

Thrombosis, Bleeding, and the Observational Effect of Early Therapeutic Anticoagulation on Survival in Critically Ill Patients With COVID-19

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Background: Hypercoagulability may be a key mechanism of death in patients with coronavirus disease 2019 (COVID-19).

Objective: To evaluate the incidence of venous thromboembolism (VTE) and major bleeding in critically ill patients with COVID-19 and examine the observational effect of early therapeutic anticoagulation on survival.

Design: In a multicenter cohort study of 3239 critically ill adults with COVID-19, the incidence of VTE and major bleeding within 14 days after intensive care unit (ICU) admission was evaluated. A target trial emulation in which patients were categorized according to receipt or no receipt of therapeutic anticoagulation in the first 2 days of ICU admission was done to examine the observational effect of early therapeutic anticoagulation on survival. A Cox model with inverse probability weighting to adjust for confounding was used.

Setting: 67 hospitals in the United States.

Participants: Adults with COVID-19 admitted to a participating ICU.

Measurements: Time to death, censored at hospital discharge, or date of last follow-up.

Results: Among the 3239 patients included, the median age was 61 years (interquartile range, 53 to 71 years), and

2088 (64.5%) were men. A total of 204 patients (6.3%) developed VTE, and 90 patients (2.8%) developed a major bleeding event. Independent predictors of VTE were male sex and higher D-dimer level on ICU admission. Among the 2809 patients included in the target trial emulation, 384 (11.9%) received early therapeutic anticoagulation. In the primary analysis, during a median follow-up of 27 days, patients who received early therapeutic anticoagulation had a similar risk for death as those who did not (hazard ratio, 1.12 [95% CI, 0.92 to 1.35]).

Limitation: Observational design.

Conclusion: Among critically ill adults with COVID-19, early therapeutic anticoagulation did not affect survival in the target trial emulation.

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Hypercoagulability in patients with coronavirus disease 2019 (COVID-19) may be a key mechanistic pathway leading to multiorgan failure and death (1, 2). Patients with COVID-19 have been reported to experience high rates of venous thromboembolism (VTE) (3) and extracorporeal circuit thrombosis (4). Autopsies show extensive fibrin thrombi within small vessels and capillaries (5). These observations have prompted some experts to recommend empirical treatment with therapeutic anticoagulation for critically ill patients with COVID-19 (1, 2).

Data on the incidence, risk factors, and prognosis associated with VTE in patients with COVID-19 are largely limited to single-center reports (4, 6–8). Granular, nationally representative data on VTE, as well as major bleeding events, are urgently needed. Furthermore, until data from randomized trials on the effect of therapeutic anticoagulation on outcomes in COVID-19 become available, clinical

care may be informed by robust estimates from observational data.

We used data from a multicenter cohort study of critically ill patients with COVID-19 admitted to intensive care units (ICUs) in the United States to evaluate the incidence of VTE and major bleeding, identify risk factors for VTE, and examine the observational effect of early initiation of therapeutic anticoagulation on survival.

See also:

Web-Only
Supplement

METHODS

Study Design, Oversight, and Patient Population

We used data from STOP-COVID (Study of the Treatment and Outcomes in Critically Ill Patients With COVID-19), a multicenter cohort study that enrolled consecutive adults (aged ≥ 18 years) with laboratory-confirmed COVID-19 admitted to participating ICUs at 67 geographically diverse hospitals in the United States (Supplement Table 1 and Supplement Figure 1, available at [Annals.org](https://www.annals.org)) (9). We included patients admitted to ICUs between 4 March 2020 and 11 April 2020. We followed patients until the first of hospital discharge, death, or 8 May 2020. The study was approved with a waiver of informed consent by the institutional review board at each participating site.

Data Collection

Study personnel at each site collected data by manual chart review and used a standardized case report form to enter data into a secure online database. Patient-level data included baseline information on demographics, coexisting conditions, symptoms, medications before hospital admission, and vital signs; daily data for the 14 days after ICU admission on physiologic and laboratory values, medications, nonmedication treatments, organ support, and acute organ injury; and outcome data on vital status at discharge. We also collected site-specific data on routine screening protocols for VTE and anticoagulation prophylaxis. A complete list of variables is provided in the Case Report Form in the Supplement, and definitions of outcomes and events are listed in Supplement Table 2 (available at [Annals.org](https://www.annals.org)). All data were validated through a series of automated and manual verifications (Methods section of the Supplement).

Definitions

We collected data on the incidence, clinical features, and 28-day mortality in patients with radiographically confirmed VTE (including deep venous thrombosis and pulmonary embolism), ischemic stroke, and major bleeding. Data on radiographically confirmed versus clinically suspected VTE are reported separately. Ischemic stroke was confirmed radiographically in all cases. We defined major bleeding as occurring in a critical area or organ (for example, intracranial, retroperitoneal, pericardial, or intramuscular bleeding with compartment syndrome) or requiring a procedural intervention; the requirement for red blood cell transfusion alone was not sufficient to qualify as a major bleed. This definition is similar to or stricter than definitions used by landmark clinical trials of novel anticoagulant reversal agents (10) and the International Society for Thrombosis and Haemostasis (11). We also collected data on the incidence of disseminated intravascular coagulation, heparin-induced thrombocytopenia, and coagulopathy (definitions provided in Supplement Table 2).

Statistical Analysis

Continuous and categorical variables are expressed as median (interquartile range [IQR]) and count (percentage), respectively. We used multivariable logistic regression to

identify predictors of radiographically confirmed VTE. We prespecified the following covariates, which were assessed on the day of ICU admission: age; sex; body mass index; current smoking status; active cancer; and leukocyte count, platelet count, D-dimer, shock, invasive mechanical ventilation, therapeutic anticoagulation, and aspirin (Methods section of the Supplement). Missing data were multiply imputed with 5 data sets, and results were pooled using Rubin's rules (12).

