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Original Article

Characteristics and Effect of Rivaroxaban on Venous Thromboembolism in Korean Patients Compared to Western Population: A Subgroup Analysis from XALIA(-LEA) Study

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Purpose: This study aimed to compare the characteristics of venous thromboembolic disease (VTE) in Korean to Caucasian population.

Materials and Methods: XALIA-LEA and XALIA were phase IV non-interventional prospective studies with identical designs that investigated the effect of rivaroxaban versus standard anticoagulation for VTE. Koreans accounted for the largest proportion of the overall enrolled population of XALIA-LEA. However, in the XALIA study, most patients were Caucasian. Therefore, Korean data from XALIA-LEA and Caucasian data from XALIA were used in this study. This study compared the clinical characteristics and primary outcomes of the XALIA program, including major bleeding, recurrent VTE, and all-cause mortality.

Results: The Korean population was older, was less obese, and had more active cancer at baseline than the Caucasian population. Provoked VTE was more common in the Korean population. Interestingly, Koreans showed less accompanying thrombophilia than Caucasians, and factor V Leiden mutations were not detected. Korean analyses comparing the effects of rivaroxaban and standard anticoagulation with primary outcomes showed a lower incidence of major bleeding, recurrent VTE, and all-cause mortality with rivaroxaban. Similar results were obtained in the propensity score matching analysis.

Conclusion: Characteristic differences were found between Korean and Caucasian VTE patients. Despite these ethnic differences, the effectiveness and safety of rivaroxaban therapy in these patients were consistent.

Key Words: Venous thromboembolism, Anticoagulants, Rivaroxaban, South Korea, Ethnicity

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INTRODUCTION

Venous thromboembolism (VTE) of deep vein thrombosis (DVT) and pulmonary embolism (PE) is associated with reduced patient survival and considerable economic burden worldwide [1,2]. Vitamin K antagonists (VKAs) had been the standard of care for VTE. However, due to several disadvantages, such as a narrow therapeutic window requiring close monitoring, frequent interaction with food and drugs, or bleeding complications [3], non-VKA oral anticoagulants (NOACs) have rapidly replaced VKAs since their emergence.

The incidence of VTE in the Asian population has been increasing under certain circumstances, such as recent surgery [4,5] or hospital admission [6,7]. The incidence of VTE in Korea has increased over time [8,9], suggesting that it is a major concern. Possible reasons for this trend are the widespread adoption of a westernized lifestyle, increasing awareness among physicians, development of diagnostic techniques, and the growing older population [8-10]. Unfortunately, due to the lack of a well-organized registry for VTE patients in Korea, the clinical characteristics and outcomes of VTE patients after anticoagulant therapy have rarely been investigated.

The XALIA program assessed the effectiveness and safety of rivaroxaban and standard anticoagulation therapy for VTE treatment in clinical practice. This program was composed of two independent phase IV non-interventional prospective studies, XALIA [11] and XALIA-LEA [12], conducted in different geographical regions with identical study designs. Caucasians dominated the XALIA study versus Asians in the XALIA-LEA study. Most of the Asian population from the XALIA-LEA was recruited from Korea. Therefore, XALIA-LEA was the largest study dealing with Korean VTE patients with reliable data quality control, which seems to be an excellent tool to assess the ethnic characteristics of VTE in the Korean population by comparing Caucasian data from XALIA.

This study aimed to investigate the clinical characteristics and outcome differences between Korean patients with VTE and Caucasian patients.

