Risk of recurrence after discontinuing anticoagulation in patients with COVID-19- associated venous thromboembolism: a prospective multicentre cohort study

Luis Jara-Palomares,[a,v,*] Behnood Bikdeli,[b,q,r,s,v] David Jiménez,[c,p,t,v] Alfonso Muriel,[d,u] Pablo Demelo-Rodríguez,[e] Farès Moustafa,[f] Aurora Villalobos,[g] Patricia López-Miguel,[h] Luciano López-Jiménez,[i] Sonia Otálora,[j] María Luisa Peris,[k] Cristina Amado,[l] Romain Chopard,[m] Francisco Rivera-Cívico,[n] and Manuel Monreal,[o] the RIETE Investigators[w]

[a]Respiratory Department, Virgen del Rocio Hospital and Instituto de Biomedicina, Sevilla, CIBER de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain
[b]Cardiovascular Medicine Division, Brigham and Women's Hospital, Harvard Medical School, USA
[c]Respiratory Department, Hospital Ramón y Cajal and Instituto Ramón y Cajal de Investigacion Sanitaria IRYCIS, Madrid, Spain
[d]Biostatistics Department, Ramón y Cajal Hospital and Instituto Ramón y Cajal de Investigacion Sanitaria IRYCIS, CIBERESP, Madrid, Spain
[e]Department of Internal Medicine, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[f]Department of Emergency, Clermont-Ferrand University Hospital, Clermont-Ferrand, France
[g]Department of Internal Medicine, Hospital Regional Universitario de Málaga, Málaga, Spain
[h]Department of Pneumonology, Hospital General Universitario de Albacete, Albacete, Spain
[i]Department of Internal Medicine, Hospital Universitario Reina Sofía, Córdoba, Spain
[j]Department of Internal Medicine, Hospital Universitario Virgen de Arrixaca, Murcia, Spain
[k]Department of Internal Medicine, Consorcio Hospitalario Provincial de Castellón, Universidad Cardenal Herrera-CEU, CEU Universities, Castellón, Spain
[l]Department of Internal Medicine, Hospital Sierrallana, Santander, Spain
[m]Department of Cardiology, University Hospital Jean Minjoz, Besançon, France
[n]Department of Internal Medicine, Hospital de Poniente, El Ejido, Almeria, Spain
[o]Chair for the Study of Thromboembolic Disease, Faculty of Health Sciences, UCAM - Universidad Católica San Antonio de Murcia, Spain
[p]CIBER Enfermedades Respiratorias (CIBERES), Madrid, Spain
[q]Thrombosis Research Group, Brigham and Women's Hospital, Harvard Medical School, USA
[r]YNHH/ Yale Center for Outcomes Research and Evaluation (CORE), New Haven, CT, USA
[s]Cardiovascular Research Foundation (CRF), New York, NY, USA
[t]Medicine Department, Universidad de Alcalá, Madrid, Spain
[u]University of Alcala, Madrid, Spain

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Summary

Background The clinical relevance of recurrent venous thromboembolism (VTE) after discontinuing anticoagulation in patients with COVID-19-associated VTE remains uncertain. We estimated the incidence rates and mortality of VTE recurrences developing after discontinuing anticoagulation in patients with COVID-19-associated VTE.

Methods A prospective, multicenter, non-interventional study was conducted between March 25, 2020, and July 26, 2023, including patients who had discontinued anticoagulation after at least 3 months of therapy. All patients from the registry were analyzed during the study period to verify inclusion criteria. Patients with superficial vein thrombosis, those who did not receive at least 3 months of anticoagulant therapy, and those who were followed for less than 15 days after discontinuing anticoagulation were excluded. Outcomes were: 1) Incidence rates of symptomatic VTE recurrences, and 2) fatal PE. The rate of VTE recurrences was defined as the number of patients with recurrent VTE divided by the patient-years at risk of recurrent VTE during the period when anticoagulation was discontinued.

