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Original Article

Secondary Prophylaxis of Venous Thromboembolism (VTE) with Low Dose Apixaban or Rivaroxaban: Results from a Patient Population with More than 2 Years of Median Follow-up

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Abstract. ***Background*: Direct oral anticoagulants (DOACs) are widely used for the treatment and secondary prophylaxis of venous thromboembolism (VTE). Nowadays, DOACs represent the gold standard for long-term anticoagulation, with low-intensity DOACs administration becoming increasingly used worldwide in such scenario. Albeit low-intensity apixaban and rivaroxaban are approved for clinical usage as secondary VTE prophylaxis, there are few literature data regarding their efficacy and safety with a long follow-up.**

***Objectives*: The aim of our study was to evaluate the efficacy and safety of low-dose DOACs for VTE secondary prophylaxis in patients at high risk of VTE recurrence.**

***Methods*: We retrospectively evaluated patients who required long-term anticoagulant secondary prophylaxis to prevent recurrent VTE, treated with apixaban 2.5 mg BID or rivaroxaban 10 mg daily with a follow-up ≥ 12 months.**

***Results*: The examined patients were 323. The median low-dose DOAC administration time was 25.40 months (IQR 13.93-45.90). Twelve (3.7%) VTE recurrences were observed; 21 bleeding events were registered (6.5%), including one episode of Major bleeding (MB) (0.3%), 8 Clinically relevant nonmajor bleeding (CRNMB) (2.5%) and 12 minor bleeding (3.7%). No statistically significant difference in the rate of VTE recurrence and/or bleeding events emerged between the rivaroxaban and apixaban groups. Patients included in the study for multiple episodes of VTE presented a significantly higher risk of a new VTE recurrence during low-intensity DOAC.**

***Conclusions*: Our data suggest that low-dose DOACs may be effective and safe in secondary VTE prophylaxis in patients at high risk of VTE recurrence; however, attention might be needed in their choice in such a scenario for patients who experienced multiple episodes of VTE.**

Keywords: Direct oral anticoagulants (DOACs); Low-dose DOACs; Venous thromboembolism secondary prophylaxis; VTE recurrence; Bleeding adverse events; Apixaban ; Rivaroxaban.

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Introduction. Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cause of death worldwide.[1] Its estimated incidence is around 1 to 2 per 1,000 people annually in the general population.[2]

Direct oral anticoagulants (DOACs) represent a more convenient and often safer treatment option for VTE prevention or treatment compared to vitamin-K antagonists or heparins.[3-7] Nowadays, DOACs represent the gold standard for long-term anticoagulation and, as well, are used for stroke prevention in patients with not valvular atrial fibrillation (NVAF)[8] and extended-duration treatment (secondary prevention) of VTE.[9-11] In particular, DOACs are the cornerstone for VTE secondary prophylaxis, and nowadays, there is an increasing tendency to perform such prophylaxis with low-dose DOAC administration. To date, only apixaban and rivaroxaban are approved for clinical usage for low-intensity DOAC secondary prophylaxis. The AMPLIFY-EXT trial[9] led to the FDA approval for low-intensity apixaban for extended-duration treatment. As for rivaroxaban, the EINSTEIN-CHOICE trial[11] assessed once-daily Rivaroxaban (at doses of 20 mg or 10 mg) vs 100 mg of aspirin doses for VTE extended-duration treatment. The risk of a recurrent event was significantly lower with Rivaroxaban at either a 20 mg or 10 mg dose than with aspirin, without a significant increase in bleeding rates, with consequent FDA approval for low-intensity Rivaroxaban in this scenario.

As secondary prophylaxis, DOAC treatment may be administered lifelong to some patients; however, few data are available concerning the efficacy and safety of low-intensity DOAC extended-duration treatment in a long follow-up.

Herein, we report our single-center experience with low-intensity DOACs as secondary VTE prophylaxis in non-oncological patients with a high risk of VTE recurrence. In particular, the study was focused on evaluating the efficacy and safety of low-intensity DOACs in patients with a follow-up≥ 12 months under this treatment regimen (median follow-up of 25.4 months).

