Selection of Oral Anticoagulants in Ischemic Stroke Patients with Nonvalvular Atrial Fibrillation

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Background: Anticoagulant therapy is indicated for management of ischemic stroke patients with nonvalvular atrial fibrillation. We retrospectively investigated how oral anticoagulants were selected for ischemic stroke patients with nonvalvular atrial fibrillation. *Methods:* This study included 297 stroke patients with nonvalvular atrial fibrillation admitted to our hospital between September 2014 and December 2017, and who were subsequently transferred to other institutions or discharged home. Baseline clinical characteristics were compared between patients prescribed warfarin and those prescribed direct-acting oral anticoagulants. *Results:* In total, 280 of 297 (94.3%) patients received oral anticoagulant therapy, including 36 with warfarin, while 244 received direct oral anticoagulants. Age, percentage of heart failure, $CHADS_2$ score before stroke onset, percentage of treatment with warfarin on admission, percentage of feeding tube at hospital discharge, and modified Rankin Scale at hospital discharge were significantly higher in the warfarin group versus the direct oral anticoagulants group, while creatinine clearance was significantly higher in the direct oral anticoagulant group. By multiple logistic regression, taking warfarin at admission and higher modified Rankin Scale at hospital discharge were associated with warfarin selection, while higher creatinine clearance was associated with direct oral anticoagulant selection (warfarin: odds ratio [OR] 7.10 [95% confidence interval {CI} 2.83-17.81]; modified Rankin Scale at hospital discharge: [OR] 1.47 [95% {CI} 1.06-2.04]; creatinine clearance: [OR] .97 [95% {CI} .95-.99]). *Conclusions:* Selection of oral anticoagulants in acute ischemic stroke patients with nonvalvular atrial fibrillation was influenced by warfarin use at admission, clinical severity at hospital discharge, and renal function.

Key Words: Acute ischemic stroke—anticoagulants—nonvalvular atrial fibrillation—secondary prevention

Introduction

Stroke in patients with nonvalvular atrial fibrillation (NVAF) is an absolute indication for secondary prevention of ischemic stroke with anticoagulant therapy.[1] The oral anticoagulants (OACs) used in Japan include warfarin and direct-acting OACs (DOACs). However, there are no definitive guidelines for the selection of warfarin or DOACs to prevent recurrent stroke in patients with NVAF, and either drug is used at the discretion of clinicians according to the clinical status of each patient. Nevertheless, an observational study (The Stroke Acute Management with Urgent Risk-factor Assessment and Improvement [SAMURAI]-NVAF study) reported that patients with poorer clinical outcomes at hospital discharge were more likely to be prescribed warfarin,[2] although the study was performed from 2011 (when the first DOAC dabigatran was approved) to March 2014. In the present study, we examined the selection of OACs for treatment of patients with cerebral infarction accompanied by NVAF in patients treated from September 2014, when all 4 DOACs were available in Japan.

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Patients and Methods

The Institutional Review Board of Saitama Medical University International Medical Center approved this study protocol (No. 17-224). The study included 297 stroke patients with NVAF who were admitted to our hospital between September 2014 and December 2017, and who were subsequently transferred to other institutions or discharged to home. The Saitama International Medical Center was developed as a tertiary and teaching hospital in 2007, and is located in the west part of Saitama Prefecture. Our department cares for patients with acute stroke, with 30-50 patients with ischemic stroke per day in the ward. Echocardiography was performed in all patients to evaluate the presence of valvular disease. NVAF was defined as the presence of AF without rheumatic mitral valve disease (mitral valve stenosis) or artificial valve replacement.[1] AF was confirmed based on medical records including electrocardiogram, bedside electrocardiogram monitoring, and 24-hour Holter monitoring.

