Risk of Recurrent Ischemic Stroke with Unintended Low-Dose Oral Anticoagulant Therapy and Optimal Timing of Review

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Background: Direct oral anticoagulant (DOAC) dose is adjusted according to manufacturer's recommendations when introduced. However, subsequent changes from appropriate DOAC doses to "unintended" inappropriate low-dose DOAC (ILD) due to increased body weight (BW) or decreased serum creatinine concentration might be overlooked. We investigated outcomes in patients receiving appropriate DOAC, "intended" ILD, or unintended ILD, to determine the optimal review time for DOAC doses and associated factors. *Methods:* This single-center, retrospective cohort study included inpatients receiving apixaban for stroke prevention between August 2015 and July 2017. Primary outcome was whether starting DOAC dose was selected according to manufacturer's recommendations and whether that dose remained appropriate thereafter. Secondary outcome was the incidence of recurrent ischemic stroke and intracranial bleeding during therapy. Average rates of change in BW, creatinine, and creatinine clearance (CrCl) were evaluated after hospitalization every 10 ± 3 days. *Results:* During the study period, 120 patients received apixaban; 112 (93.3%) commenced appropriate DOAC doses, and 8 (6.7%) commenced intended ILD doses. Of the 112 patients on appropriate DOAC doses, 7 (6.3%) changed to unintended ILD doses because of increased BW (n = 4) or decreased creatinine (n = 3). The rate of recurrent ischemic stroke differed significantly between the appropriate DOAC dose and the intended or unintended ILD dose group (1.9% [2 of 105] versus 20.0% [3 of 15], *P* = .014). BW and renal function had stabilized after 20 ± 3 days posthospitalization. *Conclusions:* Receiving ILD doses, especially unintended, might be a risk factor for recurrent ischemic stroke and DOAC dose should be reviewed around 20 ± 3 days posthospitalization. **Key Words:** Direct oral anticoagulants—apixaban—nonvalvular atrial fibrillation—appropriate dose—recurrence of ischemic stroke—inappropriate low dose.

Introduction

Recently, direct oral anticoagulant (DOAC) therapy has been used instead of warfarin because of clinical advantages and efficacy in treatment of thrombosis.[1,2] Unlike warfarin, appropriate DOAC dosing is determined on an individual basis, considering age, renal function, and body weight (BW) per manufacturer's recommendations. Inappropriate low-dose DOAC (ILD) therapy might be chosen to prevent bleeding events in the elderly, patients with moderate renal impairment or low BW, and those on concomitant medications. The Japanese multicenter SAKURA AF Registry study suggested that 19.7%-27.6% of DOAC users could be on ILD therapy.[3] Shrestha

et al reported that patients overtreated with rivaroxaban, dabigatran, or apixaban had higher bleeding risk relative to appropriately dosed patients than underdosed patients.[4] Although, "intended" ILD dosing is evaluated from the viewpoint of bleeding complications, "unintended" ILD therapy might be overlooked. Patients in the early postcerebral infarction period may have mild to severe renal dysfunction and/or circulatory failure, particularly with a history of cardiogenic stroke.[5,6] Therefore, DOAC dose review is needed when individual baseline data have stabilized.

We investigated outcomes in patients who received appropriate DOAC, intended ILD, and unintended ILD therapy, aiming to determine the optimal time to check appropriateness of DOAC doses still after introduction and associated factors.

Methods

Study Population and Inclusion Criteria

This retrospective, single-center, cohort study was approved by the Institutional Review Board, and the need for patient consent was waived. Consecutive patients hospitalized for nonvalvular atrial fibrillation and who received DOAC therapy to prevent stroke between August 2015 and July 2017 were identified from electronic medical records. To avoid selection bias, only patients who had received apixaban were enrolled. Per manufacturer's recommendations, 2 of 3 clinical characteristics are required for dose reduction (BW ≤60 kg, age ≥80 years, serum creatinine ≥1.5 mg/dL). Criteria for timing of introducing DOAC therapy were determined using the European Heart Rhythm Association practical guide on the use of new oral anticoagulants in patients with nonvalvular atrial fibrillation.[7]

Complete data, analytic methods, and study materials are available from the authors upon reasonable request.

Outcome Measures

Primary outcome was DOAC dose adjustment per manufacturer's recommendations on introduction and appropriate dose maintenance thereafter. Secondary outcomes were incidence of recurrent ischemic stroke and intracranial bleeding during therapy. We also examined average rate of change (ARC) in BW, serum creatinine, and creatinine clearance (CrCl) at intervals of 10 ± 3 days (0 to 10 ± 3 days, 10 ± 3 to 20 ± 3 days, 20 ± 3 to 30 ± 3 days) posthospitalization. ARC describes changes in 1 quantity relative to a previous value expressed as an absolute value. CrCl was calculated utilizing the Cockcroft–Gault equation[8]:

$$ARC = \left| \frac{\Delta x \, (quantity \, changes)}{previous \, value} \times 100 \right|.$$

ARCs of BW, serum creatinine, and CrCl were also measured in randomly selected controls from among patients undergoing rehabilitation in our hospital at 2 months or more after stroke and observation periods were determined as 10 ± 3 days. We compared ARCs for BW, serum creatinine, and CrCl between experimental and control groups to determine time of stabilization of these parameters to identify the best time to review appropriate DOAC dosing.

Unintended ILD therapy is typically due to BW increase and serum creatinine decrease. Factors that could influence these changes were selected, including sex (male versus female), age (>70 years versus ≤0 years), baseline National Institutes of Health Stroke Scale score (NIHSS; >8 versus ≤8), hypertension (blood pressure ≥140/90 mmHg or antihypertensive treatment), diabetes mellitus (fasting glucose level ≥126 mg/dL on 2 examinations, postprandial glucose level 200 mg/dL, HbA$_{1c}$ ≥6.5%, or antidiabetic medication), hyperlipidemia (total cholesterol ≥200 mg/dL, triglycerides ≥140 mg/dL, or lipid-lowering therapy), congestive heart failure (brain natriuretic peptide ≥100 pg/mL or medication), infection status (white blood cells >10,000/mm^3), smoking status (cessation <5 years earlier), and antiplatelet medication (yes/no).[5,6] Univariate and multivariate analyses were performed to identify factors associated with BW increase and serum creatinine decrease.

Statistical Analysis

Statistical analyses were performed with R version 3.0.3 software (R Foundation for Statistical Computing Vienna, Austria). Groups were compared using Fisher exact test, χ^2 test, and Mann–Whitney U test for discrete variables. Multiple logistic regression with backward elimination was performed. A P value < .05 was considered statistically significant.

Results

Only 120 of 200 patients (60%) who started DOAC therapy at our institution during the study period received apixaban; 59 (49.2%) were male (mean age 78.6 ± 10.7 years; mean CHADS$_2$ (congestive heart failure, hypertension, age ≥ 75 years, diabetes, prior stroke or transient ischemic attack) score 3.8 ± 1.0; median observation period 12.0 months (interquartile range [IQR], 3.0-18.0)). Median interval between hospital admission and starting apixaban was 5.0 days (IQR, 2.0-11.5).

Figure 1 shows primary and secondary outcomes results; 112 (93.3%) of the 120 patients commenced appropriate DOAC doses and 8 (6.7%) commenced intended ILD therapy because of past medical history of bleeding events (n = 4) or concomitant use of medications (such as aspirin) that increased bleeding risk (n = 4). Seven (6.3%) of the 112 patients shifted from appropriate DOAC doses to unintended ILD therapy; there were no changes to