Methods.

Study design. In this single-center, non-randomized, observational, retrospective study, we evaluated the efficacy and safety of low-intensity apixaban or rivaroxaban used in the context of VTE extended-duration secondary prophylaxis. In particular, we collected data related to all our patients receiving a low-dose DOAC, focusing on the evaluation of cases with a follow-up ≥ 12 months. The study was conducted in compliance with Institutional Review Board/Human Subjects Research Committee requirements. All patients signed the informed consent to the treatment and the use of their clinical data for scientific purposes.

Patients (≥ 18 years) were eligible for the study if they had an objectively confirmed, provoked, or unprovoked proximal deep-vein thrombosis, pulmonary embolism, or both. The extended prophylaxis with a low dose of apixaban or rivaroxaban was started because patients were considered at high risk of VTE recurrence due to of unprovoked VTE, recurrence of VTE, residual vein obstruction (RVO), presence of a permanent inferior vena cava filter, VTE with major thrombophilia, defined by congenital deficiency of antithrombin (AT), Protein C or S (PC or PS), homozygous Factor V (FV) Leiden or Factor II (FII) G20210A or combined heterozygous FV Leiden and FII G20210A.

Exclusion criteria were: subjects with active cancer (solid or hematological); cardiac mechanical valve; active bleeding or high risk for bleeding contraindicating DOAC treatment; active and clinically significant liver disease (Child-Pugh B or C); ALT or AST>2 times the upper limit of normal; total bilirubin >1.5 times the upper limit of normal (unless an alternative causative factor is identified [e.g., Gilbert's syndrome]); platelet count < $50x10^9$/L; serum creatinine >2.5 mg/dL (221 umol/L) or calculated creatinine clearance < 30 mL/min; subjects meeting the criteria for antiphospholipid syndrome (APS).

The acute VTE phase was treated (for at least 3 months) with low molecular weight heparin (LMWH), vitamin K antagonists (AVKs), or DOACs, depending on recommendations in force at the time of VTE event and on the clinician's choice. The extended secondary prophylaxis was started with low-intensity apixaban 2.5 mg BID or rivaroxaban 10 mg daily: the choice of the specific used DOAC was based on the clinician's choice.

Assessments. Patients underwent clinical assessment every 3-6 months during the treatment period. Patients were monitored for symptoms suggestive of recurrent VTE or bleeding. The assessment was on an outpatient basis with control of blood tests (including at least full blood count, liver, and kidney function) and imaging controls [computerized tomography (CT) or ultrasound (US)] when clinically appropriate.

Outcome Measures. The primary endpoint was the symptomatic recurrence of VTE, which has been employed in trials reporting extended treatment of VTE.[12] Recurrent VTE included fatal and nonfatal PE and DVT.

The primary safety outcome was major bleeding (MB). The secondary safety outcome was the composite of major or clinically relevant nonmajor bleeding (CRNMB). Major bleeding was defined as overt bleeding that was associated with a decrease in the hemoglobin level of 2 g per deciliter or more, led to transfusion of 2 or more units of red cells, occurred in a critical site, or contributed to death. CRNMB was

defined as overt bleeding that did not meet the criteria for major bleeding, but that was associated with the need for medical intervention, unscheduled contact with a physician, or discomfort or impairment of activities of daily living.[9]

We evaluated a general event-free-survival (EFS) considering as event a bleeding or thrombotic episode, a thrombotic event-free-survival (tEFS), and hemorrhagic event-free-survival (bEFS) during low-dose therapy.