We retrospectively compared the following variables between patients who received warfarin (warfarin group) and patients who received DOACs (DOAC group): patient attributes (age and sex), risk factors for cerebral infarction (hypertension, diabetes mellitus, and heart failure), past history (coronary artery disease and ischemic stroke), creatinine clearance (CCr; Cockcroft-Gault equation),[3] $CHADS_2$ scores before stroke onset,[4] the National Institutes of Health Stroke Scale score[5] on admission, use of OACs at stroke onset, recanalization therapy, feeding tube at hospital discharge, hospital stay, and modified Rankin Scale (mRS) at hospital discharge. Patients with heart failure symptoms or laboratory findings suggestive of heart failure[6-8] (left ventricular ejection fraction <40%, New York Heart Association ≥II, and heart failure symptoms within the past 3-6 months), and those on medication therapy for heart failure were defined to have congestive heart failure based on the $CHADS_2$ score. Hypertension was defined as antihypertensive therapy before stroke onset or a prior history of hypertension. Patients were considered to have diabetes if they had an HbA1c (the National Glycohemoglobin Standardization Program) of ≥6.5% or history of oral antidiabetic or insulin therapy before stroke onset. The baseline clinical characteristics of patients not receiving OAC therapy were also investigated. Patients with a CCr of <15 mL/min, a contraindication for the use of DOACs, were excluded from the study.

Statistical analysis

Data were analyzed using statistical software (SPSS version 20; IBM, Armonk, NY). Differences in age and CCr between the groups were assessed by Student's t test. The $CHADS_2$ score, NIHSS score on admission, hospital stay, and mRS at discharge were compared using the Wilcoxon rank-sum test, while the ratios were compared using the Fisher's exact test (2-sided). We also established a logistic regression model using warfarin or DOACs as objective variables, and variables with a significant difference on univariate analysis as explanatory variables. P values <.05 were considered statistically significant.

Results

The clinical characteristics of the warfarin and DOAC groups are shown in Table 1. Of the 297 patients, 280 (94.3%) received OACs. Of these 280 patients, 36 (12.9%) received warfarin, while 244 (87.1%) were treated with DOACs (dabigatran, 12; rivaroxaban, 106; apixaban, 89; and edoxaban, 37). The average age of the DOAC group was significantly lower than that of the warfarin group. In particular, the rate of DOAC administration gradually decreased with age (Fig 1).The warfarin group showed a significantly higher proportion of heart failure, $CHADS_2$ score before stroke onset, treatment with warfarin at admission, proportion of feeding tube at hospital discharge, and mRS at hospital discharge. By contrast, the DOAC group had significantly higher CCr values.

The percentages of OAC choice for the patients differed with differing discharge mRS scores (Fig 2). The rate of warfarin prescription increased with worsening mRS scores. However, DOACs users accounted for 74.7% (59 patients) of patients with an mRS of 5. The DOACs group showed a higher percentage of patients discharged to home. By contrast, the warfarin group showed a higher percentage of patients discharged to long term care unit (Fig 3). In logistic regression analysis, taking warfarin at admission (odds ratio [OR] 7.10 [95% confidence interval {CI} 2.83-17.81]) and a higher mRS at hospital discharge (OR 1.47, 95% CI 1.06-2.04) were significantly associated with the selection of warfarin, while a higher CCr value was significantly associated with the selection of DOACs (OR .97, 95% CI .95-.99) (Table 2). Seventeen patients were not prescribed OACs. Of these, 9 were ≥85 years of age, 5 had concomitant malignancies (lung cancer, 1 patient; gastric cancer, 2 patients; colorectal cancer, 1 patient; and maxillary gingival cancer, 1 patient), including 3 with end-stage cancer, and 4 patients were discontinued from anticoagulant therapy (warfarin, 3 patients; apixaban, 1 patient) because of gastrointestinal hemorrhage. All 17 patients had severe sequelae at hospital discharge (mRS of 5), 2 of whom were transferred to the palliative care unit, 12 to long term care unit or geriatric health care institutions, and 3 to the convalescent unit.

Discussion

In the present study, DOACs were selected in 94% of the patients receiving OACs. Further, adherence to warfarin therapy at admission, severity at hospital discharge, and CCr value were significant factors affecting the