

Is an Oral Anticoagulant Necessary for Young Atrial Fibrillation Patients With a CHA₂DS₂-VASc Score of 1 (Men) or 2 (Women)?

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Background—Recent studies demonstrated that oral anticoagulants (OACs) should be considered for patients with atrial fibrillation and 1 risk factor in addition to sex. Because age is an important determinant of ischemic stroke, the strategy for stroke prevention may be different for these patients in different age strata. The aim of this study was to investigate whether OACs should be considered for patients aged 20 to 49 years with atrial fibrillation and a CHA₂DS₂-VASc score of 1 (men) or 2 (women).

Methods and Results—Using the Taiwan National Health Insurance Research Database, 7374 male patients with atrial fibrillation and a CHA₂DS₂-VASc score of 1 and 4461 female patients with atrial fibrillation and a CHA₂DS₂-VASc score of 2 and all without antithrombotic therapies were identified and stratified into 3 groups by age. The threshold for the initiation of OACs for stroke prevention was set at a stroke rate of 1.7% per year for warfarin and 0.9% per year for non-vitamin K antagonist OACs. Among male patients aged 20 to 49 years with a CHA₂DS₂-VASc score of 1, the risk of ischemic stroke was 1.30% per year and ranged from 0.94% per year for those with hypertension to 1.71% for those with congestive heart failure. Among female patients aged 20 to 49 years with a CHA₂DS₂-VASc score of 2, the risk of ischemic stroke was 1.40% per year and ranged from 1.11% per year for those with hypertension to 1.67% for those with congestive heart failure.

Conclusions—For atrial fibrillation patients aged 20 to 49 years with 1 risk factor in addition to sex, non-vitamin K antagonist OACs should be considered for stroke prevention to minimize the risk of a potentially fatal or disabling event. (*J Am Heart Assoc*. 2016;5:e003839 doi: 10.1161/JAHA.116.003839)

Key Words: age • atrial fibrillation • CHA₂DS₂-VASc score • ischemic stroke • non-vitamin K antagonist oral anticoagulants

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with ≈5-fold increased risk of ischemic stroke in patients with versus without AF.¹

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AF-related stroke is more likely to be fatal, is frequently recurrent, and causes more severe functional disabilities than non-AF-related stroke.²

The risk of AF-related stroke is not homogeneous and depends on the age and comorbidities of each patient. Current clinical guidelines suggest the use of CHA₂DS₂-VASc score (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74 years, female sex) for stroke risk stratification, and the use of oral anticoagulants (OACs) is determined accordingly.^{3,4} Based on guideline recommendations, OACs should be prescribed for patients with a CHA₂DS₂-VASc score ≥2 (class I recommendation) and omitted for male patients with a CHA₂DS₂-VASc score of 0 and female patients with a CHA₂DS₂-VASc score of 1. For patients with 1 risk factor in addition to sex (ie, CHA₂DS₂-VASc score 1 [men] or 2 [women]), the European Society of Cardiology (ESC) guidelines suggest that stroke prevention with OACs should be considered, especially using non-vitamin K antagonist OACs (NOACs).³ Our previous study demonstrated that the annual risk of ischemic stroke was 2.75% for Asian men with AF and a CHA₂DS₂-VASc score of 1

and 2.55% for Asian women with AF and a CHA₂DS₂-VASc score of 2,⁵ which exceeds the treatment threshold for the initiation of warfarin (1.7% per year) or use of NOACs (0.9% per year).⁶

Although these data support the use of OACs for Asians AF patients with a CHA₂DS₂-VASc score of 1 (men) or 2 (women), the risk of ischemic stroke for these patients stratified by age has not been studied previously. It is unclear whether OACs should be prescribed for Asian AF patients aged <50 years because data are limited. This study aimed to investigate the risk of ischemic stroke in Asian AF patients with 1 stroke risk factor in addition to sex, stratified by age.

