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ORIGINAL INVESTIGATIONS

Randomized Trial of Anticoagulation Strategies for Noncritically Ill Patients Hospitalized With COVID-19

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ABSTRACT

BACKGROUND Prior studies of therapeutic-dose anticoagulation in patients with COVID-19 have reported conflicting results.

OBJECTIVES We sought to determine the safety and effectiveness of therapeutic-dose anticoagulation in noncritically ill patients with COVID-19.

METHODS Patients hospitalized with COVID-19 not requiring intensive care unit treatment were randomized to prophylactic-dose enoxaparin, therapeutic-dose enoxaparin, or therapeutic-dose apixaban. The primary outcome was the 30-day composite of all-cause mortality, requirement for intensive care unit–level of care, systemic thromboembolism, or ischemic stroke assessed in the combined therapeutic-dose groups compared with the prophylactic-dose group.

RESULTS Between August 26, 2020, and September 19, 2022, 3,398 noncritically ill patients hospitalized with COVID-19 were randomized to prophylactic-dose enoxaparin (n = 1,141), therapeutic-dose enoxaparin (n = 1,136), or therapeutic-dose apixaban (n = 1,121) at 76 centers in 10 countries. The 30-day primary outcome occurred in 13.2% of patients in the prophylactic-dose group and 11.3% of patients in the combined therapeutic-dose groups (HR: 0.85; 95% CI: 0.69-1.04; $P = 0.11$). All-cause mortality occurred in 7.0% of patients treated with prophylactic-dose enoxaparin and 4.9% of patients treated with therapeutic-dose anticoagulation (HR: 0.70; 95% CI: 0.52-0.93; $P = 0.01$), and intubation was required in 8.4% vs 6.4% of patients, respectively (HR: 0.75; 95% CI: 0.58-0.98; $P = 0.03$). Results were similar in the 2 therapeutic-dose groups, and major bleeding in all 3 groups was infrequent.

CONCLUSIONS Among noncritically ill patients hospitalized with COVID-19, the 30-day primary composite outcome was not significantly reduced with therapeutic-dose anticoagulation compared with prophylactic-dose anticoagulation. However, fewer patients who were treated with therapeutic-dose anticoagulation required intubation and fewer died (FREEDOM COVID [FREEDOM COVID Anticoagulation Strategy]; NCT04512079) (J Am Coll Cardiol 2023;81:1747-1762)

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ABBREVIATIONS AND ACRONYMS

ARDS = acute respiratory distress syndrome

ICU = intensive care unit

COVID-19, caused by the severe acute respiratory syndrome coronavirus 2, is characterized by mononuclear cell activation and endothelial cell inflammation that results in in situ thrombosis in large and small blood vessels, both arterial and venous.[1-6] In this context, a specific COVID-19-associated coagulopathy has been described that in concert with immune-mediated cytokine release induces a procoagulant state that also results in a high incidence of systemic thromboembolism, including pulmonary emboli.[1-9] Thrombotic occlusion of the pulmonary vasculature at the capillary-alveolar interface may contribute to the high rate of respiratory failure in COVID-19, the leading cause of morbidity and mortality.[10-13] Observational studies early in the pandemic have reported that mortality in hospitalized patients with COVID-19 might be reduced by anticoagulation therapy, leading to widespread acceptance of prophylactic-dose heparin as the de facto standard of care.[13-15] Some nonrandomized studies have suggested that therapeutic-dose anticoagulation might further improve outcomes, although with increased bleeding.[14,16] However, subsequent randomized trials reported conflicting results.[16]

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Therefore, we performed a large-scale randomized trial to assess the safety and effectiveness of therapeutic-dose low-molecular-weight heparin and a direct-acting oral anticoagulant compared with standard thromboprophylaxis in noncritically ill hospitalized patients with COVID-19.

METHODS

The protocol for the FREEDOM COVID (FREEDOM COVID-19 Anticoagulation Strategy) randomized trial is available in the Supplemental Appendix and has been previously described.[16] In brief, this was an investigator-sponsored, randomized, 3-arm, open-label, active-controlled multicenter trial conducted in the United States, Latin America, Southeast Asia, and Europe. The study organization and participating centers are listed in the Supplemental Appendix. The trial was sponsored and funded by the Mount Sinai Heart Health System, New York, New York, USA. The study was approved by the investigational review board or ethics committee at each participating center, and all patients provided written informed consent. There were no major protocol amendments regarding the study population, sample size, or primary and secondary endpoints during the trial.

PATIENTS AND STUDY DESIGN. The enrollment criteria are listed in the Supplemental Appendix. Eligible patients were hospitalized within 48 hours with symptoms consistent with COVID-19 that was either confirmed with a positive polymerase chain reaction or antigen test, or with suspected COVID-19 in whom 3 additional criteria were all met (temperature >38 °C, arterial oxygen saturation ≤94% on room air, and at least 1 abnormal laboratory marker [d-dimer ≥1.0 μg/mL, C-reactive protein >2 mg/L, ferritin >300 μg/L, or lymphopenia <1,500 cells/m^3]). Patients were excluded who required or were likely to require advanced pulmonary or cardiac support in an

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Baseline Clinical Characteristics of the 3 Randomized Groups

