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Original article

# Different risk factors for bleeding and discontinuation between dabigatran and rivaroxaban

Masami Nishino (MD, PhD, FJCC)[a,*], Naotaka Okamoto (MD)[a], Akihiro Tanaka (MD)[a], Naoki Mori (MD)[a], Masahiko Hara (MD, PhD)[b], Masamichi Yano (MD)[a], Nobuhiko Makino (MD, PhD)[a], Yasuyuki Egami (MD)[a], Ryu Shutta (MD)[a], Jun Tanouchi (MD, PhD, FJCC)[a]

[a] Division of Cardiology, Osaka Rosai Hospital, Sakai, Osaka, Japan
[b] Department of Cardiovascular Medicine and Medical Innovation, Osaka University Hospital, Suita, Osaka, Japan

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ABSTRACT

*Background:* It is unclear whether risk factors for bleeding and discontinuation are different between dabigatran and rivaroxaban.

*Methods and results:* We enrolled consecutive patients with atrial fibrillation who received dabigatran or rivaroxaban, had a CHADS2 score >1 and creatinine clearance >30 ml/min. During this period, only dabigatran and rivaroxaban were available as non-vitamin K oral anticoagulants (NOACs) in our hospital. We compared the clinical and demographic data and the incidence of bleeding for one year between dabigatran group and rivaroxaban group. As a result, the dabigatran group consisted of 177 patients and the rivaroxaban group consisted of 179 patients. The incidence of discontinuation was significantly higher in the dabigatran group than in the rivaroxaban group (27.7% vs. 13.4%, $p < 0.001$). Multivariate analysis, even after propensity score-matching analysis, revealed that there were no independent risk factors for bleeding in the dabigatran group, while in the rivaroxaban group, use of antiplatelet therapy was an independent factor correlating with bleeding.

*Conclusions:* The risk factors for bleeding may be different between dabigatran and rivaroxaban. To avoid bleeding, rivaroxaban should be prescribed with caution or avoided in patients using antiplatelet therapy. Upon discontinuation, rivaroxaban may be more favorable than dabigatran.



## Introduction

Warfarin has been the mainstay of anticoagulation over the past five decades but it has unpredictable anticoagulant effects resulting from multiple food and drug interactions and genetic variability. Therefore, routine monitoring of the international normalized ratio should be performed to avoid thromboembolism or bleeding, especially in patients with higher HAS-BLED score [1] (e.g. the patients with antiplatelet therapy) [2,3]. To reduce these demerits of warfarin, non-vitamin K oral anticoagulants (NOACs) including dabigatran and rivaroxaban were developed. The NOACs differ from warfarin in their active mechanism: direct inhibition of proteins in the coagulation cascade. They have more predictable pharmacokinetics leading to fixed and convenient dosing regimens, do not require strict laboratory monitoring, and have fewer drug–drug interactions, as well as rapid onset of action, and importantly, high efficacy and low risk of bleeding [4–6].

In the RE-LY and ROCKET AF trials, dabigatran and rivaroxaban, which are NOACs, were shown to be non-inferior in efficacy and safety to warfarin [4,7]. However, NOACs may not be suitable for everyone with atrial fibrillation (AF) because renal impairment has been shown to be related to an increased risk of bleeding in patients using NOACs [8]. Compared to warfarin, there is limited clinical experience with NOACs. In addition, there have been few reports directly comparing different NOACs. Thus, in this study, we compared the risk factors for bleeding and the incidence of discontinuation, between dabigatran and rivaroxaban using laboratory and clinical data of patients using each drug.

* Corresponding author at: Division of Cardiology, Osaka Rosai Hospital, 1179-3, Nagasone-cho, Sakai, Osaka 591-8025, Japan. Tel.: +81 72 252 3561; fax: +81 72 250 5492.
*E-mail address:* mnishino@orh.go.jp (M. Nishino).

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## Methods

### Study population

We enrolled consecutive patients with AF who received dabigatran or rivaroxaban, had a CHADS2 score greater than one [9] and a creatinine clearance greater than 30 ml/min, and who visited our hospital between September 2012 and August 2013. During this period, dabigatran and rivaroxaban were the only NOACs available at our hospital. Selection of dabigatran or rivaroxaban was dependent on each physician's discretion. Patients remained on concurrent medication including angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, statins, β-blockers, aspirin, and other antiplatelet drugs throughout the study period. We excluded patients with the presence of a severe heart-valve disorder, stroke within 14 days, any condition that increased the risk of hemorrhage, severe renal dysfunction [creatinine clearance (CLCr) < 30 mg/ml], active liver disease, and pregnancy. We divided our patients into a dabigatran group and rivaroxaban group. We evaluated CLCr before starting NOACs in all study patients. CLCr (ml/min) was calculated by [140 − age (years) × body weight (kg)/72/serum creatinine (mg/dl), and × 0.85 if female] [10].