To assess interhospital variation in VTE incidence and use of therapeutic anticoagulation in the first 14 days after ICU admission, we employed multilevel logistic regression modeling with patients nested in hospitals. This approach addresses the poor reliability of estimates stemming from hospitals submitting few cases. We additionally excluded hospitals that submitted data on fewer than 30 patients (for VTE incidence) and fewer than 10 patients (for therapeutic anticoagulation) to further improve the reliability of our estimates. We adjusted for the same covariates as the aforementioned VTE model.

Target Trial Specification

To examine the observational effect of early initiation of therapeutic anticoagulation on in-hospital survival, we emulated a hypothetical target trial comparing patients who received therapeutic anticoagulation in the 2 days after ICU admission to those who did not. We used the target trial framework to make our research question explicit and to guide the design of the observational analysis (13-16). The time period of 2 days was chosen for treatment assignment to provide greater homogeneity between patients, to limit indication bias, to allow longer follow-up, and for biological plausibility, because therapies initiated early and before irreversible organ injury may be more likely to be beneficial (17). To emulate the eligibility criteria of a hypothetical clinical trial of therapeutic anticoagulation, we excluded patients if they were receiving anticoagulation before hospitalization or if they had any of the following within 2 days after ICU admission: confirmed or suspected VTE, extracorporeal membrane oxygenation, major bleeding, or a platelet count less than 50×10^9 cells/L.

Target Trial Emulation

The primary analysis compares survival among patients who received or did not receive therapeutic anticoagulation in the first 2 days of ICU admission. Survival time was defined as the interval from ICU admission to death, censored at hospital discharge, or the end of follow-up, whichever occurred first. Hazard ratios and 95% CIs were estimated using a Cox model. Patients who initiated therapeutic anticoagulation on day 3 or later after ICU admission were categorized in the control group, in keeping with an intention-to-treat approach.

Inverse Probability Weighting

We adjusted for confounding using inverse probability weighting. We fit a logistic regression model with initiation of therapeutic anticoagulation in the first 2 days of ICU admission as the outcome, conditional on the following covariates that were prespecified based on

clinical judgment: age; sex; race; ethnicity; body mass index; hypertension; diabetes mellitus; atrial fibrillation or atrial flutter; coronary artery disease; congestive heart failure; current smoking status; active cancer; duration of symptoms before ICU admission; severity-of-illness covariates assessed on ICU admission, including PaO₂:FIO₂,

shock, the renal, liver, and coagulation components of the Sequential Organ Failure Assessment score (18), and inflammation (assessed by C-reactive protein, D-dimer, and ferritin); and concurrent therapies received on ICU admission, including aspirin, neuromuscular blockade, and prone positioning. Additional details are provided in

Table 1. Patient Characteristics at Baseline

Characteristic*	All Patients (N = 3239)	Confirmed VTE (N = 204)	No Confirmed VTE (N = 3035)	Major Bleeding (N = 90)	No Major Bleeding (N = 3149)
Demographics					
Median age (IQR), y	61 (53-71)	60 (50-67)	62 (52-71)	63 (55-74)	62 (51-71)
Male, n (%)	2088 (64.5)	149 (73.0)	1939 (63.9)	64 (71.1)	2024 (64.3)
Race, n (%)					
White	1194 (36.9)	66 (32.4)	1128 (37.2)	33 (36.7)	1161 (26.9)
Black	1015 (31.3)	86 (42.2)	929 (30.6)	28 (31.1)	987 (31.3)
Asian	198 (6.1)	5 (2.5)	193 (6.4)	8 (8.9)	190 (6.0)
Other	832 (25.7)	47 (23.0)	785 (25.9)	21 (23.3)	811 (25.8)
Hispanic, n (%)	663 (20.5)	37 (18.1)	626 (20.6)	14 (15.6)	649 (20.6)
Median body mass index (IQR), kg/m ²	30.3 (25.5-36.0)	30.9 (26.9-36.7)	30.3 (26.5-35.9)	28.4 (25.2-32.2)	30.4 (26.6-36.2)
Pregnant, n (%)	20 (0.6)	1 (0.5)	19 (0.6)	1 (1.1)	19 (0.6)
Coexisting conditions, n (%)†					
Diabetes mellitus, insulin dependent	464 (14.3)	19 (9.3)	445 (14.7)	19 (21.1)	445 (14.1)
Diabetes mellitus, noninsulin dependent	847 (26.2)	53 (26.0)	794 (26.2)	30 (33.3)	817 (26.0)
Hypertension	1977 (61.0)	109 (53.4)	1868 (61.6)	60 (66.7)	1917 (60.9)
Chronic lung disease					
COPD	273 (8.4)	15 (7.4)	258 (8.5)	8 (8.9)	265 (8.4)
Asthma	344 (10.6)	22 (10.8)	322 (10.6)	6 (6.7)	338 (10.7)
Other pulmonary disease	238 (7.4)	16 (7.8)	222 (7.3)	8 (8.9)	230 (7.3)
Current or former smoker	957 (29.6)	62 (30.4)	895 (29.5)	24 (26.7)	933 (29.6)
Coronary artery disease	431 (13.3)	23 (11.3)	408 (13.4)	19 (21.1)	412 (13.1)
Congestive heart failure	305 (9.4)	13 (6.4)	292 (9.6)	12 (13.3)	293 (9.3)
Chronic liver disease	107 (3.3)	3 (1.5)	104 (3.4)	4 (4.4)	103 (3.3)
Chronic kidney disease	407 (12.6)	21 (10.3)	386 (12.7)	15 (16.7)	392 (12.5)
End-stage kidney disease	98 (3.0)	4 (2.0)	94 (3.1)	9 (10.0)	89 (2.8)
Active cancer	162 (5.0)	9 (4.4)	153 (5.0)	6 (6.7)	156 (5.0)
Immunodeficiency	78 (2.4)	5 (2.5)	73 (2.4)	5 (5.6)	73 (2.3)
HIV/AIDS	48 (1.5)	5 (2.5)	43 (1.4)	0 (0.0)	48 (1.5)
Home medications affecting hemostasis, n (%)					
NSAIDs	267 (8.2)	22 (10.8)	245 (8.1)	3 (3.3)	264 (8.4)
Aspirin	715 (22.1)	41 (21.1)	674 (22.2)	34 (37.8)	681 (21.6)
Oral or parenteral anticoagulation	305 (9.4)	7 (3.4)	298 (9.8)	16 (17.8)	289 (9.2)
Median laboratory findings on the day of ICU admission (IQR)					
Leukocyte count, × 10 ⁹ /L	8.2 (5.9-11.5)	8.6 (6.5-11.6)	8.16 (5.9-11.5)	8.55 (5.9-13.2)	8.2 (5.9-11.5)
Hemoglobin, g/L	127 (111-141)	128 (113-143)	127 (111-141)	120 (87-133)	127 (112-141)
Platelet count, × 10 ⁹ /L	213 (163-271)	218 (171-277)	212 (162-270)	177 (133-277)	213 (164-270)
D-dimer, mg/L	1.32 (0.70-3.26)	2.32 (1.01-9.22)	1.29 (0.69-3.05)	3.70 (1.35-15.41)	1.30 (0.70-3.18)
C-reactive protein, mg/L	157 (90-238)	171 (103-250)	157 (89-237)	129 (69-229)	158 (91-238)
Interleukin-6, IU/mL	6.2 (2.1-17)	3.5 (0.86-9.4)	6.6 (2.3-17.1)	3.4 (1.3-5.8)	6.5 (2.1-17.4)
Procalcitonin, µg/L	0.41 (0.15-1.38)	0.40 (0.18-1.40)	0.41 (0.15-1.37)	0.80 (0.30-3.96)	0.40 (0.15-1.34)
Ferritin, µg/L	1032 (505-2000)	1258 (651-2335)	1013.5 (499-2000)	1457.4 (714-3008)	1019 (501-2000)
Fibrinogen, g/L	6.14 (4.97-7.53)	6.31 (4.16-6.92)	6.12 (4.97-7.53)	3.96 (2.85-4.87)	6.17 (5.09-7.55)
Severity-of-illness on the day of ICU admission, n (%)					
Invasive mechanical ventilation	2132 (65.8)	144 (70.6)	1987 (65.5)	68 (75.6)	2062 (63.7)
Vasopressors	1364 (42.1)	98 (48.0)	1266 (41.7)	40 (44.4)	1008 (32.0)
Renal replacement therapy	118 (3.6)	8 (3.9)	110 (3.6)	6 (6.7)	112 (3.6)