Findings Among 1106 patients with COVID-19-associated VTE (age 62.3 ± 14.4 years; 62.9% male) followed-up for 12.5 months (p25-75, 6.3–20.1) after discontinuing anticoagulation, there were 38 VTE recurrences (3.5%, 95%

*Corresponding author. Medical Surgical Unit of Respiratory Diseases, Hospital Virgen del Rocio, Av. Manuel Siurot s/n, Seville, 41013, Spain.
E-mail address: luisoneumo@hotmail.com (L. Jara-Palomares).
[v]Equal contributions.
[w]A full list of RIETE investigators is given in the Appendix.

confidence interval [CI]: 2.5–4.7%), with a rate of 3.1 per 100 patient-years (95% CI: 2.2–4.2). No patient died of recurrent PE (0%, 95% CI: 0–7.6%). Subgroup analyses showed that patients with diagnosis in 2021–2022 (vs. 2020) (Hazard ratio [HR] 2.86; 95% CI 1.45–5.68) or those with isolated deep vein thrombosis (vs. pulmonary embolism) (HR 2.31; 95% CI 1.19–4.49) had significantly higher rates of VTE recurrences.

Interpretation In patients with COVID-19-associated VTE who discontinued anticoagulation after at least 3 months of treatment, the incidence rate of recurrent VTE and the case-fatality rate was low. Therefore, it conceivable that long-term anticoagulation may not be required for many patients with COVID-19-associated VTE, although further research is needed to confirm these findings.

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Keywords: Pulmonary embolism; Venous thromboembolism; Anticoagulation; COVID-19; SARS-CoV-2

Research in context

Evidence before this study

We searched PubMed for studies published until Apr 30, 2023, using search terms venous thromboembolism and sars coronavirus or SARS-CoV-2 with search terms found in MESH headings. We also searched guidelines related to prevention, diagnosis, and acute treatment of COVID-19-associated VTE and references listed in the identified papers and guidelines published. Existing guidelines have mainly focused on the prevention, diagnosis, and acute treatment of COVID-19-associated VTE. However, there is no consensus regarding the optimal duration of anticoagulation after COVID-19-associated VTE. Evidence in the field is scarce and studies on this topic had a small sample size, short follow-up duration, and were unable to provide estimates within subgroups.

Added value of this study

To the best of our knowledge, this is the larger prospective, multicenter, multinational, non-interventional study to show that in patients with COVID-19-associated VTE who discontinued anticoagulant therapy after at least three months, the rate of recurrent VTE is low. Therefore, it is conceivable that long-term anticoagulation may not be required for many patients with COVID-19-associated VTE, although further research is needed to confirm these findings.

Implications of all the available evidence

In our work, the rate of recurrent VTE in patients with COVID-19-associated VTE was low (3.1 per 100 patients-years). This may be in line with the fact that the inflammatory response and acute illness, two of the factors predisposing to thrombosis in the setting of COVID-19, may improve over time. This work has provided relevant knowledge on patients with COVID-19-associated VTE. The presence of a low rate of VTE recurrences after discontinuation of anticoagulant treatment can contribute to the decision-making process regarding the optimal duration of anticoagulant treatment.

Introduction

Studies have revealed a high prevalence of venous thromboembolism (VTE) (deep vein thrombosis [DVT] and/or pulmonary embolism [PE]) among patients with coronavirus disease 2019 (COVID-19).[1–3] The increased risk of VTE is due to hypercoagulability, activation of the vascular endothelium, and alterations in normal blood flow (Virchow's triad).[4,5] A meta-analysis found that the pooled incidence of VTE among hospitalized patients with COVID-19 was 17%.[6]

Existing guidelines have mainly focused on the prevention, diagnosis, and acute treatment of COVID-19-associated VTE.[7–11] However, there is no consensus regarding the optimal duration of anticoagulation after COVID-19-associated VTE. Factors that can influence the decision include the rate of recurrent events after discontinuing anticoagulation, and fatal PE after VTE recurrences for COVID-19-associated VTE.

Evidence in the field of COVID-19-associated VTE is scarce and studies on this topic had a small sample size and very short follow-up, making them unable to provide clear guidance or to assess the findings within subgroup.[12,13] Preliminary analysis from RIETE found that the rate of VTE recurrences in COVID-associated VTE in whom anticoagulant treatment was discontinued was 4.8 per 100 patient-years.[12] It remains uncertain whether the underlying inflammatory response persists for long such that it exposes the patients to high risk of VTE recurrence after initial discontinuation.

Therefore, we used a large prospective international registry to study a cohort of patients with COVID-19-associated VTE who were followed-up after discontinuing anticoagulant therapy. We sought to provide estimates of the incidence rate of VTE recurrences and fatal PE after VTE recurrences.

