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ORIGINAL RESEARCH

Real-World Evaluation of the Safety and Effectiveness of Apixaban & Rivaroxaban Lead-in Dosing Compared to Parenteral Lead-in Dosing in the Treatment of Venous Thromboembolism: A Multi-Center Retrospective Cohort Study

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Background: Although parenteral anticoagulation lead-in is not recommended with apixaban and rivaroxaban, parenteral anticoagulation is often used to replace apixaban or rivaroxaban lead-in doses for the initial phase treatment of VTE. Thus, our study compares the safety and effectiveness of lead-in parenteral anticoagulation to lead-in apixaban or rivaroxaban in patients who received apixaban or rivaroxaban for VTE treatment.

Methods: A multi-center retrospective cohort study included adult patients (aged ≥ 18 years) admitted to the hospital with acute VTE and treated with either apixaban or rivaroxaban. Patients were grouped depending on the lead-in anticoagulation received for initial VTE treatment into the "Direct oral anticoagulation (DOAC) lead-in" group if patients received an appropriate lead-in dose of apixaban and rivaroxaban and patients who received parenteral lead-in the "parenteral lead-in" group.

Results: A total of 389 patients were included; the DOAC lead-in group included 296 patients, whereas 93 patients were in the parenteral lead-in group. VTE recurrence (rVTE) during hospitalization and within 30 days was numerically higher in the parenteral lead-in group compared to the DOAC lead-in group (3.3% vs 0.6%; p=0.09 and 1.1% vs 0.7%; p=0.560), with a significantly higher number of patients with rVTE at 90 days (5.4% vs 1.4%; p=0.039). However, none of the patient's characteristics were significantly associated with the incidence of rVTE. In addition, the major bleeding rate during hospitalization was significantly higher among the parenteral lead-in group than in the DOAC lead-in group (14.0% vs 3.7%; p<0.001).

Conclusion: Parenteral anticoagulation lead-in before starting maintenance of apixaban and rivaroxaban showed a significantly higher risk of bleeding and a trend toward higher VTE recurrence than the DOAC lead-in. This study adds to the evidence supporting the utilization of the DOAC lead-in regimen in treating patients with VTE. Still, larger studies with robust designs are needed to confirm these findings.

Keywords: rivaroxaban, apixaban, lead-in, parenteral anticoagulation, venous thromboembolism, recurrence

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Introduction

The initial acute venous thromboembolism (VTE) phase (within 1–3 weeks) is characterized by increased clot burden and propagation, leading to increased recurrence rates and high risks of morbidity and mortality.[1] The estimated incidence of recurrent VTE (rVTE) within the first year is up to 1.4% in the first month, 3.1% at three months, and 5.6% at one year, with the risk being at the highest post-first VTE diagnosis.[1] Therefore, early anticoagulation optimization of the therapy is crucial in the management of VTE, especially in the initial phase.

The landmark clinical trials of direct oral anticoagulants (DOACs) realized the urgent need for immediate anticoagulation during the initial phase of VTE treatment, which was supported by VTE treatment guidelines.[2–6] The Hokusai-VTE and RE-COVER trials elected to start with lead-in parenteral anticoagulation for 5–10 days before starting dabigatran and edoxaban.[4,6] In contrast, the AMPLIFY, EINSTEIN-PE, and EINSTEIN-DVT trials immediately started patients on high doses of rivaroxaban (15 mg twice daily for 21 days) or apixaban (10 mg twice daily for 7 days),[2,3,5] but patients who received parenteral therapeutic anticoagulation for less than 48 hours before randomization were included in these studies.[2,3,5] Thus, both of these agents do not require initial parenteral lead-in anticoagulants.[2,3]

Several guidelines recommend the use DOACs over conventional anticoagulation therapy to treat VTE,[7–9] but in patients with high-risk pulmonary embolism (PE), the European Society of Cardiology guidelines recommends initiating parenteral anticoagulation without delay.[10] The decision of initial anticoagulation in patients with VTE is influenced by the patient's clinical status, potential drug-drug interactions, and the patient's goals. In addition, compared to DOAC, parenteral anticoagulation agents have shorter half-lives and can be easily monitored and reversed.[11] Thus, some prescribers are reluctant to start DOAC for acute treatment of VTE in hospitalized patients, even if patients are hemodynamically stable. Clinicians tend to be cautious in treating VTE, especially in fragile patients with renal impairment, at high risk of bleeding, or who might go to a medical procedure or surgery anytime during admission.[11,12] A Global Anticoagulant Registry in the FIELD (GARFIELD)-VTE, including 10,870 patients diagnosed with VTE from various countries, found that 17.3% of the included patients started on parenteral anticoagulation before switching to DOACs.[7] Moreover, a large multi-center prospective non-interventional study including 5136 patients with VTE diagnosis reported that 368 (7.2%) of these patients received parenteral anticoagulation for 2–14 days with or without warfarin before switching to rivaroxaban.[12]

