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Regular Article

THROMBOSIS AND HEMOSTASIS

Postdischarge thromboembolic outcomes and mortality of hospitalized patients with COVID-19: the CORE-19 registry

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KEY POINTS

- **In our registry, 90-day postdischarge VTE, ATE, and ACM rates were 1.55%, 1.71%, and 4.83%, respectively.**
- **Discharge anticoagulants, mostly prophylactic doses, were associated with 46% decrease in major thromboembolism or ACM composite end point.**

Thromboembolic events, including venous thromboembolism (VTE) and arterial thromboembolism (ATE), and mortality from subclinical thrombotic events occur frequently in coronavirus disease 2019 (COVID-19) inpatients. Whether the risk extends postdischarge has been controversial. Our prospective registry included consecutive patients with COVID-19 hospitalized within our multihospital system from 1 March to 31 May 2020. We captured demographics, comorbidities, laboratory parameters, medications, postdischarge thromboprophylaxis, and 90-day outcomes. Data from electronic health records, health informatics exchange, radiology database, and telephonic follow-up were merged. Primary outcome was a composite of adjudicated VTE, ATE, and all-cause mortality (ACM). Principal safety outcome was major bleeding (MB). Among 4906 patients (53.7% male), mean age was 61.7 years. Comorbidities included hypertension (38.6%), diabetes (25.1%), obesity (18.9%), and cancer history (13.1%). Postdischarge thromboprophylaxis was prescribed in 13.2%. VTE rate was 1.55%; ATE, 1.71%; ACM, 4.83%; and MB, 1.73%. Composite primary outcome rate was 7.13% and significantly associated with advanced age (odds ratio [OR], 3.66; 95% CI, 2.84-4.71), prior VTE (OR, 2.99; 95% CI, 2.00-4.47), intensive care unit (ICU) stay (OR, 2.22; 95% CI, 1.78-2.93), chronic kidney disease (CKD; OR, 2.10; 95% CI, 1.47-3.0), peripheral arterial disease (OR, 2.04; 95% CI, 1.10-3.80), carotid occlusive disease (OR, 2.02; 95% CI, 1.30-3.14), IMPROVE-DD VTE score ≥4 (OR, 1.51; 95% CI, 1.06-2.14), and coronary artery disease (OR, 1.50; 95% CI, 1.04-2.17). Postdischarge anticoagulation was significantly associated with reduction in primary outcome (OR, 0.54; 95% CI, 0.47-0.81). Postdischarge VTE, ATE, and ACM occurred frequently after COVID-19 hospitalization. Advanced age, cardiovascular risk factors, CKD, IMPROVE-DD VTE score ≥4, and ICU stay increased risk. Postdischarge anticoagulation reduced risk by 46%. (*Blood*. 2021;137(20):2838-2847)

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has been associated with significant morbidity and mortality globally. Importantly, elevated rates of macrovessel thrombotic events, including venous thromboembolism (VTE), such as deep vein thrombosis (DVT) and pulmonary embolism (PE), and arterial thromboembolism (ATE), such as stroke and myocardial infarction (MI), have been described, especially in sick and critically ill hospitalized patients.[1-4] In addition, postmortem studies suggest that ~60% and up to 100% of patients have unsuspected VTE or pulmonary arterial thrombosis at the time of death, with pulmonary microthrombi suggesting in situ fatal PE as an important contributor to death.[5,6]

There are limited and conflicting data on the rates of thromboembolic events and death in the postdischarge period for

hospitalized patients with COVID-19, with previous studies limited by small sample sizes, retrospective designs, and nonstandardized follow-up.[7,8] Antithrombotic guidelines for extended postdischarge thromboprophylaxis for patients with COVID-19 are also conflicting, suggesting either no routine thromboprophylaxis or an individualized approach to thromboprophylaxis using individual thrombotic and bleeding risk factors.[9-11]

There have been few previous efforts to assess predictors of thrombosis or death in the postdischarge period for hospitalized patients with COVID-19, which represent a subset of medically ill patients.[12] Previous data from randomized trials suggest an elevated rate of major and fatal thromboembolic events in high-risk medically ill patients (including those with pneumonia and sepsis) within 6 weeks of hospital discharge, with a significant 28% to 38% risk reduction using extended thromboprophylaxis.[13,14]

To overcome the current knowledge gap in postdischarge rates of VTE, ATE, death, and major complications in hospitalized patients with COVID-19, we undertook an investigator-initiated, multicenter, prospective registry named CORE-19 as part of the COVID-19 Research Consortium of our health system. Our second aim was to assess clinical and laboratory risk factors, as well as relevant medications, including anticoagulants, to predict risk of thromboembolic disease or death in the postdischarge period.