Methods

Design and data source

We used data from the Registro Informatizado de la Enfermedad Tromboembolica (RIETE) registry, which prospectively collects information on patients with confirmed acute VTE.[14] The study adhered to the STROBE guidelines recommended by the EQUATOR reporting guidelines. Previous publications have described the design and conduct of the RIETE registry.[14,15] Briefly, at each participating RIETE site, investigators enrolled consecutive patients who had acute objectively confirmed VTE. All patients provided informed consent for participation in the registry in accordance with local ethics committee requirements. Since March 25, 2020, the RIETE platform has added specific data elements related to COVID-19-associated VTE.

Eligibility criteria

Patients diagnosed with acute symptomatic COVID-19-associated VTE between March 25, 2020, and July 26, 2023, that stopped anticoagulant treatment were considered for inclusion in this study. Follow-up began on the day of anticoagulation cessation, ending in July 2023 or at the point of VTE recurrence or patient death. COVID-19 confirmation was required, and COVID-19-associated VTE was considered if the COVID-19 test was positive within 30-days of the VTE event.

For this study, patients with superficial vein thrombosis, those who did not receive at least 3 months of anticoagulant therapy, and those who were followed for less than 15 days after discontinuing anticoagulation were excluded. Confirmatory testing for PE consisted of high probability ventilation-perfusion scintigraphy[16]; positive computed tomography pulmonary angiography (CTPA) for PE[17]; or lower limb venous compression ultrasonography positive for proximal DVT in patients presenting with chest symptoms.[18] Confirmatory testing for venous thrombosis in RIETE in any location (lower limb, upper limb, cava, splanchnic, lung vein, jugular or cerebral vein) consisted of positive computed tomography (CT) or compression venous ultrasonography.

All included patients in this study received at least 3 months of anticoagulation at the discretion of their treating clinicians, and were followed-up for at least 15 days after its discontinuation. Follow-up procedures were conducted in each center based on clinician criteria, and data were updated until July 2023 or earlier if a patient died or experienced a VTE recurrence. After discontinuing anticoagulant treatment, patients were instructed to contact investigators in case of signs and/or symptoms suggesting VTE recurrences were noted, and each episode of clinically suspected recurrent VTE was investigated.

Outcomes

The main outcomes were: 1) Rate of symptomatic, objectively confirmed recurrent VTE after discontinuation of anticoagulant treatment per 100 patients-years of follow-up; 2) Fatal PE was defined by mortality occurring within the initial 30 days following a VTE recurrence, confirmed through objective diagnostic testing, autopsy, or in cases where the cause of death cannot be attributed to a documented reason and where PE cannot be definitively excluded (unexplained death).[19] The rate of VTE recurrences was defined as the number of patients with recurrent VTE divided by the patient-years at risk of recurrent VTE during the period when anticoagulation was discontinued. RIETE investigators defined recurrent DVT as a new non-compressible vein segment, or an increase of the vein diameter by at least 4 mm compared with the last available measurement on venous ultrasonography, and recurrent PE as a new ventilation–perfusion mismatch on lung scan or a new intraluminal filling defect on spiral CT of the chest in patients with acute respiratory symptoms. Recurrence VTE as venous thrombosis in other locations need confirmatory testing with CT or ultrasonography.[14]

Secondary outcomes: 1) Incidence of VTE recurrences within the first 30 and within the first 180 days after discontinuation of anticoagulant treatment; 2) Location of VTE recurrence according to first VTE event; 3) Subgroup analyses were performed to evaluate the risk of VTE recurrences in some predefined subgroups: age (<65 years vs. ≥ 65 years), sex (captured according to patient self-report), active cancer (yes/no), VTE location, duration of anticoagulant treatment prior to discontinuation of anticoagulation (<6 months vs. ≥ 6 months), year of COVID infection (2020 vs. 2021–2022) and multiple enduring risk factors (at least 2 more in addition to COVID) vs. 0–1 risk factor. Factors considered in the multiple enduring risk factor were: cancer, recent surgery (until two months previously), immobilization (more than 4 days for non-surgical reason), recent travel (more than 6 h in the previous 3 weeks), previous history of VTE, familiar with VTE, hormonal treatment (in the previous 2 months), pregnancy, puerperium, various veins.

Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD) or median and percentile 25–75 (p25-75), and the categorical variables were expressed as absolute and relative frequencies. We conducted normality tests (Kolmogorov–Smirnov test) for the variables age, weight, and body mass index (BMI). We found that neither weight nor BMI followed a normal distribution, and we calculated their median and interquartile range (p25-75). To calculate 95% confidence intervals (CI) we used the Clopper-Pearson exact method. For patients with COVID-19-associated VTE, cumulative incidence of VTE recurrences was estimated using the Kaplan–Meier method. We used standardized differences to compare groups to assess the effect size or the degree of difference between them. Standardized

mean differences was calculated by d value, where values greater than 20% are considered clinically relevant.[20,21] This measure is expressed as a percentage to facilitate understanding and comparison across different studies or measurements. By standardizing the difference, we remove the influence of the units, allowing for a more universal interpretation of the effect size.

