Strategies for the prevention of ischemic stroke in atrial fibrillation in East Asia: clinical features, changes and challenges

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Summary

East Asian populations exhibit a high burden of atrial fibrillation (AF) and AF-related ischemic strokes. The countries/regions in East Asia have diversities regarding patient characteristics and varying patient care represented by different adherence rates to the ABC (Atrial Fibrillation Better Care) pathway. Two changes, "from non-anticoagulation to direct oral anticoagulants (DOACs)" and "from lower dosing to appropriate dosing DOACs", have been identified in East Asia and have been temporally linked to improved clinical outcomes in AF patients. Additional efforts are necessary to further reduce the stroke risk among AF patients, including increased communication with other specialists/societies, the initiation of prospective studies or clinical trials in Asia, and the implementation of evidence-based holistic or integrated care management based on the ABC pathway.

Keywords: Atrial fibrillation; Oral anticoagulation; ABC pathway; East Asia

Overview

The health hazards and public healthcare costs associated with atrial fibrillation (AF) and AF-related ischemic stroke are significant in East Asia. A recent meta-analysis involving 58 studies from Asia revealed that community- and hospital-based AF prevalence ranged from 0.37% to 3.56% and 2.8%–15.8%, respectively.[1] For instance, in 2020, the prevalence rate of AF in Taiwan was approximately 1.5%, which is projected to increase to 4.0% by 2050.[2] Overall, there were approximately 7.6 million AF patients in East Asia and the Pacific in 1990, and the number has increased to 20.4 million in 2019.[3] Considering an annual risk of ischemic stroke of 3.0% (1.60–4.95%),[1] approximately 600,000 AF patients would experience ischemic stroke annually in this area. Furthermore, the higher than expected incidence of AF in Asian large vessel occlusion registries (51.4% in Japan [RESCUE2 Japan] and 49.2% in Korean [ASIAN KR] registries) would further emphasize the importance to prevent AF-associated ischemic stroke in East Asia.[4]

Compared to non-Asians, Asian AF patients typically exhibit a lower body weight and a lower creatinine clearance.[5] There are also disparities between Asians and White Europeans in terms of their stroke and bleeding risks.[6,7] In the ENGAGE AF-TIMI 48 trial, Asian AF patients experienced higher stroke and bleeding risks than non-Asians, irrespective of whether they were being administered warfarin or the direct oral anticoagulant (DOAC), edoxaban.[5]

Despite these differences, the objective of standard holistic or integrated care management of AF patients should be consistent for Asian and non-Asian AF patients. The AF guidelines of the Asia Pacific Heart Rhythm Society (APHRS) recommended the adoption of the ABC (Atrial Fibrillation Better Care) pathway for structured, optimal patient care.[8,9] Although the 2023 US guidelines introduced the "SOS" concept and the 2024 AF guidelines of the European Society of Cardiology (ESC) transitioned to the "CARE" pathway,[10,11] the fundamental components and concepts remained

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unchanged. These concepts included avoiding stroke, better symptom management through rate or rhythm control, and comorbidity management. The 2021 APHRS guidelines has actually clearly mentioned the "new" E criteria (evaluation and dynamic reassessment) of the CARE pathway, which suggests that the stroke/bleeding risks of AF patients are not static and should be reassessed regularly.[8] Furthermore, the ABC pathway is substantiated by evidence, as it has been evaluated in numerous prospective and retrospective cohorts, including prospective randomized trials (mAFA-II[12] and MIRACLE-AF[13]), as well as post hoc analyses of clinical trials.[14]

In this article, we highlight the clinical features, changes/evolution of utilizations of oral anticoagulants (OACs), and challenges associated with stroke prevention in AF patients in various countries/regions in East Asia and discuss opportunities to further enhance patient care in the context of stroke prevention.

