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ORIGINAL RESEARCH

# Direct Oral Anticoagulants in Patients With Inherited Thrombophilia and Venous Thromboembolism: A Prospective Cohort Study

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**BACKGROUND:** In this prospective cohort study, we aimed to evaluate the efficacy and safety of direct oral anticoagulants (DOACs) versus heparin/vitamin K antagonists for the treatment of venous thromboembolism (VTE) in patients with inherited thrombophilia.

**METHODS AND RESULTS:** We enrolled consecutive patients with acute VTE and inherited thrombophilia treated with DOACs (cases) or heparin/vitamin K antagonists (controls), matched for age, sex, ethnicity, and thrombophilia type. End points were VTE recurrence and bleeding complications; residual vein thrombosis and post-thrombotic syndrome; VTE recurrence after anticoagulant discontinuation. Two hundred fifty-five cases (age 52.4±17.3 years, Female 44.3%, severe thrombophilia 33.1%) and 322 controls (age 49.7±18.1 years, Female 50.3%, severe thrombophilia 35.1%) were included. The cumulative incidence of VTE recurrence during anticoagulation was 1.09% in cases versus 1.83%, adjusted hazard ratio (HR) 0.67 (95% CI, 0.16–2.77). The cumulative incidence of bleeding was 10.2% in cases versus 4.97%, HR 2.24 (95% CI 1.10–4.58). No major bleedings occurred in cases (versus 3 in controls). No significant differences regarding residual vein thrombosis and post-thrombotic syndrome. After anticoagulant discontinuation, DOACs yielded a significantly lower 2-year VTE recurrence risk versus traditional anticoagulants (HR, 0.61 [95% CI, 0.47–0.82]).

**CONCLUSIONS:** DOACs and heparin/vitamin K antagonists showed a similar efficacy in treating VTE in patients with thrombophilia. Although major bleeding episodes were recorded solely with heparin/vitamin K antagonists, we noted an overall increased bleeding rate with DOACs. The use of DOACs was associated with a lower 2-year risk of VTE recurrence after anticoagulant discontinuation.

**Key Words:** anticoagulation ■ hypercoagulopathy ■ pulmonary embolism ■ thrombosis ■ vitamin K antagonists

Inherited thrombophilia is a genetically determined predisposition to develop venous thromboembolism (VTE).[1] The most common genetic defects observed in clinical practice are deficiency of naturally occurring anticoagulants (antithrombin [AT], PC [protein C], PS [protein S]), and gain-of-function polymorphisms (factor V Leiden [FVL] and the prothrombin gene variant [PT20210A]).[1,2] It is generally accepted that deficiencies of AT, PC, PS, and homozygous gain-of-function mutations cause severe thrombophilia versus mild thrombophilia in heterozygous FVL or PT20210A mutations.[3–6] Rare genetic disorders responsible for severe thrombophilia have been identified more recently, including pseudo-homozygosity

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## CLINICAL PERSPECTIVE

### What Is New?

- This is a prospective cohort study showing that direct oral anticoagulants are effective and safe for the treatment of venous thromboembolism in patients with hereditary thrombophilia, though causing an increased risk of clinically relevant nonmajor bleedings compared with heparin/vitamin K antagonists.
- The use of direct oral anticoagulants was associated with a lower 2-year risk of venous thromboembolism recurrence after anticoagulant discontinuation.

### What Are the Clinical Implications?

- Clinicians can prescribe safely direct oral anticoagulants in patients with hereditary thrombophilia—even severe—provided that female patients be warned of the possible occurrence of abnormal uterine bleeding with factor Xa inhibitors.
- If the lower risk of venous thromboembolism recurrence after anticoagulation discontinuation will be confirmed by ad hoc studies, direct oral anticoagulants could become the treatment of choice for venous thromboembolism in patients with inherited thrombophilia.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **AT** | antithrombin |
| **CRNMB** | clinically relevant nonmajor bleeding |
| **DOACs** | direct oral anticoagulants |
| **FVL** | factor V Leiden |
| **IR** | incidence rate |
| **PC** | protein C |
| **PS** | protein S |
| **PT20210A** | prothrombin gene variant |
| **PTS** | post-thrombotic syndrome |
| **RVT** | residual vein thrombosis |
| **VKAs** | vitamin K antagonists |

for activated protein C resistance, factor IX Padua, and the resistance to AT due to prothrombin mutation.[2,7–9] Inherited thrombophilia results in various clinical manifestations—predominantly VTE—which may require anticoagulant therapy. The 2016 guidelines on antithrombotic therapy for VTE by the American College of Chest Physicians recommend that the choice of anticoagulant be based on patient-specific factors such as renal/liver/coronary artery diseases, adherence, and patient's preference, while nonetheless favoring direct oral anticoagulants (DOACs) over more traditional treatments (vitamin K antagonists—VKAs).[10] However, there are no specific recommendations on the treatment of VTE in patients with inherited thrombophilia. Although multiple randomized controlled trials on the efficacy of DOACs versus warfarin in the treatment of acute VTE or secondary prevention have yielded positive results,[11–14] patients with inherited thrombophilia only accounted for 2% to 18% of those treated with DOACs.[15] A post hoc analysis of data from clinical trials concluded that the efficacy and safety of dabigatran were not significantly affected by the presence of thrombophilia.[16] Furthermore, some case reports have provided conflicting results on the efficacy of DOACs in patients with inherited thrombophilia and VTE,[15,17] whereas a very recent systematic review suggested that DOACs may be effective in this population.[18] However, the efficacy of DOACs might be hampered in patients with thrombophilia because of the peculiar hemostatic alterations stemming from these inherited disorders.[17]

The aim of this prospective cohort study was to evaluate the rate of recurrent VTE and bleeding complications in patients with inherited thrombophilia and VTE treated with DOACs versus traditional anticoagulants, such as low molecular weight heparin or VKAs.

## METHODS

### Study Participants

The data that support the findings of this study are available from the corresponding author upon reasonable request.

