

# Persistence of Oral Anticoagulants in Japanese Patients with Atrial Fibrillation: Non-Vitamin K Antagonist Oral Anticoagulant versus Warfarin

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## Editorial

Atrial fibrillation (AF) is the most common form of tachyarrhythmia and a well-known stroke risk. [1-4]. Many studies have demonstrated that vitamin K antagonists such as warfarin reduce the incidence of stroke in AF patients [4,5]. In a "real world" setting, however, a US cohort study showed that one-fourth of patients initiating warfarin for the first time for AF discontinued treatment within the first year [6]. Adherence to long-term anticoagulation therapy is a key for the prevention of stroke in at-risk AF patients. Since the approval of dabigatran by the U.S. Food and Drug Administration (FDA) in 2010, and in Japan in 2011, non-vitamin K antagonist oral anticoagulants (NOACs) have appeared in clinical practice. Large-scale randomized clinical trials (RCTs) assessing their application have shown NOACs to be as safe and effective as warfarin in patients with non-valvular AF (NVAF). Adherence to medication in RCTs is often high because selected patients are enrolled in these studies and patient adherence is attentively monitored [7].

As reported in our previous study, there was a significantly lower rate of NOAC treatment persistence compared to warfarin treatment persistence in Japanese patients with NVAF [8]. A meta-analysis of RCTs reported that the discontinuation rates of NOACs, warfarin and aspirin for the prevention of stroke in AF patients were not significantly different [9]. A cohort study of NVAF patients in the US found that the persistence rate of patients who were prescribed warfarin was lower than that of patients who were prescribed dabigatran [10]. This cohort's 12-month persistence rate for dabigatran was 63.3%, and a cohort of patients in Dresden had 12-month persistence rates for dabigatran and ribaroxaban of approximately 75% and 85%, respectively [10-12]. The persistence rates for NOACs in our study (dabigatran, 66.0%; ribaroxaban, 65.7%; and apixaban, 81.4%) are comparable to these results, but the persistence rate for warfarin (88.4%) in our study was higher than those in the US cohort studies [10,13-16].

Although the reason for this difference is unclear, it may be partially due to differences in the medical care systems (e.g., in the number of regular cardiology visits at outpatient clinics and in patient adherence to warfarin by frequent assessments of prothrombin time-international normalized ratio (PT-INR) values and subsequent dose adjustments as needed). This may also mean that the time in the therapeutic range (TTR) is generally higher in Japan than other countries [17,18]. The previous Japanese guideline for pharmacotherapy of AF (JCS 2008) recommended that the PT-INR be monitored at least weekly during induction of warfarin therapy and at least monthly after achieving a stable PT-INR (class I) [19]. Therefore, Japanese physicians usually check the PT-INR and frequently adjust doses accordingly, leading to a

high TTR. These actions may enhance patient awareness of anticoagulation and therefore their adherence to warfarin therapy.

Several factors, including those related to the patient, the drug, the disease, and the patient-physician relationship, affect adherence to medication. In practice, we recognize some barriers to adherence. In our study, the most common reason for discontinuation of NOAC treatment was the occurrence of adverse events, including bleeding events; this was similar to the findings for the Dresden cohort [8,11,12]. Minor bleeding associated with anticoagulation therapy is often observed but is not a predictor of major bleeding [20]. Moreover, cultural backgrounds affect patient behavior and adherence. In particular, Japanese patients tend to be more distressed by drug side effects than they are by ineffective drugs. Patient preference as well as patient education and understanding of the treatment are important factors in adherence to anticoagulation therapy in NVAF patients.

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