The Dose of Direct Oral Anticoagulants and Stroke Severity in Patients with Acute Ischemic Stroke and Nonvalvular Atrial Fibrillation

Yuji Kato, MD, PhD, Takeshi Hayashi, MD, PhD, Norio Tanahashi, MD, PhD, and Masaki Takao, MD, PhD

Background: The severity and the functional outcome of patients with stroke occurring during off-label underdosing of direct-acting oral anticoagulants (DOACs) remain uncertain. *Methods:* We studied 53 consecutive patients with acute ischemic stroke and nonvalvular atrial fibrillation who were treated with DOACs before the onset of stroke. Thirty patients were treated for primary prevention of stroke and 23 patients were treated for secondary prevention. DOAC treatments were categorized into 3 groups based on the following doses: (1) standard-dose group (n = 17), (2) low-dose group (n = 23), and (3) off-label underdose group (n = 13). *Results:* Age was significantly older in the low-dose group than in the standard-dose group (P = .026). The standard-dose group and the low-dose group showed higher CHA_2DS_2–VASc scores (median, 4) compared with the off-label underdose group (median, 3). More than half of the patients had a National Institutes of Health Stroke Scale score of less than 8, and many patients had a good outcome (modified Rankin Scale score ≤1). There were no differences in stroke severity and outcome among the 3 groups. The ratio of being discharged home was the highest in the standard-dose group. *Conclusions:* This study shows that patients who have off-label underdosing of DOACs do not develop more severe stroke and a poorer outcome than those with the recommended dose. Careful attention to recommended doses is required for the full benefits from DOACs. **Key Words:** Off-label underdosing—direct-acting oral anticoagulants—ischemic stroke—atrial fibrillation.

Introduction

Cardioembolic stroke, of which 70% is associated with atrial fibrillation (AF), is preventable with anticoagulant therapy.[1] Many studies have shown that approximately 60% of ischemic stroke is prevented by appropriate anticoagulation.[2] In recent large-scale, randomized clinical trials (RCTs), direct-acting oral anticoagulants (DOACs) have been shown to be at least as safe and effective as dose-adjusted warfarin, despite not requiring routine or frequent laboratory monitoring.[3-6] Because of the results of RCTs and ease in daily clinical practice, DOACs have prevailed worldwide. However, there is an issue regarding DOACs. RCTs, which have shown that DOACs have an efficacy and safety similar to warfarin, have been conducted relatively strictly.[3-6] This finding is different from general practice in which inappropriately decreased doses of drug prescriptions are common.[7]

Previous studies have shown that DOACs result in less severe ischemic stroke, even if it has occurred.[8-10] The reason for this finding may be because causative thrombi are smaller in patients under DOACs. However, the effect

From the Department of Neurology and Cerebrovascular Medicine, Saitama Medical University International Medical Center, Hidaka, Saitama, Japan.

Received October 30, 2017; revision received December 6, 2017; accepted December 23, 2017.

Address correspondence to Yuji Kato, MD, PhD, Department of Neurology and Cerebrovascular Medicine, Saitama Medical University International Medical Center, 1397-1 Yamane, Hidaka, Saitama 350-1298, Japan. E-mail: yujik@saitama-med.ac.jp.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.12.038

of the DOAC dose on stroke severity and outcome is not well known. Patients who have off-label underdosing of DOACs may develop more severe stroke or a poorer outcome than those who have the recommended dose of DOACs.

In the present study, we investigated the characteristics of ischemic stroke under DOAC treatment and compared them with each dose of DOACs (standard dose, low dose, and off-label underdose).

Methods

The present study included 53 consecutive patients with nonvalvular AF who were treated with DOACs before the onset of stroke and then admitted to our hospital for acute ischemic stroke between March 2011 and April 2017. Thirty patients were treated for primary prevention of stroke and 23 patients were treated for secondary prevention. We checked the adherence in taking a medical history as exactly as possible and excluded patients with poor adherence. Nonvalvular AF was defined as the presence of AF without mitral valve disease (mitral valve stenosis) or artificial valve replacement.[11]

For the purpose of the study, DOAC treatments were categorized into 3 groups based on doses as follows: (1) standard-dose group, (2) low-dose group, and (3) off-label underdose group.

