Comparisons of Edoxaban Versus Warfarin on Levels of Plasma Prothrombin Fragment in Patients With Nonvalvular Atrial Fibrillation

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The effect of edoxaban on plasma prothrombin fragment 1+2 (PTF1+2), a sensitive maker of in vivo thrombin generation, has not been fully investigated in nonvalvular atrial fibrillation (NVAF). We compared plasma PTF1+2 levels between 25 NVAF patients receiving warfarin and 100 NVAF patients receiving edoxaban and additionally analyzed the association between plasma PTF1+2 levels and the dose of edoxaban. Plasma PTF1+2 levels were significantly higher in patients receiving edoxaban than in those receiving warfarin (141.5 ± 50.0 pmol/l vs 93.1 ± 55.7 pmol/l, p < 0.001). The prevalence of plasma PF1+2 levels above the upper limit (229 pmol/l) of the normal range did not differ between the 2 groups (4% vs 4%), whereas the prevalence of plasma PTF1+2 levels below the lower limit (69 pmol/l) of the normal range was significantly lower in patients receiving edoxaban than in those receiving warfarin (1% vs 48%, p < 0.001). Multiple linear regression analysis identified age and warfarin treatment as independent variables associated with the plasma PTF1+2 level. In a subgroup analysis, plasma PTF1+2 levels were significantly higher in 58 receiving edoxaban of 30 mg/day than in 42 receiving edoxaban of 60 mg/day (157.6 ± 50.8 pmol/l vs 121.6 ± 39.8 pmol/l, p = 0.01); however, after adjusting for confounding factors, the dose of edoxaban was not independently associated with the plasma PTF1+2 level. In conclusion, edoxaban sufficiently inhibits thrombin generation unrelated to its dose in NVAF, although its inhibitory effect is weaker compared with warfarin. **(Am J Cardiol 2020;136:71−75)**

The conversion of prothrombin to thrombin is a central event in the coagulation of blood. As prothrombin fragment 1+2 (PTF1+2) is released during its conversion in a 1:1 ratio, the plasma PTF1+2 level is considered to be a sensitive marker of in vivo thrombin generation.[1-4] Plasma PTF1+2 levels are increased in atrial fibrillation (AF).[5−7] Previous studies have shown that plasma PTF1+2 levels were significantly lower in nonvalvular AF (NVAF) patients receiving warfarin than in those receiving rivaroxaban[8−10] or apixaban.[11] Edoxaban, another direct oral factor Xa inhibitor, has been shown to inhibit thrombin generation in healthy subjects.[12−14] However, the effect of edoxaban on the plasma PTF1+2 level has not been fully investigated in NVAF. Accordingly, we compared plasma PTF1+2 levels between NVAF patients receiving edoxaban and those receiving warfarin and additionally analyzed the association between plasma PTF1+2 levels and the dose of edoxaban.

Methods

A total of 125 consecutive patients (98 men and 27 women; mean age of 75 ± 10 years) with NVAF who had been taking warfarin or edoxaban in the morning for >6 months and who did not meet the following exclusion criteria were prospectively enrolled into this study between August 2018 and December 2019. The exclusion criteria were as follows: (1) acute illness, including inflammatory diseases, injuries, or acute cardiovascular diseases; (2) malignant diseases; (3) coagulation abnormalities; and (4) inadequate dose or use of edoxaban. Edoxaban at a dose of 30 mg/day is recommended if any of the following conditions are present: calculated creatinine clearance ≤50 ml/min using the Cockcroft-Gault formula,[15] body weight ≤60 kg, or the concomitant use of potent P-glycoprotein inhibitors. The present study protocol was approved by our institutional review board. All subjects gave their informed consent before their inclusion in the present study.