In the subgroup analysis, we compared the rate of recurrent VTE after discontinuation of anticoagulant treatment per 100 patient-years using the Mid-P exact test (or the Fisher exact test when necessary), and univariable and multivariable Cox regression analysis was performed. We conducted statistical analyses with the use of SPSS (IBM SPSS Statistics for Windows, Version 25.0, IBM Corp.) and Stata 17.1.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. LJP and BB had full access to the study data and had final responsibility for the decision to submit it for publication.

Results

Study population

From March 2020 to July 2023, 2164 patients with COVID-19-associated VTE were enrolled in RIETE. In a total of 682 patients, anticoagulant treatment was not stopped, 330 with anticoagulation less than 3 months, and 46 patients with follow-up less than 15 days after discontinuation of anticoagulant therapy. Finally, 1106 patients met eligibility criteria and were included in the study (Fig. 1). Mean age was 62.3 ± 14.4 years; 62.9% were male. Regarding the location of the index VTE, the majority of patients (74.9%) initially presented as isolated PE, 13.4% as concomitant PE and DVT, and 11.7% as isolated DVT. Locations of DVT were: lower limb DVT (n = 208), upper limb DVT (n = 26), vena cava thrombosis (n = 3), jugular vein thrombosis (n = 17), splanchnic vein thrombosis (n = 1), lung vein thrombosis (n = 3), and cerebral venous sinus thrombosis (n = 1). Median duration of anticoagulant therapy prior to discontinuation was 5.6 months (p25-p75, 3.6–7.5 months). Their baseline characteristics are shown in Table 1. Comparison between patients who discontinued or continued anticoagulation appears in Supplementary Table S1.

Primary outcome

Over a median follow-up, after discontinuation of anticoagulation, of 12.5 months (p25-p75, 6.3 to 20.1 months), 38 of 1106 (3.5%, 95% CI 2.5–4.7%) patients had recurrent VTE. The incidence rate of recurrent VTE after discontinuation of anticoagulation was 3.1 per 100 patient-years (95% confidence interval [CI], 2.2–4.2). No patient died of PE (0%, 95% CI: 0%–7.6%). Throughout the follow-up period, 34 patients (3.1%) died.

Secondary outcomes

Among 38 patients with recurrent VTE, 31 (81.6%) had PE as the index event (with or without concomitant DVT), and in these patients, recurrent VTE occurred as PE in 58.1% (n = 18), as DVT in 38.8% (n = 12) and in other sites in 2.6% (n = 1). Six patients had isolated lower limb DVT as the index event, and in these patients, recurrent VTE occurred as DVT in two patients (33%) as PE and four (66%). One patient had vena cava thrombosis as the index VTE event, and VTE recurrence was as lower limb DVT. There were no VTE recurrences in patients with other DVT sites in the index event. With respect to the timing of the recurrent events, 10 recurrent VTE events occurred within 30 days after discontinuation and 29 within 12 months, with a cumulative incidence of 0.9% (95% CI 0.5%–1.6%) and 2.6% (95% CI 1.8–3.7), respectively (Fig. 2). In 86.4% of cases, pneumonia was identified on chest X-ray, and we found no differences in recurrent VTE between patients with and without pneumonia (3.3% vs. 5.2%; p: 0.34). Univariable Cox regression analyses revealed that variables associated to higher risk of VTE recurrences in patients COVID-associated VTE were: 1) Diagnosis in 2021–2022 (vs. 2020) (Hazard ratio [HR] 2.86; 95% CI 1.45– 5.68); 2) Lower limb DVT (with or without PE) (vs. PE alone) (HR 2.31; 95% CI 1.19–4.49). Multivariable Cox regression found similar results (Table 2).