MATERIALS AND METHODS

1) Study design, participants, and data acquisition

The XALIA-LEA was a prospective, non-interventional study conducted in the Asia-Pacific region, EMEA (Europe, the Middle East, and Africa), and Latin America [12]. The study was approved by the Institutional Review Board of the Seoul National University Hospital (IRB no. H-1404-124-575). This study included patients aged ≥18 years who were diagnosed with DVT or PE and indicated for anticoagulation management after a written consent was obtained. Early switchers who received heparin/fondaparinux for >2-14 days or a VKA for 1-14 days before switching to rivaroxaban and patients who received another NOAC therapy were excluded from the primary safety analysis. Physicians determined the medication type, dose, and treatment duration. Patient information was obtained from the initial visit and routine follow-up visits at 1 month, every 3 months thereafter, and at the final visit, usually 1 month after treatment cessation. Data on demographics, clinical characteristics, and concomitant medications were acquired from medical records or patient interviews. Fragile was defined as age >75 years, body weight ≤50 kg, or first available creatinine clearance (CrCl) <50 mL/min. Chronic renal failure was defined as patients with a CrCl <30 mL/min or those undergoing dialysis. A checklist was used to obtain outcomes data on bleeding, recurrent VTE, and adverse events. The patients were instructed to report to the study center immediately when any symptoms or events related to the outcome occurred, and the physician gathered supporting evidence.

The XALIA study was conducted across 19 European countries, Israel, and Canada. Its design was the same as that of the XALIA-LEA study, but patients with isolated PE without DVT were not recruited [11]. This study used data from the Korean population from XALIA-LEA and the Caucasian population from XALIA. The clinical characteristics were compared between the Korean and Caucasian populations as well as between DVT alone and DVT with PE within the Korean and Caucasian populations to identify consistent characteristics for PE risk in DVT across ethnicities.

2) Outcome

Analyses were performed using a safety analysis set that excluded early switchers from the enrolled patients. The primary outcome was the incidence of treatment-emergent major bleeding, recurrent VTE, and all-cause mortality. Major bleeding was defined according to the International Society on Thrombosis and Hemostasis major bleeding criteria [13]. Recurrent VTE was defined as the new onset of symptoms with medical confirmation, fatal PE, or death in which case PE cannot be ruled out. All-cause death was VTE-related, bleeding-related, or of other causes. The secondary outcomes included treatment-emergent adverse events starting on or after the day of the first dose of study medication and within 2 days after the last dose. All outcomes were determined by the adjudication committee, which was blinded to the patients' treatment allocations.

3) Statistical analysis

In the XALIA, no formal power calculation, hypothesis testing for superiority or non-inferiority, or screening tests for exclusion were done [11,12]. However, confounder adjustment for baseline characteristic imbalance between treatment groups was implemented using propensity score stratification [14-16]. Furthermore, it was impossible to conduct in the XALIA-LEA because of the small sample size, high imbalances, and limited overlap in the propensity score distribution. As an alternative, a propensity score-matched analysis was applied [17].

Primary outcomes are expressed as incidence per year by calculating the number of events per 100 person-years. To compare the effect of treatment groups using rivaroxaban and standard anticoagulation, hazard ratios (HRs) and 95% confidence intervals were calculated using Cox regression analysis stratified by VTE type (XALIA-LEA only) and with active cancer at baseline as covariates. Cumulative incidences of major bleeding and recurrent VTE were provided based on Fine and Gray's sub-distribution hazard model, considering death as a competing risk, whereas Kaplan–Meier cumulative incidences are presented for all-cause mortality [18]. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for the statistical analyses.

RESULTS

1) Demographics and clinical characteristics

A total of 1,987 patients were enrolled in the XALIA-LEA study from June 2014 to October 2016. There were 839 Korean participants, accounting for the largest proportion (42.2%). The demographic and clinical characteristics of the Korean population are described in Table 1. In addition, 53.6% of the participants were women. The mean age was 65.6 years old, and 70% of them were ≥60 years old, whereas 50.3% were not obese with a mean body mass index (BMI) of 24.5 kg/m^2. As for the VTE type, DVT was the most common (52.9%), followed by PE only (23.7%) and DVT with PE (23.4%). Provoked VTE occurred in 44.3% of cases, of which the most common cause was recent surgery (26.4%), followed by recent trauma or fracture (8.1%) and immobilization (8.0%). Of all Korean patients in the XALIA-LEA study, 38.5% were classified as fragile. Navigating risk factors for VTE showed recent hospitalization (21.4%) and active cancer (19.8%) at baseline were dominant.