The clinical characteristics of patients were obtained from interviews during medical examinations or from medical records. Major bleedings were defined according to the definition of the International Society on Thrombosis and Haemostasis.[16] The $CHADS_2$[17] and CHA_2DS_2-VASc[18] scores were calculated for each patient. The creatine clearance was calculated using the Cockcroft-Gault formula.[15] The time of the therapeutic range of the prothrombin time - international normalized ratio during the preceding 6 months was calculated using the method by Rosentaal et al.[19] Blood samples were obtained at 2 to 4 hours after taking warfarin or edoxaban. The serum PTF1+2 level was measured using an enzyme immunoassay kit (Enzygnost F1+2, Siemens healthcare Diagnostics, Murberg, Germany). The normal range for the plasma level of PTF1+2 is 69 to 229 pmol/l.[8,10]

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Data were expressed as mean ± SD or median (first − third quartiles) for continuous variables. Comparisons of continuous variables between 2 groups were performed using unpaired *t* test and Mann-Whitney *U* test. Categorical data were analyzed using Fisher's exact test or chi-squared test. Simple and multiple linear regression analyses were performed to identify variables associated with the plasma PTF1+2 level. Explanatory variables with a $p < 0.2$ in simple linear regression analysis were used in multiple linear regression analysis. A $p < 0.05$ was considered statistically significant. All analyses were performed using the IBM SPSS Statistics 25 software program (International Business Machines Co. Ltd., New York).

Results

In 25 patients receiving warfarin, prothrombin time - international normalized ratio ranged from 1.72 to 3.33 and the therapeutic range was 82.2 (55.7 to 100). The dose of edoxaban was 30 mg/day in 58 patients and 60 mg/day in 42 patients. The patient characteristics are shown in Table 1. The frequency of congestive heart failure was significantly higher in patients receiving warfarin than in those receiving edoxaban. Plasma PTF1+2 levels were significantly higher in patients receiving edoxaban than in those receiving warfarin (141.5 ± 50.0 pmol/l vs 93.1 ± 55.7 pmol/l, $p < 0.001$) (Figure 1). The prevalence of plasma PTF1+2 levels above the upper limit (229 pmol/l) of the normal range did not differ between the edoxaban group and the warfarin group (4 [4%] vs 1 [4%]). The prevalence of plasma PTF1+2 levels below the lower limit (69 pmol/l) of the normal range was significantly lower in patients receiving edoxaban than in those receiving warfarin (1 [1%] vs 12 [48%], $p < 0.001$). Table 2 shows results of simple and multiple linear regression analyses to identify variables associated with the plasma PTF1+2 level. Simple linear regression analysis showed that age, body weight, calculated creatinine clearance and warfarin treatment were significantly associated with the plasma PTF1+2 level. Multiple linear regression analysis showed that age and warfarin treatment were independently associated with the plasma PTF1+2 level.

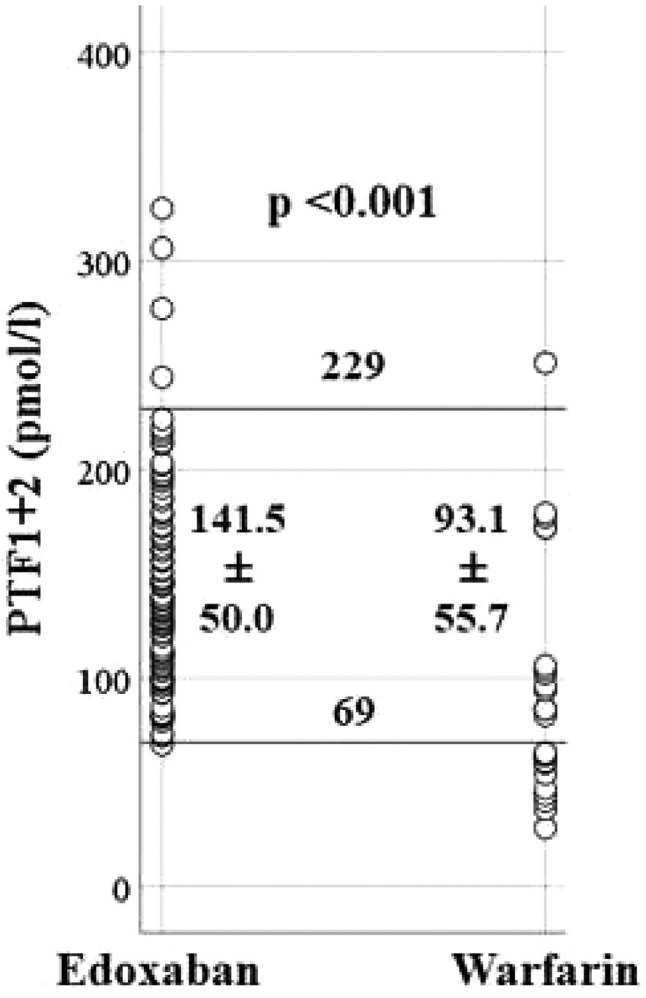

Figure 1. Comparison of plasma prothrombin fragment 1+2 (PTF1+2) levels between 100 patients receiving edoxaban and 25 patients receiving warfarin.

