Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. It is an independent risk factor for ischemic stroke. Vitamin K antagonists are highly effective for the prevention of stroke, 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. 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.

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. 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. 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-
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. 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. Japanese AF guidelines recommend an INR range of 1.6–2.6 for patients with AF older than 70 years, based on the J-RHYTHM Registry. 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. 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. Importantly, keeping the INR in the lower range in Asians may affect them negatively for increased risk of thromboembolic events.

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, Asian patients had a higher stroke rate than non-Asians (3.06% vs. 1.38%), as well as a lower average TTR (55%), reflecting patients’ tendency to keep the INR in the lower range in order to avoid bleeding events. 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, 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 2.43% with low-dose edoxaban (P for interaction value=0.35). Moreover, the randomized phase II study of edoxaban in Japanese (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.

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