

Review Article



Stroke Prevention in Atrial Fibrillation: Focus on Asian Patients

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Conflict of Interest

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ABSTRACT

Atrial fibrillation (AF) is the most common arrhythmia conferring a fivefold increased risk of stroke. Stroke prevention is the cornerstone of management of patients with AF. Asians have a generally higher incidence of AF-related risks of stroke and bleeding (particularly intracranial bleeding), compared with non-Asians. Despite the well-documented efficacy and relative safety of oral anticoagulation for stroke prevention among Asians, the suboptimal use of oral anticoagulation remains common. The current narrative review aims to provide a summary of the available evidence on stroke prevention among patients with AF focused on the Asia region, regarding stroke and bleeding risk evaluation, the performance of oral anticoagulation, and current use of thromboprophylaxis.

Keywords: Atrial fibrillation; Stroke; Prevention; Anticoagulant agents; Asian continental ancestry group

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia with increasing prevalence worldwide including in Asia.¹⁾ The incidence and prevalence of AF increased with population aging.²⁾ By 2050, 2.9 million of people may suffer from AF-associated stroke.³⁾ Overall, AF confers a fivefold increased risk of stroke which is more severe compared with those of other etiologies.⁴⁻⁷⁾ AF-related stroke often results in up to 20% high-risk of death and approximately 60% of disability.⁸⁾⁹⁾

Stroke prevention, i.e., oral anticoagulation (OAC), is the cornerstone of management for patients with AF. Therefore, optimizing stroke prevention for patients with AF in Asia has a great impact on the global health burden of this most common arrhythmia.¹⁰⁾ Among patients with AF, the risk of stroke is not homogeneous and increases with the presence of more risk factors for stroke. The more common stroke risk factors include age, heart failure (HF), diabetes mellitus, previous stroke/transient ischemic attack (TIA), vascular disease and sex category (female gender), have been used to formulate a simple risk stratification scheme, the congestive HF, hypertension, age ≥ 75 (2 points), diabetes mellitus, previous stroke/TIA (2 points), vascular disease, age 65–74, sex category (female gender) (CHA₂DS₂-

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VASc) score, for predicting individual's risk of stroke.¹¹⁾ Performance of this score has been well-validated in Asians.

Compared to control or placebo, OAC with vitamin K antagonist (VKA) reduces stroke by 64% and all-cause mortality by 26%.¹²⁾ However, VKA use has significant shortcomings, such as narrow therapeutic range, multiple foods and drugs interaction and the need for monitoring. Further, the performance of VKA is suboptimal in Asians, and is associated with a high-risk of intracranial hemorrhage (ICH), frequently related to poor anticoagulation control (reflected by poorer time in therapeutic range [TTR]) related to use of herbs and dietary habits in Asians.³⁾¹³⁾

Currently, the non-VKA oral anticoagulants (NOACs) have changed the landscape of anticoagulation in patients with AF. The improved efficacy, safety and convenience profiles of NOACs have encouraged the wide use of this anticoagulant worldwide. Also, NOACs are associated with lower risk of bleeding events, especially for ICH, compared with the VKA.¹⁴⁻¹⁷⁾ The recent development of reversal agents for NOACs make it possible to "switch off" the anticoagulation effects of these agents in some urgent situations, such emergent surgery, ICH and other major bleedings. Thus, the multiple benefits of NOAC make them more suitable as an OAC choice for Asians. Indeed, a national cohort study from Korea has shown that Asians benefit more from NOACs compared with non-Asians.¹⁸⁾

Although the provision of stroke prevention has improved among Asians during the past decades, suboptimal OAC use remains common in this region. Multiple factors, including a fear of bleeding events, inconvenience of anticoagulation quality check, lower adherence, etc. have all been related to the underuse of OAC, which contribute to a high-risk of stroke in Asian patients with AF.

The current narrative review aims to provide a summary of the available evidence on stroke prevention among patients with AF focused on the Asia region, regarding stroke and bleeding risk evaluation, the performance of OAC, and current use of thromboprophylaxis. We also provided a flowchart of decision-making process of stroke prevention in patients with AF from Asia (**Figure 1**).

ATRIAL FIBRILLATION-RELATED STROKE IN ASIAN

The prevalence of AF-related stroke has been reported in Asian cohorts from the recent randomised trials of the NOACs.¹⁴⁻¹⁷⁾ For example, in a subanalysis of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, the absolute annual rate of ischemic stroke was numerically higher in Asians compared with non-Asians (2.05% vs. 1.14% in dabigatran 110 mg group, 1.12% vs. 0.81% in the dabigatran 150 mg group, and 2.02% vs. 0.98% in the warfarin group).¹⁹⁾ A subanalysis of the Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET-AF) trial revealed a higher absolute annual rate of ischemic stroke in East Asia (not including Japan) compared with non-East Asia (2.24% vs. 1.60% in warfarin group).²⁰⁾ Also, in the Effective Anticoagulation with factor Xa Next Generation in Atrial Fibrillation (ENGAGE AF) trial, East Asians had a numerically higher annual rate of ischemic stroke compared with non-East Asians (1.31% vs. 0.89% in warfarin group).²¹⁾ Such differences among Asian populations were again confirmed in the Apixaban versus Warfarin in Patients with Atrial Fibrillation (ARISTOTLE) trial.²²⁾