Table 1
Patient characteristics

Variable	Warfarin (n = 25)	Edoxaban (n = 100)	p
Age (years)	72.4 ± 9.8	75.8 ± 10.0	0.14
Men	18 (72%)	80 (80%)	0.42
Body weight (kg)	65.9 ± 12.9	63.0 ± 12.8	0.32
Types of atrial fibrillation			0.18
Paroxysmal	9 (36%)	52 (52%)	
Persistent	16 (64%)	48 (48%)	
Hypertension	15 (60%)	72 (72%)	0.33
Diabetes mellitus	9 (36%)	38 (38%)	0.99
Current smoker	2 (8%)	7 (7%)	0.99
Congestive heart failure	19 (76%)	32 (32%)	< 0.001
Previous stroke	3 (12%)	15 (15%)	0.77
Previous major bleeding	0 (0%)	0 (0%)	0.99
Creatinine clearance (ml/min)	53.1 ± 25.2	58.8 ± 21.2	0.32
$CHADS_2$ score	2.4 ± 1.2	2.4 ± 1.3	0.83
CHA_2DS_2-VASc score	3.6 ± 1.4	3.5 ± 1.7	0.77
Medications			
Renin angiotensin inhibitors	12 (48%)	49 (49%)	0.99
β blockers	16 (64%)	64 (64%)	0.99
Antiplatelet agents	4 (16%)	10 (10%)	0.48

Values are presented as mean ± SD or number (percentage).

In a subanalysis of 100 patients receiving edoxaban, plasma PTF1+2 levels were significantly higher in 58 patients receiving edoxaban of 30 mg/day than in 42 patients receiving edoxaban of 60 mg/day (157.6 ± 50.8 pmol/l vs 121.6 ± 39.8 pmol/l, $p = 0.01$) (Figure 2). The prevalence of plasma PF1+2 levels above the upper limit of the normal range did not differ significantly between patients receiving edoxaban of 30 mg/day and those receiving edoxaban of 60 mg/day (3 [5.2%] vs 1% [2.4%], $p = 0.64$). After adjusting for confounding factors (age, men, body weight, persistent AF, hypertension, diabetes mellitus, current smoker, creatinine clearance, congestive heart failure, and previous stroke), the dose of

Table 2
Simple and multiple linear regression analyses to determine variables associated with plasma prothrombin fragment 1+2 levels.

Variable	Simple		Multiple	
	β (95% confidence interval)	p	β (95% confidence interval)	p
Age (years)	0.44 (0.28 − 0.60)	<0.001	0.32 (0.10 − 0.54)	0.005
Men, no = 0, yes = 1	0.01 (−0.12 − 0.14)	0.88		
Body weight (kg)	−0.23 (−0.40 − −0.06)	0.01	0.06 (−0.15 − 0.27)	0.58
Persistent atrial fibrillation, no = 0, yes = 1	0.04 (−0.16 − 0.24)	0.69		
Hypertension, no = 0, yes = 1	−0.03 (−0.25 − 0.19)	0.78		
Diabetes mellitus, no = 0, yes = 1	0.07 (−0.11 − 0.25)	0.44		
Current smoker, no = 0, yes = 1	0.07 (−0.12 − 0.26)	0.46		
Congestive heart failure, no = 0, yes = 1	0.14 (−0.04 − 0.32)	0.12	0.13 (−0.06 − 0.32)	0.18
Previous stroke, no = 0, yes = 1	0.12 (−0.06 − 0.30)	0.18	0.02 (−0.14 − 0.18)	0.81
Creatinine clearance (ml/min)	−0.28 (−0.45 − −0.11)	0.01	−0.07 (−0.31 − 0.17)	0.57
Warfarin, no = 0, yes = 1	−0.36 (−0.52 − −0.20)	<0.001	−0.38 (−0.55 − −0.21)	<0.001
Antiplatelet agents, no = 0, yes = 1	−0.04 (−0.22 − 0.14)	0.66		

edoxaban (0 = 30 mg/dl, 1 = 60 mg/day) was not independently associated with the plasma PTF1+2 level (β = −0.14 [95% confidence interval: −0.42 to 0.15], p = 0.33).