Methods

Database

The study protocol of the present study is similar to that of our previous studies.^{5,7–11} This study used Taiwan's National Health Insurance Research Database (NHIRD), released by the Taiwan National Health Research Institutes. The National Health Insurance (NHI) system is an obligatory nationwide health insurance program that provides comprehensive medical care coverage to all Taiwanese citizens. The NHIRD consists of detailed health care data from >23 million enrollees, representing >99% of Taiwan's residents. In this cohort data set, the patients' original data have been encrypted to protect their privacy, and the encrypting procedure was consistent. Linkage of the claims belonging to the same patient was feasible within the NHI database and can be tracked continuously. The huge sample size of this database provided a good opportunity to study the risk of ischemic stroke in AF patients with a CHA₂DS₂-VASc score of 1 (men) or 2 (women), stratified by age.

Study Cohort

From January 1, 1996, to December 31, 2003, a total of 153 036 AF patients aged ≥20 years were identified from the NHIRD as the study population. AF was diagnosed using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 427.31. To ensure the accuracy of diagnosis, we defined patients with AF only when it was a discharge diagnosis or was confirmed on at least 2 occasions in the outpatient department. The diagnostic accuracy of AF using this definition in NHIRD has been validated previously.^{12,13} The CHA₂DS₂-VASc score was calculated for each patient by assigning 1 point each for age between 65 and 74 years, history of hypertension, diabetes mellitus, heart failure, vascular disease (myocardial infarction or peripheral artery

disease), and female sex and 2 points each for history of stroke, transient ischemic attack, or age ≥75 years.¹⁴ Among the study population, we excluded patients at baseline who received treatment with warfarin or any antiplatelet agent, including aspirin, clopidogrel, dipyridamole, and ticlopidine. Finally, a total of 89 455 patients were enrolled into the study cohort; 12 115 men had a CHA₂DS₂-VASc score of 0 to 1, and 7695 women had a CHA₂DS₂-VASc score of 1 to 2. A flowchart of the enrollment of the study cohort is shown in Figure 1.

Definition of Clinical End Points

The clinical end point was the occurrence of ischemic stroke (ICD-9-CM codes 433.x, 434.x, 436), with concomitant imaging studies of the brain, such as computed tomography or magnetic resonance imaging. The accuracy of diagnosis of ischemic stroke in Taiwan's NHIRD has been reported to be ≈94%.¹⁵ Another validation study also demonstrated that the diagnostic accuracy of ischemic stroke in NHIRD was high, with a positive predictive value and sensitivity of 88.4% and 97.3%, respectively.¹⁶ The annual risk of ischemic stroke was calculated for patients who were stratified into 3 groups based on age (20–49, 50–64, and 65–74 years).

The “Tipping Point” for OAC Use for Stroke Prevention

In an analysis of the “tipping point” for OAC use for stroke prevention using a decision analytic model, Eckman et al estimated thresholds for ischemic stroke risk below which OAC therapy should be withheld and above which OAC therapy should be prescribed.⁶ Their results demonstrated that anticoagulation with warfarin is preferred at a stroke rate of >1.7% per year, whereas anticoagulation with the safer NOACs leads to lowering of the treatment threshold for anticoagulation to a stroke rate of 0.9% per year.⁶ Consequently, patients with an annual risk of ischemic stroke >0.9% in our study cohort were assumed to be candidates for NOAC use for stroke prevention. For patients with an annual risk of ischemic stroke >1.7%, OACs with either warfarin or NOACs could be considered.

Statistical Analysis

Incidence rates of ischemic stroke were calculated by dividing the number of events by person-time at risk. The risk of ischemic stroke was assessed using Cox regression analysis.

The present study was approved by the institutional review board of Taipei Veterans General Hospital, Taipei, Taiwan, and informed consent of study participants was waived.

