Saudi Pharmaceutical Journal 31 (2023) 101673

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Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Original article

Clinical characteristics and dosing of apixaban and rivaroxaban for the management of venous thromboembolism: A multi-center retrospective observational study

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ARTICLE INFO

Article history:
Received 23 April 2023
Accepted 10 June 2023
Available online 17 June 2023

Keywords:
Venous thromboembolism
Apixaban
Rivaroxaban
Characteristics
Dosage
Real-world

ABSTRACT

Background: Since the risk of recurrence of venous thromboembolism (VTE) increases with duration or inadequate anticoagulation dosage, a proper regimen of apixaban and rivaroxaban is essential in patients with VTE, especially during the acute phase. This study aims to describe the clinical characteristics and dosing of anticoagulants for patients who received apixaban or rivaroxaban for VTE treatment.

Methods: The multi-center retrospective observational study included patients diagnosed with VTE who had received apixaban or rivaroxaban between January 1, 2016, and December 31, 2021. The study's description of real-world practices includes patients' characteristics, along with anticoagulant dose and duration used for lead-in or maintenance therapy to manage VTE.

Results: The study involved 695 patients with VTE; 342 of whom were treated with apixaban (49.2%), while 353 were treated with rivaroxaban (50.8%). During the acute phase, 30.1% and 19.3% of patients did not receive lead-in therapy with apixaban and rivaroxaban, respectively, and 1.2% received reduced doses of either medication. Among the patients who received apixaban alone for lead-in, the majority (79.5%) received the recommended duration, while 17.1% received a shorter lead-in duration ($\leq$5 days), with an overall mean duration of 6.5 days. Most patients who received rivaroxaban alone for lead-in (93.0%) received the drug for the recommended duration, with an overall mean duration of 20.2 days. Most of the patients who did not receive apixaban or rivaroxaban for lead-in used parenteral anticoagulants for varying durations; however, around 25.0% of these patients did not receive any lead-in anticoagulant and started on maintenance therapy. Overall, patients who did not receive apixaban or rivaroxaban lead-in therapy were commonly associated with a higher risk of bleeding according to their clinical characteristics.

Conclusion: A notable proportion of patients with VTE who were mostly at low to intermediate risk of bleeding received non-recommended doses or durations of apixaban or rivaroxaban for lead-in therapy. Large studies are needed to establish evidence about the outcomes associated with these practices.

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https://doi.org/10.1016/j.jsps.2023.06.006
1319-0164/

1. Introduction

Warfarin has been the standard for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) for decades. However, since 2014, various direct oral anticoagulants (DOACs), including apixaban and rivaroxaban, have been introduced to clinical practice. These agents offer similar efficacy to that of warfarin in preventing the recurrence of venous thromboembolic (VTE) events, with fewer bleeding events and easier administration as well as eliminating the need for frequent monitoring. Therefore, in 2016, the American College of Chest Physicians (CHEST) Guidelines began to recommend DOACs over warfarin as a first-line therapy for the treatment of VTE (Kearon et al., 2016). In 2020 and 2021, the American Society of Hematology (ASH) and the updated CHEST guidelines supported the use of DOACs over warfarin for the treatment of VTE (Ortel et al., 2020; Stevens et al., 2021).

The approved dosing for apixaban and rivaroxaban for managing VTE consists of a regimen of high initial doses during the acute phase of VTE management (lead-in therapy), followed by fixed maintenance doses (Agnelli et al., 2013; Bauersachs et al., 2010; Büller et al., 2012). In the AMPLIFY study, a lead-in dose of apixaban 10 mg twice daily (BID) was given for one week, followed by a maintenance dose of 5 mg BID for at least three months (Agnelli et al., 2013). While in the EINSTEIN studies, a lead-in dose of rivaroxaban 15 mg BID for the initial three weeks was given, followed by a maintenance dose of 20 mg once daily (QD) for at least three months (Bauersachs et al., 2010; Büller et al., 2012).

Since the approval of the new drugs, several studies have assessed their usage and prescribing patterns in real-world settings. Albeit the approved dosing regimens for apixaban and rivaroxaban when managing VTE, real-world studies have uncovered clinical practitioners' non-adherence regarding dosing or duration. Furthermore, those studies demonstrated that treatment duration and dosage of apixaban and rivaroxaban in patients with VTE were determined by their clinical characteristics and potential risk of bleeding or thrombosis (Haas et al., 2019; Williams et al., 2022). Some scholars reported that patients characterized by an increased risk of bleeding, advanced age, renal impairment (creatinine clearance less than 30 mL/min), and prior administration of parenteral anticoagulants for more than two days received lower doses or varying durations of DOAC lead-in or maintenance therapy (Di Micco et al., 2022). However, such patients have been underrepresented in clinical trials (Agnelli et al., 2013; Bauersachs et al., 2010; Büller et al., 2012), and the modified doses and durations for these patients have not been based on strong evidence but rather on practitioners' experience. Inadequate anticoagulation dosage or duration has been associated with an increased risk of VTE recurrence; therefore, a proper regimen of apixaban and rivaroxaban is essential for patients with VTE, especially when managing VTE during the acute phase. Identifying patients' characteristics, comorbid conditions, and various DOAC regimens used by clinicians in daily practice is also essential. Thus, this paper aims to describe clinical characteristics and dosing of anticoagulants for patients who received apixaban or rivaroxaban for VTE treatment in a real-world setting.

2. Methods

2.1. Study design and study population

This retrospective observational study was conducted at three hospitals in Riyadh, Saudi Arabia. Adult patients admitted to the hospitals with newly diagnosed DVT, PE, or both and treated with either apixaban or rivaroxaban between January 2016 and December 2021 were included in the study. Patients were excluded from the study if they had received therapeutic doses of oral or injectable anticoagulants before the index VTE event, had received apixaban or rivaroxaban for purposes other than treating VTE, or had received any other oral anticoagulant therapy for treating VTE. Institutional review board approval was obtained from the participating hospitals (King Abdullah International Medical Research Center (KAIMRC)—Ref.# NRC21R/400/09, King Saud University Medical City (KSUMC)—Ref.# E-21–6295, and King Abdullah bin Abdulaziz University Hospital (KAAUH)—Ref.# HAP-01-R-059).

2.2. Data collection

We collected the following data: patient demographics and information on indexed VTE events, such as the type and location, etiology, date of the event, and history of prior VTEs. The presence of comorbid conditions, such as atrial fibrillation, coronary artery disease, hypertension, valvular disease, stroke, transient ischemic attack, diabetes mellitus, chronic kidney disease (CKD), and bleeding history within one year (including major, clinically relevant non-major bleeding, or any bleeding). Other information collected concerned risk factors for VTE, including a history of major or orthopedic surgery within one year, thrombophilia, active cancer, use of oral contraceptives, obesity (BMI $\geq$ 30), and immobility. Concomitant use of antiplatelet medications was also obtained, including aspirin and clopidogrel or ticagrelor. Furthermore, laboratory data, including serum creatinine, estimated glomerular filtration rate [eGFR], and creatinine clearance [CrCl], were collected at the initiation of the lead-in dose and the maintenance dose. The Cockcroft-Gault formula was used for creatinine clearance calculations. The hemoglobin level was taken at the time of initiation of the lead-in dose. The patients' data and agents used were extracted from their electronic health records; the data were gathered using the Research Electronic Data Capture (REDCap®) software.