We enrolled all consecutive adult patients with a confirmed diagnosis of acute deep vein thrombosis (DVT) and/or pulmonary embolism referred to the Thrombotic Unit of Padova University Hospital between January 2014 and December 2019, identified as thrombophilia carriers and treated with DOACs for at least 3 months. Consecutive patients with thrombophilia referred to our center between January 2012 and December 2019 and treated for at least 3 months with VKAs or heparin for an acute VTE acted as controls. They were matched with cases for age (±3 years), sex, ethnic origin, and thrombophilia type. Exclusion criteria were (1) thrombolytic therapy or inferior vena cava filter for the index event, (2) anticoagulant therapy for <3 months, (3) unconfirmed thrombophilia, (4) incomplete follow-up, and (5) antiphospholipid antibody-positive. Enrolled patients signed an informed consent form and the study protocol was approved by the Local Ethical Committee (4303/AO/17), in compliance with the Declaration of Helsinki. The choice and

duration of anticoagulant treatment followed international guidelines with individual adaptation based on physicians' assessment of patients' benefit-risk profile.

VTE was defined as objectively proven pulmonary embolism, lower extremity DVT, upper extremity DVT, or splanchnic DVT. Pulmonary embolism was diagnosed by contrast-enhanced lung computed tomography or by ventilation perfusion (V/Q) lung scan; DVT was confirmed by (compression) ultrasonography in accordance with current guidelines.[19] Isolated distal (calf) DVT or proximal DVT were included. Splanchnic DVT was diagnosed by contrast-enhanced abdomen computed tomography. VTE was classified as provoked if it occurred within 3 months after exposure to exogenous risk factors including surgery, immobilization >5 days, trauma, pregnancy/puerperium, use of oral contraceptives or hormonal replacement therapy, acute medical condition, or malignancy. Otherwise, VTE was classified as unprovoked.

## Thrombophilia Diagnosis

The decision for thrombophilia testing followed international recommendations.[20] In particular, patients with VTE were tested if they fulfilled any of the following criteria: (1) age (≤60 years), (2) strong family history of VTE, (3) VTE associated with weak provoking factors at a young age, (4) recurrent VTE, and (5) VTE in an unusual site. All enrolled patients were screened for AT, PC, PS deficiencies, FVL, and PT20210A mutations, as well as rare inherited thrombophilias (pseudo-homozygous FVL and AT resistance). AT, PC, PS activity, and antigen levels as well as activated protein C resistance were measured as previously reported.[9,21] The criteria used for the classification of AT, PC, and PS defects were in line with the current literature.[6,22] Reduced levels of anticoagulant factors (activity and/or antigen) were confirmed in 2 consecutive determinations and in at least 1 first-degree relative. FVL and PT20210A were detected by GeneXpert HemosIL® F5 and F2 assay (Cepheid, Sunnyvale, CA, USA).[23] We measured the activity of factors II, V, VIII, and IX on a BCS®XP coagulometer (Siemens) with the specific factor-deficient plasma (Siemens). AT resistance (Prothrombin Padua 2 mutation [c.1786C>T; p.Arg596Trp]) was previously detected by direct sequencing of exon 14 of F2 gene.[9]

## Study Outcomes

The primary outcomes were incidence rates of symptomatic recurrent VTE and bleeding complications (major, clinically relevant nonmajor, minor bleedings) during anticoagulation in patients with VTE and inherited thrombophilia. The secondary outcomes were incidence of residual vein thrombosis, incidence of post-thrombotic syndrome, and incidence of VTE recurrence after anticoagulant discontinuation.

Recurrent venous thromboembolism was defined as a new symptomatic intraluminal filling defect or symptomatic extension of a preexisting defect at lung computed tomography, 1 or more new symptomatic filling defects at a second compressive ultrasound not evident on the initial imaging, or after an interval imaging test clearly showing thrombus resolution. Major bleeding was defined as overt bleeding associated with a drop in hemoglobin ≥2 g/dL, a transfusion ≥2 units of packed red blood cells, bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal), or contributed to death. Clinically relevant nonmajor bleeding (CRNMB) was defined as any sign or symptom of hemorrhage that did not fit the definition of major bleeding but fulfilled at least 1 of the following criteria: (1) requiring medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, and (3) prompting a face-to-face evaluation.[24]

Residual vein thrombosis (RVT) was defined as the persistent presence of a venous thrombus ≥4 mm in diameter 3 months after the index event.[25,26] The development of post-thrombotic signs and symptoms (PTS) were assessed using the Villalta scale[27] at predefined times (6 and 12 months after the index event) during the follow-up.

Study outcomes were evaluated at 3, 6, and 12 months after the index event during scheduled outpatient visits. Patients were instructed to report to our center if they presented symptoms suggestive of recurrent VTE or bleeding. Patients were followed up to monitor the development of recurrence for up to 2 years after anticoagulant discontinuation.

## Statistical Analysis

Analyses included descriptive statistics of the study population (frequencies for qualitative variables, and mean±SD/median and range interquartile for quantitative variables). To limit the impact of selection bias, cases and controls were matched for age (±3 years), sex, ethnicity, and thrombophilia type using SPSS Case-Control Matching (IBM SPSS Statistics 24.0). The chi-square test (using a mid-P approach to Fisher's exact test) was used for categorical variables, whereas the Student *t* test or Mann–Whitney test was used for continuous variables, as appropriate. For the primary outcomes (symptomatic recurrence or bleeding while undergoing anticoagulation), the incidence rates (IR) and 95% CI were estimated after calculating person-times of anticoagulation. The rate ratio (RR) between cases and controls were estimated by conditional maximum-likelihood estimate with exact confidence limits. The cumulative incidence for recurrence or bleeding during anticoagulation therapy

was estimated using the Kaplan-Meier method and compared by log-rank test. The hazard ratios (HRs) and 95% CI for the time to first development of VTE or bleeding were estimated using the Cox proportional hazard model and adjusted for effect of age, sex, body mass index (BMI), and presence of severe thrombophilia. For the secondary outcomes (RVT 3 months after index event and post-thrombotic syndrome 12 months after index event), odds ratios (ORs) and 95% CI, adjusted for age, sex, BMI, presence of severe thrombophilia, VTE etiology (provoked/unprovoked), and anticoagulation duration were calculated by logistic regression. Finally, time to first development of VTE recurrence after anticoagulant discontinuation were estimated using the Cox proportional hazard regression and depicting survival curves using the Kaplan-Meier method. HRs and 95% CI were calculated and adjusted for age, sex, BMI, presence of severe thrombophilia, anticoagulation duration, VTE etiology (provoked/unprovoked), and extended therapy with low-dose DOACs. Statistical analysis was performed using OpenEpi (www.openepi.com), PASW Statistics 24.0 (IBM Inc., Armonk, NY, USA) for Windows, and MedCalc statistical software.

