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ORIGINAL ARTICLE

Prescribing patterns and clinician preferences for direct oral anticoagulant use in unusual site venous thromboembolism: a cross-sectional analysis from the Direct oral anticoagulants in Unusual Site venous Thromboembolism (DUST) study

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Abstract

Background: Unusual site venous thromboembolism (USVTE) presents therapeutic challenges. Direct oral anticoagulants (DOACs) are increasingly prescribed despite limited evidence from clinical trials.

Objectives: This cross-sectional analysis aimed to describe DOAC prescription patterns and rationale for choosing DOACs for USVTE treatment in real-life clinical practice.

Methods: The Direct oral anticoagulants in Unusual Site venous Thromboembolism study (NCT03778502) is an international, multicenter, prospective, observational registry. Adult patients with objectively diagnosed USVTE (years 2018-2023) treated with DOACs were included. Information was collected on patient characteristics, USVTE location, anticoagulant treatment, and rationale for starting DOACs.

Results: In total, 349 patients were included from 23 centers in 9 countries. The most common USVTE were splanchnic vein thrombosis (n = 219, 62.8%) and cerebral vein thrombosis (n = 103, 29.5%). The most prescribed DOACs were apixaban (n = 186, 53.3%) and rivaroxaban (n = 101, 28.9%). The median delay between USVTE diagnosis and DOAC initiation was 24 days, with 219 patients (62.8%) starting DOACs >14 days after diagnosis. Indeed, 320 (91.7%) patients received other anticoagulants before switching to DOACs (mainly low-molecular-weight heparin, n = 217, 67.8%). The main reasons for prescribing DOACs were oral administration (145/336, 43.2%), no need for blood monitoring (131/336, 39.0%), favorable safety profile (116/336, 34.5%), and prescriber-reported patient's preference (96/336, 28.6%). Apixaban was the most prescribed DOAC in splanchnic vein thrombosis (133/219, 60.7%), while dabigatran was the most prescribed DOAC in cerebral vein thrombosis (38/103, 36.9%).

Conclusion: DOACs are increasingly prescribed for USVTE owing to their ease of use and perceived safety, but mainly after initial treatment with parenteral anticoagulation. Further evidence is still needed to support their use in the acute phase.

KEYWORDS
cerebral veins, direct-acting oral anticoagulant, portal vein, splanchnic circulation, venous thromboembolism

Essentials

- Evidence on DOACs in USVTE is limited.
- The DUST study is a prospective international registry of patients with USVTE treated with DOACs.
- In total, 349 patients were included from 23 centers (9 countries), mostly with splanchnic or cerebral thrombosis.
- DOACs are increasingly prescribed for USVTE due to their ease of use and perceived safety.

1 | INTRODUCTION

Unusual site venous thromboembolism (USVTE) refers to thrombosis occurring in venous districts outside the veins of the lower extremities and the pulmonary arteries and includes, among others, cerebral vein thrombosis (CVT), splanchnic vein thrombosis (SVT), ovarian vein thrombosis (OVT), and renal vein thrombosis (RVT). USVTE presents both diagnostic and therapeutic challenges due to the heterogeneous clinical manifestations, the limited evidence regarding their acute- and long-term prognosis, and the absence of large-scale randomized controlled trials (RCTs) assessing different treatment strategies [1,2].

When the DUST (Direct oral anticoagulants in Unusual Site venous Thromboembolism) study was planned in 2018, guidelines recommended the use of unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or vitamin K antagonists (VKAs) for the treatment of USVTE [3–6]. In fact, patients with USVTE were excluded from the pivotal large phase III RCTs that evaluated the direct oral anticoagulants (DOACs) for the treatment of lower limb deep vein thrombosis or pulmonary embolism [7–11]. Nowadays, despite not being specifically licensed for this indication, the DOACs are frequently considered also for USVTE [12,13]. In the past 5 years, more evidence has been published, including 2 large observational studies on the treatment of CVT (Anticoagulation in the Treatment of Cerebral Venous Thrombosis [14] and DOAC-CVT [15]), 3 RCTs on the use of DOACs in CVT (A Clinical Trial Comparing Efficacy and Safety of Dabigatran Etexilate With Warfarin in Patients With Cerebral Venous and Dural Sinus Thrombosis [16], EINSTEIN-Jr CVT [17], and Study of Rivaroxaban for Cerebral Venous Thrombosis [18]), an interventional single-arm clinical trial evaluating rivaroxaban in acute SVT (RIVA-SVT 100 [19]), and an RCT evaluating rivaroxaban in chronic portal vein thrombosis (Rivaroxaban Prophylaxis in Noncirrhotic Portal Vein Thrombosis [20]). Furthermore, recent guidelines for the treatment of CVT [21] and SVT [22–24] have included the possibility of using the DOACs. Scarce information is available on other less common USVTE, such as OVT and RVT.

The aims of the DUST study were to describe current therapeutic approaches with the DOACs in patients with USVTE, to explore and evaluate the rationale for choosing the DOAC for the treatment of USVTE in real-life clinical practice, and to assess the safety and effectiveness of this approach. This article reports the baseline characteristics of the population, DOAC prescription patterns, and the rationale for the use of the DOACs in USVTE.

2 | METHODS

2.1 | Study design and population

The DUST study (NCT03778502) is an international, multicenter, prospective, observational registry. We included consecutive adult (≥18 years) patients with objectively diagnosed venous thrombosis (between the years 2018 and 2023) not involving the upper limbs, lower limbs and pulmonary arteries and treated with DOACs (ie, apixaban, dabigatran, edoxaban, and rivaroxaban). Patients who had objective diagnosis within 6 months prior to the start of the registry were eligible, as long as they were prospectively followed up by the participating centers and all requested information was available. Patients enrolled in interventional studies evaluating the DOACs for the treatment of USVTE were excluded.