2.3. Treatment regimens and medications

The ability to fully describe patterns in practice when using apixaban or rivaroxaban for VTE treatment required analyzing and reporting the results for different treatment regimens, the acute (lead-in) vs. maintenance phases of therapy, and the medications used, i.e., apixaban or rivaroxaban. The recommended lead-in dose for apixaban is 10 mg BID, followed by a maintenance dose of 5 mg BID, while the recommended lead-in dose for rivaroxaban is 15 mg BID, followed by a maintenance dose of 20 mg QD. For the lead-in regimen, we identified three groups of patients based on the use of lead-in therapy: 1) patients who received the recommended apixaban or rivaroxaban lead-in doses, 2) those who received reduced lead-in doses, and 3) those who did not receive lead-in doses of apixaban or rivaroxaban (with or without parenteral lead-in therapy). A reduced dosage of apixaban or rivaroxaban refers to administering a dose lower than the recommended lead-in or maintenance doses.

The recommended lead-in period for apixaban is seven days, whereas the recommended lead-in period for rivaroxaban is 21 days. To assess the duration of lead-in therapy, we classified patients as receiving either apixaban or rivaroxaban alone, undergoing parenteral therapy in combination with apixaban or rivaroxaban, or receiving parenteral therapy alone. The dosing and duration regimens for the lead-in and long-term treatment of

VTE were based on recommendations from the ASH and the CHEST guidelines (Ortel et al., 2020; Stevens et al., 2021).

2.4. Statistical analyses

This analysis describes the data collected during the lead-in and maintenance treatment of VTE. The characteristics of patients receiving apixaban or rivaroxaban at recommended or lower doses and the duration of the lead-in treatment are also described. Continuous variables are displayed as means with standard deviations, while categorical variables are summarized as numbers with percentages. The SAS software (SAS Institute Inc., Cary, NC) was used for all statistical analysis, and Microsoft Excel 2019 (Microsoft Corp., Redmond, WA) was employed for data management.

3. Results

From January 2016 to December 2021, 695 eligible patients who were diagnosed with VTE received apixaban (342 patients; 49.2%) or rivaroxaban (353 patients; 50.8%).

3.1. Characteristics and dosing of anticoagulant for patients who received apixaban

Among the patients who were prescribed apixaban, the recommended lead-in dose (10 mg BID) was administered to 235 patients (68.7%), while 103 patients (30.1%) did not receive lead-in doses with apixaban, as shown in Table 1. In addition, four patients received lower than the recommended lead-in dose: three received 5 mg BID as lead-in therapy and switched to 2.5 mg BID for maintenance therapy, and one started on 2.5 mg BID as lead-in therapy, then switched to 5 mg BID for maintenance therapy. All four of these patients were older females, with a mean age of 81.0 ± 17.3 years, with no medical history of CKD, and all had an intermediate risk of bleeding.

Patients who did not receive lead-in doses of apixaban were older than patients who received the recommended lead-in doses (67.6 ± 18.4 vs. 56.5 ± 19.6 years). In addition, the mean duration of hospital stays among patients who did not receive lead-in doses with apixaban was longer than for those who received the recommended lead-in dose (16.6 ± 32.1 vs. 7.5 ± 17.1 days). Furthermore, the rate of comorbidities was higher among patients who did not receive lead-in therapy with apixaban, including coronary artery disease, obesity, hypertension, diabetes mellitus, CKD, and active cancer. In comparison, patients who received the recommended lead-in doses of apixaban had higher rates of a history of previous VTE and the use of hormonal therapy. Lastly, the concomitant or baseline use of aspirin or clopidogrel was more frequent in patients without lead-in apixaban.

Concerning the prescribed maintenance doses of apixaban, 94.2% of the patients received the recommended maintenance dose (5 mg BID), while 5.8% received a lower dose than that recommended. Notably, patients who received the lower maintenance dose were older than those who received the recommended dosage (77.3 ± 19.8 vs. 59.1 ± 19.5 years), as depicted in Table 1. In addition, patients who received the recommended maintenance dose exhibited shorter hospital stays compared to those who received a reduced dose (9.6 ± 22.5 vs. 18.7 ± 28.9 days). Furthermore, higher rates of patients with coronary artery disease, hypertension, diabetes mellitus, and CKD were observed among patients on the lower maintenance dose of apixaban, along with a higher baseline serum creatinine level (1.25 ± 0.7 vs. 0.81 ± 0.5 mg/dL), compared to patients on the recommended dose. However, higher proportions of patients with a history of previous VTE (8.8% vs. 5.0%) or obesity (51.4% vs. 40.0%) were found among patients who received the recommended maintenance dose compared to patients who received a reduced dose, as presented in Table 1.

3.2. Characteristics and dosing of anticoagulant for patients who received rivaroxaban

The recommended rivaroxaban lead-in dose (15 mg BID) was administered to 282 (79.9%) patients; in contrast, 68 patients (19.3%) did not receive lead-in doses of rivaroxaban, as presented in Table 2. Another three patients received lower lead-in doses of rivaroxaban: two received 20 mg QD, then switched to 15 mg QD for maintenance therapy, while the last received 15 mg QD, then switched to the recommended maintenance dose of 20 mg QD. The three patients who received a lower lead-in dose of rivaroxaban had a mean age of 50.7 ± 28.0 years, comparable to those who received the recommended lead-in therapy with rivaroxaban (52.3 ± 19.7 years); the patients in both groups were slightly younger than those who did not receive lead-in rivaroxaban (56.0 ± 20.9 years). Hospital stays varied between the three groups: the three patients who received a lower lead-in dose with rivaroxaban had longer hospital stays than those who received the recommended lead-in therapy (11.0 ± 9.2 vs. 7.9 ± 10.9 days) but shorter stays than those who did not receive lead-in rivaroxaban at all (17.6 ± 25.5 days). In addition, those three patients exhibited a high rate of coronary artery disease, hypertension, diabetes mellitus, and CKD compared to the other two groups. One of the three patients had a history of bleeding within 12 months, while two received rivaroxaban for PE. Lastly, none of them had a high risk for bleeding.

Overall, the average age of patients receiving rivaroxaban was 53 ± 20 years, and most of the patients were female (58.4%). Patients who did not receive lead-in doses of rivaroxaban were older than those who received the lead-in therapy (56.0 ± 20.9 vs. 52.3 ± 19.7 years). Patients who did not receive lead-in doses of rivaroxaban had higher proportions of coronary artery disease, stroke, or thrombophilia; in addition, these patients also exhibited a more frequent concomitant use of aspirin or clopidogrel. In terms of risk factors associated with VTE recurrences, patients who did not receive lead-in therapy demonstrated a higher prevalence of prior VTE, obesity, immobility, and history of orthopedic surgery within a year. In contrast, patients who received the recommended lead-in dose of rivaroxaban had a higher proportion of hypertension than those who did not receive lead-in doses of rivaroxaban. Furthermore, these patients were more likely to have a history of major bleeding, CRNMB, or any bleeding within 12 months of the indexed VTE event. Lastly, a higher proportion of patients who received the recommended lead-in dosage had an intermediate risk of bleeding.

