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XALIA-LEA: An observational study of venous thromboembolism treatment with rivaroxaban and standard anticoagulation in the Asia-Pacific, Eastern Europe, the Middle East, Africa and Latin America

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ABSTRACT

Introduction: The prospective, non-interventional XALIA study investigated the safety and effectiveness of rivaroxaban and standard anticoagulation for the treatment of deep vein thrombosis (DVT). XALIA-LEA was conducted in regions not included in XALIA (Latin America, Eastern Europe, the Middle East, Africa, and the Asia-Pacific), and enrolled patients with isolated pulmonary embolism (PE).

Materials and methods: Adult patients with acute venous thromboembolism (VTE) indicated for ≥3 months' anticoagulant treatment were eligible; treatment strategies were at the physician's discretion. Patients receiving rivaroxaban or standard anticoagulation (unfractionated or low-molecular weight heparin/fondaparinux alone or overlapping with and followed by a vitamin K antagonist [VKA]) were included in the safety analysis. "Early switchers" to rivaroxaban (i.e. after receiving heparin/fondaparinux for > 2–14 days and/or a VKA for 1–14 days) were not included in the safety analysis set.

Results: Of the 1972 eligible patients, 1285 received rivaroxaban, 402 received standard anticoagulation, and 285 were early switchers. Most patients who received rivaroxaban were appropriately selected, received the correct dosing schedule, reported few adverse effects. Outcomes were similar to previously published results, with rivaroxaban associated with a low rate of major bleeding (1.6%), recurrent VTE (1.4%) and all-cause mortality (2.3%). Including early switchers, relatively fewer patients with index isolated PE received rivaroxaban (14.4%) versus standard anticoagulation therapy (20.9%). Some regional variations and differences in outcomes by VTE subtype were apparent with standard anticoagulation treatment.

Conclusion: XALIA-LEA reaffirms the safety and effectiveness of rivaroxaban for VTE treatment for countries not included in XALIA.

1. Introduction

The non-vitamin K antagonist (VKA) oral anticoagulant (NOAC) phase III venous thromboembolism (VTE) trials evaluated apixaban, dabigatran, edoxaban, and rivaroxaban against parenteral anticoagulant therapy overlapping with a VKA in separate studies [1–4].

Abbreviations: Bid, twice daily; BMI, body mass index; CNS, central nervous system; CrCl, creatinine clearance; DVT, deep vein thrombosis; INR, international normalized ratio; IQR, interquartile range; ISTH, International Society on Thrombosis and Haemostasis; NOAC, non-vitamin K antagonist oral anticoagulant; od, once daily; PE, pulmonary embolism; SD, standard deviation; TTR, time in therapeutic range; VKA, vitamin K antagonist; VTE, venous thromboembolism

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NOAC treatment in these studies resulted in similar efficacy and a similar or reduced bleeding risk compared with parenteral anticoagulant/VKA therapy [1–4]. As a consequence of these findings, there has been a rapid uptake of NOACs into clinical practice; the focus has now shifted to real-world data collection, with the aim of establishing whether similar findings to the phase III trials are observed in more heterogeneous patient populations.

XALIA was a phase IV non-interventional prospective study program that investigated the safety and effectiveness profile of rivaroxaban and standard anticoagulation for the treatment of VTE in clinical practice [5]. The program involved two separate studies with the same basic design – XALIA [5] and XALIA-LEA [6]. The recently reported XALIA study was the first multicenter, prospective, non-interventional study to investigate the safety and effectiveness profile of a NOAC (rivaroxaban) and standard anticoagulation for the treatment of deep vein thrombosis (DVT), and subsequently concomitant pulmonary embolism (PE), in clinical practice [5]. The study enrolled 5142 patients from Europe, Canada, and Israel and obtained findings which reflected the results from the phase III EINSTEIN DVT and EINSTEIN PE studies [4]. Here, we report the findings of the XALIA-LEA study in which patients from other regions not included in XALIA (i.e. Latin America, Eastern Europe, the Middle East, Africa, and the Asia-Pacific) were studied. In addition, XALIA-LEA included patients with isolated PE, whereas such patients were ineligible for the XALIA study.

The purpose of this study was to present data on rivaroxaban and standard anticoagulation therapy for the treatment of VTE, with a focus on evaluating the incidence of major bleeding, recurrent VTE, and all-cause mortality and patient management approaches across different geographic regions. XALIA-LEA also assessed the relationship between different subtypes of VTE, including isolated PE, and anticoagulation treatment outcomes.