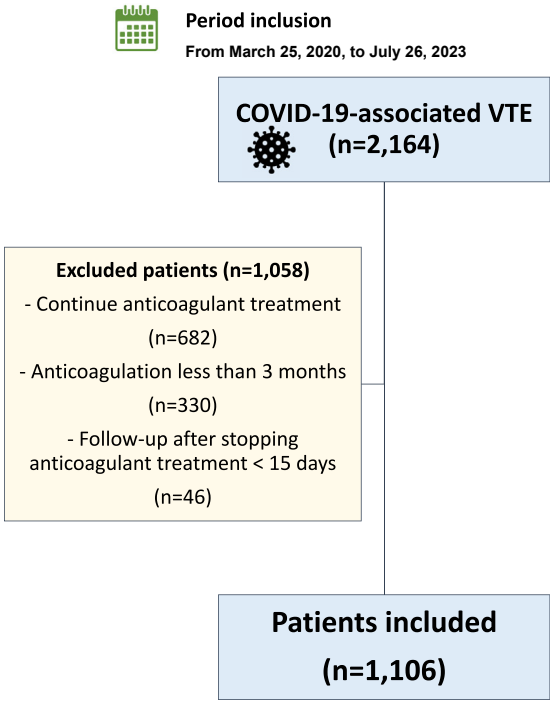


Fig. 1: **Flow diagram.**

	Recurrent VTE Yes (n = 38)	Recurrent VTE No (n = 1068)	Total (n = 1106)
Demographics			
Female, n (%) (n = 410)	14 (36.8)	396 (37.1)	410 (37.1)
Male, n (%) (n = 696)	24 (63.2%)	672 (62.9%)	696 (62.9%)
Age (years), mean (SD) (n = 1106)	65.2 (14.3)	62.2 (14.4)	62.3 (14.4)
Weight (Kilograms), median (p25-75) (n = 1106)	80 (69–90.5)	79 (69–88)	80 (70–89)
BMI, median (p25-75) (n = 823)	27.6 (23.2–32.8)	27.4 (25–30.5)	27.4 (25–30.7)
Current smoker, n (%) (n = 1068)	0 (0%)	64 (6.2%)	64 (6%)
Previous bleeding in the last month, n (%) (n = 1106)	1 (2.6%)	15 (1.4%)	16 (1.4%)
Comorbidities, n (%)			
Acute coronary syndrome, n (%) (n = 1079)	1 (2.7%)	49 (4.7%)	50 (4.6%)
Stroke, n (%) (n = 1078)	2 (5.4%)	42 (4%)	44 (4.1%)
Diabetes mellitus, n (%) (n = 1074)	9 (24.3%)	169 (16.3%)	178 (16.6%)
Hypertension, n (%) (n = 1079)	21 (58.3%)	393 (37.7%)	414 (38.4%)
Heart failure, n (%) (n = 1074)	1 (2.7%)	38 (3.7%)	39 (3.6%)
Atrial fibrillation, n (%) (n = 1075)	0 (0%)	14 14 (1.3%)	14 (1.3%)
Statins treatment, n (%) (n = 1073)	9 (24.3%)	260 (25.1%)	269 (25.1%)
Liver Cirrhosis, n (%) (n = 1106)	2 (5.3%)	2 (0.2%)	4 (0.4%)
Fatty Liver disease, n (%) (n = 1106)	2 (5.3%)	14 (1.3%)	16 (1.4%)
Rheumatoid arthritis, n (%) (n = 1106)	0 (0%)	16 (1.5%)	16 (1.4%)
Chronic lung disease, n (%) (n = 1106)	6 (15.8%)	96 (9%)	102 (9.2%)
Dementia, n (%) (n = 1106)	3 (7.9%)	33 (3.1%)	36 (3.3%)
Depression, n (%) (n = 1106)	3 (7.9%)	46 (4.3%)	49 (4.4%)
Risk factor of VTE, n (%)			
Prior VTE (n = n = 1106)	1 (2.6%)	30 (2.8%)	31 (2.8%)
Active cancer (n = 1106)	2 (5.3%)	19 (1.8%)	21 (1.9%)
Recent surgery (n = 1106)	7 (18.4%)	25 (2.3%)	32 (2.9%)
Hormonal treatment (n = 1087)	0 (0%)	20 (1.9%)	20 (1.8%)
Pregnancy or puerperium (n = 1106)	0 (0%)	14 (1.4%)	14 (1.3%)
VTE location, n (%) (n = 1036)			
Isolated DVT	7 (18.4%)	123 (11.6%)	123 (11.7%)
Isolated PE	24 (63.2%)	804 (75.3%)	828 (74.9%)
PE plus DVT	7 (18.4%)	141 (13.2%)	148 (13.4%)
DVT location, n (%)			
Lower limb DVT, n (%) (n = 1106)	14 (36.8%)	194 (18.2%)	208 (18.8%)
Upper limb DVT, n (%) (n = 1106)	0 (0%)	26 (2.4%)	26 (2.4%)
Burden of PE on CT scan (n = (%) (more proximal location), n (%) (n = 922)			
Main	5 (17.2%)	116 (13%)	121 (13.1%)
Lobar	8 (27.6%)	245 (27.4%)	253 (27.4%)
Segmental	15 (51.7%)	404 (45.2%)	419 (45.4%)
Subsegmental	1 (3.4%)	128 (14.3%)	129 (14%)
Atrial fibrillation during follow-up, n (%) (n = 652)	2 (11.1%)	13 (2%)	15 (2.2%)