At baseline, information was collected on patient characteristics (age and biological sex), details of USVTE (risk factors, clinical presentation, imaging test results, blood tests results performed at the time of starting DOACs, and known thrombophilia), details of the DOAC treatment (start date, time elapsed since USVTE diagnosis, drug, dosage, and duration), other anticoagulant treatments prescribed before the DOAC (if any), concomitant medications, and rationale for starting a DOAC. Provoked VTE was defined as VTE due to active solid or hematologic cancer; recent surgery or trauma (within 3 months); liver cirrhosis, abdominal inflammatory, or infectious diseases (eg pancreatitis, diverticulitis, cholecystitis, hepatitis, appendicitis, gastroenteritis, and inflammatory bowel diseases); autoimmune diseases; estrogen hormonal therapy (oral contraceptives or hormone replacement therapy); pregnancy or puerperium; high-risk thrombophilia (deficit of natural anticoagulants, ie, protein C, protein S, or antithrombin; antiphospholipid syndrome; and homozygous mutation of factor [F]V Leiden or Prothrombin G20210A and their combined heterozygous mutations); or other factors (evaluated on a case-by-case basis). Anemia was defined as hemoglobin levels of < 13.0 g/dL in men or < 12.0 g/dL in women [25]. Thrombocytopenia was defined as platelet count of $< 150 \times 10^9$/L. Reduced kidney function was defined as glomerular filtration rate (calculated using the Cockroft–Gault formula) of < 60 mL/min. Obesity was defined as body mass index of ≥ 30 kg/m^2 and underweight as < 18.5 kg/m^2 [26].

The complete list of study contributors is reported in Supplementary Material 1. The study was approved by the respective ethics committee at each participating institution before starting recruitment, and where requested, patients signed an informed consent before inclusion. The study was promoted through the International Society on Thrombosis and Haemostasis (ISTH). Study data were collected and managed using REDCap electronic data capture tools [27,28]. This study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [29].

2.2 | Study outcomes

The primary outcomes of the DUST study were to describe current therapeutic approaches with the DOACs in patients with USVTE and to evaluate the rationale for choosing the DOACs for the treatment of USVTE in real-life clinical practice. The therapeutic approaches were assessed by analyzing DOAC prescription patterns (ie, details of DOAC treatment, as defined in the previous section). The rationale for the use of DOACs in each patient was assessed using an open-

ended question (What is the rationale for choosing one of the DOACs in this patient?), followed by a multiple-choice question (Which one(s) of the following options better describe the rationale for choosing DOACs?), in which the investigators could select up to 3 options, as done in a previous vignette-based survey [13]. Details of the questions assessing the rationale for choosing DOACs are provided in Supplementary Material 2. For the multiple-choice question, reasons selected in >25% of cases were considered primary drivers, those selected in 10% to 25% of cases secondary drivers, and those selected in <10% of cases minor drivers. Responses to the open-ended question were used to generate a word cloud, in which the size of each word reflects its frequency, visually representing the most commonly cited terms underlying the rationale for DOAC selection.

This cross-sectional analysis presents DOAC prescription patterns and the reasons for prescribing DOACs, along with differences across the following: (1) the specific DOACs used; (2) the 2 most common sites of USVTE (CVT vs SVT); (3) the dose of DOAC (regular dose vs reduced dose, the latter including apixaban 2.5 mg twice daily, dabigatran 110 mg twice daily, edoxaban 30 mg once daily, and rivaroxaban 15 mg once daily or 10 mg once daily). The secondary outcomes of the DUST study (ie, safety and effectiveness of DOAC use in USVTE) will be assessed from the (ongoing) longitudinal follow-up.

2.3 | Statistical analysis

Normality in data distribution was assessed using the Shapiro–Wilk test. Baseline characteristics of the study population were reported by means of descriptive statistics: continuous variables were expressed as mean (SD) or as median (IQR), according to data distribution; categorical data were reported as counts and percentages.

For the comparisons between 2 groups (CVT vs SVT and regular vs reduced DOAC dose), continuous variables were assessed using either the Student's *t*-test or the Mann–Whitney U-test, depending on data distribution. Categorical variables were compared using the chi-squared test or the Fisher exact test, as appropriate. Two-tailed *P* values of $< .05$ were considered statistically significant.

To compare the reasons (categorical variable) for choosing DOACs across the 4 DOAC groups (apixaban, dabigatran, edoxaban, and rivaroxaban), the chi-squared test or the Fisher exact test were initially performed, as appropriate. For the post hoc analysis, Bonferroni correction was applied to adjust for the risk of type I error from multiple pairwise comparisons; thus, statistical significance was set at $P < .0083$ (based on 6 comparisons).

Given the paucity of prospective studies on the use of the DOACs for the treatment of USVTE, we originally planned a pilot study with a minimum sample size of 100 patients over a 4-year period. However, challenges in patient enrolment during the COVID-19 pandemic led us to extend the enrolment period to 6 years, and as more centers joined the study, we decided to remove the sample size cap.

Data analysis was performed using the software STATA/BE, version 19.5 (StataCorp LP) and SPSS Statistics Software for Windows, version 29 (IBM Corp). The word cloud was created using Python (Python Software Foundation, version 3.13.5), along with the wordcloud and matplotlib libraries.