On the other hand, the Caucasian population of the XALIA study included fewer female and younger patients and more obese patients than the Korean population (Table 1). The predominant VTE type was DVT only (91.5%). Provoked VTE was less common in the Korean population (35.1% vs. 44.3%) than in the Caucasian population, but the most common causes of VTE were immobilization (10.6%) and recent surgery (10.6%), followed by recent trauma or fracture (7.8%). While the frequency order of provoked VTE was similar between groups, a higher proportion was reported for immobilization, hormone replacement therapy,

Table 1. Demographics and clinical characteristics (enrolled population)

	XALIA-LEA Korea (n=839)	XALIA Caucasian (n=3,863)
Race (%)	Asian (99.0)	White (100.0)
Sex, female	450 (53.6)	1,734 (44.9)
Age (y)	65.6±12.7	59.3±16.6
≥60	587 (70.0)	2,035 (52.7)
Body max index (kg/m^2)	24.5±3.9	28.4±6.1
≤25	422 (50.3)	693 (17.9)
Baseline CrCl (mL/min)	83.0±40.7	99.3±42.7
Chronic renal failure[a]	24 (2.9)	54 (1.4)
Type of VTE		
DVT only	444 (52.9)	3,534 (91.5)
DVT+PE	196 (23.4)	329 (8.5)
PE only	199 (23.7)	0 (0.0)
Provoked VTE	372 (44.3)	1,356 (35.1)
Immobilization	67 (8.0)	411 (10.6)
Hormone replacement therapy	7 (0.8)	54 (1.4)
Oral contraceptive	2 (0.2)	211 (5.5)
Recent surgery (<3 mo)	184 (21.9)	409 (10.6)
Recent long hour travel	3 (0.4)	111 (2.9)
Recent trauma/fracture (<3 mo)	76 (9.1)	302 (7.8)
Fragile[b]	323 (38.5)	788 (20.4)
Medical history and risk factors		
Cardiovascular diseases	288 (34.3)	1,242 (32.2)
Venous insufficiency	3 (0.4)	315 (8.2)
Active cancer at baseline	187 (22.3)	285 (7.4)
Known thrombophilia at baseline	12 (1.4)	232 (6.0)
Protein C deficiency	2 (0.2)	59 (1.5)
Protein S deficiency	6 (0.7)	11 (0.3)
Factor V Leiden	0 (0.0)	105 (2.7)
Previous VTE at baseline	59 (7.0)	826 (21.4)
Recent hospitalization (<3 mo)	222 (26.5)	556 (14.4)

Data are presented as number (%) or mean±standard deviation.
CrCl, creatinine clearance; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism.
[a]Defined as patients with baseline CrCl <30 mL/min or undergoing dialysis. [b]Defined as age >75 y or weight ≤50 kg or first available CrCl <50 mL/min.

and oral contraceptive use in Caucasians. However, fewer fragile individuals were found among the Caucasian population. Previous VTE at baseline (21.4%), recent hospitalization (14.4%), and thrombophilia (6.0%) were the common VTE risk factors in Caucasians, which differed from those of Koreans, particularly for thrombophilia, for which Koreans had fewer cases than Caucasians (1.4% vs. 6.0%). Furthermore, factor V Leiden mutation (2.7%) was most common in Caucasians, followed by protein C deficiency (1.5%) and protein S deficiency (0.3%). On the other hand, the most common thrombophilia type in Koreans was protein S deficiency (0.7%), followed by protein C deficiency (0.2%); no cases of factor V Leiden mutation were detected. The safety analysis of the demographics is provided in Supplementary Table 1.