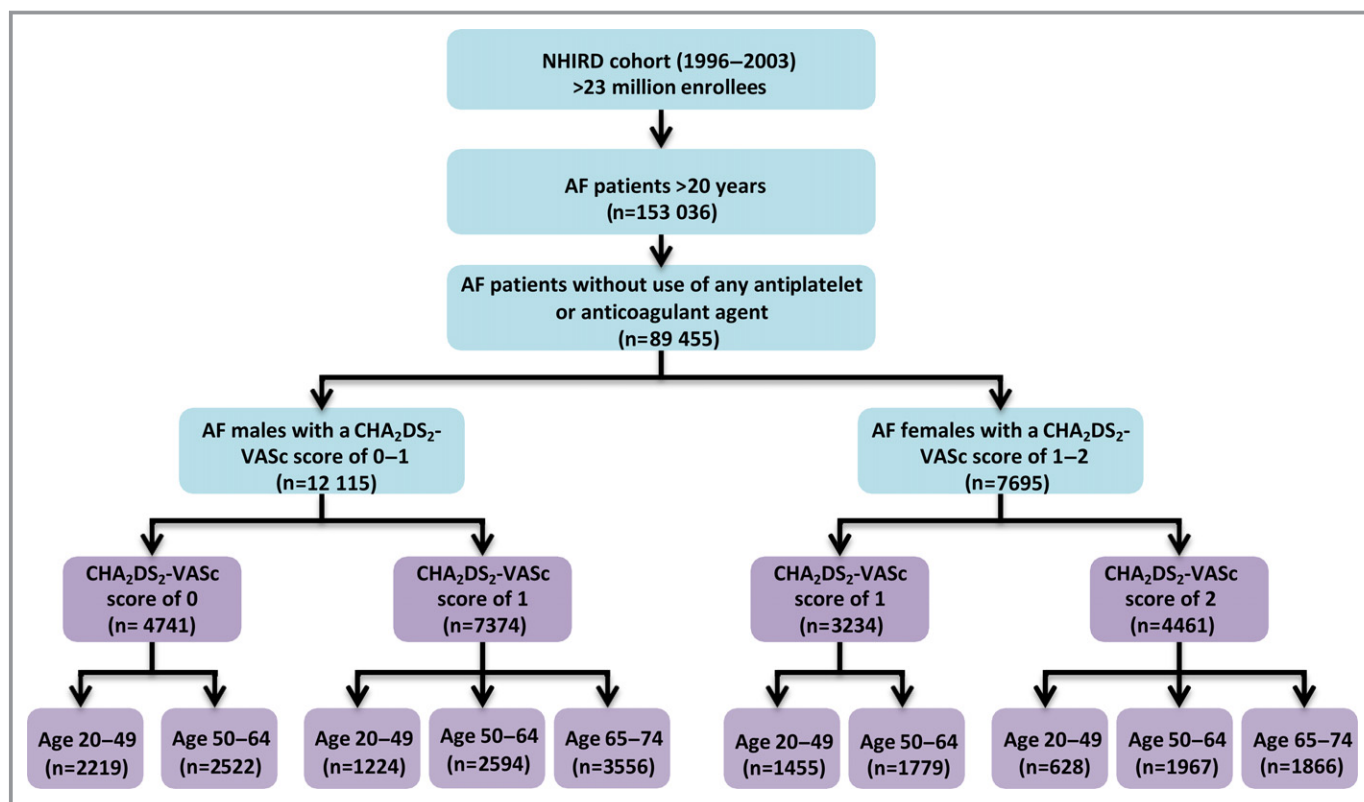


Figure 1. A flowchart of the enrollment of the study cohort. Among 89 455 AF patients who did not receive oral anticoagulants or antiplatelet agents, there were 12 115 male AF patients with a CHA₂DS₂-VASc score of 0 to 1 and 7695 female AF patients with a CHA₂DS₂-VASc score of 1 to 2. The risk of ischemic stroke was analyzed for these patients and further stratified on the basis of age. AF indicates atrial fibrillation; NHIRD, National Health Insurance Research Database.

