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No VTE Recurrence After 1-Year Follow-Up of Hospitalized Patients With COVID-19 and a VTE Event

A Prospective Study

To the Editor:

Since the beginning of the pandemic, a high prevalence of VTE has been observed in hospitalized patients with severe COVID-19.[1] SARS-CoV-2 infection induces major endothelial cell dysfunction with systemic inflammatory response, both resulting in micro- and macrovascular thrombotic events that include pulmonary thrombosis/embolism.[1,2] Although multiple studies have evaluated the efficacy and safety of anticoagulant therapy in patients with COVID-19 with diagnosed VTE during hospital stay, limited data are available regarding outcomes after hospital discharge.[3-7] Notwithstanding the particular pathogenesis of thrombosis in patients with COVID-19, whether SARS-CoV-2 infection is an effective transient VTE risk factor that requires 3 to 6 months of anticoagulant therapy[8] is still debated. We aimed to investigate the outcome of patients with COVID-19 with diagnosed VTE during hospital stay while receiving anticoagulant therapy and after its discontinuation over 1-year follow-up evaluation.

Methods

We conducted a prospective observational cohort study in our university hospital ICU and medical wards. We included all consecutive patients with COVID-19 with VTE diagnosed during hospitalization from March 25, 2020, to April 30, 2021, who were referred after hospital discharge to our outpatient thrombosis unit for follow-up. SARS-CoV-2 infection was diagnosed with the use of standard real-time polymerase chain reaction (Cobas-SARS-CoV-2 kits, Roche, France). COVID-19-related symptomatic VTE, namely pulmonary embolism (PE) and/or DVT, were diagnosed with CT pulmonary angiography and/or duplex ultrasound examination of the lower limb veins by certified ultrasound operators, respectively. Laboratory thrombophilia screening was performed within 24 h of DVT/PE diagnosis (Table 1). VTE prophylaxis and management followed local guidelines in agreement with the international guidelines regarding ICU/non-ICU patients with COVID-19.[8] In patients with DVT/PE, we recommended initial anticoagulant therapy with low-molecular-weight heparin (LMWH) or unfractionated heparin if contraindicated, which was changed on discharge to direct oral anticoagulant (DOAC; creatinine clearance $\geq$ 30 mL/min). For most patients, in the absence of evidence, a 3- to 6-month duration of anticoagulant treatment was proposed, as recommended elsewhere.[8] Outcome criteria included symptomatic VTE recurrence (primary outcome) and bleeding event onset (secondary outcome). Visits were planned at 1, 3, 6, and 12 months after VTE diagnosis and beyond if needed. Periodic evaluation included physical examination to assess both outcomes and, when required, duplex ultrasound examination, CT pulmonary angiography, and laboratory reassessment of abnormal thrombophilia parameters if needed away from the acute phase. Bleeding events were adjudicated according to the International Society on Thrombosis and Haemostasis criteria.[10] This study was part of the French COVID-19 cohort registry, approved by our institutional ethics committee (IDRCB-2020-A00256-33; CPP-11-20-20.02.04.68737). All participating patients gave their written informed consent. Reporting of the study conforms to broad EQUATOR (Enhancing the QUAlity and Transparency Of health Research) Network guidelines. Quantitative variables were expressed as medians (25th to 75th percentiles), and categoric variables were expressed as percentages (version 11.0.1.0; MedCalc Software).

Results

Over the 13-month study period, of the 59 discharged patients who experienced COVID-19-related VTE during hospital stay, 48 patients (age, 62 years [range, 52 to 67 years]; 38M/10F) were followed in our outpatient thrombosis unit and included in the study (11 patients declined the follow-up). Median follow-up duration was 12 months (range, 12 to 14 months), of which 6 months (range, 5.5 to 6.6 months) were after anticoagulant discontinuation. One patient was lost to follow-up after the first visit. Hospitalization baseline clinical and laboratory characteristics are reported in Table 1. During hospitalization, 40 patients (83%) had PE (eight cases with associated DVT); eight patients (17%) had isolated DVT. Antiphospholipid antibodies that initially were present in 26 patients (54%) persisted in only four patients (8%) after 12 weeks. Forty patients (83%) received LMWH; two patients (4%) received unfractionated heparin, and six patients (13%) received DOAC (apixaban, three patients;

TABLE 1] Initial Clinical and Laboratory Characteristics in 48 Patients With COVID-19 and VTE Events

