Stroke prevention in atrial fibrillation: An Asian perspective

Chern-En Chiang1; Kang-Ling Wang1; Gregory Y. H. Lip2

1General Clinical Research Center and Division of Cardiology, Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan; 2University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK

Summary

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. In 2050, it is estimated that there will be 72 million AF patients in Asia, accounting for almost 2.9 million patients suffering from AF-associated stroke. Asian AF patients share similar risk factor profiles as non-Asians, except that more Asians have a history of previous stroke. Clinical challenges are evident in the field of stroke prevention in AF, amongst Asians. Existing stroke and bleeding risk scores have not been well-validated in Asians. Asians are prone to bleeding when treated with warfarin, and the optimal international normalised ratio (INR) for warfarin use is yet to be determined in Asians, though Asian physicians tend to keep it in a lower range (e.g. INR 1.6–2.6) for elderly patients despite limited evidence to justify this. In general, warfarin is ‘difficult’ to use in Asians due to higher risk of bleeding and higher stroke rate in Asians than in non-Asians, as shown in randomised controlled trials. Excess of bleeding was not found in Asians when novel oral anticoagulants (NOACs) were used. Besides, the superiority of NOACs to warfarin in reducing thromboembolism was maintained in Asians. Therefore NOACs are preferentially indicated in Asians in terms of both efficacy and safety. Also, some preliminary data suggest that Asian patients with AF might not be the same. Future prospective randomised trials are needed for the selection of NOACs according to different ethnic background.

Keywords

Atrial fibrillation, Asians, major bleeding, novel oral anticoagulants, stroke

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia (1), and carries a four- to five-fold increased risk of stroke. The prevalence of AF is adult Asians is about 1%, lower than that in Caucasians (1–2%) (2, 3).

Since Asia is the most populated area in the world, the burden of AF in Asia may actually exceed that in Western countries, and indeed, it has been estimated that in 2050 there will be 72 million AF patients in Asia (4), more than double the combined numbers of patients from Europe and the United States (5, 6).

The mean/median CHADS2 (Congestive heart failure, Hypertension, Age, Diabetes, Stroke [double]) scores in recent Asian cohort studies has been around 2.0–2.2 (7-9). Based on known distribution of CHADS2 in these cohorts, the annual risk of stroke would be estimated to be at least 4% (notwithstanding the fact that the CHADS2 is not well validated in Asians). Thus, almost 2.9 million patients will suffer from AF-associated stroke in year 2050 in Asia if no oral anticoagulants (OACs) are given. Thus, this would a huge medical and economic burden, necessitating a proper action for stroke prevention in AF patients in Asia.

Risk factor profiles

Congestive heart failure, hypertension, diabetes, and previous stroke/transient ischaemic attack (TIA) are established risk factors for predicting stroke risk in AF, and are components of the CHADS2 score, which was initially derived from the non-warfarin arms of the historical randomised trials conducted approximately 20 years ago (10). There are no comprehensive prospective direct comparisons of risk factor profiles for AF in Asians versus non-Asians.

Data from AF registries and cohort studies, such as the Euro Heart Survey (11), Fushimi AF registry (8), RECORD-AF study (12), RECORD-AF-Asia Pacific registry (13), and REALISE-AF registry (7, 14), or sub-groups of anti-thrombotic trials, such as RE-LY (15, 16), ROCKET AF (17), and ARISTOTLE (18, 19), may provide some important information. About one-third of AF pa-
tients have congestive heart failure, which was slightly more common in non-Asians (except in the RE-LY trial) (▶Figure 1A). Almost 60 to 90% of patients have hypertension, again more common in non-Asians (except in the REALISE-AF registry) (▶Figure 1B). Diabetes mellitus, on the other hand, is generally more common in Asians (except in the ROCK AF trial and the ARISTOTLE trial) (▶Figure 1C).

The major difference is the prevalence of previous stroke or TIA, which is much higher in Asians (▶Figure 1D). Therefore, the risk factor profiles in Asians are similar to non-Asians, except that the percentage of patients with previous stroke is much higher in Asians.

**Asian AF patients have a high risk of stroke**

The CHADS$_2$ score has been used to predict annual stroke risk in patients with non-valvular AF, by identifying ‘high risk’ patients who would be candidates for anticoagulation (10). This scoring system has been validated in various studies from non-Asian patients (10, 20). However, data in Asians are more limited (4), and only small scaled studies have been performed (21).