3 | RESULTS

3.1 | Study population

The study flow chart is available in Supplementary Material 3. We analyzed 349 patients enrolled from 23 participating centers in 9 countries between 2018 and 2023. Median age was 54 years (IQR, 44-65 years); 187 (53.6%) were men; and 320 (91.7%) were Caucasian. The most common sites of thrombosis were SVT (219 [62.8%], of whom 5 had a Budd–Chiari syndrome) and CVT (103 [29.5%]), followed by OVT (14 [4.0%]) and RVT (8 [2.3%]). Baseline characteristics of the population are summarized in Table 1 and Supplementary Material 4.

USVTE was symptomatic in 275 (78.8%) and incidentally detected in 74 (21.2%) patients; it was unprovoked in 96 (27.5%) and provoked in 253 (72.5%) patients. In most of the provoked cases (197/253 [77.9%]) only 1 provoking factor was identified. The most common risk factors were cancer (solid cancer in 53 patients [15.2%] and hematologic cancer in 43 patients [12.3%]), abdominal inflammatory or infectious diseases (57 [16.3%]), liver cirrhosis (31 [8.9%]), estrogen hormonal therapy (28 [8.0%]), and recent surgery (26 [7.4%]). High-risk thrombophilia was reported in 41 (11.7%) patients. Furthermore, 50 (14.3%) patients had a history of VTE, 30 (8.6%) had a history of cancer (not active at enrolment), and 41 (11.7%) had a history of bleeding. At the time of starting DOACs, 38.7% (133/344) of patients had anemia, 17.4% (60/345) had thrombocytopenia, and 10.0% (33/330) had reduced kidney function.

3.2 | Anticoagulant treatment details and DOAC prescription patterns

Twenty-nine (8.3%) patients were started directly on DOACs, while the remaining 320 (91.7%) patients received other anticoagulants before switching to DOACs. In most cases (255/320 [79.7%]) only 1 other anticoagulant was prescribed before the DOAC. The other anticoagulants drugs prescribed before DOACs included LMWH (263 [75.4%]), fondaparinux (48 [13.8%]), VKAs (46 [13.2%]), and UFH (29, 8.3%). In addition, 15 (4.3%) patients received interventional treatment for USVTE (Table 2). The last anticoagulant used before switching to DOAC was LMWH in 217 (67.8%) patients, fondaparinux in 44 (13.8%), VKA in 44 (13.8%), UFH in 14 (4.4%), and argatroban in 1 (0.3%).

The most commonly prescribed DOAC was apixaban (186 [53.3%]), followed by rivaroxaban (101 [28.9%]), dabigatran (43 [12.3%]), and edoxaban (19 [5.4%]). Fifty-two patients (14.9%) were

TABLE 1 Baseline characteristics of the study population.

Characteristic	Patients with USVTE (*N* = 349)
Demographics and medical history	
Age (y)	54 (44-65)
Male	187/349 (53.6)
White race	320/349 (91.7)
Family history of VTE	35/349 (10.0)
Personal history of VTE	50/349 (14.3)[a]
Usual site VTE	37
Unusual site VTE	16
History of cancer (currently not active)	30/349 (8.6)
History of bleeding	41/349 (11.7)
Details of the current episode of USVTE	
Site of unusual VTE	
Splanchnic veins	219/349 (62.8)
Esophageal varices	44
Cerebral veins	103/349 (29.5)
Intracranial hemorrhage at diagnosis	20
Ovarian veins	14/349 (4.0)
Renal veins	8/349 (2.3)
Others	6/349 (1.7)[b]
Clinical onset	
Asymptomatic incidentally detected USVTE	74/349 (21.2)
Symptomatic USVTE	275/349 (78.8)
Risk factors for USVTE	
Unprovoked USVTE	96/349 (27.5)
Provoked USVTE	253/349 (72.5)
Solid cancer	53/349 (15.2)
Hematological cancer	43/349 (12.3)
MPNs	38
Abdominal inflammatory or infectious diseases	57/349 (16.3)
Liver cirrhosis	31/349 (8.9)
Child Pugh class	
A	18
B	12
C	1
Estrogen hormonal therapy	28/349 (8.0)
Recent surgery	26/349 (7.4)
Recent trauma	6/349 (1.7)
Pregnancy or puerperium	7/349 (2.0)
Other risk factors	63/349 (18.1)
Autoimmune diseases	2
Extra-abdominal infections	15
HIT	1
VITT	1
High-risk thrombophilia	41[c]
No. of risk factors for USVTE	
1	197/253 (77.9)
2	48/253 (19.0)
≥3	8/253 (3.2)

Values are *n*, *n/N* (%), or median (IQR).

HIT, heparin-induced thrombocytopenia; MPN, myeloproliferative neoplasms; USVTE, unusual site venous thromboembolism; VITT, vaccine-induced immune thrombotic thrombocytopenia; VTE, venous thromboembolism.

[a]Three patients had a history of both usual and unusual VTE before the current episode of USVTE.

[b]Other USVTE included retinal vein occlusion (*n* = 1), isolated inferior vena cava thrombosis (*n* = 1), isolated superior vena cava thrombosis (*n* = 1), anterior spinal vein thrombosis (*n* = 1), dorsal vein of the penis thrombosis (*n* = 1), and adrenal vein thrombosis (*n* = 1).