COPD = chronic obstructive pulmonary disease; FEU = fibrinogen equivalent units; IQR = interquartile range; NSAID = nonsteroidal anti-inflammatory drug; VTE = venous thromboembolism.

* The following data were missing: body mass index, 228 patients (7.0%); leukocyte count, 180 patients (5.6%); hemoglobin, 186 patients (5.7%); platelet count, 195 patients (6.0%); D-dimer, 1615 patients (49.9%); C-reactive protein, 1291 patients (39.9%); interleukin-6, 2595 patients (80.1%); procalcitonin, 1193 patients (36.7%); ferritin, 1423 patients (43.9%); and fibrinogen, 2648 patients (81.8%). All other variables had no missing data.

† The definitions of the coexisting conditions are provided in the Supplement.

Table 2. Thrombosis, Bleeding, and Coagulation Abnormalities

Event*	Patients, n (%)	28-Day Mortality: Deaths/Events, n (%)
Confirmed VTE	204 (6.3)	78/204 (38.2)
DVT (confirmed VTE events)	176 (86.3)	70/176 (39.8)
Lower-extremity DVT†	136 (66.6)	61/136 (44.9)
Proximal	63 (30.9)	24/63 (38.1)
Distal	47 (23.0)	25/47 (53.2)
Both proximal and distal	26 (12.8)	12/26 (46.2)
Upper-extremity DVT	49 (24.0)	15/49 (30.1)
Other DVT	5 (2.5)	2/5 (40.0)
PE (confirmed VTE events)	32 (15.7)	8/32 (25.0)
Proximal (lobar or segmental)	14 (6.7)	2/14 (14.3)
Distal (subsegmental)	7 (3.4)	0/7 (0.0)
Both proximal and distal	7 (3.4)	2/7 (28.6)
Diagnosed on V/Q scan (location not ascertained)	4 (2.0)	4/4 (100.0)
Suspected VTE events‡	63 (2.0)	31/63 (49.2)
DVT	26 (41.3)	12/26 (46.2)
PE	42 (66.6)	24/42 (57.1)
Confirmed ischemic stroke	20 (0.6)	11/20 (55.0)
Major bleeding events§	90 (2.8)	56/90 (62.2)
Site		
Bronchopulmonary	12 (13.3)	7/12 (58.3)
Body cavity (pleural, pericardial, peritoneal, retroperitoneal)	10 (11.1)	3/10 (30.0)
Central nervous system	13 (14.4)	8/13 (61.5)
Gastrointestinal	9 (32.2)	21/29 (72.4)
Genitourinary	3 (3.3)	2/3 (66.7)
Invasive sites	2 (2.2)	1/2 (50.0)
Mucocutaneous	2 (2.2)	1/2 (50.0)
Musculoskeletal and soft tissue	6 (6.7)	4/6 (66.7)
Site not specified or unknown	17 (18.9)	14/17 (82.4)
Required invasive hemostatic intervention	19 (21.1)	12/19 (63.2)
Received red blood cell transfusion for bleeding ¶	53 (58.9)	31/53 (58.4)
Thrombocytopenia (platelet count <150 × 10 ⁹ /L) at time of bleed	32 (35.6)	27/35 (77.1)
Platelet count <50 × 10 ⁹ /L	6 (6.7)	6/6 (100.0)
Platelet count 50 to 99 × 10 ⁹ /L	13 (14.4)	11/13 (84.6)
Platelet count 100 to 149 × 10 ⁹ /L	16 (17.8)	10/16 (62.5)
Therapeutic anticoagulation at time of bleed	60 (66.7)	43/60 (71.7)
Antiplatelet therapy at time of bleed	24 (26.7)	15/24 (62.5)
Aspirin	24 (26.7)	15/24 (62.5)
P2Y12 antagonist (clopidogrel or ticagrelor)	5 (5.6)	4/5 (80.0)
Fatal bleed	25 (27.8)	25/25 (100.0)
Coagulopathy**	67 (2.1)	47/67 (70.1)
Disseminated intravascular coagulation††	48 (1.5)	32/48 (66.7)
Heparin-induced thrombocytopenia	18 (0.6)	10/18 (55.6)

