Association of risk factors and bleeding complications in Asian patients taking edoxaban

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Abstract

Aim: Asian patients are known to be more prone to bleeding complications than patients of other ethnicities. Therefore, there are possibilities of other risk factors that should be given special consideration for dosage adjustment in this specific ethnic group. This study aimed to investigate the risk factors for bleeding complications in Asian patients under appropriate edoxaban dosage regimens. Methods: Data on patients taking proper dosages, based on the Lixiana package insert, were analyzed. Univariate and multivariable analyses were conducted to evaluate associations between risk factors and bleeding outcomes. Subgroup analysis was performed on high-risk patients for bleeding complications whose edoxaban dose was reduced according to the package insert. Results: A total of 346 patients were included. Among them, 32 patients experienced bleeding complications. Patients with either weights of less than or equal to 60 kg and with cancer showed around 3.3- and 3.4-fold increased risk of bleeding complications compared to heavier patients ($>$ 60 kg) and those without cancer, respectively. In subgroup analysis with high-risk patients who took low-dose edoxaban (15 mg and 30 mg), weights of less than or equal to 60 kg remained a significant factor for bleeding outcomes. Conclusion: This study showed that weights of less than or equal to 60 kg and the presence of cancers could affect bleeding complications which occurred despite proper edoxaban treatment in Asian patients. Therefore, more strict dosage guideline could be considered in populations with high proportions of Asian ethnicities.

Introduction

Direct oral anticoagulants (DOACs) are widely used for treatment and prophylaxis of atrial fibrillation (AF), ischemic stroke, deep vein thrombosis (DVT), and pulmonary embolism (PE). The recent 2019 AHA/ACC/HRS Focused Update of the 2014 guidelines for management of patients with AF states that DOACs are recommended over warfarin in eligible patients [1]. Although warfarin has been the most widely used oral anticoagulant, due to its shortcomings including a narrow therapeutic range and wide inter-and intra-individual variability [2], DOACs are currently preferred in many clinical settings [3, 4].

Among DOACs, edoxaban is the most recently introduced drug [5] and has mainly been used as an alternative to other DOACs. However, after many studies showed that both high-dose and low-dose edoxaban were not inferior to warfarin for stroke prevention and associated with a significantly lower incidence of bleeding complications [6-9], edoxaban became a representative DOAC [1]. Hence, edoxaban is likely to be prescribed more widely in the future, depending on the clinical setting or patient profile.

Bleeding complication is one of the major concerns during edoxaban usage [10]. The generally recommended dose of edoxaban for treatment of DVT/PE and AF is 60 mg once daily. In order to reduce the incidence of bleeding complications, patients with creatinine clearance (CrCl) 15 to 50 mL/min, weights of less than or equal to 60 kg, or who are taking certain concomitant P-glycoprotein (P-gp) inhibitors are recommended

to take 30 mg once daily for treatment of DVT and PE instead [5]. However, Asian patients are known to be more prone to bleeding complications than patients of other ethnicities [11], opening possibilities of other risk factors that should be given special consideration for dosage adjustment in this specific ethnic group. In this context, this study aimed to provide evidence of the association between risk factors and bleeding complications in Asian patients with an appropriate edoxaban dosage regimen.

Methods

Study patients and data collection

This study consists of 510 patients who were prescribed by Seoul National University Hospital with edoxaban between March 1, 2016 and June 30, 2017. Patients who were 18 or older and received proper dosage of edoxaban based on Lixiana package insert (Korean version) [12] were eligible for the study. Patients who received inappropriate dose of edoxaban were excluded. Data collection was conducted using electronic medical records. Data on age, sex, weight, serum creatinine, comorbidities, concurrent medication, international normalized ratio (INR) measurements, history of bleeding complications, and liver function test (cirrhosis or bilirubin >2x normal, or aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3x normal) were collected. Bleeding complications were classified as major, clinically relevant non-major, or minor bleeding using the scheme detailed in the International Society on Thrombosis and Hemostasis criteria [13].