Although the parenteral anticoagulation lead-in is generally not recommended preceeding apixaban and rivaroxaban, parenteral anticoagulation is often used to replace apixaban or rivaroxaban lead-in doses for the initial phase treatment of VTE.[12–14] It has also been noted that prescribers tend to prolong lead-in parenteral anticoagulation before switching to rivaroxaban.[12] Given that the AMPLIFY and EINSTEIN trials excluded patients who had received multiple doses or longer than 48 hours of parenteral anticoagulation before apixaban and rivaroxaban lead-in dosing,[2,3,5] the efficacy and safety of using initial parenteral anticoagulation dosing over lead-in doses of apixaban or rivaroxaban for acute phase VTE treatment remain unpredicted. Thus, our study's objective is to compare the safety and effectiveness of lead-in parenteral anticoagulation to lead-in apixaban or rivaroxaban in patients who received apixaban or rivaroxaban for VTE treatment.

Methods

Study Design

This is a multi-center retrospective observational cohort study including newly diagnosed patients with acute VTE admitted to the hospital between January 1, 2016, and December 31, 2021. The study took place at three centers in Riyadh, Saudi Arabia: King Abdullah bin Abdulaziz University Hospital (KAAUH), King Saud University Medical City (KSUMC), and King Abdulaziz Medical City. It was approved by the King Abdullah International Medical Research Center institution review board (Ref.# NRC21R/400/09), KSUMC (Ref.# E-21-6295), and KAAUH (Ref.# HAP-01-R-059). The study was conducted following the Declaration of Helsinki. The ethics committees in all centers waived the need for patient's written consent because all the data were collected from their electronic medical records after de-identification.

Patient Population and Drug Regimens

Patients were included if they were 1) adults (aged ≥ 18 years), 2) admitted to the hospital with newly diagnosed VTE, and 3) had received either apixaban or rivaroxaban for VTE treatment. We excluded patients younger than 18 years, who

received rivaroxaban or apixaban for non-VTE treatment indications, and who received other oral anticoagulation therapy for VTE treatment (ie, edoxaban, dabigatran, or warfarin). Patients who received inappropriate lead-in or maintenance dosing or duration of apixaban or rivaroxaban were excluded. We also excluded patients who were already on a treatment dose of oral or injectable anticoagulants before the indexed VTE event date.

The patients were then split into two groups depending on the lead-in anticoagulation received for acute VTE treatment. First, the "DOAC lead-in" group represented the patients who received 10 mg of apixaban for seven days twice daily (or 15 mg of rivaroxaban for 21 days twice daily) for the lead-in therapy, with (maximum of 48 hours) or without prior parenteral anticoagulation. Then, they transitioned to the recommended maintenance dose of 5 mg of apixaban twice daily (or 20 mg of rivaroxaban once daily) to be consistent with the AMPLIFY and the EINSTEIN trials inclusion criteria.[2,3,5] Second, the "parenteral lead-in" group included patients who only received a treatment dose of parenteral anticoagulant and then transitioned directly to the recommended maintenance dose of 5 mg apixaban twice daily (or 20 mg of rivaroxaban once daily).

Data Collection

Data were collected from the patient's electronic health records, including patient's demographic information (ie, age, gender, body mass index [BMI]), past medical history, and risk factors for VTE recurrence (ie, history of VTE, oral contraception use, immobility, and recent major or orthopedic surgeries). We also gathered laboratory results such as serum creatinine (Scr), estimated glomerular filtration rate (eGFR), calculated creatinine clearance (CrCl) based on the Cockcroft-Gault equation and average hemoglobin level. We assessed the patient's bleeding risk using the Kuijer et al formula.[15] Each patient's data was collected and handled using Research Electronic Data Capture (REDCap®) software hosted by KSUMC. The day of VTE diagnosis was marked as the index date (Day 0).

Definitions of Outcomes

The primary effectiveness outcomes were rVTE during hospitalization and within 30- and 90-day follow-ups, defined as deep venous thromboembolism (DVT), PE, or both DVT and PE. Both VTE events were confirmed by computed tomography angiography, Doppler ultrasound, or physician's documentation. The safety outcomes included major bleeding (MB) and clinically relevant non-major bleeding (CRNMB) during hospitalization and within 30- and 90-day follow-ups, as defined according to the International Society on Thrombosis and Hemostasis.[16,17] Additional outcomes included rehospitalization due to VTE-related causes within 90 days of VTE diagnosis and death from any cause during hospitalization.

Statistical Analysis

Descriptive statistics using frequencies with percentages for categorical variables and mean with standard deviation for continuous variables were used to summarize the data. The patients' characteristics were compared in the two lead-in regimens using an unpaired *t*-test for continuous variables and a Chi-square test for categorical variables. In addition, the odds ratios for rVTE and MB were estimated for some variables with significant differences between the groups in the baseline characteristics as a sub-analysis.