DVT = deep venous thrombosis; IQR = interquartile range; PE = pulmonary embolism; V/Q = ventilation/perfusion; VTE = venous thromboembolism.

* Of the 90 patients with a major bleeding event, data regarding the platelet count at the event were missing for 6 patients (6.7%). All other data were complete.

† 10 patients with lower-extremity DVT also had upper-extremity DVT, and 4 also had DVT in other (nonlimb) locations; these patients are included in both totals.

‡ 4 patients with confirmed DVT had a suspected PE, and 1 patient had both a suspected DVT and PE; these patients are included in both totals.

§ Median values for coagulation variables at the time of the major bleeding event were as follows: platelet count, 167 × 10⁹/L (IQR, 112 to 237); prothrombin time, 15.1 seconds (IQR, 13.4 to 17.6); international normalized ratio, 1.3 (IQR, 1.1 to 1.5); and activated partial thromboplastin time, 39.9 seconds (IQR, 31.6 to 66.0).

|| 5 patients had major bleeding events from 2 distinct sites.

¶ Patients received a median of 2 units (range, 0 to 10 units) of packed red blood cells in the 48 h after the major bleeding event.

** Defined as a peak international normalized ratio >2.0 or a peak activated partial thromboplastin time >58 seconds in the absence of oral anticoagulation or parenteral therapeutic anticoagulation.

†† As diagnosed by the treating physician.

the Methods section of the Supplement. We used the model's predicted probabilities to calculate stabilized inverse probability weights (19), which were then used to weight each individual's contribution to the survival curves and to the Cox model. We used a robust (sandwich) variance estimator to account for potential replications of patients induced by inverse probability weighting, which results in conservative 95% CIs.

Sensitivity Analyses

We conducted 5 sensitivity analyses of the target trial emulation. First, we included the aforementioned covariates in an unweighted Cox model. Second, to eliminate the potential for immortal time bias (20, 21), we categorized eligible patients into either the early therapeutic anticoagulation group or the no early therapeutic anticoagulation group on ICU day 1, and we repeated the

process for eligible patients on ICU day 2. Our final estimates were obtained by pooling the data from the nested target trials on ICU days 1 and 2, using inverse probability weighting as previously described and in the Methods section of the **Supplement**. Third, we repeated the primary target trial but extended the exposure period for initiation of therapeutic anticoagulation from the first 2 days to the first 3 days after ICU admission. Fourth, we stratified the Cox model by site. Fifth, rather than censoring patients at hospital discharge, we kept them in the risk set until 8 May 2020, the date of last follow-up.

Subgroup Analyses

We used similar methods as the aforementioned primary analysis to examine the observational effect of early therapeutic anticoagulation on survival across the following prespecified subgroups: age (≤ 60 vs. > 60 years); sex; body mass index (< 40 vs. ≥ 40 kg/m²); days from symptom onset to ICU admission (≤ 3 vs. > 3); receipt of invasive mechanical ventilation, shock, and PaO₂:FiO₂ ratio (< 100 , 100 to 199, and ≥ 200 or not mechanically ventilated) on ICU day 1; D-dimer level on ICU days 1 or 2 (≤ 1000 , 1001 to 2500, and > 2500 ng/mL); and number of ICU beds before COVID-19 (< 50 , 50 to 99, and ≥ 100). Analyses were done using SAS, version 9.4 (SAS Institute), and Stata 14.2 (StataCorp).

Role of the Funding Source

This study was not funded.

RESULTS

Patient Characteristics

A total of 3239 patients from 67 sites were included in this analysis. The median age was 61 years (IQR, 53 to 71), 2088 (64%) were men, and 2132 (65.8%) received mechanical ventilation on ICU day 1. Additional characteristics overall and according to the presence or absence of VTE and major bleeding are shown in Table 1 and Supplement Table 3 (available at Annals.org). Overall, 1273 patients (39.3%) died, 1404 (43.4%) were discharged from the hospital within 28 days, and 562 (17.4%) remained hospitalized at 28 days.

VTE, Major Bleeding, and Coagulation-Associated Complications

Routine screening for VTE in critically ill patients with COVID-19 occurred in 3 of the 67 hospitals (4.5%). A total of 204 patients (6.3%) had radiographically confirmed VTE during the first 14 days of ICU admission (Supplement Figure 2, panel A, available at Annals.org), including 176 patients (5.4%) with deep venous thrombosis and 32 patients (1.0%) with pulmonary embolism (Table 2). The 14-day radiographically confirmed VTE rate in hospitals using universal lower-extremity Doppler ultrasonography screening was 8.7%. The risk- and reliability-adjusted incidence of radiographically confirmed VTE across hospitals is shown in Supplement Figure 3, panel A (available at Annals.org), with a median incidence of 5.2% and a range of 1.1% at the lowest-incidence hospital to 17.7% at the highest. An additional 63 patients (2.0%) had a clinically suspected VTE event. A total of 20 patients (0.6%) had a radiographically

confirmed ischemic stroke. Among patients with radiographically confirmed VTE or stroke, the 28-day mortality was 38.2% and 55%, respectively.