Regarding the prescribed maintenance doses for rivaroxaban, 96.3% of the included patients received the recommended maintenance dose (20 mg QD), while 3.7% received lower maintenance doses (13 patients; nine received 15 mg, and four received 10 mg QD). Compared to patients who received the recommended maintenance doses, patients who received lower maintenance doses had higher proportions of hypertension, diabetes, CKD, thrombophilia, history of major bleeding, reduced eGFR, or creatinine clearance at the initiation of rivaroxaban maintenance therapy. These data are summarized in Table 2.

3.3. Duration for the applied lead-in therapy

In patients who received apixaban only as lead-in therapy, the average duration of the lead-in dose was 6.5 ± 1.4 days; most (79.5%) received apixaban for 6–7 days. For patients who received lead-in treatment comprising parenteral anticoagulants, then

Table 1
Clinical characteristics of the patients receiving apixaban lead-in and maintenance doses.

Patient characteristic	Overall	Apixaban Lead-in doses[†]		Maintenance doses	
		10 mg BID	None	**5 mg BID**	2.5 mg BID
Overall number of patients	342	235 (68.7)	103 (30.1)	322 (94.2)	20 (5.8)
Parenteral lead-in therapy					
None	106 (31.0)	71 (30.2)	33 (32.0)		
LMWH	156 (45.6)	114 (48.5)	42 (40.8)		
UFH	78 (22.8)	49 (20.9)	27 (26.2)		
Fondaprinux	2 (0.6)	1 (0.4)	1 (1.0)		
Maintenance doses of apixaban					
5 mg BID	322	233 (99.1)	88 (85.4)		
2.5 mg BID	20	2 (0.9)	15 (14.6)		
Age in years	60.2 ± 20.0	56.5 ± 19.6	67.6 ± 18.4	59.1 ± 19.5	77.3 ± 19.8
BMI (kg/m^2)	30.5 ± 7.0	30.9 ± 7.0	29.6 ± 7.0	30.7 ± 7.0	27.9 ± 7.5
Hospital length of stay (days)	10.2 ± 23.0	7.5 ± 17.1	16.6 ± 32.1	9.6 ± 22.5	18.7 ± 28.9
Gender					
Male	119 (34.8)	78 (33.2)	41 (39.8)	113 (35.1)	6 (30.0)
Female	223 (65.2)	157 (66.8)	62 (60.2)	209 (64.9)	14 (70.0)
Pre-existing conditions					
Atrial fibrillation	11(3.2)	7 (3.0)	3 (2.9)	10 (3.1)	1(5.0)
Coronary artery disease	38 (11.1)	14 (6.0)	23 (22.3)	33 (10.2)	5 (25.0)
Hypertension	190 (55.6)	116 (49.4)	71 (68.9)	174 (54.0)	16 (80.0)
Valvular disease	2 (0.6)	1 (0.4)	1 (1.0)	2 (0.6)	0 (0.0)
Stroke	58 (17.0)	37 (15.7)	21 (20.4)	53 (16.5)	5 (25.0)
Transient ischemic attack	7 (2.0)	5 (2.1)	2 (1.9)	7 (2.2)	0 (0.0)
Diabetes mellitus	160 (46.8)	101(43.0)	58 (56.3)	149 (46.3)	11 (55.0)
Chronic kidney disease	30 (8.8)	12 (5.1)	18 (17.5)	25 (7.8)	5 (25.0)
Active smoking	21 (6.8)	17(7.9)	4 (4.4)	20 (6.8)	1 (6.7)
Thrombophilia	5 (1.5)	4 (1.7)	1 (1.0)	5 (1.6)	0 (0.0)
Active cancer	13 (3.8)	5 (2.1)	8 (7.8)	13 (4.1)	0 (0.0)
On chemotherapy (among patients with cancer)	5 (38.5)	0 (0.0)	5 (62.5)	5 (38.5)	0 (0.0)
History of bleeding (within 12 months)					
Major	2 (0.6)	1 (0.4)	1 (1.0)	1 (0.3)	1 (5.0)
CRNMB	2 (0.6)	2 (0.9)	0 (0.0)	2 (0.6)	0 (0.0)
Any bleeding	8 (2.4)	5 (2.1)	3 (2.9)	7 (2.2)	1 (5.0)
Concomitant antithrombotic medications					
Aspirin	71 (20.8)	39 (16.6)	32 (31.1)	66 (20.5)	5 (25.0)
P2Y12 Inhibitors	19 (5.6)	7 (3.0)	12 (11.7)	18 (5.6)	1 (5.0)
Laboratory data at the time of initiating therapy					
SCr (mg/dl)	0.83 ± 0.4	0.77 ± 0.4	0.96 ± 0.5	0.81 ± 0.5	1.25 ± 0.7
eGFR (mL/min/1.73 m^2)	92.6 ± 32.3	96.4 ± 27.7	84.7 ± 40.0	95.25 ± 31.8	65.44 ± 39.5
Creatinine clearance (ml/min)	87.2 ± 40.0	93.8 ± 37.4	73.7 ± 42.2	90.24 ± 38.9	51.42 ± 45.9
Hgb (g/dL)	122.3 ± 21.8	125.4 ± 21.0	115.4 ± 22.0		
Risk Factors for VTE recurrence					
History of previous VTE	29 (8.5)	22 (9.4)	7 (6.8)	28 (8.8)	1 (5.0)
Use of oral contraceptive or ERT	27 (8.4)	23 (10.4)	4 (4.2)	27 (8.9)	0 (0.0)
Obesity (BMI $\geq$ 30 kg/m^2)	173 (50.7)	117 (49.8)	54 (52.9)	165 (51.4)	8 (40.0)
Immobility	104 (30.4)	62 (26.4)	40 (38.8)	95 (29.5)	9 (45.0)
Major general surgery (within one year)	20 (5.9)	13 (5.6)	7 (6.8)	19 (5.9)	1 (5.0)
Orthopedic surgery (within one year)	27 (7.9)	19 (8.1)	8 (7.8)	26 (8.1)	1 (5.0)
Type of the new VTE event					
DVT	108 (31.6)	69 (29.4)	36 (35.0)	96 (29.8)	12 (60.0)
Proximal	76 (70.4)	49 (71.0)	24 (66.6)	67 (69.8)	9 (75.0)
Distal	6 (5.6)	5 (7.2)	1 (2.8)	6 (6.3)	0 (0.0)
Mixed	23 (21.3)	13 (18.8)	10 (27.8)	20 (20.8)	3 (25.0)
Unspecified	3 (2.8)	2 (2.9)	1 (2.8)	3 (3.1)	0 (0.0)
PE	205 (59.9)	145 (61.7)	59 (57.3)	198 (61.5)	7 (35.0)
Segmental	86 (42.0)	53 (36.6)	33 (55.9)	83 (41.9)	3 (42.9)
Subsegmental	15 (7.3)	14 (9.7)	1 (1.7)	15 (7.6)	0 (0.0)
Mixed	70 (34.1)	51 (35.2)	18 (30.5)	67 (33.8)	3 (42.9)
Unspecified	34 (16.6)	27 (18.6)	7 (11.9)	33 (16.7)	1 (14.3)
DVT plus PE	29 (8.5)	21(8.9)	8 (7.8)	28 (8.7)	1 (5.0)
DVT type					
Proximal	15 (51.7)	8 (38.1)	7 (87.5)	15 (53.6)	0 (0.0)
Distal	5 (17.2)	5 (23.8)	0 (0.0)	5 (17.9)	0 (0.0)
Mixed	5 (17.2)	4 (19.0)	1 (12.5)	5 (17.9)	0 (0.0)
Unspecified	4 (13.8)	4 (19.0)	0 (0.0)	3 (10.7)	1 (100.0)
PE type					
Segmental	10 (34.5)	8 (38.1)	2 (25.0)	10 (35.7)	0 (0.0)
Subsegmental	1 (3.4)	1 (4.8)	0 (0.0)	1 (3.6)	0 (0.0)
Mixed	9 (31.0)	9 (42.9)	0 (0.0)	9 (32.1)	0 (0.0)
Unspecified	9 (31.0)	3 (14.3)	6 (75.0)	8 (28.6)	1 (100.0)
VTE Etiology					
Provoked	165 (48.2)	111 (47.2)	51 (49.5)	154 (47.8)	11 (55.0)
Unprovoked	65 (19.0)	48 (20.4)	16 (15.5)	60 (18.6)	5 (25.0)
Not reported	112 (32.7)	76 (32.3)	36 (35.0)	108 (33.5)	4 (20.0)