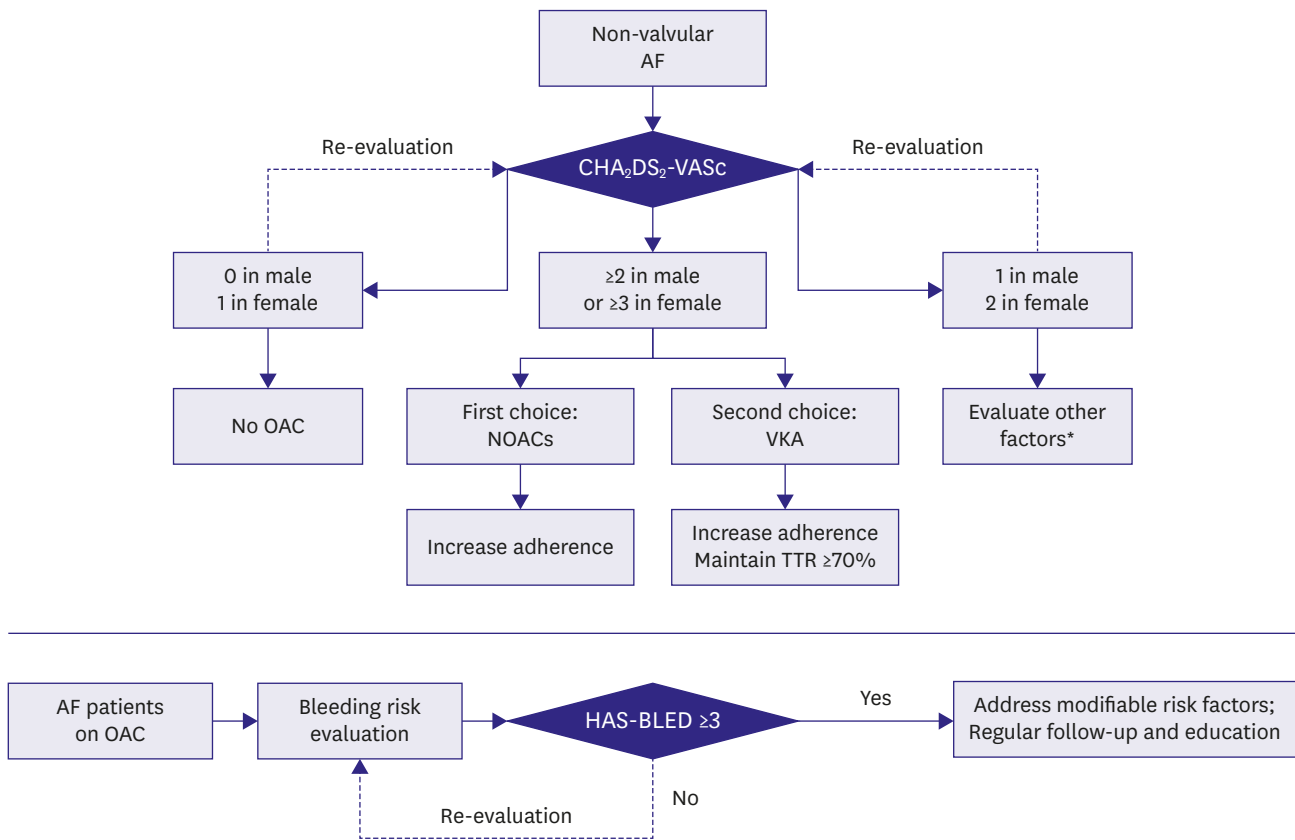


Figure 1. Decision-making process of stroke prevention in patients with AF from Asia. The decision-making process includes stroke risk evaluation, OAC choosing and bleeding risk control. Stroke and bleeding risk re-evaluation should be made at each medical contact. AF = atrial fibrillation; CHA₂DS₂-VASc = congestive HF, hypertension, age ≥75 (2 points), diabetes mellitus, previous stroke/TIA (2 points), vascular disease, age 65–74, sex category (female gender); HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; TTR = time in therapeutic range; VKA = vitamin K antagonist. *Including patients' preference, risk factor severity (such as blood pressure control), bleeding risk.

STROKE RISK STRATIFICATION IN ASIANS

The CHA₂DS₂-VASc score is widely used in different populations and got recommended by most guidelines regarding stroke risk evaluation in AF.²³⁻²⁶⁾ The CHA₂DS₂-VASc score was derived from Western populations (36 countries from Europe), with good accuracy in predicting stroke risk, especially in identifying low-risk patients.¹¹⁾

Since its original derivation, the CHA₂DS₂-VASc score has also been validated in Asian populations. For example, in a large cohort study enrolled 186,570 Chinese patients with AF, the CHA₂DS₂-VASc score outperformed the older CHADS₂ score with a better area under curve (AUC) for predicting ischemic stroke (0.698 vs. 0.659, p<0.0001)²⁷⁾. Further, the CHA₂DS₂-VASc score showed better capability in identifying low-risk patients. Indeed, in patients with a CHADS₂ score of 0, the CHA₂DS₂-VASc score ranged from 0–3 with an annual risk of stroke ranging from 1.15% to 4.47%; of note, among patients with a CHA₂DS₂-VASc score of 0, the annual stroke risk was around 1.15%.²⁷⁾

In a meta-analysis including 6 cohort studies of AF patients from Asia regions, absolute event rates were usually lower when patients were categorized as the CHA₂DS₂-VASc score

of 0–1, compared to a CHADS₂ score of 0–1.²⁸⁾ This study demonstrated that when compared with the CHA₂DS₂-VASc score, there was a 1.71-fold elevated stroke risk among patients stratified as “low-risk” using a CHADS₂ score of 0, or a 1.40-fold increased with a CHADS₂ score of 1.²⁸⁾

The performance of the CHA₂DS₂-VASc score in identifying truly low-risk AF patients for stroke was validated in a Korean Nationwide cohort study (n=5,855).²⁹⁾ The CHA₂DS₂-VASc score had the best sensitivity (98.8% vs. 85.7% in the CHADS₂ score and 74.8% in the anticoagulation and risk factor in atrial fibrillation [ATRIA] score) and negative predictive value (98.8% vs. 95.3% for the CHADS₂ score and 93.7% for the ATRIA score) for predicting stroke risk during 5 years of follow-up.²⁹⁾ In another Korean Nationwide population-based study (n=10,846), the CHA₂DS₂-VASc score was superior in identifying truly low-risk patients compared with the CHADS₂ score.³⁰⁾

The CHA₂DS₂-VASc score also showed better performance than the ATRIA score, in predicting ischemic stroke among AF patients from Taiwan (n=186,570).³¹⁾ In this study, the CHA₂DS₂-VASc score had higher c-index than the ATRIA score (0.698 vs. 0.627, DeLong test, p<0.0001) with a significantly improved net reclassification index of 11.7% (p<0.0001). Patients stratified as low-risk in the ATRIA score had a CHA₂DS₂-VASc score ranging from 0 to 7, and annual stroke rates from 1.06% to 13.33%.³¹⁾

Different age threshold for the CHA₂DS₂-VASc score in Asians?

