Reduction in the Doses of Direct Oral Anticoagulants and Risk of Ischemic Stroke Events: A Hospital Survey

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Inappropriately reduced doses (IRDs) of direct oral anticoagulants (DOACs) are common in clinical practice. We performed a retrospective review using electronic medical records of St. Marianna University School of Medicine Hospital (a 1200-bed teaching hospital in Japan) to address the prevalence of IRDs and patient-related factors that result in IRDs. We also surveyed DOAC-treated patients who were hospitalized due to a stroke during the 5-year study period to analyze the association between stroke events and IRDs. We found that one in five patients who were newly prescribed a DOAC was treated with IRDs. Patients treated with edoxaban received the most IRDs (64%, 7/11), followed by those treated with dabigatran (50%, 1/2), apixaban (32%, 19/61), and rivaroxaban (27%, 12/44). Our analysis showed that the renal function (measured as serum creatinine and creatinine clearance values) and age are possible factors influencing dose reduction. The HAS-BLED score and antiplatelet use were not associated with IRD prescription. An analysis of the 5-year hospital records revealed 20 stroke cases despite ongoing treatments with DOACs, and IRDs were noted in three of these cases. In all three cases, the patients had been on an IRD of rivaroxaban. To prevent IRDs of DOACs, we suggest that a clinical protocol be incorporated into formularies to support the prescription process.

Key words direct oral anticoagulant; atrial fibrillation; stroke prevention; inappropriate dose

INTRODUCTION

In recent years, four direct oral anticoagulants (DOACs), namely dabigatran, rivaroxaban, apixaban, and edoxaban, have been replacing warfarin for stroke prevention in patients with non-valvular atrial fibrillation (NVAF). Dose adjustments of DOACs are recommended for patients with moderate renal impairment, low body weight, and select drug interactions. In real-world settings, reduced doses of DOACs are prescribed for elderly patients.1,2 Inappropriately reduced doses (IRDs), that is, dose reductions that are often not based on manufacturers’ labeling, are prevalent according to Japanese registry studies.3,4 Clinical evidence of reduced doses of DOACs from randomized controlled studies is limited.5–8 Rivaroxaban has been approved in Japan at a lower daily dose (15/10 mg) than the globally recommended dose (20/15 mg) because of race-based differences in rivaroxaban pharmacokinetics.8,9

In our institution, medication-use evaluation (MUE) was conducted for dabigatran, apixaban, and rivaroxaban when they were added to the institution’s formulary.10 The MUE results indicated low adherence rates for the dose recommendations provided in manufacturers’ labeling. The reasons for IRD prescription remain unclear. However, physicians prescribed lower doses in consideration of the adverse effects of DOACs, such as, bleeding, in certain patients. Therefore, in this survey, we investigated the prevalence of IRDs and patient-related factors affecting the prescription of IRDs and analyzed the association between IRDs and clinical outcomes.

MATERIALS AND METHODS

Survey of IRD Prevalence and Factors Influencing IRD Prescription

(A) Patient Selection

We included patients who were newly prescribed DOACs for NVAF between September 2015 and February 2016. Patients with off-label use and overdose were excluded. As a retrospective electronic medical records (EMR) review, we excluded patients if no data were available to determine the reasons for dose reduction. Double entries in standard data collection forms completed by researchers and other discrepancies were corrected and entered in the final data (Supplementary Materials). Indications for DOAC treatment were confirmed with the diagnosis provided in the EMR during DOAC treatment initiation.

(B) Definition of IRD

We defined IRDs as doses that were reduced despite their characteristics not meeting the dose reduction criteria (Table 1). The patient-related factors influencing IRD prescription were extracted when DOAC treatment was initiated. IRDs were determined when DOAC treatment was initiated and not for the subsequent dose.