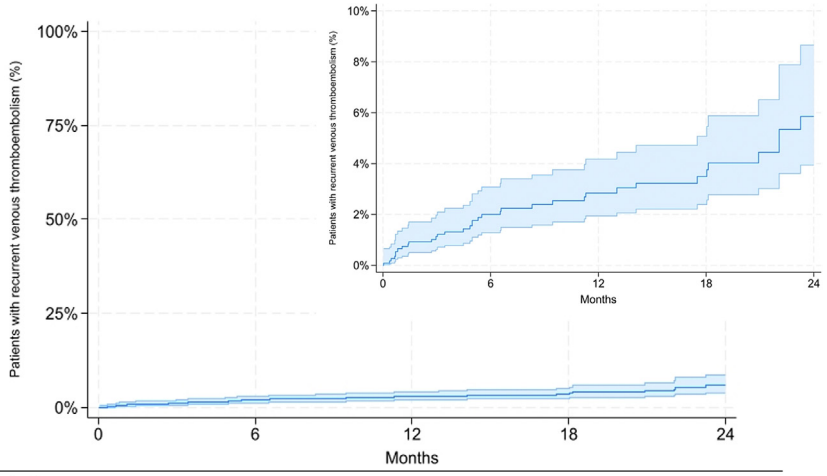
VTE: Venous thromboembolism; SD: Standard deviation; BMI: Body mass index; DVT: deep vein thrombosis; PE: pulmonary embolism; CT: Computerized tomography.

Table 1: **Demographic and clinical characteristics of patients with COVID-19-associated-venous thromboembolism in whom anticoagulant treatment was discontinued.**

Discussion

This prospective, multicenter, multinational, non-interventional study found that in patients with COVID-19-associated VTE that were followed-up after discontinuing anticoagulant therapy for at least three months, the VTE recurrence rate was of 3.1 per 100 patient-years, with no fatal PE.

Although there are many published studies on COVID-19-associated VTE, the information available about recurrent VTE after discontinuation of anticoagulant treatment is scarce and mostly coming from small studies.[12,13] Delrue et al., in a single-center prospective study, reported 48 patients with COVID-19-associated VTE diagnosed during hospitalization, with a median follow-up of 12 months (range 12–14 months). Among 39 patients in whom anticoagulant treatment was discontinued, none experienced VTE recurrences over a median follow-up period of 6 months.[13] Jara-Palomares



Patients at risk	1,106	833	567	354	168
VTE recurrences	0	23	29	32	38
Death	0	12	22	29	32

Fig. 2: **Cumulative incidence of VTE recurrences after discontinuation of anticoagulant treatment in patients with COVID-19-associated-venous thromboembolism**.

et al., in a prospective multinational cohort study, with 431 patients with COVID-associated VTE in whom anticoagulant treatment was discontinued observed a rate of VTE recurrences was 4.8 per 100 patient-years.[12] Current study included a substantively more patients (2.5 times) and with a median follow-up more than double (12.5 months vs. 5.8 months).

In the absence of direct randomized trials about treatment duration, the rates and severity of VTE recurrence are likely the most important determinants for deliberation of the duration of therapy for patients with VTE. VTE events may be provoked by a major transient risk factor, a minor transient risk factor, a persistent risk factor; or may be unprovoked.[8] Data from prior meta-analyses indicate that the pooled rate of recurrent VTE after discontinuation of anticoagulant treatment in patients with unprovoked VTE is 10.3 events per 100 person-year (95% CI, 8.3–12.1) in the first year,[22] whereas the pooled rate of recurrent VTE in patients with VTE provoked by a non-surgical factor is 5.8 per 100 person-year (95% CI, 3.2–8.3).[23] In our work, the rate of recurrent VTE in patients with COVID-19-associated VTE was lower than rate in VTE provoked by a non-surgical factor. This may be in line with the fact that the inflammatory response and acute illness, two of the factors predisposing to thrombosis in the setting of COVID-19, may improve over time.

