Clinical characteristics, prescription patterns and clinical outcomes of patients with ex-tended therapy with direct oral anticoagulants for unprovoked venous thromboembolism. Insights from the RIETE Registry

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ABSTRACT

Background: Extended therapy with direct oral anticoagulants (DOACs) is common for managing unprovoked venous thromboembolism (VTE), but real-world data on dosing decisions and their association with outcomes are limited.

Methods: From April 2013 to September 2023, we identified patients with unprovoked VTE in the RIETE registry who survived the first 6 months without recurrent VTE or major bleeding. We examined predictors of reduced- *vs*. full-dose DOACs (rivaroxaban or apixaban), and the association between dosing and recurrent VTE and major bleeding. Logistic regression was used to identify predictors of dosing, and competing risk regression models to identify predictors of outcomes.

Results: Among 3749 patients undergoing extended DOAC therapy, 921 (25%) received reduced doses. Predictors of reduced-dose use included age >75 years [adjusted odds ratio (aOR): 1.74; 95%CI: 1.48-2.05], body weight <60 kg (aOR: 1.36; 95%CI: 1.08-1.71), renal failure (aOR: 1.78; 95%CI: 1.41-2.24), and apixaban (*vs*. rivaroxaban) use (aOR: 2.33; 95%CI: 1.80-3.00). Over a median of 240 days, among all 3749 patients, 44 developed VTE recurrence and 15 bled. Apixaban (*vs*. rivaroxaban) use [adjusted hazard ratio (aHR): 0.42; 95%CI: 0.40-0.45] and antiplatelet therapy (aHR: 1.72; 95%CI: 1.68-1.77) were associated with VTE recurrence. Male sex (aHR: 0.70; 95%CI: 0.65-0.76), weight <60 kg (aHR: 2.02; 95%CI: 1.91-2.14), renal failure (aHR: 2.76; 95%CI: 2.72-2.81), reduced- (*vs*. full-dose) DOACs (aHR: 0.83; 95%CI: 0.80-0.87), and antiplatelet use (aHR: 8.18; 95%CI: 7.89-8.47) were associated with major bleeding.

Conclusions: We highlight a mismatch between dosing decisions and clinical outcomes, suggesting a need for more outcome-focused strategies in DOAC prescribing.

Key words: venous thromboembolism, extended therapy, direct oral anticoagulants, RIETE Registry.

Introduction

Venous thromboembolism (VTE), encompassing both pulmonary embolism (PE) and deep vein thrombosis (DVT), poses a significant healthcare challenge with potentially fatal outcomes if not managed appropriately. Standard initial anticoagulant therapy is typically prescribed for 3 to 6 months to mitigate the immediate risks associated with acute VTE. Beyond this period, the persistent risk of recurrence often necessitates continued anticoagulant therapy.[1,2] Recent randomized clinical trials (RCTs) such as AMPLIFY-EXT and EINSTEIN-CHOICE have demonstrated the efficacy of reduced-dose direct oral anticoagulants (DOACs) in preventing VTE recurrence while minimizing the risk of bleeding.[3-5] However, these trials largely involved selected patient populations with stringent inclusion and exclusion criteria, which may not represent the diverse patient profiles encountered in routine clinical practice.

In real-world settings, especially among patients with unprovoked VTE, clinical characteristics such as age, comorbidities, and concurrent treatments greatly influence therapeutic outcomes.[6-18] These real-world patients often differ from the relatively homogeneous populations typically enrolled in RCTs. Our recent study of patients with unprovoked VTE indicated that while approximately 35% discontinued anticoagulation beyond six months, the majority continued receiving anticoagulation with DOACs.[19] These patients are confronted with the choice between full and reduced doses, both of which were identified as reasonable choices in the RCTs and are endorsed in the guidelines.[3-5] However, choosing between these two intensities may not be inconsequential. The rationale and clinical characteristics leading to a choice between reduced and full dosing are not well studied.