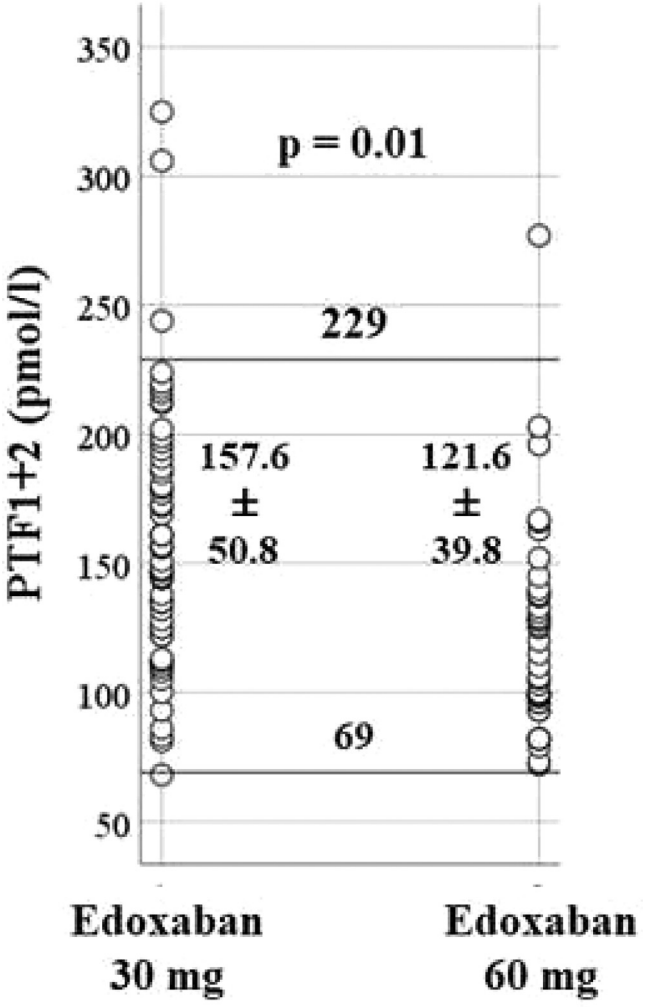

Figure 2. Comparison of plasma prothrombin fragment 1+2 (PTF1+2) levels between 58 patients receiving edoxaban of 30 mg/day and 42 patients receiving edoxaban of 60 mg/day.

Discussion

The major findings of the present study are as follows: (1) plasma PTF1+2 levels were significantly higher in NVAF patients receiving edoxaban than in those receiving warfarin; (2) the prevalence of PTF1+2 levels above the upper limit of the normal range did not differ between the 2 groups; (3) the prevalence of PTF1+2 levels below the lower limit of the normal range was significantly lower in NVAF patients receiving edoxaban than in those receiving warfarin; (4) age and warfarin treatment were independently associated with the plasma PTF1+2 level; and (5) the dose of edoxaban was not associated with the plasma PTF1+2 level.