[c]High-risk thrombophilia is detailed in Supplementary Material 4.

started on reduced-dose DOACs (Table 2). The trends in DOACs choice by year of prescription are shown in Figure 1. Considering the time elapsed between the diagnosis of USVTE and DOAC initiation, the median delay was 24 days (IQR, 9-91 days). A total of 130 patients (37.2%) initiated DOAC treatment within 14 days, 62 patients (17.8%) between 15 and 30 days, 42 patients (12.0%) between 31 and 60 days, 27 patients (7.7%) between 61 and 90 days, and 88 patients (25.2%) after more than 90 days. Differences in anticoagulant treatment based on the timing of DOAC initiation are reported in Supplementary Material 5. Of note, the proportion of patients who started reduced-dose DOAC increased with longer delays from USVTE diagnosis: 21.5% of patients who started after 14 days; 26.1% among those who started after 30 days; 33.0% after 60 days; and 39.8% after 90 days. Finally, 240 (68.8%) patients were receiving other concomitant drugs at the time of DOAC initiation.

3.3 | Rationale for using DOACs

The rationale for choosing the DOACs, using the multiple-choice question, was reported in 336 of 349 enrolled patients. Primary drivers to DOAC prescription were the oral route of administration of the drugs (145/336 [43.2%]), the lack of need for blood monitoring (131/336 [39.0%]), the favorable safety profile of the drugs (116/336 [34.5%]), and prescriber-reported patient's preference (96/336 [28.6%]). Secondary drivers to DOAC prescription were physician's

TABLE 2 Details of the treatment for USVTE.

Treatment	Patients with USVTE (*N* = 349)
Anticoagulant treatment before receiving DOACs	
Other anticoagulant drugs before DOACs	
None	29/349 (8.3)
Yes	320/349 (91.7)
UFH	29/349 (8.3)
Duration (d)	4 (3-8)
LMWH	263/349 (75.4)
Duration (d)	19 (7-63)
Fondaparinux	48/349 (13.8)
Duration (d)	29.5 (13.5-94)
VKA	46/349 (13.2)
Duration (d)	135.5 (36-427)
Other anticoagulants	2/349 (0.6)[a]
No. of anticoagulant drugs before DOACs	
1	255/320 (79.7)
2	62/320 (19.4)
3	3/320 (0.9)
Last anticoagulant used before switching to DOAC	
UFH	14/320 (4.4)
LMWH	217/320 (67.8)
Fondaparinux	44/320 (13.8)
VKA	44/320 (13.8)
Other anticoagulant	1/320 (0.3)
DOAC treatment details	
Apixaban	186/349 (53.3)
10 mg twice daily for 7 d, then 5 mg twice daily	27
5 mg twice daily	128
2.5 mg twice daily	31[b]
Dabigatran	43/349 (12.3)
150 mg twice daily	38
110 mg twice daily	5[b]
Edoxaban	19/349 (5.4)
60 mg once daily	11
30 mg once daily	8[b]
Rivaroxaban	101/349 (28.9)
15 mg twice daily for 21 d, then 20 mg once daily	19
15 mg twice daily for <21 d, then 20 mg once daily	3
20 mg once daily	71
15 mg once daily	3[b]
10 mg once daily	5[b]
Dose of DOAC	
Regular dose	297/349 (85.1)
Reduced dose	52/349 (14.9)
Time from USVTE diagnosis to DOAC initiation	
Delay (d)	24 (9-91)
Other treatments details	
Interventional treatments for USVTE	15/349 (4.3)[c]
Other concomitant drugs (at the time of DOAC initiation)	240/349 (68.8)
Antiplatelets	15/349 (4.3)
Chronic NSAIDs	3/349 (0.9)
Chronic antiepileptics	36/349 (10.3)
Statins	34/349 (9.7)
Proton pump inhibitors	94/349 (26.9)
β-Blockers	56/349 (16.0)

Values are *n*, *n*/*N* (%), or median (IQR).

DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; NSAID, nonsteroidal anti-inflammatory drugs; UFH, unfractionated heparin; USVTE, unusual site venous thromboembolism; VKA, vitamin K antagonist.

[a]Other anticoagulant treatments include bivalirudin (*n* = 1), and argatroban (*n* = 1).

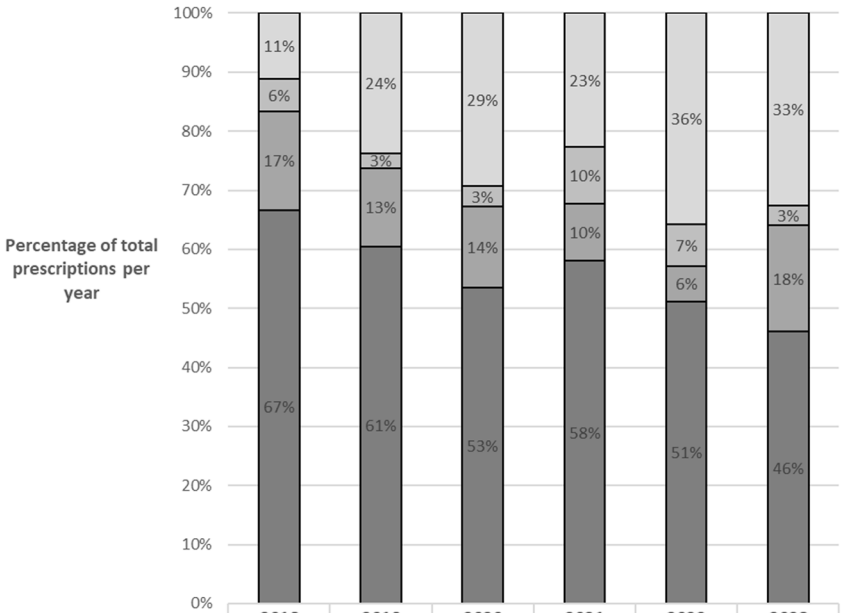
[b]Considered as reduced-dose DOACs.