An age ≥65 was set as the threshold of an increased risk of stroke in the original CHA₂DS₂-VASc score in non-Asians. However, such an age threshold may be different in Asians.

In an observational study from Hong Kong, age ≥50 years was associated with a substantial stroke risk, with an annual ischemic stroke risk of 5.87% in patients aged 50–65 years.³²⁾ This result was confirmed in another large Asian nationwide cohort from Taiwan including 186,570 patients with AF, using a cutoff of 50 years, whereby patients could be further stratified into 2 subgroups with different stroke risk (>50 years of age: 1.78%/year vs. <50 years of age: 0.53%/year).³³⁾ Therefore, in this Asian cohort study, age at 50–74 was suggested as 1 point in a modified CHA₂DS₂-VASc score which performed better than the original CHA₂DS₂-VASc score (AUC, 0.71 [0.70–0.71] vs. 0.69 [0.68–0.69], DeLong test p<0.0001), with an improved net reclassification index of 3.39% [2.16–4.59%].³⁴⁾ Thus, among Asian populations, maybe age ≥50 should be treated as a risk factor and should meet the stroke prevention threshold.

Oral anticoagulation for patients with a CHA₂DS₂-VASc score of 1 in males and 2 in females from Asia?

For obtaining a net clinical benefit (NCB), the OAC initiation threshold is 1.7% for annual risk of stroke using VKAs and 0.9% for the NOACs.¹⁾ Indeed, considering the evidence supporting NCB, patients with a CHA₂DS₂-VASc score of 1 in males or 2 in females should receive OAC, as is recommended by guidelines.²³⁻²⁶⁾³⁵⁾³⁶⁾

As demonstrated in an Asian study, in patients with only one non-gender stroke risk factor, OAC may be associated with positive NCB, considering the high stroke risk in these patients (1.96–3.50% in males, 1.91–3.34% in females).³¹⁾³⁷⁾ In another study from Taiwan, in patients with AF aged 20 to 49 and with a CHA₂DS₂-VASc score of 1 in males, the risk of ischemic stroke was 1.30% (0.94-1.71%) per year; which among those with a CHA₂DS₂-VASc score of

2 in females, this risk was 1.40% (1.11–1.67%).³⁶⁾ For these patients, may be NOAC should be considered for stroke prevention considering the treatment threshold of obtaining a positive NCB at a 0.9% annual risk of stroke.

In clinical work, a comprehensive consideration of OAC is needed for these patients with only one non-major risk factor for stroke. Although the CHA₂DS₂-VASc score provides a viable approach to evaluate individuals' risk of stroke, however, the stroke risk is not equal for patients for a particular CHA₂DS₂-VASc score point. For example, well-controlled hypertension may have a lower risk of stroke compared with uncontrolled hypertension. Also, age at 74 would confer higher stroke risk than the age at 65. Therefore, the CHA₂DS₂-VASc score should be regarded as a simple and practical score for everyday practice, and clinicians still need some degree of individualized decision-making.

Guideline recommendations in Asia

Currently, Asian countries have the 2017 consensus of the Asia Pacific Heart Rhythm Society (APHRS) on stroke prevention in AF.²⁴⁾ In the APHRS consensus document, the CHA₂DS₂-VASc score was recommended for the evaluation of stroke risk in Asian patients with non-valvular AF. Patients with at least one non-gender stroke risk factor, i.e., CHA₂DS₂-VASc score ≥ 1 in males or ≥ 2 in females, were recommended for OAC use, and NOACs were recommended over VKA.²⁴⁾ In Japan, the 2013 Japan Circulation Society guideline for pharmacotherapy of AF recommend the CHADS₂ score for risk stratification, and patients with CHADS₂ score ≥ 2 should consider NOACs use.³⁸⁾ Also, in this guideline, OAC with dabigatran or apixaban should be performed in intermediate-risk patients with a CHADS₂ score of 1 (class I). Anticoagulation therapy with rivaroxaban, edoxaban or warfarin should be considered for intermediate-risk patients with a CHADS₂ score of 1 (class IIa).³⁸⁾ In the 2016 guidelines of the Taiwan Heart Rhythm Society and the Taiwan Society of Cardiology for the management of AF, CHA₂DS₂-VASc score was recommended to assess stroke risk in nonvalvular AF.³⁹⁾ In patients with a CHA₂DS₂-VASc score ≥ 1 (beyond female sex alone), antithrombotic therapy should be considered and NOACs were preferred over VKA.³⁹⁾ In the 2018 Korean Heart Rhythm Society guidelines for stroke prevention therapy, the CHA₂DS₂-VASc score was recommended for the assessment of stroke risk.⁴⁰⁾ NOACs or anticoagulation therapy using warfarin should be recommended for antithrombotic therapy when the CHA₂DS₂-VASc score ≥ 2 .⁴¹⁾

A dynamic evaluation of stroke risk

In the real-world, a patient's stroke risk is not static. Increasing age, newly developed comorbidities, such as diabetes mellitus, HF or vascular diseases, may increase individual's risk of stroke.

In an Asian study including 31,039 patients from Taiwan, the mean baseline CHA₂DS₂-VASc score increased from 1.29 to 2.31 during follow-up.⁴²⁾ Nearly 60% of patients experienced an increased CHA₂DS₂-VASc score. Further, the change in risk (referred to as the 'delta CHA₂DS₂-VASc score') performed better in evaluating the stroke risk, when compared with baseline or follow-up CHA₂DS₂-VASc scores.⁴²⁾ Therefore, a dynamic evaluation of stroke risk is necessary and should be performed at each medical contact.⁴³⁾

In Korean nationwide population-based study in 2015 (n=276,246), the median age (from 68 to 71 years) and the prevalence of diabetes mellitus and HF in patients with AF has been increased between 2008 and 2015.²⁾ Also, the high-risk population with a CHA₂DS₂-VASc

score of ≥ 2 increased from 80.2% to 86.8%. The proportion of patient with AF who need to be treated with anticoagulation therapy increased significantly due to aging and increasing comorbidities (i.e., HF and diabetes mellitus).