This study utilized data from the RIETE registry (Computerized Registry of patients with venous thromboembolism, NCT 0282245) to identify predictors of reduced-dose vs. full-dose DOAC therapy, and VTE-related outcomes (VTE recurrence and major bleeding) in patients treated with reduced-dose *vs*. full-dose DOACs in unadjusted and adjusted analyses.

Materials and Methods

Study design

This study leverages the data from the RIETE registry, that includes over 123,000 patients with VTE from 28 countries with confirmed VTE.[20] Our investigation focused on patients with unprovoked VTE who continued DOACs beyond the initial six months of therapy without recurrent VTE or major bleeding. The objective was to delineate the determinants that influence clinicians to prescribe reduced- *versus* full-doses of DOACs from April 2013 to September 2023, and to correlate these choices with clinical outcomes, including recurrent VTE and major bleeding.

Eligibility criteria and cohort definitions

Participants included in the study met the following criteria: i) initiation of anticoagulant therapy (with or without DOACs) for unprovoked VTE, with no VTE recurrences nor major bleeding within the first six months; ii) Receiving DOAC therapy with apixaban or rivaroxaban beyond six months; and iii) a minimum duration of extended therapy with DOACs of three months or until a VTE-related outcome occurred. The reason edoxaban was excluded is that unlike apixaban and rivaroxaban, reduced-dose edoxaban can be prescribed as dose-adjustment treatment for VTE, rather than being low-intensity therapy.[10]

Unprovoked venous thromboembolism definition

Unprovoked VTE was defined as a VTE event occurring in the absence of recognized provoking factors such as active cancer, recent surgery or immobilization, pregnancy, the postpartum period, hormone therapy, or prolonged travel.[20]

Direct oral anticoagulants dosing definitions

We defined full-dose DOACs as rivaroxaban 20 mg once daily or apixaban 5 mg twice daily. Reduced-dose DOACs were considered when patients received either Rivaroxaban 15 mg or 10 mg daily, or Apixaban 2.5 mg daily.

Data collection

Data was comprehensively collected, including demographic details, clinical characteristics, VTE events specifics, comorbidities, concomitant medications, and laboratory values at the time of the index VTE. The type of DOAC prescribed and any dosage adjustments were also recorded. Special considerations were made for documenting cognitive impairment, including dementia, and anemia, defined by hemoglobin levels below 13 g/dL for men and 12 g/dL for women.

Treatment and follow-up

Patient management reflected real-world conditions, adhering to the protocols of the enrolling centers. This included discretion in the choice of DOAC, dosing, and duration of therapy. Follow-up was rigorously conducted by the responsible physicians through direct clinic visits or remote communications, ensuring data reliability.

Study outcomes

The primary objective was to ascertain independent predictors for prescribing reduced-dose DOACs, considering potential influences such as patient demographics, initial VTE presentation, existing comorbidities, concurrent medications, and practice location. Secondary outcomes included the incidence of recurrent VTE and major bleeding events during the extended therapy period.

Recurrent PE was considered in patients with signs and/or symptoms of PE and a new V/Q mismatch on lung scintigraphy, or a new intraluminal filling defect on helical chest CT-scan or on pulmonary angiography. Recurrent DVT was defined as a new non-compressible vein segment or an increase of the vein diameter of >4 mm compared with the last available measurement on compression ultrasonography. Major bleeding events were defined as overt bleeding requiring transfusion of two units or more of blood, or bleeding that was retroperitoneal, spinal, intracranial, intrathecal, intraocular, intrapericardial, or fatal. Fatal PE was defined as any death occurring less than 10 days after a recurrent PE, in the absence of any alternative explanation for death. Fatal bleeding was defined as any death occurring less than 10 days

after a major bleeding episode, in the absence of any alternative explanation for death.

Statistical analysis

We presented categorical variables as percentages and continuous variables as means and standard deviations or medians with interquartile ranges (IQR) for non-normally distributed data. Time-to-event regression models, considering competing risks, facilitated the exploration of associations between baseline variables and the risks for recurrent VTE or major bleeding.

