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Original Article

Indications for suboptimal low-dose direct oral anticoagulants for non-valvular atrial fibrillation patients

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ABSTRACT

Background: Direct oral anticoagulants (DOACs) have been developed for stroke prevention in patients with non-valvular atrial fibrillation (NVAF). We conducted a retrospective cohort study of patients with NVAF who were newly treated with DOACs in a real-world clinical setting.
Methods: We retrospectively analyzed patients with NVAF newly treated with one of three DOACs—dabigatran, rivaroxaban, or apixaban—between January 1, 2013, and December 31, 2015.
Results: A total of 670 patients with NVAF who were newly prescribed one of the three DOACs were analyzed; 74 patients (10.9%) received dabigatran, 290 (43.3%) received rivaroxaban, and 306 (45.8%) received apixaban. Fifteen patients had thromboembolic events, almost half of which were due to discontinuation of DOACs. Six patients had major bleeding, although almost all were discharged with good neurological prognoses. A total of 129 patients were treated with a suboptimal low-dose DOAC; none experienced a thromboembolic event as long as the DOAC was taken regularly, and none of the patients in any of the three DOAC groups had major bleeding events.
Conclusions: With good adherence, the clinical course associated with DOACs is comparatively good. In the future, suboptimal low-dose DOAC therapy may serve as an appropriate choice for some patients with a high risk of stroke and bleeding.

1. Introduction

Atrial fibrillation (AF) is associated with an increased risk of stroke and death. In patients who are newly diagnosed with AF, the mortality risk is especially high during the first 4 months [1]. In order to prevent devastating thromboembolic events, anticoagulants are initiated as soon as possible among high-risk patients. However, while anticoagulants can effectively prevent thromboembolism, they may also trigger bleeding events. Therefore, whether patients with a high risk of bleeding should be prescribed anticoagulants remains controversial.

Warfarin and other vitamin K antagonists have long been known to be effective anticoagulants in preventing stroke among patients with non-valvular atrial fibrillation (NVAF), and are recommended for patients with a high risk of stroke [2]. Nevertheless, their use may be troublesome because of their slow onset and their interactions with several foods and drugs, requiring close monitoring of the international normalized ratio (INR) [3]. These disadvantages, as well as others, sometimes lead to poor medication adherence and thus ineffective prevention of stroke [4].

Direct oral anticoagulants (DOACs) were developed to provide an effective and prompt anticoagulant regimen that does not require frequent drug monitoring [5]. Four DOACs have hitherto been found to be at least as effective and safe as warfarin in the prevention of stroke among patients with NVAF [6–9]. Moreover, many studies and reports have compared the efficacy and safety of warfarin and DOACs [10–13]. However, in current clinical practice, concerns persist regarding which DOAC to prescribe and whether they should be continued in patients who have had bleeding events or who are at a high risk of bleeding. These patients are often prescribed suboptimal low-dose DOACs (lower than the recommended dose); however, the efficacy of suboptimal low-dose DOACs has not been established.

Therefore, we compared the baseline characteristics, medication persistence, efficacy, and safety outcomes of patients with NVAF

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who were newly treated with one of three DOACs: dabigatran, rivaroxaban, or apixaban. In addition, we analyzed the clinical time course of patients who were prescribed suboptimal low-dose DOACs in a real-world clinical practice setting.

2. Materials and methods

2.1. Subjects

This was a retrospective cohort study of patients with NVAF who were newly treated with DOACs—dabigatran, rivaroxaban, or apixaban— between January 1, 2013, and December 31, 2015. Since the baseline characteristics of patients prescribed warfarin can be expected to be completely different from those of patients treated with DOACs, patients who were prescribed warfarin were excluded from the present study. In addition, edoxaban was introduced in our hospital at the end of 2014 and only a small number of patients had been prescribed it at the time the present study was started; thus, we also excluded these patients from the present study. All patients were treated in the Department of Cardiology at the NTT Medical Center in Tokyo. Patients who did not return to our center after being prescribed a DOAC (for reasons such as being referred to the local doctor, etc.) were excluded. The study was registered as a retrospective study under the Protocol Registration System of the UMIN Clinical Trials Registry (UMIN000025009). We combined covariate information with the CHA_2DS_2 [14] and CHA_2DS_2-VASc scores [15] to assess stroke risk and the HAS-BLED score [16] as a measure of the risk of bleeding.