Another recent nationwide study from Korea (n=167,262) also demonstrated an increasing CHA₂DS₂-VASc score among patients with AF during 10 years of follow-up. There were 46.6% of 'low-risk' patients and 72.0% of 'intermediate-risk' patients re-classified to higher stroke risk categories.⁴³⁾

BLEEDING RISK ASSESSMENT IN THE ASIAN POPULATIONS

It is important to evaluate the risk of bleeding in AF patients taking OAC. Patients with high bleeding risk need more regular review and early follow-up (e.g., 4 weeks rather than 4–6 months), and modifiable bleeding risk factors should be addressed, such as anemia, uncontrolled hypertension, alcohol use, and renal dysfunction.⁴⁴⁾⁴⁵⁾ In terms of bleeding risk prediction, relying on modifiable bleeding risk factors alone is an inferior strategy compared to an established bleeding risk score for risk stratification.⁴⁶⁻⁴⁸⁾

Several bleeding risk evaluation tools have been proposed in the last decade.⁴⁹⁻⁵²⁾ In patients with AF from Asia, the hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio (INR), elderly, drugs/alcohol concomitantly (HAS-BLED) score was compared with other bleeding risk scoring systems in a large cohort study from Taiwan (n=40,450), whereby the HAS-BLED score outperformed other scoring systems, including the HEMORR₂HAGES score, the ATRIA score and the outcomes registry for better informed treatment (ORBIT) score, as evident from the net reclassification index.⁴⁸⁾

In a large cohort of Chinese inpatients with AF (n=4,824), the HAS-BLED score showed good performance in predicting major bleeding events (AUC, 0.72 [0.65–0.79]) and ICH (AUC, 0.83 [0.75–0.91]).⁵³⁾ The HAS-BLED score was significantly better in predicting major bleeding events and ICH, compared with the ATRIA and the ORBIT scores (Delong test, $p < 0.05$, respectively). Additionally, the HAS-BLED score resulted in net reclassification improvement of 17.1–65.5% in predicting major bleeding events and 29.5–67.3% in ICH (all $p < 0.05$).⁵³⁾

Considering the dynamic risk of bleeding, a follow-up HAS-BLED score may be more viable for evaluating individual bleeding risk. In a “real-world” AF cohort study from Taiwan (n=19,566), follow-up HAS-BLED (AUC, 0.63 [0.62–0.64]) and the change in HAS-BLED risk (i.e., ‘delta HAS-BLED score’) (AUC, 0.62 [0.61–0.63]) had higher predictive accuracy of major bleeding compared with the baseline HAS-BLED score (AUC, 0.54 [0.53–0.55]; Delong test, $p < 0.05$ respectively) or simply relying on modifiable bleeding risk factors.⁵⁴⁾

In clinical settings, other risk factors may also need consideration for bleeding risk evaluation. For example, in Korean patients with AF taking NOACs (n=1,353), underweight was found to have an increased risk of major bleeding compared with those with normal weight or overweight to obesity.⁵⁵⁾ Dose reduction in such patients should be considered more in Asian to decrease the risk of bleeding.

EFFECTIVENESS AND SAFETY OF ORAL ANTICOAGULATION IN ASIAN POPULATIONS

The efficiency of OAC in reducing stroke and systemic embolism (SE) has been well identified. Dose-adjusted VKA reduces stroke/SE by 64% and all-cause mortality by 26%, compared with placebo or control.²³⁾ In patients using VKAs, the TTR >65–70% guarantees an optimal OAC quality and need to be maintained. Nevertheless, poor TTR has been associated with worse outcomes.⁵⁶⁾⁵⁷⁾

In the last decade, NOAC has superseded traditional VKAs for stroke prevention in patients with nonvalvular AF, given their quick action, less drug and/or food interactions, and lack of necessity for anticoagulation monitoring. The four available NOACs, i.e., dabigatran, rivaroxaban, apixaban and edoxaban, show good efficacy and safety for stroke prevention in AF patients in large randomized trials.¹⁴⁻¹⁷⁾ The good performance of NOACs in randomised trials has been complemented and augmented by so-called ‘real-world’ evidence from large post-marketing observational cohorts.⁵⁸⁻⁶⁰⁾ Importantly, all the NOACs were associated with significantly reduced risk (25–82%) for ICH shown in different subgroups of patients.⁶¹⁾⁶²⁾ The efficacy and safety of NOACs among Asian populations with AF have also been demonstrated in subgroup analysis from the major trials (**Table 1**).¹⁴⁻¹⁷⁾¹⁹⁻²²⁾⁶³⁾

In a subanalysis of the RE-LY study, dabigatran had better (150 mg) or similar (110 mg) efficacy compared with warfarin (**Table 1**).¹⁹⁾ Also, dabigatran 150 mg was associated with a 43% reduced major bleeding, 60% reduced ICH, and 40% reduced total bleeding (hazard ratio [HR], 0.60 [0.51–0.70]) amongst Asian patients. Dabigatran 110 mg was associated with a 43% reduced major bleeding, 80% reduced ICH and 52% reduced total bleeding (HR, 0.48 [0.40–0.56]).¹⁹⁾ Further, dabigatran 150 mg in Asians had a greater NCB compared with non-Asians (p interaction, 0.004).¹⁹⁾

In the ROCKET-AF trial, 932 patients with AF were enrolled in East Asia.²⁰⁾ Rivaroxaban had a similar risk of stroke/SE compared with warfarin (HR, 0.78 [0.44–1.39]).²⁰⁾ Also, rivaroxaban had a similar risk of major or nonmajor clinically relevant bleeding risk compared with