Then, univariable logistic regression analysis was used to measure the effect of different lead-in regimens on the incidence of rVTE and MB at 90 days; the result was reported in the unadjusted analysis as crude odds ratio (COR) with a 95% confidence interval (95% CI). A multilevel logistic regression model was used to assess the association between patient's characteristics and their outcomes (rVTE and MB at 90 days) while using the lead-in regimens as a grouping variable in the multilevel model; results were reported in the unadjusted analysis. Then, backward-stepwise multivariable logistic regression, with $p<0.1$ for keeping variables in the model, was used to examine the actual effect of different regimens on the incidence of rVTE and MB at 90 days while adjusting for the effect of patients' characteristics in the model; and results were reported in the adjusted analysis as adjusted OR (AOR) with 95% CI. A p-value of < 0.05 was set for statistical significance. The data were analyzed using the SAS statistical analytics software, version 9.4 (SAS Institute Inc., Cary, NC).

Results

Patients' Demographics and Clinical Characteristics

A total of 698 patients diagnosed with VTE and treated with apixaban or rivaroxaban were included in the initial screening, and 309 patients were excluded for the reasons listed in the patient flow diagram (Figure 1). Thus, a total of 389 patients were included based on the eligibility criteria. The DOAC lead-in group included 296 patients, whereas 93 patients received parenteral lead-in therapy. The mean age of the included patients was 54.5 years (±20.1), and most of the included patients were female (62%). When comparing the two study groups, several patients' characteristics were comparable among the two groups, Table 1. However, patients included in the parenteral lead-in group were significantly

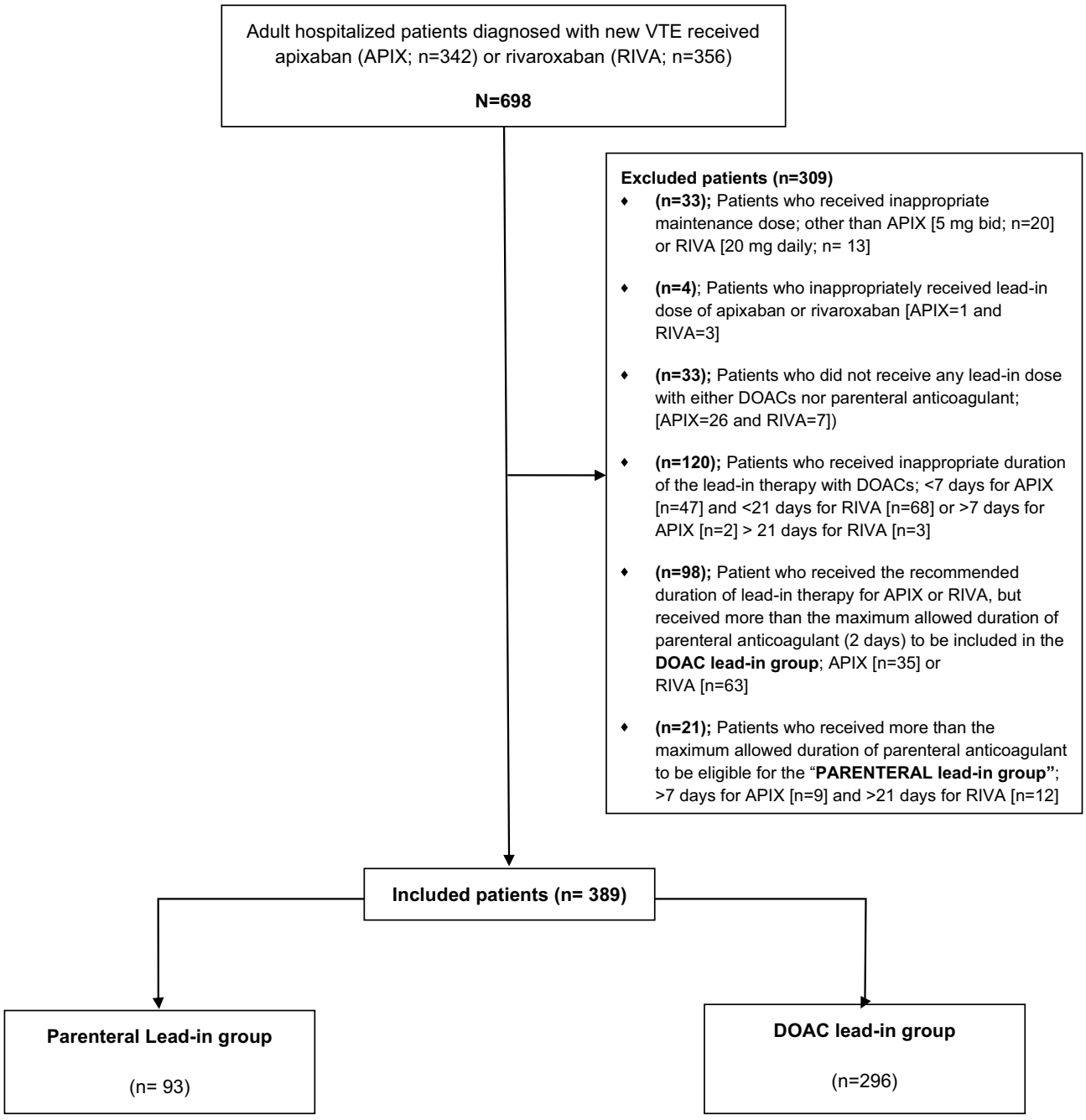

Figure 1 Patients inclusion and exclusion flow diagram.