2. Materials and methods

2.1. Study design and participants

XALIA-LEA was a multicenter, prospective, non-interventional study, which enrolled patients with VTE from Indonesia, Malaysia, the Philippines, Singapore, South Korea, Taiwan, Russia, Ukraine, Jordan, Kazakhstan, Lebanon, Saudi Arabia, Algeria, Egypt, Kenya, and Mexico. The study design has been previously reported in detail [5,7]. In brief, patients were included if they were aged ≥18 years old, with objectively confirmed DVT and/or PE and an indication to receive anticoagulation treatment with rivaroxaban or standard anticoagulation for ≥3 months. Written informed consent was obtained from all enrolled patients after initial screening. In keeping with the non-interventional study design, the type, dose, and duration of therapy for each patient were at the physician's discretion. Patients treated with rivaroxaban or standard anticoagulation (initial treatment with unfractionated heparin, low-molecular weight heparin, or fondaparinux, usually overlapping with and followed by a VKA) were eligible for inclusion. An external steering committee supported defining the study designs, clinical protocols, study oversight, and data verification and analyses. All reported outcome events were adjudicated by the same central adjudication committee as in the XALIA study, with the addition of one further adjudicator from South Korea; this committee was blinded to the treatment decisions. Investigators had to assess all eligible patients for potential inclusion; reasons for exclusion are shown in Fig. 1.

2.2. Procedures

Patients who received rivaroxaban alone and those who had received heparin/fondaparinux for ≤48 h before enrollment were included in the rivaroxaban cohort. Patients who initially received heparin/fondaparinux for > 2–14 days and/or a VKA for 1–14 days before switching to rivaroxaban were designated as “early switchers” and excluded from the primary safety analysis. Patients who received another NOAC therapy were also excluded from the primary analysis.

All patient data were collected at the initial visit and during routine follow-up visits or via post, telephone or email at approximately month 1, every 3 months thereafter, and at the final visit (usually 30 days after treatment cessation). Information about demographic data, clinical characteristics, relevant concomitant medications, resource use, and outcomes (bleeding, recurrent VTE, and adverse events) was obtained from medical records or during patient interviews through use of standardized questionnaires. A checklist was used to record bleeding, recurrent VTE symptoms, and adverse events; patients were instructed to report to the study center immediately if any of these events or their symptoms occurred. Any adverse event that occurred in XALIA-LEA was entered into the Electronic Data Capture system. The physician was required to obtain all supporting evidence to confirm that the adverse event had occurred [5].

2.3. Outcomes

The primary outcomes in XALIA-LEA were treatment-emergent major bleeding, recurrent VTE, and all-cause mortality. An adverse event was classified as treatment-emergent if it started on or after the day of the first dose of study medication and within 2 days after the last dose. Major bleeding was defined according to the International Society on Thrombosis and Haemostasis (ISTH) major bleeding criteria [8]. Recurrent VTE was defined as the new onset of symptoms confirmed by diagnostic testing or fatal PE or unexplained death where PE cannot be ruled out. Death was classified as VTE-related, bleeding-related, or from other causes.

Secondary outcomes included: major adverse cardiovascular events (e.g. cardiovascular death, stroke, myocardial infarction, unstable angina or acute coronary syndrome); other symptomatic thromboembolic events (e.g. Budd–Chiari syndrome, retinal-vein thrombosis, sinus-vein thrombosis, portal-vein thrombosis, catheter-associated thrombosis, or upper-limb thrombosis [if the initial DVT was not an upper-limb thrombosis]); other adverse events; and healthcare resource use (e.g. admissions to hospital, length of hospital stay, and the number of healthcare professional visits). All outcomes were adjudicated by members of the adjudication committee, who were blinded to which treatment the patients received.

2.4. Statistical analysis

As per the XALIA study [5], no formal power calculation, hypothesis testing for superiority or non-inferiority, or further investigations of the reasons for exclusion (beyond eligibility screening) were applied to XALIA-LEA. Unlike XALIA, propensity score adjustment was not utilized in the XALIA-LEA analyses because of the small sample size of the standard anticoagulation treatment group and lack of overlap in the propensity distributions.

An analysis of variance was used to analyze the effect of treatment on initial length of hospitalization. Time in therapeutic range (TTR) in the patients who received VKA treatment was ascertained using the method described by Rosendaal et al. [9]. Source data were verified at approximately 10% of study centers in countries where this was legally possible (all countries in the study). SAS version 9.4 was used for all statistical analyses. This study is registered with ClinicalTrials.gov, number NCT02210819.

3. Results

3.1. Patients

A total of 1987 patients were enrolled between 27 June 2014 and 31 October 2015 from hospital and community centers across 16 countries from the Asia-Pacific region (Indonesia, Malaysia, Philippines, Singapore, South Korea, and Taiwan), Eastern Europe (Russia and Ukraine), the Middle East (Jordan, Kazakhstan, Lebanon, and Saudi