We used a mixed effects model to identify predictors of reduced-dose (*versus* full doses) DOAC use. The analysis used adjusted odds ratios (aOR) as the effect measure and corresponding 95% confidence intervals (CIs) were calculated. Then, we used Fine-Gray models to identify predictors of clinical outcomes (VTE recurrences, major bleeding) in the entire population, considering death as a competing event. The analysis used adjusted hazard ratios (aHR) as the effect measure and corresponding 95% CIs. Additionally, in both types of models (logistic regression and Fine-Gray), we adjusted the standard errors using robust clustering techniques, which apply robust variance estimators. In our case, the patients were clustered by center.

Pre-specified covariates for multivariable models included type (rivaroxaban or apixaban) and dosing (full *vs*. reduced doses) of DOAC, age, sex, body weight, initial presentation of VTE, hypertension, dementia, anemia, renal failure, concomitant use of antiplatelets, corticosteroids or statins, geographic location (countries), and size of the hospital. SPSS software (version 22, SPSS Inc. Chicago, IL, USA) was used for the statistical management of the data.

Conflict of interests

No funds from the registry are allocated directly to any investigators for the recruitment of patients or the conduct of studies. The financial support provided by our sponsors is strictly used to compensate the statistical analysts, IT support staff, and quality control personnel who maintain the registry's infrastructure and integrity. This funding ensures that the scientific investigations conducted under the auspices of the registry are carried out without any financial incentive that could influence clinical decision-making or the objectivity of the research.

The dataset supporting the conclusions of this article is available upon reasonable request. Interested researchers can access the data by submitting a formal request to the RIETE registry coordinating center. The request will be reviewed by the registry's steering committee to ensure compliance with privacy regulations and ethical guidelines. Upon approval, a data usage agreement will be established, and access to the data will be provided. Specific data queries can be addressed to the corresponding author, who will facilitate the provision of the necessary link to the RIETE registry's data access portal.

Results

Study cohort and medication dosage

From April 2013 to September 2023, 3749 patients with unprovoked VTE within the RIETE registry did not develop VTE recurrences nor major bleeding during the initial six months, and then initiated extended therapy (beyond six months) with DOACs (with rivaroxaban 2027, apixaban 1722). Overall, 921 (25%) received reduced-doses, and 2828 were prescribed full-doses. A substantial majority of patients (95%) were already on DOACs before Day 180. Over half of patients (57%) treated with reduced-dose DOACs for extended therapy had also received reduced doses before Day 180, while the vast majority (96%) of those on full-doses had also received full-dose DOACs before Day 180 (Supplementary Table S1). Rivaroxaban was the most frequently used (2027 patients, 54%), with apixaban being the most frequently reduced (587 of 921 patients, 64%). The median duration of extended therapy was similar in both groups (240 days each).

Patient demographics and clinical presentations

Patients on reduced doses were predominantly female [odds ratio (OR): 1.41; 95%CI: 1.21-1.64], older (average age: 71±16 *vs*. 63±16 years; p<0.001) and had lower body weight than those on full-dose DOACs. They more frequently presented with isolated lower-limb DVT, and had higher rates of hypertension, chronic lung or heart disease, dementia, anemia, or renal failure (Table 1). Patients receiving reduced-dose DOACs were also more likely to be on concurrent medications such as corticosteroids, psychotropics, or statins. The baseline characteristics of patients receiving each drug and dosage are detailed in Supplementary Table S2.

Predictors of use of reduced-dose direct oral anticoagulants

On multivariable analysis, predictors of reduced-dose DOACs prescription included age >75 years [adjusted odds ratio (aOR): 1.74; 95%CI: 1.48-2.05], body weight <60 kg (aOR: 1.36; 95%CI: 1.08-1.71), renal failure at baseline (aOR: 1.78; 95%CI: 1.41-2.24), and use of apixaban (compared to rivaroxaban) (aOR: 2.33; 95%CI: 1.80-3.00) (Table 2).