Table 1 Patients' Demographics and Clinical Characteristics

Patient Characteristics	Overall (n=389)	Lead-in Group		*p*-value
		Parenteral (n=93)	DOAC(n=296)	
Age in years, mean (SD)	54.5 (20.1)	60.5 (20.3)	52.6 (19.7)	<0.001
BMI (kg/m^2), mean (SD)	30.9 (7.0)	30.2 (7.4)	31.1 (6.9)	0.306
Hospital Length of Stay (days)	7.1 (15.8)	15.2 (28.1)	4.6 (7.4)	<0.001
Gender				0.009
Male	148 (38.0)	46 (49.5)	102 (34.5)	
Female	241 (62.0)	47 (50.5)	194 (65.5)	
Pre-existing conditions				
Atrial Fibrillation	8 (2.1)	3 (3.2)	5 (1.7)	0.403
Coronary Artery Disease	29 (7.5)	16 (17.2)	13 (4.4)	<0.001
Hypertension	149 (38.3)	45 (48.4)	104 (35.1)	0.022
Valvular Disease	3 (0.8)	1 (1.1)	2 (0.7)	0.560
Stroke	44 (11.3)	16 (17.2)	28 (9.5)	0.040
Transient Ischemic Attack	7 (1.8)	4 (4.3)	3 (1.0)	0.059
Diabetes Mellitus	138 (35.5)	41 (44.1)	97 (32.8)	0.047
Chronic Kidney Disease	21 (5.4)	6 (6.5)	15 (5.1)	0.606
Active Smoking	27 (6.9)	4 (4.3)	23 (7.8)	0.418
Active Cancer	16 (4.1)	9 (9.7)	7 (2.4)	0.002
On chemotherapy (among patients with cancer)	7 (43.8)	4 (44.4)	3 (42.9)	1.000
Thrombophilia	14 (3.6)	4 (4.3)	10 (3.4)	0.752
History of MB (within 12 months)	17 (4.4)	3 (3.2)	14 (4.7)	0.576
History of CRNMB (within 12 months)	12 (3.1)	2 (2.2)	10 (3.4)	0.737
History of any bleeding (within 12 months)	8 (2.1)	2 (2.2)	6 (2.0)	1.000
Concomitant medications				
Aspirin	79 (20.3)	34 (36.6)	45 (15.2)	<0.001
P2Y12 Inhibitors				0.002
Clopidogrel	17 (4.4)	10 (10.8)	7 (2.4)	
Ticagrelor	2 (0.5)	1 (1.1)	1 (0.3)	
Risk Factors for VTE Recurrence				
History of Previous VTE	43 (11.1)	8 (8.6)	35 (11.8)	0.382
Type of Historical VTE				0.563
DVT	33 (76.7)	6 (75.0)	27 (77.1)	0.338
Proximal DVT	2 (6.1)	1 (16.7)	1 (3.7)	
Distal DVT	2 (6.1)	1 (16.7)	1 (3.7)	
Mixed DVT	2 (6.1)	0 (0.0)	2 (7.4)	
Unspecified DVT	27 (81.8)	4 (66.7)	23 (85.2)	
PE	7 (16.3)	2 (25.0)	5 (14.3)	0.571
Segmental PE	1 (14.3)	0 (0.0)	1 (20.0)	
Subsegmental PE	1 (14.3)	0 (0.0)	1 (20.0)	
Unspecified PE	5 (71.4)	2 (100)	3 (60.0)	
DVT plus PE	3 (7.0)	0 (0.0)	3 (8.6)	
Time of Historical VTE				0.005
Within 3 months	3 (7.0)	0 (0.0)	3 (8.6)	
Within 6 months	1 (2.3)	1 (12.5)	0 (0.0)	
Within 12 months	2 (4.7)	0 (0.0)	2 (5.7)	
Within >12 months	33 (76.7)	4 (50.0)	29 (82.9)	
Use of oral contraceptives or ERT	44 (11.3)	6 (6.5)	38 (12.8)	0.104
Obesity (BMI >30 kg/m2)	201 (51.7)	51 (54.8)	150 (50.7)	0.490
Immobility	98 (25.2)	33 (35.5)	65 (22.0)	0.010
Major General Surgery (within one year)	37 (9.5)	7 (7.5)	30 (10.1)	0.398
Orthopedic Surgery (within one year)	34 (8.7)	13 (14.0)	21 (7.1)	0.058

Notes: Results are presented as frequency (percentage) unless otherwise indicated. *p*-values are from the *t*-test for continuous data and chi-square or fisher-exact test for categorical data.

