The Comparison of Inappropriate-Low-Doses Use among 4 Direct Oral Anticoagulants in Patients with Atrial Fibrillation: From the Database of a Single-Center Registry

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Background: Inappropriate doses of direct oral anticoagulants (DOACs) are often prescribed. This study evaluated the prevalence, outcomes, and predictors of the prescription of inappropriately low doses of 4 types of DOACs in patients with atrial fibrillation (AF). *Methods:* We retrospectively analyzed prospectively collected data from a single-center registry with 2272 patients prescribed DOACs for AF (apixaban: 1014; edoxaban: 267; rivaroxaban: 498; dabigatran: 493). Patients were monitored for 2 years and classified into appropriate-dose (n = 1,753; including appropriate low doses), inappropriate-low-dose (n = 490) and inappropriate-high-dose groups (n = 29). Major bleeding (MB) and thromboembolic events (TEEs) were evaluated. *Results:* The mean age was 72 ± 10 years. The $CHADS_2$ and HAS-BLED scores were 1.95 ± 1.32 and 1.89 ± .96, respectively. Overall, the incidences of MB and TEE were 2.3 and 2.1 per 100-patinet year, respectively. The inappropriate-low-dose group had younger age, heavier body weight, and higher creatinine clearance value than the appropriate-dose group. Multiple logistic regression analyses demonstrated the following independent determinants of the prescription of an inappropriately low dose: apixaban: HAS-BLED score; edoxaban: age; rivaroxaban: age, creatinine clearance value, HAS-BLED score, $CHADS_2$ score, and antiplatelet therapy; dabigatran: age. There were not significant differences in the incidence of major bleeding and stroke/systemic emboli among the inappropriate-low-dose group of 4 DOACs compared with the appropriate-dose group of 4 DOACs. *Conclusions:* In a single-center registry, 23% of patients with AF treated with a DOAC received an inappropriate dose. Several clinical factors, such as age and the creatinine clearance value, can identify patients at risk of under-treatment with DOACs.

Key Words: Direct oral anticoagulant—atrial fibrillation—major bleeding—stroke—systemic embolism

Introduction

Atrial fibrillation (AF) is the most frequently sustained type of arrhythmia; AF affects 1.5%-2% of the general population, and this prevalence increases to 10% at 80 years of age and 18% at 85 years of age.[1-3] Direct oral anticoagulants (DOACs) were developed to overcome some of the limitations associated with vitamin K antagonists, which include an unpredictable anticoagulant response, the need for regular therapeutic monitoring and

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dose adjustments, and interactions with food and drugs. In addition, DOAC therapy has demonstrated higher safety and efficacy in thromboembolic prevention in patients with AF, without an increase in intracranial bleeding.[4-7] Although meticulous dose adjustments are not required for DOACs, cut-off values in the consideration of an appropriate dose selection differ according to age, renal function, body weight, and interacting drugs. Indeed, both age and chronic kidney disease in patients with AF increase the risk of stroke and bleeding during antithrombotic treatment.[8] Therefore, a reduced dose (an inappropriately low dose) of DOAC is sometimes prescribed, based on several patient-specific factors.

The aim of the present study was to compare the clinical outcomes between patients prescribed an inappropriately low dose of DOAC and those prescribed an appropriate dose of DOAC in a single center. Furthermore, we evaluated the prevalence of the prescription of an inappropriately low dose of DOAC, and investigated the factors associated with this prescription.

Methods

Ethical Considerations

The institutional database used in the present study was approved by our local ethics committee, and informed consent was obtained from all patients (Fig 1).

Study Population and Data Collection

For this retrospective analysis, we identified 2272 consecutive patients who were prescribed a DOAC for AF (including paroxysmal AF) between September 2011 and January 2016 at the Tachikawa General Hospital, Nagaoka, Japan. Patients with valvular disease requiring surgery, those with a prosthetic mechanical heart valve, and those with mitral stenosis were excluded from the database. All patients in the DOAC database were included in the analysis.

Collected data included the patients' baseline characteristics including age, sex, body weight, and renal function (creatinine clearance and creatinine levels); history, including comorbidities (coronary artery disease and peripheral artery disease); and clinical outcomes, including those at the 2-year follow-up interval. In addition, the congestive heart failure, hypertension, age ≥75 years, diabetes mellitus ($CHADS_2$) score; and the hypertension, renal disease and liver disease, stroke history, prior major bleeding or predisposition to bleeding, age >65 years, medication usage predisposing to bleeding (HAS-BLED) score were determined.

DOAC Prescriptions

Four DOACs (apixaban [N = 1014], rivaroxaban [N = 498], edoxaban [N = 267], and dabigatran [N = 493]) were prescribed for AF, per the doctor's discretion. The prescription dose was decided with consideration of the manufacturer's labeling recommendations in Japan, which include the following reduced-dose recommendations. For apixaban, a reduced dose is recommended in patients with at least 2 of the following characteristics: age ≥80 years, weight ≤60 kg, or serum creatinine level ≥1.5 mg/dL. For rivaroxaban, a reduced dose is recommended for patients with moderate renal impairment (creatinine clearance of 15-49 mL/min). For edoxaban, a reduced dose is recommended for patients with moderate or severe renal impairment (creatinine clearance of 15-49 mL/min), those with weight ≤60 kg, or those with concomitant use of interacting drugs (eg, verapamil). For dabigatran, a reduced dose is recommended for elderly patients (age ≥70 years), patients with moderate renal impairment (creatinine clearance of 30-49 mL/min), those with concomitant use of interacting drugs (eg, verapamil), or those with a high risk of bleeding. However, an

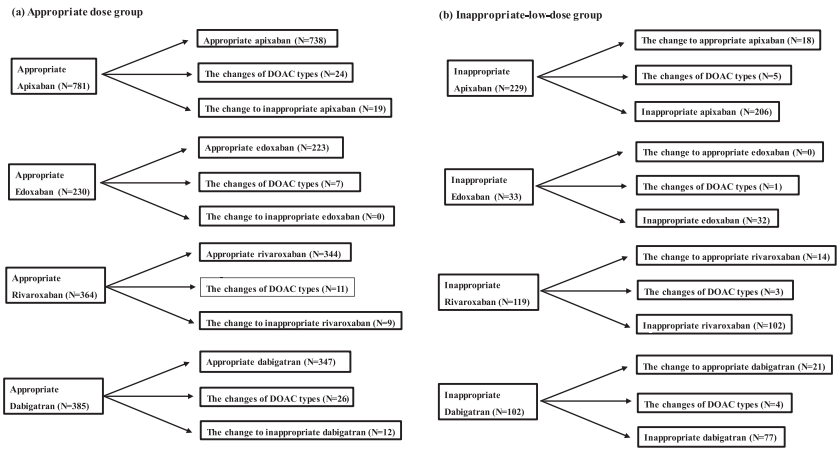

Figure 1. *Changes in oral anticoagulation (OAC) status during 2 years.* ***(a)*** *Changes in OAC status in appropriate dose group during 2 years.* ***(b)*** *Changes in OAC status in inappropriate-dose-group during 2 years.*