In patients with COVID-19-associated VTE, the subgroup analysis has allowed us to identify situations where the rate of recurrent VTE was high. In patients diagnosed with COVID-19-associated VTE in the years 2021 and 2022, the rate of recurrent VTE was higher than in patients diagnosed in 2020. Although there is no clear justification for this finding, it could be hypothesized that in 2020, COVID-19 was more virulent, and therefore it could be considered a major transient risk factor. However, in the years 2021 and 2022, COVID-19 infection had less impact, and based on the rate of recurrent VTE, COVID-19 infection behaves as a minor transient risk factor, which is why the rate of recurrent VTE is higher. In patients with lower limb DVT (with or without PE), compared with PE alone, had an increase rate of VTE recurrences. Reasons for this finding are unclear but could be postulated. It is possible that some of the patients with COVID-19-associated PE had immunothrombosis, rather than truly embolic PE, and that recurrent events are less likely in this context once the inflammatory response and endothelial dysfunction improve.[24,25]

About VTE recurrence location, in 58% of the patients VTE recurrences occurred as PE, both in patients who initially presented with PE (58%) and DVT (66%) in the index event. The location of VTE is important when considering whether to discontinue anticoagulant treatment because the clinical and prognostic impact of a PE is not the same as that of a DVT. Therefore, in the risk-benefit balance, clinicians will more carefully weigh those patients who, in the case of recurrent VTE, may present a higher risk of complications. It is worth noting that 26% of VTE recurrences occurred within the first month of discontinuation (n = 10), and 76% occurred within 12 months (n = 29).

This work has several strengths: RIETE is a multidisciplinary project aimed at creating an extensive data

	VTE recurrences	Rate per-100 patient-years	Lower 95% CI	Upper 95% CI	P value	Univariate COX regression HR (95% CI)	Multivariate COX regression HR (95% CI)
Duration of anticoagulation					0.25	0.6 (0.31–1.15)	0.6 (0.31–1.15)
< 6 months	18	2.5	1.5	4			
≥ 6 month	20	3.8	2.3	5.9			
COVID-19 (Year 2020 vs. 2021–2022)					0.002	2.86 (1.45–5.68)	2.65 (1.35–5.2)
2020 (n = 702)	19	2.1	1.3	3.3			
2021–2022 (n = 404)	19	5.8	3.5	9.1			
Multiple enduring risk factors (at least 2 more in addition to COVID-19) vs. other					0.28	1.34 (0.57–3.13)	1.34 (0.57–3.15)
More than 1 risk factor (n = 943)	8	4.4	1.9	8.7			
0–1 risk factors (n = 163)	30	2.8	1.9	4.1			
Sex (male vs. female)					0.89	1.17 (0.59–2.32)	1.18 (0.60–2.34)
Male (n = 696)	24	3.1	2.0	4.7			
Female (n = 410)	14	3.0	1.6	5			
Age (≥ 65 years vs. < 65 years)					0.039	1.77 (0.91–3.45)	1.82 (0.94–3.54)
Older 65 years (n = 504)	23	4.3	2.7	6.4			
Younger 65 years (n = 602)	15	2.2	1.2	3.6			
Active cancer					0.19	1.8 (0.38–8.48)	1.95 (0.41–9.24)
Yes (n = 21)	2	8.7	1.0	31.4			
No (n = 1085)	36	3.0	2.0	4.1			
Initial VTE location					0.001	2.31 (1.19–4.49)	2.25 (1.16–4.37)
Pulmonary embolism only (n = 828)	24	2.1	1.4	3.2			
Lower limb DVT (with or without PE) (n = 208)	14	5.2	2.8	8.7			

Factors considered in the multiple enduring risk factor: cancer, recent surgery (until two months previously), immobilization (more than 4 days for non-surgical reason), recent travel (more than 6 h in the previous 3 weeks), previous history of VTE, familiar with VTE, hormonal treatment (in the previous 2 months), pregnancy, puerperium, various veins. Abbreviations: DVT: Deep vein thrombosis; HR: Hazard Ratio; PE: Pulmonary embolism; VTE: Venous thromboembolism.