(C) Definition of Patient-Related Factors Influencing IRD Prescription

The patient-related factors influencing IRD prescription review included DOAC dose regimen, age, height, body weight, sex, indications, serum creatinine (Scr) value, and concomitant medication. Creatinine clearance (CrCl) was calculated using the Cockcroft-Gault estimation formula. Furthermore,
the CHADS₂ and CHA₂DS₂-VASc scores, which reflect stroke risk, and the HAS-BLED score for bleeding risk were assessed. To identify patient-related factors influencing IRD prescription, we compared the IRD and standard groups.

**Five-Year Hospital Record Data Review of the Association between IRDs and Clinical Outcomes**

**(A) Patient Selection**

We identified patients who had records of both DOAC prescription for NVAF and admission due to stroke between March 2012 and February 2017. For inclusion in the analysis, DOAC prescription for NVAF continuously for more than 1 month before a stroke diagnosis was a requirement. We excluded patients who did not adhere to the prescribed DOAC treatment (documented in the EMR).

**(B) Definition of Stroke Events**

We used the discharge summary and diagnosis included in the EMR to identify patients with cerebral infarction (ICD-10 code: I63). We defined a stroke event as that caused by a cardiogenic cerebral embolism (documented in the EMR) confirmed by magnetic resonance imaging (MRI) or computed tomography (CT) examination or anticoagulant therapy administration involving the subcutaneous injection of heparin or intravenous administration of recombinant tissue plasminogen activator within 1 week of admission.

**(C) Previous DOAC Use among Stroke Patients**

We analyzed the patients’ demographic data, including their DOAC dosing profile, to compare IRDs and standard doses.

**Statistics and Ethics** Continuous variables are reported as mean ± standard deviation (S.D.) and categorical variables are reported as the number of patients. The prevalence of IRDs was analyzed for each DOAC. Differences in variables between the two DOAC groups (IRD vs. standard dose) were evaluated using the t-test or Wilcoxon rank-sum test. Significant differences were considered at p < 0.05. JMP Pro 13 software was used for statistical analysis. This study was approved by the ethics committee of St. Marianna University School of Medicine Hospital (STMUH) (Authorization No. 3769).