Table 1 (*continued*)

Patient characteristic	Overall	Apixaban Lead-in doses†		Maintenance doses	
		10 mg BID	None	**5 mg BID**	2.5 mg BID
Bleeding Risk*					
High risk	11 (3.2)	4 (1.7)	7 (6.8)	11 (3.4)	0 (0.0)
Intermediate risk	287 (83.9)	197 (83.8)	86 (83.5)	268 (83.2)	19 (95.0)
Low risk	44 (12.9)	34 (14.5)	10 (9.7)	43 (13.4)	1 (5.0)

Results are presented as frequency (percentage) or mean ± SD.
p-values are from the *t*-test for continuous data and chi-square or fisher-exact test for categorical data.
* From the bleeding risk assessment score.
† Four additional patients received a lower dose of lead-in apixaban (2.5 or 5 mg) and their important details were discussed in text only.
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; SCr: serum creatinine; Hgb: hemoglobin; eGFR: estimated glomerular filtration rate; SD: standard deviation.

apixaban, the parental anticoagulant was used for an average duration of 2.7 ± 3.6 days; subsequently, apixaban was used for an additional 6.3 ± 1.7 days. The majority of these patients received 1–2 days of parenteral anticoagulants (72.3%) and 6–7 days of apixaban (77.1%). Overall, the lead-in duration for this group of patients was 8.9 ± 3.8 days. A different lead-in strategy was observed where patients received parenteral anticoagulants for lead-in and then switched directly to maintenance doses of apixaban; these patients received the parenteral anticoagulants for an average of 5.4 ± 5.0 days, with 32.9% receiving the treatment for 1–2 days and 35.7% receiving 3–5 days of this therapy. These data are illustrated in Figs. 1 and 2.

In contrast, in terms of the use of rivaroxaban only as lead-in therapy, the average duration of the lead-in dose was 20.2 ± 3.5 d ays, and most of the patients (93.0%) received the drug for 19–21 days. For patients who received lead-in treatment comprising parenteral anticoagulants, then rivaroxaban, parenteral anticoagulants were used for an average duration of 3.9 ± 4.6 days, after which rivaroxaban was used for an additional 19.2 ± 4.4 days; most of these patients (78.1%) received 1–5 days of parenteral anticoagulant therapy, followed by 19–21 days of rivaroxaban (72.7%). Overall, the lead-in duration for this group of patients was 23.1 ± 5.8 days. Similar to the patients who underwent treatment with apixaban, some patients received only parenteral anticoagulants for lead-in, then switched to rivaroxaban for maintenance therapy, receiving a parenteral anticoagulant for an average of 20.7 ± 21.2 days. About 40% of these patients received parenteral anticoagulants for less than 10 days. These data are available in Figs. 3 and 4.

3.4. Duration of maintenance therapy based on the type and history of VTE

Overall, most of our cases had no prior history of VTE (90.4%), while the remaining 9.6% of the cases were characterized by a history of VTE (Table 3). Among patients without a history of VTE, most cases revealed plans to receive or patients' having received anticoagulants for a three-month period. Similarly, among patients with a history of VTE, most cases included plans to receive or reports of having received anticoagulants for three months. However, a larger proportion of patients with a history of VTE were associated with plans to receive or had received anticoagulants for a six-month period or indefinitely compared to patients without a history of VTE.

3.5. Maintenance therapy adjustments during follow-up

A total of 73 patients (10.5%) had their maintenance dose adjusted during follow-up (Table 4). Of those, 43 patients were on apixaban (12.6% of the apixaban users), while 30 patients were on rivaroxaban (8.5% of the rivaroxaban users). Most of these dose adjustments (93.0% and 83.3% of the cases that had dose adjustments for apixaban and rivaroxaban, respectively) entailed reducing the patients' dosage, and similar patterns were observed for apixaban and rivaroxaban. The reason for adjusting the dose was not documented in most cases (79.5%). Among the documented reasons for making such changes were increased risk of bleeding, declining renal function, and drug-drug interactions.

4. Discussion

This retrospective study examines the prescribing patterns of apixaban and rivaroxaban in VTE patients. Most patients received the recommended dose and duration of initial and maintenance therapy with the drugs under consideration. However, our findings reveal that 30.1% of apixaban users and 19.3% of rivaroxaban users did not receive lead-in therapy with DOACs; furthermore, a few patients received reduced lead-in or maintenance doses. In terms of duration for lead-in therapy, most of the patients who received apixaban or rivaroxaban lead-in therapy received it for the recommended duration: alone or with a few days of parenteral anticoagulant therapy, with limited deviation observed in the doses and duration of therapy during the maintenance phase.