In the present study, plasma PTF1+2 levels were significantly higher in patients receiving edoxaban than in those receiving warfarin, and multiple linear regression analysis identified warfarin treatment as an independent variable associated with the plasma PTF1+2 level. These results suggest that warfarin inhibits thrombin generation more strongly than edoxaban in NVAF patients, as having been shown in previous studies comparing between warfarin and rivaroxaban[8−10] or apixaban.[11] However, it should be noted that the prevalence of plasma PF1+2 levels above the upper limit of the normal range did not differ between the warfarin and edoxaban groups. This suggests that edoxaban sufficiently inhibits thrombin generation in NVAF patients and may partly support the result of the ENGAGE AF-TIMI 48 trial, which demonstrated the noninferiority of edoxaban treatment to warfarin treatment in terms of protecting against thromboembolic events in NVAF.[20]

In the present study, plasma PTF1+2 levels below the lower limit of the normal range were observed in 48% of 25 NVAF patients receiving warfarin, suggesting that warfarin sometimes excessively inhibits thrombin generation in NVAF as was previously demonstrated.[8] On the other hand, plasma PTF1+2 levels below the lower limit of the normal range were observed in only 1% of 100 patients receiving edoxaban. Excessive suppression of thrombin generation would reduce the ability to protect against bleeding events, possibly leading to an increased risk of major bleeding. Thus, our results may partly support the results of the ENGAGE AF-TIMI 48 trial, which demonstrated a

significant reduction in major bleeding in the edoxaban group in comparison to the warfarin group.[20]

There are no studies comparing the plasma PTF1+2 level between NVAF patients receiving a direct oral anticoagulant at a standard dose and those receiving it at an adequate reduced dose. In the present study, plasma PTF1+2 levels were significantly higher in patients receiving edoxaban of 30 mg/day than in patients receiving edoxaban of 60 mg/day. However, after adjusting for confound variables, the dose of edoxaban was not significantly associated with the plasma PTF1+2 level. Importantly, the prevalence of plasma PF1+2 levels above the upper limit of the normal range did not differ significantly between patients with edoxaban of 30 mg/day and those with edoxaban of 60 mg/day. Thus, an adequate dose-reduction of edoxaban does not seem to be associated with insufficient suppression of thrombin generation, supporting the validity of the adequate dose-reduction of edoxaban for NVAF.

Plasma PTF1+2 levels are increased in AF.[5–7] A previous population-based study showed a positive correlation between age and plasma PTF1+2 levels.[21] These results may partly explain an age-related increase in the incidence of strokes in patients with AF, which have been reported in several large population-based studies.[22–25] In the present study, age was found to be an independent factor for the plasma PTF1+2 level even in NVAF patients receiving warfarin or edoxaban. Age is also an important risk factor for major bleeding events in NVAF patients receiving anticoagulant therapy.[20,26–29] Thus, an adequate inhibition of thrombin generation is essential to reduce thromboembolic events without increasing the risk of major bleeding events especially in elderly patients with NVAF. In the ENGAGE AF-TIMI 48 trial, edoxaban significantly reduced the rates of major bleeding and intracranial hemorrhage with a preserved efficacy in the prevention of strokes and systemic embolisms in comparison to warfarin in elderly patients with NVAF.[29]

The present study has several limitations. First, the sample size of the present study was relatively small and the warfarin group and the edoxaban group had different sample sizes and patient characteristics. Therefore, further studies are needed to confirm our results. Second, we did not evaluate the plasma PTF1+2 level before and after starting edoxaban treatment. Thus, the precise effect of edoxaban on plasma PTF1+2 levels in NVAF patients remains unclear. Third, we measured the plasma PTF1+2 level at 2 to 4 hours after the administration of edoxaban, which reflects the plasma PTF1+2 level approximately at the maximal circulating concentration of edoxaban. It is unclear whether plasma PTF1+2 levels are similar at the peak and trough phases of the circulating edoxaban concentration. A previous study showed no significant circadian variation in plasma PTF1+2 levels in NVAF patients receiving rivaroxaban.[9,10] Fourth, we used the plasma PTF1+2 level as a marker of in vivo thrombin generation. It has not been established whether the plasma PTF1+2 level is a reliable marker of the efficacy and safety of anticoagulants or a useful predictor of subsequent thromboembolic and major bleeding events in NVAF.[7] Further investigations are warranted to answer these unsolved issues.

In conclusion, edoxaban sufficiently inhibits thrombin generation unrelated to its dose in NVAF, although its inhibitory effect is weaker compared with warfarin.

Authors Contribution

Akira Tamura: Conceptualization, methodology, data curation, data analysis, writing. Ena Yamamoto: Data curation, data analysis. Yoshiyuki Kawano: Data curation, data analysis.

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