Evaluation of the Efficacy and Safety of Direct Oral Anticoagulants in Japanese Patients—Analysis of Pharmaceuticals and Medical Devices Agency Data

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Background: Two forms of direct oral anticoagulant (DOAC) have recently been introduced: direct thrombin inhibitors (DTI; e.g., dabigatran) and factor Xa inhibitors (FXa; e.g., rivaroxaban and apixaban). Despite the advantages of DOACs over warfarin with regard to cerebrovascular complications, those associated with DOACs have been reported with the increasing use of DOACs. Nevertheless, little is known about real-world comparative efficacy and safety of DOACs. *Methods:* Cerebrovascular adverse events collected by the Pharmaceutical and Medical Devices Agency (PMDA) during 2014 were analyzed to describe and compare efficacy and safety among patients prescribed DTI and FXa. *Results:* Thirty-six cerebrovascular events associated with DTI and 419 events with FXa were reported during 2014. Ratios of hemorrhagic to ischemic events were similar in both DTI (2.2) and FXa (1.9) groups, with hemorrhagic events exceeding ischemic events. Ratios of intracerebral hemorrhage to total hemorrhagic events in patients with FXa (0.84) were significantly higher than those taking DTI (0.48; $P < .01$), but ratios of subdural (epidural) hemorrhage in FXa (0.14) were significantly lower than in DTI (0.44; $P < .01$). Among patients developing cerebral infarction, ratios of embolic to total ischemic events among FXa (0.34) and DTI (0.31) were comparable, but no patients taking DTI developed atherothrombotic infarction, compared with patients taking FXa (ratio of atherothrombotic to total ischemic events = 0.15). *Conclusions:* The present study indicates that different drug effects on cerebrovascular events may exist between DTI and FXa. DTI may play important roles in reducing and preventing intracerebral hemorrhage and atherothrombotic events. **Key Words:** Cerebrovascular complication—DOAC—direct thrombin inhibitor—factor Xa inhibitor—efficacy and safety—PMDA.

Introduction

The recent introduction of direct oral anticoagulants (DOACs) has provided new treatment options beyond warfarin for stroke prevention in atrial fibrillation (AF). In the last 5 years, 2 different forms of DOACs have been approved for use in Japan for the prevention of embolic stroke in patients with non-valvular AF (NVAF): oral direct thrombin inhibitors (DTI; e.g., dabigatran) and oral factor Xa inhibitors (FXa; e.g., rivaroxaban, apixaban, and edoxaban).

Although large-scale clinical studies have shown advantages of DOACs over warfarin with regard to hemorrhagic

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complications,[1-4] several cases of hemorrhagic and ischemic complications associated with DOACs have been reported with the increasingly widespread use of these agents.[5,6] According to the report by McDonald et al, 30%-35% of spontaneously reported adverse events associated with DOACs are related to hemorrhage.[7,8] Nevertheless, little is known about the real-world comparative effectiveness and safety of DOACs among patients. Japanese data on the safety of DOACs such as hemorrhagic complications are also sparse.[9]

Differences between DTI and FXa in terms of safety and efficacy are often discussed, and the issue remains controversial.[10]

In Japan, post-marketing surveillance (PMS) of drugs relies on spontaneous reporting of adverse drug events to the Pharmaceuticals and Medical Devices Agency (PMDA), a Japanese regulatory agency established on April 1, 2004, working together with the Ministry of Health, Labour and Welfare.[11] The PMDA collects information on the quality, efficacy, and safety of drugs from marketing authorization holders and medical institutions when cases of adverse drug reactions are detected during the post-marketing period. They also provide information on all cases of adverse drug reactions reported by pharmaceutical companies or healthcare professionals since April 1, 2004, on the PMDA website.

Pharmaceutical companies are mandated to report adverse events, whereas health professionals and consumers are recommended, but not required, to report adverse events.

The purpose of this study was to determine the real-world risk of cerebrovascular events associated with the 2 forms of DOACs, DTI and oral FXa, using the electronic database of spontaneously reported adverse events by the PMDA in Japan.

Materials and Methods

Data Sources

This study was based on spontaneous reporting of adverse drug events to the PMDA in Japan. We searched for reports on adverse drug reactions from January 1, 2014 to December 31, 2014, issued by the PMDA among patients treated with DOACs including dabigatran, rivaroxaban, and apixaban.

We did not collect data about cerebrovascular adverse events due to edoxaban, because only a few months have passed since the introduction of additional indications for patients with NVAF and with embolic stroke due to NVAF in Japan.

The PMDA report contained more than 2127 adverse events associated with DOACs during 2014. PMDA reports for each cerebrovascular adverse event in which DOACs were considered a potential cause were identified. Information on age, gender, dose, concomitant medication, and type of adverse cerebrovascular events including hemorrhagic and ischemic stroke of each patient was extracted.

Adverse events are any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (Food and Drug Administration 21 312.32 a Code of Federal Regulations). FDA also suggests that an adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose. For this reason, the present study focused on the ischemic events as well as hemorrhagic events.

Hemorrhagic events included subdural (epidural) hemorrhage, intracerebral hemorrhage, and subarachnoid hemorrhage (SAH). Ischemic events included embolic infarction, atherothrombotic infarction including ischemic stroke due to unknown origin, lacunar stroke, transient ischemic attack, and uncertain type of stroke. Uncertain type included stroke of unknown origin.

The crude annual incidence (events/10,000 patient-years) of cerebrovascular events in 2014 among patients prescribed DTI and FXa was calculated as below:

$$= \frac{\text{number of events reported for individual DOAC}}{\text{estimated number of patients prescribed with individual DOAC}} \times 10{,}000$$

We defined the number of patients with cerebrovascular events reported during 2014 as the number of events that occurred and was reported to the PMDA during 2014.

The number of patients prescribed individual DOACs was calculated as below:

$$= \frac{\text{annual sales of individual DOACs in 2014}}{\text{annual cost of individual DOACs in 2014}}$$

The annual sales and costs of individual DOACs in 2014 were retrieved from the annual reports of domestic sales revenue for individual DOACs published in 2015.[12]

The Iwate Medical University Human Research Ethics Committee deemed the study as exempt from the need for ethics approval.

Design

This is a retrospective, observational study.

Statistical Analysis

The chi-square test was used for comparisons. Results with values of $P < .05$ were considered statistically significant. All analyses were performed using SPSS Statistics 20 software (SPSS Inc., Chicago, IL).