Clinical features of AF patients in different Asian regions

The clinical characteristics of AF patients vary since East Asia comprises different countries with diverse ethnicities and healthcare systems. The "APHRS AF registry" was the first systematic prospective registry of AF patients from multiple countries/regions in Asia. It enrolled in- and outpatients who presented with AF to a cardiologist, and was derived from 52 centers in Hong Kong, Japan, Singapore, South Korea, and Taiwan with a broad mix of tertiary and general hospitals.[15]

Overall, in the APHRS AF registry, the mean age of patients was 68.53 years, with 65.47% being male. Paroxysmal AF was present in 41.88% of patients, and most (64.26%) were asymptomatic (i.e., European Heart Rhythm Association [EHRA] class I), with significant differences noted between countries/regions (Fig. 1). For example, the mean age of AF patients in Hong Kong was 73.59 years compared to 65.28 years in South Korea. Additionally, the comorbidities were diverse, with the highest CHA_2DS_2-VASc scores reported from Hong Kong (mean 3.5) and lowest in Japan (mean 2.03) (Fig. 2). The HAS-BLED score revealed significant variation, with the highest mean in Hong Kong (1.81) and the lowest in Japan (1.08).

These differences in profiles of patients enrolled by cardiologists at medical centers may be indicative of the distinct challenges that each country/region would encounter in relation to AF patient management.

Two changes in stroke prevention strategies in Asia

Stroke risk among AF patients remained unchanged in the era without DOACs.[2,16] Take Taiwan for example, the 1-year risk of ischemic stroke for newly-diagnosed AF patients ranged from 3.84% to 4.48% between year 2000 and 2010 with a trend $P > 0.05$.[2] A significant factor is the underutilization of OACs, a prevalent issue in East Asia.[17–19]

Two changes in stroke prevention in AF were observed following the increased availability of DOACs: (1) **Change 1**: from non-anticoagulation to DOACs; and (2) **Change 2**: from "lower-dose or underdosing" to "higher-dose or appropriate dosing" of DOACs. Table 1 summarizes these two changes in different countries/regions of East Asia.[17,20–24]

In a nationwide study conducted in Taiwan, the prescription rates of OACs within six months for newly diagnosed AF patients increased from 13.6% (2008 Q1) to 35.6% (2015 Q3) and subsequently increased to

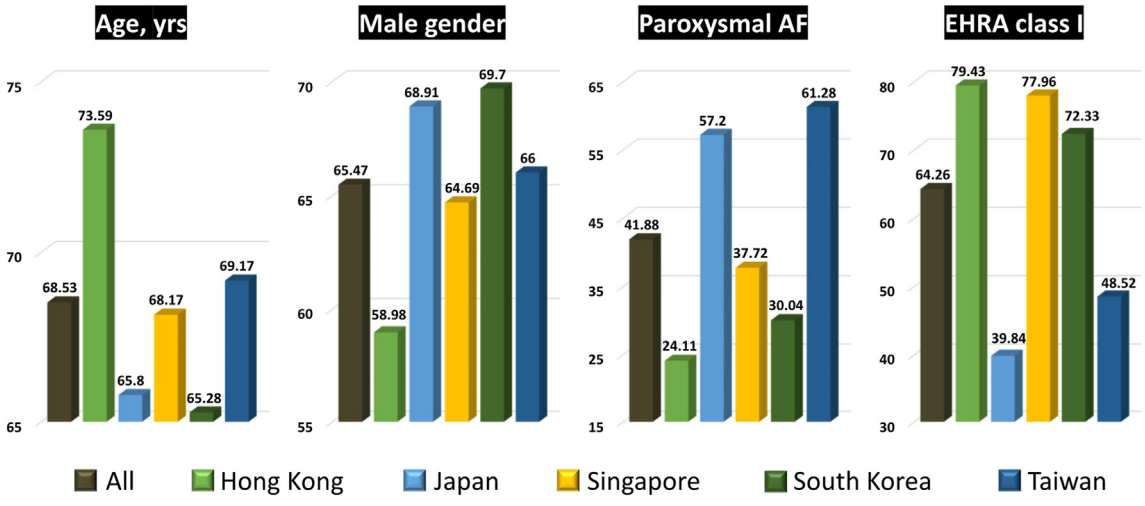

***Fig. 1:* Baseline characteristics of AF patients in the APHRS AF registry**. AF = atrial fibrillation; APHRS = Asia Pacific Heart Rhythm Society; EHRA = European Heart Rhythm Association.