Major bleeding occurred in 90 patients (2.8%) (Supplement Figure 2, panel B), 56 of whom (62.2%) died within 28 days. The most common sites of bleeding were gastrointestinal (32.2%) and intracranial (14.4%). A total of 60 of the 90 patients (66.7%) with a major bleeding event were receiving therapeutic anticoagulation at the time of the event (Table 2). Other coagulation-associated complications included coagulopathy (2.1%), disseminated intravascular coagulation (1.5%), and heparin-induced thrombocytopenia (0.6%).

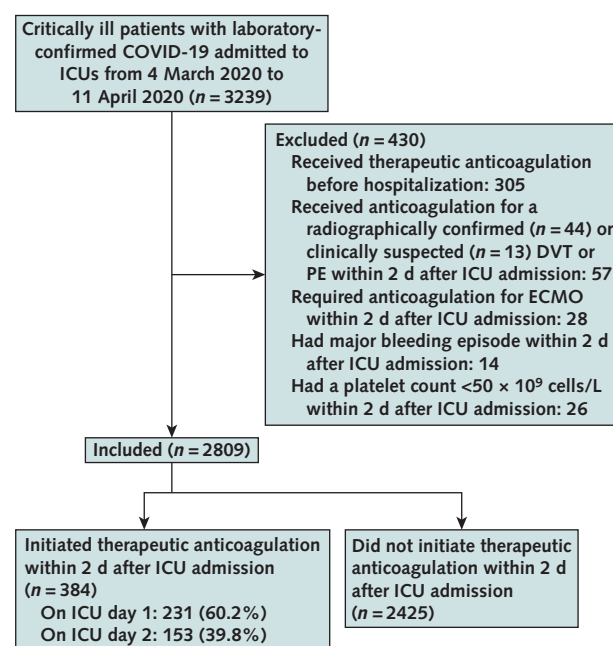
Predictors of VTE

In multivariable analysis, covariates associated with radiographically confirmed VTE were male sex (odds ratio [OR], 1.60 [CI, 1.13 to 2.27]) and higher D-dimer concentration on ICU day 1 (OR, 1.79 [CI, 1.14 to 2.81], for D-dimer of 1001 to 2500 vs. ≤ 1000 ng/mL; OR, 2.50 [CI, 1.40 to 4.50], for 2501 to 10 000 vs. ≤ 1000 ng/mL; and OR, 4.20 [CI, 2.17 to 8.14], for $> 10 000$ vs. ≤ 1000 ng/mL). Other covariates examined were not associated with VTE (Supplement Figure 2, panel D). The increased risk for VTE in men was observed across multiple categories of body mass index and D-dimer (Supplement Figure 4, available at Annals.org).

Interhospital Variation in Use of Anticoagulation

All participating centers reported routinely administering, at a minimum, standard prophylactic doses of

Figure 1. Flow diagram for target trial emulation of therapeutic anticoagulation.



COVID-19 = coronavirus disease 2019; DVT = deep venous thrombosis; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; PE = pulmonary embolism.

Table 3. Patient Characteristics According to Therapeutic Anticoagulation Status

Characteristic*	Pre-IPW		Post-IPW	
	Anticoagulated (N = 384)	Not Anticoagulated (N = 2425)	Anticoagulated	Not Anticoagulated
Demographics				
Median age (IQR), y	62.0 (52.0-71.0)	62.0 (51.0-71.0)	62 (52-72)	62 (51-71)
Age group, n (%)				
18-39 y	35 (9.1)	222 (9.2)	(8.2)	(9.1)
40-59 y	139 (36.2)	855 (35.3)	(36.0)	(35.4)
60-79 y	182 (47.4)	1146 (47.3)	(47.9)	(47.3)
≥80 y	28 (7.3)	202 (8.3)	(7.9)	(8.2)
Male, n (%)	264 (68.8)	1549 (63.9)	(63.9)	(64.5)
White race, n (%)	138 (35.9)	860 (35.5)	(32.4)	(35.5)
Non-Hispanic ethnicity, n (%)	235 (61.2)	1620 (66.8)	(66.2)	(66.1)
Median body mass index (IQR), kg/m ²	29.8 (26.1-35.9)	30.3 (26.4-35.9)	31.1 (26.7-35.9)	30.3 (26.4-35.9)
Body mass index, n (%)				
<30 kg/m ²	183 (47.7)	1112 (45.9)	(44.0)	(46.1)
30-39.9 kg/m ²	128 (33.3)	861 (35.5)	(37.6)	(35.3)
≥40 kg/m ²	52 (13.5)	341 (14.1)	(13.7)	(14.0)
Coexisting disorders, n (%)				
Hypertension	235 (61.2)	1438 (59.3)	(57.5)	(59.5)
Diabetes mellitus	144 (37.5)	973 (40.1)	(36.1)	(39.7)
Coronary artery disease	41 (10.7)	290 (12.0)	(11.5)	(11.8)
Atrial fibrillation/flutter	14 (3.6)	59 (2.4)	(3.0)	(2.6)
Congestive heart failure	20 (5.2)	173 (7.1)	(6.3)	(6.9)
Current smoker	13 (3.4)	128 (5.3)	(4.4)	(5.0)
Active cancer	16 (4.2)	105 (4.3)	(4.1)	(4.3)
Severity of illness on ICU admission, n (%)				
Days from symptom onset to ICU admission				
0-3	71 (18.5)	463 (19.1)	(21.0)	(19.1)
>3	313 (81.5)	1962 (80.9)	(79.0)	(80.9)
Mechanical ventilation and hypoxemia				
Not mechanically ventilated	80 (20.8)	898 (37.0)	(33.9)	(34.8)
Mechanically ventilated and Pao ₂ :Flo ₂ ≥200	55 (14.3)	297 (12.2)	(11.4)	(12.5)
Mechanically ventilated and Pao ₂ :Flo ₂ <200	204 (53.1)	983 (40.5)	(42.3)	(42.2)
Shock†	62 (16.1)	200 (8.2)	(8.9)	(9.3)
Renal SOFA score‡				
0 (Cr <106.1 μmol/L [1.2 mg/dL])	196 (51.0)	1534 (63.3)	(64.8)	(61.7)
1 (Cr 106.1-168 μmol/L [1.2-1.9 mg/dL])	88 (22.9)	517 (21.3)	(20.0)	(21.5)
2-4 (Cr > 176.8 μmol/L [2 mg/dL], UOP <500 mL, RRT)§	100 (26.0)	374 (15.4)	(15.2)	(16.8)
Liver SOFA score‡				
0 (bilirubin <20.5 μmol/L [<1.2 mg/dL])	334 (87.0)	2245 (92.6)	(92.2)	(91.9)
1 (bilirubin 20.5-34.1 μmol/L [1.2-1.9 mg/dL])	43 (11.2)	137 (5.6)	(6.3)	(6.3)
2-4 (bilirubin ≥34.2 μmol/L [≥2 mg/dL])	7 (1.8)	43 (1.8)	(1.5)	(1.8)
Coagulation SOFA score‡				
0 (platelet count ≥150 × 10 ⁹ /L)	328 (85.4)	2010 (82.9)	(85.2)	(83.2)
1 (platelet count 100-149 × 10 ⁹ /L)	43 (11.2)	333 (13.7)	(12.4)	(13.4)
2 (platelet count <100 × 10 ⁹ /L)	13 (3.4)	82 (3.4)	(2.4)	(3.4)
Inflammation				
Inflamed	331 (86.2)	1765 (72.8)	(74.6)	(74.6)
Not inflamed	28 (7.3)	254 (10.5)	(10.9)	(10.0)
Therapies administered on ICU admission, n (%)				
Aspirin	70 (18.2)	349 (14.4)	(13.9)	(14.9)
Neuromuscular blockade	120 (31.3)	500 (20.6)	(23.0)	(22.1)
Prone positioning	92 (24.0)	499 (20.6)	(21.8)	(21.0)