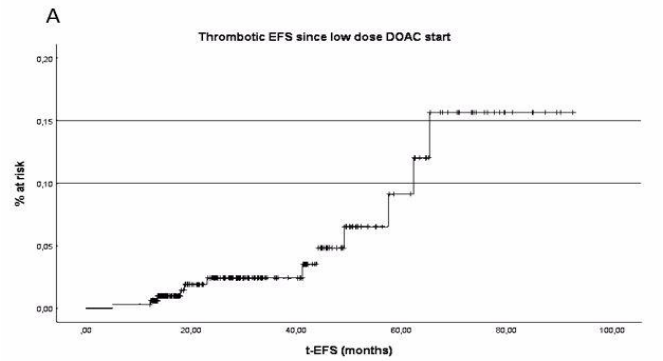
Statistical analysis. Descriptive statistics, such as the frequency (n), arithmetic mean, median, range, and standard deviation (SD), are presented for normally distributed variables. Differences in terms of bleeding and thrombotic events between groups were evaluated with univariate logistic regression. The chi-square test was used for categorical variables, and the T student or Mann-Whitney U-test was used for continuous variables. The odds ratio (OR) for each independent variable was determined with a confidence interval (CI) of 95%. Kaplan-Meier curves and survival tables were also employed to assess the difference in terms of thrombotic and bleeding adverse event-free survival (t-EFS or b-EFS), considered as the time range between the start of low dose DOACs and the occurrence of AE. Log-rank Mantel-Cox on Kaplan-Meyer curves was used to assess statistical significance. A p-value of 0.05 was considered significant. A receiver operating characteristic (ROC) curve was performed on continuous variables to determine a cut-off predictive of increased adverse event incidence.

Results. We selected a total of 447 patients that were receiving low-dose DOAC treatment. Our analysis has been focused on the 323 non-oncologic patients who were reaching a follow-up ≥ 12 months. Patients' characteristics are shown in **Table 1**.

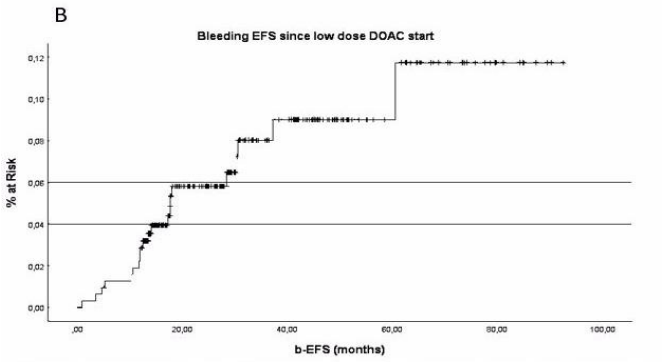
Median age was 56.5 years (IQR 44.60-70.59), 191 (59.1 %) were male, and 132 (40.9%) were female. Two-hundred-ten (65.0%) patients presented with isolated proximal DVT, 16 (5.0%) with isolated PE, and 97 (30.0%) with both proximal DVT and PE. During the VTE acute phase, 97 (30%) patients were treated with AVKs or LMWH, and 226 (70.0%) were treated with full

Table 1. Low-dose DOACs Patients characteristics with a follow-up ≥12 months.