Methods

This study was a prospective registry of consecutive patients diagnosed with COVID-19 infection within the Northwell Health System. The Northwell Health Institutional Review Board approved our study (#20-0363) and, as described in International Conference on Harmonisation guidelines for Good Clinical Practice, provided regulatory oversight. The study was performed with waiver of informed consent. The patient population consisted of discharged adult (age >18 years) patients with a polymerase chain reaction–confirmed COVID-19 diagnosis admitted to 1 of the 12 hospitals within the Northwell Health System for nonobstetric/nongynecologic reasons from 1 March to 31 May 2020 and responding to follow-up phone calls. Transfers between in-system hospitals were considered as a single visit. For patients with multiple hospitalizations for COVID-19, only the first hospitalization was considered. Our hospital system policy, which went into effect on 7 April 2020, at the height of the pandemic, recommended extended thromboprophylaxis with the direct oral anticoagulant (DOAC) rivaroxaban (10 mg orally) or low molecular weight heparin (LMWH) enoxaparin (40 mg subcutaneously daily; if creatinine clearance ≥15 mL/min) for 30 days in patients with COVID-19 with an IMPROVE VTE score of ≥4 or D-dimer twice the upper limit of normal (ULN) or higher. The IMPROVE-DD VTE score is a validated VTE risk assessment model both patients without COVID-19, and more recently for patients with COVID-19.[15,16]

Data of interest were assessed by electronic medical record and health informatics exchange (HIE) review, a filtered radiology informatics database, and REDCap data entry with a comprehensive data collection form (including data derived from telephonic patient calls) through 90 days postdischarge (Figure 1). Our data set included demographic characteristics, all available diagnoses, comorbidities, VTE risk factors, laboratory values (highest values during index hospitalization), and medications, including in-hospital and

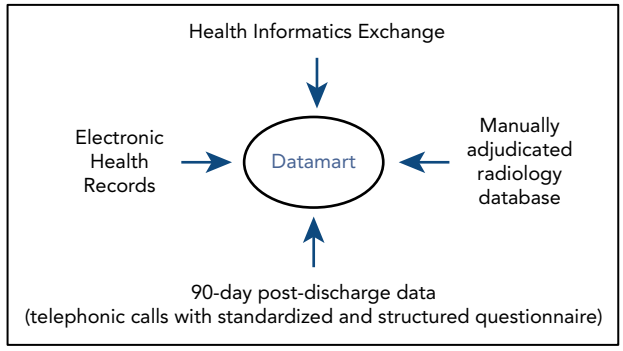

Figure 1. Data sources included in the unified repository (datamart).

postdischarge thromboprophylaxis, and image results were assessed up to 90 days after hospital discharge.

The primary efficacy outcome was a composite of VTE (DVT and PE), ATE (stroke, MI, non-MI coronary revascularization, major adverse limb event, and systemic embolism), and all-cause mortality (ACM) within 90 days of hospital discharge. DVT was defined as a noncompressible venous segment on compression ultrasonography or presence of an intraluminal filling defect on venography. PE was defined as an intraluminal filling defect on computed tomography (CT) angiography or spiral CT. Our hospital policy did not include any systematic screening for VTE during this study. Stroke was defined by a new focal neurologic defect lasting ≥24 hours, as confirmed by a neurologist with imaging studies. MI was defined by detection of a rise and/or fall of cardiac biomarker values with at least 1 value above the 99th percentile of the upper reference limit and with at least 1 of the following: 1) symptoms of acute myocardial ischemia, 2) new or presumed new significant ST segment–T wave changes or new left bundle branch block development of pathologic Q waves in the electrocardiogram, 3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with ischemic etiology, or 4) identification of an intracoronary thrombus by angiography or autopsy. Major adverse limb event was defined by confirmation of arterial obstruction by imaging (including ultrasound, CT, magnetic resonance imaging, or conventional angiography), surgical findings, or pathology. Systemic embolism was defined as abrupt vascular insufficiency associated with radiologic evidence of arterial occlusion in the absence of other likely mechanisms. Death was determined by telephonic patient calls. The principal safety outcome was major bleeding (MB) using International Society on Thrombosis and Haemostasis criteria.[17] Secondary outcomes included rehospitalization (with or without intensive care unit [ICU] admission), congestive heart failure exacerbation, atrial fibrillation/flutter, interstitial lung disease, myocarditis, and acute respiratory distress syndrome using standardized definitions.

Our dedicated team of 35 abstractors attempted to contact discharged patients via at least 3 phone calls on different days and at different times to obtain 1 set of data elements during the study period using a standardized and structured questionnaire. All study data were aggregated and systematically stored in a unified repository (datamart) developed by the Center for Research Informatics and Innovation. Our database includes data extracted through automatic extract-transform-load (ETL) processes that query and transfer data from radiology databases, electronic

health records (through identification of International Classification of Diseases 9th or 10th Revision codes), and the HIE and REDCap sources. The unified repository resides in an instance of Microsoft SQL Server database and uses a common data model that ensures semantic interoperability between data originating from disparate sources and accurate interpretation of statistical analyses.

The team of abstractors called the patients and entered any postdischarge outcomes in the standardized REDCap questionnaire. Subsequently, in the population of respondents, demographic characteristics, all available diagnoses, comorbidities, VTE risk factors, laboratory values (highest values during index hospitalization), medications including in-hospital and postdischarge thromboprophylaxis, and postdischarge events were captured through automatic ETL processes that extracted data from radiology images, electronic health records, and HIE. All postdischarge outcomes that were captured manually through phone calls (in REDCap) or through automatic ETL processes were pooled in a common file that was then used by the abstractors to manually screen the patients' records and confirm or reject the presence of an outcome. The postdischarge outcomes were adjudicated by 2 abstractors, and any disagreements were resolved by a third experienced abstractor (A.C.S.).