## RESULTS

Among 652 patients with VTE and hereditary thrombophilia admitted to our unit during the study period, 55 patients (8.4%) were excluded for unconfirmed thrombophilia (n. 16), anticoagulation treatment <3 months (n. 10), incomplete follow-up (n. 21), concomitant antiphospholipid antibodies (n. 3), refusal to participate (n. 5). Overall, 597 patients with VTE and hereditary thrombophilia were enrolled: 275 (46.1%) cases treated with DOACs and 322 (53.9%) controls treated with heparin/VKAs. Among cases, the mean age was 52.4±17.3 years versus 49.7±18.1 years (*P*=0.063); females were 122 (44.3%) versus 162 (50.3%, *P*=0.14); and patients with severe thrombophilia were 91 (33.1%) versus 113 (35.1%, *P*=0.52). The main characteristics of the study population are reported in Table 1. Among cases, 168 (61.1%) patients were treated with rivaroxaban, 55 (20%) with apixaban, 36 (13.1%) with edoxaban, and 16 (5.8%) with dabigatran (Table 2). Median anticoagulation duration was similar in both groups (12 [6–20.75] months in cases versus 10 [6–24] months in controls). A significantly higher proportion of cases received long-term anticoagulation 28.4% versus 20.1% (*P*=0.02) (Table 2).

**Table 1. Characteristics of the Study Population**

| | DOACs (n. 275) | VKAs/Heparin (n. 322) | *P* Value |
|---|---|---|---|
| Female, n (%) | 122 (44.3) | 162 (50.3) | 0.14 |
| Age, mean y (±SD) | 52.4 (±17.3) | 49.7 (±18.1) | 0.063 |
| Body mass index, mean kg/m$^2$ (±SD) | 26.4 (±4.7) | 26.5 (±4.9) | 0.79 |
| Mild thrombophilia, n (%) | 184 (66.9) | 209 (64.9) | 0.60 |
| FVL hetero | 105 | 118 | |
| PT hetero | 79 | 91 | |
| Severe thrombophilia, n (%) | 91 (33.1) | 113 (35.1) | 0.52 |
| PC deficiency* | 15 | 30 | |
| PS deficiency* | 29 | 32 | |
| AT deficiency | 13 | 16 | |
| FVL homo | 9 | 9 | |
| PT homo | 1 | 2 | |
| Compound hetero | 18† | 18‡ | |
| Pseudo-homo FVL | 4 | 5 | |
| AT resistance | 2 | 1 | |
| Previous VTE, n (%) | 60 (21.8) | 59 (18.3) | 0.28 |
| VTE etiology, n (%) | | | |
| Provoked | 103 (37.5) | 144 (44.7) | 0.073 |
| Unprovoked | 172 (62.5) | 178 (55.2) | |
| VTE risk factors, n (%) | | | |
| Trauma or surgery | 24 (23.3) | 37 (25.7) | 0.27 |
| Immobilization | 21 (20.4) | 19 (13.2) | 0.40 |
| Pregnancy/hormones | 37 (35.9) | 50 (34.7) | 0.56 |
| Acute medical condition | 11 (10.7) | 17 (11.8) | 0.47 |
| Cancer | 10 (9.7) | 21 (14.6) | 0.12 |
| VTE type, n (%) | | | |
| PE | 58 (21.1) | 49 (15.2) | 0.063 |
| PE and DVT | 70 (25.4) | 71 (22) | 0.33 |
| DVT | 147 (53.5) | 202 (62.7) | 0.022 |
| DVT site, n (%) | | | |
| Femoral and/or popliteal | 171 (78.8) | 224 (82) | 0.37 |
| Isolated distal | 35 (16.1) | 35 (12.8) | 0.30 |
| Upper extremity | 8 (3.7) | 7 (2.6) | 0.48 |
| Splanchnic | 3 (1.4) | 7 (2.6) | 0.38 |

Qualitative variables are expressed as frequencies, quantitative as mean and SD. Comparisons are reported as *P* (chi-square or Student *t* test, as appropriate). AT indicates antithrombin; DOACs, direct oral anticoagulants; DVT, deep vein thrombosis; FVL, factor V Leiden; hetero, heterozygous; homo, homozygous; PC, protein C; PE, pulmonary embolism; PS, protein S; PT, prothrombin mutation G20210A; VKAs, vitamin K antagonists; VTE, venous thromboembolism.

*No homozygous PC or PS deficiency were enrolled.

†15 FVL+PT hetero, 2 FVL hetero+PS deficiency, 1 PT hetero+PS deficiency.

‡14 FVL+PT hetero, 2 FVL homo+PT hetero, 1 PT hetero+PC deficiency, 1 PT hetero+PS deficiency.