Table 1. Efficacy and safety of NOACs in Asians from the randomised trials

Study (No. of Asians)	NOACs	Ischemic stroke		Stroke/SE		Major bleeding		Intracranial hemorrhage		All-cause mortality	
		Risk*	HR	Risk*	HR	Risk*	HR	Risk*	HR	Risk*	HR
RE-LY ¹⁹⁾ (n=2,782)	Dabigatran 150 mg	1.12% vs. 2.02%	0.55 (0.32–0.95)	1.39% vs. 3.06%	0.45 (0.28–0.72)	2.17% vs. 3.82%	0.57 (0.38–0.84)	0.45% vs. 1.10%	0.40 (0.18–0.92)	4.01% vs. 5.09%	0.78 (0.57–1.07)
	Dabigatran 110 mg	2.05% vs. 2.02%	1.01 (0.63–1.61)	2.50% vs. 3.06%	0.81 (0.54–1.21)	2.22% vs. 3.82%	0.57 (0.39–0.85)	0.23% vs. 1.10%	0.20 (0.07–0.60)	5.01% vs. 5.09%	0.98 (0.73–1.32)
ROCKET-AF ²⁰⁾ (n=932)	Rivaroxaban	2.12% vs. 2.24%	Not given	2.63% vs. 3.38%	0.78 (0.44–1.39)	3.44% vs. 5.14%	Not given	0.59% vs. 2.46%	0.24 (0.08–0.71)	2.58% vs. 3.57%	0.73 (0.41–1.27)
J-ROCKET AF ⁶⁴⁾ (n=1,278)	Rivaroxaban	Not given	0.40 (0.17–0.96)	1.26% vs. 2.61%	0.49 (0.24–1.00)	3.00% vs. 3.59%	0.85 (0.50–1.43)	0.8% vs. 1.6%	Not given	Not given	Not given
ENGAGE AF-TIMI 48 ²¹⁾ (n=1,943)	Edoxaban 60 mg	0.80% vs. 1.31%	0.64 (0.31–1.32)	1.34% vs. 2.62%	0.53 (0.31–0.90)	2.86% vs. 4.80%	0.61 (0.41–0.89)	0.60% vs. 1.92%	0.31 (0.15–0.66)	1.73% vs. 2.77%	0.63 (0.40–0.98)
	Edoxaban 30 mg	2.26% vs. 1.31%	1.77 (1.01–3.10)	2.52% vs. 2.62%	0.93 (0.63–1.54)	1.59% vs. 4.80%	0.34 (0.21–0.54)	0.46% vs. 1.92%	0.24 (0.11–0.56)	1.84% vs. 2.77%	0.66 (0.42–1.02)
ARISTOTLE ²²⁾ (n=1,993)	Apixaban 5 mg	2.22% vs. 1.90%	1.17 (0.74–1.85)	2.52% vs. 3.39%	0.74 (0.50–1.10)	2.02% vs. 3.84%	0.53 (0.35–0.80)	0.67% vs. 1.88%	0.36 (0.18–0.71)	2.86% vs. 2.81%	1.02 (0.70–1.50)

Numbers in bold stands for significance.

ARISTOTLE = Apixaban versus Warfarin in Patients with Atrial Fibrillation; ENGAGE AF-TIMI 48 = Effective Anticoagulation with factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48; NOAC = non-vitamin K antagonist oral anticoagulant; RCT = randomized controlled trial; HR = hazard ratio; J-ROCKET AF = Rivaroxaban vs. Warfarin in Japanese Patients with Atrial Fibrillation; RE-LY = Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET-AF = Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation; SE = systemic embolism.

*Annual incidence, NOACs vs. warfarin.

warfarin (HR, 1.01 [0.79–1.30]).²⁰⁾ In the Rivaroxaban vs. Warfarin in Japanese Patients with Atrial Fibrillation (J-ROCKET AF) trial conducted in Japan (n=1,278), rivaroxaban had similar stroke/SE rates compared with warfarin (**Table 1**), while the risks of major bleeding and non-major clinically relevant bleeding (HR, 1.20 [0.92–1.56]) were comparable between the rivaroxaban and warfarin groups (**Table 1**).⁶⁴⁾

In a subanalysis of the Effective Anticoagulation with factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial, 1,943 patients with AF were recruited from East Asia, including Japan, China, Taiwan and South Korea.²¹⁾ Compared with warfarin, edoxaban 60 mg was associated with a 47% reduced risk of stroke/SE²¹⁾. Edoxaban 30 mg had a similar risk of stroke/SE compared with warfarin. The risk of major bleeding was significantly reduced by edoxaban (39% in edoxaban 60 mg and 66% in edoxaban 30 mg) compared with warfarin (**Table 1**).²¹⁾

In the ARISTOTLE trial, 1,993 patients with AF were from East Asia. Apixaban 5 mg had a similar risk of stroke/SE in East Asians and a 47% significantly reduced risk of major bleeding.²²⁾ In addition, a 29% reduced risk of major bleeding or clinical relevant nonmajor bleeding with was observed in apixaban treated group.²²⁾

These trial data are supported by real-world studies. In a real-world study from the Korean National Health Insurance Service database (n=34,833), NOACs (n=11,611) had similar risk of ischemic stroke (HR, 0.98 [0.78–1.22]) and lower risk of ICH (HR, 0.50 [0.36–0.68]) compared with warfarin. All-cause mortality was significantly lower in patients taking dabigatran (HR, 0.52 [0.39–0.68]) or apixaban (HR, 0.32 [0.18–0.53]).¹⁸⁾

The comparison of the performance of NOACs in Asians and non-Asians was also reported in a recent meta-analysis using aggregate data from phase III clinical trials.⁶⁵⁾ When compared with VKAs, standard-dose NOACs reduced stroke/SE more in Asians than in non-Asians (odds ratio [OR], 0.65 [0.52–0.83] vs. 0.85 [0.77–0.93]; p interaction, 0.045). Standard NOACs were also associated with a 20% reduced all-cause mortality compared with VKAs in Asians (OR, 0.80 [0.65–0.98]).⁶⁵⁾ Also, standard-dose NOACs had lower major bleeding (OR, 0.57 [0.44–0.74] vs. 0.89 [0.76–1.04]; p interaction, 0.004) and hemorrhagic stroke (OR, 0.32 [0.19–0.52] vs. 0.56 [0.44–0.70]; p interaction, 0.046). An increased risk of GI bleeding was only observed in non-Asians (OR, 1.44 [1.12–1.85]) but not in Asians (OR, 0.79 [0.48–1.32]) (p interaction, 0.041).⁶⁵⁾