Cr = creatinine; ICU = intensive care unit; IPW = inverse probability of treatment weighting; RRT = renal replacement therapy; SOFA = Sequential Organ Failure Assessment; UOP = urine output.

* A total of 1.4% of covariate data were missing in this analysis, as follows: body mass index, 132 of 2809 patients (4.7%); inflammation, 431 of 2809 patients (15.3%); Pao₂:Flo₂, 292 of 1831 patients who were mechanically ventilated (15.9%). All other data were complete.

† Shock was defined as the requirement for ≥2 vasopressors.

‡ Categories 2, 3, and 4 of the renal, liver, and coagulation components of the SOFA score were binned due to low frequency.

§ Includes both acute RRT as well as end-stage kidney disease requiring RRT.

|| Inflamed was defined as ≥1 of the following on either ICU days 1 or 2: C-reactive protein >100 mg/L, D-dimer >1.00 mg/L, or ferritin >10 g/L. Noninflamed was defined as ≥1 value that was below the threshold on either ICU day 1 or 2 and no value that was above the threshold. Unknown was defined as all 3 values being missing on both ICU days 1 and 2.

anticoagulation (enoxaparin, 40 mg subcutaneously once daily, or equivalent, or unfractionated heparin, 5000 units subcutaneously 2 to 3 times daily, with or without weight-based dose adjustment) for all critically ill patients with COVID-19. Eight centers (12%) transitioned to higher-than-standard doses for some or all patients with COVID-19 during the study period, using either a risk-adapted approach (based on such criteria as D-dimer) or empirical dose escalation (that is, enoxaparin, 30 to 40 mg twice daily, or equivalent) for all patients.

A total of 1412 patients (43.6%) received therapeutic anticoagulation within 14 days after ICU admission (Supplement Figure 2, panel C). The median time to initiation was 3 days (IQR, 1 to 7), and the most common reasons were concern for a hypercoagulable state (40.8%), atrial fibrillation or atrial flutter (18.8%), and suspected or confirmed VTE (16.9%). Most patients received unfractionated heparin (62.6%) or low-molecular-weight heparin (34.4%), with a minority receiving direct thrombin inhibitors and other agents (Supplement Table 4, available at [Annals.org](#)). The risk- and reliability-adjusted rate of therapeutic anticoagulation use varied widely across hospitals, with a median rate of 39.8% and a range of 15.1% to 78.5% at the lowest-use and highest-use hospitals, respectively (Supplement Figure 3, panel B).

Target Trial Emulation

Among the 3239 patients enrolled, 2809 (86.7%) were included in the target trial (Figure 1). A total of 384 patients (11.9%) were treated with early therapeutic anticoagulation. The characteristics of patients before and after applying inverse probability of treatment weighting are shown in Table 3, and indications for therapeutic anticoagulation in the first 2 days of ICU admission in patients included in the target trial emulation are listed in Supplement Table 5 (available at [Annals.org](#)). Before applying the weighting, patients treated with early therapeutic anticoagulation were more likely to have shock and greater severity of hypoxemia and renal dysfunction on ICU admission than were patients not treated with early therapeutic anticoagulation. Other characteristics

were similar between groups (Table 3). After weighting was applied, baseline and acute severity-of-illness characteristics were well balanced between groups (Table 3 and Supplement Figure 5 [available at [Annals.org](#)]), with standardized differences below 0.1 for all 22 covariates.