Data were summarized using descriptive statistics. Categorical variables were summarized using frequencies and percentages; continuous variables were summarized using means and standard deviations. Logistic regression analyses were performed to assess the association between independent variables and the composite outcome consisting of VTE or ATE or ACM (yes or no). Univariate analyses were performed first, followed by multivariate analyses. In the final logistic regression model, the following variables were included regardless of their univariate *P* values: age, body mass index, IMPROVE-DD VTE score, use of anticoagulants or antiplatelet agents, D-dimer >4 to 6 times the ULN or >6 times the ULN, history of VTE, coronary artery disease, history of peripheral arterial disease, history of carotid occlusive disease, congestive heart failure, chronic renal disease, race, and ICU admission. Variables with univariate *P* values <.2 were also included in the final model if selected through backward selection process. Results are reported as adjusted odds ratios (ORs) with 95% confidence intervals (CIs).

All statistical analyses were conducted using SAS software (version 9.4; Cary, NC). A 2- tailed *P* value <.05 was considered statistically significant.

Results

Demographic characteristics, comorbidities, and VTE risk factors

Of a total of 11 249 adult nonobstetric/nongynecologic hospitalized patients with COVID-19 (1 March to 31 May 2020), 3081 died in hospital. We thus identified 8168 eligible patients, of whom we contacted 8034. Our abstractors were able to capture the outcomes of 4906 unique patients (61% response rate) at a mean follow-up of 92.0 ± 13.8 days (Table 1). The cohort had a mean age of 61.7 ± 17.5 years, was predominantly male (53.7%), and consisted of 36.6% White, 21.4% Black, and 8.1% Asian patients; an additional 29.6% of patients who did not self-identify race were grouped in the "other" category.

Table 1. Demographic characteristics, comorbidities, and VTE risk factors (N = 4906)

Population characteristic	n (%)
Age, y	
Mean	61.7
SD	17.5
Median	63.0
IQR	25.0
Sex	
Male	2633 (53.7)
Female	2273 (46.3)
Race	
Black	1051 (21.4)
Asian	396 (8.1)
White	1797 (36.6)
Other or unspecified	1451 (29.6)
Unknown	211 (4.3)
Ethnicity	
Hispanic or Latino	1051 (21.4)
Not Hispanic or Latino	3373 (68.8)
Unknown	166 (3.4)
Declined	316 (6.4)
Comorbidities	
Hypertension	1895 (38.6)
Diabetes mellitus	1234 (25.1)
Coronary artery disease	340 (6.9)
Heart failure	219 (4.5)
Atrial fibrillation	321 (6.5)
Valvular heart disease	12 (0.2)
Chronic renal disease	334 (6.8)
Chronic lung disease	359 (7.3)
Chronic liver disease	48 (1.0)
Thyroid disease	354 (7.2)
BMI >35 kg/m2	752 (18.9)
ICU stay	578 (11.8)
Bleeding history	438 (8.9)
Ischemic stroke history	174 (3.6)
Carotid occlusive disease history	181 (3.7)
Peripheral arterial disease history	83 (1.7)
VTE risk factors	
Personal history of VTE	531 (10.8)
Family history of VTE	69 (1.4)
Thrombophilia	69 (1.4)
Cancer history	644 (13.1)
Autoimmune disease	102 (2.1)
Paraplegia/hemiplegia	18 (0.4)

BMI, body mass index; IQR, interquartile range; SD, standard deviation.

Main comorbidities included hypertension in 38.6%, diabetes mellitus in 25.1%, body mass index >35 kg/m^2 in 18.9%, ICU admission at index hospitalization in 11.8%, coronary artery disease in 6.9%, heart failure in 4.5%, atrial fibrillation in 6.5%,

Table 2. Key laboratory parameters during index hospitalization

	n	Mean ± SD	Median ± IQR
Laboratory parameters*			
WBC, × $10^3/\mu L$	4187	11.0 ± 6.7	9.5 ± 6.8
Hb, g/dL	4186	12.9 ± 2.1	12.9 ± 2.7
Hct, %	4186	39.7 ± 6.1	39.6 ± 7.7
Platelets, × $10^3/\mu L$	4187	341.8 ± 153.1	318.0 ± 206.0
Serum creatinine, mg/dL	4041	1.8 ± 2.5	1.0 ± 0.7
TnI, ng/mL	261	1.0 ± 3.9	0.1 ± 0.2
TnT, ng/mL	206	0.3 ± 0.8	0.1 ± 0.1
D-dimer, ng/mL	508	3373.6 ± 7113.2	779.0 ± 2500.0
IL-6, pg/mL	92	63.3 ± 112.6	22.0 ± 36.0
CRP, mg/L	626	138.7 ± 99.1	122.1 ± 137.5
Lactic acid, mmol/L	1269	2.2 ± 1.7	1.8 ± 1.3
LDH, μ/L	2339	469.1 ± 541.7	401.0 ± 250.0
Antiphospholipid antibodies			
Anticardiolipin IgG, GPL	30	17.3 ± 17.0	11.5 ± 10.8
Anticardiolipin IgM, MPL	32	19.6 ± 20.6	16.9 ± 14.3
β2GPI IgA, SAU	4	11.5 ± 2.4	11.7 ± 3.5
β2GPI IgM, SMU	5	39.5 ± 58.5	14.3 ± 1.2
LA dRVVT, sec	21	41.5 ± 10.3	39.9 ± 12.8
LA SCT, ratio	14	0.89 ± 0.19	0.91 ± 0.24

