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Original article

Impact of rivaroxaban compared with warfarin on the coagulation status in Japanese patients with non-valvular atrial fibrillation: A preliminary analysis of the prothrombin fragment 1 + 2 levels

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ABSTRACT

Background: Rivaroxaban is an oral anticoagulant that effectively prevents thromboembolic complications using fixed doses without requiring laboratory monitoring. In this study, we aimed to examine the coagulation status in patients with non-valvular atrial fibrillation (NVAF) treated with rivaroxaban compared with warfarin.

Methods and results: The study group consisted of 85 consecutive Japanese patients with NVAF who received rivaroxaban ($n = 33$) or warfarin ($n = 52$) from June 2013 to February 2014. We compared the coagulation status between the rivaroxaban and warfarin treatments. The prothrombin time (PT) values did not significantly differ between the two groups. However, the prothrombin fragment 1 + 2 (F1 + 2) level, a marker of thrombin generation, was significantly higher in the rivaroxaban group than the warfarin group (202 ± 88 pmol/l vs. 114 ± 79 pmol/l, $p < 0.001$). Next, we collected blood samples from 18 patients taking rivaroxaban at 3 h and 15 h after the drug intake and evaluated the time-dependent changes in the coagulation status. The PT values at 3 h after the drug intake were significantly more prolonged than those at 15 h ($p < 0.001$). However, there were no significant differences in the F1 + 2 levels between the two time points (194 ± 73 pmol/l [at 3 h] vs. 165 ± 61 pmol/l [at 15 h], $p = 0.112$).

Conclusions: Our preliminary results suggest that the thrombin generation level is stable regardless of the time elapsed after rivaroxaban intake, and warfarin treatment may inhibit thrombin generation more aggressively than rivaroxaban.

Introduction

Rivaroxaban is a non-vitamin K antagonist oral anticoagulant (NOAC) that inhibits factor Xa (FXa) directly and is used for anticoagulation in patients with non-valvular atrial fibrillation (NVAF). The J-ROCKET AF study demonstrated that rivaroxaban was not inferior to warfarin for the principal safety outcome and that there was a trend for a reduction in strokes and non-central nervous system embolisms observed in Japanese patients treated with rivaroxaban [1], which was consistent with the results of the global ROCKET AF trial [2].

Thrombin generation from its precursor prothrombin is the central step in coagulation; hence, excess thrombin generation leads to thrombosis, whereas insufficient thrombin generation can result in bleeding (reviewed in [3]). Each anticoagulant inhibits the thrombin generation through different mechanisms; warfarin targets vitamin K-dependent multiple coagulation factors and rivaroxaban is a specific inhibitor of FXa. Rivaroxaban is administered once daily and has a peak and trough in its concentration curve; however, the wide therapeutic window of rivaroxaban allows the use of fixed doses without any need for laboratory monitoring [4]. It has been reported that the prothrombin time (PT) and activated partial thromboplastin time (APTT) are prolonged depending on the drug plasma concentrations [5]. However, little

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is known about the difference in the effect of rivaroxaban on the thrombin generation between its peak and trough phases. Moreover, the difference in the coagulation status between warfarin and rivaroxaban treatment is unknown. In this study, we aimed to examine the coagulation status in the patients with NVAF treated with rivaroxaban compared with warfarin.

Methods

Study population

This single-center study consisted of 85 consecutive patients with NVAF who received rivaroxaban (n = 33) or warfarin (n = 52) at the physician's discretion, from June 2013 to February 2014 at Sumiyoshi Clinic Hospital. Patients with stable estimated creatinine clearance (CrCl) levels of ≥20 ml/min were considered for enrollment in the study. The CrCl was evaluated using the Cockcroft-Gault formula: CrCl (ml/min) = ([140 − age] × body weight [kg] × [0.85 if female])/(72 × serum creatinine [mg/dl]). The present study protocol was approved by the institutional review board. All subjects were required to give written informed consent.

Data collection

The clinical characteristics of the patients were obtained from their medical records. The $CHADS_2$ score was calculated as follows: one point for a history of hypertension, diabetes, or recent heart failure; and two points for a history of a stroke or transient ischemic attack (TIA) [6]. The $CHADS_2$-VASc score was calculated as follows: one point for a history of hypertension, diabetes mellitus, heart failure, vascular disease (myocardial infarction, complex aortic plaque, or peripheral artery disease), female gender, or age between 65 and 74 years; and two points for a history of a stroke or TIA, or age ≥75 years [7]. For all patients, the PT (Coagpia PT-N, Sekisui Medical Co., Tokyo, Japan), APTT (Coagpia APTT-N, Sekisui Medical Co.) and prothrombin fragment 1 + 2 (F1 + 2) levels were measured 3 h following the oral dosing. To evaluate the differences in the time-dependent changes in the coagulation status in the individual patients with rivaroxaban treatment, the values of the PT, APTT, and F1 + 2 were sampled from 18 patients at 3 h and 15 h after the drug intake on different days.