Variable	Measurement
Patients characteristics	
Age, y	62 (52-67)
Male sex, No. (%)	38 (79)
BMI, kg/m^2	27.0 (24.3-30.0)
Hypertension, No. (%)	17 (35)
Diabetes mellitus, No. (%)	13 (27)
History of cardiac disease, No. (%)	8 (17)
VTE history, No. (%)	6 (12)
COVID-19-related lung involvement[a]	
< 10%, No. (%)	4 (8)
10%-25%, No. (%)	15 (31)
25%-50%, No. (%)	15 (31)
50%-75%, No. (%)	14 (30)
Critically ill patients, No. (%)	17 (35)
Time from first symptoms to VTE diagnosis, d	12 (9-16)
Time from hospital admission to VTE diagnosis, d	0 (0-4)
Description of VTE, No. (%)	
Pulmonary embolism	40 (83)
Proximal	36 (75)
Isolated	32 (67)
Bilateral	19 (40)
DVT	16 (33)
Proximal	8 (17)
Isolated	8 (17) (6 in the ICU)
Bilateral	2 (4)
Initial anticoagulant therapy, No. (%)	
Low molecular weight heparin (therapeutic dose)	40 (83)
Direct oral anticoagulant	6 (13)
Apixaban	3 (6)
Rivaroxaban	3 (6)
Unfractionated heparin (therapeutic dose)	2 (4)
Anticoagulant therapy on hospital discharge	
Direct oral anticoagulant, No. (%)	45 (94)
Apixaban	35 (73)
Rivaroxaban	10 (21)
Low molecular weight heparin (therapeutic dose), No. (%)	3 (6)
Length of hospital stay, d	11 (7-18)
Laboratory data	
Hemoglobin, g/dL	12.7 (11.4-13.3)
Platelet count, g/L	323 (255-386)
Leukocytes, g/L	8.2 (6.8-10.3)
Serum creatinine, μM	72.0 (59.0-84.0)
Fibrinogen, g/L	5.89 (4.8-7.8)
D-dimer, ng/mL	3,410 (1,990-8,450)
Antiphospholipid antibodies,[b] No. (%)	
Lupus anticoagulant[b,c,d]	24 (50)
Anti-cardiolipin and/or anti-beta-2-GPI antibodies[b,e]	7 (15)
Persistence of anti-phospholipid antibodies ≥ 12 wks	4 (8)
Antithrombin activity,[b,d,f] International Units/dL	92 (85-102)
Protein C clotting activity,[b,d,f] International Units/dL	82 (66-93)
Protein S[b,d,f]	
Clotting activity,[b,d] International Units/dL	58 (41-75)
Free antigen,[b,d] International Units/dL	88 (71-111)
F2 G20210A variant,[b] No. (%)	4 (8)
F5 G1691A variant,[b] No. (%)	2 (4)

Results are expressed as median (interquartile range), unless otherwise indicated.

[a]COVID-19-related lung involvement (%) refers to parenchymal ground-glass opacities based on CT scan findings as defined by Revel et al.[9]

[b]Thrombophilia screening parameters.

[c]Diagnosis performed with diluted Russell viper venom time (dRVVT LAC-Screen/LAC-Confirm Siemens), PTT-LA Stago and Staclot-LA Stago (Diagnostica Stago, Inc, Parsippany-Troy Hills, NJ).

[d]The result could be unreliable in the setting of acute clot and/or anti-coagulation: abnormal parameters were reassessed systematically away from the acute phase and after anticoagulant cessation.

[e]Quantified with the use of chemiluminescence assays (Acustar, Werfen).

[f]No patient had confirmed natural inhibitor deficiency after anticoagulant cessation.

rivaroxaban, three patients) for initial VTE management. After discharge, 45 patients (94%) received DOAC (35 apixaban, 35 patients; rivaroxaban, 10 patients) and three patients (6%) received LMWH. Anticoagulants were discontinued after 3 months in one patient with DVT (2%) and after 6 months in 38 additional patients (79%). Anticoagulants were continued in eight patients (16%) in relation to antiphospholipid syndrome (n = 3), VTE history (n = 2), and underlying cancer (n = 3).