Results

Table 1 shows the number of ischemic strokes per 100 person-years for AF patients with a CHA₂DS₂-VASc score of 0 to 1 (men) or 1 to 2 (women) and stratified by age. The number of ischemic strokes per 100 person-years for patients aged 20 to 49 and 50 to 64 years who did not have any risk factors other than sex (ie, CHA₂DS₂-VASc 0 in men, 1 in women) were 0.63 and 1.96, respectively. For patients with 1 risk factor in addition to sex (ie, CHA₂DS₂-VASc 1 for men, 2 for women), the numbers of ischemic strokes per 100 person-years were 1.33 for patients aged 20 to 49 years, 2.90 for those aged 50 to 64 years, and 3.60 for those aged 65 to 74 years. Among patients aged 20 to 49 years, the number of ischemic strokes per 100 person-years ranged from 1.00 for those with hypertension to 1.69 for those with congestive heart failure.

Table 2 shows the number of ischemic strokes per 100 person-years for male AF patients with a CHA₂DS₂-VASc score of 0 to 1, stratified by age. Among male patients aged 20 to 49 years with a CHA₂DS₂-VASc score of 1, the number of ischemic strokes per 100 person-years was 1.30, ranging from 0.94 for those with hypertension to 1.71 for those with congestive heart failure.

Table 3 shows the number of ischemic strokes per 100 person-years for female AF patients with a CHA₂DS₂-VASc score of 1 to 2, stratified by age. Among female patients aged 20 to 49 years with a CHA₂DS₂-VASc score of 2, the number of ischemic strokes per 100 person-years was 1.40 and ranged from 1.11 for those with hypertension to 1.67 for those with congestive heart failure.

Figure 2 shows the risk of ischemic stroke represented by hazard ratios for each risk factor component stratified by age. Among patients aged 20 to 49 years, the hazard ratios ranged from 1.59 for patients with hypertension to 2.67 for those with congestive heart failure.

Discussion

In this real-world nationwide cohort study of nonanticoagulated Taiwanese AF patients, we demonstrated that AF patients with 1 risk factor in addition to sex (CHA₂DS₂-VASc score 1 for men and 2 for women) had an ischemic stroke rate of 1.33% for patients aged 20 to 49 years, 2.90% for those aged 50 to 64 years, and 3.60% for those aged 65 to 74 years. Consequently, AF patients with 1 risk factor in

Table 1. Risk of Ischemic Stroke in AF Patients With a CHA₂DS₂-VASc Score of 0 to 1 (Men) or 1 to 2 (Women), Stratified by Age

Age Groups	CHA ₂ DS ₂ -VASc Score	Number of Patients	Number of Ischemic Strokes	Person-Years	Incidence*
All patients					
Age 20–49 years	No risk factors in addition to sex (score 0 for men or 1 for women)	3674	234	36 942.2	0.63
	Sex plus 1 additional risk factor (score 1 for men or 2 for women)	1852	211	15 838.9	1.33
	Congestive heart failure	766	99	5843.3	1.69
	Hypertension	705	66	6614.3	1.00
	Diabetes mellitus	224	30	1891.1	1.59
	Vascular disease	157	16	1490.3	1.07
Age 50–64 years	No risk factors in addition to sex (score 0 for men or 1 for women)	4301	729	37 265.0	1.96
	Sex plus 1 additional risk factor (score 1 [men] or 2 [women])	4561	1014	34 912.9	2.90
	Congestive heart failure	1350	268	9535.9	2.81
	Hypertension	2230	517	18 425.5	2.81
	Diabetes mellitus	679	178	4317.2	4.12
	Vascular disease	302	51	2634.2	1.94
Age 65–74 years	Score 1 (men) or 2 (women)	5422	1214	33 727.0	3.60

*Number of ischemic strokes per 100 person-years of follow-up. AF indicates atrial fibrillation.

addition to sex who are aged <50 years should still be considered for stroke prevention using OACs because the annual risk of ischemic stroke (1.33%) was above the tipping point for the use of NOACs (0.9% per year). This approach could minimize the risk of a potentially fatal or disabling thromboembolic event and the public health burden of stroke related to AF.