This pattern of observation is in line with the findings of previous studies. In a prospective observational study, prior to the initiation of rivaroxaban, 7.2% of patients (called "early switchers") received parenteral therapy with or without warfarin for more than 48 h (Ageno et al., 2016). Compared to the rest of the sample in the study, the patients in the early switchers' group were older, had a higher proportion of kidney impairment or history of major bleeding, and were diagnosed with PE rather than DVT (Turpie et al., 2017). Williams et al. reported that 22% of 171 patients with VTE received parenteral anticoagulants for lead-in therapy with a reduced or shortened lead-in duration for the DOACs (Williams et al., 2022), demonstrating a clear deviation from the recommended 7- and 21-day lead-in therapy for apixaban and rivaroxaban, respectively. In that study, the patients who received a reduced or shortened lead-in therapy were older, had more cardiac comorbidities, and were taking antiplatelet drugs compared to the rest of the study sample population (Williams et al., 2022). Thus, both the early switchers in the Turpie et al. study and those who received the reduced or shortened lead-in therapy in the Williams et al. study exhibited a high-risk characteristic profile among those who received parenteral lead-in therapy in the two studies (Turpie et al., 2017; Williams et al., 2022). In our study, the use of reduced doses of apixaban or rivaroxaban for lead-in or maintenance therapy was observed in older patients who had other comorbid conditions, such as coronary artery disease, hypertension, diabetes mellitus, atrial fibrillation, stroke, CKD, history of major bleeding, or history of major surgeries, as well as immobility for few days or concomitant use of antiplatelets. Prior research has reported

Table 2
Clinical characteristics of the patients receiving rivaroxaban lead-in and maintenance doses.

Patient characteristic	Overall	Rivaroxaban Lead-in doses †		Maintenance doses		
		15 mg BID	None	**20 mg QD**	15 mg QD	10 mg QD
Overall number of patients	353	282 (79.9)	68 (19.3)	340 (96.3)	9 (2.5)	4 (1.1)
Parenteral lead-in therapy						
None	53 (15.0)	43 (15.2)	10 (14.7)			
LMWH	265 (75.1)	214 (75.9)	49 (72.1)			
UFH	34 (9.6)	25 (8.9)	8 (11.8)			
Fondaprinux	1 (0.3)	0 (0.0)	1 (1.5)			
Maintenance doses of rivaroxaban						
20 mg QD	340 (96.3)	279 (98.9)	59 (86.8)			
15 mg QD	9 (2.5)	3 (1.1)	5 (7.4)			
10 mg QD	4 (1.1)	0 (0.0)	4 (5.9)			
Age in years	53.0 ± 20.0	52.3 ± 19.7	56.0 ± 20.9	52.3 ± 19.6	72.7 ± 23.9	71.0 ± 17.1
BMI (kg/m^2)	30.2 ± 7.2	30.2 ± 6.8	30.6 ± 8.5	30.3 ± 7.0	28.2 ± 11.2	27.1 ± 9.7
Hospital length of stay (days)	9.8 ± 15.3	7.9 ± 10.9	17.6 ± 25.5	9.6 ± 15.3	18.0 ± 15.4	2.0 ± 3.4
Gender						
Male	147 (41.6)	112 (39.7)	33 (48.5)	142 (41.8)	5 (55.6)	0 (0.0)
Female	206 (58.4)	170 (60.3)	35 (51.5)	198 (58.2)	4 (44.4)	4 (100.0)
Pre-existing conditions						
Atrial fibrillation	5 (1.4)	4 (1.4)	1 (1.5)	5 (1.5)	0 (0.0)	0 (0.0)
Coronary artery disease	26 (7.4)	17 (6.0)	7 (10.3)	26 (7.6)	0 (0.0)	0 (0.0)
Hypertension	112 (31.7)	91 (32.3)	19 (27.9)	106 (31.2)	4 (44.4)	2 (50.0)
Valvular disease	4 (1.1)	3 (1.1)	1 (1.5)	4 (1.2)	0 (0.0)	0 (0.0)
Stroke	23 (6.5)	16 (5.7)	7 (10.3)	22 (6.5)	1 (11.1)	0 (0.0)
Transient ischemic attack	2 (0.6)	0 (0.0)	2 (2.9)	2 (0.6)	0 (0.0)	0 (0.0)
Diabetes mellitus	110 (31.2)	87 (30.9)	21 (30.9)	105 (30.9)	3 (33.3)	2 (50.0)
Chronic kidney disease	13 (3.7)	10 (3.5)	2 (2.9)	11 (3.2)	2 (22.2)	0 (0.0)
Active smoking	27 (10.9)	22 (11.1)	5 (10.9)	27 (11.2)	0 (0.0)	0 (0.0)
Thrombophilia	17 (5.9)	12 (5.4)	5 (8.2)	16 (5.8)	0 (0.0)	1 (25.0)
Active cancer	19 (5.4)	15 (5.3)	4 (5.9)	19 (5.6)	0 (0.0)	0 (0.0)
On chemotherapy (among patients with cancer)	8 (42.1)	6 (40.0)	2 (50.0)	8 (42.1)	0 (0.0)	0 (0.0)
History of bleeding (within 12 months)						
Major	33 (11.7)	28 (12.7)	4 (6.9)	32 (11.7)	1 (20.0)	0 (0.0)
CRNMB	17 (6.2)	15 (7.0)	2 (3.5)	17 (6.4)	0 (0.0)	0 (0.0)
Any bleeding	8 (2.9)	7 (3.3)	1 (1.8)	8 (3.0)	0 (0.0)	0 (0.0)
Concomitant antithrombotic medications						
Aspirin	62 (17.6)	42 (14.9)	19 (27.9)	59 (17.4)	1 (11.1)	2 (50.0)
P2Y12 Inhibitors	13 (3.7)	8 (2.9)	5 (8.2)	13 (3.8)	0 (0.0)	0 (0.0)
Laboratory data at the time of initiating therapy						
SCr (mg/dl)	0.77 ± 0.3	0.76 ± 0.3	0.81 ± 0.4	0.75 ± 0.3	0.97 ± 0.4	0.61 ± 0.1
eGFR (mL/min/1.73 m^2)	107.8 ± 57.6	107.9 ± 58.8	108.2 ± 53.2	110.9 ± 63.6	80.4 ± 41.8	98.3 ± 13.6
Creatinine clearance (ml/min)	107.6 ± 55.2	108.6 ± 56.3	104.7 ± 51.1	111.4 ± 60.1	63.5 ± 36.6	70.4 ± 36.4
Hgb (g/dL)	120.5 ± 22.0	121.1 ± 21.7	118.4 ± 22.3			
Risk Factors for VTE recurrence						
History of previous VTE	38 (10.8)	29 (10.3)	9 (13.2)	37 (10.9)	0 (0.0)	1 (25.0)
Use of oral contraceptive or ERT	37 (11.0)	35 (12.9)	2 (3.2)	37 (11.4)	0 (0.0)	0 (0.0)
Obesity (BMI $\geq$ 30 kg/m^2)	159 (47.3)	124 (46.6)	34 (50.7)	155 (48.0)	2 (22.2)	2 (50.0)
Immobility	96 (27.2)	72 (25.5)	23 (33.8)	91 (26.8)	5 (55.6)	0 (0.0)
Major general surgery (within one year)	55 (16.6)	45 (17.2)	10 (14.9)	55 (17.3)	0 (0.0)	0 (0.0)
Orthopedic surgery (within one year)	35 (10.6)	24 (9.3)	11 (16.2)	35 (11.0)	0 (0.0)	0 (0.0)
Type of the new VTE event						
DVT	155 (43.9)	126 (44.7)	28 (41.2)	149 (43.8)	2 (22.2)	4 (100.0)
Proximal	111 (71.6)	92 (73.0)	18 (64.3)	106 (71.1)	2 (100.0)	3 (75.0)
Distal	14 (9.0)	11 (8.7)	3 (10.7)	13 (8.7)	0 (0.0)	1 (25.0)
Mixed	20 (12.9)	15 (11.9)	5 (17.9)	20 (13.4)	0 (0.0)	0 (0.0)
Unspecified	10 (6.5)	8 (6.3)	2 (7.1)	10 (6.7)	0 (0.0)	0 (0.0)
PE	172 (48.7)	134 (47.5)	36 (52.9)	165 (48.5)	7 (77.8)	0 (0.0)
Segmental	58 (33.7)	39 (29.1)	18 (50.0)	55 (33.3)	3 (42.9)	0 (0.0)
Subsegmental	32 (18.6)	29 (21.6)	2 (5.6)	29 (17.6)	3 (42.9)	0 (0.0)
Mixed	45 (26.2)	36 (26.9)	9 (25.0)	45 (27.3)	0 (0.0)	0 (0.0)
Unspecified	37 (21.5)	30 (22.4)	7 (19.4)	36 (21.8)	1 (14.3)	0 (0.0)
DVT plus PE	26 (7.4)	22 (7.8)	4 (5.9)	26 (7.6)	0 (0.0)	0 (0.0)
DVT type						
Proximal	14 (53.8)	11 (50.0)	3 (75.0)	14 (53.8)	0 (0.0)	0 (0.0)
Distal	2 (7.7)	2 (9.1)	0 (0.0)	2 (7.7)	0 (0.0)	0 (0.0)
Mixed	3 (11.5)	3 (13.6)	0 (0.0)	3 (11.5)	0 (0.0)	0 (0.0)
Unspecified	7 (26.9)	6 (27.3)	1 (25.0)	7 (26.9)	0 (0.0)	0 (0.0)
PE type						
Segmental	11 (42.3)	10 (45.5)	1 (25.0)	11 (42.3)	0 (0.0)	0 (0.0)
Subsegmental	2 (7.7)	2 (9.1)	0 (0.0)	2 (7.7)	0 (0.0)	0 (0.0)
Mixed	1 (3.8)	1 (4.5)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)
Unspecified	12 (46.2)	9 (40.9)	3 (75.0)	12 (46.2)	0 (0.0)	0 (0.0)
VTE Etiology						
Provoked	223 (63.2)	178 (63.1)	45 (66.2)	218 (64.1)	4 (44.4)	1 (25.0)
Unprovoked	66 (18.7)	58 (20.6)	6 (8.8)	66 (19.4)	0 (0.0)	0 (0.0)