### VTE Recurrence and Bleedings During Anticoagulation

Considering the overall anticoagulation duration of 378 patients-year in cases versus 659 patients-year in controls, we recorded 3/275 symptomatic VTE recurrence in the former versus 6/322 in the latter. The IR of recurrent VTE during anticoagulation was 7.9/1000 patients-year (95% CI, 1.59–23.2) in cases versus

**Table 2. Type and Duration of Anticoagulation Therapy in the Study Population**

| | DOACs (n. 275) | VKAs/Heparin (n. 322) | *P* Value |
|---|---|---|---|
| Type of anticoagulant, n (%) | | | |
| Apixaban | 55 (20) | … | |
| Dabigatran | 16 (5.8) | … | … |
| Edoxaban | 36 (13.1) | … | |
| Rivaroxaban | 168 (61.1) | … | |
| Warfarin | … | 249 (77.3) | |
| Low molecular weight heparin/Fondaparinux | … | 73 (22.7) | |
| Anticoagulation duration, median mo [IQR] | 12 [6–20.75] | 10 [6–24] | 0.70 |
| Long-term anticoagulation, n (%) | 78 (28.4) | 65 (20.1) | 0.02 |
| Extension with low-dose DOACs, n (%) | 65 (23.6) | 41 (12.7) | 0.0005 |
| Follow-up duration, median mo [IQR] | 17.5 [9–24] | 24 [11–24] | 0.053 |

Qualitative variables are expressed as frequencies, quantitative as median and range interquartile. Comparisons are reported as *P* (chi-square and Mann–Whitney test, as appropriate). DOACs indicates direct oral anticoagulants; IQR, range interquartile; and VKAs, vitamin K antagonists.

9.1/1000 patients-year (95% CI, 3.34–19.8), with an unadjusted RR 0.87 (95% CI, 0.18–3.50). The cumulative incidence of recurrence during the anticoagulation period was 1.09% (95% CI, 0.22–3.31%) in cases versus 1.83% (95% CI, 0.74–4.3%; Figure [A]), adjusted HR 0.67 (95% CI, 0.16–2.77) (Table 3). Detailed characteristics of patients who experienced VTE recurrence are reported in Table S1—2/6 controls (33%) showed levels of anticoagulation below the therapeutic range at the time of recurrence.

Considering the overall anticoagulation duration, bleeding events occurred in 28/275 cases and 16/322 controls. The IR of bleeding during anticoagulation was 7.4/100 patients-year (95% CI, 4.92–10.71) in cases versus 2.43/100 patients-year (95% CI, 1.39–3.94), with an unadjusted RR 3.05 (95% CI, 1.66–5.76). The cumulative incidence of bleeding during the anticoagulation period was 10.2% (95% CI, 7.09–14.36%) in cases versus 4.97% (95% CI, 3.02–7.97%; Figure [B]), with an adjusted HR 2.24 (95% CI, 1.10–4.58) (Table 3). Other risk factors independently associated with bleeding were age (HR, 1.02 [95% CI, 1.01–1.04]) and BMI (HR, 0.87 [95% CI, 0.78–0.96]).

We observed no major bleedings in cases versus 3/16 (18.75%) in controls (IR=4.55/1000 persons-year [95% CI, 0.93–13.3]): 2 cerebral hemorrhages and 1 gastrointestinal bleeding (melena). Considering only CRNMB, we documented 16/28 (57.1%) events in cases versus 5/16 (31.25%) in controls. The IR was 4.23/100 patients-year (95% CI, 2.42–6.87) in cases versus 0.75/100 patients-year (95% CI, 0.24–1.77), with an unadjusted RR 5.58 (95% CI, 2.11–17.03). The cumulative incidence of CRNMB during the anticoagulation period was 5.82% (95% CI, 3.55–9.3%) in cases versus 1.55% (95% CI, 0.56–3.69%; Figure [C]), adjusted HR 3.75 (95% CI, 1.25–11.29) (Table 3). Among 16 CRNMB events observed in cases, 7 (43.7%) were menometrorrhagia and 3 (18.7%) were macrohematuria in men. We recorded no CRNM menometrorrhagia among controls (Table 4).

## VTE Recurrence and Bleedings During Anticoagulation in Severe Thrombophilia

As it pertains to severe thrombophilia and considering the overall anticoagulation time of 151 patients-year in cases and 296 patients-year in controls, we recorded 2/91 VTE recurrence in the former versus 2/113 in the latter. The IR of VTE recurrence during anticoagulation was 1.32/100 patients-year (95% CI, 0.15–4.78) in cases versus 0.69/100 patients-year (95% CI, 0.08–2.52), with an unadjusted RR 1.89 (95% CI, 0.19–19.2). The cumulative incidence of recurrence during anticoagulation in severe thrombophilia was 2.2% (95% CI 0.13–8.14%) in cases versus 1.77% (95% CI 0.09–6.62%).

With regard to bleeding complications, 10 episodes were documented in cases versus 5 in controls. The IR of bleeding was 6.62/100 patients-year (95% CI, 3.17–12.2) in cases versus 1.74/100 patients-year (95% CI, 0.56–4.08), with an unadjusted RR 3.78 (95% CI, 1.30–12.27). The cumulative incidence of bleeding during the anticoagulation period in severe thrombophilia was 10.9% (95% CI, 5.89–19.2%) in cases versus 4.42% (95% CI, 1.64–10.2%).

## Residual Vein Thrombosis and Post-Thrombotic Syndrome

After 3 months of anticoagulation, RVT was detected in 82/217 cases with DVT (37.8% [95% CI, 31.6–44.4]) and in 99/273 controls with DVT (36.2% [95% CI, 30.79–42.12]) with an unadjusted OR 1.11 (95% CI, 0.77–1.60). After adjustment for age, sex, BMI, VTE etiology (provoked/unprovoked), and presence

