Undoubtedly the recent trend for anticoagulation treatment in patients with nonvalvular atrial fibrillation (NVAF) has shifted away from warfarin toward using novel oral anticoagulants (NOACs). Several randomized controlled trials have tested the efficacy and safety of NOACs in comparison with warfarin in patients with NVAF, such as the direct thrombin inhibitor (RE-LY) trial or direct factor Xa inhibitor (ROCKET AF trial) and the ARISTOTLE trial. According to their results, generally NOACs have been more effective at preventing thromboembolism and causing less hemorrhagic events than warfarin in NVAF patients. Thus, although warfarin has quite a long history of clinical use, and NOACs have several disadvantages including their high cost and adverse effects, which are less frequent in warfarin therapy, most clinicians have been changing their minds and are treating NVAF patients with NOACs instead of warfarin.

One major reason why treatment with NOACs has become favorable is that patients treated with warfarin often need to undergo blood sampling to measure the international normalized ratio of the prothrombin time (PT-INR). This process is somewhat troublesome for both the clinician and the patient. In particular, in several outpatient clinics in Japan, blood samples are sent to an offsite laboratory and the resultant PT-INR data will be returned to the original clinics with a significant delay. Accordingly, the adjustment of the dose of warfarin for the relevant patient will also be delayed, sometimes even until the next visit of the patient. In addition, warfarin therapy often tends to be underused because it is believed it increases the risk of intracranial bleeding, especially in Japanese.

For these reasons, the ratio of the period in which the PT-INR is kept within an optimal value (ie, the time in the therapeutic range: TTR) in Japanese patients with warfarin therapy is often inadequate. As shown in Figure 1, the mean TTR in Japanese patients is 58%, which is not very high in comparison with other countries according to the analysis of the warfarin arm of the RE-LY trial. This insufficient TTR will primarily result in a long period of underuse. Needless to say, to obtain an adequate TTR, both at the relevant patient level and for the mean value of the center or institute, is quite important in order to achieve an adequate

Figure 1. Country distribution of the mean time in the therapeutic range (TTR). See text for details. (Reproduced with permission from Wallentin L, et al. Lancet 2010; 376: 975–983.)
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Warfarin for AF

Antithrombotic therapy with warfarin.\textsuperscript{6} Figure 2\textsuperscript{5} depicts the result of another analysis of the RE-LY trial, in which it is revealed that warfarin therapy yielded an almost equal time to the primary outcome in comparison with dabigatran in the centers in which the mean TTR was a high percentage. This result indicates that if the PT-INR is strictly kept within the therapeutic range and an excellent TTR is achieved during the therapy with warfarin, a sufficient clinical effect comparable to that with NOACs can be expected.

Concerning the target PT-INR, the Japanese Guidelines for the Pharmacotherapy of Atrial Fibrillation\textsuperscript{7} recommend maintaining the PT-INR between 2.0 and 3.0 for patients aged <70, and between 1.6 and 2.6 for patients aged ≥70. Is this target PT-INR truly valid in Japanese patients? To resolve this question, an observational cohort study in Japan, namely the J-RHYTHM Registry,\textsuperscript{8} aimed to determine the current status of anticoagulation therapy with warfarin and the optimal anticoagulation levels for preventing thromboembolic events in Japanese patients with AF. In that study, warfarin was used in 6,404 of the 7,406 (86.5\%) NVAF patients enrolled. The authors concluded that an INR of 1.6–2.6 is safe and effective in preventing thromboembolic events in patients with NVAF, particularly those aged ≥70. An INR of 2.6–2.99 is also effective but associated with a slightly increased risk of major hemorrhage. The study gave us the following messages: a special target PT-INR of 1.6–2.6 in Japan is indeed reasonable for the prevention of thromboembolism; a lower PT-INR might not be protective against strokes; and a higher PT-INR could present a small risk of hemorrhages in Japanese patients with AF. Therefore, the importance of strict PT-INR control should be re-emphasized.

In this issue of the Journal, as a strategy to achieve ideal PT-INR maintenance (ie, to obtain an excellent TTR), Okuyama et al\textsuperscript{9} assess the advantage of introducing point-of-care (POC) testing for PT-INR measurements using a device called the CoaguChek (Roche Diagnostics). An improvement in the TTR was expected with the introduction of POC testing because it would overcome the time delay in receiving the PT-INR value at the relevant clinics. In the 8 outpatient clinics in which the CoaguCheck was set up, 109 patients who were treated with warfarin were enrolled to investigate whether the TTR improved after POC testing was introduced. The TTR improved significantly from 51.9\% to 69.3\% in those clinics. The improvement in TTR was especially significant in patients whose TTR was low (<70\%) before the introduction of POC, thus indicating that the improvement in TTR with POC testing was mainly through a reduction in the time spent below the target INR. In addition, they not only enrolled patients with NVAF, but also patients with heart valve replacement or mitral stenosis for whom NOACs were not indicated. Thus, this report emphasized the advantage of POC testing in patients other than those with antithrombotic therapy with warfarin.
NVAF for whom warfarin is prescribed. This beneficial role of POC testing proposed by Okuyama et al\(^9\) gives a bright outlook to continuing the current use of warfarin in patients who need anticoagulation treatment.

Although the leading role in anticoagulation treatment of patients with NVAF has shifted toward NOACs in the present era, warfarin may still have a significant role in anticoagulation treatment because of its economic advantage and utility even for patient groups other than those with NVAF. Some patients with NVAF for whom warfarin has already been prescribed for a long time and do not care about any food limitations or frequent blood sampling, may still prefer warfarin. However, maintaining the target PT-INR should be strictly attempted in the patients on warfarin therapy. From this viewpoint, the benefit of POC testing proposed in the present report by Okuyama et al\(^9\) is quite important.

**References**

1. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; 361: 1139–1151.

2. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in non-valvular atrial fibrillation. *N Engl J Med* 2011; 365: 883–891.

3. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; 365: 981–992.

4. 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.

5. Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalized ratio control for stroke prevention in atrial fibrillation: An analysis of the RE-LY trial. *Lancet* 2010; 376: 975–983.

6. White HD, Gruber M, Feyzi J, Kaatz S, Tse HF, Husted S, et al. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulation control: Results from SPORTIF III and V. *Arch Intern Med* 2007; 167: 239–245.

7. 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.

8. Inoue H, Okumura K, Atarashi H, Yamashita T, Origasa H, Kumagai N, et al. Target international normalized ratio values for preventing thromboembolic and hemorrhagic events in Japanese patients with non-valvular atrial fibrillation: Results of the J-RHYTHM Registry. *Circ J* 2013; 77: 2264–2270.

9. Okuyama Y, Matsu M, Matsuo H, Sakaguchi Y, Takai H, Horiguchi Y, et al. Introduction of point-of-care testing in Japanese outpatient clinics is associated with improvement in time in the therapeutic range in anticoagulant-treated patients. *Circ J* 2014; 78: 1342–1348.