The CHADS$_2$ score has various limitations (22), being derived from the historical trial cohorts that only randomised <10% of patients screened, and many stroke risk factors were not recorded nor consistently defined. The CHADS$_2$ score has been superseded by the CHA$_2$DS$_2$-VASc score, which includes additional common stroke risk factors, such as age 65–74, vascular disease and female sex (23) (▶Table 1). Various studies have shown how CHA$_2$DS$_2$-VASc is better at defining the ‘low risk’ patients who do not need any antithrombotic therapy (24, 25), and is as good as – and possibly better – than the CHADS$_2$ score in defining patients who develop thromboembolism. Thus, the CHA$_2$DS$_2$-VASc score is the recommended stroke risk score in the recent 2013 guideline statement from the Asia-Pacific Heart Rhythm Society (26).

One study from Taiwan using insurance claim data suggests a lower stroke risk when CHADS$_2$ score was applied (27), but this database might not be able to capture all the stroke events outside the hospital. A recent study from China using a hospital-based database suggested a similar stroke risk in Chinese AF patients compared to Caucasians (9). In this study, the c-statistics for predicting stroke/thromboembolism with CHADS$_2$ and CHA$_2$DS$_2$-VASc were 0.58 (p=0.109) and 0.72 (p<0.001), respectively.
The question of whether anticoagulated Asians have a higher risk of stroke compared to non-Asians may be answered by exploring data from multi-national clinical trials of novel oral anticoagulants (NOACs) when all AF patients in Asian and non-Asian countries were enrolled under the same inclusion and exclusion criteria, and all the risk factors for stroke and CHADS\textsubscript{2} scores were available (15-19).

In the RE-LY trial, there were 2,782 patients from Asian countries (China, Japan, South Korea, Taiwan, Hong Kong, Philippines, Singapore, Malaysia, Thailand, and India), representing 15% of the trial cohort. The mean CHADS\textsubscript{2} score was 2.2, and 69.8% patients had a CHADS\textsubscript{2} score ≥2 (16). The mean CHADS\textsubscript{2} score in Non-East Asians was 2.1, and 67.7% patients had a CHADS\textsubscript{2} score ≥2 (15, 16). The risks of stroke and systemic embolisation for both warfarin and NOAC groups in Asians were generally higher than those in non-Asians (Figure 2A). When Asian and non-Asian patients on warfarin are compared, Asian patients had higher stroke, major bleeding and intracranial bleeding compared to non-Asians, as well as a poorer average Time in Therapeutic Range (TTR) (55%) reflecting poorer quality of anticoagulation control in these patients. This is pertinent given the risk of bleeding and thromboembolism is related to TTR (28, 29).

In the ROCKET AF trial, there were 932 patients from East Asian countries (China, South Korea, Taiwan, Hong Kong). The mean CHADS\textsubscript{2} score of 3.2, and 76.0% patients had CHADS\textsubscript{2} score ≥3 (17). The mean CHADS\textsubscript{2} score in Non-East Asians was 3.47, and 87.0% patients had a CHADS\textsubscript{2} score ≥3 (17). Despite the mean CHADS\textsubscript{2} score being lower and fewer patients had a CHADS\textsubscript{2} score ≥3 in Asians, the risk of stroke and systemic embolisation was higher in East Asians (Figure 2B).

Lastly, in the ARISTOTLE trial, there were 1993 patients from Asian countries (China, Japan, South Korea, Taiwan, Hong Kong, Philippines, Singapore, Malaysia) (19). The mean CHADS\textsubscript{2} score was 2.1, and 60.7% of patients have a CHADS\textsubscript{2} score ≥2 (18, 19). The mean CHADS\textsubscript{2} score in non-East Asians was also 2.1, and 66.7% patients had a CHADS\textsubscript{2} score ≥2. However, the risk of stroke and systemic embolisation was higher in Asians (Figure 2C) (18, 19).

It is not very clear why AF patients in Asia had higher stroke rate. Besides from ethnic differences, there are other possible explanations. In these trials, the percentages of patients with previous stroke/TIA were higher amongst Asians than in non-Asians (RE-LY: 24.2% vs 10.4%; ROCKET AF: 65.0% vs 54.0%; ARISTOTLE: 28.8% vs 18.3%) (Figure 1D). Many studies have shown that the hazard ratio of previous stroke/TIA in predicting future stroke is highest among all the risk factors in the CHADS\textsubscript{2} or CHA\textsubscript{2}DS\textsubscript{2}-VASc scores (23, 30, 31). Another possibility is that more Asian patients had an INR <2.0 than non-Asians (Table 2), as lower INR was not protective against stroke (32). But this may be related to the higher stroke risk in warfarin users, and may not be applied to NOAC users.