	Prophylactic-Dose Enoxaparin (n = 1,141)	Therapeutic-Dose Enoxaparin (n = 1,136)	Therapeutic-Dose Apixaban (n = 1,121)
Age, y	53 (39-64) (1,141)	52 (40-64) (1,136)	52 (40-64) (1,121)
Male	678/1,141 (59.4)	674/1,136 (59.3)	677/1,121 (60.4)
Geography of enrollment			
United States	156/1,141 (13.7)	151/1,136 (13.3)	149/1,121 (13.3)
Latin America[a]	507/1,141 (44.4)	502/1,136 (44.2)	495/1,121 (44.2)
India	455/1,141 (39.9)	453/1,136 (39.9)	454/1,121 (40.5)
Other[b]	23/1,141 (2.0)	30/1,136 (2.6)	23/1,121 (2.1)
Race[c]			
White	484/1,141 (42.4)	490/1,136 (43.1)	464/1,121 (41.4)
Southeast Asian	477/1,141 (41.8)	481/1,136 (42.3)	472/1,121 (42.1)
Black or African American	61/1,141 (5.3)	58/1,136 (5.1)	64/1,121 (5.7)
American Indian/Alaska Native	6/1,141 (0.5)	4/1,136 (0.4)	4/1,121 (0.4)
Pacific Islander	0/1,141 (0.0)	1/1,136 (0.1)	0/1,121 (0.0)
Other	82/1,141 (7.2)	70/1,136 (6.2)	84/1,121 (7.5)
Multiracial	2/1,141 (0.2)	6/1,136 (0.5)	5/1,121 (0.4)
Not reported	29/1,141 (2.5)	26/1,136 (2.3)	28/1,121 (2.5)
Hispanic or Latino ethnicity[c]	522/1,141 (45.7)	506/1,134 (44.6)	507/1,120 (45.3)
Body mass index, kg/m^2	26.6 (24.1-30.8) (1,103)	26.4 (23.7-30.2) (1,107)	26.6 (24.1-30.7) (1,085)
Hypertension[d]	390/1,139 (34.2)	348/1,129 (30.8)	361/1,114 (32.4)
Hyperlipidemia[d]	128/1,139 (11.2)	123/1,129 (10.9)	126/1,114 (11.3)
Smoking			
Current (within 2 wks)	65/1,139 (5.7)	66/1,125 (5.9)	65/1,113 (5.8)
Past	135/1,139 (11.9)	109/1,125 (9.7)	132/1,113 (11.9)
Never	939/1,139 (82.4)	950/1,125 (84.4)	916/1,113 (82.3)
Diabetes mellitus, all	247/1,139 (21.7)	215/1,129 (19.0)	209/1,113 (18.8)
Medically treated	215/1,139 (18.9)	178/1,129 (15.8)	178/1,113 (16.0)
Insulin-treated	67/1,139 (5.9)	49/1,129 (4.3)	52/1,113 (4.7)
Chronic kidney disease	35/1,139 (3.1)	26/1,129 (2.3)	27/1,113 (2.4)
Prior myocardial infarction	23/1,139 (2.0)	20/1,126 (1.8)	25/1,114 (2.2)
Prior PCI	26/1,139 (2.3)	17/1,128 (1.5)	24/1,114 (2.2)
Prior CABG	9/1,137 (0.8)	11/1,128 (1.0)	9/1,114 (0.8)
Peripheral arterial disease	8/1,137 (0.7)	8/1,128 (0.7)	5/1,114 (0.4)
Cerebrovascular disease	11/1,139 (1.0)	11/1,126 (1.0)	8/1,111 (0.7)
Respiratory disease	100/1,139 (8.8)	90/1,129 (8.0)	108/1,114 (9.7)
Asthma	55/1,139 (4.8)	42/1,126 (3.7)	60/1,112 (5.4)
COPD	37/1,138 (3.3)	32/1,127 (2.8)	30/1,114 (2.7)
Sleep apnea	12/1,138 (1.1)	12/1,128 (1.1)	18/1,111 (1.6)
Other	14/1,138 (1.2)	15/1,129 (1.3)	18/1,114 (1.6)
Vital signs			
Temperature, °C	37.0 (36.4-37.7) (1,130)	37.0 (36.5-37.7) (1,121)	37.0 (36.4-37.7) (1,112)
Heart rate, beats/min	93 (80-105) (1,133)	93 (80-105) (1,125)	94 (81-105) (1,111)
Systolic blood pressure, mm Hg	127 (119-136) (1,133)	126 (118-136) (1,123)	127 (119-136) (1,111)
Diastolic blood pressure, mm Hg	80 (71-85) (1,133)	80 (72-86) (1,123)	80 (72-86) (1,111)
Respiratory rate, per minute	21 (19-24) (1,125)	21 (19-25) (1,109)	22 (19-24) (1,099)
Oxygen saturation, %	94 (91-96) (1,116)	94 (91-96) (1,112)	93 (91-96) (1,102)
Measured on supplemental O_2	398/1,135 (35.1)	358/1129 (31.7)	363/1,112 (32.6)

Values are median (IQR) (number of observations) or n/N (%). [a]Brazil, Colombia, Mexico, and Panama. [b]Hong Kong, Italy, Spain, and Poland. [c]Patient self-identified. [d]Medically treated.

CABG = coronary artery bypass graft surgery; COPD = chronic obstructive pulmonary disease; PCI = percutaneous coronary intervention.

TABLE 2 Baseline Laboratory and Chest Radiology Results

	Prophylactic-Dose Enoxaparin (n = 1,141)	Therapeutic-Dose Enoxaparin (n = 1,136)	Therapeutic-Dose Apixaban (n = 1,121)
Laboratory			
WBC, $\times 10^3/\mu L$	7.0 (5.1-9.2) (1,123)	6.9 (5.1-9.1) (1,106)	6.9 (5.2-9.1) (1,098)
Hemoglobin, g/dL	13.5 (12.3-14.8) (1,124)	13.6 (12.4-14.8) (1,104)	13.5 (12.4-14.8) (1,086)
Platelet count, $\times 10^3/\mu L$	208 (169-274) (1,123)	206 (167-263) (1,107)	209 (167-262) (1,098)
Serum creatinine, mg/dL	0.9 (0.7-1.0) (1,100)	0.9 (0.7-1.0) (1,083)	0.9 (0.7-1.0) (1,080)
C-reactive protein, mg/dL	11.1 (3.5-19.0) (1,008)	10.9 (3.8-18.4) (1,007)	11.4 (4.2-19.0) (971)
D-dimer, ng/mL	0.6 (0.4-0.9) (990)	0.6 (0.4-0.9) (995)	0.6 (0.3-0.9) (973)
Ferritin, μg/L	359 (168-667) (785)	332 (174-606) (756)	369 (201-695) (753)
Procalcitonin, ng/mL	0.1 (0.1-0.3) (509)	0.1 (0.1-0.3) (500)	0.1 (0.1-0.3) (503)
Fibrinogen, mg/dL	374 (293-586) (509)	378 (294-566) (501)	370 (300-569) (487)
Troponin, ng/L	3.1 (0.0-10.0) (379)	3.2 (0.0-8.0) (382)	3.4 (0.0-8.6) (353)
BNP, pg/mL	173 (29-278) (199)	156 (51-270) (200)	187 (61-283) (182)
NT-proBNP, pg/mL	120 (72-231) (255)	138 (88-303) (271)	127 (81-224) (255)
Chest x-ray			
Abnormal	467/583 (80.1)	466/575 (81.0)	480/577 (83.2)
ARDS	210/467 (45.0)	223/466 (47.9)	222/480 (46.3)
Other	257/467 (55.0)	243/466 (52.1)	258/480 (53.8)
Normal	116/583 (19.9)	109/575 (19.0)	97/577 (16.8)
Chest CT			
Abnormal	386/428 (90.2)	392/439 (89.3)	389/431 (90.3)
ARDS	329/386 (85.2)	324/392 (82.7)	320/389 (82.3)
Other	57/386 (14.8)	68/392 (17.3)	69/389 (17.7)
Normal	42/428 (9.8)	47/439 (10.7)	42/431 (9.7)
Chest x-ray or chest CT (worst result)			
Abnormal	760/884 (86.0)	760/878 (86.6)	757/867 (87.3)
ARDS	475/884 (53.7)	481/878 (54.8)	466/867 (53.7)
Other	285/884 (32.2)	279/878 (31.8)	291/867 (33.6)
Normal	124/884 (14.0)	118/878 (13.4)	110/867 (12.7)
COVID-19 pathogen testing performed (hospital lab)	1,108/1,136 (97.5)	1,100/1,126 (97.7)	1,082/1,109 (97.6)
Positive	1,107/1,107 (100.0)	1,096/1,096 (100.0)	1,082/1,082 (100.0)