In a retrospective Japan cohort study with propensity-matched comparison (n=11,972 for patients on apixaban and warfarin, respectively), apixaban was associated with significantly lower risk of any bleeding (HR, 0.81 [0.73–0.90]), major bleeding (HR, 0.66 [0.51–0.85]) and stroke/SE (HR, 0.64 [0.48–0.85]) compared with warfarin.⁶⁶⁾

In a recent study, including 1,834 patients with non-valvular AF from Korea, dabigatran had similar efficacy in reducing stroke/SE. Dabigatran 110 mg was associated with lower risk of major bleeding (HR, 0.19 [0.07–0.55]). In this study, the number of patients in dabigatran 150 mg was 294 compared with 550 in dabigatran 110 mg group and 990 in warfarin group, which may undermine the safety profile of dabigatran 150 mg.⁶⁷⁾

Recently, in a randomized, multicenter study from Korea (n=183), the efficacy and safety of rivaroxaban were compared with warfarin among patients experienced recent mild AF-

related stroke within the previous 5 days. During 4 weeks of follow-up, rivaroxaban showed no differences in primary endpoint (composite of new ischemic lesion or new ICH seen on results of magnetic resonance imaging) (relative risk [RR], 0.91 [0.69–1.20]) and new ICH (RR, 1.10 [0.70–1.71]) compared with warfarin.⁶⁸⁾

In the real-world setting, choosing the standard or low-dose of NOACs is highly subjective at the level of clinician.⁶⁹⁾ In the SAKURA AF registry (n=3,266), 20–30% of NOAC users received an inappropriate reduced dose of NOAC.⁷⁰⁾ However, a reduced dose of NOACs should not be encouraged for general patients. In a meta-analysis of 3,155 Asian patients enrolled from the RE-LY and ENGAGE AF trials, standard-dose NOACs were associated with significantly reduced risk of stroke/SE and ischemic stroke compared with low-dose NOACs (RR, 0.62 [0.45–0.85] for stroke/SE; RR, 0.55 [0.38–0.79] for ischemic stroke); however, rates of major bleeding (RR, 1.31 [0.74–2.33]), ICH (RR, 1.54 [0.72–3.30]), and life-threatening bleeding (RR, 1.49 [0.87–2.55]) with the two dosing regimens were similar.⁷¹⁾ Also, only certain clinical risk criteria justify dose reduction.

LEFT ATRIAL APPENDAGE OCCLUSION IN ASIAN POPULATIONS

Left atrial appendage (LAA) has been considered as the major site of clot formation in AF. Occlusion of the LAA was therefore suggested to reduce stroke risk in patients with non-valvular AF.

In the WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation (PROTECT-AF) study, the annual primary efficacy event (stroke/SE and cardiovascular death) rate was 3.0% in the left atrial appendage occlusion (LAAO) group (n=463) and 4.9% in the warfarin group (n=244) (RR, 0.62 [0.35–1.25]), the annual primary safety endpoint (major bleeding, pericardial effusion, and device embolization) rate was higher in the LAAO group compared with warfarin group (7.4 per 100 patient-years vs. 4.4 per 100 patient-years; RR, 1.69 [1.01–3.19]).⁷²⁾ In the WATCHMAN Left Atrial Appendage Closure Device in Patients with Atrial Fibrillation vs. Long-term Warfarin Therapy (PREVAIL) study, LAAO was non-inferior to warfarin for ischemic stroke prevention or SE during 18 months of follow-up. The rate of composite of stroke, SE and cardiovascular/unexplained death was 6.4% in the LAAO group vs. 6.3% in the control group (RR, 1.07 [0.57–1.89]).⁷³⁾

In a patient-level meta-analysis of 5-year outcomes from the PROTECT-AF and PREVAIL studies, LAAO (n=732) was associated with a non-significant increased risk of ischemic stroke/SE (HR, 1.71 [0.94–3.11]), compared with warfarin (n=382). Disabling stroke was lower in the LAAO group (HR, 0.45 [0.21–0.94]). The risk of hemorrhagic stroke was significantly lower in the LAAO group (HR, 0.20 [0.07–0.56]); however, the risks of all-cause major bleeding (including procedure-related) were comparable in the LAAO group and the warfarin group (HR, 0.91 [0.64–1.29]).⁷⁴⁾

Currently, there is limited evidence regarding the effectiveness and safety of LAAO in Asians. Previously, a small size report (n=20) showed that the success rate of LAAO was 95% at two Asian centers.⁷⁵⁾ In this study, one procedure was abandoned because of catheter-related thrombus formation, while one patient experienced coronary artery air embolism. No stroke or death occurred at a mean follow-up of 12.7 months.⁷⁵⁾

In a recent registry of patients with AF from Korea (n=142), including 10 patients with and 132 without LAA thrombus, LAAO was performed in multicenter facilities between 2010 to 2016. In this study, 6 patients experienced periprocedural complications. During the mean 23.2±17.5-month follow-up, 7 major adverse cardiac events occurred (1 cardiovascular death, 6 ischemic strokes).⁷⁶⁾ Another multicenter study in Korea (n=96) demonstrated that during 21.9-month follow-up after LAAO, the incidence of death, stroke, and major bleeding was 5.2%, 4.2%, and 1.0%, respectively.⁷⁷⁾ On transesophageal echocardiography of 93 patients within 6 months after the procedure, 24 residual leaks were observed (25.8%; 2 mild, 18 moderate, and 4 major).⁷⁷⁾

Another single center study from from China included 122 AF patients with CHA₂DS₂-VASc score ≥1 for LAAO using WATCHMAN device.⁷⁸⁾ The mean CHA₂DS₂-VASc score were 4.09 in the primary prevention group and 1.93 in secondary prevention group. The success rate of the procedure was 98.5–100% with a low complication rate (not given). Stroke rates were low in the primary (1.47%) and secondary prevention groups (2.13%).⁷⁸⁾

The safety of LAAO procedures is always a major concern. In the PROTECT-AF study, procedural-related adverse events at 7 days after the procedure occurred in 8.7% of patients, including pericardial tamponade requiring intervention in 4.0%.⁷²⁾ In the Amulet Global Observational Registry (n=1,088), 3.2% of patients experienced major procedural complications, including 1.2% pericardial effusion or tamponade, 0.9% vascular complications, 0.2% periprocedural stroke and 0.2% death.⁷⁹⁾ However, device-related complications may reduce with accumulating operator experience.