Table 2: **Subgroup analyses in patients with COVID-19-associated-venous thromboembolism.**

registry of consecutive patients with venous thromboembolism and get result generalizability through various mechanisms. Firstly, we include diverse patient populations, reflecting real-world demographics, comorbidities, and clinical characteristics, thereby increasing the applicability of findings to real-world settings. Secondly, involve large sample sizes over extended periods, enhancing statistical power and allowing for better representation of various patient groups and clinical scenarios, which contributes to result generalizability. Thirdly, by capturing data from routine clinical practice, they mirror actual management strategies and treatment patterns, making findings more relevant to real-world clinical decision-making. Fourth, this pragmatic design facilitates real-time data capture without strict criteria, enabling inclusion of a broader spectrum of patients and enhancing external validity. We identified potential confounders, and our analysis was controlled through regression adjustment. In the conducted study, only variables collected in the database were analyzed, so no data imputation was performed for missing values.

There are several limitations. First, patient follow-up beyond the first three months in RIETE is according to routine care; i.e., there is no study-wide mandatory visit. However, patients are monitored regularly by their treating clinicians –who are RIETE investigators –and encouraged to notify their clinicians of any changes in symptoms that may warrant additional diagnostic tests. Our analyses of patients who had extended follow-up vs. those without showed that clinical characteristics were mostly comparable. Second, this study lacks an efficacy comparison group, making it potentially challenging to determine if discontinuing anticoagulant treatment is effective compared to continuation, although we do have reference cohorts through which we can compare the rate of recurrent VTE.[22,23] Nevertheless, comparing our results with data from systematic reviews and meta-analyses, if done properly and considering potential limitations, can be a valid strategy for assessing the effectiveness of a clinical decision, especially when conducting a clinical trial is not feasible or is complicated. Third, it is possible that during the study period, there were cases of COVID-19 that went undetected because tests were not conducted. However, initially, this would not affect our results or their interpretation since patients had to meet both criteria (diagnosis of COVID-19 and VTE) to be included. Underdiagnosis of COVID-19 could be assumed in the case of asymptomatic infection, but this is not the case for patients who have experienced symptomatic acute VTE. Fourth, it would be interesting to have information regarding

the severity of COVID-19 infection to determine if the severity of the infection was correlated with VTE recurrence. Unfortunately, we lack detailed information on the severity of the infection (e.g., the need for mechanical ventilation, orotracheal intubation, high-flow therapy) or the treatment received for COVID (e.g., corticosteroids, tocilizumab, etc.). However, information about the presence or absence of pneumonia was analyzed and no differences in VTE recurrence were observed.

In summary, this prospective, multicenter, multinational, non-interventional study of patients with COVID-19-associated VTE the rate of VTE recurrences after discontinuation of anticoagulant upon at least 3 months of anticoagulation was low with zero fatal PE. These values are crucial for understanding the severity and clinical impact of recurrent VTE in this population, and may help clinicians and patients for decision-making.

Contributors

Conception, study design, data analysis, data interpretation, drafting of manuscript: LJP, BB, DJ, MM, AM. Data Collection: PDR, FM, AV, PLM, LLJ, SO, MLP, CA, RC and FRC. Review of manuscript and final approval of manuscript: LJP, BB, DJ, MM, AM, PDR, FM, AV, PLM, LLJ, SO, MLP, CA, RC and FRC. LJP and AM have access to and verify the underlying study data.

Data sharing statement

Data are available with publication from the corresponding author after approval of a proposal on reasonable request.

Declaration of interests

BB is supported by a Career Development Award from the American Heart Association and VIVA Physicians (#938814). BB was supported by the Scott Schoen and Nancy Adams IGNITE Award and is supported by the Mary Ann Tynan Research Scientist award from the Mary Horrigan Connors Center for Women's Health and Gender Biology at Brigham and Women's Hospital, and the Heart and Vascular Center Junior Faculty Award from Brigham and Women's Hospital. BB reports that he is a consulting expert, on behalf of the plaintiff, for litigation related to two specific brand models of IVC filters. BB has not been involved in the litigation in 2022 or 2023 nor has he received any compensation in 2022 or 2023. BB reports that he is a member of the Medical Advisory Board for the North American Thrombosis Forum and serves in the Data Safety and Monitory Board of the NAIL-IT trial funded by the National Heart, Lung, and Blood Institute, and Translational Sciences. MM received fees from Sanofi, Leo Pharma, Rovi and the Catholic University of Murcia (Spain) sponsored the RIETE registry with unrestricted educational grants. Payments were made to the FUENTE foundation. DJ received honoraria for lectures from BMS and Sanofi. LJP received grants from Leo Pharma and MSD and personal fees from Daichii, Rovi, GlaxoSmithKline, BMS and Johnson and Johnson outside the submitted work. No other conflict of interest declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102659.

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