In summary, the risk of stroke and systemic embolisation for anticoagulated AF patients appears to be higher in Asians, though Asians had similar mean CHADS\textsubscript{2} scores and fewer patients with higher CHADS\textsubscript{2} score.

**Does the optimal INR in Asians need to be determined?**

The optimal INR range of 2.0–3.0 for warfarin use has been well established in Caucasians (32, 33). Though most of the studies done in Asia suggested a lower range of INR (1.6 to 2.6), they were either retrospective (34, 35), or small-scaled studies (36).

The Japanese AF guidelines recommend an INR of 1.6–2.6 for patients with AF older than 70 years (37), based on a small retrospective cohort study of only 203 patients (38), as well as data from one small randomised trial in secondary prevention setting (36). In the latter trial, Japanese Nonvalvular Atrial Fibrillation-Embolism Secondary Prevention Cooperative Study, 55 and 60 patients with AF were allocated into the conventional (INR 2.2 to 3.5) and low-intensity (INR 1.5 to 2.1) warfarin groups, respectively. Major haemorrhagic complications occurred in 6.6% per year of the conventional-intensity group compared to the low-intensity warfarin group (0% per year, P=0.01).

A recent report from J-RHYTHM registry reiterated that an INR of 1.6–2.6 is safe and effective at preventing thromboembolic
events in Japanese patients with non-valvular AF (39). However, only baseline INR was provided, and TTR was not reported.

In summary, it is generally believed that Asians are prone to bleeding when treated with warfarin (40), and the optimal range of INR for Asians might be narrower than that for non-Asians. We will never know the correct answer until we have large prospective randomized controlled trials in Asia to prospectively compare thromboembolic and bleeding events in different ranges of INR (41).

Appraisal of the evidence for Asians doing badly on warfarin

The efficacy and safety of warfarin in Asians versus non-Asians have not been adequately tested. We now have an opportunity to test it by exploring some data from the recent multinational randomised controlled trials comparing NOACs with warfarin (15, 17, 18). In these trials, the risk of major bleeding and the efficacy

Figure 2: Annual risk of stroke and systemic embolisation for Asians and non-Asians in three clinical trials of novel anticoagulants. A) RE-LY trial (15) and RE-LY Asia sub-analysis (16). B) ROCKET AF trial and ROCKET AF East Asia sub-analysis (17). C) ARISTOTLE trial (18), and ARISTOTLE Asia sub-analysis (19).
in reducing thromboembolic events from warfarin users in Asians could be compared with those in non-Asians with a similar target INR range and known TTR.

There were 2,782 Asian patients in the RE-LY trial (15), 1,781 in the ROCKET AF trial (17), and 2,916 in the ARISTOTLE trial (18). The target INR of 2.0–3.0 was generally followed in all countries, except a lower INR of 2.0–2.6 was allowed in elderly Japanese (age ≥70). Of note, the ROCKET AF trial did not enroll Japanese patients.

The Asian data in these trials were either published (16), or presented in an abstract form (19), or included in the original paper or supplementary appendix (17, 18). Information of INR in different regions in the ROCKET AF trial could be found on page 71 in the FDA document (www.fda.gov/drugs/cardiovascularandrenaldrugsadvisorycommittee/ucm270797.pdf). The Japanese data in the ARISTOTLE was not published, but could be found in the FDA reviews (20155Orig1s000MedR.pdf; http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/20155Orig1s000TOC.cfm).

The distribution of INR in Asians and non-Asians was shown in Table 2. The TTR was generally lower in Asians compared to non-Asians. More Asian patients had an INR <2.0, and fewer had an INR >3.0. These data would suggest that trial investigators in Asia tended to keep an INR in the lower range to avoid bleeding.

The incidence of major bleeding in warfarin users in these 3 trials are shown in Figure 3A (41). Overall Asians had higher risk of bleeding than non-Asians, despite a lower INR, and the Japanese had highest bleeding risk, as shown in the ARISTOTLE trial. The slight lower risk of major bleeding in Japanese in the RE-LY trial might be due to an adjusted INR (2.0–2.6) for age ≥70 (41). Thus, these data could suggest that Asians are perhaps more prone to bleeding from the use of warfarin, even with a lower INR.

