Risk factors for major bleeding and clinically relevant non-major bleeding in Japanese patients treated with edoxaban

Tomoki Takase,*a Hiroaki Ikesue,a Haruna Nakagawa,a Megumi Kinoshita,a Nobuyuki Muroi,a Takeshi Kitai,b Yutaka Furukawa,b and Tohru Hashidaa

a Department of Pharmacy, Kobe City Medical Center General Hospital; 2-2-1, Minatojima Minamimachi, Chuo-ku, Kobe-city, Hyogo, 650-0047, Japan: and
b Department of Cardiovascular Medicine, Kobe City Medical Center General Hospital; 2-2-1, Minatojima Minamimachi, Chuo-ku, Kobe-city, Hyogo, 650-0047, Japan.

* Tomoki Takase
Department of Pharmacy, Kobe City Medical Center General Hospital
2-2-1, Minatojima Minamimachi, Chuo-ku, Kobe-city, Hyogo, 650-0047, Japan
Telephone: 81-78-302-4321, Fax: 81-78-302-5534
E-mail: t-takase@kcho.jp
Summary

Edoxaban is used to prevent and treat stroke or systemic embolism such as venous thromboembolism. Although bleeding is the most common complication of anticoagulants, only a few studies have addressed the safety of direct oral anticoagulants in East Asian patients. In this study, we investigated the risk factors for bleeding in Japanese patients receiving edoxaban. A retrospective review of the records of 198 patients who received 30 mg/day edoxaban in our hospital between April 2015 and March 2017 was performed. Subsequently, these patients were followed up to 1 year. Seven (3.5%) and 22 (11.1%) patients developed major bleeding and clinically relevant bleeding, respectively. In the univariate Cox regression analyses, low baseline hemoglobin levels ($p = 0.002$) and low baseline creatinine clearance ($p = 0.020$) were significantly associated with major bleeding. Multivariate Cox regression analysis revealed that a low baseline hemoglobin level was a significant risk factor for major bleeding and clinically relevant bleeding [hazard ratio 1.67 per 1 g/dL decrease (95% confidence interval 1.14–2.56, $p = 0.008$) and hazard ratio 1.31 per 1 g/dL decrease (95% confidence interval 1.06–1.62, $p = 0.013$), respectively]. Baseline hemoglobin level in quartiles also showed a quartile-dependent decrease in major bleeding and clinically relevant bleeding event. These results suggest that low baseline hemoglobin level is a significant risk factor for both major bleeding and clinically relevant bleeding in Japanese patients receiving edoxaban. Thus, these patients should be carefully monitored.

Keywords: edoxaban, risk factor, major bleeding, hemoglobin, clinically relevant bleeding, Japanese
Introduction

Edoxaban is one of the direct oral anticoagulants (DOACs; dabigatran, rivaroxaban, apixaban, and edoxaban) that is used to prevent and treat stroke or systemic embolism such as venous thromboembolism. Edoxaban is the most frequently prescribed DOAC in Kobe City Medical Center General Hospital [1,054 (45.9%) out of 2,294 patients in 2018], and also in Japan. As bleeding is the most common complication of anticoagulants, balancing the clinical benefit for thromboembolism with the risk of bleeding is essential for effective and safe use of anticoagulants. To maximize the safety aspect of these medications, it is necessary to identify the risk factors for bleeding. At present, anemia, age, kidney dysfunction, concomitant use of antiplatelet, history of bleeding, and race have been identified as risk factors for bleeding in patients treated with vitamin K antagonists or DOACs. Most studies investigating the risk factors for bleeding were based on patients in Western countries, who typically have a larger body weight than East Asian patients. The risk of intracranial bleeding is higher in Asian patients receiving warfarin or DOACs than non-Asians. Besides, the risk factor for bleeding might also be different between different races. Only few studies have addressed the safety of DOACs in East Asian patients and very little has been reported on the risks for bleeding in Japanese patients receiving edoxaban. Thus, to identify the risk factors for bleeding, assessing adverse events due to edoxaban is of particular importance in this patient population.

In this study, we investigated the risk factors for bleeding in Japanese patients receiving edoxaban.

