RESEARCH LETTER

Rate of Recurrence After Discontinuing Anticoagulation Therapy in Patients With COVID-19–Associated Venous Thromboembolism

There is uncertainty regarding the optimal duration of anticoagulation therapy (AT) after COVID-19-associated venous thromboembolism (VTE). We analyzed the rate of VTE recurrence in patients with COVID-19-associated VTE who discontinued AT.[1-3]

Methods | This prospective, multinational cohort study used data from the Registro Informatizado de la Enfermedad Tromboembolica (RIETE) registry, which prospectively collects information on patients with VTE.[4] Since March 25, 2020, RIETE has incorporated data on COVID-19-associated VTE. This study included patients who developed proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE) within 30 days of confirmed COVID-19 between March 25, 2020, and April 23, 2021, and discontinued AT after at least 3 months (eMethods in the Supplement).[1-3] Patients with upper limb or unusual sites of DVT, those who did not receive at least 3 months of AT, and those who were followed up for less than 15 days after AT discontinuation were excluded. The observation period for the inception cohort began on the day of AT discontinuation and ended with recurrent VTE, death, or on November 24, 2021. This study was approved by the Ethics Committee of Hospital Germans Trias i Pujol. Oral informed consent was obtained. This study followed the STROBE reporting guideline.

Supplemental content

The primary outcome was the rate of symptomatic recurrent VTE per 100 patient-years of follow-up. Testing for VTE was triggered by patient-reported symptoms and ascertained by local clinicians without central validation. Analyses were conducted with SPSS, version 25.0, and Stata, version 17.1.

Results | Of 1372 enrolled patients with COVID-19-associated VTE, 664 (48.4%) were receiving AT at the end of the study period and 708 (51.6%) had discontinued AT. After excluding 109 patients who had less than 15 days of follow-up after AT discontinuation, 147 who received less than 3 months of AT, and 21 with upper limb DVTs, 431 remained (mean [SD] age, 61.6 [14.3] years; 60.3% men) (**Table**). Median duration of AT was 4.6 months (IQR, 3.5-6.3 months). There were no significant differences in clinical characteristics of patients who discontinued vs continued anticoagulation.

Over a median postdiscontinuation follow-up of 5.8 months (IQR, 3.4-10.0 months), 11 patients (2.6%; 95% CI, 1.3%-4.5%) had recurrent VTE (6 DVT, 3 PE, and 2 DVT and PE). At 30 days, 1 patient had PE and DVT and 1 had DVT only). The rate of recurrent VTE was 4.8 (95% CI, 2.4-8.6) per 100 patient-years (**Figure**).

Table. Demographic and Clinical Characteristics of Patients With COVID-19–Associated VTE for Whom Anticoagulant Treatment Was Stopped

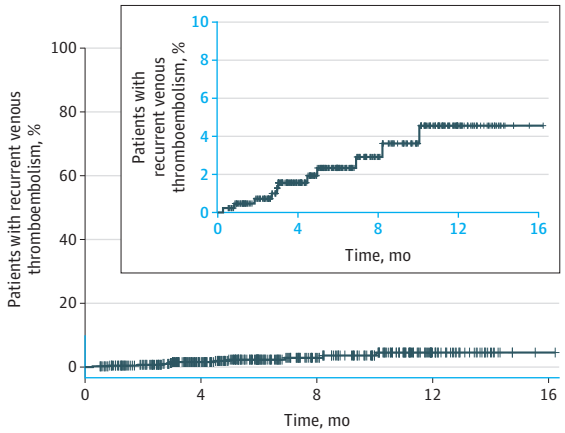
Characteristic	Patients with recurrent VTE[a]	
	Yes (n = 11)	No (n = 420)
Sex		
Female	3/11 (27.3)	169/420 (40.2)
Male	8/11 (72.7)	252/420 (60.0)
Age, mean (SD), y	63.8 (16.0)	61.5 (14.3)
Weight, mean (SD), kg	83.2 (17.5)	77.9 (15.7)
Height, mean (SD), m[b]	1.64 (0.1)	1.67 (0.1)
BMI >30[b]	3 (37.5)	85 (29.5)
Comorbidities		
Chronic lung disease	1 (9.1)	40 (9.5)
Obstructive sleep apnea	2 (18.2)	17 (4.0)
Dementia	1 (9.1)	19 (4.5)
Depression	0	20 (4.8)
Risk factor for VTE		
Family history of VTE	0/11	13/382 (3.4)
Prior VTE	0	9/420 (2.1)
Active cancer	3/11 (27.3)	23/420 (5.5)
Recent surgery	2/11 (18.2)	9/420 (2.1)
Hormonal treatment	0/11	11/420 (2.7)
Pregnancy	0/11	5/420 (1.2)
Puerperium	0/11	4/420 (1.0)
Varicose veins	1/11 (9.1)	23/383 (6.0)
VTE location		
Isolated DVT	4/11 (36.4)	21/420 (5.0)
Isolated PE	5/11 (45.5)	362/420 (86.2)
PE and DVT	2/11 (18.2)	37/420 (8.8)
Burden of PE on CT scan (more proximal location)		
Main	0/5	37/366 (10.1)
Lobar	3/5 (60)	97/366 (26.5)
Segmental	2/5 (40)	168/366 (45.9)
Subsegmental	0/5	64/366 (17.5)
Unilateral or bilateral PE		
Unilateral	2/5 (40)	172/366 (47)
Bilateral	3/5 (60)	194/366 (53)
Anticoagulant treatment duration, median (IQR), mo	4.6 (3.1-6.1)	4.6 (3.5-6.3)
Follow-up time after stopping anticoagulant treatment, median (IQR), mo	8 (5.1-11.3)	5.7 (3.4-9.9)
Anticoagulant treatment duration, mo		
3-6	8/11 (72.7)	283/420 (67.4)
>6	3/11 (27.3)	137/420 (32.6)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CT, computed tomography; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

[a] Data are presented as number/total number of patients (percentage) unless otherwise indicated.

[b] Data are for 296 patients.

Figure. Incidence Curve for Recurrent Venous Thromboembolism



During follow-up, there were 11 deaths (2.5%; 95% CI, 1.3%-4.4%), with no cases of recurrent fatal PE. The case-fatality rate of VTE recurrences was 0% (95% CI, 0%-28.5%).

Discussion | In patients with COVID-19–associated VTE who discontinued AT, the rate of VTE recurrences (4.8 per 100 patient-years) was similar to that in patients with VTE associated with a transient nonsurgical factor (5.8% [95% CI, 3.2%-8.3%] per patient-year)[5] and may be in line with the inflammatory response and acute illness in the context of COVID-19 improving over time. Our findings support the practice of providing a limited course of AT to these patients.[3]

Data about duration of AT for this population are scarce. A single-center study reported that 39 patients with COVID-19–associated VTE discontinued AT after a median duration of 6 months (range 3-6 months), and no symptomatic VTE recurrences were reported at 6 months (range, 5.5-6.6 months).[6]

Limitations are that follow-up beyond the first 3 months in RIETE is according to routine care and outcomes were ascertained by local clinicians without central validation. However, patients were monitored regularly by their clinicians and encouraged to report changes in symptoms that might warrant additional diagnostic tests. Routine screening for asymptomatic recurrences is not the standard of care in practice or in most clinical studies. Although our study assessed, to our knowledge, the largest sample of patients with COVID-19–associated VTE who discontinued AT, the 95% CIs were wide. Additional epidemiological and comparative effectiveness studies may improve the confidence and clarity of our findings.

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