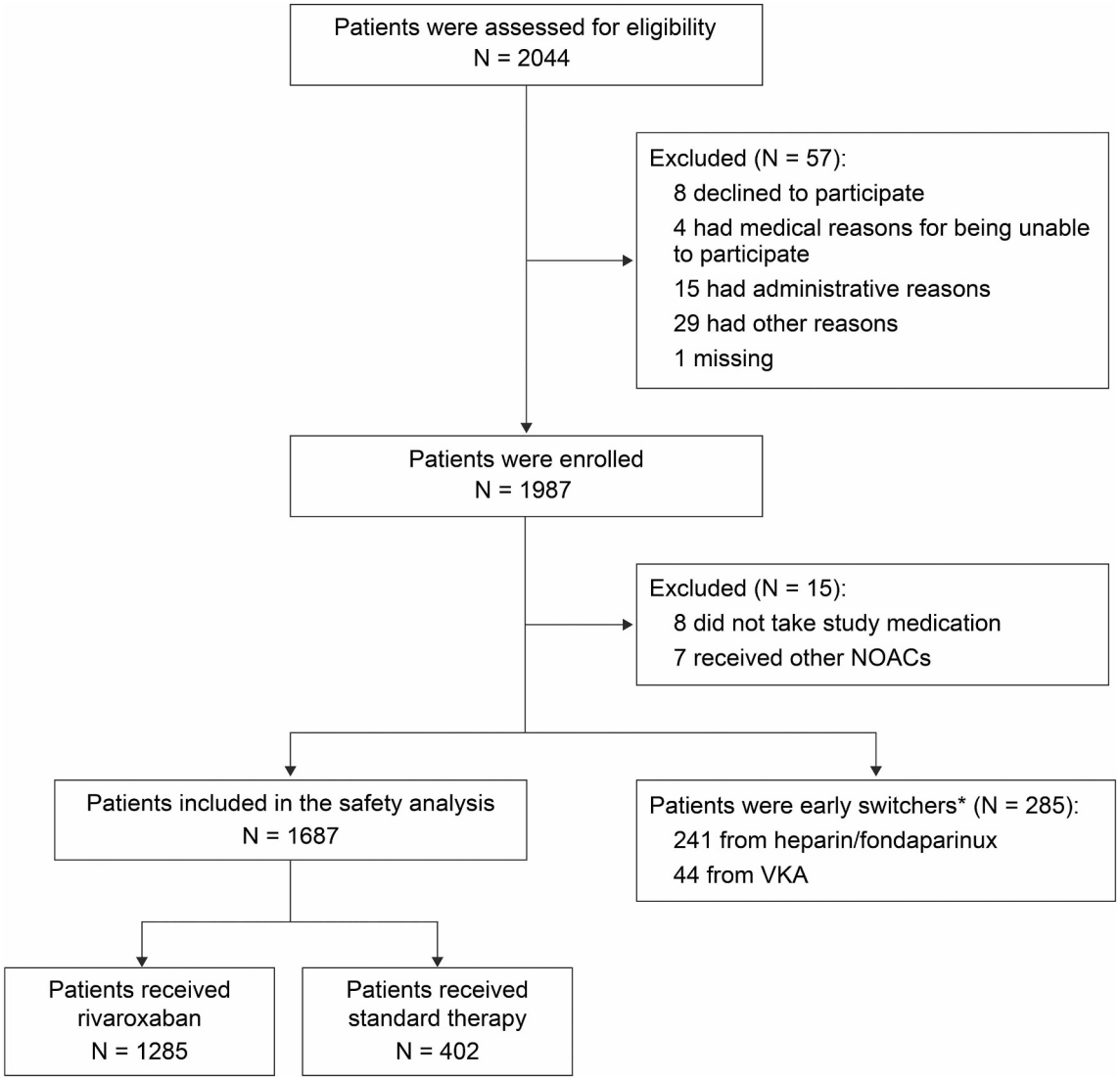

Fig. 1. Study profile.
*Early switchers were defined as patients for whom rivaroxaban was planned, but who initially received heparin or fondaparinux for at least 2–14 days, a VKA for 1–14 days, or both before switching to rivaroxaban. In total, 115 patients in the rivaroxaban group, 29 in the standard anticoagulation group and 23 patients in the early switchers group were lost to follow-up.
NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist.

Arabia), Africa (Algeria, Egypt, and Kenya), and Latin America (Mexico). South Korea had the largest proportion (42% of the overall population) of patients enrolled in the study.

Overall, 8 patients did not receive anticoagulant therapy and 7 received other NOAC therapies and were excluded from the analyses. Of the remaining 1972 patients, 1285 (65.2%) received rivaroxaban and 402 (20.4%) received standard anticoagulation; in addition, 285 (14.5%) were early switchers, and therefore excluded from the main safety analysis (Fig. 1). The number of patients who prematurely discontinued (as determined by the attending physician) from the study (not including those who died during the study) were 227 (17.7%) in the rivaroxaban group, 58 (14.4%) in the standard anticoagulation group, and 49 (17.2%) from the early switchers group; reasons for premature discontinuation were loss to follow-up, patient choice, physician choice, and other reasons. Overall, 167 (8.5%) patients were lost to follow-up. The median duration of follow-up was 215 days (interquartile range [IQR] 149–323) days in the rivaroxaban group, 214 (IQR 130–289) in the standard anticoagulation group. Table 1 shows enrollment by geographic region and country for patients included in the main safety analysis.