When choosing LAAO for patients with AF, the most driven factor would generally be the fear of ICH or reoccurrence of major bleeding. Nevertheless, the NOACs showed a significantly decreased risk of ICH and major bleeding, which may compromise the supporting evidence of choosing LAAO rather than OACs in the general patient with AF. In addition, LAAO cannot eliminate the need for antithrombotic therapy, including a period of peri-procedural anticoagulation and long-term antiplatelet therapy, which is probably no safer than NOACs. Further, LAAO would only aim at reducing the thrombin formation at LAA and has no influence on other clot origins in AF. Also, LAAO induced left atrium size increasing and left ventricular filling pressure need further study.⁸⁰⁾

Therefore, LAAO should only be considered in patients with clear absolute contra-indications for long-term OAC.²³⁾²⁴⁾ Also, the performance of LAAO should be compared with NOACs, considering the later showed significant benefits over warfarin.

CURRENT SITUATION OF ORAL ANTICOAGULATION USE IN ASIA

Over the last decade, in Asia-Pacific countries, the utilization rate of VKA has been around 15–20%.⁸¹⁾ Such situation has improved recently, with the introduction of NOACs. In the Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) registry reported at 2015, OAC use was seen in 57.4% of patients with AF with ≥1 stroke risk factors, including 31.9% on VKAs and 25.5% on NOACs.⁸²⁾ The total OAC use was lower in Asia (55.2%) compared to in Europe (90.1%).⁸³⁾ Amongst those

taking OAC, NOACs were used in about 50.2% of patients in Asia, although still lower than other regions, such as North America 66.5%.⁸³⁾

There are regional differences in OAC use in Asia. In the last decade from 2001 to 2012, in an observational study (n=921) of a relatively rural area, Yunnan Province of southwest China, less than 10% of patients with AF received VKA treatment, which has increased from 0.0% at 2007 to 9.5% at 2012.⁸⁴⁾ During 2011 to 2014, in Beijing, China, a survey involving 32 hospitals and 7,977 AF patients demonstrated OAC use of 36.5% among those with CHA₂DS₂-VASc score ≥ 2 , which was increased from 30.2% at 2011 to 57.7% at 2014.⁸⁵⁾ In a “real-world” observational study from Hong Kong (n=9,727) at 2014, only 19.7% were taking warfarin.⁸⁶⁾ Also, in the same area, among the elderly patients with AF using the same database (≥ 80 years, n=2,339), there was only 23.8% received warfarin treatment.⁸¹⁾

A trend study in Korea between 2000 to 2013 showed that 86.1% of patients with AF had CHA₂DS₂-VASc score ≥ 2 , however, only 39.1% of these patients were taking warfarin.⁸⁷⁾ In a recent national study of patients with AF from Korea (n=276,246), using the National Health Insurance Service database between 2008 to 2015, most of the patients had CHA₂DS₂-VASc score ≥ 2 (78.2% in 2008 and 83.2% in 2015).⁸⁸⁾ In the whole study population, OAC use increased from 34.7% to 50.6% and NOAC use accounted for 50% of total OAC use.⁸⁸⁾ In a cross-sectional analysis of Korean adults using the 2015 National Health Insurance Service database (n=41,505,679), OAC utilization among AF patients was lower in the suburban/rural regions compared with that observed in the urban regions (48.2% vs. 51.8%, $p < 0.001$).⁸⁹⁾ Furthermore, the AF prevalence and income levels showed a J-shaped curve, whereas NOAC tended to be more commonly prescribed in those with higher income groups. In the Comparison study of Drugs for symptom control and complication prEvention of Atrial Fibrillation (CODE-AF) Registry, 6,275 patients with nonvalvular AF were consecutively enrolled between 2016 to 2017 from 10 tertiary hospitals in Korea.⁹⁰⁾ The mean CHA₂DS₂-VASc score was 2.7 ± 1.7 . OAC was used in 70.1% of patients. Among patients with high stroke risk, OAC rate was 82.7%.⁹⁰⁾

OAC use has improved in Japan over the last decade. In the study using Shinken Database, OAC use increased from 40.7% at 2004 to 55.9% at 2012. Among patients with CHADS₂ score ≥ 2 , OAC use rate was 64.4% during 2010 to 2012. The use of NOAC also significantly increased, with nearly 60% of anticoagulated patients treated with NOACs at 2010–2012.⁹¹⁾ In a recent study from Japan, the Registry of Japanese Patients with Atrial Fibrillation Focused on anticoagulant therapy in New Era (RAFFINE) registry study, including 3,901 patients with AF from 4 university hospitals and 50 general hospitals/clinics from 2013 to 2015, 87.6% of patients received OAC therapy, including 44.6% treated with warfarin, and 43.0% treated with NOACs.⁹²⁾

TTR CONTROL IN ASIANS ON VITAMIN K ANTAGONISTS

Apart from the rate of OAC use, quality of anticoagulation is important for stroke prevention. The TTR is an essential measurement for anticoagulation quality of VKA.⁹³⁾ Effective anticoagulation when using VKA means TTR ≥ 65 –70%. But TTR can be influenced by multiple factors, which have been summarized as the sex, age, medical history, treatment, tobacco use, race risk (SAME-TT₂R₂) score.⁴⁾ A patient on VKA with SAME-TT₂R₂ score > 2 tends to have suboptimal TTR, who may need more frequent INR checks and monitoring or

a switch to NOAC. Non-Westerns, including Asians, have at least 1 point in the SAME-TT₂R₂ score, and tend to have poorer TTR.⁹⁴⁻⁹⁶⁾ The SAME-TT₂R₂ score has been validated in Asian cohorts⁹⁷⁾ and was recommended by the APHRS guidelines.²⁴⁾

