How Can We Bridge the Results of Global Clinical Trials and Region/Country Specific Clinical Practice by Region/Country Specific Registry Data?

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In this issue of the Journal, Kodani et al present an interesting report regarding the thrombotic and bleeding event rates in patients in Japan treated with warfarin in real-world practice against atrial fibrillation (AF) with valvular heart disease (the majority was mitral stenosis). Warfarin is recommended for primary and secondary stroke prevention in cases of valvular and non-valvular AF in various clinical practice guidelines, including those published in Japan. Recommendation is based on the consensus that the risk of bleeding events caused by warfarin therapy is lower than that of thrombotic events prevented by the use of warfarin. Indeed, absolute merit is high in patient populations facing higher thrombotic event risk. In patients with AF, there are subpopulations at high risk of thrombosis, such as patients with mitral stenosis, heart failure, diabetes, etc. Of these risk factors for thrombotic events in AF patients, mitral stenosis is by far the most important. Thus, we have reached the consensus that anticoagulation therapy in mitral stenosis is needed no matter whether the patient has AF or not if that patient has severe mitral stenosis with an enlarged left atrium or a previous history of embolic events. There are several direct oral coagulation factor inhibitors, such as direct thrombin inhibitor and direct Xa inhibitor, registered for the prevention of stroke and systemic embolism in patients with non-valvular AF. Of note, patients with mitral stenosis, which has a clinically meaningful high risk of thrombotic events, have been excluded from all the phase III trials of these direct anticoagulants. Furthermore, except for the J-ROCKET trial of rivaroxaban, the efficacy and safety of new generation direct oral anticoagulants have been compared with warfarin targeting an international normalized ratio (INR) 2–3. This INR target (target INR 2.5) originally comes from the recommendation for mitral stenosis and chronic phase of artificial heart valve. Failure of one clinical trial comparing the efficacy and safety of dabigatran with warfarin in patients with mechanical heart valve led us to consider the difference in the mechanisms of direct enzyme inhibition by new-generation direct oral anticoagulants and the complex multi-target anticoagulation of warfarin. Nevertheless, the present report is the first demonstration of thrombotic and bleeding events in Japanese AF patients with valvular heart disease (mostly mitral stenosis), thus providing important insight for the treatment of these patients in Japan.

Kodani et al show that a target INR of 1.6–2.6 was associated with the lowest risk of the combined event of stroke and major hemorrhage in Japanese patients with valvular AF (Figure). This result was mainly driven by increased bleeding complications in patients with INR >2.6. It has previously been reported that a target INR of 1.6–2.6 may be optimal for preventing recurrent stroke in Japanese patients with non-valvular AF. These results confirm that a lower target INR brings better results in Japanese patients treated by warfarin, which is of great importance because it suggests that the optimal target INR for Japanese patients with AF may be different from the current recommendation in clinical practice guidelines developed based on the results from global trials.

In this context, one might argue that great caution is necessary when using the new-generation oral anticoagulants tested...
in global trials also comparing the efficacy and safety of warfarin with a target INR of 2–3 in nonvalvular AF. If the optimal target INR in Japanese patients is different to that for patients in other regions of the world such as North America and the Europe, we have to recognize a lack of scientific evidence for the use of new-generation oral anticoagulants in Japan. If low intensity anticoagulation is as effective and safer, even in a population with higher thrombotic tendency, the high intensity (INR 2–3) recommended in the current Japanese guideline should be re-written soon to avoid causing harm to Japanese patients. The recommendation of new-generation of oral anticoagulants in comparison with warfarin with a target INR of 2–3 should also be cautiously re-written.

We are assuming that the results shown in the current study reflect real-world clinical practice in Japan. However, we should be careful about potential selection bias even in this kind of registry data. One might argue that any of the randomized clinical trials used to develop new drugs should be conducted against the best standard care in the previous era. In this context, if new-generation anticoagulants are developed in the future, Japan standalone trials comparing the efficacy and safety with warfarin targeting an INR of 1.6–2.6 might be requested before drug registration. Hypothetical standard care of a warfarin target INR of 2–3 does not seem realistic in Japan.

Kodani et al convincingly show that recommendation of INR control in patients with valvular AF based on global experience may be too intense for Japanese patients. By combining with the results of previous report from other Japanese studies, we may conclude that a target INR of 2–3 is higher than optimal for the care of any type of AF in the Japanese population. The current article also shows that even under the current guideline recommendation, almost half of the physicians target lower INRs even in valvular AF. This suggests that current physicians make their decision based on their own experience, not practice guidelines that were developed mainly from the results of experimental clinical trials done around the globe. The results of this study partly demonstrate that “non adherence of practice guideline brings better outcome” and gave us a future challenge for clinical science in Japan and also the East Asian region.\(^1\)

In the field of thrombosis and antithrombotic therapy, there is huge heterogeneity in the incidence of thrombotic, bleeding events and the efficacy/safety of drug intervention.\(^6,7\) In the modern era with low rates of hard endpoints such as cardiovascular death, myocardial infarction and symptomatic stroke, it is reasonable to conduct global trials for clinical hypothesis testing. However, physicians in each region/country should be cautious in translating these clinical trials results to clinical practice in their region/country.\(^8\) Region/country specific interpretation of clinical trial results with region/country specific registries seems extremely reasonable.

**Disclosures**

Shinya Goto received remuneration for attending meetings (presentations), being paid for the time and effort of the activity, which exceeds an annual total of 500,000 yen. per company or organization: Sanofi-Aventis, Astrazeneca. Shinya Goto also received research funds (trust research funds, joint research funds etc) provided by a single company or organization that exceed an annual total of 2,000,000 yen from Sanofi-Aventis. Shinichi Goto has nothing to disclose.

**References**