Clinical outcomes

During extended therapy (median duration: 240 days in both subgroups), 44 patients experienced VTE recurrences (21 recurrent PEs, 23 recurrent DVTs) and 15 patients suffered major bleeding (4 gastrointestinal, 4 uterine, 3 intracranial, and 3 hematoma). Recurrent VTE occurred in 3 of 334 patients (0.9%) receiving reduced-dose rivaroxaban, 31 of 1693 (1.8%) on full-dose rivaroxaban, 4 of 587 (0.7%) on reduced-dose apixaban, and 6 of 1135 (0.5%) on full-dose apixaban. Major bleeding occurred in 0.6%, 0.4%, 0.3%, and 0.4%, of these groups, while the mortality rates were: 0.9%, 0.8%, 1.7%, and 0.9%, respectively. No patient died from bleeding, but one patient died of recurrent PE while on full-dose rivaroxaban. Notably, 19 of the VTE recurrences (43%) and 8 of the major bleeding events (53%) occurred within the first 60 days of extended therapy (Figure 1).

Predictors of outcomes

On multivariable analysis, the use of apixaban (compared to rivaroxaban) was independently associated with a lower risk

of recurrent VTE (aHR: 0.42; 95%CI: 0.40-0.45) whereas concomitant therapy with antiplatelet drugs (aHR: 1.72; 95%CI: 1.68-1.77) was independently associated with a higher risk for VTE recurrence (Table 3). For major bleeding, reduced-dose DOAC therapy was associated with a lower risk (aHR: 0.83; 95%CI: 0.80-0.87), whereas low body weight (aHR: 2.02; 95%CI: 1.91-2.14), renal failure (aHR: 2.76; 95%CI: 2.72-2.81), concomitant use of antiplatelet drugs (aHR: 8.18; 95%CI: 7.89-8.47) and corticosteroid use (aHR: 1.81; 95%CI: 1.77-1.85) were associated with a higher risk.

Discussion

Our study provides critical insights into the extended therapy of unprovoked VTE with DOACs. Although data from RCTs suggest that reduced-dose DOACs are a reasonable option beyond the first six months, only 25% of patients in our cohort received them. Advanced age, low body weight, and renal impairment often prompted the prescription of reduced doses, particularly with apixaban. While low body weight and renal impairment were associated with a two-fold higher risk of major bleeding (justifying the preference for dose reduction), we did not find a significant association between advanced age and the risk for major bleeding. Importantly, concomitant use of antiplatelet therapy was linked to an eight-fold higher risk of major bleeding, yet it did not prompt dose reduction in our patient population.

Similar to the findings from RCTs and other cohort studies, the use of reduced-dose DOACs was associated with a lower risk of major bleeding.[6,12,15,18,21,22] However, reduced-dose DOACs were not predictive of VTE recurrence in multivariable analysis. This consistency with previous research supports the safety and efficacy of reduced-dose DOACs, even among VTE patients at high risk of bleeding. These results highlight the importance of personalizing DOAC therapy based on individual patient risk factors to optimize therapeutic outcomes.

Table 1. Baseline characteristics of the patients, according to prescribed doses.