Materials and Methods

This retrospective cohort study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research by the Ministry of
Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare of Japan. The protocol was approved by the institutional review board of Kobe City Medical Center General Hospital, Japan (Approval No. zn190621). The need for informed consent was waived for this retrospective study. Patient characteristics including age, sex, body weight, medical history, incidence of bleeding complications, concomitant medications, and laboratory data were reviewed using the electronic medical record system. All variables were recorded at baseline (before edoxaban administration).

**Patients**

A total of 640 consecutive patients who received edoxaban (30 mg/day) in our hospital between April 1, 2015 and March 31, 2017 were included in the present study. Patients were excluded if they received edoxaban for less than 3 months (n = 402), began edoxaban treatment at another institution (n = 35), or had missing body weight (n = 2) or serum creatinine (n = 3) data. The remaining 198 patients were followed up to 1 year.

**Bleeding definition**

Bleeding complications were evaluated by compiling the following bleeding events: (a) major bleeding, (b) clinically relevant non-major bleeding (CRNMB), and (c) minor bleeding. Major bleeding was defined by the International Society on Thrombosis and Hemostasis criteria as clinically overt bleeding accompanied by a decrease in hemoglobin levels of at least 2 g/dL or the requirement of a transfusion with at least 2 units of packed red blood cells, at a critical site (intracranial, intraocular, intraspinal, intra-articular, intramuscular with compartment syndrome, pericardial, or retroperitoneal), or death. CRNMB was defined as acute or subacute clinically overt bleeding that did not satisfy the criteria of major bleeding, thereby leading to hospitalization for bleeding, physician-guided
medical or surgical treatment for bleeding, or a change in antithrombotic therapy (including the study drug) due to bleeding. Minor bleeding was defined as all acute, clinically overt bleeding events that did not meet the criteria of major bleeding or CRNMB. These bleeding events, such as major bleeding or CRNMB, were defined as clinically relevant bleeding.\(^{16}\)

### Objectives

The primary objective of this study was to detect the risk factors associated with major bleeding in patients receiving 30 mg/day edoxaban. Secondary objectives were to detect risk factors for clinically relevant bleeding and the incidences of bleeding events.

### Statistical analysis

Statistical analyses were performed using JMP 13.2.1 (SAS Institute Inc., Cary, NC, USA). For continuous data, values are presented as mean ± standard deviation (SD). Student’s t-test, Fisher’s exact test, and Wilcoxon rank-sum test were used to assess differences between major bleeding group and non-major bleeding group. To identify the risk factors associated with major bleeding and clinically relevant bleeding, univariate Cox regression analyses were performed using the clinical variables that are known to be associated with bleeding, such as hemoglobin levels, age, creatinine clearance (CrCl), concomitant use of antiplatelet, and history of bleeding.\(^{1-11}\) Significant factors in univariate analyses were evaluated as potential covariates in multivariate Cox regression analyses. The correlation between significant factor in multivariate analysis and, CHADS\(_2\) score or HAS-BLED score, were assessed by using Spearman's rank correlation coefficient. All \(p\)-values < 0.05 were considered statistically significant.

### Results

#### Patient characteristics

Patient characteristics are shown in Table 1. Incidence of major bleeding was 3.5%
Mean baseline hemoglobin levels and CrCl were significantly lower in patients that developed major bleeding than those that did not develop this bleeding. The median follow-up period was 365 days (range, 90 to 365).

**Risk factors for bleeding events**

In the univariate Cox regression analyses, low baseline hemoglobin levels [hazard ratio (HR) 1.82 per 1 g/dL decrease, 95% confidence interval (CI) 1.23–2.78, \( p = 0.002 \)] and low baseline CrCl (HR 1.67 per 10 mL/min decrease, 95% CI 1.11–2.87, \( p = 0.020 \)) were significantly associated with major bleeding (Table 2). Similarly, low baseline hemoglobin levels (HR 1.35 per 1 g/dL decrease, 95% CI 1.09–1.67, \( p = 0.006 \)) and low baseline CrCl (HR 1.22 per 10 mL/min decrease, 95% CI 1.00–1.50, \( p = 0.044 \)) were significantly associated with clinically relevant bleeding (Table 3).

