Suboptimal Anticoagulant Management in Japanese Patients with Nonvalvular Atrial Fibrillation Receiving Warfarin for Stroke Prevention

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Background: Atrial fibrillation (AF) is the most common cardiac arrhythmia, with increasing prevalence in Japan. Although prothrombin time–international normalized ratio (PT-INR) targets for monitoring warfarin therapy in patients with nonvalvular AF (NVAF) are well defined, real-world patient characteristics and PT-INR levels remain unknown among Japanese patients with NVAF who initiate and continue warfarin (warfarin maintainers) versus those who switch from warfarin to direct oral anticoagulants (DOACs; warfarin switchers). *Methods:* Patients with NVAF receiving oral anticoagulants between February 2013 and June 2015 were identified using a nationwide electronic medical record (EMR) database from 69 hospitals in Japan. Demographics and characteristics of patients, PT-INR, time in therapeutic range (TTR), and frequency in range (FIR) of PT-INR between warfarin maintainers and warfarin switchers were assessed. *Results:* A total of 1705 patients met inclusion criteria and were examined (1501 warfarin maintainers versus 204 warfarin switchers). $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores were comparable between groups. However, these scores were significantly higher among warfarin switchers at the time of switching than at the time of warfarin initiation. Furthermore, TTR and FIR of PT-INR were lower in warfarin switchers than in maintainers. Nevertheless, TTR and FIR were below 50% (PT-INR, 1.6-2.6) in both patient groups. *Conclusions:* In this EMR-based clinical study, patients who switched to DOACs had both poor or inadequate PT-INR control and higher risk factors of stroke. Many patients receiving warfarin did not achieve sufficient PT-INR therapeutic range. DOACs could be recommended in Japanese patients with NVAF with inadequate PT-INR control and increased risk of stroke. **Key Words:** Prothrombin time–international normalized ratio—oral anticoagulant—atrial fibrillation—warfarin—time in therapeutic range—DOAC.

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Introduction

Globally, the age-adjusted prevalence of atrial fibrillation (AF) was approximately 33 million in 2010, entailing a major public health burden.[1] As in Western countries, AF prevalence has been increasing in Japan as the population ages; prevalence was 0.56% (720,000) in 2003 and is expected to rise to 1.09% (>1 million) by 2050.[2] The risk of stroke is approximately 5 times higher in patients with AF.[3] Although anticoagulation therapy reduces stroke risk in patients with nonvalvular AF (NVAF),[4-10] substantial undertreatment with anticoagulants such as warfarin persists,[11] possibly because of the need to balance maintenance of high anticoagulation intensity to prevent stroke with the importance of low-intensity anticoagulant treatment to minimize the risk of major bleeding, especially in patients at high risk of bleeding.

Warfarin, a vitamin K antagonist, is routinely used for anticoagulation and is effective in reducing stroke and death risk in patients with NVAF.[7] Despite possessing a number of limitations,[12] including food and drug interactions, the need for close laboratory monitoring to ensure the prothrombin time–international normalized ratio (PT-INR) is maintained within a narrow therapeutic range, and a high risk of bleeding when the high end of this range is exceeded, warfarin has been used extensively for patients with NVAF in clinical practice in Japan.[13] Recently, non–vitamin K-dependent, direct oral anticoagulants (DOACs; dabigatran, rivaroxaban, apixaban, and edoxaban) have become available for the prevention of stroke and systemic embolism in patients with NVAF. Although the risk of major bleeding remains, DOACs offer an improved risk-benefit profile (e.g., less risk of intracranial bleeding) compared with warfarin. Of note, though, risk profiles also differ among DOACs.[14-16] Compared with warfarin, DOACs have a more rapid onset[17]; shorter half-lives, which can aid timing of surgery[17,18]; fewer drug and food interactions[19]; no need for routine laboratory monitoring[17]; and potential for fixed dosing.[19] Further, the efficacy and safety of DOACs have been demonstrated in large randomized controlled trials[4-6,9] and under real-world conditions[8,10,20] in Western populations. However, results may not be entirely applicable to Japanese populations in light of known differences in patient characteristics and clinical outcomes between Asians and Westerners. For example, Asians taking warfarin for AF have higher rates for stroke and bleeding than non-Asians.[21]

According to the latest (2013) Japanese Circulation Society (JCS) guidelines, DOACs should be considered, whenever indicated, as first-line therapy in high- or intermediate-risk patients with NVAF.[22] JCS guidelines also recommended PT-INR targets of 2.0-3.0 in warfarin-treated patients younger than 70 years and 1.6-2.6 for those aged 70 years and older.[22] Previous, large-scale, prospective, observational studies in Japan (such as the Japanese Rhythm Management Trial for Atrial Fibrillation study [J-RHYTHM] Registry) have validated these targets[23-25] and provided other data on the status of anticoagulation therapy in Japan. However, real-world data focusing on patient characteristics and PT-INR levels in Japanese patients with NVAF who started and continued on warfarin (warfarin maintainers) versus those who switched from warfarin to DOACs (warfarin switchers) in the era of DOAC availability are limited. Therefore, the objective of this retrospective observational study was to assess patient characteristics and anticoagulation management in patients, including variation across time of PT-INR levels. Additionally, time in therapeutic range (TTR) and frequency in range (FIR) time were compared between warfarin maintainers and warfarin switchers.

Methods

Data Sources

The nationwide Japanese electronic medical record (EMR) database was established in 2001. It now contains case-based information from regional hospitals in Japan with approximately 3 million unique patient records. It has been used for previous retrospective observational studies to investigate patient demographic and clinical characteristics, medication utilization patterns, and treatment outcomes.[26,27] De-identified data (i.e., patient demographics, drug prescriptions, comorbid conditions, and laboratory test data from in-patient and out-patient settings) were available from 69 hospitals throughout Japan, specifically, 12 facilities with 1-99 beds, 27 facilities with 100-299 beds, 11 facilities with 300-499 beds, 16 facilities with 500-899 beds, and 3 facilities with 900 beds or more. This study was conducted as a database study, informed consent was opt-out style in each institution, and the study design did not require institutional review board approval.

Study Population

For inclusion, eligible patients were 18 years and older as of the index date, which was defined as the date of initiation of any oral anticoagulant (OAC) such as warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban. Eligible patients had at least 1 confirmed diagnosis of AF between January 1, 2001 (database inception) and the index date, and no use of any anticoagulation for at least 4 months before the index date. Patients also had received at least 1 OAC prescription from February 1, 2013 to June 30, 2015 (or the last date of the last data cutoff available at the time of execution of the study; Fig 1). The AF diagnosis was confirmed by any medical record associated with an International Classification of Diseases (ICD-10) code of I48 (AF and flutter), including persistent AF, chronic AF, typical atrial flutter, and atypical atrial flutter.

Patients were excluded if they had 1 or more diagnosis of valvular heart disease (ICD-10 code of I05, I06, I34,