Values are median (IQR) (number of observations) or n/N (%). Data are site measured and reported and were not assessed at a central laboratory or core lab.

ARDS = acute respiratory distress syndrome; BNP = brain natriuretic peptide; CT = computed tomography; NT-proBNP = N-terminal pro-brain natriuretic peptide; WBC = white blood cell count.

intensive care unit (ICU) within 24 hours after admission; had an anticipated duration of hospitalization ≤72 hours; had been treated with any therapeutic-dose or multiple prophylactic doses of an anticoagulant within 7 days; had active bleeding or other conditions contraindicating anticoagulation; or had end-stage kidney disease. A positive hospital-based polymerase chain reaction test for COVID-19 was required after admission except in those with a recent confirmed outpatient test. Patients randomized with suspected COVID-19 who tested negative in-hospital had their study drugs stopped and were withdrawn from the study.

Eligible patients were randomized equally to 1 of 3 groups: 1) prophylactic-dose enoxaparin (40 mg subcutaneously every day; 30 mg subcutaneously every day for creatinine clearance <30 mL/min); 2) therapeutic-dose enoxaparin (1 mg/kg subcutaneously every 12 hours; 1 mg/kg subcutaneously every day for creatinine clearance <30 mL/min); 3) therapeutic-dose apixaban (5 mg by mouth twice daily; 2.5 mg every 12 hours for patients with at least 2 of 3 of age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL). Computer-generated randomization was performed with randomly assigned blocks stratified by center, admission type (ward vs ICU), and age (<65 years vs ≥65 years). Study drug was administered within 12 hours of randomization and until discharge. Changes to the assigned drug regimen were only allowed for major

TABLE 3 30-Day Effectiveness Outcomes of Therapeutic-Dose Anticoagulation Compared With Prophylactic-Dose Enoxaparin

	Prophylactic-Dose Enoxaparin (n = 1,141)	Therapeutic-Dose Anticoagulation[a] (n = 2,257)	HR (95% CI)	*P* Value
Primary effectiveness endpoint[b]	148 (13.2)	249 (11.3)	0.85 (0.69-1.04)	0.11
In-hospital	140 (12.3)	240 (10.6)	0.85 (0.68-1.06)	0.15
Postdischarge to 30 days	8 (0.7)	9 (0.4)	0.57 (0.22-1.47)	0.24
Death, all-cause	78 (7.0)	108 (4.9)	0.70 (0.52-0.93)	0.01
In-hospital	70 (6.1)	99 (4.4)	0.70 (0.51-0.96)	0.03
Postdischarge to 30 days	8 (0.7)	9 (0.4)	0.57 (0.22-1.47)	0.24
Etiology: cardiovascular	2 (0.2)	5 (0.2)	1.26 (0.25-6.51)	0.78
Etiology: noncardiovascular	71 (6.4)	96 (4.4)	0.68 (0.50-0.92)	0.01
From pulmonary causes	48 (4.4)	61 (2.8)	0.64 (0.44-0.93)	—
From infection (includes sepsis)	23 (2.1)	34 (1.6)	0.74 (0.44-1.26)	—
From malignancy	0 (0.0)	0 (0.0)	—	—
From other noncardiovascular cause	0 (0.0)	1 (0.0)	—	—
Etiology: undetermined	5 (0.5)	7 (0.3)	0.70 (0.22-2.21)	—
ICU level of care	132 (11.7)	220 (9.9)	0.84 (0.68-1.04)	0.11
Intubation with mechanical ventilation	94 (8.4)	141 (6.4)	0.75 (0.58-0.98)	0.03
BiPAP or CPAP[c]	26 (2.3)	51 (2.3)	0.99 (0.62-1.59)	0.97
High-flow nasal cannula oxygen (>30 L/min)[c]	62 (5.5)	122 (5.5)	1.00 (0.74-1.36)	0.99
Vasopressor or inotropic medication[c]	63 (5.6)	106 (4.8)	0.85 (0.62-1.16)	0.29
Mechanical circulatory support	1 (0.1)	2 (0.1)	—	—
Cardiac arrest	1 (0.1)	2 (0.1)	—	—
All-cause death or mechanical ventilation	109 (9.7)	167 (7.6)	0.77 (0.60-0.98)	0.03
Pulmonary emboli or deep venous thrombosis	10 (0.9)	18 (0.8)[d]	0.91 (0.42-1.97)	0.81
Deep venous thrombosis	7 (0.6)	8 (0.4)	0.58 (0.21-1.59)	0.28
Pulmonary emboli	3 (0.3)	11 (0.5)	1.85 (0.52-6.63)	0.34
Systemic arterial thrombosis or emboli	1 (0.1)	1 (0.0)	—	—
Myocardial infarction	2 (0.2)	7 (0.3)	1.77 (0.37-8.53)	0.47
Stroke	0 (0.0)	1 (0.0)[e]	—	—
Death, systemic arterial or venous thromboembolism, or ischemic stroke	79 (7.1)	113 (5.2)	0.72 (0.54-0.96)	0.02
Dialysis or renal replacement therapy[f]	13 (1.2)	20 (0.9)	0.77 (0.38-1.55)	0.47