β2GP1, β-2-glycoprotein 1; CRP, C-reactive protein; GPL, G phospholipids; Hb, hemoglobin; Hct, hematocrit; Ig, immunoglobulin; IQR, interquartile range; LA dRVVT, lupus anticoagulant dilute Russell's viper venom time; LA SCT, lupus anticoagulant silica clotting time; LDH, lactate dehydrogenase; MPL, M phospholipids; SD, standard deviation; Tn, troponin;

*Highest value during initial hospitalization. Normal laboratory values are as follows: TnI, 0.00-0.03 ng/mL; TnT, 0.0-0.06 ng/mL; D-dimer, 0.0-229.0 ng/mL; IL-6, 0.0-13.0 pg/mL; CRP, 0.0-0.4 mg/L; lactic acid, 0.5-2.0 mmol/L; LDH, 50.0-242.0 μ/L; anticardiolipin IgG, 0.0-12.5 GPL; anticardiolipin IgM, 0.0-12.5 MPL; β2GPI IgA, 0.0-20.0 SAU; and β2GPI IgM, 0.0-.20.0 SMU.

history of ischemic stroke in 3.6%, history of carotid occlusive disease in 3.7%, peripheral arterial disease in 1.7%, history of bleeding in 8.9%, chronic renal disease in 6.8%, chronic lung disease in 7.3%, chronic liver disease in 1.0%, and thyroid disease in 7.2%.

Main comorbidities associated with increased risk of VTE included a personal history of VTE in 10.8%, known thrombophilia in 1.4%, cancer in 13.1%, autoimmune disease in 2.1%, family history of VTE in 1.4%, and paraplegia or hemiplegia in 0.4%.

The population characteristics and main comorbidities of 3262 patients who were eligible and did not respond to follow-up phone calls or were not contacted are summarized in the data supplement. There did not seem to be major differences in demographic characteristics and comorbidities between the group of patients for whom follow-up was available and this group.

Laboratory parameters

In-hospital laboratory parameters included mild leukocytosis (white blood cell count, 11.0 ± 6.7 × $10^3/\mu L$), mildly increased serum creatinine (1.8 ± 2.5 mg/dL), elevated troponin I (1.0 ± 3.9 ng/mL), markedly increased D-dimer (3373.6 ± 7113.2 ng/mL), increased interleukin-6 (IL-6; 63.3 ± 112.6 pg/mL), C-reactive protein (138.7 ± 99.1 mg/L), lactic acid (2.2 ± 1.7 mmol/L), and lactate dehydrogenase (469.1 ± 541.7 μ/L; Table 2).

In-hospital and discharge medications

In-hospital medications included IL-6 antagonists (tocilizumab or sarilumab) in 56.3%, hydroxychloroquine in 55.6%, statins in 30.6%, glucocorticoids in 27.1%, aspirin in 21.9%, other antiplatelet agents in 5.7%, famotidine in 14.3%, antibiotics in 10.5%, IL-1 antagonist (anakinra) in 6.0%, and antivirals in 2.0% (Tables 3-6).

At index hospitalization, thromboprophylaxis consisted of prophylactic enoxaparin in 53.6%, treatment dose enoxaparin in 5.5%, subcutaneous prophylactic unfractionated heparin in 20.1%, IV treatment-dose unfractionated heparin in 4.7%, prophylactic apixaban in 6.3%, treatment-dose apixaban in 1.1%, prophylactic rivaroxaban in 2.3%, treatment-dose rivaroxaban in 1.0%, and treatment-dose warfarin in 1.6% (Tables 3-6; supplemental Table 1, available on the *Blood* Web site).

Postdischarge thromboprophylaxis was prescribed in 12.7% of the population and consisted of prophylactic-dose rivaroxaban in 6.9%, prophylactic-dose apixaban in 3.7%, and prophylactic-dose enoxaparin in 1.3%. The rate of postdischarge thromboprophylaxis in patients with an IMPROVE-DD VTE score ≥4 was 21.5% compared with patients with an IMPROVE-DD VTE score <4 who had a postdischarge thromboprophylaxis rate of 9.7% ($P < .0001$).

VTE, ATE, ACM, BM, and other postdischarge event rates

VTE was diagnosed in 76 patients (1.55%) postdischarge and included 44 DVTs (0.90%), 42 PEs (0.85%), 2 splanchnic vein thrombosis (0.04%), and 3 other vein thromboses (0.06%; right cephalic vein, n = 1; brachiobasilic arteriovenous fistula, n = 1; and superior vena cava, n = 1; Table 7).

ATE was diagnosed postdischarge in 84 patients (1.71%) and included stroke in 22 (0.45%), myocardial infarction in 24 (0.49%), non-MI coronary revascularization in 6 (0.12%), major adverse limb event in 26 (0.53%), and systemic embolism in 16 (0.33%).

Table 3. Key in-hospital and discharge medications

Medication	n (%)	
	In hospital	Discharge
IL-6 antagonists*	2762 (56.3)	262 (5.3)
Hydroxychloroquine	2728 (55.6)	262 (5.3)
Statins	1500 (30.6)	135 (2.8)
Aspirin	1073 (21.9)	91 (1.9)
Other antiplatelets†	279 (5.7)	29 (0.6)
Famotidine	699 (14.3)	65 (1.3)
Antibiotics	517 (10.5)	31 (0.6)
Anakinra	295 (6.0)	0 (0.0)
Antivirals	98 (2.0)	1 (0.02)
IV immunogloblin	26 (0.5)	0 (0.0)
Glucocorticoids	1329 (27.1)	118 (2.4)

*Tocilizumab or sarilumab.