3.2. Baseline demographics and clinical characteristics

Baseline demographics and clinical characteristics for the rivaroxaban and standard anticoagulation therapy groups are shown in Table 2 (the equivalent for the 'early switchers' cohort are shown in Supplementary Table 1). Patients treated with rivaroxaban differed significantly from the standard anticoagulation group for the following demographic and clinical characteristics: geographic region (a higher proportion of patients from the Asia-Pacific region and a lower proportion from Eastern Europe); proportion of patients with severe renal impairment (a lower proportion of patients with first available creatinine clearance [CrCl] < 30 mL/min); lower proportion of provoked VTE as the index event; and lower proportion of isolated PE. Proportions for index PE with DVT were more similar between treatment groups. No significant differences in age, renal function status (mean first available CrCl), known cancer at baseline or previous major bleeding episodes between patients in the rivaroxaban and standard anticoagulation groups were observed. Like the standard anticoagulation group, the early switchers group included relatively more patients with isolated index PE and provoked VTE than the rivaroxaban group. The early switchers group also included a

Table 1
Enrollment by geographic region and country.

Characteristics[a]	Rivaroxaban (n = 1285)	Standard anticoagulation therapy[b] (n = 402)
Asia-Pacific	720 (56.0)	167 (41.5)
Indonesia	46 (3.6)	7 (1.7)
Malaysia	15 (1.2)	14 (3.5)
Philippines	13 (1.0)	4 (1.0)
Singapore	12 (0.9)	20 (5.0)
South Korea	607 (47.2)	110 (27.4)
Taiwan	27 (2.1)	12 (3.0)
Eastern Europe	142 (11.1)	45 (11.2)
Russia	103 (8.0)	36 (9.0)
Ukraine	39 (3.0)	9 (2.2)
Middle East	142 (11.1)	73 (18.2)
Jordan	13 (1.0)	4 (1.0)
Kazakhstan	47 (3.7)	2 (0.5)
Lebanon	34 (2.6)	5 (1.2)
Saudi Arabia	48 (3.7)	62 (15.4)
Africa	189 (14.7)	78 (19.4)
Algeria	32 (2.5)	7 (1.7)
Egypt	145 (11.3)	58 (14.4)
Kenya	12 (0.9)	13 (3.2)
Latin America	92 (7.2)	39 (9.7)
Mexico	92 (7.2)	39 (9.7)

VKA, vitamin K antagonist.
[a] All results are presented as n (%).
[b] Standard anticoagulation consisted of initial treatment with unfractionated heparin, low-molecular weight heparin or fondaparinux, which could overlap with and be followed by an oral VKA.

higher proportion of patients with previous major bleeding events than the rivaroxaban group.

Baseline demographics and clinical characteristics in the rivaroxaban cohort by region are shown in Table 3. Patients from the Asia-Pacific region receiving rivaroxaban had the highest mean age and proportion of patients ≥60 years old (65.7% compared with 35.5% of patients in Eastern Europe/Middle East/Africa and 56.5% in Latin America). In the rivaroxaban cohort, CrCl was ≥50 mL/min in 433 (60.1%) patients in the Asia-Pacific region, 254 (53.7%) patients in Eastern Europe/Middle East/Africa, and 37 (40.2%) in Latin America. A minority of patients had a CrCl < 30 mL/min (16 [2.2%], 4 [0.8%] and 2 [2.2%], respectively). Of note, the proportion of missing CrCl data was substantial (26.7%, 41.2% and 53.3%, respectively). An index diagnosis of PE (with or without DVT) was the case in 257 (35.7%) rivaroxaban-treated patients in the Asia-Pacific region, 124 (26.2%) in Eastern Europe/Middle East/Africa and 22 (23.9%) in Latin America. Regarding the risk factors for recurrent VTE in rivaroxaban-treated patients, index VTE was unprovoked in 420 (58.3%) patients from the Asia-Pacific region, 309 (65.3%) in Eastern Europe/Middle East/Africa and 76 (82.6%) in Latin America. Active cancer at baseline was present in 173 (24.0%) patients in the Asia-Pacific region, 36 (7.6%) in Eastern Europe/Middle East/Africa and 7 (7.6%) in Latin America. Furthermore, a previous venous thromboembolic event had occurred in 68 (9.4%), 64 (13.5%) and 18 (19.6%) patients enrolled, respectively.

3.3. Dosing patterns

The median duration of therapy was 184 days (IQR 105–234) with rivaroxaban and 152 days (IQR 53–214) with standard anticoagulation. A total of 53 (4.1%) patients receiving rivaroxaban and 55 (13.7%) patients receiving standard anticoagulation switched therapy during the study; the median duration of study treatment before switching was 175 days (IQR 26–197) with rivaroxaban and 28 days (IQR 17–58) with standard anticoagulation.

The majority of rivaroxaban-treated patients were dosed in accordance with the label [10]. Overall, 1091 (84.9%) patients received an initial dose of rivaroxaban 15 mg twice daily (bid) for 21 ± 3 days and 724/1285 (56.3%) of rivaroxaban-treated patients had a planned switch at 21 ± 3 days to the rivaroxaban 20 mg once daily (od) maintenance dose. Other rivaroxaban regimens included 122 (9.5%) patients who received rivaroxaban 20 mg od during the initial study period, 33 (2.6%) patients received rivaroxaban 15 mg od, and 23 (1.8%) received rivaroxaban 10 mg od during the initial period. Most patients in the rivaroxaban group received rivaroxaban without initial parenteral anticoagulation (1076/1285 [83.7%]); for the 209 (16.3%) patients who did, the median duration of initial parenteral anticoagulation was 2 days (IQR 1–3).