Values are number of events (Kaplan-Meier estimated percentages) unless otherwise indicated. [a]Therapeutic-dose enoxaparin (n = 1,136) plus therapeutic-dose apixaban (n = 1,121). [b]The composite of all-cause mortality, requirement for ICU level of care, systemic arterial or venous thromboembolism confirmed by imaging or requiring surgical intervention, or ischemic stroke at 30 days. [c]For at least 12 hours. [d]1 patient had both deep venous thrombosis and a pulmonary embolus. [e]This event was a hemorrhagic stroke and was not included as a component of the primary endpoint. No patient had an ischemic stroke. [f]In patients not on prior dialysis or renal replacement therapy (these events are not part of the primary endpoint).

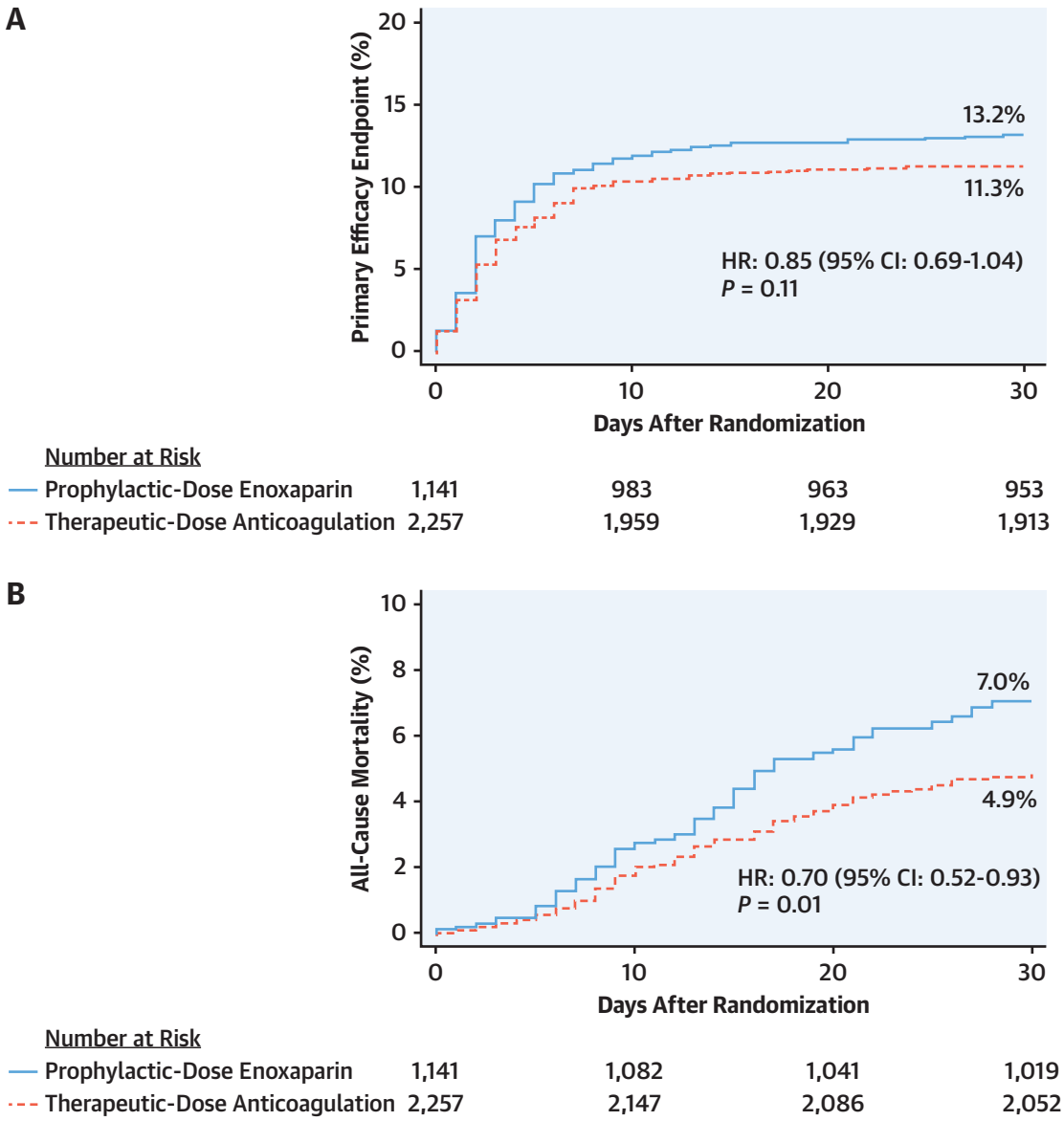
BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; ICU = intensive care unit.

bleeding or other side effects, a clinical event requiring therapeutic-dose anticoagulation, or after a primary outcome event.

Other patient care procedures were per local practice. Routine screening for thromboembolism or other conditions without clinical symptoms was not performed. Anticoagulant use after discharge was discouraged absent a clinical indication.[17] Monitoring of study records to confirm site-reported events, to detect unreported events, and to collect original site documents for adjudication was performed at each site by an independent contract research organization. Follow-up visits were scheduled 30 days and 90 days after discharge and are currently complete through 30 days for all patients.

