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XALIA-LEA, a non-interventional study comparing rivaroxaban with standard anticoagulation for initial and long-term therapy in venous thromboembolism

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Background

- The non-interventional XALIA study compared the safety and effectiveness of rivaroxaban to standard anticoagulation for the treatment of deep vein thrombosis (DVT) in routine clinical practice[1]
  - XALIA enrolled patients between June 2012 and March 2014 from Europe, Israel and Canada
  - The approval of rivaroxaban in the pulmonary embolism (PE) indication occurred during the study, and as a result patients with DVT and concomitant PE (but not isolated PE) were subsequently eligible for inclusion
- XALIA-LEA emulated the main XALIA study, but enrolled patients from regions under-represented or not included in the XALIA population
- In contrast to XALIA, the later start date of XALIA-LEA enabled the inclusion of patients with isolated PE (beginning after the approval of rivaroxaban in the PE indication)

Aim

- To provide rivaroxaban safety and effectiveness information from routine clinical practice in an unselected venous thromboembolism (VTE) population from the Asia-Pacific region, Eastern Europe, the Middle East, Africa and Latin America

Methods

- Patients aged ≥18 years, with objectively confirmed acute DVT and/or PE, and with an intended anticoagulant treatment duration of ≥3 months were eligible
- Patients received rivaroxaban (alone or with ≤48 hours of initial heparin or fondaparinux therapy) or standard anticoagulation (heparin/fondaparinux alone or overlapping with/followed by a vitamin K antagonist [VKA])
- Therapy type, dose and duration were at the physician's discretion
- Patients who initially received heparin/fondaparinux for >2–14 days and/or a VKA for 1–14 days before switching to rivaroxaban were defined as 'early switchers'
  - These patients were excluded from the main safety analysis
- Outcome events were adjusted for covariates, which were selected based on a Cox regression using stepwise selection ($p<0.10$ for adding/keeping variables in the model)
  - Major bleeding: Cox regressions were adjusted for known cancer at baseline, Asian race, concomitant non-steroidal anti-inflammatory drug use and stratified by index VTE type
  - VTE recurrence: Cox regressions were adjusted for known cancer at baseline, previous VTE at baseline, fragility and stratified by index VTE type
  - All-cause mortality: Cox regression was adjusted for fragility, first available creatinine clearance (<50 ml/min, ≥50–<80 ml/min or ≥80 ml/min), Country=South Korea, concomitant steroid use and stratified by known cancer at baseline and index VTE type
- Unlike in 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

Results

- Between 27 June 2014 and 3 October 2015, XALIA-LEA enrolled 1987 patients from 16 countries (111 centres) across the Asia-Pacific region, Eastern Europe, the Middle East, Africa and Latin America (Table 1)
  - A large proportion of patients were enrolled from South Korea (42%)
- Overall, 8 patients did not receive anticoagulant therapy and 7 received other non-vitamin K antagonist oral anticoagulants, and were excluded from the primary analysis. Early switchers (n=285) were included in a separate sensitivity analysis
- The primary analysis comprised 1285 rivaroxaban-treated and 402 standard anticoagulation-treated patients
- Baseline characteristics (unadjusted safety population) were largely similar between treatment groups, with the following exceptions (Table 2):
  - The standard anticoagulation group had higher rates of renal impairment, PE and provoked VTE than the rivaroxaban group (cancer was considered separately from provoking factors)
  - Geographical region and race had a significant impact on treatment choice; more patients from the Asia-Pacific region or with Asian ethnicity (regardless of geographical location) received rivaroxaban versus standard anticoagulation therapy

Table 1. Enrolment by geographical region and country

Characteristic*	Rivaroxaban (N=1285)	Standard anticoagulation therapy# (N=402)	Early switcher‡ (N=285)
Asia-Pacific	**720 (56.0)**	**167 (41.5)**	**157 (55.1)**
Indonesia	46 (3.6)	7 (1.7)	1 (0.4)
Malaysia	15 (1.2)	14 (3.5)	6 (2.1)
Philippines	13 (1.0)	4 (1.0)	1 (0.4)
Singapore	12 (0.9)	20 (5.0)	6 (2.1)
South Korea	607 (47.2)	110 (27.4)	118 (41.4)
Taiwan	27 (2.1)	12 (3.0)	25 (8.8)
Eastern Europe	**142 (11.1)**	**45 (11.2)**	**28 (9.8)**
Russia	103 (8.0)	36 (9.0)	25 (8.8)
Ukraine	39 (3.0)	9 (2.2)	3 (1.1)
Middle East	**142 (11.1)**	**73 (18.2)**	**63 (22.1)**
Jordan	13 (1.0)	4 (1.0)	2 (0.7)
Kazakhstan	47 (3.7)	2 (0.5)	48 (16.8)
Lebanon	34 (2.6)	5 (1.2)	4 (1.4)
Saudi Arabia	48 (3.7)	62 (15.4)	9 (3.2)
Africa	**189 (14.7)**	**78 (19.4)**	**30 (10.5)**
Algeria	32 (2.5)	7 (1.7)	0 (0.0)
Egypt	145 (11.3)	58 (14.4)	20 (7.0)
Kenya	12 (0.9)	13 (3.2)	10 (3.5)
Latin America	**92 (7.2)**	**39 (9.7)**	**7 (2.5)**
Mexico	92 (7.2)	39 (9.7)	7 (2.5)