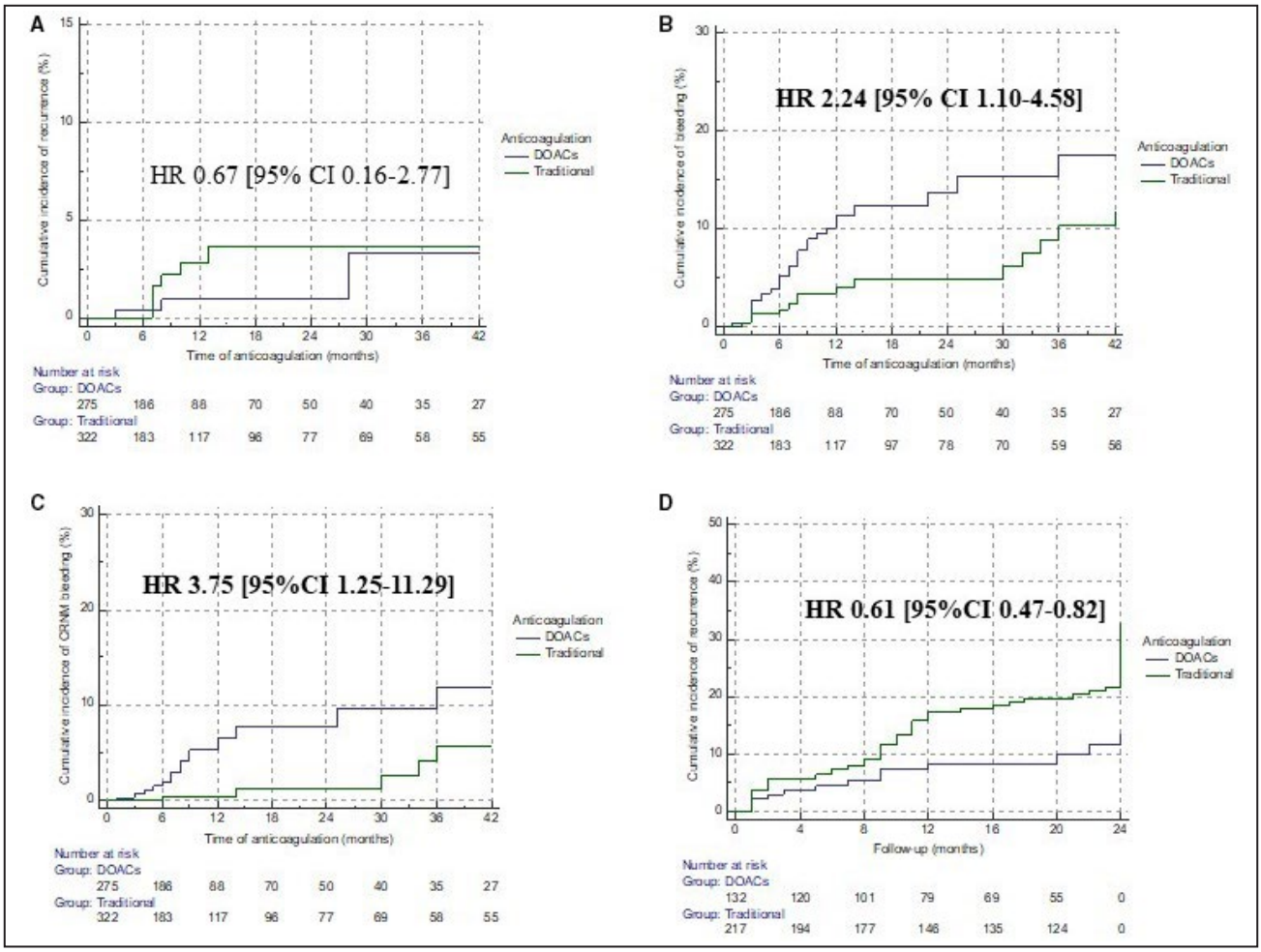


**Figure. Cumulative incidence of the study outcomes in patients treated with DOACs vs traditional anticoagulation.** **A**, Cumulative incidence of recurrent venous thromboembolism during anticoagulation (Log rank test *P*=0.39). **B**, Cumulative incidence of bleeding during anticoagulation (Log rank test *P*=0.015). **C**, Cumulative incidence of nonmajor clinically relevant (CRNM) bleeding (Log rank test *P*=0.0045). **D**, Cumulative incidence of recurrent venous thromboembolism after stopping anticoagulation during 2 years follow-up (Log rank test *P*=0.0033). DOAC indicates direct oral anticoagulant; and HR, hazard ratio.

of severe thrombophilia the OR was 1.05 (95% CI, 0.68–1.61).

After 12 months of anticoagulation, PTS was diagnosed in 45/217 cases with DVT (20.7% [95% CI, 15.85–26.64]) versus 61/273 controls with DVT (22.3% [95% CI, 17.79–27.66]), with an unadjusted OR 0.95 (95% CI, 0.61–1.46). After adjustment for age, sex, BMI, VTE etiology (provoked/unprovoked), presence of severe thrombophilia, and duration of anticoagulation the OR was 1.04 (95% CI, 0.62–1.74).

## VTE Recurrence After Discontinuation of Anticoagulation

One hundred thirty-two cases and 217 controls who discontinued anticoagulant therapy were followed up for 2 years. Patients' characteristics were comparable, as seen in Table S2.

During the 2-year follow-up, recurrent VTE occurred in 13/132 cases (9.85% [95% CI, 5.73–16.24]) versus 46/217 controls (21.2% [95% CI, 16.26–27.14]), with an unadjusted HR 0.54 (95% CI, 0.33–0.87) (log-rank test *P*=0.0033). The HR remained statistically significant even after adjustment for age, sex, BMI, duration of anticoagulation, etiology of VTE (provoked/unprovoked), presence of severe thrombophilia, and extended anticoagulation therapy with low-dose DOACs (HR, 0.61 [95% CI, 0.47–0.82]) (Figure [D]). Other independent predictors of recurrent VTE were age (HR, 1.02; 95% CI, 1.00–1.04), male sex (HR, 1.52; 95% CI, 1.09–2.26), and unprovoked venous thrombosis (HR, 1.69; 95% CI, 1.49–2.28).