Abbreviations: BMI, body mass index; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; ERT, estrogen replacement therapy; MB, major bleeding; CRNMB, clinically relevant non-major bleeding; SD, standard deviation.

older (mean age 60.5 years vs 52.6 years; $p<0.001$) and had a significantly longer mean hospital stay (15.2 vs 4.6 days; $p<0.001$). This group also had significantly higher rates of comorbidities, including coronary artery disease, hypertension, stroke, diabetes mellitus, and active cancer. In addition, patients who were in the parenteral lead-in group received more concomitant antiplatelet medications compared to the DOAC lead-in group (Table 1). In contrast, the history of bleeding was numerically higher in the DOAC lead-in group compared to the parenteral lead-in group, at 4.7% vs 3.2% for MB and 3.4% vs 2.2% for CRNMB. The risk factors for VTE recurrence among the two groups were comparable, except for the rate of immobility, which was significantly higher in the parenteral lead-in group (35.5% vs 22%; $p=0.010$). Additional parameters related to baseline renal function were all comparable among the parenteral lead-in and DOAC lead-in groups, as presented in the additional material (Table S1). On the other hand, the mean hemoglobin level on or before VTE events was significantly higher among the DOAC lead-in group (Table S1).

Characteristics of the New VTE Events

Among 389 patients diagnosed with acute VTE, PE was present in 48.6% of the total patients (segmental PE in 42.9%) as compared to DVT in 44.5% (proximal DVT in 68.8%), with 6.9% having mixed VTE event. PE was the most common VTE type in the parenteral lead-in group (59.1%), and DVT was most present in the DOAC lead-in group (47.6%), as shown in Table 2. More than half of the patients (58.1%) presented with provoked VTE, with more provoked events in the parenteral lead-in group (64.5%). The risk of bleeding was comparable between the two groups, with most patients having intermediate to low risks (Table 2).

Table 2 Type of Current VTE Events and the Risk of Bleeding

VTE Characteristics	Overall (n=389)	Lead-in Group		*p*-value
		Parenteral (n=93)	DOAC (n=296)	
Type of the current VTE event				0.060
DVT	173 (44.5)	32 (34.4)	141 (47.6)	0.132
Proximal DVT	119 (68.8)	18 (56.3)	101 (71.6)	
Distal DVT	16 (9.2)	2 (6.3)	14 (9.9)	
Mixed DVT	28 (16.2)	9 (28.1)	19 (13.5)	
Unspecified DVT	10 (5.8)	3 (9.4)	7 (5.0)	
PE	189 (48.6)	55 (59.1)	134 (45.3)	0.061
Segmental PE	81 (42.9)	29 (52.7)	52 (38.8)	
Subsegmental PE	25 (13.2)	2 (3.6)	23 (17.2)	
Mixed PE	55 (29.1)	15 (27.3)	40 (29.9)	
Unspecified PE	28 (14.8)	9 (16.4)	19 (14.2)	
DVT plus PE	27 (6.9)	6 (6.5)	21 (7.1)	
DVT type of the DVT plus PE				0.287
Proximal DVT	14 (51.9)	5 (83.3)	9 (42.9)	
Distal DVT	5 (18.5)	0 (0.0)	5 (23.8)	
Mixed DVT	5 (18.5)	1 (16.7)	4 (19.0)	
Unspecified DVT	3 (11.1)	0 (0.0)	3 (14.3)	
PE type of the DVT plus PE				0.216
Segmental PE	11 (40.7)	3 (50.0)	8 (38.1)	
Subsegmental PE	1 (3.7)	0 (0.0)	1 (4.8)	
Mixed PE	8 (29.6)	0 (0.0)	8 (38.1)	
Unspecified PE	7 (25.9)	3 (50.0)	4 (19.0)	
VTE Etiology				0.323
Provoked	226 (58.1)	60 (64.5)	166 (56.1)	
Unprovoked	80 (20.6)	15 (16.1)	65 (22.0)	
Not reported	83 (21.3)	18 (19.4)	65 (22.0)	

(*Continued*)

Table 2 (Continued).

VTE Characteristics	Overall (n=389)	Lead-in Group		*p*-value
		Parenteral (n=93)	DOAC (n=296)	
Bleeding Risk*				0.061
High risk	14 (3.6)	7 (7.5)	7 (2.4)	
Intermediate risk	298 (76.6)	67 (72.0)	231 (78.0)	
Low risk	77 (19.8)	19 (20.4)	58 (19.6)	

Notes: Results are presented as frequency (percentage). *From the bleeding risk assessment score.
Abbreviations: VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; SD, standard deviation; BMI, body mass index.