*All results are presented as n (%); #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; ‡patients who initially received heparin/fondaparinux for >2–14 days and/or a VKA for 1–14 days before switching to rivaroxaban.

VKA, vitamin K antagonist.

- After adjusting for important covariates, there was a statistically significant difference between rivaroxaban and standard anticoagulation therapy for the primary outcomes (Figure 1):
  - Major bleeding (2.9%/year vs 8.2%/year; hazard ratio [HR] =0.36; 95% confidence interval [CI] 0.18–0.71; $p=0.003$)
  - Recurrent VTE (2.6%/year vs 8.8%/year; HR=0.32; 95% CI 0.16–0.64; $p=0.001$)
  - All-cause mortality (4.2%/year vs 15.8%/year; HR=0.37; 95% CI 0.21–0.63; $p<0.001$)

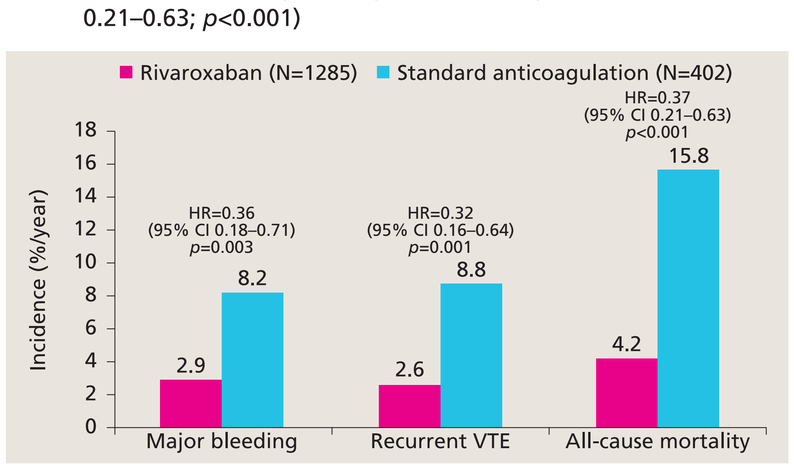

Figure 1. Primary outcomes associated with rivaroxaban and standard anticoagulation therapy for the treatment of VTE.

CI, confidence interval; HR, hazard ratio; VTE, venous thromboembolism.

- In total, 6 patients (0.5%) in the rivaroxaban group and 2 patients (0.5%) in the standard anticoagulation group had a major adverse cardiovascular event
- There were no other symptomatic thromboembolic events in the rivaroxaban or standard anticoagulation groups
- In contrast to the main XALIA study[1]:
  - There were no significant differences in age, body weight, known cancer at baseline or previous major bleeding episodes between treatment groups
  - As expected, a higher proportion of patients with PE were enrolled in XALIA-LEA (with/without DVT) (34.9%) versus XALIA (with DVT only) (10.7%)
  - The number of enrolled patients with known cancer at baseline was also higher in XALIA-LEA (16.6%) than in XALIA (11.4%)
  - The incidences of all-cause mortality and major bleeding (for the respective rivaroxaban and standard anticoagulation groups) were considerably higher in XALIA-LEA (compared with the crude events rates from XALIA); only the incidence of recurrent VTE with rivaroxaban therapy was similar between the two studies (Figure 2)

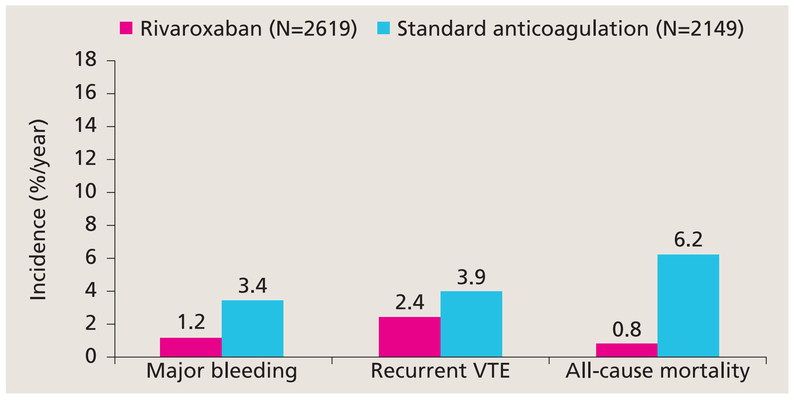

Figure 2. Primary outcomes from XALIA (crude event rates) associated with rivaroxaban and standard anticoagulation therapy for the treatment of DVT.[1]

CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; VTE, venous thromboembolism.