Stroke Prevention for AF Patients With 1 Risk Factor in Addition to Sex

The 2012 focused update of the ESC AF management guidelines suggested that OACs should be prescribed for AF patients with 1 risk factor in addition to sex.³ Recommendations for these patients were less clear in the 2014 American

Table 2. Risk of Ischemic Stroke in Men With AF and a CHA₂DS₂-VASc Score of 0 or 1, Stratified by Age

Age Groups	CHA ₂ DS ₂ -VASc Score	Number of Patients	Number of Ischemic Strokes	Person-Years	Incidence*
Age 20–49 years	No risk factors in addition to sex (score 0)	2219	119	21 888.9	0.54
	Sex plus 1 additional risk factor (score 1)	1224	134	10 328.0	1.30
	Congestive heart failure	474	60	3511.9	1.71
	Hypertension	485	42	4459.2	0.94
	Diabetes mellitus	156	21	1268.3	1.66
	Vascular disease	109	11	1088.6	1.01
Age 50–64 years	No risk factors in addition to sex (score 0)	2522	434	20 799.9	2.09
	Sex plus 1 additional risk factor (score 1)	2594	584	18 655.0	3.13
	Congestive heart failure	791	154	5312.9	2.90
	Hypertension	1233	301	9574.2	3.14
	Diabetes mellitus	392	99	2310.8	4.28
	Vascular disease	178	30	1457.1	2.06
Age 65–74 years	Score 1	3556	764	20 737.0	3.68

*Number of ischemic strokes per 100 person-years of follow-up. AF indicates atrial fibrillation.

Table 3. Risk of Ischemic Stroke in Women With AF and a CHA₂DS₂-VASc Score of 1 or 2, Stratified by Age

Age Groups	CHA ₂ DS ₂ -VASc Score	Number of Patients	Number of Ischemic Strokes	Person-Years	Incidence*
Age 20–49 years	No risk factors in addition to sex (score 1)	1455	115	15 053.3	0.76
	Sex plus 1 additional risk factor (score 2)	628	77	5510.9	1.40
	Congestive heart failure	292	39	2331.3	1.67
	Hypertension	220	24	2155.1	1.11
	Diabetes mellitus	68	9	622.8	1.45
	Vascular disease	48	5	401.7	1.24
Age 50–64 years	No risk factors in addition to sex (score 1)	1779	295	16 465.1	1.79
	Sex plus 1 additional risk factor (score 2)	1967	430	16 257.9	2.64
	Congestive heart failure	559	114	4223.0	2.70
	Hypertension	997	216	8851.4	2.44
	Diabetes mellitus	287	79	2006.4	3.94
Age 65–74 years	Vascular disease	124	21	1177.1	1.78
	Score 2	1866	450	12 989.9	3.46

*Number of ischemic strokes per 100 person-years of follow-up. AF indicates atrial fibrillation.

College of Cardiology and American Heart Association AF guidelines, which suggested that “no antithrombotic therapy, aspirin or an OAC” be considered (class IIb

recommendation).⁴ Numerous registry studies and randomized trials suggested that the risk of ischemic stroke is higher for Asian compared with non-Asian AF patients.^{8,17–20} We