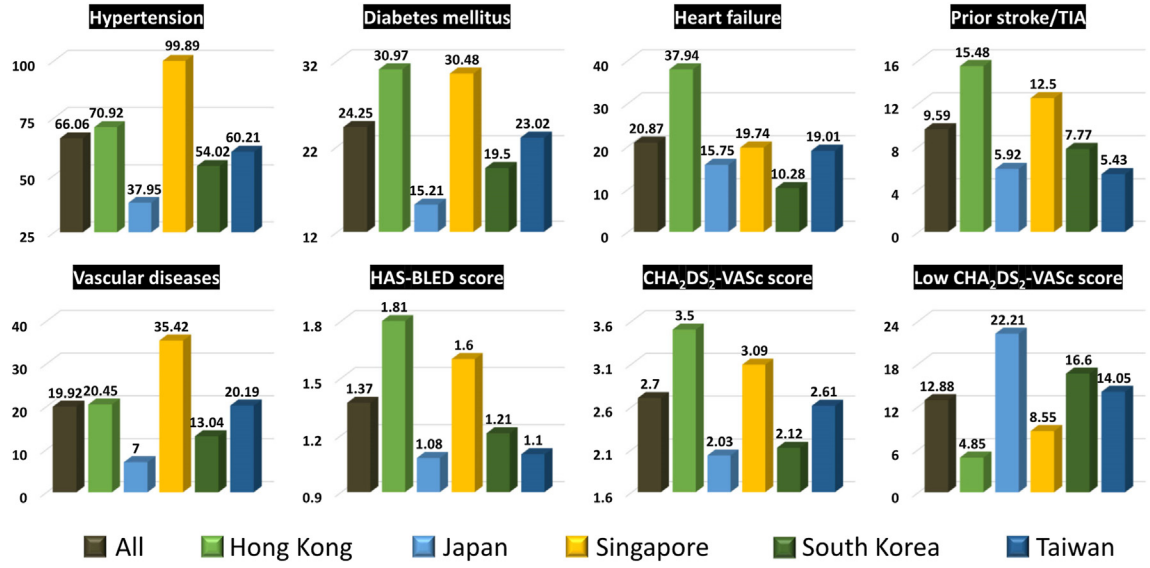

***Fig. 2:* Comorbidities and risk scores of patients with AF in the APHRS AF registry.** AF = atrial fibrillation; APHRS = Asia Pacific Heart Rhythm Society; TIA = transient ischemic attack. A low CHA_2DS_2-VASc score was defined as a score of 0 (male) or 1 (female).

nearly 60% in 2020, with DOACs accounting for around 95% of OAC prescriptions.[17,24] Notably, the 1-year risk of stroke following AF diagnosis gradually declined temporally in association with the increasing DOAC prescriptions (Fig. 3).[24]

China, Japan, and South Korea also reported comparable results regarding the improvement in the condition of AF patients without the use of anticoagulants. As indicated by the Korean nationwide health insurance dataset, South Korea's prescription rate of OACs increased from 44.6% in 2013 to 77.5% in 2022.[23] Registry data from Japan (Fushimi-AF) also revealed a similarly substantial increase in OAC prescriptions.[22] The decline on risk of ischemic stroke in the era of

	Change 1 From non-anticoagulation to DOACs	Change 2 From "lower-dose or underdosing" to "higher-dose or appropriate dosing" DOACs
China	GLORIA-AF in China[20]: Phase II (2013–2014): OACs 21% (15.2% warfarin and 5.8% DOACs) => Phase III (2015–2016): 40.7% (23.5% warfarin and 17.2% DOACs) Shanghai, China 2015–2020[21]: The prescription rate of OACs increased from 19.46% in 2015 to 56.57% in 2020 (warfarin: 18.52% => 24.44%; DOACs: 0.94% => 32.13%)	No report
Hong Kong	The prescription rate of OACs (warfarin or DOACs) for newly-diagnosed AF patients increased from 31.9% in 2002, to 33.1% in 2012, and 67.2% in 2022 The prescription rate of DOACs for newly diagnosed AF increased from 10.8% in 2012, to 60.7% in 2022	No report
Japan	Fushimi AF registry[22]: OACs in 53% (51% warfarin and 2% DOACs) of patients in year 2011 => 70% (18% warfarin and 52% DOACs) in year 2021	The percentages of standard-dose DOACs increased from 14% in year 2012 to 39% in year 2017 among DOAC users
South Korea	Nationwide cohort[23]: OACs in 44.6% of newly-diagnosed AF patients in 2013 => 77.5% in 2022	No report
Taiwan	Nationwide cohort[17,24]: The prescription rate of OACs for newly diagnosed AF patients increased from 13.6% (2008 Q1) to 35.6% (2015 Q3) and further increased to 57.7% in 2020	Lower-dose DOACs accounted for nearly 90% of NOAC prescriptions in year 2012 and the percentages gradually decreased to around 55% in year 2019–2020

AF = atrial fibrillation; DOACs = direct oral anticoagulants; OACs = oral anticoagulants.