[c]Interventional treatments include surgery (*n* = 6); surgical shunt or transhepatic intrajugular portosystemic shunt (*n* = 2); caval filter (*n* = 1); thromboaspiration or thrombectomy (*n* = 5); thrombolysis (*n* = 5); and ballooning or stenting (*n* = 2).

personal experience (47/336 [14.0%]), expected higher patient's adherence (41/336 [12.2%]), and the proven efficacy of the drug (40/336 [11.9%]). Minor drivers are presented in Figure 2.

The 2 most common reasons for prescribing apixaban were the oral route of administration (87/177 [49.2%]) and the favorable safety profile of the drug (79/177 [44.6%]); for dabigatran, they were the proven efficacy of the drug in this setting (18/43 [41.9%]) and the favorable safety profile of the drug (15/43 [34.9%]); for edoxaban and rivaroxaban, they were the lack of need for blood monitoring during follow-up and the oral route of administration of the drug (10/19 [52.6%] and 10/19 [52.6%], respectively, for edoxaban; 54/97 [55.7%] and 36/97 [37.1%], respectively, for rivaroxaban).

Some differences emerged in the rationale behind the choice of a specific DOAC (Table 3). For instance, proven efficacy of the drug in this setting was chosen in 41.9% (18/43) of dabigatran prescriptions vs 12.4% (12/97) of rivaroxaban and 5.6% (10/177) of apixaban (all $P <$



	2018	2019	2020	2021	2022	2023
Rivaroxaban	2	9	17	14	30	29
Edoxaban	1	1	2	6	6	3
Dabigatran	3	5	8	6	5	16
Apixaban	12	23	31	36	43	41
Total prescriptions per year (n. of patients)	18	38	58	62	84	89

FIGURE 1 Trends in direct oral anticoagulant (DOAC) use by year of prescription (2018-2023).

.001). The favorable safety profile of the drug was chosen in 44.6% (79/177) of apixaban prescriptions vs 17.5% (17/97) of rivaroxaban ($P < .001$). Expected higher patient's adherence was chosen in 21.6% (21/97) of rivaroxaban vs 7.3% (13/177) of apixaban ($P < .001$).

In addition, in 323 of 349 enrolled patients, the investigators also answered the open-ended question. As shown in the word cloud (Supplementary Material 6), the most commonly cited words were patient ($n = 69$) and drug ($n = 64$), indicating that prescribing decisions were primarily guided by patient-related factors, such as patient's clinical characteristics or individual preferences, and drug-related factors, such as pharmacologic properties and safety or efficacy profile.

Differences in the rationale for choosing DOAC and in DOAC treatment details between the 2 countries with the largest patient cohorts (Italy and France) are shown in Supplementary Material 7.

3.4 | Comparison between CVT and SVT

There were several differences in patient baseline characteristics according to the site of unusual VTE (Supplementary Material 8). For instance, patients with SVT showed more comorbidities than patients with CVT, such as solid cancer (44/219 [20.1%] vs 4/103 [3.9%]; $P < .001$), liver cirrhosis (31/219 [14.2%] vs 0/103 [0%]; $P < .001$), abdominal inflammatory or infectious diseases (49/219 [22.4%] vs 3/103 [2.9%]; $P < .001$), a history of bleeding (32/219 [14.6%] vs 6/103 [5.8%]; $P = .023$), anemia (96/217 [44.2%] vs 23/100 [23.0%]; $P < .001$), thrombocytopenia (58/217 [26.7%] vs 1/101 [1.0%]; $P < .001$), reduced kidney function (27/207 [13.0%] vs 2/97 [2.1%]; $P = .002$), and they were more likely incidentally detected (62/219 [28.3%] vs 5/103 [4.9%]; $P < .001$).

The anticoagulant treatment also showed distinct patterns according to USVTE locations (Supplementary Material 8), with patients with SVT receiving more frequently fondaparinux (38/219 [17.4%] vs 4/103 [3.9%]; $P < .001$) and patients with CVT receiving more frequently VKA (17/219 [7.8%] vs 27/103 [26.2%]; $P < .001$) before switching to DOACs. With regards to DOAC prescription, apixaban was more commonly prescribed to patients with SVT (133/219 [60.7%] vs 32/103 [31.1%]; $P < .001$), while dabigatran was more commonly prescribed to patients with CVT (5/219 [2.3%] vs 38/103 [36.9%]; $P < .001$); no differences emerged in the prescription of edoxaban and rivaroxaban.

Regarding the rationale behind the choice of DOACs (Supplementary Material 9), the oral route of administration of the drug was chosen more frequently for SVT (102/208 [49.0%] vs 30/103 [29.1%]; $P < .001$), while proven efficacy of the drug in this setting (19/208 [9.1%] vs 21/103 [20.4%]; $P = .005$) and patient demographic characteristics (10/208 [4.8%] vs 15/103 [14.6%]; $P = .003$) were chosen more frequently for CVT. The rationale for choosing DOAC in patients with OVT and RVT is reported in Supplementary Material 10.