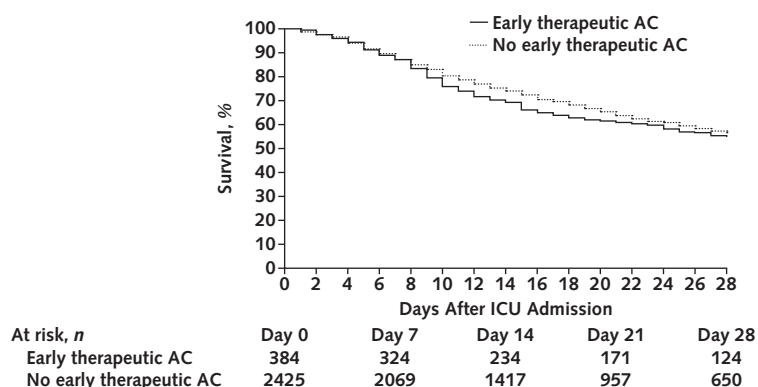
During a median follow-up of 27 days (IQR, 15 to 35), 1066 of the 2809 patients (38.0%) died, including 179 (46.6%) treated with early therapeutic anticoagulation and 887 (36.6%) not treated with early therapeutic anticoagulation. In the primary analysis, patients treated with early therapeutic anticoagulation had a similar survival to those not treated with early therapeutic anticoagulation (hazard ratio, 1.12 [CI, 0.92 to 1.35]) (Figures 2 and 3). Results were similar across all sensitivity and subgroup analyses (Figure 3).

DISCUSSION

This multicenter cohort study of 3239 critically ill adults with COVID-19 found that 6.3% of patients developed a radiographically confirmed VTE and 2.8% had a major bleeding event in the 14 days after ICU admission. Male sex and higher D-dimer levels at the time of ICU admission were each independently associated with a higher risk for VTE. Patients who received early therapeutic anticoagulation had similar in-hospital survival compared with those who did not. These data suggest that rates of VTE in critically ill patients with COVID-19 may be considerably lower in the United States than in other countries, and that initiation of early therapeutic anticoagulation may not have a survival benefit.

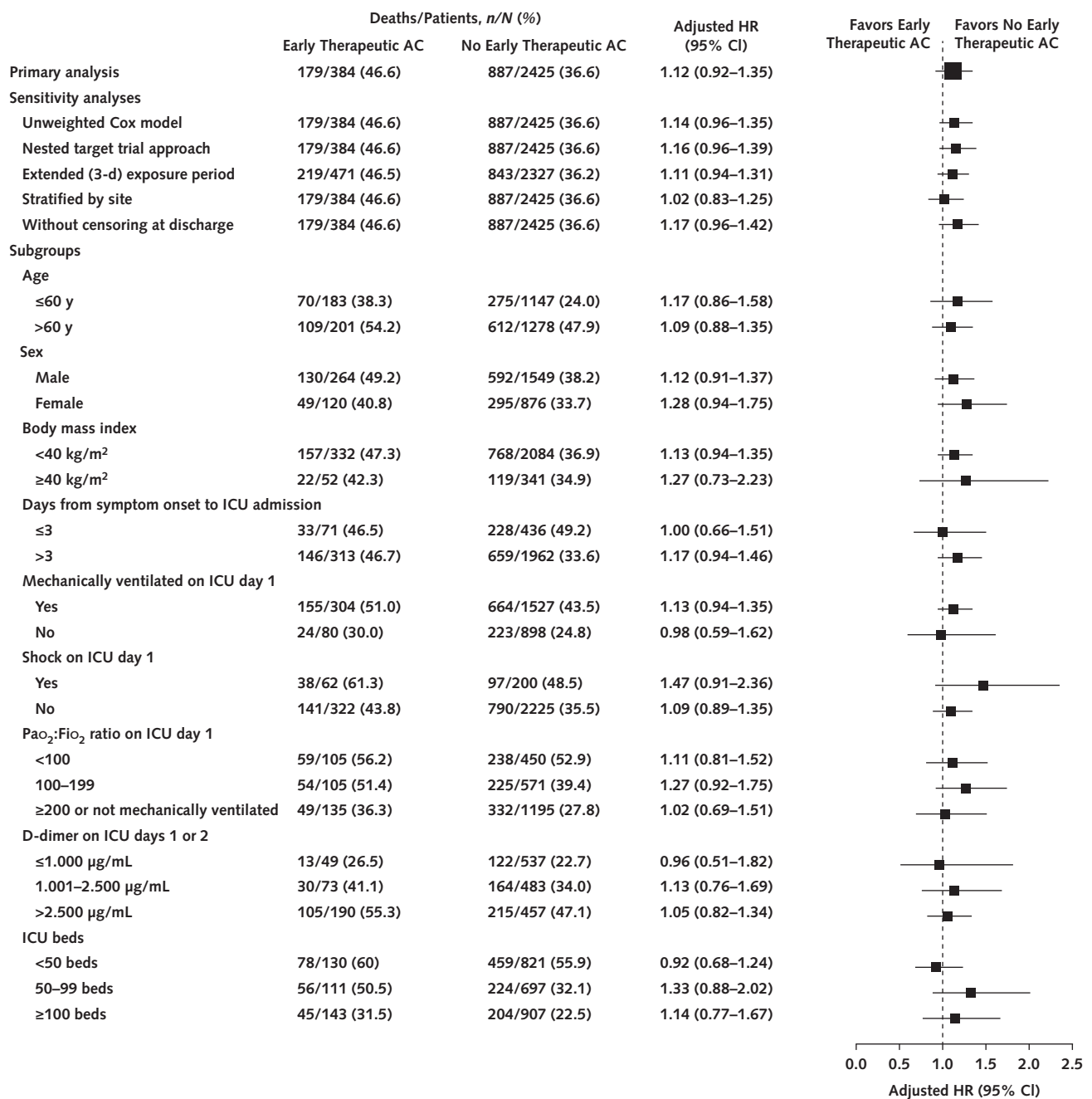
Single-center and regional studies, primarily from Europe, reported VTE rates ranging from 5% to 42% in critically ill patients with COVID-19 (4, 6-8, 22, 23), and a recent meta-analysis that included 1981 patients found a rate of 23.9% (24). The 6.3% incidence of VTE that we observed is similar to that reported by a study conducted in 2 New York City hospitals, which found a 7.7% incidence of VTE among patients who were mechanically ventilated (25). Our findings are also consistent with prior reports in critically ill patients without COVID-19 receiving

Figure 2. Target trial emulation.