Multivariate Cox regression analysis revealed that low baseline hemoglobin levels were significant risk factors for major bleeding and clinically relevant bleeding [HR 1.67 per 1 g/dL decrease (95% CI 1.14–2.56, \( p = 0.008 \)) and HR 1.31 per 1 g/dL decrease (95% CI 1.06–1.62, \( p = 0.013 \)), respectively, Tables 2 and 3].

Figure 1 shows the relationships between incidence of bleeding and baseline hemoglobin levels. The baseline hemoglobin levels were grouped into four quartiles: the lower quartile (Q1) included the 25% of patients with the lowest hemoglobin level (≤10.7 g/dL); Q2 (10.8–12.1 g/dL) and Q3 (12.2–13.1 g/dL) extended 25% below and above the median hemoglobin level, respectively; Q4 included the 25% of patients with the highest hemoglobin level (>13.1 g/dL). The incidence rates of major bleeding and clinically relevant bleeding in Q1, Q2, Q3, and Q4 were 8.0%, 3.8%, 2.1%, and 0%, respectively (Fig. 1A), and 22.0%, 9.6%, 8.5%, and 4.1%, respectively (Fig. 1B).

Baseline hemoglobin level was not significantly correlated with either CHADS2 score.
Discussion

We evaluated the risk factors for bleeding in Japanese patients receiving edoxaban. In the multivariate Cox regression analysis, low baseline hemoglobin level was identified as a significant risk factor for major bleeding and clinically relevant bleeding (Tables 2 and 3). Baseline hemoglobin level in quartiles also showed a quartile-dependent decrease in major bleeding and clinically relevant bleeding event (Fig. 1).

The risk factors for bleeding in patients receiving vitamin K antagonists or DOACs has been reported, with anemia, age, kidney dysfunction, concomitant use of antiplatelet, and history of bleeding being identified as common risk factors for bleeding events. For edoxaban, Nisio et al. conducted a subgroup analysis of the phase 3 Hokusai-VTE study and found that the female sex, concomitant use of antiplatelet, hemoglobin levels ≤ 10 g/dL, history of arterial hypertension, and systolic blood pressure > 160 mmHg were risk factors for major bleeding. Aisenberg et al. conducted a subgroup analysis of the phase 3 ENGAGE AF-TIMI 48 study. They found that the male sex, increased age, prior gastrointestinal bleeding, concomitant aspirin, low baseline hemoglobin, kidney dysfunction, and high HAS-BLED and CHADS2 scores were risk factors for major gastrointestinal bleeding in patients receiving edoxaban. However, most study subjects were patients in Western countries and they typically have a larger body weight than East Asians, including Japanese patients. Shinohara et al. conducted a retrospective cohort study and reported that low body mass index was the risk factor for bleeding in Japanese non-severe frail octogenarians with atrial fibrillation (n = 346) receiving anticoagulants (i.e., dabigatran, rivaroxaban, apixaban, edoxaban, or warfarin). In their study, however, the risk factor was evaluated in conjunction with 5 anticoagulants, and the number of
patients who received edoxaban was limited (n = 27). To add, the risk factor was evaluated based on incidences of all bleeding events including major bleeding, CRNMB, and minor bleeding, with minor bleeding as the most dominant (72.9%). CRNMB and major bleeding, and not minor bleeding, are independently associated with all-cause mortality in patients with atrial fibrillation treated with anticoagulation therapy. Therefore, identifying the risk factors for clinically relevant bleeding with edoxaban is of particular importance in Asian patients. To the best of our knowledge, this is the first study to investigate each risk factor for major bleeding and clinically relevant bleeding events in Japanese patients receiving edoxaban.

