Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

EDITORIAL

Oral Anticoagulation in Japanese Patients With Atrial Fibrillation

– Insight to the Use of Non-Vitamin K Antagonist Oral Anticoagulants –

Miriam Gómez-Molina, MD; Mariano Valdés, MD, PhD; Francisco Marín, MD, PhD

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. It is an independent risk factor for ischemic stroke.[1] Vitamin K antagonists are highly effective for the prevention of stroke,[2] mainly of ischemic origin, in patients with AF but they have significant limitations. The main pitfall described is the unpredictable anticoagulant response showed by this therapeutic family. Over the last years, non-vitamin K antagonist oral anticoagulants (NOACs), including direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban and edoxaban), have been developed.[3] They have rapid, predictable pharmacokinetics and pharmacodynamics, and minimal food or drug interactions with an easier therapeutic strategy. NOACs have been compared with warfarin and demonstrated that they are at least non-inferior for the prevention of stroke or systemic embolism (some of them even superior to warfarin) and safer in terms of reduction of intracranial bleeding compared with warfarin.

Article p 339

Renewed interest has arisen about the medical and economic burden of AF in Asians. Senoo et al have been concerned about the efficacy and safety of NOACs in this subgroup of patients.[4] There are demonstrated racial differences in the background incidence and types of stroke related to AF. It is well known that AF differs considerably between Asian and non-Asian countries, in terms of epidemiology, clinical profile, and optimal anticoagulation levels (Figure 1). In fact, there is the perception in Japan that cardiovascular events rates are lower and bleeding complications are more frequent than in Western populations.[5] However, the risk of stroke and systemic embolism for AF patients taking warfarin appears to be higher in Asians than non-Asians. On the other hand, antico-

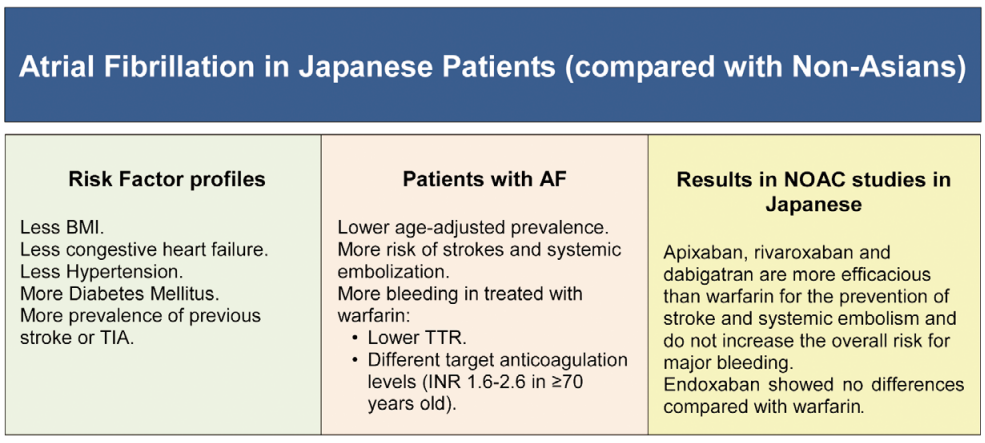

Figure 1. Differential features of Japanese patients with atrial fibrillation compared with non-Asian patients. BMI, body mass index; INR, international normalized ratio; NOAC, non-vitamin K antagonist oral anticoagulant; TIA, transient ischemic attack; TTR, time in the therapeutic range.

Received December 16, 2014; accepted December 16, 2014; released online January 14, 2015
Department of Cardiology, University Hospital Virgen de la Arrixaca Bio-Health Research Institute Virgen de la Arrixaca. IMIB-Arrixaca, Murcia, Spain
Mailing address: Francisco Marín, MD, PhD, Department of Cardiology, Hospital Universitario Virgen de la Arrixaca, Ctra Madrid-Cartagena s/n, 30120, Murcia, Spain. E-mail: fcomarino@hotmail.com
ISSN-1346-9843 doi:10.1253/circj.CJ-14-1378