Of the 402 patients treated with standard anticoagulation, 92 (22.9%) patients received unfractionated heparin/low-molecular weight heparin or fondaparinux only (40.2% of these patients had active cancer at baseline) and 310 (77.1%) patients received a VKA with (217/310 [70.0%]) or without (93/310 [30.0%]) parenteral therapy. For patients who received a VKA following parenteral therapy the median duration of initial heparin/fondaparinux use was 8 days (IQR: 6–18 days). Patients receiving VKA only, therefore, make up 23% of patients treated with standard anticoagulation. In patients treated with a VKA, the mean TTR (± standard deviation) in the standard anticoagulation group for the standard target INR of 2.0–3.0 was 43.7% (± 40.6%). Mean TTR by region was 56.5% (± 39.5%) in patients from Eastern Europe, the Middle East and Africa, 45.6% (± 42.8%) in patients from Latin America, and 25.9% (± 34.7%) in patients from the Asia-Pacific region (data mainly obtained in patients from South Korea). However, treatment centers in the Asia-Pacific region commonly targeted an INR range of 1.5–2.5, which resulted in a TTR of 50.9% (± 40.7%) when this target range was considered for patients in this region. Data showing TTR by region for different INR ranges are shown in Table 4.

3.4. Outcome events

Incidence proportions for the primary outcome in the rivaroxaban cohort by region are presented in Table 5. Details of treatment-emergent clinical outcomes in the safety analysis set are in Supplementary Table 2.

3.4.1. Major bleeding

The incidence proportion of treatment-emergent major bleeding was 1.6% in patients receiving rivaroxaban and 3.7% in patients receiving standard anticoagulation. Overall, 18 of the 20 major bleeding events in the rivaroxaban group occurred in patients in the Asia-Pacific cohort, whereas one major bleeding event each occurred in the Eastern Europe/Middle East/Africa cohort and the Latin America cohort (Table 5). A total of three fatal bleeding events were observed (Supplementary Table 2), which were all of gastrointestinal origin – two occurred in the rivaroxaban group and one in the standard anticoagulation group (it was unknown if these patients had an underlying gastrointestinal pathology). Other bleeding event rates are shown in Supplementary Table 2; they were consistently low with both rivaroxaban and standard anticoagulation therapy.

3.4.2. Recurrent venous thromboembolism

The incidence proportion of recurrent treatment-emergent VTE was 1.4% in the rivaroxaban group and 4.0% in the standard anticoagulation group. Overall, 14 of the 18 recurrent venous thromboembolic events in the rivaroxaban group occurred in patients in the Asia-Pacific cohort, and four occurred in the Latin America cohort; there were no recurrent venous thromboembolic events in patients in Eastern Europe/Middle East/Africa (Table 5). PE-related recurrent venous thromboembolic events (fatal PE, non-fatal PE, and DVT with concomitant PE) occurred in 4 (0.3%) patients in the rivaroxaban group and 12 (3.0%) patients in the standard anticoagulation group (Supplementary Table 2). Recurrent VTE post-treatment (i.e. patients who experienced an event in the period > 2 days after stopping treatment) occurred in 7/908 (0.8%) patients in the rivaroxaban group and 10/292 (3.4%) patients in the standard anticoagulation group.

Table 2
Baseline demographics and clinical characteristics.

Characteristic	Rivaroxaban (n = 1285)	Standard anticoagulation therapy[a] (n = 402)	P-value
Geographic region			< 0.0001
Asia-Pacific	720 (56.0)	167 (41.5)	
Eastern Europe/ Middle East/Africa	473 (36.8)	196 (48.8)	
Latin America	92 (7.2)	39 (9.7)	
Age, years, mean ± SD	59.6 ± 17.1	58.0 ± 1 8.0	0.1090
Age category			0.3033
< 60 years old	592 (46.1)	197 (49.0)	
≥60 years old	693 (53.9)	205 (51.0)	
Male sex	623 (48.5)	180 (44.8)	0.1941
Body weight, kg, mean ± SD	71.6 ± 16.9	73.5 ± 17.6	0.0532
Body weight category			0.1908
≤70 kg	585 (45.5)	189 (47.0)	
> 70 to 90 kg	353 (27.5)	124 (30.8)	
> 90 kg	160 (12.5)	64 (15.9)	
Missing	187 (14.6)	25 (6.2)	
First available CrCl, mL/min, mean ± SD	89.8 ± 42.4	89.8 ± 61.7	0.9831
First available CrCl category			0.0052
< 30 mL/min	22 (1.7)	19 (4.7)	
30 to < 50 mL/min	103 (8.0)	41 (10.2)	
50 to < 80 mL/min	275 (21.4)	90 (22.4)	
≥80 mL/min	449 (34.9)	131 (32.6)	
Missing	436 (33.9)	121 (30.1)	
Index diagnosis			0.0005
DVT only	882 (68.6)	238 (59.2)	
PE with DVT	238 (18.5)	80 (19.9)	
PE only	165 (12.8)	84 (20.9)	
Type of VTE[b]			0.0002
Provoked	480 (37.4)	192 (47.8)	
Unprovoked	805 (62.6)	210 (52.2)	
Previous VTE	150 (11.7)	55 (13.7)	0.2821
Known cancer at baseline	216 (16.8)	69 (17.2)	0.8684
Known thrombophilic condition	49 (3.8)	12 (3.0)	0.4376
Previous major bleeding episode	28 (2.2)	9 (2.2)	0.9036
Missing/unknown	31 (2.4)	17 (4.2)	