This study was approved by the Institutional Review Board of the Seoul National University Hospital (approval number: H-1809-044-971).

Statistical analysis

Chi-square test or Fisher's exact test was used to compare categorical variables between patients with bleeding complications and those without complications. Multivariable logistic regression analysis was used to examine independent risk factors for bleeding complications. Factors having a p-value less than 0.05 in univariate analysis along with clinically relevant confounders (age, sex, and CrCl) were included in multivariable analysis. Subgroup analysis was conducted on high-risk patients for bleeding complications whose edoxaban dose was reduced to less than or equal to 30 mg. Odds ratios and adjusted odds ratios were calculated through univariate and multivariable analyses, respectively. A p-value of less than 0.05 was considered statistically significant. To test the model's goodness of fit, we performed a Hosmer–Lemeshow test. All statistical analyses were conducted using IBM SPSS statistics, version 20 software (International Business Machines Corp., New York, USA).

Results

Among the 510 patient enrolled in this study, 164 patients were excluded due to the usage of inappropriate dose of edoxaban. Accordingly, data on 346 patients, who were receiving recommended dosages of edoxaban, were used for the analysis. The median age of the included patients was 73 years (range, 34-93 years), and there were 168 (48.6%) females. Thirty two patients (9.2%) experienced bleeding complications after taking edoxaban. Among them, 16 patients experienced major bleeding complications. Two and eight patients experienced intracranial hemorrhage and gastrointestinal bleeding complications, respectively. Six patients showed urological bleeding and 11 had unclassified bleeding outcomes. Eleven patients experienced stroke or recurrent DVT/PE.

As shown in Table 1, patients less than or equal to 60 kg had more bleeding complications than those who were heavier than 60 kg (p=0.018). Also, patients with cancer had more bleeding outcomes than those without cancer (p=0.030).

Multivariable analysis (Table 2) included sex, age, CrCl, and factors with $p<0.05$ in univariate analysis (weight and cancer). After adjusting for related covariates, patients with cancer or weights less than or equal to 60 kg showed approximately 3.4-fold higher bleeding complications than patients without cancer or

with weights higher than 60 kg. The Hosmer–Lemeshow test showed that the fitness of the multivariable analysis model was satisfactory (χ^2=11.335, 6 degrees of freedom, p=0.079).

Since more than 10% of patients had bleeding complications even after dose reduction, we performed subgroup analysis to investigate factors on bleeding complications in high-risk patients receiving a low dose of edoxaban. We found that weight was a significant factor for bleeding outcomes in both univariate and multivariable analysis (Table 3 and Table 4). Patients with weight [?]60 kg showed 3.3-times higher bleeding complications even with low dose of edoxaban compared to those with weight >60 kg. Hosmer–Lemeshow test showed that the fitness of the multivariable analysis model was satisfactory (χ^2=3.636, 6 degrees of freedom, p=0.726).

Discussion

The main finding of this study is that weight ([?] 60 kg) and cancer were associated with bleeding complications under appropriate edoxaban dosage regimen. Patients with weights of less than or equal to 60 kg and cancer had around a 3.4-fold increased risk of bleeding complications compared to heavier patients (>60 kg) and those without cancer. In the subgroup analysis with high-risk patients who took low-dose edoxaban (15 mg and 30 mg), weights of less than or equal to 60 kg was remained a significant factor for bleeding outcomes than those who weigh more than 60 kg.

Edoxaban is implicated in the reduction of stroke and systemic embolism risks in nonvalvular AF and treatment of DVT and PE [5]. According to the 2019 AHA/ACC/HRS Guideline for the Management of AF, edoxaban has been added to the list of DOACs used for stroke prevention and is recommended over warfarin except in patients with moderate to severe mitral stenosis or prosthetic heart valves [1]. Several studies have shown that edoxaban was not inferior to warfarin regarding the prevention of stroke or systemic embolization and was associated with significantly lower rates of bleeding and death from cardiovascular causes [6-9]. Yet, although edoxaban is the preferred oral anticoagulant over warfarin, it still can increase the risk of bleeding and can cause serious or even potentially fatal bleeding. Hence, risk factors should be carefully considered when administering edoxaban.