Table 2. Baseline demographics and clinical characteristics

Characteristic	Rivaroxaban (N=1285)	Standard anticoagulation therapy* (N=402)	*p*-value	Early switchers# (N=285)
Geographic region			<0.0001	
Asia-Pacific	720 (56.0)	167 (41.5)		157 (55.1)
Eastern Europe/Middle East/Africa	473 (36.8)	196 (48.8)		121 (42.5)
Latin America	92 (7.2)	39 (9.7)		7 (2.5)
Race			<0.0001	
White	393 (30.6)	154 (38.3)		85 (29.8)
Black	18 (1.4)	18 (4.5)		11 (3.9)
Asian	744 (57.9)	179 (44.5)		184 (64.6)
Multiple	0	1 (0.2)		N/A
Missing	130 (10.1)	50 (12.4)		5 (1.8)
Age, years, mean ± SD	59.6±17.1	58·0±18.0	0.1090	59.0±18.18
Age category			0.3033	
<60 years	592 (46.1)	197 (49.0)		133 (46.7)
≥60 years	693 (53.9)	205 (51.0)		152 (53.3)
Male sex	623 (48.5)	180 (44.8)	0.1941	133 (46.7)
Weight			N/S	
<50 kg	73 (5.7)	23 (5.7)		16 (5.6)
≥50–70 kg	512 (39.8)	166 (41.3)		119 (41.8)
>70–<90 kg	353 (27.5)	124 (30.8)		80 (28.1)
≥90 kg	160 (12.5)	64 (15.9)		43 (15.1)
Missing	187 (14.6)	25 (6.2)		27 (9.5)
First available CrCl			0.0052	
<30 ml/min	22 (1.7)	19 (4.7)		8 (2.8)
30–<50 ml/min	103 (8.0)	41 (10.2)		35 (12.3)
50–<80 ml/min	275 (21.4)	90 (22.4)		57 (20.0)
≥80 ml/min	449 (34.9)	131 (32.6)		123 (43.2)
Missing	436 (33.9)	121 (30.1)		62 (21.8)
Index diagnosis			0.0005	
DVT only	882 (68.6)	238 (59.2)		163 (57.2)
PE with or without DVT	403 (31.4)	164 (40.8)		122 (42.8)
Type of VTE‡			0.0002	
Provoked	480 (37.4)	192 (47.8)		136 (47.7)
Unprovoked	805 (62.6)	210 (52.2)		149 (52.3)
Previous VTE	150 (11.7)	55 (13.7)	0.2821	26 (9.1)
Known cancer at baseline	216 (16.8)	69 (17.2)	0.8684	43 (15.1)
Known thrombophilic condition	49 (3.8)	12 (3.0)	0.4376	6 (2.1)
Previous major bleeding episode	28 (2.2)	9 (2.2)	0.9036	9 (3.2)
Missing/unknown	31 (2.4)	17 (4.2)		14 (4.9)

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. *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; #patients who initially received heparin/fondaparinux for >2–14 days and/or a VKA for 1–14 days before switching to rivaroxaban; ‡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).

CrCl, creatinine clearance; DVT, deep vein thrombosis; N/A, not available; N/S, non-significant; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.

Conclusions

- XALIA-LEA provides information on VTE treatment in regions not studied in XALIA
- Results for the three primary outcomes demonstrated that rivaroxaban is safe and effective in a broad range of patients, supporting the observations from XALIA and the phase III EINSTEIN studies[1,2]
- Baseline characteristics between treatment groups were more similar in XALIA-LEA than was the case in XALIA (including age and cancer rates);[1] increased familiarity with rivaroxaban in clinical practice since the XALIA study may have influenced prescription patterns
- Major bleeding rates and all-cause mortality were considerably higher in XALIA-LEA compared with XALIA (for the respective rivaroxaban and standard anticoagulation groups),[1] possibly due to the higher proportion of patients with PE and known cancer at baseline enrolled in XALIA-LEA

Disclosures

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