3.5 | Comparison by dose of DOACs

Patients starting DOAC directly with a reduced-dose were older (median age, 61 vs 52 years; $P = .023$), were more likely to have a history

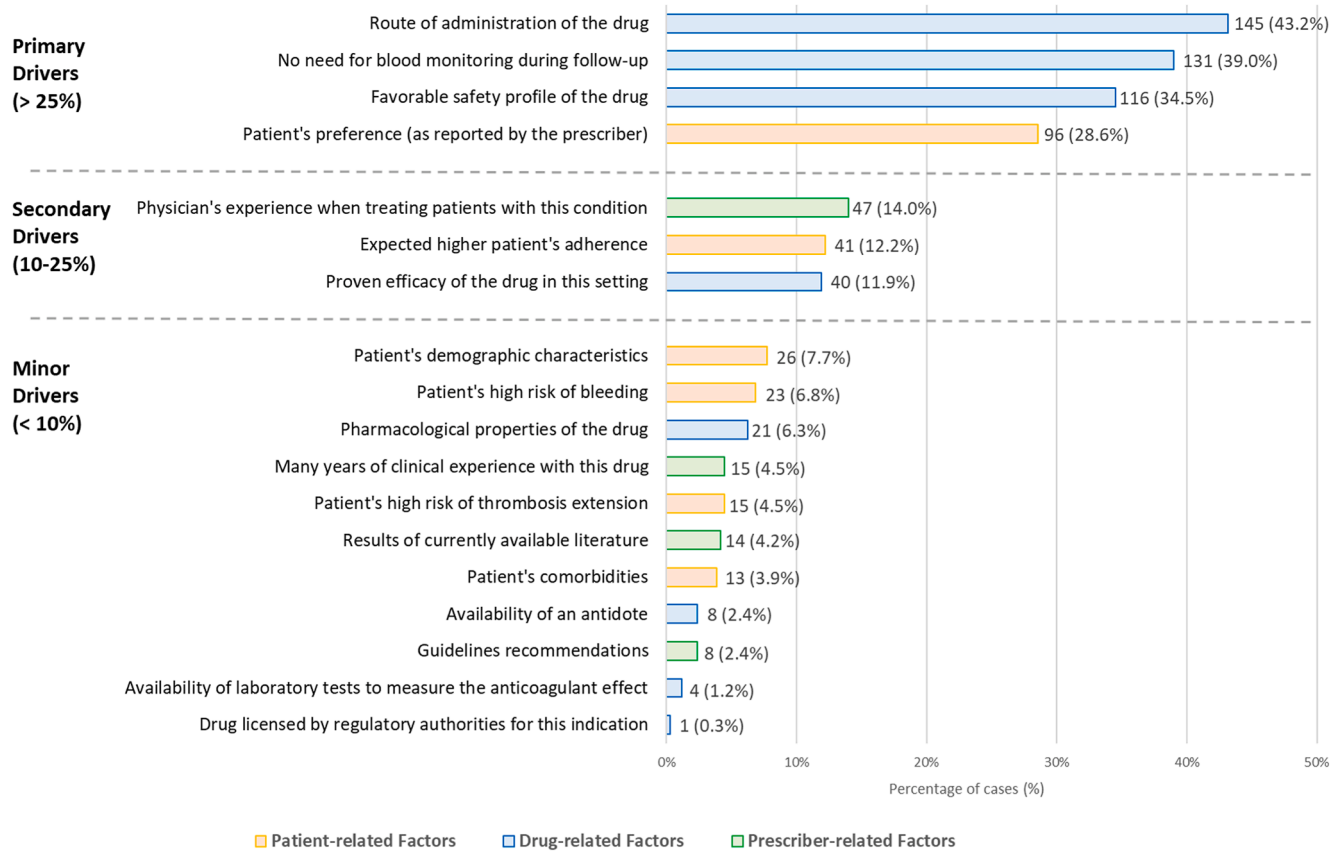


FIGURE 2 Rationale for choosing direct oral anticoagulants (DOACs) for the treatment of unusual site venous thromboembolism. The rationale for choosing the DOACs was reported for 336 of 349 enrolled patients.

of bleeding (11/52 [21.2%] vs 30/297 [10.1%]; P = .022), and showed higher prevalence of anemia, thrombocytopenia, and reduced kidney function, than patients starting regular-dose DOAC (Supplementary Material 8). They had also more frequently SVT (41/52 [78.8%] vs 178/297 [59.9%]; P = .009), liver cirrhosis (13/52 [25.0%] vs 18/297 [6.1%]; P < .001) and incidentally detected thrombosis (23/52 [44.2%] vs 51/297 [71.7%]; P < .001).

Patients who started reduced-dose DOAC were more likely to have received VKA before switching (12/52 [23.1%] vs 32/297 [10.8%]; P = .014) and showed a longer delay from USVTE diagnosis to DOAC treatment (median, 177.5 vs 19 days; P < .001). The most commonly prescribed DOAC was apixaban, but the proportion was not different from that observed in patients receiving regular-dose DOAC (31/52 [59.6%] vs 155/297 [52.2%]; P = .32). Edoxaban was statistically more common among patients receiving reduced-dose DOAC (8/52 [15.4%] vs 11/297 [3.7%]; P = .003), while rivaroxaban was more common among patients receiving regular-dose DOAC (8/52 [15.4%] vs 93/297 [31.3%]; P = .019).

Regarding the rationale behind the choice of DOACs (Supplementary Material 9), route of administration of the drug was more frequently chosen for patients receiving reduced-dose DOAC (34/52 [65.4%] vs 111/284 [39.1%]; P < .001), while proven efficacy of the drug was chosen more frequently for patients receiving regular-dose DOAC (1/52 [1.9%] vs 39/284 [13.7%]; P = .016).