It has been reported that Asians exhibit more bleeding risks than other ethnicities; a study showed that death from hemorrhagic stroke was more common in Asian patients compared to others [14]. Reports of bleeding complications with antithrombotic agents also consistently revealed that Asians experienced more bleeding complications than other ethnic groups. A meta-analysis showed that DOAC-associated intracranial hemorrhage (ICH) was significantly higher in the Asian population [15]. In addition, in the case of warfarin treatment, a retrospective cohort study using AF patients showed that the incidence for ICH in Asians was 4.06-times higher than in Caucasians [16]. For antiplatelet therapy, a meta-analysis showed that bleeding events occurred twice as frequently in Asians than in the non-Asian group [17].

Most dosage studies of oral anticoagulants have primarily involved Caucasians; therefore, current edoxaban dosage regimens may have been predominantly derived from data on white patients. This study showed that standard dosage regimens of edoxaban induced complications in Asian individuals, which may stem from ethnicity-dependent profiles. The U.S. Savaysa package insert suggested that DVT/PE patients with CrCl 15 to 50 mL/min, weights of less than or equal to 60 kg, or who are taking certain concomitant P-gp inhibitors are recommended to take 30 mg once daily [5]. Also, for patients with nonvalvular AF, CrCl 15-50 mL/min was the sole criterion for dose reduction [5]. In contrast, the Korean package insert suggests that patients with AF, in addition to DVT/PE, should reduce edoxaban dose under two more criteria, namely lower weight ([?] 60 kg) and P-gp inhibitor concomitant usage, alongside CrCl 15-50 mL/min. [12]. Thus it may be stated that considering high bleeding risks of Asian populations, the Korean dose recommendation is much more conservative.

In this study, subgroup analyses showed that 27 patients still experienced bleeding complications despite dosage adjustments. It has been previously established that the incidence of bleeding events during edoxaban administration shows a dose-dependent trend [18]. Moreover, Yamashita et al. reported body weight-dependent differences in the incidence of bleeding risks, suggesting that weight is an important factor to consider in assessing the risk of bleeding while taking edoxaban [18]. Hence, for ethnic groups that are known

to be more prone to bleeding complications, modification of anticoagulation intensity may be considered. Since the current results showed that lower weight was a significant risk factor for bleeding outcome even in patients using low-dose edoxaban, more strict dosage guidelines for patients with lower weights could be beneficial or perhaps necessary.

This study revealed that cancer was significantly associated with bleeding complications for patients with edoxaban therapy. Cancer patients with anticoagulation are more prone to bleeding outcomes compared to those without cancer. A study showed that cancer patients on anticoagulation therapy had approximately 2.2-fold higher bleeding complications than those without malignancies [19]. Another retrospective analysis concluded that the incidence of bleeding complications for cancer patients was higher than in patients without cancer. Hutten et al. showed that patients with cancer, compared with nonmalignant patients, had a statistically significantly increased overall incidence (100 patient-years) of recurrence (27.1 vs 9.0, respectively) as well as bleeding (13.3 vs 2.1, respectively) [20]. Our study was also consistent with the findings that patients with cancer showed a 3.4-fold increased risk of bleeding complications than those without cancer.

It is possible that bleeding is caused by the cancer itself, as tumor invasion, abnormal tumor vasculature or tumor regression can increase risk of bleeding [21]. Furthermore, anti-tumor treatment including chemotherapy and anti-inflammatory drugs can exacerbate bleeding outcomes. Finally, cancer patients with thrombocytopenia from malignancies or chemotherapy may result in bleeding complications [21]. In this context, cancer should be considered for dosage adjustment when administering edoxaban. Moreover, more frequent monitoring in this high-risk group may be recommended.