2) Demographics of DVT only and DVT with PE

Table 2 shows the demographic and clinical characteristics of DVT patients with or without PE. In the Korean population from the XALIA-LEA study, there was a slight difference in the female proportion, age, BMI, baseline CrCl, and proportion of fragile patients between the DVT only and DVT with PE groups. In the DVT with PE group, provoked VTE proportion (48.5% vs. 42.6%), immobilization (10.7% vs. 7.4%), and recent trauma or fracture (9.7% vs.

Table 2. Demographics and clinical characteristics of DVT only and DVT with PE (enrolled patients)

DVT type	XALIA-LEA Korea (n=640)		XALIA Caucasian (n=3,863)	
	DVT (n=444)	DVT+PE (n=196)	DVT (n=3,534)	DVT+PE (n=329)
Race (%)	Asian (98.4)	Asian (98.0)	White (100.0)	White (100.0)
Sex, female	237 (53.4)	101 (51.5)	1,612 (45.6)	122 (37.1)
Age (y)	65.8±14.6	63.3±15.6	59.2±16.6	60.4±16.6
Body max index (kg/m^2)	24.5±4.0	24.7±3.8	28.4±6.1	29.2±6.0
Baseline CrCl (mL/min)	84.2±41.5	86.6±39.1	99.4±43.1	98.8±39.9
Provoked VTE	189 (42.6)	95 (48.5)	1,245 (35.2)	111 (33.7)
Central venous catheter	4 (0.9)	0 (0.0)	21 (0.6)	2 (0.6)
Immobilization	33 (7.4)	21 (10.7)	377 (10.7)	34 (10.3)
Hormone replacement therapy	3 (0.7)	1 (0.5)	52 (1.5)	2 (0.6)
Oral contraceptive	1 (0.2)	0 (0.0)	192 (5.4)	19 (5.8)
Recent surgery (<3 mo)	117 (26.4)	37 (18.9)	382 (10.8)	27 (8.2)
Recent long hour travel	2 (0.5)	1 (0.5)	98 (2.8)	13 (4.0)
Recent trauma/fracture (<3 mo)	36 (8.1)	19 (9.7)	288 (8.1)	14 (4.3)
Fragile[a]	164 (36.9)	64 (32.7)	713 (20.2)	75 (22.8)
Medical history and risk factors				
Cardiovascular diseases	144 (32.4)	76 (38.8)	1,114 (31.5)	128 (38.9)
Acute coronary syndrome	2 (0.5)	4 (2.0)	60 (1.7)	10 (3.0)
Peripheral artery disease	5 (1.1)	0 (0.0)	71 (2.0)	9 (2.7)
Chronic heart failure	6 (1.4)	1 (0.5)	73 (2.1)	6 (1.8)
Venous insufficiency	2 (0.5)	1 (0.5)	289 (8.2)	26 (7.9)
History of hypertension	133 (30.0)	68 (34.7)	879 (24.9)	113 (34.3)
Diabetes mellitus	46 (10.4)	25 (12.8)	310 (8.8)	32 (9.7)
Active cancer at baseline	88 (19.8)	31 (15.8)	259 (7.3)	26 (7.9)
Known thrombophilia at baseline	6 (1.4)	1 (0.5)	211 (6.0)	21 (6.4)
Protein C deficiency	1 (0.2)	0 (0.0)	55 (1.6)	4 (1.2)
Protein S deficiency	5 (1.1)	0 (0.0)	10 (0.3)	1 (0.3)
Factor V Leiden	0 (0.0)	0 (0.0)	96 (2.7)	9 (2.7)
Recent hospitalization (<3 mo)	95 (21.4)	69 (35.2)	495 (14.0)	61 (18.5)

Data are presented as number (%) or mean±standard deviation.
DVT, deep vein thrombosis; PE, pulmonary embolism; CrCl, creatinine clearance; VTE, venous thromboembolism.
[a]Defined as age >75 y or weight ≤50 kg or first available CrCl <50 mL/min.