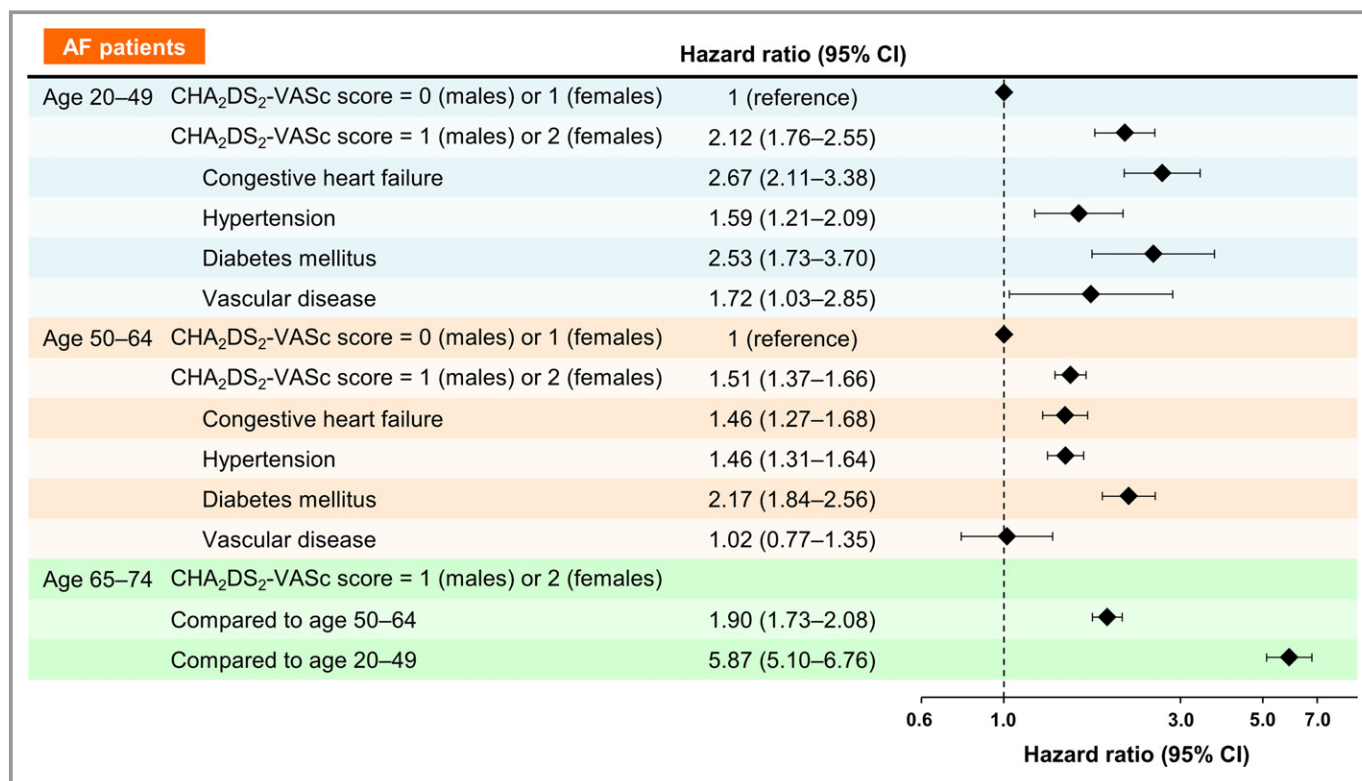


Figure 2. Risk of ischemic stroke represented by hazard ratios for each risk factor component stratified by age. Among patients aged 20 to 49 years, the hazard ratios ranged from 1.59 for patients with hypertension to 2.67 for those with congestive heart failure compared with patients with a CHA₂DS₂-VASc score of 0 (men) or 1 (women). AF indicates atrial fibrillation.

showed, for example, that the annual risk of ischemic stroke was 2.75% for Asian men with AF and a CHA₂DS₂-VASc score of 1 and 2.55% for Asian women with AF and a CHA₂DS₂-VASc score of 2⁵; therefore, these patients should receive OACs for stroke prevention, given the greater mortality and disability for AF-related strokes.