The incidence of major bleeding in our study was similar to that of phase 3 clinical trials (3.5% vs 3.1%). In multivariate Cox regression analyses, low baseline hemoglobin level was identified as a significant risk factor for major bleeding and clinically relevant bleeding (Tables 2 and 3). Regardless of the type of DOACs, many studies have indicated that a low baseline hemoglobin level is one of the risk factors for bleeding events. This study revealed that low baseline hemoglobin levels are risk factors for major bleeding and clinically relevant bleeding in Japanese patients receiving edoxaban. These results are consistent with previous studies that were mainly performed in patients from Western countries. Although the mechanism of the association between low hemoglobin levels and the high incidence of bleeding is unclear, hemoglobin level was not found to influence the pharmacokinetic parameters of edoxaban. Low hematocrit levels have been reported to prolong bleeding time, which may be due to a decrease in the diffusion and activity of platelets by red blood cells. Pharmacodynamic interactions between edoxaban and low hemoglobin levels might additively increase the risk of bleeding. Our results suggested that the hemoglobin levels of each patients should be carefully monitored to prevent clinically relevant bleeding.
This study had some limitations. First, only few patients were retrospectively analyzed at a single center. Second, although active bleeding was not observed at the onset of edoxaban treatment, low baseline hemoglobin levels in subjects might reflect occult gastrointestinal bleeding. Third, blood concentrations of edoxaban or anti-factor Xa activities were not measured.

**Conclusion**

To summarize, our data suggest that low baseline hemoglobin level is a significant risk factor for both major bleeding and clinically relevant bleeding in Japanese patients receiving edoxaban. Based on these results, careful monitoring of patients treated with edoxaban should be performed.

**Conflict of Interest**

YF received speaker's bureaus from Daiichi Sankyo Co., Ltd.
References

1) Di Nisio M, Raskob G, Büller HR, Grosso MA, Zhang G, Winters SM, Cohen A. Prediction of major and clinically relevant bleeding in patients with VTE treated with edoxaban or vitamin K antagonists. *Thromb. Haemost.*, **117**, 784–793 (2017).

2) Aisenberg J, Chatterjee-Murphy P, Friedman Flack K, Weitz JI, Ruff CT, Nordio F, Mercuri MF, Choi Y, Antman EM, Braunwald E, Giugliano RP. Gastrointestinal bleeding with edoxaban versus warfarin: Results from the ENGAGE AF-TIMI 48 trial (effective anticoagulation with factor Xa next generation in atrial fibrillation-thrombolysis in myocardial infarction). *Circ. Cardiovasc. Qual. Outcomes.*, **11**, e003998 (2018).

3) Zenati N, Gaboreau Y, Provencher CB, Albaladejo P, Bosson JL, Pernod G. Anaemia as an independent key risk factor for major haemorrhage in patients treated with vitamin K antagonists: Results of the SCORE prospective cohort. *Thromb. Res.*, **151**, 83–88 (2017).

4) Ruíz-Giménez N, Suárez C, González R, Nieto JA, Todolí JA, Samperiz AL, Monreal M; RIETE Investigators. Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism. Findings from the RIETE registry. *Thromb. Haemost.*, **100**, 26–31 (2008).

5) Westenbrink BD, Alings M, Granger CB, Alexander JH, Lopes RD, Hylek EM, Thomas L, Wojdyla DM, Hanna M, Keltai M, Steg PG, De Caterina R, Wallentin L, van Gilst WH. Anemia is associated with bleeding and mortality, but not stroke, in patients with atrial fibrillation: Insights from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. *Am. Heart J.*, **185**, 140–149 (2017).

6) Hori M, Matsumoto M, Tanahashi N, Momomura SI, Uchiyama S, Goto S, Izumi T,
Koretsune Y, Kajikawa M, Kato M, Cavaliere M, Iekushi K, Yamanaka S; J-ROCKET AF Study Investigators. Predictive factors for bleeding during treatment with rivaroxaban and warfarin in Japanese patients with atrial fibrillation—Subgroup analysis of J-ROCKET AF. *J. Cardiol.*, **68**, 523–528 (2016).

7) Westenbrink BD, Alings M, Connolly SJ, Eikelboom J, Ezekowitz MD, Oldgren J, Yang S, Pongue J, Yusuf S, Wallentin L, van Gilst WH. Anemia predicts thromboembolic events, bleeding complications and mortality in patients with atrial fibrillation: insights from the RE-LY trial. *J. Thromb. Haemost.*, **13**, 699–707 (2015).

8) Goodman SG, Wojdyla DM, Piccini JP, White HD, Paolini JF, Nessel CC, Berkowitz SD, Mahaffey KW, Patel MR, Sherwood MW, Becker RC, Halperin JL, Hacke W, Singer DE, Hankey GJ, Breithardt G, Fox KA, Califf RM; ROCKET AF Investigators. Factors associated with major bleeding events: insights from the ROCKET AF trial (rivaroxaban once-daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). *J. Am. Coll. Cardiol.*, **63**, 891–900 (2014).