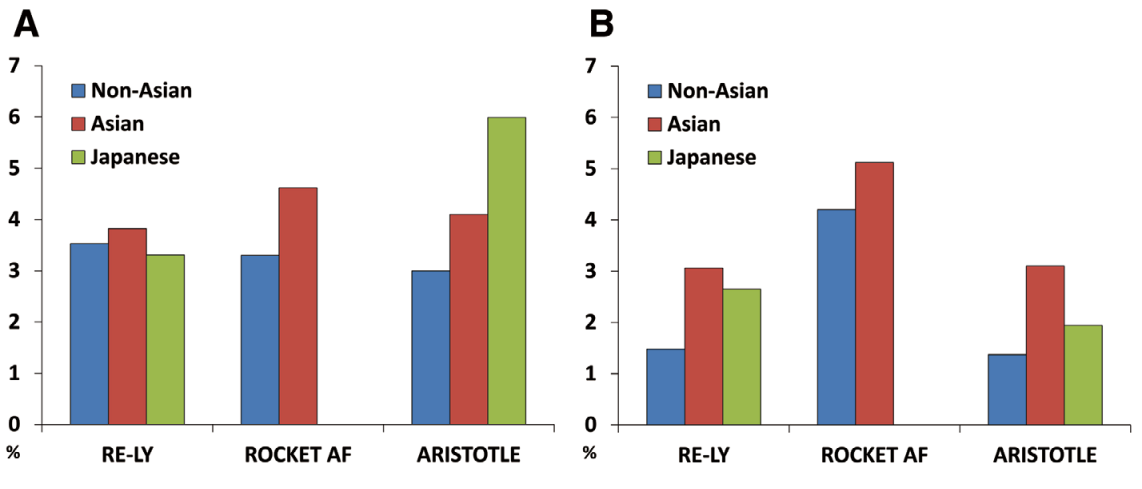

Figure 2. Annual risk of mayor bleeding and thromboembolism in warfarin users from non-Asian, Asian and Japanese patients. (**A**) Major bleeding in 3 multinational randomized constrolled trials. (**B**) Stroke and systemic embolism in 3 multinational randomized controlled trials. (Reproduced with permission from Wang KL, et al.[7])

agulant therapy is not commonly given to Asian patients with AF, probably because of a perceived risk of critical bleeding, which might be higher in this geographic area.[6] Actually, Asian people have a narrower optimal range of the international normalized ratio (INR) for the protection against ischemic strokes than the 2.0–3.0 for Caucasians, because of their increased bleeding tendency.[6,7] Japanese AF guidelines recommend an INR range of 1.6–2.6 for patients with AF older than 70 years,[8] based on the J-RHYTHM Registry.[9] An estimation of the quality of oral anticoagulation is the time in the therapeutic range (TTR). Relatively weak INR control in Japanese patients has been observed, especially in patients aged <70 years, even though the recommended therapeutic range is between 2.0 and 3.0.[10] Most of the time spent out of TTR is usually below the range because of a tendency to keep the INR at the lower range in order to avoid bleeding events.[10] Importantly, keeping the INR in the lower range in Asians may affect them negatively for increased risk of thromboembolic events.[5,6]

It has been questioned if NOACs have the same effect in all Asians. In this issue of this Journal, Senoo et al study the efficacy and safety of NOACs in Japanese patients with AF. Baseline differences between populations have also been explored in the subgroup analysis of the NOAC trials. When patients on warfarin were compared in the RE-LY trial,[11] Asian patients had a higher stroke rate than non-Asians (3.06% vs. 1.48%), as well as a lower average TTR (55%), reflecting poorer quality of anticoagulation control in these patients. Similar results were found in the ROCKET AF trial,[12] where the risk of stroke was higher (3.4% vs. 2.4%) in East Asians despite a lower $CHADS_2$ score (3.2 vs. 3.5). In the ARISTOTLE trial,[13] the risk of stroke and systemic embolism was also higher in Asians (3.39% vs. 1.38%). The Asian subgroup analysis of the RE-LY and the ARISTOTLE trials demonstrated superiority in both efficacy and safety over warfarin. And excess bleeding in Asians was found only in warfarin users. Both trials also showed a higher risk of stroke and systemic embolism in Japanese compared with non-Asians patients.[7] Moreover, the risk of major bleeding was higher in Japanese patients, as shown in the ARISTOTLE trial. The slightly lower risk of major bleeding in Japanese in the RE-LY trial might be related to the adjusted INR (2.0–2.6) for age ≥70 years (**Figure 2**).[7] The ROCKET AF trial did not include a Japanese population. Senoo et al analyzed the Japanese patients from these 3 trials in a 1-year follow-up of 1,940 AF patients and have found that patients randomized to NOACs had a significant 55% relative risk reduction for the composite endpoint of stroke and systemic embolism (RR 0.45, 95% confidence interval [CI] 0.24–0.85) and a non-significant trend towards lower risks for major bleeding (RR 0.66, 95% CI 0.29–1.47), intracranial bleeding (RR 0.46, 95% CI 0.18–1.16) and gastrointestinal bleeding (RR 0.52, 95% CI 0.25–1.08), when compared with warfarin.