Characteristics	N=323	Rivaroxaban (N=135)	Apixaban (N=188)
Male sex – no. (%)	191 (59.1)	80 (59.3)	111 (59.0)
Female sex – no. (%)	132 (40.9)	55 (40.7)	77 (41.0)
Age (years) - Median (IQR)	56.5 (44.60-70.59)	56.74 (44.33-71.94)	56.17 (43.07-71.46)
BMI – no. (%)			
< 20	19 (5.9)	6 (4.4)	13 (6.9)
20 to ≤ 30	239 (74.0)	95 (70.4)	144 (76.6)
> 30	65 (20.1)	34 (25.2)	31 (16.5)
Index event — no. (%)			
Isolated deep-vein thrombosis	210 (65.0)	90 (66.7)	120 (63.8)
Isolated pulmonary embolism	16 (5.0)	6 (4.4)	10 (5.3)
Both deep-vein thrombosis and pulmonary embolism	97 (30.0)	39 (28.9)	58 (30.9)
Previous treatment with full dose DOAC — no. (%)	226 (70.0)	106 (78.5)	120 (63.8)
Median duration of full dose DOAC administration — months	13.51 (8.26-36.89)	26.95 (11.97-53.21)	11.41 (5.81-17.91)
Previous treatment with VKA or LMWH — no. (%)	97 (30)	29 (21.5)	68 (36.2)
Median duration of full dose VKA or LMWH administration — months (IQR)	32.9 (5.5-103.8)	11.4 (4.5-81.6)	37.4 (9.03-106.0)
Switch from another DOAC full dose to low dose — no. (%)	63 (19.5)	46 (34.1)	17 (9.0)
Median duration of low dose DOAC administration — months (IQR)	25.40 (13.93-45.90)	23.23 (13.63-36.20)	29.18 (14.60-57.70)
Mortality, unrelated to DOAC treatment no. (%)	4 (1.2)	2 (1.5)	2 (1.1)
Reason for long term low dose prophylaxis — no. (%)			
Recurrent venous thromboembolism	145 (44.9)	63 (46.7)	82 (43.6)
Unprovoked thrombosis	74 (22.9)	27 (20.0)	47 (25.0)
Hereditary thrombophilia	55 (17.0)	32 (23.7)	23 (12.2)
Residual vein obstruction (RVO)	38 (11.8)	10 (7.4)	28 (14.9)
Permanent Inferior Vena Cava Filter	11 (3.4)	3 (2.2)	8 (4.3)



1y t-EFS (n at risk)	2y t-EFS (n at risk)	5y t-EFS (n at risk)	t-EFS at FU (n at risk)
99.4% (323)	98.1% (319)	96.9% (186)	96.3% (35)



1y b-EFS (n at risk)	2y b-EFS (n at risk)	5y b-EFS (n at risk)	b-EFS at FU (n at risk)
97.2% (323)	98.1% (309)	96.9% (186)	93.2% (37)

Figure 1. A. Thrombotic Event Free Survival (t-EFS) during low dose treatment. **B**. Bleeding Event Free Survival (b-EFS) during low dose treatment. Horizontal lines highlight the median risk interval in the Kaplan-Meier curve.

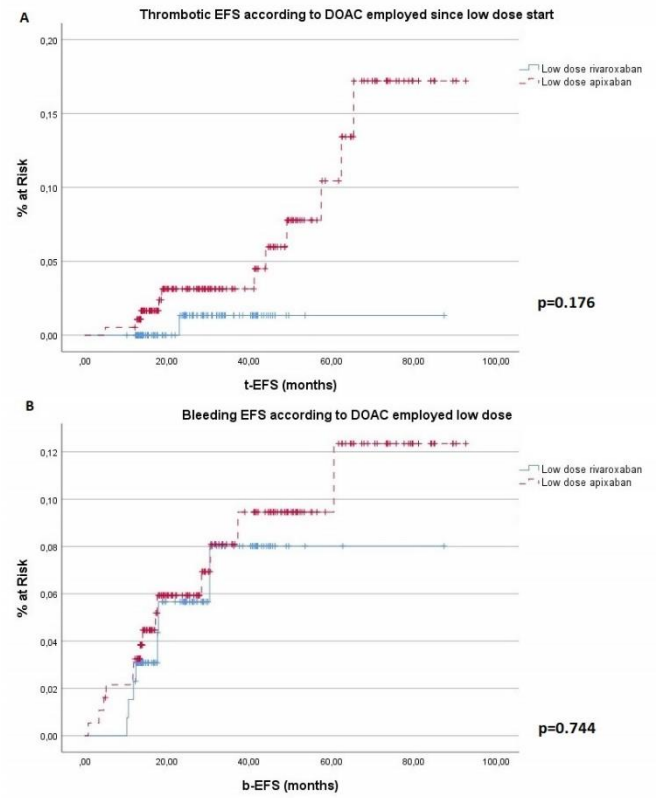


Figure 2. **A**. Thrombotic Event Free Survival (t-EFS) comparison between apixaban and rivaroxaban low dose treatment. **B**. Bleeding Event Free Survival (b-EFS) comparison between apixaban and rivaroxaban low dose treatment