9) Hylek EM, Held C, Alexander JH, Lopes RD, De Caterina R, Wojdyla DM, Huber K, Jansky P, Steg PG, Hanna M, Thomas L, Wallentin L, Granger CB. Major bleeding in patients with atrial fibrillation receiving apixaban or warfarin: The ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): Predictors, Characteristics, and Clinical Outcomes. *J. Am. Coll. Cardiol.*, **63**, 2141–2147 (2014).

10) Beshir SA, Aziz Z, Yap LB, Chee KH, Lo YL. Evaluation of the predictive performance of bleeding risk scores in patients with non-valvular atrial fibrillation on oral anticoagulants. *J. Clin. Pharm. Ther.*, **43**, 209–219 (2018).

11) Sherwood MW, Nessel CC, Hellkamp AS, Mahaffey KW, Piccini JP, Suh EY, Becker
RC, Singer DE, Halperin JL, Hankey GJ, Berkowitz SD, Fox KAA, Patel MR. Gastrointestinal bleeding in patients with atrial fibrillation treated with rivaroxaban or warfarin: ROCKET AF trial. *J. Am. Coll. Cardiol.*, **66**, 2271–2281 (2015).

12) Shen AY, Yao JF, Brar SS, Jorgensen MB, Chen W. Racial/ethnic differences in the risk of intracranial hemorrhage among patients with atrial fibrillation. *J. Am. Coll. Cardiol.*, **50**, 309–315 (2007).

13) Yamashita T, Koretsune Y, Yang Y, Chen SA, Chung N, Shimada YJ, Kimura T, Miyazaki K, Abe K, Mercuri M, Ruff CT, Giugliano RP. Edoxaban vs. warfarin in east asian patients with atrial fibrillation - an ENGAGE AF-TIMI 48 subanalysis. *Circ. J.*, **80**, 860–869 (2016).

14) Bahit MC, Lopes RD, Wojdyla DM, Held C, Hanna M, Vinereanu D, Hylek EM, Verheugt F, Goto S, Alexander JH, Wallentin L, Granger CB. Non-major bleeding with apixaban versus warfarin in patients with atrial fibrillation. *Heart.*, **103**, 623–628 (2017).

15) Schulman S, Kearon C, Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J. Thromb. Haemost.*, **3**, 692–694 (2005).

16) Apostolakis S, Lane DA, Guo Y, Buller H, Lip GY. Performance of the HEMORR2HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in nonwarfarin anticoagulated atrial fibrillation patients. *J. Am. Coll. Cardiol.*, **61**, 386–387 (2013).

17) Shinohara M, Fujino T, Yao S, Yano K, Akitsu K, Koike H, Kinoshita T, Yuzawa H, Suzuki T, Kobayashi K, Ikeda T. Assessment of the bleeding risk of anticoagulant treatment in non-severe frail octogenarians with atrial fibrillation. *J. Cardiol.*, **73**, 7–13 (2019).
18) Ruff CT, Giugliano RP, Braunwald E, Morrow DA, Murphy SA, Kuder JF, Deenadayalu N, Jarolim P, Betcher J, Shi M, Brown K, Patel I, Mercuri M, Antman EM. Association between edoxaban dose, concentration, anti-Factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial. *Lancet.*, **385**, 2288–2295 (2015).

19) Niebecker R, Jönsson S, Karlsson MO, Miller R, Nyberg J, Krekels EH, Simonsson US. Population pharmacokinetics of edoxaban in patients with symptomatic deep-vein thrombosis and/or pulmonary embolism--the Hokusai-VTE phase 3 study. *Br. J. Clin. Pharmacol.*, **80**, 1374–1387 (2015).

20) Jönsson S, Simonsson US, Miller R, Karlsson MO. Population pharmacokinetics of edoxaban and its main metabolite in a dedicated renal impairment study. *J. Clin. Pharmacol.*, **55**, 1268–1279 (2015).