8.1%) was higher than DVT only group. The medical history and risk factor comparison revealed that the DVT with PE group had a greater proportion of cardiovascular diseases (38.8%), including acute coronary syndrome (2.0%), hypertension (34.7%), diabetes mellitus (12.8%), and recent hospitalization (35.2%). Similarly, among the Caucasians from the XALIA study, the DVT with PE group had a greater proportion of cardiovascular diseases (38.9%), such as acute coronary syndrome (3.0%), hypertension (34.3%), diabetes (9.7%), and recent hospitalization (18.5%).

3) Outcome

The primary outcomes were treatment-emergent major bleeding, recurrent VTE, and all-cause mortality. The primary outcome incidence and HR are shown in Table 3. The safety analysis set with and without propensity score matching showed that the primary outcome incidence was significantly lower in the rivaroxaban versus standard anticoagulation group of Koreans. The difference in the incidence was highest for major bleeding among the primary outcome components. All HR values comparing rivaroxaban with standard anticoagulation were consistently low: 0.31 for major bleeding, 0.28 for recurrent VTE, and 0.26 for all-cause mortality. Similar findings for incidence were seen in Caucasians regardless of propensity score stratification. HR values were similar: 0.52 for major bleeding, 0.67 for recurrent VTE, and 0.28 for all-cause mortality. However, the difference in incidence between the rivaroxaban and standard anticoagulation groups was predominantly larger in Koreans. The HR was also lower in Koreans than in Caucasians.

Fig. 1 shows the cumulative incidence of major bleeding, recurrent VTE, and all-cause mortality in both treatment groups. Major bleeding and recurrent VTE showed higher cumulative incidences in the standard anticoagulation versus rivaroxaban group, and the intergroup difference increased over time. The rivaroxaban group showed a higher all-cause mortality rate in the initial phase, but this was reversed after approximately 15 days. From the 60th day of initiation, the cumulative incidence of all-cause mortality with standard anticoagulation treatment increased dramatically, and the difference from that with rivaroxaban was consistently significant over time.

An additional analysis showed no significant difference in the trend for a lower incidence of major bleeding or recurrent VTE in the rivaroxaban versus standard anticoagulation group by age, renal function, weight, and active cancer at baseline (Supplementary Table 2). For recurrent VTE, the incidence in the standard anticoagulation group was significantly higher in patients aged <60 years (18.39%/

Table 3. Primary outcome incidence rate (%/y) and HR

	Safety analysis set					Safety analysis set with propensity score adjustment			
	Rivaroxaban		Standard anticoagulation		HR (95% CI)	Rivaroxaban		Standard anticoagulation	
	N	Rate (range)	N	Rate (range)		N	Rate (range)	N	Rate (range)
XALIA-LEA Korea									
Major bleeding	9/607	3.39 (1.55-6.44)	6/110	13.08 (4.80-28.47)	0.31 (0.11-0.88)	3/100	6.72 (1.39-19.64)[a]	4/82	12.86 (3.50-32.93)[a]
Recurrent VTE	8/607	3.04 (1.31-5.99)	4/110	8.72 (2.38-22.32)	0.28 (0.08-0.96)	2/100	4.49 (0.54-16.23)[a]	3/82	9.57 (1.97-27.96)[a]
All-cause mortality	9/607	3.39 (1.55-6.43)	5/110	10.80 (3.51-25.19)	0.26 (0.09-0.80)	3/100	6.69 (1.38-19.56)[a]	4/82	12.72 (3.47-32.58)[a]
XALIA Caucasian									
Major bleeding	15/1,997	1.27 (0.71-2.09)	30/1,587	2.79 (1.88-3.98)	0.52 (0.27-0.98)	15/1,893	1.32 (0.74-2.18)[b]	26/1,487	2.58 (1.69-3.79)[b]
Recurrent VTE	30/1,997	2.55 (1.72-3.64)	42/1,587	3.96 (2.85-5.35)	0.67 (0.42-1.09)	29/1,893	2.57 (1.72-3.69)[b]	35/1,487	3.52 (2.45-4.90)[b]
All-cause mortality	10/1,997	0.85 (0.41-1.56)	57/1,587	5.27 (3.99-6.83)	0.28 (0.14-0.56)	9/1,893	0.79 (0.36-1.50)[b]	42/1,487	4.15 (2.99-5.61)[b]

HR, hazard ratio; CI, confidence interval; VTE, venous thromboembolism.
[a]Propensity score matching. [b]Propensity score-stratified analysis.