**RESULTS**

**(Prevalence Survey Results** There were 1063 patients treated with DOACs (rivaroxaban: 352, apixaban: 298, edoxaban: 283, and dabigatran: 130) at STMUH between September...
|                | **Apixaban n = 79** |                | **Dabigatran n = 5** |                | **Edoxaban n = 31** |                | **Rivaroxaban n = 56** |
|----------------|---------------------|----------------|---------------------|----------------|---------------------|-----------------|----------------------|
|                | Total n = 171       |                |                     |                |                     |                 |                      |
|                | IRD: inappropriately reduced dose | Standard dose |                     | IRD: inappropriately reduced dose | Standard dose |                     | IRD: inappropriately reduced dose | Standard dose |                     | IRD: inappropriately reduced dose | Standard dose |                     | IRD: inappropriately reduced dose | Standard dose |                     |
| **Age**        | 74.89 ± 5.64*       | 70.88 ± 7.14*  | 83.74 ± 2.83        | 67.57 ± 7.59    | 73.00 ± 3.65        | 73.95 ± 9.65    | 69.67 ± 10.09       | 66.56 ± 11.59       | 81.5 ± 6.29       |
| **BW (kg)**    | 55.67 ± 22.16       | 55.63 ± 26.58  | 54.39 ± 24.80       | 49.26 ± 7.56    | 37.67 ± 32.62       | 37.67 ± 32.62   | 63.25 ± 4.65*       | 57.25 ± 9.96       | 52.08 ± 26.49     |
| **Female**     | 18.3 ± 13.30        | 0.4 ± 0.27     | 10.2 ± 0.44         | 0.8 ± 0.27      | 0.9 ± 0.017         | 0.6 ± 0.22      | 0.8 ± 0.20           | 0.8 ± 0.19         | 1.0 ± 0.16       |
| **SCr (mg/dL)**| 0.90 ± 0.27         | 1.01 ± 0.30    | 0.84 ± 0.27         | 0.70 ± 0.22     | 0.92 ± 0.16         | 0.90 ± 0.017    | 1.67 ± 1.50          | 1.28 ± 1.17         | 2.67 ± 0.89     |
| **CrCl (mL/min)| 59.93 ± 21.37       | 49.18 ± 17.14*| 60.20 ± 13.98*      | 37.77 ± 15.36   | 72.74 ± 18.76       | 66.63 ± 22.34   | 71.24 ± 12.55        | 78.49 ± 19.06       | 37.91 ± 6.92    |
| **CHADS<sub>2</sub>** | 1.89 ± 1.28       | 1.63 ± 1.25    | 1.70 ± 1.12         | 1.67 ± 0.58     | 2.57 ± 0.98         | 3.50 ± 1.73     | 2.15 ± 1.14          | 1.67 ± 0.50         | 1.28 ± 1.17     |
| **CHA<sub>2</sub>-VASc** | 3.15 ± 1.59       | 3.00 ± 1.29    | 3.00 ± 1.53         | 2.66 ± 1.53     | 3.29 ± 1.38         | 4.75 ± 1.50     | 3.65 ± 1.57          | 2.85 ± 1.80         | 2.31 ± 1.47     |
| **HAS-BLED**   | 1.42 ± 0.88         | 1.42 ± 0.61    | 1.39 ± 0.89         | 2.00 ± 1.73     | 1.14 ± 0.90         | 2.25 ± 0.96     | 1.60 ± 0.82          | 1.33 ± 0.98         | 0.97 ± 0.78     |
| **Hypertension** | 10.9 ± 11           | 11.24 ± 11    | 1.00 ± 2             | 5.0 ± 12        | 8.0 ± 12            | 11.0 ± 12       |                      |                      |               |
| **History of stroke/TIA** | 51.12 ± 11          | 18.4 ± 0      | 0.0 ± 0              | 6.3 ± 6         | 4.0 ± 4             | 4.8 ± 4         |                      |                      |               |
| **Heart failure** | 43.2 ± 12           | 8.12 ± 2      | 0.0 ± 0              | 1.2 ± 6         | 1.4 ± 6             | 4.8 ± 4         |                      |                      |               |
| **Vascular disease** | 23.0 ± 3            | 7.5 ± 0       | 0.0 ± 0              | 1.0 ± 3         | 1.5 ± 3             | 3.0 ± 0         |                      |                      |               |
| **Diabetes mellitus** | 38.4 ± 5            | 5.5 ± 0       | 0.0 ± 0              | 6.3 ± 6         | 3.5 ± 1             | 5.1 ± 0         |                      |                      |               |
| **LAA closure** | 12.1 ± 1            | 1.0 ± 0       | 0.0 ± 0              | 1.0 ± 3         | 3.0 ± 0             | 3.0 ± 0         |                      |                      |               |
| **Antiplatelet** | 24.2 ± 6            | 4.6 ± 0       | 0.0 ± 0              | 4.0 ± 3         | 1.2 ± 2             | 2.0 ± 4         |                      |                      |               |
| **NSAIDs**     | 18.3 ± 3            | 3.2 ± 2       | 0.0 ± 1              | 1.2 ± 0         | 0.0 ± 0             | 4.2 ± 0         |                      |                      |               |
| **Gastroprotection agents (PPI, H2B)** | 8618 ± 10          | 18.10 ± 0      | 0.0 ± 2              | 5.4 ± 11        | 5.17 ± 6            |                      |                      |                      |               |
| **Prior anticoagulation** | 8.1 ± 1            | 3.1 ± 2       | 0.0 ± 0              | 0.2 ± 0         | 0.0 ± 0             | 1.0 ± 1         |                      |                      |               |
| **Heparins**   | 42.3 ± 8            | 2.8 ± 2       | 1.2 ± 1              | 3.1 ± 11        | 4.5 ± 1             | 5.0 ± 1         |                      |                      |               |
| **Warfarin**   | 29.7 ± 3            | 2.0 ± 0       | 0.0 ± 0              | 4.1 ± 5         | 4.2 ± 3             | 3.0 ± 0         |                      |                      |               |
| **Other DOACs** | 10.13 ± 29          | 10.1 ± 2      | 1.1 ± 2              | 7.1 ± 11        | 12.25 ± 7           |                      |                      |                      |               |