Table 2 (*continued*)

Patient characteristic	Overall	Rivaroxaban Lead-in doses †		Maintenance doses		
		15 mg BID	None	**20 mg QD**	15 mg QD	10 mg QD
Not reported	64 (18.1)	46 (16.3)	17 (25.0)	56 (16.5)	5 (55.6)	3 (75.0)
Bleeding Risk*						
High risk	16 (4.5)	13 (4.6)	3 (4.4)	16 (4.7)	0 (0.0)	0 (0.0)
Intermediate risk	250 (70.8)	202 (71.6)	46 (66.7)	238 (70.0)	8 (88.9)	4 (100.0)
Low risk	87 (24.6)	67 (23.8)	19 (27.9)	86 (25.3)	1 (11.1)	0 (0.0)

Results are presented as frequency (percentage) or mean ± SD.
*From the bleeding risk assessment score.
† Three additional patients received a lower dose of lead-in rivaraoxaban (15 or 20 mg QD) and their important details were discussed in text only.
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;; SCr: serum creatinine; Hgb: hemoglobin; eGFR: estimated glomerular filtration rate; SD: standard deviation.

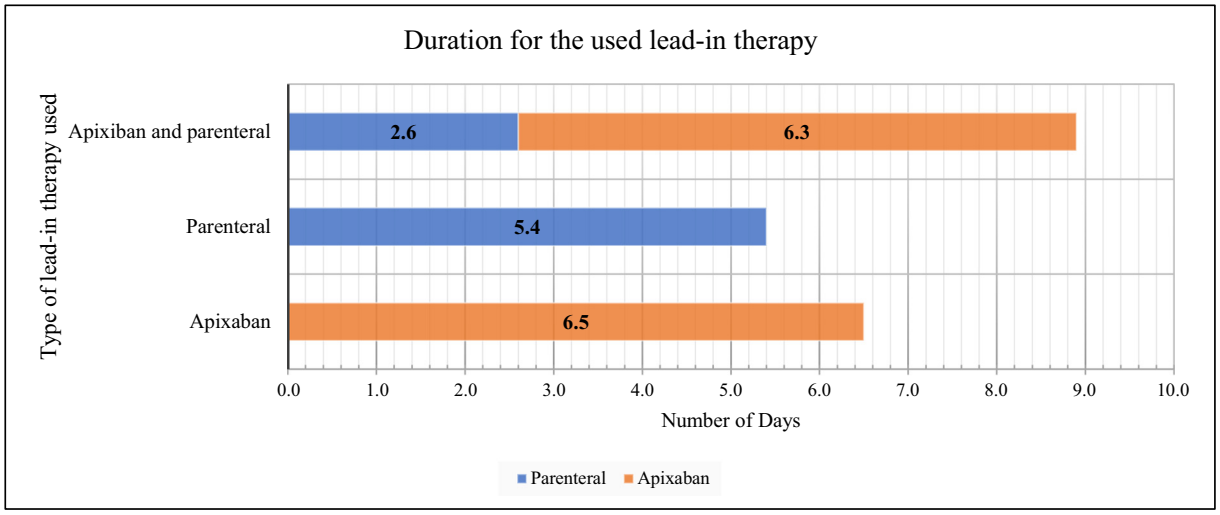

Fig. 1. Duration of lead-in therapy for patients on apixaban.