The DOAC dose was evaluated based on the manufacturer's labeling recommendations in Japan. For dabigatran, the standard dose is 300 mg/day. Dabigatran does not have definite dose reduction criteria, but a reduced dose (220 mg/day) is suggested for any one of the following: age 70 years or older, creatinine clearance of 30-50 mL/min, history of major bleeding, and use of p-glycoprotein inhibitors. The standard dose of rivaroxaban is 15 mg/day, and a reduced dose (10 mg/day) is indicated when creatinine clearance is 15-50 mL/min. For apixaban, the standard dose is 10 mg/day, and a reduced dose (5 mg/day) is indicated for patients who meet two of the following criteria: body weight of 60 kg or lower, age 80 years or older, and serum creatinine levels of 1.5 mg/dL or higher. The standard dose of edoxaban is 60 mg/day, and a reduced dose (30 mg/day) is recommended for patients with either a body weight of 60 kg or lower or creatinine clearance of 15-50 mL/min. Patients who were prescribed a lower drug dose but did not meet the criteria for dose reduction were grouped in the off-label underdose group. Patients who were prescribed a standard drug dose but met the criteria for dose reduction (off-label overdose) were grouped in the standard-dose group.

We obtained the data from electronic medical charts and summaries and retrospectively reviewed the following variables. The variables included demographic information (age and sex), body weight, body mass index, preadmission modified Rankin Scale (mRS) score, DOAC prescriber (from a university hospital, regional hospital, specialist clinic [cardiology, neurology, or neurosurgery], or general clinic), and medical history. Cardiovascular risk factors were defined as follows: (1) hypertension, a history of using antihypertensive agents, systolic blood pressure of 140 mm Hg or higher, or diastolic blood pressure of 90 mm Hg or higher before or 2 or more weeks after the onset of stroke; (2) diabetes mellitus, use of hypoglycemic agents, random glucose levels of 200 mg/dL or higher, or glycosylated hemoglobin level of 6.5% or higher on admission; (3) dyslipidemia, use of antihyperlipidemic agents, or serum low-density lipoprotein cholesterol levels of 140 mg/dL or higher; (4) current smoking; (5) prior stroke; (6) coronary artery disease, angina, or prior myocardial infarction; and (7) heart failure, a history of congestive heart failure, or an ejection fraction of less than 40%. The prestroke $CHADS_2$ score, the CHA_2DS_2–VASc scores, or the HAS-BLED score was calculated for each patient based on the published guideline.[12-14] Routine blood biochemistry examinations, including levels of D-dimer, brain natriuretic peptide, and serum creatinine, and creatinine clearance (Cockcroft–Gault equation[15]), as well as left atrial dimension and ejection fraction by echocardiographic findings were also evaluated.

Stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS) score. Stroke size and location were assessed based on diffusion-weighted magnetic resonance imaging or computed tomography.[16] Infarct size was defined as follows: small when the longest diameter was 15 mm or smaller; large when the infarct was larger than one third of the territory of the middle cerebral artery, the anterior cerebral artery, the posterior cerebral artery, or the cerebellar hemisphere; and medium for the others.[17] Occluded vessels were assessed based on magnetic resonance angiography or computed tomographic angiography. Acute reperfusion therapy, such as intravenous recombinant tissue plasminogen activator and endovascular therapy, clinical outcome using the mRS score, duration of hospital stay, and discharge destinations (home, rehabilitation hospital, or nursing home) were also evaluated. The study was approved by the institutional ethics committee (17-033).

Data were expressed as median (interquartile range) or n (%). One-way analysis of variance followed by Bonferroni post hoc tests for continuous variables or the Pearson χ^2 test for categorical variables was used to compare differences among the 3 groups. Statistical analysis was performed using the PASW Statistics software (version 20; SPSS Inc., Chicago, IL).

Results

Of the 53 patients included, 17 (32%) were treated with a standard dose, 23 patients (43%) were treated with a low dose, and 13 patients (25%) were treated with an