Clinical major adverse events were defined as all-cause death, cardiac death, myocardial infarction, or cerebral infarction. Major bleeding complications were defined as cerebral hemorrhage or gastrointestinal bleeding.

Time in the therapeutic range

The time in the therapeutic range (TTR) of the PT-international normalized ratio (INR) is the proportion of the estimated period in which the PT-INR is within the target range (2.0–3.0 for <70 years, 1.6–2.6 for ≥70 years) [8] to the total follow-up period. For each patient receiving warfarin, we retraced the PT-INR values from their medical records and the TTR was calculated using the method described by Rosendaal et al. [9]. Using specially programmed software (Eisai, Tokyo, Japan), we input the successive PT-INR values of each patient and calculated the TTR. This software automatically draws lines successively between any two consecutive PT-INR values during the observation period, and calculates the percentage of the total time within the target range over the entire period [10]. The total follow-up period was 353.6 ± 96.1 days.

Statistical analysis

Data are expressed as means ± standard deviation, medians [interquartile range (IQR)], or numbers and percentages. Comparisons between the two groups were tested by the unpaired t-test or Mann–Whitney U-test according to the data distribution with or without normality. All categorical variables were compared by a chi-square analysis or Fisher's exact test. Statistical significance was considered at a level of $p < 0.05$. All statistics were calculated with JMP software (SAS Institute, Cary, NC, USA).

Results

Patient characteristics and study drugs

The two groups were well balanced with respect to their baseline characteristics (Table 1). The mean age of the patients was 78.1 ± 9.4 years (median, 79 years; range, 52–94 years). In the rivaroxaban group, a renal dose (10 mg once daily) was administered to 15 patients with impaired renal function (CrCl <50 ml/min). In the rivaroxaban-treated patients with preserved renal function (18 patients, CrCl ≥50 ml/min), 12 patients were taking a regular dose of rivaroxaban (15 mg once daily), but the other 6 were receiving a reduced dose (10 mg) because of an advanced age (76–87 years). Patients treated with warfarin had a mean TTR of 58.8% and a median TTR of 63.7%. There were two sudden deaths and one cardiac death due to heart failure out of 52 patients who were receiving warfarin, whereas there were no clinical major adverse events in the patients with rivaroxaban during the follow-up period. There were no major bleeding complications in either group.

Comparison of the coagulation status between rivaroxaban and warfarin

Fig. 1 shows the coagulation status in both groups at 3 h after the drug intake. The mean PT-INR was 2.0 ± 0.6 in the warfarin group. The PT-INR values in 26 patients (50.0%) were in the therapeutic range at that time, those in 16 patients (30.8%) were below the normal range, and those in 10 patients (19.2%) were above it (Supplemental Fig. S1). The PT and APTT values did not significantly differ between the rivaroxaban group and warfarin group (23.2 ± 7.7 s vs. 24.9 ± 7.4 s, 36.8 ± 6.0 s vs. 36.8 ± 7.7 s, respectively). However, the F1 + 2 levels were significantly higher in the

Table 1
Baseline patient characteristics.

Characteristic	Rivaroxaban (n = 33)	Warfarin (n = 52)	p-value
Age, years (mean ± SD)	79.0 ± 9.2	77.5 ± 9.6	0.471
Female, n (%)	16 (48.5)	18 (34.6)	0.203
Body weight, kg (mean ± SD)	59.1 ± 10.3	58.1 ± 11.1	0.683
Cardiac failure congestive, n (%)	12 (36.4)	13 (25.0)	0.263
Hypertension, n (%)	15 (45.5)	24 (46.2)	0.950
Diabetes mellitus, n (%)	11 (33.3)	23 (39.7)	0.318
History of a cerebral infarction (including TIA), n (%)	2 (6.1)	5 (9.6)	0.561
$CHADS_2$ (mean ± SD)	1.94 ± 1.09	2.10 ± 1.31	0.570
$CHADS_2$ score, n (%)			0.946
0	2 (6.1)	4 (7.7)	
1	10 (30.3)	13 (25.0)	
2	12 (36.4)	19 (36.5)	
≥3	9 (27.3)	16 (30.8)	
Creatinine (mean ± SD)	0.92 ± 0.33	0.91 ± 0.21	0.890
CrCl, ml/min (mean ± SD)	55.4 ± 20.9	55.9 ± 21.2	0.916
CrCl, n (%)			0.414
CrCl >50 ml/min	18 (54.5)	33 (63.5)	
CrCl ≤50 ml/min	15 (45.5)	19 (36.5)	

SD, standard deviation; TIA, transient ischemic attack; CrCl, creatinine clearance.