2.2. Medication

Decisions regarding prescription and dosages were left to the discretion of the treating physicians, who in principle abided by the drug package insert. Lower-dose DOACs are recommended for elderly patients with chronic kidney disease (CKD) and for those with a high risk of bleeding. In Japan, lower doses of dabigatran should be considered for elderly patients (age $\geq$ 70 years), patients with moderate renal impairment (creatinine clearance 30–49 mL/min), those with concomitant use of interacting drugs (e.g., verapamil), or those with a high risk of bleeding. Lower doses of rivaroxaban should be considered for patients with moderate renal impairment (creatinine clearance 30–49 mL/min), while low-dose apixaban is recommended in patients with at least two of the following: age $\geq$ 80 years, weight $\leq$ 60 kg, or serum creatinine $\geq$ 1.5 mg/dL.

The Rely study [6] demonstrated that, compared with warfarin, low-dose dabigatran was associated with lower rates of major hemorrhage, while high-dose dabigatran was associated with lower rates of stroke and systemic embolism; this indicated that low-dose dabigatran may not be “suboptimal” treatment. However, in the present study, we defined “suboptimal low-dose DOAC” as low-dose DOAC prescribed without an indication for a low dose, according to the drug package insert in Japan; this is because physicians usually abide by current guidelines and drug package inserts in real-world clinical practice.

2.3. Follow-up

Follow-up data were obtained at routine or additional visits to our hospital. The patients were followed until the end of the specified period (2 years after the first prescription, until March 30, 2016), or until discontinuation of anticoagulants (loss to follow-up). In patients who discontinued therapy before the end of the 2-year follow-up, the observation period ended 1 month after the last dose of medication.

2.4. Outcomes

Information regarding the discontinuation of anticoagulants, thromboembolic events, bleeding, and all-cause mortality was obtained from the medical records. Discontinuation events were defined as the cessation of anticoagulants and/or a switch to a different anticoagulant. Temporary discontinuation for reasons such as surgery was not considered as a discontinuation event. Thromboembolic events were diagnosed by doctors in the Department of Neurosurgery and the Stroke Unit at our hospital, and were classified as ischemic stroke, transient ischemic attack (TIA), or systemic embolism. Ischemic stroke was defined as a sudden loss of neurological function lasting more than 24 hours. TIA was defined as a transient episode of neurological dysfunction lasting for less than 24 hours without acute infarction. Bleeding events included major bleeding, clinically-relevant non-major bleeding (CRNM bleeding), and minor bleeding. Major bleeding was defined according to the criteria of the International Society on Thrombosis and Haemostasis as clinically overt bleeding accompanied by a decrease in hemoglobin level of at least 2 g per deciliter, or the requirement of a transfusion of at least 2 units of packed red cells, occurring at a critical site. CRNM bleeding was defined as visible bleeding that did not meet the criteria for major bleeding, but which led to a medical intervention or unscheduled contact with a physician and temporary cessation of treatment. All clinically overt bleeding not meeting the criteria for either major or CRNM bleeding was defined as minor bleeding.

2.5. Statistical analysis

Statistical analyses were performed using SPSS® Statistics version 21 (IBM Corp, Armonk, NY). Data are expressed as mean $\pm$ standard deviation (SD) for continuous variables and as percentages for categorical variables. Student's t-tests were performed for continuous variables and chi-square tests were performed for categorical variables. *P*-values < 0.05 were considered statistically significant. Event curves were created using the Kaplan–Meier method.

3. Results

Between January 1, 2013 and December 31, 2015, a total of 683 patients with NVAF were newly prescribed one of the three DOACs under investigation (dabigatran, rivaroxaban, and apixaban). Approximately 44% of the patients had previously received warfarin. A total of 13 patients never visited our hospital after receiving the DOAC prescription, and were thus excluded from analysis. Therefore, we retrospectively analyzed 670 patients; 74 (10.9%) received dabigatran, 290 (43.3%) received rivaroxaban, and 306 (45.8%) received apixaban.

Baseline characteristics are shown in Table 1. The mean follow-up period was 15.2, 19.6, and 13.4 months in the dabigatran, rivaroxaban, and apixaban groups, respectively. Patients in the apixaban group were older, had a higher proportion of females, and had more CKD than those in the other two DOAC groups. Patients prescribed apixaban had the highest $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores (2.3 ± 1.3, 3.7 ± 1.7, 2.7 ± 1.3, respectively), followed by patients in the rivaroxaban (2.1 ± 1.3, 3.2 ± 1.7, 2.5 ± 1.3, respectively) and dabigatran groups (1.2 ± 1.0, 2.1 ± 1.5, 1.7 ± 1.1, respectively). Overall, 14 patients in the dabigatran group, 27 patients in the rivaroxaban group, and 23 patients in the apixaban group had 0 points on the $CHADS_2$ score; 6 patients in the dabigatran group, 9 patients in the rivaroxaban group, and 7 patients in the apixaban group had 0 points on the CHA_2DS_2-VASc score (data not shown). Patients who were taking

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