*IRD vs standard dose p value < 0.05; IRD: inappropriately reduced dose; BW: body weight; SCr: serum creatinine; CrCl: creatinine clearance; TIA: transient ischemic attack; INR: international normalized ratio; NSAID: non-steroidal anti-inflammatory drug; PPI: proton pump inhibitor; H2B: histamine H2 blocker; DOAC: direct oral anticoagulant.
As shown in Fig. 1, 171 patients who had been newly prescribed DOACs during the 6-month study period met the inclusion criteria (rivaroxaban: 56, apixaban: 79, edoxaban: 31, and dabigatran: 5).

As shown in Table 2, 39 patients received IRDs (apixaban: 19, rivaroxaban: 12, edoxaban: 7, and dabigatran: 1). Patients treated with edoxaban received the most IRDs (63%), followed by those treated with dabigatran (50%), apixaban (32%), and rivaroxaban (27%). Table 2 summarizes the patient-related factors influencing IRD prescription.

A comparison of the IRD and standard-dose groups revealed a significant intergroup difference in age and CrCl values for apixaban treatment (Table 2).

Of the five patients treated with dabigatran, only one patient received a standard dose of 300 mg/d, whereas 3 patients received a reduced dose of 220 mg/d per criteria and 1 patient received IRD.

Among the 31 edoxaban-treated patients, only four received a standard dose of 60 mg/d, whereas 20 received a reduced dose of 30 mg/d. Body weight in the IRD group (n = 7, four with a body weight of >80 kg) was significantly greater than that in the standard-dose group (n = 4).

Of the 56 patients treated with rivaroxaban, 32 were administered a standard dose of 15 mg/d, whereas 12 were administered a reduced dose of 10 mg/d per criteria and 12 received IRDs. There was a significant difference in prescribing settings between the IRD and standard-dose groups. The IRDs were prescribed at an outpatient clinic.

Results of the 5-Year Hospital Data Review There were 2322 patients with NVAF who were prescribed DOACs at STMUH from March 2012 to February 2017 (apixaban: 821, edoxaban: 424, dabigatran: 638, and rivaroxaban: 1109). We identified 39 in-patients with cerebral infarction (ICD10 code: I63) corresponding to the main injury/sickness per the discharge summary. There were 20 patients who met the inclusion criteria. Patients who were excluded from the study were as follows: 6 with cerebral embolism events, 5 with documented non-adherence to DOAC treatment, 4 with no documented information in the record, and 4 patients for whom DOAC treatment was initiated after a stroke event (Fig. 2).

Twenty patients were hospitalized for stroke events despite receiving DOAC treatment (Table 3). DOAC overdose occurred in three patients. The average age of these patients was 78.5 years, 70% of these patients were male, and the average CHADS2 score was 3.05. Half of the patients had a history of stroke or TIA. We identified three patients (15%) who had received IRDs. All these patients received rivaroxaban (Table 4) and had received a dose of 10 mg once a day between 33 and 1067 d before the stroke event.

DISCUSSION

In this survey, we found that one in five patients who were newly prescribed a DOAC received an IRD. Furthermore, we found that the renal function (as reflected by serum creatinine and CrCl values) and age were factors influencing dose reduction. Using hospital records for a 5-year period, we identified 20 cases in which stroke events occurred despite DOAC treatment, and three of these patients had received IRDs.
In Japan, the prevalence rates of IRDs of DOACs were higher, 20–28% and 48–59%, as reported in a SAKURA AF registry-based study\(^4\) and a Fushimi registry-based study, respectively.\(^4\) Post-marketing surveillance also showed that treatment was started at a lower rivaroxaban dosage in 51% of patients whose CrCl was \(\leq 50\) mL/min.\(^2\) In our study, 22.8% (39/171) of the patients who were newly prescribed DOACs received IRDs. This may have been related to low-intensity anticoagulation therapy with warfarin, which is the mainstay treatment in Japan. For Japanese patients aged \(\geq 70\) years with NVAF, low-intensity anticoagulation warfarin therapy with an international normalized ratio (INR) target of 1.6–2.6 is suggested in the national guidelines.\(^3\)