doses of DOACs. All patients were considered at high risk of VTE recurrence and switched to extended treatment low-intensity DOACs for recurrent VTE 145 (44.9%), unprovoked thrombosis event 74 (22.9%), thromboembolic events in patients affected by major hereditary thrombophilia 55 (17.0%), RVO after acute phase VTE treatment 38 (11.8%) and permanent Inferior Vena Cava Filter in situ 11 patients (3.4%). The 55 patients with major thrombophilia were represented by 5 patients (9.1%) with AT deficiency, 5 (9.1%) with PC deficiency, 18 (32.7%) with PS deficiency, 3 (5.5%) with homozygous F II G20210A, 13 (23.6%) with homozygous FVL, and 11 (20%) patients with combined heterozygous FVL and F II G20210A.

During low dose, 135 patients (41.8%) received rivaroxaban and 188 (58.2%) apixaban. The median low-dose DOAC administration time was 25.40 months (IQR 13.93-45.90).

During low dose, 12 (3.7%) VTE recurrence events were observed after a median low-dose treatment of 27.68 months (IQR 17.0-47.3). These patients were switched on to full-dose DOAC therapy. The low-dose DOAC thrombotic event-free-survival (tEFS) was 99.4% at 1 year, 98.1% at 2 years, and 96.9% at 5 years, as shown in **Figure 1A**. Four patients died, but no death was VTE-related: 3 patients died because of old age, and 1 patient's death was caused by SARS-CoV-2 pneumonia. No statistically significant difference in the rate of VTE recurrence emerged between the rivaroxaban and apixaban groups (1/135 vs. 11/188), as shown in **Figure 2** (99.3% vs. 94.1% - p=0.176). We analyzed tEFS according to the reason for low dose DOAC start, and patients with multiple episodes of VTE presented a significantly higher risk of a new VTE recurrence during low-intensity DOAC (p=0.03 – **Figure 3**) (11/12 events verified in this subgroup). In this subgroup, the mean number of previous thrombosis was 2.3 (range 2-5), with unprovoked VTE representing 64% of the episodes, while 22% were provoked episodes; the presence of a provoking factor was not clear in the other cases. For the 11 patients developing VTE with low-dose DOACs, all 11 (100%) thrombotic events were represented by unprovoked VTEs.

During low dose, one MB (after 11.7 months of low-dose apixaban treatment) was observed (0.3%), represented by rectal bleeding requiring one blood transfusion and apixaban withdrawal for 5 days. In total 21 patients (6.5%) had a bleeding event during low dose after a median treatment period of 13.6 months (IQR 10.6-17.9): one MB (0.3%), 8 CRNMB (2.5%) and 12 minor bleeding (3.7%). Three CRNMB (0.9%) were registered within the first year; the other 5 CRNMB

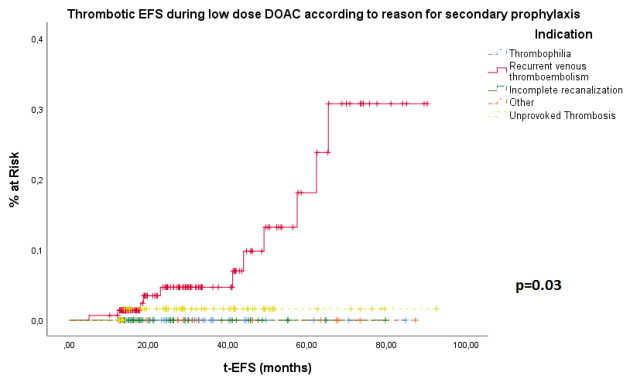


Figure 3. Thrombotic EFS for low-dose DOAC according to reason for secondary prophylaxis.