# DISCUSSION

In patients with VTE, DOACs have shown promising results with regard to improving safety profile and

**Table 3. Outcomes in Patients with Thrombophilia With VTE in Relation to Anticoagulation**

| | DOACs (n. 275) | VKAs/Heparin (n. 322) | HR [95% CI]* |
|---|---|---|---|
| Recurrent VTE/1000 patient-y (95% CI) | 7.9 (1.59–23.2) | 9.1 (3.34–19.8) | 0.67 [0.16–2.77] |
| Any bleeding/100 patient-y (95% CI) | 7.4 (4.92–10.71) | 2.43 (1.39–3.94) | 2.24 [1.10–4.58] |
| Major bleeding/1000 patient-y (95% CI) | 0 | 4.55 (0.93–13.3) | … |
| Clinically relevant nonmajor bleeding/100 patient-y (95% CI) | 4.23 (2.42–6.87) | 0.75 (0.24–1.77) | 3.75 [1.25–11.29] |
| | **DOACs With DVT (n. 217)** | **VKAs/Heparin With DVT (n. 273)** | **OR [95% CI]** |
| Residual vein thrombosis, n (%) | 82 (37.8) | 99 (36.2) | 1.05 [0.68–1.61]‡ |
| Post-thrombotic syndrome, n (%) | 45 (20.7) | 61 (22.3) | 1.04 [0.62–1.74]§ |

DOACs indicates direct oral anticoagulants; DVT, deep vein thrombosis; HR, hazard ratio; OR, odds ratio; VKAs, vitamin K antagonists; and VTE, venous thromboembolism.

*HR adjusted for age, sex, body mass index, and presence of severe thrombophilia.

‡OR adjusted for age, sex, body mass index, VTE etiology (provoked/unprovoked), and presence of severe thrombophilia.

§OR adjusted for age, sex, body mass index, VTE etiology (provoked/unprovoked), presence of severe thrombophilia and duration of anticoagulation.

quality of life, and reducing costs associated with long-term anticoagulation, even in highly prothrombotic conditions like cancer. However, the recent Trial on Rivaroxaban in Antiphospholipid Syndrome showed no benefit and excessive risk for rivaroxaban versus warfarin in the treatment of high-risk antiphospholipid syndrome,[28] indicating that DOACs may have less efficacy than traditional anticoagulants in high-risk thrombophilia.

In our prospective cohort study, we enrolled consecutive patients with acute VTE and a confirmed diagnosis of inherited thrombophilia and the efficacy of DOACs was similar to that of heparin/VKAs for VTE treatment. In addition, the efficacy of DOACs has also been confirmed in severe thrombophilia. Regarding the safety profile, DOACs have been linked to an increased risk of CRNMB in patients with thrombophilia. Interestingly enough, DOACs appeared to significantly reduce the 2-year risk of VTE recurrence after anticoagulant discontinuation. This finding may have a significant bearing on the choice of VTE treatment in patients with inherited thrombophilia.

A recent systematic review and meta-analysis by Elsebaie et al[18] showed the efficacy of DOACs for the prevention of VTE recurrence (RR 1.02; 95% CI, 0.80–1.30; $I^2$=46%, versus VKAs) in patients with inherited thrombophilia. However, severe defects were poorly represented and the efficacy of apixaban was not evaluated. A post hoc analysis compared dabigatran with warfarin for the treatment of VTE in patients with inherited thrombophilia and found no significant differences in symptomatic VTE/VTE-related deaths

**Table 4. Bleeding Complications During Anticoagulant Treatment in the Study Population**

| | DOACs (n. 275) | VKAs/Heparin (n. 322) |
|---|---|---|
| Overall, n (% out of total population) | 28 (10.2) | 16 (4.97) |
| Major, n (% out of overall bleedings) | 0 | 3 (18.75) |
| Site | … | 2 Intracranial hemorrhages<br>1 GI hemorrhage (melena) |
| Clinically relevant nonmajor, n (% out of overall bleedings)<br>Site | 16 (57.1)<br>7 Meno-metrorrhagia<br>2 GI hemorrhage (melena)<br>3 Macrohematuria<br>1 Severe anemia in CLL<br>1 Hemarthrosis<br>1 Hemoptysis<br>1 Epistaxis | 5 (31.25)<br>1 Expansion of known chronic cerebral hematoma<br>1 Hemarthrosis<br>1 Thigh hematoma<br>1 Macrohematuria<br>1 Epistaxis |
| Minor, n (% out of overall bleedings)<br>Site | 12 (42.9)<br>3 Hemorrhoid rectorrhage<br>2 Hematuria<br>2 Epistaxis<br>1 Subconjunctival hemorrhage<br>1 Iron deficiency anemia<br>1 Gingivorrhagia and hematuria<br>2 Meno-metrorrhagia | 8 (50)<br>2 Subconjunctival hemorrhage<br>2 Hematuria<br>1 Hemorrhoid rectorrhage<br>1 Epistaxis<br>1 Hemoptysis<br>1 Metrorrhagia<br>1 GI chronic bleeding |

CLL indicates chronic lymphocytic leukemia; DOACs, direct oral anticoagulants; GI, gastrointestinal; and VKAs, vitamin K antagonists.

in patients with or without thrombophilia (HR, 1.09 [95% CI 0.76–1.57]).[16] However, patients with acquired thrombophilia were also included. There are other case reports published on the use of DOACs in patients with severe thrombophilia.[15,17,18] Boey et al confirmed the efficacy of DOACs in PC deficiency, with only 1 treatment failure,[29] whereas several case reports in the literature indicate more treatment failures than successes among patients with PS deficiency treated with DOACs.[30,31]

Our study also confirmed the efficacy of DOACs in a subgroup of patients with severe thrombophilia covering the whole spectrum of severe disorders, even rare forms such as homozygous PT G20210A, pseudo-homozygous FVL, and AT resistance. Furthermore, all DOACs were evaluated in our study and the treating physician made the ultimate decision each time, apixaban and rivaroxaban being the most used drugs. The 3 cases of recurrence during anticoagulation stemmed from poor compliance in 1 case (patient 1), a further diagnosis of polycythemia vera in another (patient 2), and the development of antiphospholipid antibodies syndrome (patient 3). These observations underline the importance of follow-up in anticoagulated patients with inherited thrombophilia and periodic reassessment of the thrombotic risk as relates to the presence of additional hypercoagulable conditions (eg, cancer or antiphospholipid antibodies), especially when the index event is an unprovoked VTE.