Survival in patients who received therapeutic anticoagulation in the first 2 days of ICU admission compared with those who did not. AC = anticoagulation; ICU = intensive care unit.

Figure 3. Results of sensitivity and subgroup analyses.



Shown are the hazard ratios for survival according to early initiation of therapeutic AC versus no early initiation of therapeutic AC in the primary analysis, the sensitivity analyses, and across subgroups. AC = anticoagulation; HR = hazard ratio; ICU = intensive care unit.

standard doses of heparin-based thromboprophylaxis (26). Notably, standard doses of low-molecular-weight heparin thromboprophylaxis used by some of the European cohorts (for example, nadroparin, 2850 IU daily) (4, 7) are lower than the standard prophylactic dose used by most centers in this study. In addition, the high rate of initiation of therapeutic anticoagulation in our cohort (43.6% of all patients by day 14) may have contributed to our lower rates of VTE. Of importance, our VTE risk

prediction model only included those with radiographically confirmed VTE (6.3%) and not those with suspected VTE (2.0%), as many patients with suspected VTE may have had alternative explanations for cardiopulmonary decompensation, including worsening of COVID-19 lung and myocardial disease.

We identified 2 predictors of VTE in critically ill patients with COVID-19: male sex and higher D-dimer level on ICU day 1. Both of these factors have been

associated with adverse outcomes in COVID-19 (27-30) but have not been rigorously studied in the context of VTE. Elevated D-dimer on ICU day 1 may be indicative of elevated coagulation activation and therefore truly predictive of elevated VTE risk or may be representative of an existing thrombus. It is tempting to speculate that early, empirical therapeutic anticoagulation could be beneficial in select patients, such as men with elevated D-dimer on ICU admission. However, in our target trial emulation, we found no benefit of early therapeutic anticoagulation overall or in any subgroup.

We also examined rates of major bleeding. Although we found the rate to be approximately half as frequent as VTE, the associated 28-day mortality was much higher in patients with major bleeding (62.2% vs. 38.2%). Furthermore, two thirds of the major bleeding events occurred in patients receiving therapeutic anticoagulation. The high mortality associated with major bleeding in critically ill patients with COVID-19 highlights the need to identify which patients, if any, may benefit from therapeutic anticoagulation in the absence of standard indications. This need is further underscored by the considerable interhospital variation we detected in the use of therapeutic anticoagulation, which may reflect the lack of available evidence to guide decision making.

We also sought to examine the observational effect of early therapeutic anticoagulation on survival. When data from randomized trials are unavailable, analyzing observational data using a target trial emulation framework may provide more robust estimates on which to guide practice than traditional approaches (31-33). Traditional observational studies that do not explicitly emulate a target trial have resulted in erroneous findings, such as the conclusion that postmenopausal hormone therapy was associated with a 30% lower risk for coronary heart disease (34). These findings become null when the observational analysis is designed to explicitly emulate the corresponding target trial (35), a practice that helps minimize some of the biases that commonly affect observational studies. Our target trial emulation found that early initiation of therapeutic anticoagulation, compared with prophylactic-dose anticoagulation, did not affect survival. One potential explanation for our findings is that therapeutic anticoagulation may have reduced the risk for VTE but at the cost of an increased risk for major bleeding. Alternatively, other pathways of injury, such as inflammation (36), may be more important determinants of survival in critically ill patients with COVID-19 and may not have been affected by anticoagulation dose. Of note, our findings are consistent with the recommendations endorsed by several professional societies against broad empirical institution of therapeutic anticoagulation in patients with COVID-19 (37, 38).

Our findings differ from those recently reported by a single-center study that found an association between therapeutic anticoagulation and decreased mortality in patients with COVID-19 who are mechanically ventilated (2). However, the latter study was limited by its inability to account for immortal time bias or severity-of-illness differences between groups. Furthermore, the reported short-term mortality of 62.7% in the patients who did not receive therapeutic anticoagulation is higher than in many cohorts and suggests the potential for residual confounding.

Our study has several strengths. We used granular data from many consecutive critically ill patients with laboratory-confirmed COVID-19, thereby minimizing selection or surveillance bias at each center. We included patients from 67 geographically diverse sites throughout the United States, thereby increasing the generalizability of our findings and allowing us to examine interhospital variation in the use of therapeutic anticoagulation. Furthermore, all data were obtained by detailed chart review rather than reliance on administrative or billing codes, which have well-described limitations in general (31-33, 39) and in the context of VTE (40). Very few data were missing for the covariates in our target trial emulation, which was the primary analysis in this study. Our target trial emulation included robust methods to account for immortal time bias and confounding by indication. Finally, results were similar across multiple sensitivity and subgroup analyses.

Our study has several limitations. First, as with all observational analyses, we cannot exclude the possibility of residual confounding. Second, we only captured data on VTE and major bleeding events for the first 14 days after ICU admission and thus likely underestimated their true incidence in this population. Third, VTE events (and pulmonary emboli, in particular) were likely underdiagnosed given the logistic challenges of imaging in critically ill patients with COVID-19 (41). Nevertheless, the considerably lower incidence of VTE in our study than in prior studies raises questions about the appropriateness of institutional policies advocating universal dose escalation of prophylactic anticoagulation in critically ill patients with COVID-19.

Using data from a nationally representative multicenter cohort study of critically ill adults with COVID-19 in the United States, we found the rates of radiographically confirmed VTE and major bleeding to be 6.3% and 2.8%, respectively. Male sex and higher D-dimer levels were independently associated with VTE. Patients who received therapeutic anticoagulation in the first 2 days of ICU admission had similar in-hospital survival compared with those who did not. Our findings do not support early empirical use of therapeutic anticoagulation in critically ill patients with COVID-19. These findings highlight the need for well-designed, adequately powered randomized clinical trials of therapeutic anticoagulation in critically ill patients with COVID-19.

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