(1.5%) after more than one year. Two patients presented with a CRNMB required low-dose withdrawal up to a maximum of 3 days. The low-dose DOAC bleeding event-free-survival (bEFS) was 97.2% at 1 year, 98.1% at 2 years, and 96.9% at 5 years, as shown in **Figure 1B**. No statistically significant difference in the rate of bleeding events emerged between the rivaroxaban and apixaban groups (7/135 vs. 14/188), as shown in **Figure 2** (94.7% vs. 92.6% - p=0.744). A significant correlation was found between previous estrogenic-progestin therapy and b-EFS (94.5% vs 66.7% - p=0.0001).

During follow-up, 33 patients, after a median low-dose treatment of 20.35 months (IQR 14.02 – 29.45), interrupted low-dose DOAC secondary prophylaxis due to complete venous recanalization and, therefore, not being considered at high risk of VTE recurrence anymore. None of these 33 patients experienced a VTE recurrence after low-dose DOAC withdrawal.

Discussion. The current study analyzed data collected in our center regarding long-term treatment of patients with a VTE episode managed in real-life conditions with low-dose DOACs.

International guidelines recommend extending anticoagulation for secondary prevention to patients at high risk of VTE recurrence;[13] nevertheless, selecting which patients may need long-term anticoagulant secondary prophylaxis is a complex clinical decision. Such guidelines, in patients selected for extended-phase anticoagulation, suggest the use of reduced-dose over full-dose of apixaban or rivaroxaban.[13] Since low-intensity DOAC FDA approval (2013 for apixaban 2.5 mg BID and 2017 for rivaroxaban 10 mg),[9,11] these doses for apixaban and rivaroxaban have been extensively used worldwide. Compared to their extensive usage in clinical practice, literature data regarding low-intensity DOAC efficacy and safety in real life are quite scant. Hence, our objective was to provide data on long-term low-intensity DOAC efficacy and safety, which are lacking in pivotal studies such as the AMPLIFY-EXT trial[9] and the EINSTEIN-CHOICE trial.[11] In fact, secondary prophylaxis was given for up to 12 months in both trials. In our study, we report a median extended administration of 2 years, which is, to our knowledge, the longest period reported.

In the AMPLIFY-EXT trial,[9] recurrent VTE or death related to VTE occurred in 14 patients (1.7%) receiving 2.5/5 mg of apixaban; MBs were registered in 0.15% of patients, as well, in the EINSTEIN-CHOICE trial;[11] patients receiving 10 mg rivaroxaban had similar VTE recurrence rate to those receiving 20 mg (1.2% vs 1.5%), moreover, MB rate was superimposable (0.4% vs 0.5%).

Our data compare favorably with these findings: we report a VTE recurrence rate of 0.6% at 1 year and 1.9% at 2 years, confirming the efficacy of low doses on a longer time frame. As well, the bleeding event rate was low, with only one MB and 2.5% of CRNMB rate, confirming the efficacy of the reduced schedule.

A systematic review and meta-analysis of studies on patients presenting with an unprovoked VTE reported a rate of VTE recurrence of 10.1% at one year after anticoagulation therapy discontinuation.[14]

In 2022, our group evaluated patients requiring long-term anticoagulation for recurrent VTE, receiving DOACs as per VTE secondary prophylaxis.[15] In this retrospective, single-center study, 209 patients were included. DOACs were administered for a median time of 20 months, including VTE acute phase treatment; 157 patients continued DOACs at full dosage (75%), 52 (25%) switched to apixaban 2.5 mg BID or rivaroxaban 10 mg daily after a median time of 13 months. VTE recurrence occurred in 7/209 (3.1%), with an average time of occurrence of 18 months. Bleeding events occurred in 25/209 (12%) patients with an average time of occurrence of 9 months. Among the patients treated with low-intensity DOACs, the VTE recurrence rate was 5.7%; the hemorrhagic event rate was 11.5%. In the present paper, expanding the sample size, follow-up, and including different patients in this experience, we observed a better outcome.