Data are n (%) unless stated otherwise. P-values are for comparisons between the rivaroxaban and standard anticoagulation therapy groups for each major category. P-values for categorical variables were calculated using Chi-square tests; P-values for continuous variables were calculated using F-tests. CrCl, creatinine clearance; DVT, deep vein thrombosis; PE, pulmonary embolism; SD, standard deviation; VKA, vitamin K antagonist; VTE, venous thromboembolism.

[a] Standard anticoagulation consisted of initial treatment with unfractionated heparin, low-molecular weight heparin, or fondaparinux, which could overlap with and be followed by an oral VKA.

[b] Provoking factors included recent surgery (< 3 months), recent trauma/fracture (< 3 months), pregnancy, post-partum (< 3 months), oral contraceptives, hormone replacement therapy, central venous catheter, post-thrombotic syndrome, and immobilization (not family history of VTE, hospitalization before the index VTE or cancer).

3.4.3. All-cause mortality

Incidence proportions for treatment-emergent all-cause mortality were 2.3% with rivaroxaban and 7.2% with standard anticoagulation. Overall, 15 of the 29 deaths in the rivaroxaban group occurred in patients in the Asia-Pacific region and 14 occurred in patients from Eastern Europe/Middle East/Africa; there were no treatment-emergent deaths in patients in Latin America (Table 5). Cancer was the most frequent cause of death in the rivaroxaban and standard anticoagulation groups; other causes of death included PE, cardiovascular-related mortality, and infectious disease (Supplementary Table 2). Treatment-emergent recurrent VTE-related deaths (which included unexplained deaths where PE could not be ruled out) occurred in 4 (0.3%) patients in the rivaroxaban group and 8 (2.0%) in the standard anticoagulation group.

3.4.4. Outcomes by index venous thromboembolic event

Incidence proportions for the primary outcomes in patients by type of index venous thromboembolic event are shown in Supplementary Table 3. In patients in the rivaroxaban group, incidences of major bleeding were similar across all three VTE groups (DVT only, DVT plus PE and PE only; 1.6%, 1.3%, and 1.8%, respectively). This pattern was also observed for recurrent VTE (1.6%, 0.8%, and 1.2%, respectively) and all-cause mortality (2.2%, 2.1%, and 3.0%, respectively).

In patients in the standard anticoagulation group, incidence proportions of major bleeding were numerically highest in patients with DVT plus PE (6.3%, compared with 2.5% in those with DVT only and 4.8% in those with PE only). For recurrent VTE, incidence proportions were highest in patients with isolated PE (9.5%) compared with those with DVT alone and DVT plus PE (2.5% in both groups). A similar pattern was observed for all-cause mortality (10.7% for isolated PE and 5.9% and 7.5% for DVT alone and DVT plus PE, respectively).

3.4.5. Outcomes in patients in the standard anticoagulation group according to treatment received

Incidences of major bleeding, recurrent VTE, and all-cause mortality differed between the three subgroups of patients receiving standard anticoagulation. For all three outcome events, the incidence was highest to lowest in the following order: heparin/fondaparinux only; heparin/fondaparinux overlapping with and followed by a VKA; and VKA only. Incidence proportions of major bleeding were 6.5%, 3.2%, and 2.2%, respectively; for recurrent VTE, they were 4.3%, 4.1%, and

Table 3
Baseline demographics and clinical characteristics of the rivaroxaban cohort by region.

Characteristic	Asia-Pacific (n = 720)	Eastern Europe/Middle East/Africa (n = 473)	Latin America (n = 92)
Age, years, mean ± SD	64.3 ± 15.3	52.0 ± 17.3	61.4 ± 15.9
Age category			
< 60 years old	247 (34.3)	305 (64.5)	40 (43.5)
≥60 years old	473 (65.7)	168 (35.5)	52 (56.5)
Male sex	335 (46.5)	260 (55.0)	28 (30.4)
Body weight, kg, mean ± SD	64.4 ± 13.7	82.1 ± 16.3	75.0 ± 14.5
Body weight category			
≤70 kg	451 (62.6)	97 (20.5)	37 (40.2)
> 70 to 90 kg	132 (18.3)	182 (38.5)	39 (42.4)
> 90 kg	33 (4.6)	112 (23.7)	15 (16.3)
Missing	104 (14.4)	82 (17.3)	1 (1.1)
First available CrCl, mL/min, mean ± SD	83.4 ± 39.9	102.7 ± 44.2	85.8 ± 42.8
First available CrCl category			
< 30 mL/min	16 (2.2)	4 (0.8)	2 (2.2)
30 to < 50 mL/min	79 (11.0)	20 (4.2)	4 (4.3)
50 to < 80 mL/min	196 (27.2)	65 (13.7)	14 (15.2)
≥80 mL/min	237 (32.9)	189 (40.0)	23 (25.0)
Missing	192 (26.7)	195 (41.2)	49 (53.3)
Index diagnosis			
DVT only	463 (64.3)	349 (73.8)	70 (76.1)
PE with DVT	131 (18.2)	94 (19.9)	13 (14.1)
PE only	126 (17.5)	30 (6.3)	9 (9.8)
Type of VTE[a]			
Provoked	300 (41.7)	164 (34.7)	16 (17.4)
Unprovoked	420 (58.3)	309 (65.3)	76 (82.6)
Previous VTE	68 (9.4)	64 (13.5)	18 (19.6)
Known cancer at baseline	173 (24.0)	36 (7.6)	7 (7.6)
Known thrombophilic condition	23 (3.2)	21 (4.4)	5 (5.4)
Previous major bleeding episode	21 (2.9)	5 (1.1)	2 (2.2)
Missing/unknown	18 (2.5)	13 (2.7)	0 (0)