DISCUSSION

The DUST study represents one of the largest published cohorts to date describing the use of DOACs in 349 patients with USVTE. The most commonly prescribed DOAC was apixaban (53.3%), followed by rivaroxaban (28.9%) and dabigatran (12.3%). Of note, DOAC therapy was started after a median delay of 24 days since the diagnosis of USVTE, and only 8.3% of patients began anticoagulation directly with a DOAC, while the majority (91.7%) received other types of anticoagulants before transitioning to DOACs. The practice of waiting until clinical stabilization before switching to oral anticoagulation has been frequently reported in previous studies enrolling patients with CVT or SVT [17,18,30,31]. In the present study, a significant proportion of patients (14.9%) started DOACs directly with a reduced dose. This finding can be partly explained by the time elapsed since USVTE diagnosis (median delay was 177.5 days in patients receiving reduced-dose DOAC), which suggests secondary VTE prevention. In addition, patients receiving reduced-dose DOAC appear to be more fragile than those receiving regular-dose DOAC, as evidenced by the higher prevalence of prior bleeding, anemia, thrombocytopenia, and reduced kidney function. We also noticed a higher proportion of SVT, liver cirrhosis, and incidentally detected thrombosis. These factors could be potentially related, since patients with SVT are more frequently incidentally detected than patients with CVT, and liver cirrhosis is one of the main risk factors for SVT.

TABLE 3 Differences in the rationale for choosing DOAC across different drugs.

	Comparison across 4 groups (significance level: $P < .05$)					Post hoc analysis: pairwise comparisons with Bonferroni correction (significance level: $P < .0083$)					
Rationale	Apixaban ($n = 177$)	Dabigatran ($n = 43$)	Edoxaban ($n = 19$)	Rivaroxaban ($n = 97$)	P	A vs D, P	A vs E, P	A vs R, P	D vs E, P	D vs R, P	E vs R, P
Route of administration of the drug	87 (49.2)	12 (27.9)	10 (52.6)	36 (37.1)	.032	.012	.77	.055	.061	.29	.21
Pharmacologic properties of the drug	15 (8.5)	2 (4.7)	1 (5.3)	3 (3.1)	.34	—	—	—	—	—	—
Availability of an antidote	2 (1.1)	6 (14.0)	0 (0)	0 (0)	<.001	<.001	1.00	.54	.17	<.001	NC
No need for blood monitoring during follow-up	54 (30.5)	13 (30.2)	10 (52.6)	54 (55.7)	<.001	.97	.051	<.001	.092	.005	.81
Availability of laboratory tests to measure the anticoagulant effect	2 (1.1)	0 (0)	0 (0)	2 (2.1)	.83	—	—	—	—	—	—
Many years of clinical experience with this drug	10 (5.6)	2 (4.7)	0 (0)	3 (3.1)	.74	—	—	—	—	—	—
Favorable safety profile of the drug	79 (44.6)	15 (34.9)	5 (26.3)	17 (17.5)	<.001	.25	.13	<.001	.51	.024	.35
Proven efficacy of the drug in this setting	10 (5.6)	18 (41.9)	0 (0)	12 (12.4)	<.001	<.001	.60	.050	<.001	<.001	.21
Patient's high risk of bleeding	14 (7.9)	0 (0)	1 (5.3)	8 (8.2)	.21	—	—	—	—	—	—
Patient's high risk of thrombosis extension	9 (5.1)	1 (2.3)	1 (5.3)	4 (4.1)	.92	—	—	—	—	—	—
Patient's demographic characteristics	12 (6.8)	10 (23.3)	1 (5.3)	3 (3.1)	.002	.003	1.00	.20	.15	<.001	.52
Patient's comorbidities	9 (5.1)	1 (2.3)	1 (5.3)	2 (2.1)	.57	—	—	—	—	—	—
Patient's preference (as reported by the prescriber)	48 (27.1)	8 (18.6)	8 (42.1)	32 (33.0)	.18	—	—	—	—	—	—
Expected higher patient's adherence	13 (7.3)	4 (9.3)	3 (15.8)	21 (21.6)	.006	.75	.19	<.001	.67	.078	.76
Drug licensed by regulatory authorities for this indication	1 (0.6)	0 (0)	0 (0)	0 (0)	1.00	—	—	—	—	—	—
Guidelines recommendations	5 (2.8)	0 (0)	0 (0)	3 (3.1)	.86	—	—	—	—	—	—
Results of currently available literature	4 (2.3)	7 (16.3)	0 (0)	3 (3.1)	.004	.001	1.00	.70	.089	.010	1.00
Physician's experience when treating patients with this condition	35 (19.8)	3 (7.0)	4 (21.1)	5 (5.2)	.002	.046	1.00	.001	.19	.70	.039

Values are *n* (%). The rationale was available in 177 of 186 patients receiving apixaban, 43 of 43 patients receiving dabigatran, 19 of 19 patients receiving edoxaban, and 97 of 101 patients receiving rivaroxaban.

A, apixaban; D, dabigatran; E, edoxaban; NC, not computable (because the number of choices was 0 in both groups); R, rivaroxaban.

The present analysis explored, for the first time, the rationale for choosing DOACs in real-life patients with USVTE. The most frequently chosen reasons included the oral administration (43.2%), the lack of need for blood monitoring during follow-up (39.0%), the favorable safety profile of the drug (34.5%), and prescriber-reported patient preference (28.6%). A previous physicians' survey, based on 4 clinical vignettes involving patients with CVT and SVT, also identified these as the most common reasons for selecting DOACs with percentages similar to the present study (oral administration in 50.6%, lack of need for blood monitoring in 48.1%, and favorable safety profile in 43.4%) [13].