The limitations of our study are that it was conducted in a single center and designed retrospectively. Another shortcoming is a lack of information on detailed mechanisms and genetic polymorphisms. Nevertheless, this study revealed potential risk factors for bleeding complications in Asian patients undergoing edoxaban therapy. In addition, this study provided preliminary data to modify current dosage regimen to reduce the risk of bleeding outcomes; these factors can be applied for developing individualized drug therapy with edoxaban.

Authorship

Conceptualization: Ok Sang Lee, Woorim Kim, Bo Min Jang, Sandy Jeong Rhie, Kyung Eun Lee; Methodology: Ok Sang Lee, Woorim Kim; Formal analysis and investigation: Ok Sang Lee, Woorim Kim, Kyung Hyun Min ; Writing - original draft preparation: Woorim Kim, Ok Sang Lee; Writing - review and editing: Myung Koo Lee, Kyung Eun Lee; Funding acquisition: Kyung Eun Lee; Resources: Bo Min Jang, Yoon Sook Cho; Supervision: Kyung Eun Lee

All authors have read and approved the final version of this manuscript.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Table 1. Factors associated with bleeding events caused by edoxaban use

	No events N = 314	Events N = 32	*p*-value
Age (years)			
< 65	69 (22.0)	3 (9.4)	0.094
[?] 65	245 (78.0)	29 (90.6)	
Sex			
Male	165 (52.5)	13 (40.6)	0.199
Female	149 (47.5)	19 (59.4)	
Weight (kg)			
[?] 60	119 (37.9)	19 (59.4)	0.018
> 60	195 (62.1)	13 (40.6)	
CrCl (mL/min)			
15–50	91 (34.5)	8 (29.6)	0.613
> 50	173 (65.5)	19 (70.4)	
Medical history			
Congestive heart failure			
Yes	49 (15.6)	2 (6.2)	0.196
No	265 (84.4)	30 (93.8)	
Hypertension			
Yes	204 (65.0)	16 (50.0)	0.094
No	110 (35.0)	16 (50.0)	
Diabetes			
Yes	101 (32.2)	9 (28.1)	0.640
No	213 (67.8)	23 (71.9)	
Previous ischemic stroke or TIA			
Yes	47 (15.0)	5 (15.6)	1.000
No	267 (85.0)	27 (84.4)	
Vascular disease			
Yes	4 (1.3)	1 (3.1)	0.386
No	310 (98.7)	31 (96.9)	
Immobilization			
Yes	7 (2.2)	1 (3.1)	0.544
No	307 (97.8)	31 (96.9)	
Recent ([?]1 month) trauma and/or surgery			
Yes	4 (1.3)	0 (0.0)	1.000
No	310 (98.7)	32 (100.0)	
Abnormal liver function[a]			
Yes	10 (3.2)	2 (6.2)	0.306
No	304 (96.8)	30 (93.8)	
INR			
Normal	168 (53.5)	18 (56.2)	0.767
High[b]	146 (46.5)	14 (43.8)	
Previous bleeding			
Yes	43 (13.7)	8 (25.0)	0.112

	No events N = 314	Events N = 32	*p*-value
No	271 (86.3)	24 (75.0)	
Cancer			
Yes	28 (8.9)	7 (21.9)	0.030
No	286 (91.1)	25 (78.1)	
Medication			
Antiplatelet agents			
Yes	20 (6.4)	3 (9.4)	0.459
No	294 (93.6)	29 (90.6)	
Steroids			
Yes	7 (2.2)	1 (3.1)	0.544
No	307 (97.8)	31 (96.9)	

CrCl: Creatinine clearance; TIA: Transient ischemic attack; INR: International normalized ratio

[a]Cirrhosis or bilirubin >2× normal, or aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3× normal