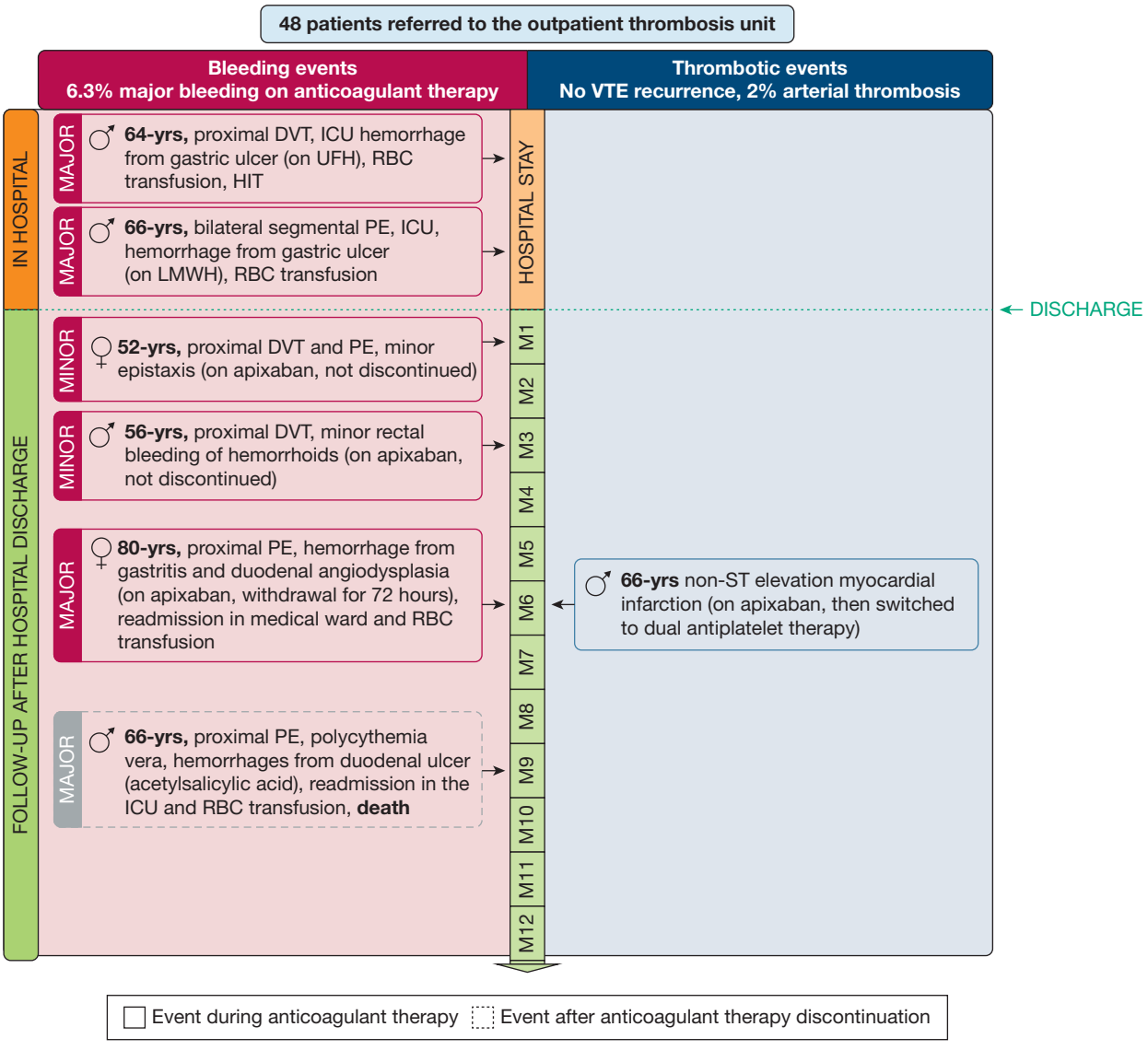

Figure 1 – *Bleeding and thromboembolic events during 1-year follow-up in 48 patients with COVID-19 who presented with a venous thromboembolic event that was diagnosed during hospitalization for COVID-19. The timeline indicates the date of clinical event occurrence after discharge. HIT = heparin-induced thrombocytopenia; LMWH = low molecular weight heparin; M = month; PE = pulmonary embolism; UFH = unfractionated heparin.*