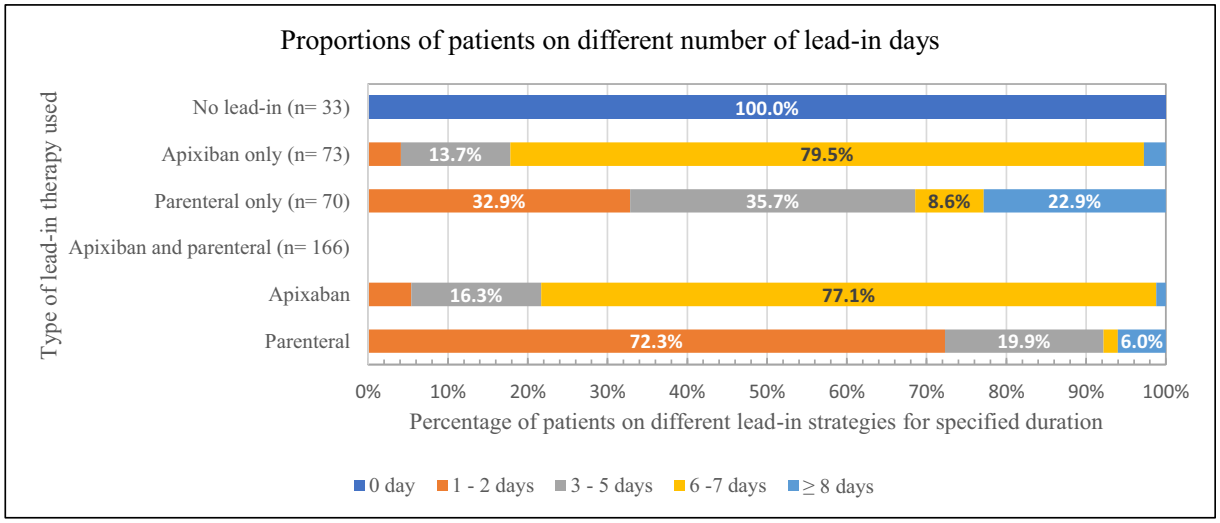

Fig. 2. Proportion of patients on different number of days of lead-in therapy for patients on apixaban (n = 342).

the potential association of these characteristics with an increased risk of bleeding (Decousus et al., 2011; Kearon et al., 2012).

Older patients or those with poor kidney function are considered part of a special population in terms of DOAC therapy because of the longer half-life and drug exposure in those patients (Cohen

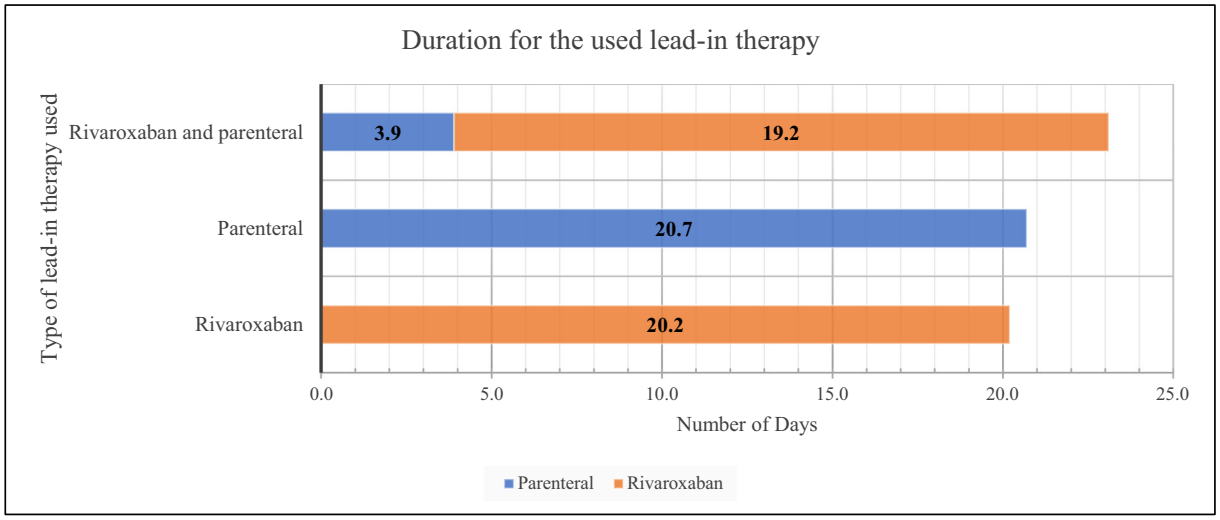

Fig. 3. Duration of lead-in therapy for patients on rivaroxaban.

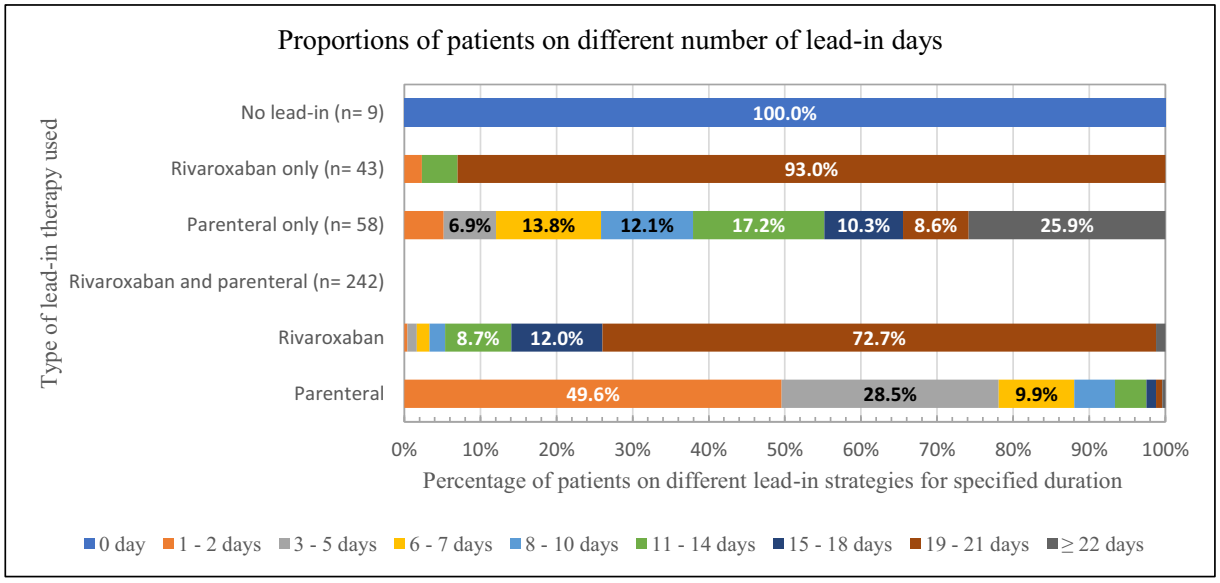

Fig. 4. Proportion of patients on different number of days of lead-in therapy for patients on rivaroxaban (n = 353).

Table 3
Planned or actual duration of apixaban or rivaroxaban maintenance therapy based on the type and history of VTE events.

Patient characteristic	Overall	Without history of VTE			With history of VTE		
		DVT	PE	DVT and PE	DVT	PE	DVT and PE
Overall number of patients	695	231	349	48	32	28	7
Planned or actual duration							
3 months	373 (53.7)	128 (55.4)	188 (53.9)	30 (62.5)	11 (34.4)	12 (42.9)	4 (57.1)
6 months	194 (27.9)	63 (27.3)	98 (28.1)	12 (25.0)	10 (31.3)	9 (32.1)	2 (28.6)
12 months	22 (3.2)	7 (3.0)	11 (3.2)	1 (2.1)	1 (3.1)	2 (7.1)	0 (0.0)
Lifelong	75 (10.8)	23 (10.0)	39 (11.2)	3 (6.3)	6 (18.8)	3 (10.7)	1 (14.3)
No documented stop date	31 (4.5)	10 (4.3)	13 (3.7)	2 (4.2)	4 (12.5)	2 (7.1)	0 (0.0)

et al., 2014). The high lead-in doses of apixaban or rivaroxaban used in the landmark trials during the acute phase of VTE were effective and safe; however, the average age of the patients in these trials was 54 to 58 years, and less than 10% of these patients had a CrCl of less than 50 mL/min (Agnelli et al., 2013; Bauersachs et al., 2010; Büller et al., 2012). Notably, clinical trials that have included patients with non-valvular atrial fibrillation have used adjusted doses of DOACs that were approved by regulatory bodies; however, no similarly approved dose adjustment recommendations are currently available for patients with VTE (Bikdeli et al., 2022). Nevertheless, reduced doses of apixaban or rivaroxaban have often been seen in clinical settings for individuals with similar high-risk char-

Table 4
Patients with maintenance dose adjustment during follow-up.