***Table 1:* Changes about stroke prevention in atrial fibrillation in East Asia.**

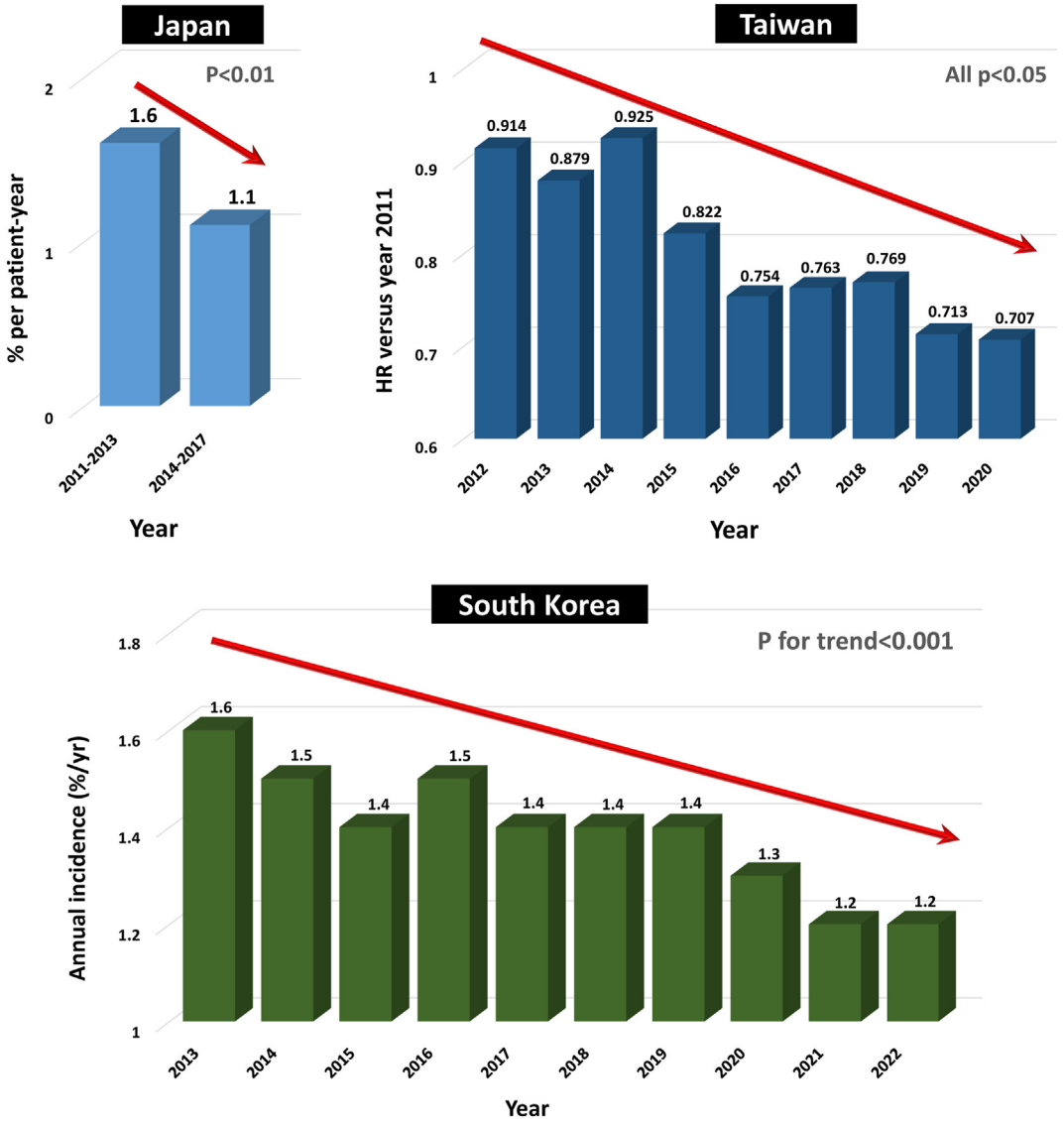

***Fig. 3:* Temporal trends of ischemic stroke in the era of DOACs in East Asia**. DOACs = direct oral anticoagulants; HR = hazard ratio. Data used in this figure were adapted from Akao et al.,[22] Chao et al.,[24] and Lee et al.[25]