Outcomes during follow-up are summarized in Figure 1. No symptomatic VTE recurrence was observed during or after anticoagulant therapy discontinuation. One 66-year-old patient with a 6-year history of ischemic cardiomyopathy experienced non-ST-elevation myocardial infarction 5 months after apixaban initiation and underwent coronary stenting with apixaban switch to dual antiplatelet therapy. During the anticoagulant therapy period, five patients (11%) presented bleeding that included three major hemorrhages that affected the GI tract (two patients in-hospital; one patient after discharge) and two minor episodes (both after discharge). One patient with major bleeding further experienced confirmed heparin-induced thrombocytopenia that required heparin to be switched to argatroban, then danaparoïd, and finally to apixaban without bleeding recurrence. In addition, once anticoagulation was stopped, one 66-year-old man with past polycythemia vera (6-month apixaban for PE, then switched to aspirin), died 9 months later from major duodenal hemorrhage (Fig 1).

Discussion

To the best of our knowledge, this is one of the first prospective real-life studies to evaluate outcomes over a 12-month period after COVID-19-related VTE diagnosis in hospitalized patients. We report the absence of VTE recurrence during the follow-up on anticoagulant therapy and after discontinuation. Only few studies reported shorter follow-up periods (from 10 to 159 days) in

cohorts of 24 to 737 patients with COVID-19-related VTE,[3-7] which shows a very low rate of VTE recurrence (0.0% to 2.4%) during anticoagulant therapy, which is consistent with our data. Moreover, we provided new data that confirm the low VTE recurrence risk up to 6 months after anticoagulant discontinuation. This low risk in patients with COVID-19 is similar to what has been observed in patients with VTE that is provoked by a transient nonsurgical factor.[11] Our data support limited anticoagulant therapy duration of 3 to 6 months in patients with COVID-19, in agreement with current guidelines,[8] although selected individuals (eg, with a VTE history) may require long-term anticoagulation. The rate of major bleedings (6.3%) on anticoagulant therapy in our cohort was comparable with those reported in previous studies (2.6% to 11.0%)[3-7]; however, heterogeneity of patient recruitment and anticoagulant treatment across studies makes comparisons difficult.

Despite limitations because of its single-center design and small sample size, our study presents significant strengths such as the inclusion of critically and noncritically ill patients with COVID-19. Moreover, by contrast to other studies, we report outcomes after a relatively long-term anticoagulant therapy discontinuation.

To conclude, our study with prospective 1-year follow-up supports the low VTE recurrence risk in either critically or noncritically ill patients with COVID-19 with VTE while receiving anticoagulant therapy and 6 months after its discontinuation. Our data remain to be confirmed in larger cohorts.

Maxime Delrue, MD, PhD
Alain Stépanian, PhD
Sebastian Voicu, MD, PhD
Kladoum Nassarmadji, MD
Damien Sène, MD, PhD
Philippe Bonnin, MD, PhD
Jean-Philippe Kevorkian, MD, PhD
Pierre-Olivier Sellier, MD, PhD
Jean-Michel Molina, MD, PhD
Marie Neuwirth, MD
Dominique Vodovar, MD, PhD
Stéphane Mouly, MD, PhD
Alexandre Mebazaa, MD, PhD
Bruno Mégarbane, MD, PhD
Virginie Siguret, PhD
Paris, France

AFFILIATIONS: From the Hematology Laboratory & Thrombosis unit (M. Delrue, A. Stépanian, M. Neuwirth, and V. Siguret), the Department of Internal Medicine (K. Nassarmadji, D. Sène and S. Mouly), the Department of Medical and Toxicological Critical Care (S. Voicu, and B. Mégarbane), the Laboratory of Clinical Physiology (P. Bonnin), Department of Diabetology-Endocrinology (J.-P. Kevorkian), Department of infectious disease (P.-O. Sellier and J.-M Molina), Paris Poison Control Center (D. Vodovar), Department of Anesthesiology and Critical Care (A. Mebazaa), Paris Cité, Hospital group Lariboisière-Fernand Widal, APHP; EA 3518 (M. Delrue and A. Stépanian), INSERM UMRS-1140 (M. Neuwirth and V. Siguret), INSERM UMRS-1144 (S. Voicu, D. Vodovar, S. Mouly, and B. Mégarbane), INSERM UMRS-1148 (P. Bonnin), and INSERM UMRS-942 (A. Mebazaa), Université Paris Cité.

CORRESPONDENCE TO: Virginie Siguret, PhD; email: virginie.siguret@aphp.fr

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