21) Krekels EH, Niebecker R, Karlsson MO, Miller R, Shimizu T, Karlsson KE, Ruff CT, Simonsson US, Jönsson S. Population pharmacokinetics of edoxaban in patients with non-valvular atrial fibrillation in the ENGAGE AF-TIMI 48 study, a phase III clinical trial. *Clin. Pharmacokinet.*, **55**, 1079–1090 (2016).

22) Anand A, Feffer SE. Hematocrit and bleeding time: an update. *South Med. J.*, **87**, 299–301 (1994).

23) Boneu B, Fernandez F. The role of the hematocrit in bleeding. *Transfus. Med. Rev.*, **1**, 182–185 (1987).

24) Gotoh S, Hata J, Ninomiya T, Hirakawa Y, Nagata M, Mukai N, Fukuhara M, Ikeda F, Ago T, Kitazono T, Kiyohara Y. Hematocrit and the risk of cardiovascular disease in a Japanese community: The Hisayama Study. *Atherosclerosis.*, **242**, 199–204 (2015).

25) Rockey DC. Occult and obscure gastrointestinal bleeding: causes and clinical management. *Nat. Rev. Gastroenterol. Hepatol.*, **7**, 265–279 (2010).
Table 1 Patient characteristics.

|                         | Overall (n = 198) | Major bleeding (n = 7) | Without major bleeding (n = 191) | p-Value |
|-------------------------|------------------|------------------------|----------------------------------|---------|
| Age, years (mean ± SD)  | 70.1 ± 12.6      | 75.3 ± 14.1            | 69.9 ± 12.5                      | 0.265⁹⁰ |
| Male/Female, n          | 78/120           | 2/5                    | 76/115                           | 0.708⁰⁰ |
| Body weight, kg (%)     |                  |                        |                                  |         |
| >60 kg                  | 42 (21.2%)       | 0 (0%)                 | 42 (22.0%)                       | 0.349⁰⁰ |
| ≤50 kg                  | 156 (78.8%)      | 7 (100%)               | 149 (78.0%)                      |         |
| Enoxaban indication, n (%) |              |                        |                                  |         |
| DVT                     | 79               | 2 (28.6%)              | 77 (40.3%)                       |         |
| Atrial fibrillation     | 67               | 3 (42.9%)              | 64 (31.5%)                       |         |
| PE                      | 17               | 0 (0%)                 | 17 (8.9%)                        |         |
| DVT + PE                | 14               | 0 (0%)                 | 14 (7.3%)                        |         |
| Atrial flutter          | 4                | 0 (0%)                 | 4 (2.1%)                         |         |
| Cardiogenic embolism    | 4                | 0 (0%)                 | 4 (2.1%)                         |         |
| Other                   | 13               | 2 (28.6%)              | 11 (5.8%)                        |         |
| Comorbidity, n (%)      |                  |                        |                                  |         |
| Hypertension            | 89               | 3 (42.9%)              | 86 (45.0%)                       |         |
| Cancer                  | 79               | 1 (14.3%)              | 78 (40.8%)                       |         |
| Diabetes                | 57               | 1 (14.3%)              | 36 (18.8%)                       |         |
| Heart failure/LVEF      | 28               | 2 (28.6%)              | 26 (13.9%)                       |         |
| Coronary artery disease | 24               | 3 (42.9%)              | 21 (11.0%)                       |         |
| Stroke/TIA/Systemic embolism | 19           | 0 (0%)                 | 19 (9.9%)                        |         |
| Peripheral artery disease | 15           | 0 (0%)                 | 15 (7.9%)                        |         |
| Cerebral hemorrhage     | 6                | 0 (0%)                 | 6 (3.1%)                         |         |
| History of bleeding     | 15               | 1 (14.3%)              | 14 (7.3%)                        | 0.439⁰⁰ |
| CHADS2 score (mean ± SD)| 1.3 ± 1.1        | 1.6 ± 1.4              | 1.3 ± 1.1                        | 0.533⁰⁰ |
| CHA2DS2-VASc score (mean ± SD) | 2.1 ± 1.3     | 2.7 ± 1.5              | 2.1 ± 1.2                        | 0.196⁰⁰ |
| HAS-BLED score (mean ± SD) | 1.7 ± 1.1     | 1.9 ± 1.3              | 1.7 ± 1.1                        | 0.714⁰⁰ |
| Concomitant medication, n (%) |          |                        |                                  |         |
| PPI or H2RA             | 94               | 5 (71.4%)              | 89 (46.6%)                       | 0.260⁰⁰ |
| Antiplatelet            | 31               | 2 (28.6%)              | 29 (15.2%)                       | 0.301⁰⁰ |
| P-gp inhibitor          | 22               | 2 (28.6%)              | 20 (10.5%)                       | 0.176⁰⁰ |
| NSAIDs                  | 10               | 1 (14.3%)              | 9 (4.7%)                         | 0.308⁰⁰ |
| Hemoglobin, g/dL (mean ± SD) | 11.9 ± 2.0   | 9.8 ± 1.9              | 12.0 ± 1.9                       | 0.007⁰⁰ |
| Treatment period (day)  | 293.3 ± 92.9     | 203.6 ± 104            | 296.6 ± 91.1                     | 0.009⁰⁰ |
| CrCl (mL/min), n (%)    |                  |                        |                                  | 0.008⁰⁰ |
| >50                     | 149              | 7 (28.6%)              | 147 (77.0%)                      |         |
| >15 to 50               | 49               | 5 (71.4%)              | 44 (23.0%)                       |         |