OUTCOMES. Endpoints are listed in the Supplemental Appendix. The primary effectiveness endpoint was the 30-day composite of all-cause mortality, requirement for ICU level-of-care, systemic thromboembolism confirmed by imaging or requiring surgical intervention, or ischemic stroke confirmed by imaging. ICU level-of-care was defined as: 1) mechanical ventilation following endotracheal intubation; 2) use of bilevel positive airway pressure, continuous positive airway pressure, or high-flow nasal cannula oxygen (>30 L/min) for respiratory support; or 3) use of intravenous vasopressors, inotropes, or mechanical circulatory support. Systemic thromboembolism included deep venous thrombosis, pulmonary emboli, myocardial infarction, and other

FIGURE 1 **30-Day Outcomes in the Combined Therapeutic-Dose and Prophylactic-Dose Groups**



(A) Primary effectiveness endpoint (composite of all-cause mortality, requirement for intensive care unit level of care, systemic arterial or venous thromboembolism confirmed by imaging, or requiring surgical intervention or ischemic stroke). **(B)** All-cause mortality. The combined therapeutic-dose anticoagulation groups include patients randomized to therapeutic-dose enoxaparin (n = 1,136) and therapeutic-dose apixaban (n = 1,121).

arterial or venous thromboembolic events. Some patients could be admitted or transferred to the ICU for observation without requiring "ICU level-of-care" as so defined. The primary safety endpoint was the in-hospital rate of major bleeding defined as types 3 or 5 by the Bleeding Academic Research Consortium (Supplemental Appendix).[18] The trial outcomes were not changed after enrollment commenced. An independent committee blinded to randomization group adjudicated all adverse events after review of original source documents.

OBJECTIVES AND STATISTICAL ANALYSIS. The principal study objective was to show that the 30-day primary effectiveness outcome would be reduced in the combined therapeutic-dose anticoagulation groups compared with the prophylactic-dose

enoxaparin group. Assuming a 25% event rate with prophylactic-dose enoxaparin based on prior registry studies of similar patients and a 20% event rate in both therapeutic-dose anticoagulation groups, randomizing 1,200 patients in each group (3,600 patients total) would provide >95% power to show superiority with a 2-sided $\alpha = 0.05$.[1,13,14] If this null hypothesis was rejected, subsequent hypotheses would be tested in a hierarchy to control type I error, as described in the Supplemental Appendix.

All analyses were performed from the time of randomization in the modified intention-to-treat population, consisting of those patients not withdrawn per protocol or before at least 1 dose of study drug was administered. Time to first event rates through 30 days are reported as Kaplan-Meier estimates and were compared with the log-rank test. As most events were expected during the in-hospital phase, missing data were not replaced. HRs and 95% CIs were calculated by Cox regression. The in-hospital primary safety endpoint was evaluated with the Fisher exact test. Rates of bleeding between groups were compared using Poisson regression. Adjustment was not made for multiple testing of secondary endpoints.

An interim analysis of the principal study endpoint was conducted when 1,800 patients reached 30-day follow-up. This used an alpha-spending O'Brien-Fleming stopping guideline for the primary endpoint. $P < 0.048$ was required to claim 5% significance at the final analysis. All P values other than for the primary endpoint should be considered nominal exploratory analyses and not for formal hypothesis testing. All statistical analyses were performed with SAS software, v9.4 (SAS Institute).

RESULTS

ENROLLMENT AND BASELINE FEATURES. Between August 26, 2020, and September 19, 2022, 3,452 patients were consented and randomized at 76 centers in 10 countries; enrollment was terminated before the planned 3,600 patients because of slow recruitment in 2022. Nineteen patients were withdrawn before receiving any study drug because all enrollment criteria were not met, and 35 patients who persistently tested negative for COVID-19 were withdrawn per protocol (Supplemental Figure 1). The modified intention-to-treat analytic cohort thus consists of 3,398 noncritically ill patients hospitalized with confirmed COVID-19, including 1,141 randomized to prophylactic-dose enoxaparin, 1,136 randomized to therapeutic-dose enoxaparin, and 1,121 randomized to therapeutic-dose apixaban. Thirty-day follow-up was complete in all but 39 patients randomized to prophylactic-dose enoxaparin, 55 randomized to therapeutic-dose enoxaparin, and 43 randomized to therapeutic-dose apixaban (Supplemental Figure 1).

TABLE 4 In-Hospital Safety Outcomes of Therapeutic-Dose Anticoagulation Compared With Prophylactic-Dose Enoxaparin

	Prophylactic-Dose Enoxaparin (n = 1,141)	Therapeutic-Dose Anticoagulation[a] (n = 2,257)	IRR (95% CI)	*P* Value
Primary safety endpoint: major bleeding (BARC[b] types 3 or 5)	1 (0.1)	9 (0.4)	3.96 (0.50-31.27)	0.18
BARC[b] bleeding type				
2, 3, or 5	4 (0.4)	21 (0.9)	2.36 (0.81-6.88)	0.47
2	3 (0.3)	12 (0.5)	–	
3	1 (0.1)	7 (0.3)	–	
3a	0 (0.0)	2 (0.1)	–	
3b	1 (0.1)	4 (0.2)	–	
3c	0 (0.0)	1 (0.0)	–	
4	0 (0.0)	0 (0.0)	–	
5	0 (0.0)	2 (0.1)	–	
Heparin-induced thrombocytopenia	0 (0.0)	0 (0.0)	–	

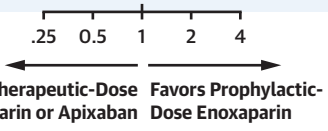
Values are n (%) unless otherwise indicated. [a]Therapeutic-dose enoxaparin (n = 1,136) plus therapeutic-dose apixaban (n = 1,121). [b]The definitions for the BARC bleeding types are listed in the Supplemental Appendix.
BARC = Bleeding Academic Research Consortium; IRR = incidence rate ratio.

Baseline clinical characteristics were well-matched between groups (**Table 1**). Median age was 53 years (range 40-64 years) and 59.7% were male. The population was of diverse race and ethnicity. Most patients were nonsmokers, and pre-existing lung disease was present in only 8.8% of patients. On admission, most patients were afebrile but slightly tachypneic and had mild arterial oxygen desaturation. The white blood cell count was normal in most patients, but C-reactive protein levels were increased, D-dimer levels were frequently elevated, and more than half of patients had radiologic evidence of acute respiratory distress syndrome (ARDS) (**Table 2**).