While it is well known that the DOACs offer several pharmacokinetic and pharmacodynamic advantages over traditional anticoagulant drugs and they are nowadays the standard of care for usual site VTE, the evidence supporting their use in USVTE remains relatively modest [12]. Studying the rationale behind physicians' treatment decisions in real-life clinical practice is particularly valuable in gray areas where evidence is limited. This analysis suggests that physicians' decisions were influenced by a combination of patient-related factors (eg, patients' preference, although reported by the prescribers), drug-related factors (eg, oral administration and lack of need for monitoring), and prescriber-related factors (eg, physicians' personal experience). The present analysis also showed that patient preference was cited in approximately a third of cases, highlighting the importance of patient-centered care in anticoagulation management. Patient-centered approaches (such as

using educational material or shared decision-making tools) have the potential to improve medication adherence [32,33].

The differences in the rationale for prescribing each DOACs reflect the peculiarities of the individual drugs. Among all DOACs, dabigatran had the highest proportion of physicians selecting proven efficacy of the drug in this setting and results of currently available literature. Dabigatran, in fact, was the first DOAC to be evaluated in USVTE with an RCT (RESPECT-CVT), which randomized 120 patients with CVT to dabigatran or VKA and was published in 2019 [16]. Notably, the enrolment period of the DUST study spanned from 2018 to 2023, meaning that the results of this RCT became available early during the course of this study. More recent evidence supporting the use of rivaroxaban in adult patients with CVT comes from another RCT (the SECRET study), which randomized 55 patients to rivaroxaban or standard anticoagulation (LMWH or VKA) but was published only in 2023 [18]. Apixaban had the highest proportion of physicians selecting favorable safety profile of the drug, likely due to its very low risk of major bleeding and gastrointestinal bleeding reported in several cohorts of patients with atrial fibrillation and usual site VTE [34–36]. Edoxaban and rivaroxaban had the highest proportion of physicians selecting expected higher patient's adherence, possibly due to their once daily dosing, in contrast to the twice daily dosing required for apixaban and dabigatran.

The DOAC prescription patterns and the rationale for choosing DOAC showed some differences according to the site of unusual VTE and the dose of DOAC. Patients with SVT were more likely to receive apixaban, while patients with CVT were more likely to receive dabigatran. Additionally, route of administration of the drug was chosen more frequently in patients with SVT, while proven efficacy of the drug in this setting in patients with CVT. Indeed, the reported favorable safety profile of apixaban [34–36] may be particularly advantageous in patients with SVT, who are at higher risk of bleeding. Furthermore, the oral route of administration may also be beneficial in this population, considering that two-thirds of patients with SVT were initially treated with parenteral anticoagulants. For patients with CVT, the preference for dabigatran may reflect the availability of a dedicated RCT in this population [16], which likely contributed to the perception of efficacy in this setting. Regarding the dose of DOAC, route of administration of the drug was more commonly cited for patients receiving reduced-dose DOAC, while proven efficacy of the drug in this setting was more commonly cited for patients receiving regular-dose DOAC, despite recent evidence on the efficacy of low-dose DOAC in SVT [20,37]. However, this analysis should be interpreted as a snapshot of clinicians' decision making in areas of limited evidence, rather than as an endorsement of any specific DOAC strategy.

The main strengths of the DUST study include the multicenter design, which allowed the enrolment of a large number of patients with USVTE from various countries, the ability to describe real-world DOAC prescription patterns, and the impact of individual patients' characteristics on treatment choices. The systematic assessment of the physicians' prescribing rationale (through a structured evaluation with multiple-choice options) provides insights into the decision making in these complex clinical scenarios. However, several limitations should be acknowledged. First, being an observational registry of patients receiving DOAC treatment for USVTE, this study is subject to confounding by indication, since only patients for whom DOACs were deemed beneficial were included. This might have been reflected in the prescribing rationales predominantly favorable toward DOACs. Second, although many patients received non-DOAC anticoagulants as initial therapy, this study did not include a comparator group of patients with USVTE who remained on non-DOAC anticoagulants. As such, it does not allow for a direct comparison of prescription patterns or treatment rationale between DOACs and other anticoagulants. Third, despite being one of the largest cohorts of USVTE, the number of patients which certain specific conditions (eg, OVT or RVT) or receiving less commonly prescribed DOACs (eg, edoxaban) was too small to allow for informative subgroup analyses.

In conclusion, DOACs are increasingly prescribed for USVTE in real-life practice, typically after initial treatment with parenteral anticoagulation. These findings provide insight into current prescribing patterns and physician rationale.

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AUTHOR CONTRIBUTIONS

N.R.: conceptualization, methodology, investigation, data curation, formal analysis, funding acquisition, project administration, writing—original draft. L.B.: methodology, investigation, resources, funding acquisition, writing—review and editing. A.C., V.DS., S.B., M.P.D., M.T.S., F.C., M.S., A.G., O.C., C.F., A.M., I.M., J.C., P.R.-A., G.G., L.J.-P., G.M.P., A.S., P.R., J.L., and M.A.S.: investigation, resources, writing—review and editing. S.K.: methodology, investigation, resources, writing—review and editing. W.A.: conceptualization, methodology, investigation, resources, funding acquisition, supervision, writing—original draft. All authors have read and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

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