Why Asian patients have a higher risk of bleeding on warfarin needs further investigation. From a population-based study, Asians had a two-fold increase in the risk of intra-cerebral haemorrhage compared to white people (42). The risk of intra-cranial haemorrhage increased to four-fold compared to white people when warfarin was used, under a similar intensity of anti-

| Table 2: Distribution of INR in warfarin users in RE-LY, ROCKET AF, and ARISTOTLE trials. |
|-----------------------------------|----------|----------|
|                                   | Asians   | Non-Asians|
| RE-LY                             |          |          |
| TTR (INR=2.0–3.0)                 | 56.5%    | 68.9%    |
| INR<2.0                           | 30.8%    | 15.4%    |
| INR>3.0                           | 8.1%     | 11.6%    |
| ROCKET AF                         |          |          |
| TTR (INR=2.0–3.0)                 | 52.4%    | 55.2%*   |
| INR<2.0                           | 33.9%    | 29.1%*   |
| INR>3.0                           | 13.7%    | 15.7%*   |
| ARISTOTLE                         |          |          |
| TTR (INR=2.0–3.0)                 | 60%      | 67%      |
| INR<2.0                           | 28.6%    | 18.0%    |
| INR>3.0                           | 11.4%    | 15.0%    |

*: overall patients; ARISTOTLE: Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; NNH: number needed to harm for producing one intra-cranial haemorrhage in comparison to historical placebo; NNT: number needed to treat for preventing one stroke or one systemic embolization in comparison to historical placebo; INR: international normalized ratio; RE-LY: Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF: Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; TTR: time in therapeutic range.

Figure 3: Annual risk of major bleeding and thromboembolism in warfarin users from non-Asians, Asians, and Japanese. A) Major bleeding. B) Stroke and systemic embolisation. Data were obtained from RE-LY trial (15), RE-LY Asia sub-analysis (16), ROCKET AF trial and ROCKET AF East Asia sub-analysis (17), ARISTOTLE trial (18), and ARISTOTLE Asia sub-analysis (19). (Modified from Wang et al. (41) with permission).
coagulation (40). Differences in polymorphism of the P450 cytochrome CYP2C9 (43), and the variation in the gene for vitamin K epoxide reductase complex 1 (VKORC1) may affect the optimal dose of warfarin or patients’ responses to warfarin (44), but cannot explain the excessive bleeding in Asians who had lower INR. The HAS-BLED score, a useful scoring system for the prediction of bleeding (45-47), has not been systemically analysed in the Asian subgroups in these NOACs trials. The prevalence of hypertension was actually lower in Asians than non-Asians (► Figure 1B). Mean age was also lower in Asians than non-Asians (16-19), although history of stroke was more common in Asians (► Figure 1D). Therefore, except for the ethnic difference, the precise cause(s) of more bleeding in warfarin users in Asians who were less intensely anticoagulated still remains to be determined.

The price we perhaps pay for keeping INR in lower range in Asia is an increased risk of thromboembolic events, as shown in ► Figure 3B. This finding is echoed by a recent meta-analysis of warfarin use, in which the risk of stroke and systemic embolism in Asians was 70% higher than non-Asians (48). Indeed, warfarin is difficult to be used properly in Asians, and both bleeding and thromboembolism rates are generally higher than non-Asians.

NOACs are preferentially indicated in Asians

The recent development of NOACs, including direct thrombin inhibitor (dabigatran) and factor Xa inhibitors (rivaroxaban and apixaban), can potentially circumvent many drawbacks of warfarin, especially in Asians. NOACs have predictable pharmacokinetics, and routine monitoring was not needed. In contrast, the variability of the anticoagulation activity of warfarin, especially in Asians, make it difficult to use in clinical practice. As TTR negatively correlated with major bleeding and thromboembolic rate (49), the sub-optimal TTR in Asians (► Table 2) might suggest potential benefits of NOACs in Asians.

The Asian subgroup analysis of the RE-LY trial demonstrated superiority of dabigatran 150 mg bd over warfarin in reducing thromboembolism (16). Indeed, the relative risk reductions in primary endpoints (stroke and systemic embolisation), ischaemic stroke, and haemorrhagic stroke for Asians were numerically greater than those in non-Asians. Also, the risk of major bleeding in the group of dabigatran 150 bd was significantly lower than the warfarin group in Asians, with a greater relative risk reduction than that from non-Asians. In fact, the risk of major bleeding in dabigatran 150 mg bd group in Asians was lower than that in non-Asians (2.17%/year vs 3.52%/year). The lower risk of major bleeding was similarly found in dabigatran 110 mg bd group (2.22%/year in Asians vs 2.99%/year in non-Asians) (16). These data suggest that excess bleeding in Asians was found only in warfarin users, not amongst dabigatran users. Interestingly, there was no signal of increased risk of myocardial infarction or gastrointestinal bleeding as those found in non-Asians (16).