Recently, Palareti et al.[16] (WHITE study) evaluated clinicians' decisions and clinical events occurring during at least one year of follow-up during maintenance treatment following diagnosis of a first-ever DVT and PE event. In this international, prospective, observational study, the type, dose, and duration of patient treatment were left to the attending physician's discretion. Hence, many different drugs were used as secondary prophylaxis, with DOACs representing the most frequently prescribed drugs for extended treatment despite not reporting DOACs' type and dosing. Outcome assessment was performed on 715 patients on follow-up who were compliant with the treatment prescribed by the participant clinical centers. Overall, across a median follow-up of 17.47 months, a total of 40 venous thrombotic recurrences (5.6%) were registered. Bleeding complications were represented by 5 MB (0.7%) and 5

CRNMB (0.7%) (MB + CRNMB – 1.4%). A sub-analysis of the 310 evaluable patients who received DOACs as secondary prophylaxis was performed. After a median follow-up of 16.49 months, 17 VTE recurrences (5.5%), 0 MB (0.0%), and 3 CRNMB (1.0%) were registered. We report a similar cohort with longer follow-up, including patients treated with low doses exclusively, and also, in this case, our data on thrombotic and bleeding outcomes are comparable.

In our real-life study, the efficacy and safety of DOACs in the secondary prophylaxis of VTE seem to be comparable or even with a better outcome than studies published on DOAC's long-term administration. In particular, the overall 3.7% incidence of VTE recurrence seems lower than the VTE recurrence rate registered in other studies, regardless of dosing. The bleeding outcome is comparable. A correlation was observed between b-EFS and estrogen-progestin therapy, probably due to increased gynecological bleeding risk in women requiring such treatment.

Therefore, given our long median follow-up (25.4 months), considering that just patients receiving low-dose DOACs as secondary prophylaxis were included, we can suggest that apixaban 2.5 mg BID or rivaroxaban 10 mg daily seem to be effective in reducing the risk of VTE recurrence in high-risk patients compared to anticoagulation therapy discontinuation and seem to be not inferior to full-dose DOACs in such scenario. We want to highlight that the patients included in the study for multiple episodes of VTE presented a significantly higher risk of a new VTE recurrence during low-intensity DOAC, warning about the use of such a schedule in this subset of patients, in which probably thrombotic predisposition is sustained by not well-defined mechanisms which limit DOACs' efficacy. The bleeding incidence in our study was 6.5%, including 12 minor bleeding (3.7%). These data are comparable to the general bleeding rate reported in the literature with low-intensity DOACs, pinpointing that low-dose DOAC administration may reduce bleeding adverse events in patients requiring secondary VTE prophylaxis.

Nevertheless, our study presents some limitations. The first limitation is represented by its retrospective nature; data were collected in a single center; moreover, it was an observational study, and all the treatment decisions were left to the attending physician. For all these reasons, the interpretation of our findings requires caution and further studies. A prospective study with extended low-dose DOACs could be designed with defined practical guidelines and randomized DOACs to overcome such limitations.

Conclusions. Based on this retrospective observation, administration of low-intensity DOACs (apixaban 2.5 mg BID or rivaroxaban 10 mg daily) in long-term secondary VTE prophylaxis for high-risk patients is effective and safe in the real-world setting. Further studies should investigate the choice of a low-dose DOAC secondary prophylaxis for patients presenting with multiple episodes of VTE. In this scenario, a careful clinical evaluation between full-dose and low-dose DOAC secondary prophylaxis might be useful.

Further prospective multicentric management studies are needed to identify the best use, efficacy, and safety profile of DOACs for secondary prevention in real-life conditions in non-oncological patients at high risk for VTE recurrence after a VTE event.

Author Contributions. AL wrote the manuscript. GMA + CM + AC revised and corrected the manuscript. AL + G.M.A. + AC provided and interpreted case data, GMA performed the statistical analysis, and AC conceived and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement. The data that support the findings of this study are available in the text and from the corresponding author, A.L. + AC, upon reasonable request.

Informed Consent. Written informed consent was collected according to local practice.

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