**Dose Reduction Criteria** Data for four DOAC agents with different dose reduction criteria are shown in Table 1. Our review of the 5-year hospital records showed that three patients were admitted due to stroke events, and they had been on IRDs of rivaroxaban. We were not able to establish a causal relationship, but our chart review showed no reasons for the prescription of reduced doses for these patients. The renal impairment subgroup analysis in the J-ROCKET AF study (\(n = 141\) for rivaroxaban and \(n = 143\) for warfarin group) showed that the percentage of stroke events per year was 2.77% (5/141) and 0.87% (6/696) for 10 and 15 mg/d doses, respectively.\(^8\) Low-dose rivaroxaban (15 or 10 mg/d) has been only approved for patients with NVAF in Japan and Taiwan. A retrospective study conducted in Taiwan showed no differences in outcomes associated with either dose compared with those associated with warfarin.\(^4\)

**Patient-Related Factors Influencing the IRD Prescriptions** Our prevalence survey revealed that the renal function and age were factors influencing the prescription of IRDs for apixaban. Furthermore, although the threshold of SCr \(\geq 1.5\) mg/dL was not reached, we found that the doctor reduced the dose. For edoxaban, the dose reduction criterion was set at 60 kg, as a threshold; however, doctors reduced the dose for heavier patients in our cohort. The proportion of IRDs was the highest for edoxaban (63.6%). This may be because the 30 mg/d dose had been widely used for the prophylaxis of deep vein thrombosis (DVT).

The CHADS\(_2\)-VASc, CHA\(_2\)-VASc, and HAS-BLED scores did not appear to be associated with IRD prescription. We analyzed the components of each score, but there was no association. Concomitant treatment (non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, and gastroprotective agents) did not appear to influence IRDs.

**Support** Formulary management has not been established in Japan. Social insurance reimburses costs related to nearly all drugs that have market authorization.\(^5\) Therefore, the four DOACs can be prescribed based on the clinical decision of the physicians. Most individual prescribers have their own informal repertoire of drugs that they feel comfortable prescribing, as they are familiar with the dosing requirements and common adverse effects. The four DOACs and warfarin have different indications and dose reduction criteria, which may complicate clinical practice; therefore, the "preferred list of drugs" and clinical protocol reinforce familiarity and competence in prescribing.\(^6\)

A systematic review reported that educating healthcare professionals, guideline/protocol implementation, and medical care programs resulted in significant improvements in appropriate oral anticoagulant prescription.\(^7\) Antithrombotic stewardship conducted by a hospital demonstrated that the implementation of a computerized decision support (CCDS) system for DOACs as a part of the EMR ensured safe prescription.\(^8\) In general, the implementation of computerized advice for drug dosage has several benefits. However, there is no evidence that this support affects mortality or clinical adverse events.\(^9\)

**CONCLUSION**

Our hospital survey revealed that 22.8% of the patients who were newly prescribed a DOAC were treated with IRDs. We also found that physicians may have reduced DOAC doses for patients who did not meet the dose reduction criteria based on their decreased renal function, old age, and low body weight. Using our 5-year hospital records, we identified 20 cases in which patients experienced a stroke despite DOAC treatment, and three of these patients received IRDs. To prevent treatment with IRDs of DOACs, we suggest that a clinical protocol be incorporated into formularies to support the prescription process and achieve optimum clinical efficacy.

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**Conflict of Interest** The authors declare no conflict of interest.
Supplementary Materials  The online version of this article contains supplementary materials.

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