Unfortunately, data are scarce regarding edoxaban, another factor Xa inhibitor, and it was not included in this meta-analysis. In the Edoxaban Versus Warfarin in patients with AF ENGAGE AF TIMI 48 trial,[14] edoxaban was non-inferior to warfarin with respect to prevention of stroke and was associated with lower rates of bleeding. In the prespecified superiority analysis for efficacy performed in the intention-to-treat population in the subgroup of Asian patients, the annualized rate of the primary endpoint was 2.37% in the warfarin group, as compared with 1.86% in the high-dose edoxaban group (P for interaction value=0.25) and 2.43% in the low-dose edoxaban group (P for interaction value=0.32). On the other hand, the annualized rate of major bleeding events was 4.12% with warfarin, as compared with 3.51% with high-dose edoxaban (P for interaction value=0.50) and 1.87% with low-dose edoxaban (P for interaction value=0.35). Moreover, the randomized phase II study of edoxaban in Japanese[15] (which included 536 patients) showed no significant differences between edoxaban and warfarin.

In conclusion, NOACs should be preferentially indicated in Asians in terms of both efficacy and safety. All Asians are not necessarily the same, because there are different groups based on ethnic differences, and different bleeding/stroke risks. Among Japanese with AF, NOACs (although not all) are more effective than warfarin for the prevention of stroke and sys-

temic embolism and do not increase the overall risk for major bleeding. However, because of the heterogeneity between the chosen trials, the limited number of patients and the different choice of anticoagulant drugs, future prospective randomized trials are required for us to choose NOACs according to ethnic background and other baseline characteristics of the patients.

Acknowledgments

The authors are supported by RD12/0042/0049 (RETICS) from ISCIII and PI13/00513/FEDER from ISCIII.

Disclosures

Competing Interests: F.M. has received funding for research, consultancy, and lecturing from Abbott, Astra Zeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb/Pfizer, and Daiichi Sankyo. M.G.-M. has no competing interests. M.V. has received funding for research, consultancy, and lecturing from Abbott, and Boston Scientific.

References

1. Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation: Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012; **33:** 2719–2747.
2. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007; **146:** 857–867.
3. Ahrens I, Lip GYH, Peter K. New oral anticoagulant drugs in cardiovascular disease. *Thromb Haemost* 2010; **104:** 49–60.
4. Senoo K, Lau YC, Dzeshka M, Lane D, Okumura K, Lip GYH. Efficacy and safety of non-vitamin K antagonist oral anticoagulants vs. warfarin in Japanese patients with atrial fibrillation: Meta-analysis. *Circ J* 2015; **79:** 339–345.
5. Suzuki S, Yamashita T, Kato T, Fujino T, Sagara K, Sawada H, et al. Incidence of major bleeding complication of warfarin therapy in Japanese patients with atrial fibrillation. *Circ J* 2007; **71:** 761–765.
6. Chiang CE, Wang KL, Lip GYH. Stroke prevention in atrial fibrillation: An Asian perspective. *Thromb Haemost* 2014; **111:** 789–797.
7. Wang KL, Chiang CE. Optimal international normalized ratio for atrial fibrillation in Asians and Japanese: Do we really know? *Circ J* 2013; **77:** 2242–2243.
8. JCS Joint Working Group. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2008): Digest version. *Circ J* 2010; **74:** 2479–2500.
9. Atarashi H, Inoue H, Okumura K, Yamashita T, Kumagai N, Origasa H, et al. Present status of anticoagulation treatment in Japanese patients with atrial fibrillation: A report from the J-RHYTHM Registry. *Circ J* 2011; **75:** 1328–1333.
10. Okumura K, Komatsu T, Yamashita T, Okuyama Y, Harada M, Konta Y, et al. Time in the therapeutic range during warfarin therapy in Japanese patients with non-valvular atrial fibrillation: A multicenter study of its status and influential factors. *Circ J* 2011; **75:** 2087–2094.
11. Hori M, Connolly SJ, Zhu J, Liu LS, Lau CP, Pais P, et al. Dabigatran versus warfarin: Effects on ischemic and hemorrhagic strokes and bleeding in Asians and non-Asians with atrial fibrillation. *Stroke* 2013; **44:** 1891–1896.
12. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; **365:** 883–891.
13. Goto S, Zhu J, Liu L, Oh BH, Wojdyla DM, Aylward P, et al. Efficacy and safety of apixaban compared with warfarin for stroke prevention in patients with atrial fibrillation from East Asia: A subanalysis of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. *Am Heart J* 2014; **168:** 303–309.
14. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013; **369:** 2093–2104.
15. Yamashita T, Koretsune Y, Yasaka M, Inoue H, Kawai Y, Yamaguchi T, et al. Randomized, multicenter, warfarin-controlled phase II study of edoxaban in Japanese patients with non-valvular atrial fibrillation. *Circ J* 2012; **76:** 1840–1847.