Characteristics of Lead-in Regimens

A total of 296 patients were included in the DOAC lead-in group, of which 50.3% received apixaban and 49.7% received rivaroxaban, as shown in Table 3. Among the DOAC lead-in group, 66.9% received parenteral anticoagulation for < 48 hours, in which 56.8% received low-molecular-weight heparin (LMWH). The mean duration of parenteral anticoagulation use was 1.3 days (±0.4) before starting apixaban and 1.2 days (±0.4) before starting rivaroxaban. In the parenteral lead-in group, apixaban was prescribed as the maintenance DOAC in 57% of the patients as compared to rivaroxaban in 43%. LMWH was utilized as the parenteral anticoagulant in 72% of the patients before switching to the DOAC maintenance dose. The mean duration of parenteral anticoagulant before switching to the maintenance dose of DOAC was 3.7 (±2.4) days in apixaban and 11.1 (±5.8) days in rivaroxaban.

Clinical Outcomes

rVTE

VTE recurrence during hospitalization and within 30 days was numerically higher in the parenteral lead-in group compared to the DOAC lead-in group (3.3% vs 0.6% and 1.1% vs 0.7%, respectively); however, the difference was not statistically significant

Table 3 DOAC vs Parenteral Lead-in Dosing for VTE Treatment

Anticoagulation Characteristics	Overall	Apixaban	Rivaroxaban
Patients, N	389	202	187
DOAC lead-in dosing	296 (76.1)	149 (50.3)	147 (49.7)
Type of parenteral anticoagulant used (for less than 2 days), n (%)			
LMWH	168 (56.8)	68 (45.6)	100 (68.0)
UFH	29 (9.8)	22 (14.8)	7 (4.8)
Fondaparinux	1 (0.3)	1 (0.7)	0 (0.00)
None	98 (33.1)	58 (38.9)	40 (27.2)
Duration for received lead-in dose of DOAC in days, Mean (SD)		7.0 (0.0)	21 (0.0)
Duration for received parenteral anticoagulant in days, Mean (SD)		1.3 (0.4)	1.2 (0.4)
Parenteral lead-in Dosing	93 (23.9)	53 (57.0)	40 (43.0)
Type of parenteral anticoagulant used, n (%)			
LMWH	67 (72.0)	32 (60.4)	35 (87.5)
UFH	24 (25.8)	20 (37.7)	4 (10.0)
Fondaparinux	2 (2.2)	1 (1.9)	1 (2.5)
Duration for the lead-in parenteral anticoagulant in days, Mean (SD)		3.7 (2.4)	11.1 (5.8)

Note: Results are presented as frequency (percentage) unless otherwise indicated.
Abbreviations: VTE, venous thromboembolism; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; UFH, unfractionated heparin; SD, standard deviation; IQR, interquartile range.

(Table 4). In addition, the overall number of patients with VTE recurrence within 90 days was significantly higher among the parenteral lead-in group (5.4%) compared to the DOAC lead-in group (5.4% vs 1.4%; p=0.039) (Table 4). In the multilevel logistic regression model assessing the association between the patient's characteristics and the incidence of rVTE, none of the patient's characteristics was significant. While the odds of having rVTE were linked to being on parenteral lead-in therapy in the univariate model (OR 4.148; 95% CI 1.09–15.78), this difference became insignificant when all patients' characteristics were included in the multivariable model (Table S2).

Bleeding

The MB rate during hospitalization was significantly higher among the parenteral lead-in group than the DOAC lead-in group (14.0% vs 3.7%; p<0.001). Additionally, the total proportion of patients who developed MB within 90 days was significantly higher in the parenteral lead-in group compared to the DOAC lead-in group (14.0% vs 4.7%; p=0.004), as presented in Table 4. Meanwhile, the rate of CRNMB during hospitalization was significantly higher in the parenteral lead-in group than in the DOAC lead-in group (10.8% vs 3.0%; p=0.006). However, the proportion of patients who developed CRNMB within 90 days was numerically higher in the parenteral lead-in group (16.1% vs 9.8%; p=0.092). Detailed sub-group analyses of patients who developed rVTE and MB are presented in Table S3.

Meanwhile, the multilevel logistic regression model showed no significant association between the occurrence of MB and any of the patients' characteristics except for patients with a history of MB (OR 14.84; 95% CI 4.78–46.40) and orthopedic surgery (OR 4.02; 95% CI 1.50–10.74) within a year (Table S4). When comparing the odds of MB within 90