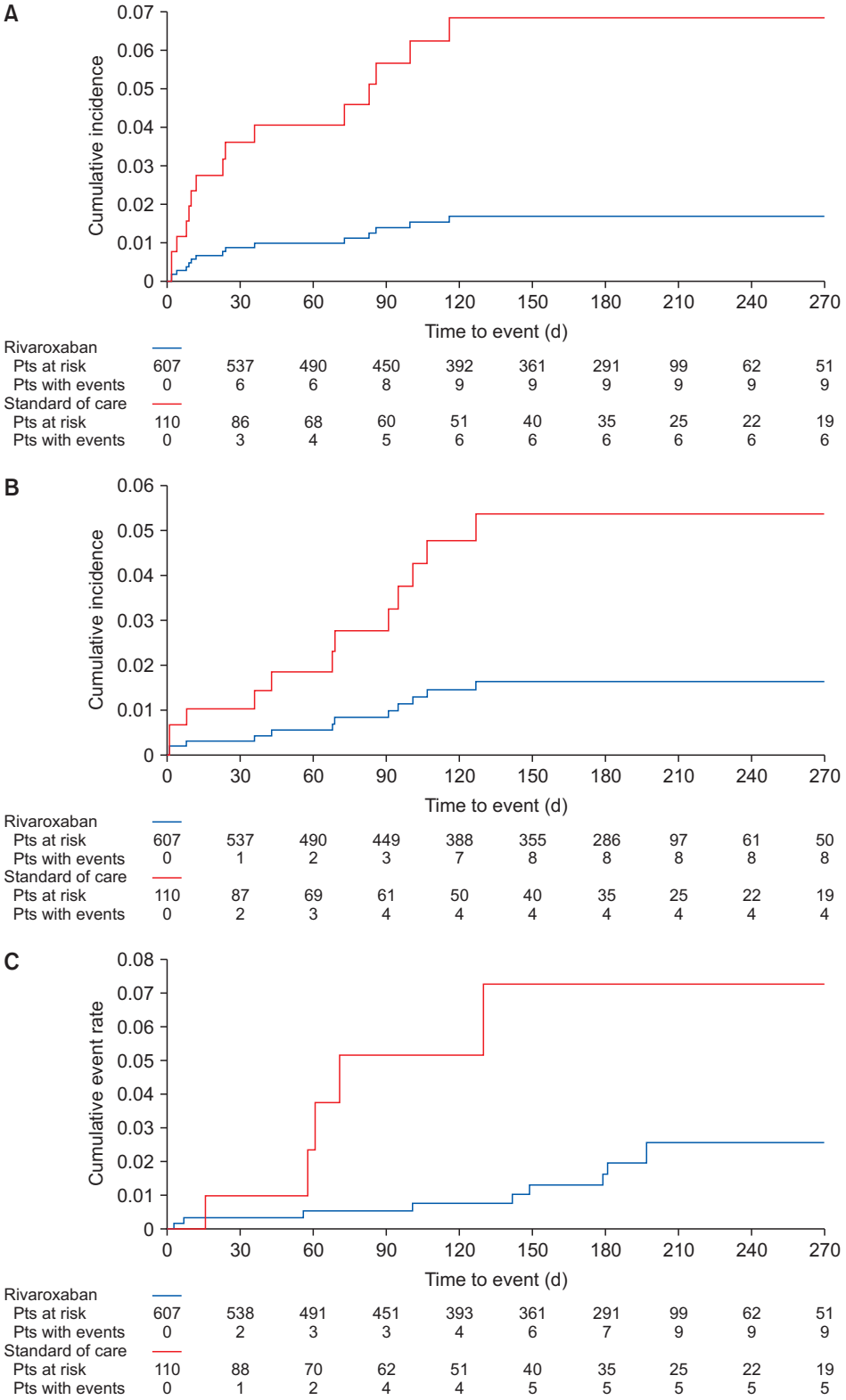

Fig. 1. Primary outcome of XALIA-LEA KOREA safety analysis set. Cumulative incidence of any treatment-emergent adjudicated major bleeding events (A), recurrent venous thromboembolism events (B), and all-cause mortality (C). Pts, patients.

y) and those with normal renal function (21.13%/y).

In Korea, the rivaroxaban (21.7%) and standard anticoagulation (40.0%) groups experienced treatment-emergent adverse events (Table 4). Furthermore, serious adverse events occurred in 7.25% and 17.3% of the rivaroxaban and standard anticoagulation groups, respectively. Drug-related adverse events were reported in 9.6% and 15.5% of the rivaroxaban and standard anticoagulation groups, respec-

Table 4. Adverse event (XALIA-LEA Korea, safety analysis set)

	Rivaroxaban (n=607)	Standard anticoagulation (n=110)
Any treatment-emergent AE	132 (21.7)	44 (40.0)
Any serious treatment-emergent AE	44 (7.2)	19 (17.3)
Any drug-related treatment-emergent AE	58 (9.6)	17 (15.5)
Any serious drug-related treatment-emergent AE	12 (2.0)	9 (8.2)
Incidence of treatment-emergent AE by primary system organ class		
Gastrointestinal disorders	26 (4.3)	14 (12.7)
Respiratory, thoracic, and mediastinal disorders	26 (4.3)	12 (10.9)
Incidence of treatment-emergent serious AE by primary system organ class		
Infections and infestations	8 (1.3)	2 (1.8)
Respiratory, thoracic, and mediastinal disorders	3 (0.5)	7 (6.4)

Data are presented as number (%).
AE, adverse event.