DVT, deep vein thrombosis; PE, pulmonary embolism; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack; PPI, proton pump inhibitor; H2RA, histamine H2-receptor antagonist; P-gp, P-glycoprotein; NSAIDs, nonsteroidal anti-inflammatory drugs; CrCl, creatinine clearance.

a) Student’s t-test, b) Fisher’s exact test, c) Wilcoxon rank-sum test.
### Table 2. Risk factors of major bleeding events.

| Risk Factor                                         | Univariate       | Multivariate    |
|-----------------------------------------------------|------------------|-----------------|
| Low baseline hemoglobin levels (per 1 g/dL decrease)| HR 1.82, 95% CI 1.23–2.78, p-Value 0.002 | HR 1.67, 95% CI 1.14–2.56, p-Value 0.008 |
| Low baseline CrCl (per 10 mL/min decrease)           | HR 1.67, 95% CI 1.11–2.87, p-Value 0.020 | HR 1.48, 95% CI 0.97–2.56, p-Value 0.073 |
| Concomitant use of antiplatelet                      | HR 2.30, 95% CI 0.45–11.90, p-Value 0.319 |
| History of bleeding                                  | HR 1.93, 95% CI 0.23–16.02, p-Value 0.543 |
| Age (per 10 years increase)                          | HR 1.48, 95% CI 0.74–3.11, p-Value 0.242 |

HR: hazard ratio, CI: confidence interval, CrCl: creatinine clearance
Table 3. Risk factors of clinically relevant bleeding events.

| Risk Factor                                      | Univariate |               | Multivariate |               |
|--------------------------------------------------|------------|---------------|--------------|---------------|
|                                                  | HR         | 95% CI        | p-Value      | HR            | 95% CI        | p-Value      |
| Low baseline hemoglobin levels (per 1 g/dL decrease) | 1.35       | 1.09–1.67     | 0.006        | 1.31          | 1.06–1.62     | 0.013        |
| Low baseline CrCl (per 10 mL/min decrease)       | 1.22       | 1.00–1.50     | 0.044        | 1.19          | 0.97–1.50     | 0.101        |
| Concomitant use of antiplatelet                   | 1.61       | 0.60–4.38     | 0.347        |               |               |              |
| History of bleeding                               | 1.14       | 0.27–4.86     | 0.864        |               |               |              |
| Age (per 10 years increase)                       | 1.10       | 0.82–1.63     | 0.528        |               |               |              |

HR; hazard ratio, CI; confidence interval, CrCl; creatinine clearance
Fig. 1 Relationship between incidence of bleeding and baseline hemoglobin levels in patients treated with edoxaban.

Relationship between incidence of major bleeding (A), clinically relevant bleeding (B) and baseline hemoglobin levels. Baseline hemoglobin levels were grouped into four quartiles. Baseline hemoglobin level: Q1, ≤10.7 g/dL; Q2, 10.8–12.1 g/dL; Q3, 12.2–13.1 g/dL; Q4, >13.1 g/dL.