†Clopidogrel, prasugrel, ticagrelor, or cangrelor.

Postdischarge ACM was 4.83%. MB was diagnosed in 85 patients (1.73%). Of these 85 patients with MB, 15 (17.6%) were prescribed postdischarge anticoagulants.

Secondary postdischarge events included a rate of rehospitalization of 15.5%, with 4.69% admitted to the ICU; acute respiratory distress syndrome in 113 (2.3%); heart failure exacerbation in 63 (1.28%); new-onset atrial fibrillation/flutter in 22 (0.45%); and interstitial lung disease in 26 (0.53%).

VTE, ATE, or ACM

Univariate analysis Overall the VTE, ATE, or ACM rate was 7.13% (350 of 4906 patients). Univariate analysis showed that the composite end point was associated with age >75 years (OR, 4.33; 95% CI, 3.47-5.40), race (other; OR, 0.47; 95% CI, 0.36-0.62), coronary artery disease (OR, 2.45; 95% CI, 1.78-3.39), congestive heart failure (OR, 1.99; 95% CI, 1.31-3.00), atrial fibrillation (OR, 2.50; 95% CI, 1.80-3.46), chronic renal disease (OR, 2.86; 95% CI, 2.10-3.91), thyroid disease (OR, 1.58; 95% CI, 1.10-2.26), admission to the ICU (OR, 2.66; 95% CI, 2.10-3.38), history of bleeding (OR, 2.39; 95% CI, 1.78-3.21), history of ischemic stroke (OR, 3.13; 95% CI, 2.10-4.67), carotid occlusive disease (OR, 3.23; 95% CI, 2.19-4.77), and peripheral arterial disease (OR, 2.96; 95% CI, 1.67-5.23; Table 8). VTE risk factors that were associated with the composite end point included personal history of VTE (OR, 4.29; 95% CI, 3.35-5.50), family history of VTE (OR, 4.07; 95% CI, 2.30-7.20), known thrombophilia (OR, 4.07; 95% CI, 2.30-7.20), history of cancer (OR, 1.57; 95% CI, 1.18-2.08), and IMPROVE-DD VTE score ≥4 (OR, 3.64; 95% CI, 2.91-4.55). Lastly, the composite end point was associated with a D-dimer level >6 times the ULN (OR, 1.81; 95% CI, 1.43-2.31) and a neutrophil/lymphocyte ratio ≥3 (OR, 1.39; 95% CI, 1.07-1.81).

Multivariate analysis Multivariate analysis showed significant association between VTE, ATE, or ACM with advanced age (>75 years; OR, 3.66; 95% CI, 2.84-4.71; $P < .0001$), race (other; OR, 0.68; 95% CI, 0.50-0.93; $P = .015$), IMPROVE-DD VTE score ≥4 (OR, 1.51; 95% CI, 1.06-2.14; $P = .023$), personal history of VTE (OR, 2.99; 95% CI, 2.00-4.47; $P < .0001$), coronary artery disease (OR, 1.50; 95% CI, 1.04-2.17; $P = .032$), peripheral arterial disease (OR, 2.04; 95% CI, 1.10-3.80; $P = .024$), carotid occlusive disease (OR, 2.02; 95% CI, 1.30-3.14; $P = .0002$), chronic renal disease (OR, 2.10; 95% CI, 1.47-3.0; $P < .0001$), and admission to the ICU (OR, 2.22; 95% CI, 1.78-2.93; $P < .0001$). The use of anticoagulant medications prescribed at discharge was significantly associated with a 46% reduction in the composite primary efficacy outcome, with ACM comprising the majority of this outcome (OR, 0.54; 95% CI, 0.47-0.81; $P = .003$; Table 9). Sensitivity analysis was also performed in the subgroup of patients receiving prophylactic-dose anticoagulant medications at discharge, and the anticoagulant medication effect was consistent with a reduction in this composite primary efficacy outcome (OR, 0.55; 95% CI, 0.37-0.83; $P = .0046$).

The results of a multivariate analysis that was not part of the prespecified analysis and included only VTE and ATE without

Table 4. Key in-hospital corticosteroids (n = 1329)

Medication	n (%)		
	Patients	Dose, mg	Duration, d
Hydrocortisone	36 (27.1)	51.1 (29.6)	7.2 (14.7)
Prednisone	290 (21.8)	31.8 (17.6)	15.5 (33.2)
Prednisolone	1 (<0.01)	60.0 (0.0)	3.6 (0.0
Methylprednisolone	1301 (97.9)	55.4 (70.4)	6.4 (12.6)
Dexamethasone	70 (5.3)	7.9 (7.2)	12.4 (21.0)
Bethamethasone	5 (<0.01)	13.2 (2.7)	1.0 (0.0)

In-hospital corticosteroid frequency: betamethasone, once daily; dexamethasone, once, twice, 3 times, and 4 times daily; hydrocortisone, once, twice, 3 times, and 4 times daily; methylprednisolone, once, twice, 3 times, and 4 times daily, every 4 hours; prednisolone, once daily; and prednisone, once and twice daily.