tively. Regarding the incidence of adverse events by primary system organ class, gastrointestinal (GI) and respiratory disorders were common. A lower event rate was found in the rivaroxaban versus standard anticoagulation group (4.3% vs. 12.7% for GI disorders and 4.3% vs. 10.9% for respiratory disorders). On the other hand, the most frequently seen serious adverse event by primary system organ class was infection in the rivaroxaban group (1.3%) versus respiratory disorder in the standard anticoagulation group (6.4%). Overall, the occurrence of adverse events was lower with rivaroxaban than with anticoagulation regardless of drug-related event, severity, or system organ class.

DISCUSSION

Regarding Korean VTE patient characteristics, the most recent related study to our knowledge was the Korean VTE registry report published in 2011 [10]. In this registry of 596 VTE patients, 76% were >50 years old, and VTE developed more frequently in women than in men. The major risk factors for VTE are old age, cancer, immobilization, surgery, severe medical disease, stroke, and trauma. Of these, cancer-associated VTE was seen in 24% (134/596), while idiopathic VTE was found in 28% (158/596).

In the current study, we could see the demographics and clinical characteristics of Korean VTE patients in a larger group than in the previous registry report. We found that the reported major risk factors from the past registry were identically distinct, especially advanced age and cancer at baseline, compared with other ethnicities. Advanced age and cancer at baseline are widely known high-risk factors for bleeding as well, which might affect the primary outcomes by showing all the elements numerically higher incidence rates in the Korean population.