DOACs in Japan and South Korea was observed (Fig. 3).[22,25]

In GLORIA-AF registry in China, warfarin continued to make up over 50% of all OAC prescriptions, despite the fact that the absolute increase for DOACs was more substantial (from 5.8% to 17.2%) than for warfarin (from 15.2% to 23.5%).[20] In the more recent report from China focusing on AF patients in Shanghai, the prescription rate of OACs increased from 19.46% in 2015 to 56.57% in 2020 (warfarin increased from 18.52% to 24.44% while DOACs increased from 0.94% to 32.13%).[21] The gaining ground process of DOACs has been accelerated at the end of 2017, when dabigatran and rivaroxaban were added to the list of medicines covered by the medical insurance system in Shanghai.[21] Diverse healthcare systems with varying policies for the reimbursement/coverage of drug costs would appear to significantly influence the prescription choice of OACs.

Appropriate or on-label dosing of DOACs is crucial, as off-label dosing is generally associated with adverse clinical outcomes.[26] In Asia, underdosing is a prevalent practice (approximately 27%) due to the concern of bleeding. However, this practice is associated with a higher risk of ischemic stroke and mortality.[27] With an increase in clinical experience and "real-world" data, physicians may feel more confident in prescribing

DOAC at a "higher" or "appropriate dosing", a phenomenon observed in Taiwan and Japan.[24] Additional data from other Asian countries is required to investigate this trend and its impact on the clinical outcomes in Asian AF patients.

Use of the ABC pathway in Asia

The ABC pathway has been endorsed by APHRS for holistic or integrated patient care due to its well-documented effectiveness in Asian populations. In an analysis of 4013 patients in the APHRS AF registry, 38.6% were adherent to all three main pillars of the ABC pathway, and this was correlated with improved clinical outcomes (defined as a composite of all-cause death, any thromboembolic events, acute coronary syndrome, or percutaneous interventional procedures, and advancing heart failure).[28] Nevertheless, the percentages of AF patients who were adherent to all three domains of the ABC pathway varied across five countries/regions, ranging from 26.3% in Hong Kong to 49.1% in South Korea (Fig. 4).

For the "A" (avoid stroke) domain, the highest adherence rate was noted in Japan (96.3%), followed by South Korea (87.2%), Hong Kong (85.8%), Taiwan (84.8%), and Singapore (83.6%). It should be emphasized that the stroke and bleeding risks of AF patients are dynamic,[29,30] and risk re-assessment is an important part of the "A" domain recommended by 2021 APHRS AF guidelines suggesting that patients' CHA_2DS_2-VASc scores should be reassessed regularly (at least annually and every 4 months if possible).[8]

Notably, the adherence rate to the "C" (comorbidity management) domain was significantly lower than that of the "A" and "B" domains (better symptom management with rate or rhythm control), which only ranged between 31.9% (Hong Kong) and 58.4% (South Korea). In COOL-AF registry, the adherence to "C" domain was associated with a lower composite risk of all-cause death, ischemic stroke/systemic embolism, intracranial hemorrhage (ICH), major bleeding, acute myocardial infarction and heart failure compared to non-adherence (hazard ratio 0.72).[31] This observation underscores the importance of managing comorbidities and healthy lifestyles, which are strongly emphasized by the guidelines. The linkage of mobile health solutions and telemedicine could be helpful for better management of comorbidities. Such a digital health intervention in AF has been prospectively tested in the mAFA-II trial and found to be associated with reduction in adverse clinical events.[12] Also, the prospective randomized trial (MIRACLE-AF) is ongoing to evaluate the effectiveness of the telemedicine-based care model in rural area in China.[13]

Efforts to mitigate stroke risk among AF patients in East Asia

Further initiatives focusing on abovementioned two changes in stroke prevention are required to minimize the stroke risk of AF patients in East Asia:

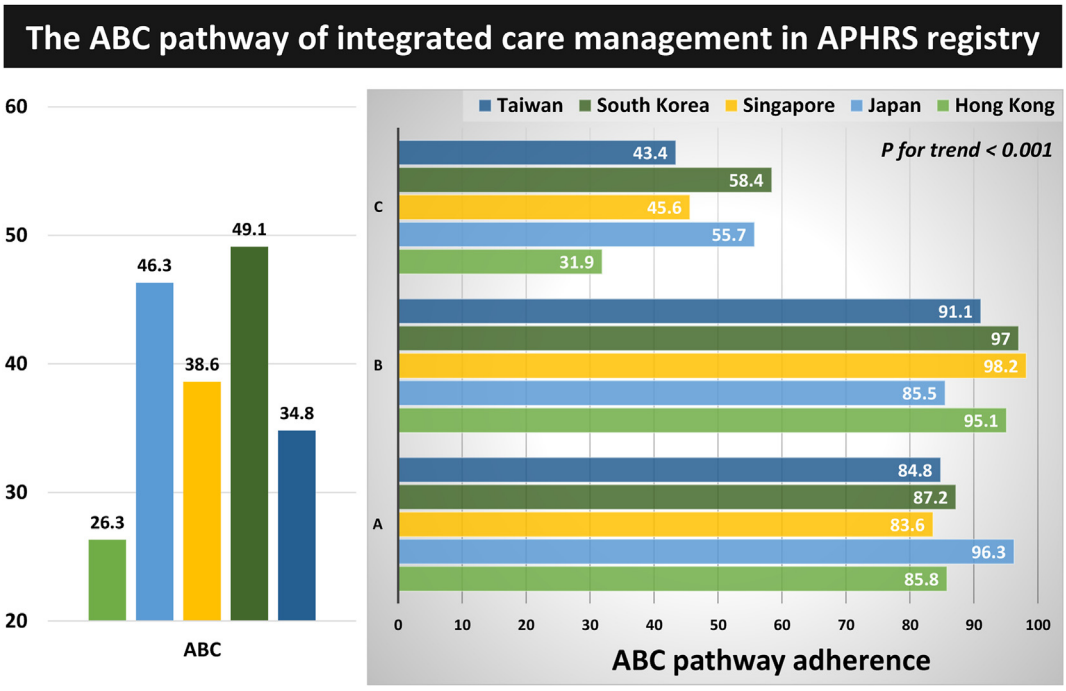

Fig. 4: **Adherence rate among AF patients to the ABC pathway**. APHRS = Asia Pacific Heart Rhythm Society.

Change 1: from nonanticoagulation to OACs

Despite significant improvements in OAC prescriptions (Change 1), many patients still do not receive anticoagulants. Aside from the patient-related factors associated with non-anticoagulation that have been widely recognized in Asians, such as abnormal renal function, anemia, and a history of bleeding, etc.,[32] the "non-patient" factors also warrant consideration. A previous report demonstrated that AF patients managed by cardiologists were more likely to receive rate and/or rhythm control agents and OACs, and their annual risk of ischemic stroke was lower than that of those who were managed by non-cardiologists.[33] Ideally, an AF patient should receive standardized management that is consistent irrespective of the specialists who are responsible for patient care. More efforts are necessary to enhance the awareness of the ABC pathway, particularly among non-cardiologists ("Management of AF: Easy as ABC").

Additionally, Asian physicians refrain from prescribing OACs for AF patients due to their apprehensions regarding bleeding, especially for the risk of ICH which was reported to be higher in Asians than non-Asians.[7,34] Some of these patients were either excluded or rarely included in the randomized trials, such as those with extremely advanced age (>90 years), stage IV chronic kidney disease, and very low body weight (<40 kg). Therefore, there is a relative lack of data regarding the use of OAC in these frail populations. The concern about fall risks in frail patients would also have impacts on physicians' attitudes to not to prescribe OACs.[35] In ARISTOTLE trial, around 5% of AF patients had a history of falling, and they had a more than threefold increased risk of fall during the trial period and a higher risk of major bleeding and ICH.[36] Actually, trauma-related ICH accounted for around 28% of all ICH events in ARISTOTLE trial.[37] Insights into stroke prevention strategies for these patients will be enhanced by conducting of prospective multi-country registries or even randomized trials from Asia.