Table 5. Key in-hospital and discharge anticoagulants

Anticoagulant	n (%)			
	In hospital		Discharge	
	Prophylactic	Treatment	Prophylactic	Treatment
Enoxaparin	2630 (53.6)	272 (5.5)	62 (1.3)	13 (0.3)
UFH (subcutaneous)	984 (20.1)	—	3 (0.06)	—
UFH (IV)	—	230 (4.7)	—	—
Fondaparinux	1 (0.02)	5 (0.1)	—	—
Apixaban	309 (6.3)	52 (1.1)	180 (3.7)	—
Dabigatran	—	—	—	—
Rivaroxaban	112 (2.3)	51 (1.0)	336 (6.9)	1 (0.02)
Argatroban (IV)	—	—	—	—
Warfarin	—	77 (1.6)	—	17 (0.4)

UFH, unfractionated heparin.

mortality as a sensitivity analysis are shown in the data supplement.

Discussion

Our prospective multihospital registry of 4906 adult hospitalized patients with COVID-19 that have a mean follow-up of 92 days represents the largest study to date of postdischarge major thromboembolic events and death conducted in this population. Our results reveal 3 important findings. First, VTE, ATE, and ACM occur with a higher frequency during this postdischarge period than previously thought. Second, key predictors of postdischarge major thromboembolic events and death include advanced age >75 years, cardiovascular risk factors (personal history of VTE, coronary artery disease, carotid occlusive disease, and peripheral arterial disease), CKD, IMPROVE-DD VTE score ≥4, and ICU stay. Third, postdischarge anticoagulants, mostly at prophylactic dosages, reduce the risk of major thromboembolic events and death by 46%.

It is by now well recognized that COVID-19 induces a prothrombotic state resulting from interactions between the immune, inflammatory, and coagulation systems in sick, hospitalized patients that lead to a multifold increased risk of in-hospital VTE and ATE.[4,18] In addition, autopsy data in hospitalized patients with COVID-19 suggested that ~60% and up to 100% of thrombotic events including PE and pulmonary arterial thrombosis may not be suspected before death, indicating that thrombotic mechanisms

Table 6. Anticoagulants at discharge and IMPROVE-DD score

IMPROVE-DD score	Anticoagulant at discharge		
	Yes	No	*P**
<4	380 (9.7)	3537 (90.3)	**<.0001**
≥4	213 (21.5)	776 (78.5)	

*Bold font indicates significance.

Table 7. ATE, VTE, mortality, MB, and other postdischarge outcomes

	n (%)
VTE	76 (1.55)*
DVT	44 (0.90)
PE	42 (0.85)
Splanchnic vein thrombosis	2 (0.04)
Other vein thrombosis	3 (0.06)
Arterial thromboembolism	84 (1.71)*
Stroke	22 (0.45)
MI	24 (0.49)
Non-MI coronary revascularization	6 (0.12)
Major adverse limb event	26 (0.53)
Systemic embolism	16 (0.33)
All-cause mortality	237 (4.83)
MB	85 (1.73)
Other outcomes	
Rehospitalization	759 (15.5)
ICU admission	230 (4.69)
Heart failure exacerbation	63 (1.28)
Atrial fibrillation/flutter	22 (0.45)
Interstitial lung disease	26 (0.53)
Myocarditis	1 (0.02)
Acute respiratory distress syndrome	113 (2.3)

*Patients may have multiple events.

Table 8. VTE, ATE, or mortality: univariate analysis

Predictor	OR	95% CI	P*
Age >75 y	4.33	3.47-5.40	**<.0001**
Female sex	0.97	0.78-1.21	.810
Race			
White	1.00	1.00-1.00	
Black	0.73	0.55-0.96	.811
Asian	0.73	0.48-1.10	.843
Other	0.47	0.36-0.62	**.0001**
Comorbidities			
Hypertension	1.37	1.10-1.70	**.005**
Diabetes mellitus	1.30	1.03-1.65	**.030**
Coronary artery disease	2.45	1.78-3.39	**<.0001**
Congestive heart failure	1.99	1.31-3.00	**.001**
Atrial fibrillation	2.50	1.80-3.46	**<.0001**
Valvular heart disease	1.18	0.15-9.20	.872
Chronic renal disease	2.86	2.10-3.91	**<.0001**
Chronic lung disease	0.97	0.64-1.48	.897
Chronic liver disease	1.52	0.60-3.87	.378
Thyroid disease	1.58	1.10-2.26	**.013**
BMI >35 kg/m²	0.85	0.67-1.08	.186
ICU admission	2.66	2.10-3.38	**<.0001**
Bleeding history	2.39	1.78-3.21	**<.0001**
Ischemic stroke history	3.13	2.10-4.67	**<.0001**
Carotid occlusive disease history	3.23	2.19-4.77	**<.0001**
Peripheral arterial disease history	2.96	1.67-5.23	**.0002**
VTE risk factors			
Personal history of VTE	4.29	3.35-5.50	**<.0001**
Family history of VTE	4.07	2.30-7.20	**<.0001**
Thrombophilia	4.07	2.30-7.20	**<.0001**
Cancer history	1.57	1.18-2.08	**.0019**
Autoimmune disease	0.53	0.19-1.44	.211
Paraplegia/hemiplegia	1.63	0.37-7.12	.520
IMPROVE-DD ≥4	3.64	2.91-4.55	**<.0001**
D-dimer, ng/mL			
0-920 (<4× ULN)	1.00	1.00-1.00	
921-1380 (4-6× ULN)	1.51	0.99-2.30	.054
>1380 (>6× ULN)	1.81	1.43-2.31	**<.0001**
NLR ≥3	1.39	1.07-1.81	**.013**
Medications at discharge			
Anticoagulants	0.85	0.60-1.21	.367
Antiplatelets	1.56	0.87-2.80	.137

BMI, body mass index; NLR, neutrophil/lymphocyte ratio.