Superiority in both efficacy and safety has also been observed in the Asian subgroup analysis of the ARISTOTLE trial (19). The relative risk reduction in primary endpoints (stroke + systemic embolisation) for Asians were numerically greater than those in non-Asians (~26% vs ~19%). The annual risk of major bleeding from apixaban was 2.02% for Asians and 2.15% for non-Asians. For warfarin users, the annual risk of major bleeding was 3.84% for Asians, and 3.00% for non-Asians. Similar to what we have found in the RE-LY trial, the excess of bleeding in Asians was found only in warfarin users, not in apixaban users. The safety and efficacy signals were not found in the ROCKET AF trial, perhaps suggesting that not all Xa inhibitors are the same. Using historical placebo as a control (10), we can perhaps calculate the number needed to treat (NNT) to prevent a stroke or systemic embolisation, and number needed to harm (NNH) to produce an intracranial haemorrhage in Asians and non-Asians (► Table 3).

Table 3 shows that dabigatran 110 mg bd, dabigatran 150 mg bd, and apixaban 5 mg bd had lower NNT and higher NNH compared to warfarin, favouring their use in Asians in terms of both efficacy and safety. In contrast, the differences in NNT for these NOACs and warfarin were not very remarkable in non-Asians, though NNH was much higher for these NOACs than warfarin. Therefore, preference of NOACs in non-Asians was largely based on safety instead of efficacy.

Are Asians not all the same?

In order to check if all Asians performed equally well on NOACs, we managed to stratify Asians in three different groups, based on the ethnic differences, risk of bleeding, and stroke prevalence: (i) Chinese (Taiwan, Hong Kong, and China), (ii) South and Southeast Asians (India, Philippines, Malaysia, Thailand), and (iii) East Asians (Japan and South Korea).
Figure 4: Event rate of stroke plus systemic embolisation, and major bleeding in whole duration of trial from three clinical trials of novel anti-coagulants in different groups of Asians. SE: systemic embolisation.
We re-analysed efficacy and safety of dabigatran and apixaban, compared to warfarin, in these groups (Figure 4). For the Chinese, either dose of dabigatran seemed to decrease risk of stroke and systemic embolisation. The risk of major bleeding was lower in dabigatran users (Figure 4A). Apixaban seemed not effective in reducing thromboembolism and bleeding in Chinese (Figure 4B).

In South and Southeast Asians, both doses of dabigatran, especially 150 mg bd, seemed to decrease risk of stroke and systemic embolisation. The risk of major bleeding was also decreased by either dose of dabigatran (Figure 4C). Similarly, apixaban performed equally well in reducing thromboembolism and major bleeding in South and Southeast Asians (Figure 4D). For East Asians, both doses of dabigatran seemed to decrease risk of thromboembolism. However, dabigatran 110 mg bd did not reduce the risk of major bleeding compared to warfarin (Figure 4E). Nevertheless, it is possible that the risk of major bleeding in warfarin users in East Asia was under-estimated in the RE-LY trial, due to an adjusted INR of 2.0–2.6 for elderly (≥70 years) in Japan. East Asians respond very well to apixaban in both efficacy and safety (Figure 4F).

**Summarisation**

This is a post-hoc analysis, and the event rate has not been adjusted to annual rate. Future prospective randomised trials are needed to show if Asians are not the same in their responses to NOACs and warfarin.

**Conclusions**

There is a huge burden of AF in Asians. In general, Asian AF patients share similar risk factor profiles as non-Asians, except that more Asians have a history of previous stroke. With a similar CHADS\(^2\) (or CHA\(^2\)DS\(^2\)-VASc) score, Asians have the same or possibly higher risk of thromboembolism. Whilst the optimal INR is yet to be determined in Asians, Asian physicians tend to keep it in a lower range. However, data from recent trials show that warfarin is difficult to use in Asians due to higher risk of bleeding and stroke than non-Asians. The role of validated clinical risk scores (for example, SAMe-TT\(_R\)_R\(_S\)) to help predict those who would do well (or not) on warfarin with a high TTR is uncertain in Asians, and further studies are needed (50–52).

On the basis of current evidence, NOACs are preferentially indicated in Asians in terms of both efficacy and safety of these new drugs. Asians are not necessarily the same. Future prospective randomised trials are required for us to choose NOACs according to ethnic background, as the impact on stroke prevention in Asia may be huge (53, 54).

**Conflicts of interest**

Prof. Chiang has been on the speakers bureau for AstraZeneca, Bayer, Boehringer Ingelheim, Chugai, Daiichi-Sankyo, GSK, MSD, Novartis, Pfizer, Roche, Sanofi-aventis, Servier, Tanabe, Takeda, TTY. Dr. Wang has nothing to disclose. Prof. Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Medtronic, Biotronik, Portola and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, Medtronic, Daiichi-Sankyo and Sanofi Aventis.

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