Table 4 Outcomes During Hospitalization and Up to 90 Days of the VTE Event

Outcome	Lead-in Group		p-value
	Parenteral	DOAC	
Patients, N	93	296	
rVTE Event			
During Hospitalization	3 (3.3)	2 (0.6)	0.091
Within 30 days*	1 (1.1)	2 (0.7)	0.560
Within 90 days**	2 (2.2)	2 (0.7)	0.243
Total number of patients with rVTE within 90 days***	5 (5.4)	4 (1.4)	0.039
MB Event			
During Hospitalization	13 (14.0)	11 (3.7)	<0.001
Within 30 days*	0 (0.0)	4 (1.4)	0.576
Within 90 days**	2 (2.2)	5 (1.7)	0.674
Total number of patients with MB within 90 days***	13 (14.0)	14 (4.7)	0.004
CRNMB Event			
During Hospitalization	10 (10.8)	9 (3.0)	0.006
Within 30 days*	7 (7.5)	23 (7.8)	0.938
Within 90 days**	7 (7.5)	23 (7.8)	0.938
Total number of patients with CRNMB within 90 days***	15 (16.1)	29 (9.8)	0.092
Rehospitalization**			
Within 30 days*	1 (1.1)	7 (2.4)	0.686
Within 90 days**	2 (2.2)	13 (4.4)	0.537
Death during hospitalization	2 (2.2)	0 (0.0)	0.032

Notes: Results are presented as frequency (percentage). p-values are from the chi-square or fisher-exact test. *Within 30 days: 30 days of the indexed event date (excluding hospitalization days). **Within 90 days: 90 days of the indexed event date (excluding hospitalization days). ***The Cumulative number of patients with the outcome within 90 days, including events occurring during the index hospitalization. ****Rehospitalization due to VTE-related causes (recurrence, deterioration, or bleeding). Two patients in the recommended group and two in the parenteral lead-in group had two MB events each, and three patients from the recommended group and two patients in the parenteral lead-in group had two CRNMB events each during the 90 days of follow-up after the indexed VTE event, including events that occurred during the index hospitalization.

Abbreviations: rVTE, recurrent venous thromboembolism; VTE, venous thromboembolism; MB, major bleeding; CRNMB, clinically relevant non-major bleeding.

days between the two lead-in regimens, the use of parenteral lead-in was associated with higher odds of having MB in the univariate model (OR 3.27; 95% CI 1.48–7.25) and the multivariable model (OR 4.45; 95% CI 1.22–16.29).

Rehospitalization and Mortality

The rate of rehospitalization within 30 and 90 days showed higher trends in the DOAC lead-in group (2.4% vs 1.1%; p=0.686 and 4.4% vs 2.2%; p=0.537, respectively). The rate of all-cause mortality during hospitalization was significantly higher in the parenteral lead-in group compared to the DOAC lead-in group (2.2% vs 0%; p<0.032) (Table 4).

Discussion

In this study, we assessed the safety and effectiveness of two lead-in regimens in patients receiving either apixaban or rivaroxaban for VTE treatment. The risk of developing rVTE events during hospitalization and up to 90 days was not significantly higher among the parenteral and the DOAC lead-in groups. Still, there was a significantly higher proportion of patients with rVTE at 90 days in the parenteral lead-in group (5.4% vs 1.4%; p=0.039). In addition, there was a significantly higher rate of MB and CRNMB during hospitalization in patients receiving the parenteral lead-in regimen compared to the DOAC lead-in regimen, with a significantly higher proportion of patients with MB at 90 days (14% vs 4.7%; p = 0.004).

Consistent with our study findings, a multi-center observational prospective study (XALIA study) reported a higher rate of rVTE (2.2%, 95% CI 0.94–4.24) in patients who received parenteral anticoagulation for > 48 hours with or without warfarin before switching to rivaroxaban.[13] In that study, those patients were labeled as "early switchers" compared to patients who received rivaroxaban lead-in (1.4%, 95% CI 1.00–1.94) with/without a parenteral lead-in dose for less than two days.[13] It is important to note that it was not clear if early switchers in the XALIA study were switched to rivaroxaban 15 mg twice daily to complete the 21 days or directly to 20 mg once daily, as follows in our parenteral lead-in group.[13] This variation, if it exists, may limit the comparison of our results to those of the XALIA study.[13] In addition, a retrospective cohort study showed a higher rate of rVTE within 90 days in patients receiving a reduced lead-in duration of apixaban and rivaroxaban compared to the full lead-in duration (5% vs 1%; p=0.205).[14] However, patients in the reduced lead-in group received some lead-in doses of apixaban and rivaroxaban and then transitioned to maintenance doses.[14]

The higher incidence of rVTE we witnessed with the parenteral lead-in group may be driven by the group's significantly older age, higher LOS, and higher number of comorbidities seen at baseline in the parenteral lead-in group, all of which may indicate that these patients may originally be sicker. However, the regression analysis showed that the patient's age and LOS were not significantly different between the two lead-in groups in terms of having rVTE. Moreover, the increased odds of rVTE in patients with a history of TIA, DM, cancer, or CRNMB were not significantly higher among the DOAC lead-in group compared to the parenteral lead-in group. The higher occurrence of rVTE in the parenteral lead-in group may be attributed to the switch between anticoagulation agents (from parenteral lead-in to maintenance DOAC), which puts the patients at risk of rVTE and/or bleeding.[18]

The initiation of parenteral anticoagulation for acute VTE treatment in more frail or hemodynamically unstable patients before starting oral anticoagulation is commonly observed and recommended in patients with PE.[10,12–14] Physicians are sometimes pushed to substitute lead-in DOACs by parenteral anticoagulation due to patients' severe illnesses, renal or liver dysfunction, extreme body weight, the necessity for acute surgical interventions, or simply because some of them are not used to the new approach of starting oral anticoagulant without parenteral therapy.[7] The presence of cancer in patients with VTE also affects the anticoagulation choice due to the potential drug-drug interaction between DOACs and several anti-cancer therapies.[19] In our study, we noticed a significantly higher number of patients with cancer in the parenteral lead-in group. Higher odds of rVTE were also observed in patients with active cancer, but it was not statistically significant.