MEDICATIONS AND STUDY DRUG ADMINISTRATION. Before randomization, 18.8% of patients had received anticoagulation, 13.9% received an antiplatelet agent, 21.9% were administered steroids, and 9.7% received remdesivir (Supplemental Table 1). Site compliance with study drug administration per protocol was high in all 3 groups (Supplemental Table 2). The assigned study drug regimen was used throughout the entire hospitalization in 88.2% of patients. Most changes occurred after a primary outcome was reached or after bleeding, both allowed per protocol. Discharge medication use is shown in Supplemental Table 3;

FIGURE 2 **Subgroup Analysis for the 30-Day Primary Effectiveness Endpoint**

	Prophylactic-Dose Enoxaparin n/N (KM %)	Therapeutic-Dose Enoxaparin or Apixaban n/N (KM %)	HR (95% CI)	$P_{interaction}$
Overall	148/1,141 (13.2)	249/2,257 (11.3)	0.85 (0.69-1.04)	
Age (median)				0.10
<53 years	35/555 (6.4)	80/1,133 (7. 1)	1.13 (0.76-1.68)	
≥53 years	113/586 (19.6)	169/1,124 (15.4)	0.77 (0.61-0.97)	
Sex				0.59
Male	92/678 (13.7)	162/1,351 (12.2)	0.88 (0.68-1.14)	
Female	56/463 (12.3)	87/906 (9.8)	0.79 (0.56-1.10)	
Body mass Index (median)				0.17
<26.6 kg/m^2	48/547(8.9)	67/1,100 (6.2)	0.69 (0.47-1.03)	
≥26.6 kg/m^2	96/556 (17.5)	178/1,092 (16.5)	0.94 (0.73-1.20)	
Diabetes mellitus				0.66
No	105/892 (11.9)	188/1,818 (10.5)	0.88 (0.89-1.12)	
Yes	43/247 (17.8)	60/424 (14.4)	0.79 (0.54-1.17)	
Geography				0.08
United States	26/156 (17.5)	27/300 (9.5)	0.53 (0.31-0.91)	
India	3/455 (0.7)	12/907 (1.3)	2.01 (0.57-7.13)	
Other countries*	119/530 (22.7)	210/1,050 (20.4)	0.89 (0.71-1.11)	
Creatinine clearance† (median)				0.76
<92 mL/min	79/482 (16.6)	122/906 (13.7)	0.81 (0.61-1.08)	
≥92 mL/min	45/438 (10.3)	86/950 (9.2)	0.87 (0.61-1.25)	
D-dimer (median)				0.68
<0.57 ng/mL	44/493 (9.0)	77/964 (8.1)	0.90 (0.62-1.30)	
≥0.57 ng/mL	78/497 (16.0)	130/994 (13.2)	0.82 (0.62-1.08)	
C-reactive protein (median)				0.62
<11.1 mg/dL	51/505 (10.3)	77/988 (7.9)	0.76 (0.53-1.08)	
≥11.1 mg/dL	80/503 (16.0)	134/990 (13.7)	0.85 (0.64-1.12)	
Hypertension				0.96
No	75/749 (10.1)	134/1,534 (8.9)	0.87 (0.66-1.15)	
Yes	73/390 (18.9)	115/709 (16.5)	0.86 (0.64-1.15)	
Pre-existing respiratory disease				0.80
No	130/1,039 (12.7)	216/2,045 (10.7)	0.84 (0.68-1.05)	
Yes	18/100 (18.2)	33/198 (17.1)	0.91 (0.51-1.61)	
Tobacco use				0.85
Current	10/65 (15.4)	19/131 (14.8)	0.95 (0.44-2.05)	
Past	37/135 (28.3)	62/241 (26.4)	0.94 (0.63-1.42)	
Never	101/939 (10.9)	168/1,866 (9.1)	0.83 (0.65-1.06)	
Hemoglobin (median)				0.94
<13.5 g/dL	52/534 (9.9)	90/1,054 (8.7)	0.87 (0.62-1.22)	
≥13.5 g/dL	95/590 (16.3)	157/1,136(14.0)	0.86 (0.66-1.10)	
White blood cell count (median)				0.57
<7 × 10^9/L	62/551 (11.4)	100/1,110 (9.1)	0.79 (0.58-1.09)	
≥7 × 10^9/L	85/572 (15.0)	146/1,094 (13.6)	0.90 (0.69-1.17)	
CHA_2DS_2-VASc score				0.69
0	32/356 (9.1)	62/752 (8.4)	0.92 (0.60-1.41)	
≥1	116/785 (15.0)	187/1,505 (12.7)	0.83 (0.66-1.05)	
Chest x-ray or CT scan				0.29
ARDS	103/475 (21.9)	170/947 (18.1)	0.82 (0.64-1.04)	
Abnormal without ARDS	17/285 (6.0)	21/570 (3.8)	0.61 (0.32-1.16)	
Normal	4/124 (3.3)	12/228 (5.4)	1.66 (0.53-5.13)	
Duration of study drug anticoagulation therapy (median)‡				0.68
<5 days	111/549 (20.5)	177/1,021 (17.7)	0.85 (0.67-1.08)	
≥5 days	37/580 (6.4)	71/1,185 (6.0)	0.94 (0.63-1.39)	



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anticoagulation was prescribed in 11.3% of patients, usually for physician choice.

OUTCOMES. Hospitalization details are shown in Supplemental Table 4. Within 30 days after randomization, 397 patients (Kaplan-Meier estimated rate, 11.9%) had an adjudicated primary outcome event, 380 (11.4%) first occurring in-hospital, and 17 (0.5%) after discharge. As shown in **Table 3** and **Figure 1**, the 30-day primary endpoint occurred in 13.2% of patients in the prophylactic-dose group and 11.3% of patients in the combined therapeutic-dose groups (HR: 0.85; 95% CI: 0.69-1.04; $P = 0.11$). All-cause mortality within 30 days occurred in 7.0% of patients treated with prophylactic-dose and 4.9% of patients treated with therapeutic-dose anticoagulation (HR: 0.70; 95% CI: 0.52-0.93; $P = 0.01$); this difference was driven by fewer deaths attributed to pulmonary causes with therapeutic-dose anticoagulation. ICU level of care was administered to 11.7% of patients treated with prophylactic-dose and 9.9% of patients treated with therapeutic-dose anticoagulation (HR: 0.84; 95% CI: 0.68-1.04; $P = 0.11$). Endotracheal intubation was required in fewer patients in the therapeutic-dose anticoagulation group (8.4% vs 6.4%; HR: 0.75; 95% CI: 0.58-0.98; $P = 0.03$). In-hospital major bleeding (the primary safety endpoint) was infrequent, occurring in 0.1% and 0.4% of patients in the prophylactic-dose and therapeutic-dose anticoagulation groups, respectively (**Table 4**). No major bleeds occurred after discharge through 30-day follow-up. There were no significant between-group differences in organ support-free days or days alive and out-of-hospital (Supplemental Table 5).