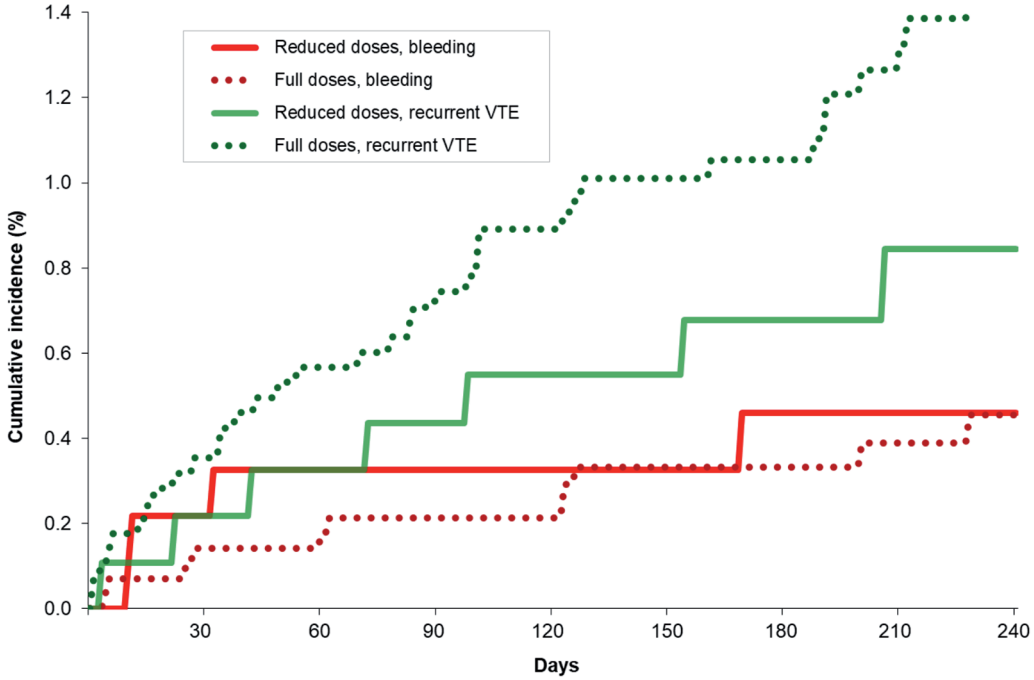
	All patients	Reduced doses	Full doses
Patients, N	3749	921	2828
Demographics			
Female, n (%)	1584 (42)	448 (49)	1136 (40)
Age (mean years±SD)	65±16	71±16	63±16
Body weight (mean kg±SD)	82±17	77±16	83±17
Initial VTE presentation, n (%)			
Pulmonary embolism	2551 (68)	586 (64)	1965 (69)
Isolated, lower-limb DVT	1111 (30)	317 (34)	794 (28)
Isolated, upper-limb DVT	91 (2.4)	19 (2.1)	72 (2.5)
Comorbidities, n (%)			
Hypertension	1832 (52)	523 (60)	1309 (49)
Chronic lung disease	336 (9)	99 (11)	237 (8.4)
Chronic heart failure	223 (6.3)	69 (7.9)	154 (5.8)
Prior MI or stroke	375 (11)	115 (13)	260 (10)
Depression	284 (7.6)	81 (8.8)	203 (7.2)
Dementia	115 (3.1)	49 (5.3)	66 (2.3)
Inflammatory bowel disease	53 (1.4)	14 (1.5)	39 (1.4)
Prior VTE	877 (23)	201 (22)	676 (24)
Laboratory tests			
Anemia, n (%)	626 (17)	198 (22)	428 (15)
CrCl levels (mean mL/min±SD)	89±40	75±35	93±40
Concomitant drugs, n (%)			
Antiplatelets	121 (3.7)	30 (3.7)	91 (3.7)
Corticosteroids	213 (6.6)	66 (8.3)	147 (6.0)
Psychotropics	634 (19)	201 (25)	433 (18)
Statins	890 (26)	265 (31)	625 (24)
Countries, n (%)			
Spain	1766 (47)	487 (53)	1279 (45)
Rest of Europe	1704 (45)	378 (41)	1326 (47)
America	169 (4.5)	27 (2.9)	142 (5.0)
Asia or Africa	110 (2.9)	29 (3.1)	81 (2.9)
Hospital size, n (%)			
≤500 beds	1062 (28)	217 (24)	845 (30)
501-1000 beds	1407 (38)	391 (42)	1016 (36)
1000 beds	1280 (34)	313 (34)	967 (34)

SD, standard deviation; DVT, deep vein thrombosis; MI, myocardial infarction; VTE, venous thromboembolism; CrCl creatinine clearance.

Table 2. Uni- and multivariable analyses for the decision to use reduced- versus full dose direct oral anticoagulants. Results expressed as odds ratio and 95% confidence limits (in brackets).