*Bold font indicates significance.

play a major role in mortality.[5,6] As such, major thrombotic events and death may represent competing risks in these patients.

Our study found that hospitalized patients with COVID-19 had a postdischarge ACM rate of nearly 5%; an ATE rate of 1.71% that included stroke, MI, non-MI coronary revascularization, major adverse limb event, and systemic embolism; and a VTE rate of 1.55%, more than half of the events of which included

Table 9. VTE, ATE, or mortality: multivariable analysis

Predictor	OR	95% CI	P*
Age >75 y	3.66	2.84-4.71	**<.0001**
BMI >35 kg/m²	0.95	0.73-1.24	.691
Black race†	0.79	0.57-1.09	.149
Asian race†	1.18	0.75-1.84	.476
Other race†	0.68	0.50-0.93	**.015**
IMPROVE-DD ≥4	1.51	1.06-2.14	**.023**
Anticoagulants (discharge)	0.54	0.47-0.81	**.003**
Antiplatelets (discharge)	1.50	0.77-2.90	.231
D-dimer 4-6× ULN‡	1.17	0.74-1.85	.507
D-dimer >6× ULN‡	1.09	0.81-1.45	.577
Personal history of VTE	2.99	2.00-4.47	**<.0001**
Coronary artery disease	1.50	1.04-2.17	**.032**
Peripheral arterial disease history	2.04	1.10-3.80	**.024**
Carotid occlusive disease history	2.02	1.30-3.14	**.0002**
Heart failure	0.93	0.58-1.51	.787
Chronic renal disease	2.10	1.47-3.0	**<.0001**
ICU admission	2.22	1.78-2.93	**<.0001**
Lymphocyte count	0.97	0.96-0.99	**<.0001**

*Bold font indicates significance.

†Compared with White race.

‡Compared with 4× ULN.

PE, with a composite primary outcome rate of 7.13% in the 90-day period postdischarge. These rates are higher than previous reports of postdischarge thrombotic events in hospitalized patients with COVID-19, with absolute VTE rates of 0.2% to 0.98% seen in 3 studies of 1529, 1877, and 102 patients, respectively, whereas results of another small study of 163 patients were more in line with our findings, suggesting a cumulative incidence of arterial and venous thrombosis of 2.5% (95% CI, 0.8% to 7.6%) at 30 days.[7,8,12,19] The reasons for these discrepant results may include the small sample sizes, retrospective designs, shorter observation periods, or lack of systematic follow-up and uniform data collection seen in previous studies compared with our prospective registry design. In addition, our results suggest at least a fourfold increased risk of major thromboembolic events and death in the postdischarge period in patients with COVID-19 compared with untreated hospitalized medically ill patients (including those with sepsis and pneumonia) in the pre–COVID-19 era, with event rates of ~1.77%.[13] Our study also found that ~1 in 6 patients was rehospitalized in the immediate postdischarge period, which is in accordance with a previous large study in patients with COVID-19 during the 60 days postdischarge (19.9%)[20] and comparable with 30-day readmission rates in patients with pneumonia (17.8%).[21]

The postdischarge MB rate of 1.73% seen in our study was higher than that in a previous report of postdischarge MB of 0.7% (95% CI, 0.1% to 5.1%) seen in hospitalized patients with COVID-19.[8] However, this study included a small sample size and retrospective design, which may have underestimated results. In addition, our MB rate is multifold higher than previous rates of MB of ~0.2% seen in contemporary studies of extended postdischarge thromboprophylaxis of hospitalized medically ill patients before the COVID-19 era.[13] Of the 85 patients with MB in our study, only 17.6% were prescribed postdischarge anticoagulants. These data suggest that although the majority of MB occurred in the patient population not prescribed postdischarge anticoagulants, a clinically important relationship between postdischarge anticoagulation and MB cannot be ruled out. An important bleeding diathesis in hospitalized patients with COVID-19 also cannot be excluded, although the rates of thrombotic events (and presumably unrecognized thrombotic events leading to death) are at least twofold higher than MB events.

Our study found that advanced age >75 years, cardiovascular risk factors (personal history of VTE, coronary artery disease, carotid occlusive disease, and peripheral arterial disease), CKD, IMPROVE-DD VTE score ≥4, and ICU stay were all significantly associated with postdischarge major thromboembolic events and death, with ORs of ~2.0 to 3.66, whereas "other" race in patients who did not self-identify race seemed protective, with an OR of 0.68. Advanced age, history of cardiovascular disease, and ICU level of care have been consistently associated with poor outcomes and increased thrombotic events and mortality in hospitalized patients with COVID-19.[3,22,23] CKD has also been associated with increased risk of thrombotic events and mortality in patients with COVID-19.[24,25] The IMPROVE VTE score has been extensively validated in medically ill patients,[26] and addition of an elevated D-dimer >2 times the ULN to improve model discrimination has identified medically ill patients (including those with pneumonia and sepsis) with a nearly threefold increased risk for VTE.[27] Consistent reports support that elevated D-dimer, which may reflect the hyperinflammatory state and cytokine storm that leads to thromboinflammation, especially >4 or 6 times the ULN, is a strong predictor of mortality and thrombosis in patients with COVID-19.[2,28] In our study, a D-dimer greater than sixfold the ULN was predictive of our primary outcome in univariate analysis, but it lost significance in the multivariate analysis. However, the IMPROVE-DD VTE score, which incorporates elevated D-dimer, was a significant predictor of postdischarge cardiovascular events and death, with an OR of 1.5 in the multivariate analysis. More recently, the IMPROVE-DD VTE score has been validated in hospitalized patients with COVID-19, with patients with a score ≥4 having a high risk of thrombosis.[16]

