the risk of ICH with NOAC use. In the study by Lip et al,[24] the HR of ICH with the use of NOACs in comparison with warfarin was 0.47. In the previous meta-analysis performed by Ruff et al,[10] the risk of ICH can be reduced by 52% with NOACs in comparison with warfarin with a risk ratio of 0.48 (95% CI, 0.39–0.59; $P<0.0001$). In the recent study by Wang et al,[25] the odds ratio of ICH with the use of NOACs in comparison with warfarin was 0.33 for Asians, which was lower than that of non-Asians (odds ratio, 0.52; 95% CI, 0.42–0.64). According to these data, the estimated risk of ICH with OACs for AF patients having a history of ICH can be reduced from 5.9% with warfarin to ≈2.8% and even as low as 1.9% when NOACs are used. Based on this assumption, the threshold for initiating OAC with a NOAC could be lowered to a CHA_2DS_2-VASc score of 2 (annual risk of ischemic stroke=3.2%; Figure I in the online-only Data Supplement). In the US Food and Drug Administration Medicare analysis,[26] the ICH rates on dabigatran in comparison with warfarin were 0.33% per year and 0.96% per year, respectively; however, these data were based on predominantly non-Asian cohort, and no data on TTR were available. In a Chinese AF cohort from Hong Kong, the annual ICH rate on well-controlled warfarin (top quartile TTR) was 0.74%, and, on a NOAC (dabigatran), was 0.32%.[27] This would be in keeping with a treatment threshold of CHA_2DS_2-VASc score of ≥2.

Besides OACs, occlusion of the left atrial appendage by means of a device may represent an alternative to oral anticoagulation for stroke prevention,[28,29] mainly in patients with absolute contraindications to oral anticoagulation because of a very high bleeding risk.[30,31] Although head-to-head comparisons between left atrial appendage closure and NOACs are not

available, left atrial appendage occlusion may potentially be a useful way to reduce stroke risk and avoid long-term use of OACs among AF patients with previous ICH, especially when the risk factors of bleeding are uncorrectable.

Study Limitations

Our study is the first and largest population-based study to investigate the risk/benefit of warfarin use for East Asian AF patients with a history of ICH, and the strength of our study is the use of a well-validated nationwide data set that enrolled a large sample of subjects.

However, there are still some limitations in our study. First, the diagnosis of ICH was based on the diagnostic codes registered by the physicians responsible for the treatment of patients, and detailed results of imaging studies of brain were not available in this registry data set to ascertain the location and type of ICH; however, our principal objective was to address a simple clinical question of the NNH and NNT for antithrombotic treatments in our Chinese AF patients with ICH. Second, the information about international normalized ratio and TTR for warfarin was lacking in this nationwide registry, and Asian patients consistently have poorer TTRs than non-Asian patients.[9] In the Randomized Evaluation of Long-Term Anti-coagulation Therapy (RE-LY) trial, the TTR for warfarin was only 44% in Taiwan.[32] Because a higher TTR is significantly associated with a lower risk of ischemic stroke and ICH for AF patients receiving warfarin,[33] the threshold of initiating OACs would be lower than a CHA_2DS_2-VASc score of 6 if the quality of warfarin use could be much improved. Third, we were not able to report the Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol (HAS-BLED) score for each patient because details on the amount of alcohol intake and biochemical indices of renal/liver function, which should be used to calculate the score, were not available in this registry database. However, decision making about the use of OACs should be based on CHA_2DS_2-VASc score; indeed, the HAS-BLED score should not be used to exclude patients from OAC therapy but allows clinicians to think of the correctable risk factors for bleeding.[34] Therefore, the lack of data on HAS-BLED score may not significantly interfere the interpretation of our study. Fourth, previous studies have demonstrated that the risk of ICH with warfarin use was higher among Asians than non-Asians.[22,35] The present study only enrolled Taiwanese Chinese patients, and whether the results can be extrapolated to other populations remains uncertain. Last, the risk of ICH and the CHA_2DS_2-VASc score threshold for initiating NOACs for stroke prevention in patients with a history of ICH were estimated and proposed based on previous studies in the literature. A prospective randomized trial is therefore necessary to confirm our findings.

Conclusion

In this Asian cohort of AF patients with previous ICH, warfarin use may be beneficial for patients with a CHA_2DS_2-VASc score $\geqq 6$. Patients receiving antiplatelet agents had a similar risk of ischemic stroke but higher risk of ICH in comparison with untreated patients. Whether the use NOACs could lower the threshold for treatment deserves further study.

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Disclosures

Dr Lip has served as a consultant for Bayer, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Medtronic, Portola, and Boehringer Ingelheim and has been on the speakers' bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Treatment with oral anticoagulants with vitamin K antagonists (eg, warfarin) or non–vitamin K antagonist oral anticoagulants could effectively reduce the risk of ischemic stroke in patients with atrial fibrillation (AF). However, the risk of further intracranial hemorrhage (ICH) and the benefit of stroke risk reduction with the use of oral anticoagulants for AF patients with previous ICH remain unclear, given that such patients were excluded from randomized trials. In this nationwide population-based study, we investigated the risk of ischemic stroke and ICH among 12 917 AF patients with a history of ICH, who were allocated into 3 groups, that is, no treatment (63.6%), antiplatelet therapy (27.5%), and warfarin (8.9%). We found that the use of antiplatelet agents did not significantly reduce the risk of ischemic stroke, but it did increase the risk of ICH for patients with previous ICH; thus, antiplatelet therapy should not be used in AF patients with a history of ICH for stroke prevention. The use of warfarin was associated with a lower risk of ischemic stroke, but also a higher risk of ICH in comparison with AF patients who did not receive antithrombotic therapy. After considering the risk/benefit ratio, warfarin use may be beneficial for Asian AF patients with a CHA_2DS_2-VASc score ≧6. Whether the use of non–vitamin K antagonist oral anticoagulants could lower the threshold for treatment deserves further study.