	Univariable analysis	Multivariable analysis
Demographics		
Male sex	0.71 (0.58-0.87)**	0.99 (0.81-1.21)
Age >75 years	2.62 (2.25-3.05)**	1.74 (1.48-2.05)**
Body weight <60 kg	2.10 (1.65-2.68)**	1.36 (1.08-1.71)*
Initial VTE presentation		
Pulmonary embolism	Ref.	Ref.
Isolated DVT	1.30 (1.11-1.53)*	1.12 (0.98-1.27)
Comorbidities		
CrCl levels <50 mL/min	3.05 (2.53-3.67)**	1.78 (1.41-2.24)**
Drugs		
Rivaroxaban	Ref.	Ref.
Apixaban	2.62 (2.00-3.44)**	2.33 (1.80-3.00)**
Concomitant drugs		
Antiplatelets	1.01 (0.68-1.51)	0.83 (0.52-1.32)
Corticosteroids	1.41 (1.05-1.88)*	1.14 (0.81-1.60)

VTE, venous thromboembolism; DVT, deep vein thrombosis; CrCl, creatinine clearance; Ref., reference; *p<0.01; **p<0.001.



Days		30	60	120	180	240
Reduced doses	*At risk, N*	*921*	*916*	*875*	*776*	*624*
	Recurrent VTE	2 (0.2%)	3 (0.3%)	5 (0.6%)	6 (0.7%)	7 (0.8%)
	Major bleeding	2 (0.2%)	3 (0.3%)	3 (0.3%)	4 (0.5%)	4 (0.5%)
Full doses	*At risk, N*	*2,825*	*2,811*	*2,684*	*2,331*	*1,768*
	Recurrent VTE	10 (0.4%)	16 (0.6%)	25 (0.9%)	29 (1.1%)	36 (1.5%)
	Major bleeding	4 (0.1%)	5 (0.2%)	6 (0.2%)	9 (0.3%)	11 (0.5%)

Figure 1. Cumulative incidence rates of venous thromboembolism (VTE) recurrence and major bleeding during extended direct oral anticoagulants (DOAC) therapy in the two cohorts.

Table 3. Uni- and multivariable analyses for the risk of venous thromboembolism recurrence and for major bleeding. Results expressed as adjusted hazard ratio and 95% confidence limits (in brackets).

	Recurrent VTE		Major bleeding	
	Univariable analysis	Multivariable analysis	Univariable analysis	Multivariable analysis
Demographics				
Male sex	0.66 (0.66-0.67)***	0.85 (0.71-1.02)	0.49 (0.48-0.49)***	0.70 (0.69-0.70)***
Age >75 years	0.51 (0.50-0.51)***	0.94 (0.83-1.10)	1.53 (1.52-1.54)***	0.95 (0.94-1.02)
Body weight <60 kg	0.45 (0.44-0.45)***	0.88 (0.75-1.05)	4.71 (4.66-4.77)***	2.02 (1.91-2.14)***
Initial VTE presentation				
Pulmonary embolism	Ref.	Ref.	Ref.	Ref.
Isolated DVT	0.99 (0.99-1.00)	0.88 (0.80-1.05)	1.06 (1.05-1.07)***	1.07 (0.98-2.13)
Comorbidities				
CrCl levels <50 mL/min	-	-	3.84 (3.81-3.87)***	2.76 (2.74-2.78)***
Drugs				
Rivaroxaban	Ref.	Ref.	Ref.	Ref.
Apixaban	0.34 (0.34-0.34)***	0.42 (0.40-0.42)***	1.02 (1.01-1.03)**	0.95 (0.88-1.02)
Doses of DOACs				
Reduced doses	0.57 (0.56-0.57)***	0.97 (0.91-1.05)	1.10 (1.06-1.13)**	0.83 (0.82-0.83)***
Concomitant drugs				
Antiplatelets	1.43 (1.40-1.46)***	1.72 (1.68-1.77)***	7.56 (7.30-7.83)***	8.18 (7.89-8.47)***
Corticosteroids	-	-	2.53 (2.49-2.56)***	1.81 (1.79-1.83)***

VTE, venous thromboembolism; DVT, deep vein thrombosis; CrCl, creatinine clearance; DOACs, direct oral anticoagulants; Ref., reference; **p<0.01; ***p<0.001.