An important observation in our study is that anticoagulants (either LMWH or a DOAC), mainly at prophylactic doses and prescribed at hospital discharge, were significantly associated with a reduction in the composite outcome of ATE, VTE, or ACM by 46% in hospitalized patients with COVID-19. ACM represented the key component of our composite outcome. Previous autopsy-based studies in hospitalized patients with COVID-19 revealed that unsuspected antemortem thrombotic events such as in situ PE and pulmonary arterial thrombi may play a key role in subsequent death.[4-6,18] Our health system policy at the time of our study advocated for extended anticoagulant thromboprophylaxis for 30 days after hospitalization in high-risk hospitalized patients with COVID-19.[29] Previous high-quality data from randomized trials in high-risk hospitalized medically ill patients (including those with sepsis/pneumonia, IMPROVE VTE score ≥4, and elevated D-dimer) revealed a 28% to 38% risk reduction for major and fatal thromboembolic events (including ATE and VTE) using extended post–hospital discharge thromboprophylaxis with a DOAC.[13,14] Antithrombotic guidelines and hospital protocols in hospitalized patients with COVID-19 diverge on this topic, with some suggesting extended thromboprophylaxis in high-risk patients with COVID-19[10,18,29,30] and others not advocating for extended thromboprophylaxis.[9,11,31] Our findings support extended thromboprophylaxis with an anticoagulant (either LMWH or preferably a DOAC because of oral route of administration) in high-risk patients with COVID-19 at low bleeding risk at the time of discharge, especially because a majority of postdischarge MB events in our study (82.4%) occurred in patients not receiving postdischarge anticoagulants. High-risk criteria include advanced age >75 years, presence of cardiovascular risk factors (personal history of VTE, coronary artery disease, carotid occlusive disease, and peripheral arterial disease), CKD, IMPROVE-DD VTE score ≥4, or ICU stay.

Our study has several strengths and limitations. Our prospective registry design and large sample size of consecutive and diverse patients hospitalized with COVID-19 within a multihospital health system reinforce the generalizability of our findings. In addition, the use of a standardized data collection instrument and unified datamart reflects the high integrity of data collection, and use of adjudicated outcomes using record review reflects the high quality of outcome capture. Another potential strength when interpreting study results is the well-defined criteria for postdischarge thromboprophylaxis. Limitations include the lack of a comparator group, the potential introduction of hidden bias with our study's 61% response rate, the inability to capture medication adherence including omission of anticoagulant use, and the inability to undergo further statistical analyses of less frequent cardiovascular complications with multivariate analyses. Another study limitation when interpreting results is the relatively small subgroup of patients who received postdischarge thromboprophylaxis.

In summary, our prospective multihospital registry of 4906 adult hospitalized patients with COVID-19 followed for a mean of 92 days reveals that VTE, ATE, and ACM occur with a higher frequency during this postdischarge period than previously reported. Key predictors of postdischarge thromboembolic events and death include advanced age, cardiovascular risk factors, CKD, IMPROVE-DD VTE score ≥4, and ICU stay. The use of postdischarge anticoagulants, mostly at prophylactic doses, was associated with a reduction of the risk of major thromboembolic events and death by 46%. Well-conducted randomized trials of the efficacy and safety of extended postdischarge thromboprophylaxis in hospitalized patients with COVID-19 are needed.

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Authorship

Contribution: D.G. and A.C.S. conceived and designed the study; D.G., J.T., S.F., T.P., S.W., G.T., R.T., C.L., M.S., C.B., D.G., C.C., S.I., E.G., A.S., B.G., M.A.B., M.Q., M.Z., M.G., and A.C.S. acquired, analyzed, or interpreted data; M.Z., J.T., and M.Q. performed statistical analysis; A.C.S., S.L.A., A.D., G.S.M., T.M., K.W.D., M.M., and E.A. supervised the study; D.G., A.C.S., S.L.A., and M.G. drafted the manuscript; D.G., J.T., M.Q., and M.Z. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; and all authors approved the final manuscript.

Conflict-of-interest disclosure: S.L.A. is a current equity holder in Bristol-Myers Squibb and C4 Therapeutics. A.C.S. has consulting for Janssen, Boehringer Ingelheim, Bayer, Bristol-Myers Squibb, Portola, and ATLAS Group and received research funding from Janssen and Boehringer Ingelheim. M.M. has consulted for Bayer and Pfizer and received support for congress attendance from Bayer, Pfizer, and Leo. E.A. has consulted for Bayer and received support for congress attendance from Bayer and Boehringer Ingelheim. The remaining authors declare no competing financial interests.

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Footnotes

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Appendix

The Northwell COVID-19 Research Consortium members: Mohanambal Manoharan, Kerry Meyers, Christina Ghiuzeli, Erin Jou, Ivan Ramirez De Oleo, and Jordan Gitlin.

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