Surprisingly enough, we found a significant increase of total bleeding events in patients with thrombophilia treated with DOACs versus heparin/VKAs. However, it bears noting that no major bleedings occurred in patients treated with DOACs whereas we recorded 3 major events—including 2 intracranial hemorrhages—in patients treated with heparin/VKAs. The aforementioned meta-analysis by Elsebaie et al[18] found no significant differences between DOACs and VKAs recipients regarding the risk of major bleeding (RR, 0.84; 95% CI, 0.32–2.19; $I^2$=0%) or risk of CRNMB (RR, 0.92; 95% CI, 0.62–1.36; $I^2$=23%). The post hoc analysis showed a trend of fewer major bleeding and CRNMB in patients with thrombophilia treated with dabigatran versus VKAs (HR, 0.51; 95% CI, 0.05–5.59 and HR, 0.48; 95% CI, 0.19–1.19).[16] We observed a significantly higher number of CRNMB in patients with thrombophilia treated with DOACs versus controls—the most reported were genitourinary hemorrhages (menometrorrhagia and macrohematuria). There is abundant evidence in the literature indicating that abnormal uterine bleeding is a common side effect of Factor Xa inhibitors.[32–36] Nevertheless, a recent post hoc analysis of the pooled RE-COVER studies and the REMEDY trial showed significantly less abnormal uterine bleeding in females with VTE treated with dabigatran versus VKAs (HR, 0.53; 95% CI, 0.34–0.83)[37]; however, abnormal uterine bleeding was not a predefined end point in the RE-COVER and RE-MEDY trials. In our study, almost all patients were treated with Factor Xa inhibitors and only 5.8% with dabigatran. All 7 uterine CRNMB observed in patients treated with DOAC occurred with Factor Xa inhibitors (5 rivaroxaban, 1 apixaban, 1 edoxaban). A very recent study by DeCamillo et al[38] conducted among young adults treated with rivaroxaban or apixaban for acute VTE, confirmed a high incidence of vaginal/heavy menstrual bleeding (71.4% of all bleeding events recorded); in this study, 4 patients out of 5 with abnormal uterine bleeding were being treated with rivaroxaban. Ad hoc studies aiming to evaluate this outcome with different DOACs are needed. In the meantime, patients should be warned of this particular side effect when prescribing anticoagulation with Factor Xa inhibitors. Hormonal therapy has not shown any association with increased risk of recurrent VTE in women receiving therapeutic anticoagulation, and may therefore be considered without contraindication.[39] Nevertheless, the long-term prothrombotic risk once anticoagulation and hormonal therapy are discontinued is unknown.

Our study also evaluated the presence of RVT and PTS as secondary outcomes. A recent study by Yoo et al[40] confirmed our previous findings[41] that thrombophilia is significantly associated with persistent RVT whereas no association was found between PTS and thrombophilia.[42] In this study, we observed no significant difference in 3-month RVT and in the occurrence of PTS in patients with thrombophilia treated with DOACs versus traditional anticoagulants. Studies conducted on patients without thrombophilia showed a more favorable profile for DOACs in reducing the risk of both RVT (OR 0.63; 95% CI, 0.48–0.81)[43] and PTS (OR 0.46; 95% CI, 0.33–0.63).[44] We hypothesize that the presence of thrombophilia may hamper the efficacy of DOACs versus VKAs with regard to RVT and PTS. However, as these were not our primary outcomes, the study may have been underpowered for detecting any significant difference.

Finally, a very promising finding of the study was that DOACs appear to significantly reduce the 2-year risk of VTE recurrence after anticoagulant discontinuation compared with VKAs. Notably, the beneficial association was independent of the duration of anticoagulation, etiology of VTE (provoked/unprovoked), presence of severe thrombophilia, and extended anticoagulant treatment with low-dose DOACs. Thus, carriers of thrombophilia may benefit from DOACs for the treatment of acute VTE and the prevention of VTE recurrence after anticoagulant discontinuation. This may be attributable to the more stable anticoagulation offered by DOACs, a potential more effective anticoagulation because of the direct inhibition of Factor Xa/IIa, or the beneficial effect of extended anticoagulant

therapy with low-dose dosages; or it may be due to chance. If these hypotheses are confirmed by ad hoc studies, DOACs could become the treatment of choice for VTE in patients with inherited thrombophilia.

Although we are fully aware that a recent meta-analysis[18] confirmed the efficacy of DOACs in treating VTE in patients with thrombophilia, ours is the first prospective study with a large cohort comprising all thrombophilia types to investigate the efficacy of DOACs in this specific population. We would be remiss not to mention some of the limitations of our study. Namely, all DOACs were not equally represented—rivaroxaban was the most used—thus our findings may be skewed and not generalizable. Study outcomes were not assessed centrally, however, precise outcomes definitions were provided and all diagnoses were confirmed. Although the control group was enrolled over a longer time span than cases for a close match (2012–2019 versus 2014–2019), our department did not implement any changes in clinical practice on diagnosis, management of patients with thrombophilia, anticoagulation duration, and detection methods of RVT and PTS between 2012 and 2014. The duration of follow-up after anticoagulant discontinuation was slightly longer for controls, though the difference was not statistically significant. Finally, the sample size of patients with severe thrombophilia was small because of the rarity of the condition. Nevertheless, diagnoses were all confirmed and all forms of severe thrombophilia were represented.

In conclusion, in this cohort of patients with a confirmed diagnosis of inherited thrombophilia—including most severe and rare forms—DOACs showed an efficacy profile comparable to that of heparin/VKAs. Additionally, DOACs proved safe in patients with thrombophilia, despite a significant increase in clinically relevant nonmajor menometrorrhagia. Similar rates of 3-month residual vein thrombosis and 12-month post-thrombotic syndrome were observed in both cohorts. DOACs were associated with a significant 2-year decrease of VTE recurrence after anticoagulant discontinuation versus heparin/VKAs. The importance of these findings in daily clinical practice cannot be overstated as they confirm the efficacy and safety of DOACs for VTE treatment and recurrence prevention in patients carrying severe and mild forms of inherited thrombophilia.