Data are n (%) unless stated otherwise.
CrCl, creatinine clearance; DVT, deep vein thrombosis; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.
[a] Provoking factors included recent surgery (< 3 months), recent trauma/fracture (< 3 months), pregnancy, post-partum (< 3 months), oral contraceptives, hormone replacement therapy, central venous catheter, post-thrombotic syndrome, and immobilization (not family history of VTE, hospitalization before the index VTE or cancer).

Table 4
Adjusted TTR by INR range and geographic region.

Geographic region, % ± SD	INR range		
	< 2.0	2.0–3.0	> 3.0
Asia-Pacific	65.2 ± 40.3	25.9 ± 34.7	8.9 ± 23.9
Europe, Middle East and Africa	32.5 ± 39.2	56.5 ± 39.5	10.9 ± 22.4
Latin America	35.5 ± 44.1	45.6 ± 42.8	18.9 ± 34.3

Geographic region, % ± SD	INR range		
	< 1.5	1.5–2.5	> 2.5
Asia-Pacific	28.4 ± 38.1	50.9 ± 40.7	20.7 ± 35.4
Europe, Middle East and Africa	13.9 ± 30.4	48.3 ± 37.8	37.7 ± 38.8
Latin America	23.8 ± 41.3	37.0 ± 41.7	39.2 ± 44.0

INR, international normalized ratio; SD, standard deviation; TTR, time in therapeutic range.

3.2%, respectively; and for all-cause mortality, they were 17.4%, 4.6% and 3.2%, respectively. Of note, 40.2% of patients who received heparin/fondaparinux only had active cancer at baseline (Supplementary Table 4).

3.4.6. Major adverse cardiovascular events

The incidence proportions of major adverse cardiovascular events were 0.5% in both the rivaroxaban and standard anticoagulation groups.

Table 5
Primary outcome incidence proportions of the rivaroxaban cohort by region (safety population).

Characteristic	Asia-Pacific (n = 720)	Eastern Europe/ Middle East/Africa (n = 473)	Latin America (n = 92)	All (n = 1285)
Major bleeding	18 (2.5)	1 (0.2)	1 (1.1)	20 (1.6)
Recurrent VTE	14 (1.9)	0 (0.0)	4 (4.3)	18 (1.4)
All-cause mortality	15 (2.1)	14 (3.0)	0 (0.0)	29 (2.3)

Data are n (%) unless stated otherwise.
VTE, venous thromboembolism.

3.4.7. Other symptomatic thromboembolic events

There were no other symptomatic thromboembolic events in the rivaroxaban or standard anticoagulation groups, and just one event (0.4%) in the early switchers group.

3.4.8. Other adverse events

Data on other adverse events are presented in Supplementary Table 4.

3.4.9. Healthcare resource use

Overall, 614 (47.8%) patients in the rivaroxaban group and 280 (69.7%) patients in the standard anticoagulation group were hospitalized. The least squares mean (± standard error from the logarithmized data) for length of stay for hospitalized patients was 8.1 (± 0.04) days for rivaroxaban-treated patients and 12.5 (± 0.05) days for standard anticoagulation-treated patients. The number of healthcare professional

visits (with some patients receiving more than one visit) totaled 1231 in the rivaroxaban group and 373 in the standard anticoagulation group; the mean number of visits (± standard deviation) was 0.2 (0.82) and 0.6 (1.90), respectively.

4. Discussion

XALIA-LEA adds to the growing body of real-world evidence supporting the use of rivaroxaban for the treatment and secondary prevention of VTE. The study included patients from the Asia-Pacific region, Eastern Europe, the Middle East, Africa, and Latin America and those with isolated PE, who were not included in the XALIA study [5]. Furthermore, XALIA-LEA also provides novel data from routine clinical practice on management strategies and treatment outcomes for patients in these demographic groups who received standard anticoagulation.