### Dabigatran and rivaroxaban groups

In the dabigatran group, dabigatran was administered in two 75-mg capsules to be taken twice daily (customary dose: 300 mg/day) when the patients' CLCr ≥ 50 ml/min and 110-mg capsules twice daily (reduced dose: 220 mg/day) when CLCr was 30–49 ml/min. In the rivaroxaban group, patients were assigned to receive 15 mg once daily (Japanese customary dose: 15 mg/day) in patients with a CLCr ≥ 50 ml/min and 10 mg once daily (Japanese reduced dose: 10 mg/day) in those with a CLCr of 30–49 ml/min. We evaluated the incidence of the customary dose in both groups. It was intended that patients would continue to take the assigned therapy throughout the course of the study, unless discontinuation was considered to be clinically indicated. The incidence of discontinuation including switching to other oral anticoagulants due to side effects by dabigatran or rivaroxaban during the study period was also evaluated.

### Follow-up

Follow-up visits occurred 14 days after administration of NOACs, at 1 and 3 months, and every 3 months until one year. Laboratory data including prothrombin time (PT), activated partial thromboplastin time (APTT), renal function test, liver-function testing, and hemoglobin level were obtained just before and at one month and one year after administration.

We checked the clinical and demographic data including other medications, and the incidence of side effects including bleeding for one year. Major bleeding was defined as intrinsic bleeding associated with a reduction in hemoglobin to 2.0 g/dl or more, systemic bleeding in a critical area including intracranial hemorrhage, or fatal bleeding using the International Society on Thrombosis and Haemostasis definition [11]. Minor bleeding was defined as other bleeding including nasal bleeding, gastrointestinal bleeding, and subcutaneous bleeding including petechial and purpura. We also evaluated the HAS-BLED score [1] in all patients. We checked for any ischemic events for the first year including cerebral infarction and systemic embolization. The Ethical Committee at Osaka Rosai Hospital approved this study.

### Statistical analysis

All data are expressed as the mean ± standard deviation or numbers and percentage of patients. A univariate analysis was performed with the Mann–Whitney's *U*-test for continuous variables and the chi-square test for nominal variables in the dabigatran and rivaroxaban groups. Multivariate logistic regression analysis was performed to determine the independent risk factors for bleeding events using covariates that could be related to bleeding, i.e. age, male, customary dose, CHADS2 score, HAS-BLED score, CLCr, use of antiplatelet therapy, PT, and APTT in each group. After initial analysis, we performed propensity score-based method, i.e. nearest-neighbor caliper matching [12], to minimize the potential selection bias because of the retrospective nature of the study. The discrimination and calibration of the propensity-score model were adequately assessed by receiver-operating characteristics (ROC) curve (DeLong method). *p*-values of <0.05 were considered statistically significant in each group. Propensity score matching was performed using R software packages (version 3.1.0; R Development Core Team) and the other statistical analyses were performed by SPSS version 11.0.1 software (SAS institute, Cary, NC, USA).

## Results

A total of 356 patients with AF (177 in the dabigatran group and 179 in the rivaroxaban group) were enrolled in this study. Baseline characteristics including CHADS2 and HAS-BLED scores are shown in Table 1. Among the patients, age, CHADS2, and HAS-BLED scores were significantly higher in the rivaroxaban group than in the dabigatran group. In addition, the incidence of the prescribed customary dose in the dabigatran group was significantly lower than that in rivaroxaban group (39.5% vs. 60.5%, $p < 0.001$). The laboratory data before, one month, and one year after the beginning of drug administration are shown in Table 2. Significant reduction in hemoglobin at one month after administration was found in both groups but there were no significant differences in the values of hemoglobin between one month and one year after administration in both groups. In addition, there were no significant before-and-after one month, one year differences in the values of APTT and PT. The incidence of discontinuation was significantly higher in the dabigatran group than in the rivaroxaban group (27.7% vs. 13.4%, $p < 0.001$) (Fig. 1). The reasons for switching from dabigatran were subcutaneous bleeding in 11, nasal bleeding in 6, and dyspepsia in 33; those for switching from rivaroxaban were subcutaneous bleeding in 13, nasal bleeding in 5, and dyspepsia in 5. The incidence of dyspepsia in dabigatran group

**Table 1**
Baseline characteristics of dabigatran and rivaroxaban groups.

| | Dabigatran group ($n = 177$) | Rivaroxaban group ($n = 179$) | *p*-value |
|---|---|---|---|
| Age | 71.5 ± 10.0 | 73.5 ± 9.3 | 0.043 |
| Male (%) | 64.4 | 62.6 | 0.662 |
| Paroxysmal AF (%) | 26 | 24.6 | 0.808 |
| CHADS2 | 1.7 ± 1.2 | 2.1 ± 1.4 | 0.004 |
| HAS-BLED | 1.6 ± 1.1 | 2.2 ± 1.4 | >0.001 |
| CLCr (ml/min) | 74.6 ± 24.5 | 71.7 ± 28.0 | 0.313 |
| Body weight (kg) | 60.4 ± 13.9 | 60.5 ± 12.6 | 0.977 |
| Antiplatelet therapy (%) | 10.2 | 14 | 0.330 |
| Ablation (%) | 32.2 | 30.1 | 0.764 |

AF, atrial fibrillation; CHADS2, congestive heart failure, hypertension, age of 75 years old or older, diabetes mellitus [1 point for presence of each], and stroke/transient ischemic attack [2 points]; HAS-BLED, hypertension (uncontrolled systolic blood pressure >160 mmHg), abnormal renal and/or liver function, previous stroke, bleeding history or predisposition, labile international normalized ratios, elderly, and concomitant drugs and/or alcohol excess [1 point for presence of each]; CLCr, creatinine clearance.