## ARTICLE INFORMATION

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### Disclosures

None.

### Supplementary Material

**Tables S1–S2**

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# SUPPLEMENTAL MATERIAL

**Table S1. Characteristics of patients with VTE recurrence during anticoagulant treatment.**

| Patient | Sex | Age, y | BMI, Kg/m$^2$ | Thrombophilia | Index event | Drug | Event | Observations | Months after starting anticoagulation |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 46 | 25.7 | PS deficiency | Femoral-popliteal unprovoked DVT | DOAC (dabigatran) | Femoral-popliteal unprovoked DVT | Poor compliance | 3 |
| 2 | F | 85 | 26 | Pseudo-homo FVL | Femoral DVT unprovoked | DOAC (apixaban) | Femoral-popliteal DVT | Polycythemia Vera | 8 |
| 3 | M | 55 | 26 | PT G20210A hetero | Femoral unprovoked DVT | DOAC (rivaroxaban) | PE and DVT | Positivity for aPL* | 11 |
| 4 | F | 75 | 22 | PT G20210A hetero | Femoral-popliteal DVT provoked by cancer | Warfarin | Bilateral DVT | breast cancer; INR in range | 2 |
| 5 | F | 42 | 35 | Double hetero | Popliteal unprovoked DVT | Warfarin | Superficial vein thrombosis up to femoral vein | INR below range | 7 |
| 6 | F | 69 | 23 | PT G20210A hetero | Femoral unprovoked DVT | Warfarin | Cerebral venous sinus thrombosis | INR in range | 15 |
| 7 | F | 73 | 24.8 | PT G20210A hetero | PE and popliteal DVT provoked by cancer | Warfarin | Distal DVT after air travel | poor INR control | 26 |
| 8 | M | 48 | 22 | FVL hetero | Femoral unprovoked DVT | Warfarin | Femoral DVT | congenital vena cava agenesis; INR in range | 7 |
| 9 | M | 18 | 24.7 | PC deficiency | Popliteal unprovoked DVT | Warfarin | Femoral DVT | INR in range | 10 |

aPL, antiphosholipid antibodies; BMI, body mass index; DOACs, direct oral anticoagulants; DVT, deep vein thrombosis; F, female; FVL, factor V Leiden; hetero, heterozygous; INR, international normalized ratio; M, male; PE, pulmonary embolism; PC, protein C; PS, protein S; PT G20210A, prothrombin mutation G20210A; y, year.

*Not present at inclusion.

**Table S2. Characteristics of patients who underwent anticoagulant discontinuation and 2-year follow-up.**

| | **DOACs** (n. 132) | **VKAs/heparin** (n. 217) | **p** |
|---|---|---|---|
| **Female** – n(%) | 65 (49.2) | 114 (52.5) | 0.55 |
| **Age** – mean years (±SD) | 50.9 (± 18.4) | 47.6 (± 18.2) | 0.10 |
| **BMI** – mean Kg/m$^2$ (±SD) | 25.9 (± 4.6) | 26.5 (± 5.1) | 0.27 |
| **Mild thrombophilia** – n(%) | 98 (74.2) | 144 (66.3) | 0.12 |
| FVL hetero | 59 | 77 | |
| PT hetero | 39 | 67 | |
| **Severe thrombophilia** – n(%) | 34 (25.8) | 73 (33.7) | 0.12 |
| PC deficiency | 10 | 9 | |
| PS deficiency | 9 | 23 | |
| AT deficiency | 7 | 10 | |
| FVL homo | 1 | 6 | |
| PT homo | 1 | 1 | |
| Compound hetero | 6* | 12** | |
| Pseudo-homo FVL | 0 | 2 | |
| AT resistance | 0 | 0 | |
| **Previous VTE** – n (%) | 18 (13.6) | 22 (10.1) | 0.32 |
| **Index VTE etiology** – n (%) | | | |
| Provoked | 65 (49) | 121 (55.8) | 0.23 |
| Unprovoked | 67 (51) | 96 (44.2) | |
| **Index VTE risk factors** – n (%) | | | |
| Trauma or surgery | 14 (21.5) | 41 (34) | 0.068 |
| Immobilization | 12 (18.5) | 10 (8) | 0.049 |
| Pregnancy/hormones | 24 (37) | 48 (39.6) | 0.71 |
| Acute medical condition | 7 (11) | 13 (11) | 0.98 |
| Cancer | 8 (12) | 9 (7.4) | 0.28 |
| **Index VTE type**– n (%) | | | |
| PE | 25 (19) | 24 (11) | 0.044 |
| PE and DVT | 31 (23) | 47 (22) | 0.69 |
| DVT | 76 (58) | 146 (67) | 0.07 |
| **Type of anticoagulant** – n (%) | rivaroxaban 82 (62)<br>apixaban 24 (18)<br>edoxaban 20 (15)<br>dabigatran 6 (5) | heparin 51 (24)<br>AVKs 166 (76) | - |
| **Extension with low-dose therapy** – n (%) | 27 (20.5) | 13 (6) | 0.0006 |
| **Anticoagulation duration** – median months [IQR] | 7 [5-12] | 6 [5-14] | 0.04 |

Qualitative variables are expressed as frequencies when not specified.
Comparisons are reported as p (Chi-square or Student-T-test, as appropriate).
* 6 FVL + PT hetero
** 11 FVL + PT hetero, 1 PT hetero + PS deficiency.

AT, antithrombin; BMI, body mass index; DOACs, direct oral anticoagulants; DVT, deep vein thrombosis; FVL, factor V Leiden; hetero, heterozygous; homo, homozygous; PC, protein C; PE, pulmonary embolism; PS, protein S; PT, prothrombin mutation G20210A; SD, standard deviation; VKAs, vitamin K antagonists; VTE, venous thromboembolism.