We also confirmed that the Korean population was less genetically vulnerable in a prospective real-world study. Ethnic thrombogenicity differences regarding VTE risk were reported previously [19,20]; specifically, Caucasians had a predominantly higher VTE risk associated with genetic variants with the two polymorphisms of factor V Leiden and prothrombin than East Asians. Particularly in Koreans, the factor V Leiden mutation and prothrombin G20210A mutation are reportedly extremely scarce [21]. A study of natural anticoagulant deficiency in 127 Korean VTE patients reported that the most common deficiency was of protein C (50.7%), followed by antithrombin III (29.6%), and protein S (19.7%) [22], which are known to be at least partially heritable [23]. Based on this evidence, the Korean practice guidelines for DVT diagnosis and treatment do not recommend routine thrombophilia tests for factor V Leiden or prothrombin G20210A mutation in Korean DVT patients (class III, level C) [21].

This study also found that both Korean- and Caucasian-accompanied atherosclerosis risk factors, such as acute coronary syndrome, hypertension, and diabetes, were more frequent in DVT with PE than in DVT alone. It might be derived from PE pathology of athero-thromboembolism, the detachment from deep venous thrombi to pulmonary circulation in patients with underlying DVT [24].

As such, this Korean subgroup analysis of the XALIA-LEA study data confirmed the consistent effectiveness and safety of rivaroxaban for VTE in a phase 3 trial [25] along with the XALIA program [11,12] as well as the German subgroup analysis of the XALIA study [26]. The primary outcomes consistently had a lower incidence in the rivaroxaban group (Table 3). However, the incidence of major bleeding and all-cause mortality in the standard anticoagulation group was higher than in the Korean group. This was believed due to

the small number of patients and unmeasured confounding factors. Considering that only 19.9% of patients using VKA met the adjusted time in therapeutic range (TTR) of an international normalized ratio of 2 to 3 (Supplementary Table 3), which was less than half of the XALIA-LEA adjusted TTR of an international normalized ratio of 2 to 3 (43.7%), VKA use in Korean VTE patients should be more cautious in terms of bleeding and mortality risk. Furthermore, a subgroup analysis of the primary outcomes showed that recurrent VTE incidence in the standard anticoagulation group was much higher in the younger age and normal kidney function subgroups, which are usually not at higher risk for VTE. This might imply that anticoagulant therapy compliance rates are low but that rivaroxaban compliance rates are potentially better as shown in other studies [27-29].

This study has limitations. First, there was potential selection bias in treatment allocation due to the open-label study design and physicians' choice of treatment for the enrolled patients as indicated in the XALIA and XALIA-LEA studies. To overcome this limitation, a propensity score-stratified analysis for XALIA and propensity score matching of the XALIA-LEA were conducted. Second, only numerical descriptive comparisons were available, as the XALIA and XALIA-LEA studies were observational and conducted independently despite having the same study design. Finally, it was difficult to perform a direct statistical comparison of the clinical outcomes between rivaroxaban and a specific standard anticoagulation treatment because the standard anticoagulation group was heterogeneous, including VKA-only and bridging management using unfractionated heparin, low-molecular-weight heparin, or fondaparinux injection followed by VKA.

CONCLUSION

This study contributed to clarifying the clinical characteristics of the Korean VTE population using recent and larger well-qualified datasets. We also confirmed the overall consistent effectiveness and safety of rivaroxaban compared to classic standard anticoagulants across ethnicities in a prospective real-world study setting. However, further well-qualified studies with larger populations are needed to enable direct comparisons of multi-ethnic groups.

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SUPPLEMENTARY MATERIALS

Supplementary Tables can be found via https://doi.org/10.5758/vsi.220039.

CONFLICTS OF INTEREST

JSK and MG are the employees of Bayer. The other authors have nothing to disclose.

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Concept and design: SKM. Analysis and interpretation: JSK, MG. Data collection: JSK. Writing the article: JSK, SKM. Critical revision of the article: JYK, UJP, TL, JMK, SCP, WIC, KHP. Final approval of the article: all authors. Statistical analysis: JSK, MG. Obtained funding: JSK. Overall responsibility: SKM.

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