An additional aspect that deserves consideration is the potential inter-individual variability in anticoagulant response to DOACs. As recently highlighted by Palareti *et al.*,[23] the anticoagulant effect of DOACs may be highly variable and, in some patients, unpredictable, leading either to subtherapeutic or excessive drug exposure, with consequent thrombotic or bleeding complications. This issue may be particularly relevant in fragile patients, such as those selected for reduced-dose regimens because of advanced age, renal dysfunction, or low body weight. Further studies are needed to clarify whether individualized approaches, potentially including assessment of drug exposure in selected high-risk patients, could improve the safety and efficacy of extended anticoagulation.

Moreover, the preference for apixaban in patients perceived to be at high risk for bleeding did not result in a lower bleeding risk. Instead, apixaban use was associated with a significantly lower risk of VTE recurrence (less than half the risk) compared to rivaroxaban, without a corresponding difference in bleeding risk. This suggests a potential gap in clinical practice, where dosing strategies may not always align with the best patient outcomes. While clinicians might reduce doses to prevent bleeding, this cautious approach does not necessarily improve outcomes in terms of VTE recurrence or major bleeding events.

Our findings also highlight significant differences between real-world patients and those typically enrolled in RCTs, particularly in terms of demographics, comorbidities, and outcomes. Patients in our cohort were generally older and had higher rates of comorbidities such as hypertension, arterial disease, dementia, and renal impairment compared to those in the RCT that led to the approval of apixaban and rivaroxaban for extended VTE therapy.[3-5] Not unexpectedly, the rate of VTE recurrence in our cohort (2.08 per 100 patient-years) was comparable to rates reported in RCTs, but our observed rate of major bleeding (0.71 per 100 patient-years) was up to three times higher than that seen in trials. These differences underscore the limitations of RCTs in capturing the complexities of real-world practice, where patients often present with multiple comorbidities and higher risk profiles.

Despite these valuable insights, the observational nature of our study requires a cautious interpretation of the results. While our data provides a comprehensive view of real-world practices, they also introduce potential biases and confounding factors that are difficult to fully control. Residual confounding due to unmeasured variables, such as lifestyle factors or incomplete medication profiles, could have influenced the outcomes. Additionally, the registry-based data collection may not capture all the nuances of patient-provider interactions, which could impact the applicability of these findings to other healthcare settings. Another limitation is the potential temporal bias to the evolving evidence base for reduced-dose DOAC regimens during the study period. While reduced-dose apixaban for extended VTE treatment was supported earlier, the evidence supporting reduced-dose rivaroxaban became available only after publication of the EINSTEIN-CHOICE in 2017.[4] Thus, reduced-dose rivaroxaban prescriptions before 2017 may have reflected empirical dose adjustment rather than a standardized extended-treatment strategy. This may have influenced both the overall proportion of patients receiving reduced-dose DOACs and the comparison between rivaroxaban and apixaban.

Conclusions

In summary, our study emphasizes the importance of tailoring anticoagulant therapy to individual patient risk factors. Further research is needed to validate and refine these strategies, particularly in vulnerable populations with elevated bleeding risks. These findings highlight the need for continued vigilance and research to ensure that anticoagulant therapy remains both safe and effective, particularly for the most at-risk VTE patients.