Variable	Overall n = 695	Apixaban n = 342	Rivaroxaban n = 353
Patients with maintenance dose adjustment	73 (10.5)	43 (12.6)	30 (8.5)
Type of change in dose			
Dose reduction	65 (89.0)	40 (93.0)	25 (83.3)
Dose escalation	4 (5.5)	3 (7.0)	1 (3.3)
Undocumented new dose	4 (5.5)	0 (0.0)	4 (13.3)
Reasons for change of maintenance Dose			
Renal adjustment	3 (4.1)	2 (4.7)	1 (3.3)
Increased bleeding risk	11 (15.1)	4 (9.3)	7 (23.3)
Drug-drug interaction	1 (1.4)	1 (2.3)	0 (0.0)
Others	19 (26.0)	7 (16.3)	12 (40.0)
No documented reason	39 (53.4)	29 (67.4)	10 (33.4)

acteristics or fragilities. The observed use of reduced dosage or duration for apixaban and rivaroxaban suggests the possible reluctance of physicians to prescribe the approved doses for either of these medications in high-risk patients. In a study that used data from the RIETE registry, Trujillo-Santos et al. found that older patients, as well as those with renal insufficiency, received lower than the recommended doses for apixaban and rivaroxaban (Trujillo-Santos et al., 2017). Similarly, recent major bleeding, anemia, thrombocytopenia, or renal insufficiency were the most common characteristics associated with lower doses of rivaroxaban in another study (Di Micco et al., 2022). Although this conservative approach might represent a justifiable option, the evidence is mixed regarding the safety and efficacy of such strategies. Trujillo-Santos et al. reported a statistically significant increase in the risk of thromboembolic recurrence (HR 10.5, 95% CI 1.28–85.9) and a similar rate of major bleeding (HR: 1.04; 95 %CI: 0.36–3.03) among patients treated with non-recommended doses or regimens for apixaban or rivaroxaban in comparison to individuals treated with the recommended doses and regimens (Trujillo-Santos et al., 2017). In the same vein, Di Micco et al.'s results indicated that patients who received non-recommended doses or regimens of rivaroxaban (delayed start and low doses) had a significantly higher rate of major bleeding and mortality (OR: 22.5; 95% CI: 2.97–170.5) compared to those who received the recommended doses of rivaroxaban for VTE management during the first three months (Di Micco et al., 2022). Another study found no difference in the incidence of recurrent symptomatic VTE or major bleeding between the reduced-dose and the standard-dose groups in the sub-analysis of the J'xactly study (Fukamachi et al., 2022). That being said, the current evidence about the suitability of using reduced dosage or duration remains limited as well as controversial, highlighting the need for high-quality evidence investigating the impact of such dosing on VTE outcomes.

In our cohort, parenteral lead-in alone was often used instead of apixaban and rivaroxaban for the management of VTE during the acute phase. Specifically, 30.1% and 19.3% of patients who later received apixaban or rivaroxaban for maintenance therapy, respectively, initially received parenteral anticoagulants only as lead-in therapy before switching to maintenance doses of either medication. Our findings indicate that a relatively high percentage of patients underwent an unusual treatment strategy that was not supported by guidelines or approved labels. In general, various factors can influence a physician's plan to begin therapy on a patient that involves parenteral anticoagulant treatment. For instance, prescribers tend to start the lead-in phase with parenteral anticoagulation in patients with complex conditions, in those requiring invasive procedures, or when evaluating a patient to decide whether they are a candidate for DOACs or not (Burnett et al., 2016). Furthermore, it is common for physicians to adopt parenteral anticoagulation as a lead-in therapy simply because they have more experience with such an approach. Trujillo-Santos et al. reported similar findings when they studied the clinical characteristics and treatment outcomes of fragile patients with VTE. In particular, they found a higher rate of parenteral anticoagulation prescribed to fragile patients while reporting that 98% of the patients received parenteral anticoagulants as their initial (or lead-in) treatment (Trujillo-Santos et al., 2017). In addition, comorbidities, such as coronary artery disease, stroke, and aspirin use, were prominent in those who did not receive apixaban or rivaroxaban for lead-in treatment. When considering the possibility of utilizing antiplatelet therapy in these patients, physicians likely avoided high-intensity lead-in therapy. This choice may be explained by the fact that the use of low doses of aspirin in conjunction with rivaroxaban has been associated with an increased risk of clinically relevant non-major bleeding as well as major bleeding in a sub-analysis of the EINSTEIN trials (Davidson et al., 2014).

This study has evaluated practices associated with the real-world use of apixaban or rivaroxaban in the treatment of VTE from the Saudi perspective. The study also offers an advantage in its involvement of multiple centers, representing a broader spectrum of patients and practices than that represented by data collected from a single medical center. However, the study also has some limitations that should be acknowledged. For example, in this study, we did not assess the effect of non-recommended doses or durations on the recurrence of VTE or bleeding. The association between the selection of a non-recommended regimen and patients' clinical characteristics or comorbidities was not examined. The retrospective nature of the study precluded us from interviewing prescribers to identify the reasons behind prescribing apixaban and rivaroxaban in the non-recommended strategies. Lastly, a retrospective study using data obtained from patient records is subject to the risk of inaccuracy or missing information.

5. Conclusion

In this real-world study, prescribing patterns of apixaban and rivaroxaban in patients with VTE demonstrated that patients were frequently prescribed non-recommended dosages or durations that differed from the approved guidelines or product labels. Most of the characteristics of patients who received the non-recommended dosage or duration of apixaban and rivaroxaban for lead-in or maintenance therapy pertained to risk factors that might increase the risk of bleeding. Larger studies are required at the national and international levels to ensure that real-world practice aligns with the latest evidence concerning the safety and efficacy of these medications. Furthermore, high-quality evidence examining the effectiveness and safety of these practices is essential.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

The authors extend their appreciation to the Deputyship for Research and Innovation, Ministry of Education in Saudi Arabia for funding this research work through the project no. (IFKSUOR3–101–2).

Funding

This work was supported by the Deputyship for Research and Innovation, Ministry of Education in Saudi Arabia, project no. (IFKSUOR3–101–2).

Authors' contributions

All authors have participated in (a) conception and design, or analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version.

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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