Results for the 3 groups individually are shown in Supplemental Tables 6 and 7 and Supplemental Figure 2. Event rates with therapeutic-dose enoxaparin and apixaban were similar. Fewer deaths were observed with each of the therapeutic-dose anticoagulation regimens compared with prophylactic-dose enoxaparin.

SUBGROUP ANALYSIS. As shown in **Figures 2 and 3**, the results were reasonably consistent among 16 prespecified subgroups. However, event rates varied substantially by country and other baseline risk factors. Among 1,362 patients recruited from India, the 30-day primary composite outcome in patients assigned to prophylactic-dose enoxaparin was only 0.7%, precluding the possibility to show a benefit of therapeutic-dose anticoagulation. In contrast, among 2,036 patients enrolled from 9 other countries, the primary outcome rate was 21.5% with prophylactic-dose enoxaparin and 18.0% with therapeutic-dose anticoagulation (HR: 0.82: 95% CI: 0.67-1.01). Fewer primary outcome events were observed in 456 patients recruited in the United States treated with therapeutic-dose compared with prophylactic-dose anticoagulation (17.5% vs 9.5%; HR: 0.53; 95% CI: 0.31-0.91). On-site monitoring confirmed that patients enrolled in India all had COVID-19, but were younger, had fewer comorbidities, and were less likely to have radiologic ARDS than patients from other countries (Supplemental Table 8). A more detailed analysis of outcomes from each country and with other geographic groupings is shown in Supplemental Table 9. Older patients (at least 53 years of age, the study median) had higher rates of the 30-day primary outcome than younger patients and were more likely to benefit from therapeutic-dose anticoagulation (primary outcome 19.6% vs 15.4%; HR: 0.77; 95% CI: 0.61-0.97). The 30-day rate of the primary outcome was greatest in patients with radiologic evidence of ARDS, and 30-day mortality was substantially reduced with therapeutic-dose anticoagulation in this group (12.3% vs 7.9%; HR: 0.63; 95% CI: 0.45-0.89) (**Figure 3**).

DISCUSSION

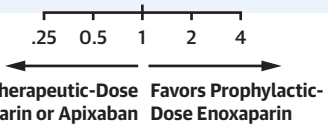
The major results from the present large-scale, international, randomized trial are summarized in the **Central Illustration**. Among noncritically ill patients

FIGURE 2 Continued

The primary effectiveness endpoint was the composite of all-cause mortality, requirement for intensive care unit level of care, systemic arterial or venous thromboembolism confirmed by imaging or requiring surgical intervention, or ischemic stroke. The combined therapeutic-dose anticoagulation groups include patients randomized to therapeutic-dose enoxaparin (n = 1,136) and therapeutic-dose apixaban (n = 1,121). Subgroups for continuous data were categorized according to the median to avoid bias. Subgroups according to geography of enrollment were not prespecified and were categorized post hoc. *Colombia, Mexico, Brazil, Panama, Hong Kong, Spain, Italy, Poland. †Estimated by the Cockcroft-Gault formula. ‡In-hospital, post-randomization; drug duration censored at the time of a primary endpoint event. ARDS = acute respiratory distress syndrome; CT = computed tomography; KM = Kaplan-Meier estimated event rate.

FIGURE 3 Subgroup Analysis for 30-Day Mortality

	Prophylactic-Dose Enoxaparin n/N (KM %)	Therapeutic-Dose Enoxaparin or Apixaban n/N (KM %)	HR (95% CI)	$P_{interaction}$
Overall	78/1,141 (7.0)	108/2,257 (4.9)	0.70 (0.52-0.93)	
Age (median)				0.26
<53 years	15/555 (2.8)	15/1,133 (1.4)	0.49 (0.24-1.00)	
≥53 years	63/586(11.1)	93/1,124 (8.6)	0.77 (0.56-1.05)	
Sex				0.17
Male	52/678 (7.9)	62/1,351 (4.7)	0.59 (0.41-0.86)	
Female	26/463 (5.8)	46/906(5.3)	0.90 (0.56-1.46)	
Body mass Index (median)				0.80
<26.6 kg/m^2	23/547 (4.3)	34/1,100 (3.2)	0.73 (0.43-1.25)	
≥26.6 kg/m^2	53/556 (9.9)	72/1,092 (6.8)	0.68 (0.47-0.96)	
Diabetes mellitus				0.96
No	52/892 (6.0)	75/1,818 (4.2)	0.71 (0.50-1.01)	
Yes	26/247 (11.0)	33/424 (8.1)	0.72 (0.43-1.20)	
Geography				0.58
United States	10/156 (7.1)	12/300 (4.5)	0.63 (0.27-1.47)	
India	2/455 (0.4)	6/907 (0.7)	1.51 (0.30-7.48)	
Other countries*	66/530 (12.7)	90/1,050 (8.8)	0.68 (0.49-0.93)	
Creatinine clearance† (median)				0.68
<92 mL/min	51/482 (10.8)	69/906 (7.8)	0.71 (0.50-1.02)	
≥92 mL/min	15/438 (3.5)	27/950 (2.9)	0.83 (0.44-1.56)	
D-dimer (median)				0.50
<0.57 ng/mL	25/493 (5.1)	30/964 (3.2)	0.62 (0.36-1.05)	
≥0.57 ng/mL	37/497 (7.7)	59/994 (6.1)	0.78 (0.52-1.17)	
C-reactive protein (median)				0.99
<11.1 mg/dL	25/505 (5.1)	34/988 (3.5)	0.69 (0.41-1.15)	
≥11.1 mg/dL	44/503 (8.9)	60/990 (6.2)	0.68 (0.46-1.01)	
Hypertension				0.91
No	34/749 (4.7)	51/1,534 (3.4)	0.73 (0.47-1.12)	
Yes	44/390 (11.5)	57/709 (8.3)	0.70 (0.47-1.04)	
Pre-existing respiratory disease				0.57
No	68/1,039 (6.7)	91/2,045 (4.6)	0.67 (0.49-0.92)	
Yes	10/100 (10.3)	17/198 (8.9)	0.86 (0.39-1.87)	
Tobacco use				0.42
Current	6/65 (9.4)	4/131 (3.1)	0.33 (0.09-1.16)	
Past	20/135 (15.5)	30/241 (13.1)	0.83 (0.47-1.45)	
Never	52/939 (5.7)	74/1,866 (4.1)	0.71 (0.50-1.01)	
Hemoglobin (median)				0.54
<13.5 g/dL	29/534 (5.5)	45/1,054 (4.4)	0.78 (0.49-1.25)	
≥13.5 g/dL	48/590 (8.4)	61/1,136 (5.5)	0.65 (0.45-0.95)	
White blood cell count (median)				0.34
<7 × 10^9/L	36/551(6.7)	43/1,110 (4.0)	0.59 (0.38-0.91)	
≥7 × 10^9/L	41/572 (7.3)	62/1,094 (5.8)	0.79 (0.53-1.16)	
CHA_2DS_2-VASc score				0.04
0	17/356 (4.9)	13/752 (1.8)	0.36 (0.17-0.74)	
≥1	61/785 (8.0)	95/1,505 (6.5)	0.81 (0.59-1.12)	
Chest x-ray/Chest CT scan				0.13
ARDS	57/475 (12.3)	74/947 (7.9)	0.63 (0.45-0.89)	
Abnormal without ARDS	2/285 (0.7)	10/570 (1.8)	2.53 (0.55-11.55)	
Normal	2/124 (1.7)	4/228 (1.8)	1.08 (0.20-5.91)	
Duration of study drug anticoagulation therapy (median)‡				0.08
<5 days	56/549 (10.6)	62/1,021 (6.4)	0.59 (0.41-0.84)	
≥5 days	22/580 (3.9)	46/1,185 (3.9)	1.02 (0.61-1.69)	