Indeed, in a subanalysis of the ENGAGE AF-TIMI 48 trial (n=21,105), the mean TTR was also low (56%) in patients from East Asia, including China, Korea, and Taiwan.⁶³⁾ In a multicenter retrospective observational study in Korea, including 1,230 patients with AF from 16 Korean centers, the mean TTR was 49.1%. None of the 16 centers achieved a mean TTR >60%.⁹⁸⁾ In Thailand, the mean TTR ranged from 40.1% to 62.7% in a cohort study with 433 AF patients.⁹⁹⁾ In Malaysia, during a 6 months follow-up with 184 AF patients, the TTR was 65.1% in a professional anticoagulation clinic and 48.3% amongst a 'general' medical clinic.¹⁰⁰⁾ In Singapore, the mean TTR of AF patients on warfarin was also poor (58%).¹⁰¹⁾

A low TTR in Asians may explain the suboptimal anticoagulation efficacy of VKAs. Indeed, in a study included 1,034 AF patients in China, warfarin did not show better efficacy in stroke prevention compared with aspirin. On the other hand, because of the relatively higher baseline risk of ICH¹⁰²⁾ and lower TTR in Asians, the benefits of VKA in Asia were likely to be compromised. However, NOACs were associated with better NCB compared with VKA among Asians.¹⁰³⁾

A high rate of aspirin uses in Asia

The sole use of aspirin is highly prevalent in many patients with AF in Asia.¹⁰³⁾¹⁰⁴⁾ As is shown in phase I of the GLORIA-AF registry, 49.6% of Chinese AF patients received aspirin alone,¹⁰⁵⁾ which has decreased to 25.8% at 2015.⁸²⁾ In the Registry on cardiac rhythm disORDers (RecordAF-AP) from eight Asian-Pacific countries, aspirin use was more common than VKAs use (56–66% vs. 35–47%).¹⁰⁶⁾ A large cohort study from Taiwan between 2001–2008 also demonstrated a high rate of aspirin use (62%).¹⁰⁷⁾ Also, in Hong Kong, a recent real-world data showed that 61% of patients received aspirin alone.¹⁰⁸⁾ In Korea, the use of aspirin was high, despite consistently decreased from 48.2% to 31.5%.⁸⁸⁾

BARRIERS TO OPTIMISING ANTICOAGULATION USE IN ASIA

Elderly age is a common reason for low OAC use. In a study from China, age ≥75 years was associated with a 74% lower rate of OAC use in patients with AF¹⁰³⁾; however, a large cohort study (n=25,722) in an Asian population demonstrated that among AF patients age ≥90 years, warfarin was associated with a lower risk of ischemic stroke (HR, 0.69 [0.49–0.96]) and a positive NCB. Further, NOACs were associated with even lower risk of ICH (HR, 0.32 [0.10–0.97]) without difference in ischaemic stroke risk compared to warfarin.¹⁰⁹⁾ In a large real-world study using the Korean National Health Insurance Service database, among patients age ≥75 years, NOACs were associated with similar ischemic stroke (HR, 1.10 [0.80–1.49]) but reduced risk of ICH (HR, 0.63 [0.40–0.95]) and all-cause mortality (HR, 0.72 [0.59–0.86]) compared with VKA.¹⁸⁾

A recent meta-regression analysis included 26 studies, exploring the effectiveness and safety of OAC in older patients (≥65 years). Warfarin use was superior to no antithrombotic therapy (RR, 0.59 [0.51–0.76]) and aspirin (RR, 0.44 [0.24–0.64]) for stroke/SE prevention.¹¹⁰⁾ NOACs were superior to warfarin for stroke/SE prevention (HR, 0.81 [0.73–0.89]) and were associated with lower risk of major bleeding (HR, 0.87 [0.77–0.97]).¹¹⁰⁾

Many clinicians may have a misunderstanding that aspirin can reduce stroke in AF and often underestimated the risk of bleeding related to aspirin. One study from Japan demonstrated the futility of aspirin in reducing stroke risk among low-risk patients.¹¹¹ In another study from Hong Kong, aspirin showed a non-significant reduction in ischemic strokes, compared with no therapy.⁸⁶

Asian populations were associated with higher risk of ICH compared with the Western populations on VKA, which may also related to a low rate of VKA use.^{3,112} However, such situation could be avoided by using NOACs, which were associated with significantly lower risk of ICH (up to 80%).⁶² Finally, the inconvenience of INR checks in patients taking VKA and lack of anticoagulation clinics may also induce a high rate of aspirin use in Asia. Low persistence and adherence to VKA therapy have been associated with poor outcomes.^{113,114}

CONCLUSION

Stroke prevention in Asian patients with AF has many challenges, yet opportunities for improved care are evident. In many countries, OAC use is suboptimal, with high rates of aspirin or non-treatment, and where VKAs are used TTR is poorly managed.¹¹⁵ The NOACs offer an opportunity to improve efforts for stroke prevention, and modelling projections indicate this would have a major impact in reducing stroke and death, with substantial healthcare benefits.¹¹⁶ We should also be aware of the need for a holistic and integrated approach to managing the 'whole' AF patient, which should be '... as simple as ABC', that is, Avoid stroke with Anticoagulation, Better symptom management with decisions on rate or rhythm control, and Cardiovascular and comorbidity risk management.^{117,118} This is relevant since AF independently increases all-cause mortality and strokes only account for 1 in 10 deaths related to AF, while 7 in 10 deaths are cardiovascular.^{119,120}

Priorities should be to identify the non-treated eligible for stroke prevention, finding those on aspirin and treating them with OAC, and finally identifying those on VKA with poor TTR, and to swop them to NOACs.

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