[b]INR > 1.1

Table 2. Multivariable analysis to identify predictors of bleeding complications

	Crude OR (95% CI)	*p*-value	Adjusted* OR (95% CI)	*p*-value
Female	1.618 (0.773–3.390)	0.202		
Age [?] 65	2.722 (0.805–9.206)	0.107		
CrCl 15–50 (mL/min)	0.800 (0.337–1.900)	0.614		
Weight [?] 60 kg	2.395 (1.141–5.027)	0.021	3.378 (1.372–8.312)	0.008
Cancer	2.860 (1.136–7.203)	0.026	3.429 (1.275–9.224)	0.015

CrCl: Creatinine clearance

*Adjusted for sex, age, CrCl, weight, and cancer

Table 3. Subgroup analysis of factors associated with bleeding events in patients on low-dose edoxaban

	No events N = 231	Events N = 27	*p*-value
Age (years)			
< 65	43 (18.6)	3 (11.1)	0.433
[?] 65	188 (81.4)	24 (88.9)	
Sex			
Male	107 (46.3)	9 (33.3)	0.199
Female	124 (53.7)	18 (66.7)	
Weight (kg)			
[?] 60	125 (54.1)	20 (74.1)	0.048
> 60	106 (45.9)	7 (25.9)	
CrCl (mL/min)			
15–50	96 (50.8)	9 (40.9)	0.380
> 50	93 (49.2)	13 (59.1)	
Medical history			
Congestive heart failure			

	No events N = 231	Events N = 27	*p*-value
Yes	36 (15.9)	3 (11.1)	0.777
No	191 (84.1)	24 (88.9)	
Hypertension			
Yes	139 (61.2)	14 (51.9)	0.346
No	88 (38.8)	13 (48.1)	
Diabetes			
Yes	66 (29.1)	7 (25.9)	0.732
No	161 (70.9)	20 (74.1)	
Previous ischemic stroke or TIA			
Yes	44 (19.4)	6 (22.2)	0.726
No	183 (80.6)	21 (77.8)	
Vascular disease			
Yes	2 (0.9)	1 (3.7)	0.283
No	229 (99.1)	26 (96.3)	
Immobilization			
Yes	6 (2.6)	1 (3.7)	0.549
No	221 (97.4)	26 (96.3)	
Recent ([?]1 month) trauma and/or surgery			
Yes	4 (1.8)	0 (0.0)	1.000
No	223 (98.2)	27 (100.0)	
Abnormal liver function[a]			
Yes	4 (1.7)	1 (3.7)	0.427
No	227 (98.3)	26 (96.3)	
INR			
Normal	127 (55.0)	116 (59.3)	0.672
High[b]	104 (45.0)	11 (40.7)	
Previous bleeding			
Yes	35 (15.4)	7 (25.9)	0.174
No	192 (84.6)	20 (74.1)	
Cancer			
Yes	20 (8.7)	5 (18.5)	0.157
No	211 (91.3)	22 (81.5)	
Medication			
Antiplatelet agents			
Yes	19 (8.4)	3 (11.1)	0.714
No	208 (91.6)	24 (88.9)	
Steroids			
Yes	3 (1.3)	1 (3.7)	0.359
No	228 (98.7)	26 (96.3)	

CrCl: Creatinine clearance; TIA: Transient ischemic attack; INR: International normalized ratio

[a]Cirrhosis or bilirubin >2× normal, or aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3× normal

[b]INR > 1.1

Table 4. Multivariable analysis of subgroup analysis of factors associated with bleeding events in patients on

low-dose edoxaban

	Crude OR (95% CI)	p-value	Adjusted* OR (95% CI)	p-value
Female	1.726 (0.744–4.001)	0.203		
Age [?] 65	1.830 (0.527–6.355)	0.342		
CrCl 15–50 mL/min	0.671 (0.274–1.645)	0.382		
Weight [?] 60 kg	2.395 (1.141–5.027)	0.021	3.265 (1.078–9.886)	0.036

CrCl: Creatinine clearance

*adjusted for sex, age, CrCl, and weight