We found that the rates of MB and CRNMB during hospitalization were significantly higher in the parenteral lead-in group. Similar to our study, the sub-analysis of patients who switched from standard therapy to rivaroxaban in the XALIA study found a higher rate of MB in the "early switcher" group compared to the rivaroxaban lead-in dose (1.4%, 95% CI 0.44–3.14 vs 0.7%, 95% CI 0.44–1.13.[13] In addition, a retrospective cohort study reported a significantly higher

rate of overall bleeding within 90 days in patients who received a reduced lead-in duration of apixaban or rivaroxaban at 16% compared to 2% in the full-duration lead-in group.[14] This bleeding rate was mostly driven by the significantly high rate of CRNMB bleeding in the reduced lead-in group vs the full-duration lead-in group (8% vs 0%; p=0.009).[14] In our study, the higher rate of bleeding witnessed in the parenteral lead-in group may be affected by their significantly lower hemoglobin level at baseline and a higher rate of active cancer. Nonetheless, only the history of MB and orthopedic surgery were significantly associated with higher odds of MB within 90 days in patients receiving DOACs lead-in compared to the parenteral lead-in. It is also noteworthy that at baseline, the bleeding risk and history of bleeding among the parenteral and DOAC lead-in groups were similar.

The rate of rehospitalization within 30 and 90 days was higher among the DOAC lead-in group. However, it did not reach statistical significance. This trend may be related to a significantly higher LOS in the parenteral group initially, which may limit catching rehospitalization events within the 90-day follow-up period. Consistent with our findings, the sub-analysis of the XALIA study found that "early switcher" patients had a higher rate of rehospitalization when compared with the DOAC rivaroxaban group.[13] Moreover, mortality during hospitalization was also significantly higher among patients who received a parenteral lead-in regimen (2.2% vs 0%; p = 0.032). This death rate may be attributed to the sicker patients who initially presented in the parenteral lead-in group. In the XALIA, all-cause mortality was higher in the early switchers (0.8%) compared to the rivaroxaban group (0.5%), similar to our findings. Our study and the XALIA analysis suggest that interrupting anticoagulation therapy may expose patients to higher mortality risk.[13]

Although this is one of the few studies that assessed the real-world effect of using rivaroxaban and apixaban on patients' clinical outcomes,[13,14] unlike previous studies, the focus of this study was on the lead-in regimens used before switching to maintenance rivaroxaban or apixaban. Nonetheless, this study has several limitations. The retrospective design and the study's small sample size may limit the generalization of the study findings. The heterogeneity of the study sample between groups may have influenced the decision to choose parenteral lead-in over the DOAC lead-in and the study outcomes. Therefore, regression analysis was performed to identify whether these factors were significantly associated with the outcomes. It is worth mentioning that the number of patients with unprovoked VTE was lower among the parenteral lead-in group. It is well known that the risk of VTE recurrence is almost doubled in patients with unprovoked VTE.[20] In addition, the risk of bleeding among the two groups at baseline was comparable; however, the bleeding risk assessment tool has some limitations, as it only focuses on the patient's age, gender, and history of cancer. Finally, failure to follow up on patients and reliance on patients' records to assess medication adherence may have impacted the results of this study.

Conclusion

This study presented insights into the real-world clinical practice of using apixaban and rivaroxaban for VTE treatment. Even though prescribing parenteral anticoagulation lead-in before switching to maintenance doses of apixaban or rivaroxaban is commonly used in frail patients, our findings suggest using a parenteral lead-in regimen for those patients may be associated with an increased risk of bleeding and rVTE compared to the DOAC lead-in regimen. Thus, practitioners must be diligent when deciding on the initial VTE lead-in regimen and consider the patients' potential risk of bleeding along with their risk of thrombosis. This study adds to the evidence supporting the utilization of the DOAC lead-in regimen in treating patients with VTE. Still, larger studies with robust designs and longer follow-up duration are needed to confirm these findings.

Ethical Consideration

The study was approved by King Abdullah International Medical Research Center (KAIMRC) (Ref.# NRC21R/400/09), KSUMC (Ref.# E-21-6295), and KAAUH (Ref.# 22-0139). No informed consent was required from the patients since all patients' data were collected from the electronic records.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Omar A. Alshaya contributed equally as the primary author.

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Disclosure

The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

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