A substantial number of patients enrolled in XALIA-LEA were prescribed rivaroxaban for VTE treatment (1570/1972 total patients [the former figure includes the early switchers as well as those in the rivaroxaban group]); rivaroxaban dosing was mostly in accordance with the label. However, as shown in XALIA [5,11], physicians appear to be cautious in prescribing rivaroxaban to certain patients. The standard anticoagulation groups in both studies had higher incidences of renal impairment, PE, and provoked VTE than the respective rivaroxaban groups. The early switchers included a greater percentage of patients with PE and previous major bleeding episodes versus the rivaroxaban group in both XALIA and XALIA-LEA. Furthermore, in XALIA-LEA, the number of patients with a provoked VTE was higher in the early switchers than the rivaroxaban group.

Similar to XALIA [5] and the EINSTEIN PE and EINSTEIN DVT studies [12,13], XALIA-LEA showed that rivaroxaban was well tolerated and effective for the treatment of VTE. This study further demonstrates the applicability of the EINSTEIN PE and EINSTEIN DVT phase III trial results to unselected patient populations. Incidence proportions for the primary outcomes with rivaroxaban in XALIA-LEA were similar to those reported in the EINSTEIN pooled analysis (major bleeding: 1.6% and 1.0%; recurrent VTE: 1.4% and 2.1%; and all-cause mortality: 2.3% and 2.3%, respectively) [4]. Direct comparisons should, however, be interpreted cautiously, because adjustments for all confounding factors cannot be made and few events occurred in both studies.

Notably, a high proportion of patients who received standard anticoagulation were prescribed a VKA only (despite guidelines recommending initial use of heparin/fondaparinux before transitioning to a VKA). However, these patients had lower incidences of major bleeding, recurrent VTE, and all-cause mortality than those who received heparin/fondaparinux only or heparin/fondaparinux overlapping with and followed by a VKA; therefore, deviation from clinical recommendations did not appear to be the underlying reason for high primary outcome incidence proportions observed in the present study. There were also variations in TTR by region, with low TTR (25.9%) for the standard target INR range of 2.0–3.0 observed in patients from the Asia-Pacific region (the majority of whom were from South Korea) compared with patients from Europe, the Middle East and Africa, and Latin America. This may be explained by local patient management practices in Asian countries – despite guideline recommendations to target an INR of 2.0–3.0 in many countries in the region (including South Korea) [14]. In practice, it is common for physicians to target an INR range of 1.5–2.5 because of fears over bleeding risk. Furthermore, some Asian guidelines (e.g. Japan) advise targeting the lower INR range for this reason [15,16]. This approach was reflected in the higher TTR (50.9%) when an INR for the target range of 1.5–2.5 was considered in the analysis of patients from the Asia-Pacific region.

The inclusion of patients with isolated PE was a novel feature of XALIA-LEA, because these patients were not eligible to enroll in XALIA. Across the three VTE types (DVT only, DVT plus PE, and PE only), all primary outcome incidence proportions were numerically low with rivaroxaban therapy and generally similar for all three VTE subtypes in both treatment groups. There was a small numerical trend toward higher incidences of major bleeding and all-cause mortality in the group of patients with PE only. In the standard anticoagulation group, there were more pronounced differences for the primary outcome incidences between the different VTE types, where recurrent VTE incidence and all-cause mortality were highest in patients with isolated PE. However, major bleeding incidence was highest in patients with DVT plus PE in the standard anticoagulation group. As discussed above, factors such as local management practices could potentially have influenced these findings. For example, although only 52.6% of patients in the safety analysis set of XALIA-LEA were from the Asia-Pacific region, 18 of the 20 major bleeding events occurred in this group; this was likely driven by the older, sicker population in this region compared with patients from Europe/Middle East/Africa and Latin America.

The strengths of the XALIA and XALIA-LEA studies resulted from the prospective design, data collection and blinded adjudication of outcome events, and have together with the limitations (e.g. selection bias in treatment allocation) been summarized in the primary publication for XALIA [5]. An additional limitation in XALIA-LEA was that a propensity score-stratified analysis was not possible because of the small sample size of the standard anticoagulation treatment group (of the 1972 patients enrolled, only 20.4% received standard anticoagulation) and the lack of overlap in the propensity distributions, which would have resulted in the exclusion of most patients who received standard anticoagulation. Furthermore, the ‘standard anticoagulation’ group was heterogeneous including 24% of patients who received a VKA only; therefore, direct statistical comparisons of clinical outcomes between the rivaroxaban and standard anticoagulation cohorts were avoided.

5. Conclusions

XALIA-LEA expands the dataset obtained from the XALIA study to include additional global regions. XALIA-LEA showed that most patients who received rivaroxaban were appropriately selected, received the correct dosing schedule and reported few adverse effects. The primary outcome incidences in patients treated with rivaroxaban were low and consistent with previously published data. There were also regional variations in patient management approaches observed with standard anticoagulation, which may have influenced outcome incidences in these patients. Furthermore, it appears that in the Asia-Pacific region, the approach to INR management in clinical practice differs from the guideline-recommended approach. XALIA-LEA also provides novel information on outcomes by VTE subtype, including patients with isolated PE who were not eligible for enrollment in XALIA. The results of XALIA-LEA demonstrated that, in patients treated with rivaroxaban, outcome incidence proportions were relatively consistent regardless of VTE type.

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Appendix A. Supplementary data

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