References

1. Stevens SM, Woller SC, Baumann Kreuziger L, et al. Antithrombotic therapy for VTE disease: Compendium and review of CHEST guidelines 2012-2021. Chest 2024:S0012-3692.
2. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020;41: 543-603.
3. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. NEJM 2013;368: 699-708.
4. Weitz JI, Lensing AWA, Prins MH, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. NEJM 2017;376:1211-22.
5. Ebraheem M, Alzahrani I, Crowther M, et al. Extended DOAC therapy in patients with VTE and potential risk of recurrence: a systematic review and meta-analysis. J Thromb Haemost 2020;18:2308-17.
6. Barra ME, Fanikos J, Connors JM, et al. Evaluation of dose-reduced direct oral anticoagulant therapy. Amer J Med 2016;129:1198-204.
7. Donato A, Forman D. Review: extended therapy with DOACs, but not VKAs, reduces mortality after VTE treatment with initial anticoagulation. Ann Intern Med 2019; 171:JC42.
8. Mai V, Guay CA, Perreault L, et al. Extended anticoagulation for VTE: a systematic review and meta-analysis. Chest 2019;155:1199-216.
9. Khan F, Tritschler T, Kimpton M, et al. Long-term risk for major bleeding during extended oral anticoagulant therapy for first unprovoked venous thromboembolism: a systematic review and meta-analysis. Ann Intern Med 2021;174:1420-9.
10. Bikdeli B, Zahedi Tajrishi F, Sadeghipour P, et al. Efficacy and safety considerations with dose-reduced direct oral anticoagulants: a review. JAMA Cardiol 2022;7:747-59.
11. Bortoluzzi C, Bernardi E, Camporese G, et al. Safety and efficacy of rivaroxabán for extended-phase anticoagulation of patients with unprovoked or recurrent venous thromboembolism: real-life data from the MAC project. Life 2022;12: 1657.
12. Groat D, Martin KA, Rosovsky RP, et al. Physician perceptions and use of reduced-dose direct oral anticoagulants for extended phase venous thromboembolism treatment. Res Pract Thromb Haemost 2022;6:e12740.
13. Su X, Yan B, Wang L, et al. Comparative efficacy and safety of oral anticoagulants for the treatment of venous thromboembolism in the patients with different renal functions: a systematic review, pairwise and network meta-analysis. BMJ Open 2022;12:e048619.
14. Pawar A, Gagne JJ, Gopalakrishnan C, et al. Association of type of oral anticoagulant dispensed with adverse clinical outcomes in patients extending anticoagulation therapy beyond 90 days after hospitalization for venous thromboembolism. JAMA 2022;327:1051-60.
15. Fang MC, Reynolds K, Fan D, et al. Clinical outcomes of direct oral anticoagulants vs warfarin for extended treatment of venous thromboembolism. JAMA Network Open 2023;6: e2328033.
16. Park H, Jones BL, Huang PL, et al. Trajectories of oral anticoagulation adherence and associated clinical outcomes during long-term anticoagulation among Medicare beneficiaries with venous thromboembolism. Ann Pharmacother 2023;57: 1349-60.
17. Palareti G, Barinov V, Urbanek T, et al. Recurrences and bleeding during extended treatment of patients with venous thromboembolism: results of the international, prospective, observational WHITE study. Int Angiol 2023;42:37-44.
18. Iyer GS, Tesfaye H, Khan NF, et al. Trends in the use of oral anticoagulants in the US, 2010-2020. JAMA Network Open 2023;6:e234059.
19. Gabara C, Aibar J, Nishimoto Y, et al. Clinical outcomes after discontinuing anticoagulant therapy in patients with first unprovoked venous thromboembolism. J Thromb Haemost 2024:S1538-7836.
20. Bikdeli B, Jimenez D, Hawkins M, et al. Rationale, design and methodology of the computerized registry of patients with venous thromboembolism (RIETE). Thromb Haemost 2018; 118:214-24.
21. Trujillo-Santos J, Di Micco P, Dentali F, et al. Real-life treatment of venous thromboembolism with direct oral anticoagulants: the influence of recommended dosing and regimens. Thromb Haemost 2017;117:382-9.
22. Camporese G, Simioni P, Di Micco P, et al. Edoxaban for the long-term therapy of venous thromboembolism: Should the criteria for dose reduction be revised? Clin Transl Sci 2020; 14:335-42.
23. Palareti G, Testa S, Legnani C, et al. The use of reduced DOAC doses in atrial fibrillation patients does not always lead to good anticoagulation levels and avoid adverse events. Int J Cardiol 2024;416-132484.

Online supplementary material:

Supplementary Table S1. Baseline characteristics of the patients and VTE-related outcomes during extended therapy, according to prescribed drugs and doses.

Supplementary Table S2. Treatment details in patients receiving reduced- or full-dose DOACs for extended therapy of unprovoked VTE.