Despite the importance of appropriate dosing of DOACs and the general recommendation to avoid underdosing, a practical alternative is that even a low-dose DOAC is better than non-anticoagulation, which is clearly proved by the ELDERCARE-AF trial.[38] In the context of administering for a special and frail population, this "compromised flexibility" rather than "strict binary classification (on-label or off-label)" may at least further reduce the non-anticoagulation rate.

In addition to non-anticoagulation, the discontinuation rates of OACs were also higher for Asians than non-Asians, as reported from the GLORIA-AF registry.[39] Although the specific reasons for the discontinuation were unclear, apprehension regarding bleeding in susceptible patients is one of the potential factors. It is crucial to highlight that the continuation of OACs, despite the increased bleeding risk, was associated with a superior clinical outcome.[40] More practical guidelines endorsed by international societies, such as the APHRS, to emphasize the aforementioned points would be beneficial in improving the penetration rate of OACs.

Change 2: from underdosing to appropriate dosing of DOACs

Dosing of DOACs is a complicated issue. Administering DOACs at appropriate doses comprises the gold standard approach for "typical" AF patients who are enrolled in randomized trials. However, the numbers of AF patients enrolled from East Asia in these trials were relatively small (6.5% in ROCKET AF, 10.9% in ARISTOTLE and 9.2% in ENGAGE AF-TIMI 48).[41–43] Therefore, whether the dose of DOACs defined in these trials mainly enrolling non-Asians was actually the "optimal" dose for Asians deserves further studies. Besides, the AF patients we encounter on a daily basis are quite different from those in the "controlled" selective clinical trial setting. Decision-making regarding the administration of DOACs for patients who were not eligible for trial enrollment can be challenging, and it is typically the domain of the art of medicine. The decision was typically based on shared decision-making; however, it should still be substantiated by the available evidence. The dissemination of more consensus opinion documents could facilitate the transmission of precise definitions and statements regarding DOAC administration and the process of making decisions based on the currently available evidence.[26] Meanwhile, it is crucial that additional high-quality studies investigating the dosing issue of DOACs be conducted in East Asia.

Conclusions

East Asia is home to a substantial number of AF patients and a significant burden of AF-associated ischemic stroke. The countries/regions in East Asia have diversities regarding patient characteristics and varying patient care represented by different adherence rates to the ABC pathway. Two changes in stroke prevention in AF, "from non-anticoagulation to DOACs" and "from lower dosing to appropriate dosing DOACs", have been identified in East Asia and have been temporally linked to improved clinical outcomes in AF patients. Additional initiatives are required to further mitigate the stroke risk among AF patients, including enhanced communication with other specialists/societies, the initiation of prospective studies/clinical trials in Asia, and the implementation of evidence-based holistic or integrated care management based on the ABC pathway.

Contributors

Tze-Fan Chao: figures, writing; **Eue-Keun Choi**: literature search, data interpretation, writing; **Yutao Guo**: literature search; **Wataru Shimizu**: literature search, data interpretation; **Hung-Fat Tse**: literature search, data interpretation; **Gregory Y.H. Lip**: data interpretation, writing.

Editor note

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Declaration of interests

Tze-Fan Chao: Speaking fees from Daiichi-Sankyo, Boehringer Ingelheim, Pfizer and Bayer. **Eue-Keun Choi**: Research grants or speaking fees from Abbott, Bayer, BMS/Pfizer, Biosense Webster, Chong Kun Dang, Daewoong Pharmaceutical Co., Daiichi-Sankyo, DeepQure, Dreamtech Co., Ltd., Jeil Pharmaceutical Co. Ltd, Medtronic, Samjinpharm, Samsung Electronics Co., Ltd., Seers Technology, and Skylabs. **Yutao Guo**: None. **Wataru Shimizu**: Research grants from Daiichi-Sankyo and Nippon Behringer, and speaking fees from Daiichi-Sankyo, Nippon Behringer, BMS/Pfizer, Johonson & Johnson, Boston Scientific, Abbott, Japan Lifeline, and Medtronic. **Hung-Fat Tse**: Research grants, consultant and speaking fee from Abbott; Amgen; AstraZeneca; Bayer; Boehringer Ingelheim; Boston Scientific; Daiichi Sankyo; Medtronic; Novartis; Pfizer; Sanofi. **Gregory Y.H. Lip**: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Anthos. No fees are received personally. He is a National Institute for Health and Care Research (NIHR) Senior Investigator.

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