Age is an important driver of ischemic stroke risk for AF patients, and the risk of ischemic stroke substantially increases for Asian AF patients aged >50 years.⁹ Whether OACs should be prescribed for AF patients with a CHA₂DS₂-VASc score of 1 (men) or 2 (women) who are aged <50 years is unclear because data are limited, and few such patients were included in clinical trials. In the present study, we demonstrated that the annual risks of ischemic stroke were 1.30% and 1.40% for men and women, respectively, aged 20 to 49 years. Because the proposed treatment thresholds for balancing ischemic stroke reduction against serious bleeding were 1.7% per year for the use of warfarin and 0.9% per year for the use of NOACs,⁶ stroke prevention using NOACs should be considered for these patients.

As in previous studies, not all risk factors in the CHA₂DS₂-VASc score were associated with equal risks of ischemic stroke^{19,21}; therefore, the annual stroke risk was not the same for our patients aged 20 to 49 years with a CHA₂DS₂-VASc score of 1 (men) or 2 (women) and different risk components. The stroke risks were relatively higher for patients with heart failure (1.69% per year) and lower for those with hypertension (1.00% per year). Event rates for 1 stroke risk factor have varied in different studies because of different methodologies and study settings¹⁹; however, exclusion of OAC use at any time, even during follow-up, has resulted in bias from “conditioning on the future” toward lower stroke event rates.^{22,23} Because the annual risks of ischemic stroke for male patients aged 20 to 49 years with a CHA₂DS₂-VASc score of 1 due to hypertension (0.94%) or vascular disease (1.01%) in the present study were just slightly higher than the treatment threshold for using NOACs (0.9% per year), treatment of these patients in this “gray zone” should be based on shared decision making regarding the risks and benefits of OACs.

Study Limitations

Several limitations of the present study were addressed previously.^{5,7–11} First, the diagnosis of AF and the occurrence of ischemic stroke were based on the diagnostic codes registered by the physicians responsible for the treatment of patients; nonetheless, the accuracy of the diagnosis of AF and ischemic stroke in Taiwan’s NHIRD has been validated previously as high.^{12,13,15,16} We defined patients as having AF only when it was a discharge diagnosis or was confirmed on at least 2 occasions in the outpatient department. To ensure the diagnostic accuracy of AF, patients having AF

coding only 1 time at the outpatient clinic were not enrolled. Nevertheless, compared with patients coded with AF only 1 time, patients coded with AF more times might have had longer AF duration and higher AF burden, which could increase stroke risk. Second, the clinical end point of the present study included only ischemic stroke and did not account for transient ischemic attack and other systemic thromboembolism. Because the event rate of the study population could be even higher if transient ischemic attack and other systemic thromboembolic events were included, that would further support the main finding of the present study showing that NOACs should be considered for Asian AF patients aged 20 to 49 years with 1 risk factor in addition to sex. Third, detailed information about personal habits, symptoms, and cardiac function were unavailable in the registry database. Fourth, many young AF patients would have received various treatments (eg, rate/rhythm control, ablation) to relieve their symptoms, and this may have influenced event rates. Last, the present study enrolled only Asian patients, and it remains uncertain whether the results can be extrapolated to other populations. Moreover, the data from which the tipping points were derived for the initiation of OACs were acquired in studies that consisted mainly of white patients; therefore, the treatment thresholds may be different for Asian patients.

Conclusion

For Asian AF patients aged 20 to 49 years with 1 risk factor in addition to sex and a CHA₂DS₂-VASc score of 1 (men) or 2 (women), NOACs should be considered for stroke prevention to minimize the risk of a potentially fatal or disabling event. A treatment threshold gray zone exists for male patients aged 20 to 49 years with a CHA₂DS₂-VASc score of 1 because of hypertension or vascular diseases; the annual risks of stroke for these patients were just slightly higher than the tipping point for using NOACs. Treatment should be based on shared decision making with patients regarding the risks and benefits of OACs.

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Disclosures

Lip has served as a consultant for Bayer/Janssen, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola,

Boehringer Ingelheim, Microlife and Daiichi-Sankyo; and speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo.

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