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hospitalized with COVID-19, the difference between groups in the incidence of the 30-day primary outcome (a composite of all-cause mortality, requirement for ICU level of care, systemic thromboembolism, or ischemic stroke) in patients treated with therapeutic-dose anticoagulation compared with prophylactic-dose anticoagulation did not reach statistical significance. However, fewer patients treated with therapeutic-dose anticoagulation required endotracheal intubation and fewer died within 30 days. In addition, the prognosis among patients varied greatly, especially according to patient age, radiology findings, and geography of recruitment. Event rates were highest and the response to therapeutic-dose anticoagulation was greatest in older patients, in those with radiologic evidence of ARDS, and in patients enrolled outside of India. Outcomes were similar with therapeutic-dose enoxaparin and apixaban, and major bleeding was infrequent with all 3 anticoagulant regimens. In concert with the results from prior studies, these findings support the use of therapeutic-dose anticoagulation in selected higher-risk hospitalized patients with COVID-19.

The utility of therapeutic-dose anticoagulation in hospitalized patients with COVID-19 is uncertain, and has recently been summarized.[13,16] In the largest trial (n = 1,103) of critically ill patients with COVID-19 (defined by the requirement for ICU-level respiratory or cardiovascular organ support), the REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia), ACTIV-4a (A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitalized Adults with COVID-19), and ATTACC (Antithrombotic Therapy to Ameliorate Complications of COVID-19) investigators reported that therapeutic-dose anticoagulation did not reduce hospital mortality or otherwise improve outcomes compared with usual-care thromboprophylaxis, and more major bleeds were observed with therapeutic-dose anticoagulation.[19] Therefore, therapeutic-dose anticoagulation is not currently recommended for routine management of critically ill hospitalized patients with COVID19.[20] In contrast, the same investigators reported that therapeutic-dose anticoagulation reduced the number of days without organ support in a trial of 2,219 noncritically ill patients hospitalized with COVID-19, albeit with a 1% absolute increase in major bleeding.[21] Performed in a Bayesian framework, the probability that therapeutic-dose anticoagulation was superior was 97.3% in patients with baseline D-dimer levels greater than or equal to twice the upper limit of normal, 92.9% in patients with lower D-dimer levels, and 97.3% in those with unknown D-dimer levels. However, the individual rates of mortality, progression to intubation, and major thrombotic events were not significantly reduced in all patients or any subgroup, warranting further studies to examine the risk/benefit profile of therapeutic-dose anticoagulation in moderate-risk patients with COVID-19.[22] More recently, among 465 randomized noncritically ill patients with elevated D-dimer levels in a separate study, therapeutic-dose heparin did not improve the primary composite outcome of death, invasive or noninvasive mechanical ventilation, or ICU admission within 28 days compared with prophylactic dose heparin.[23] However, the composite of death or any mechanical ventilation occurred in 10.1% of patients treated with therapeutic-dose heparin compared with 16.0% treated with prophylactic-dose heparin ($P = 0.06$), and major bleeding was not increased. Finally, some observational studies have suggested that a direct-acting oral anticoagulant may provide greater safety and effectiveness than low-molecular-weight heparin in patients hospitalized with COVID-19.[14] However, therapeutic-dose rivaroxaban did not improve outcomes compared with thromboprophylaxis (and bleeding was increased) in a randomized trial of 614 mostly stable patients hospitalized with COVID-19, although this study was underpowered for effectiveness.[24] On the basis of these and other studies, the National Institutes of Health currently recommends therapeutic-dose heparin (low-molecular-weight heparin preferred) for hospitalized COVID-19 patients with D-dimer levels above the upper limit of normal who require low-flow oxygen but do not require ICU level-of-care.[13,16,20,25] Prophylactic-dose anticoagulation is recommended for other noncritically ill hospitalized patients with COVID-19 who do

FIGURE 3 Continued

The combined therapeutic-dose anticoagulation groups include patients randomized to therapeutic-dose enoxaparin (n = 1,136) and therapeutic-dose apixaban (n = 1,121). Subgroups for continuous data were categorized according to the median to avoid bias. Subgroups according to geography of enrollment were not prespecified and were categorized post hoc. *Colombia, Mexico, Brazil, Panama, Hong Kong, Spain, Italy, Poland. †Estimated by the Cockcroft-Gault formula. ‡In-hospital, post-randomization; drug duration censored at the time of a primary endpoint event. Abbreviations as in **Figure 2**.

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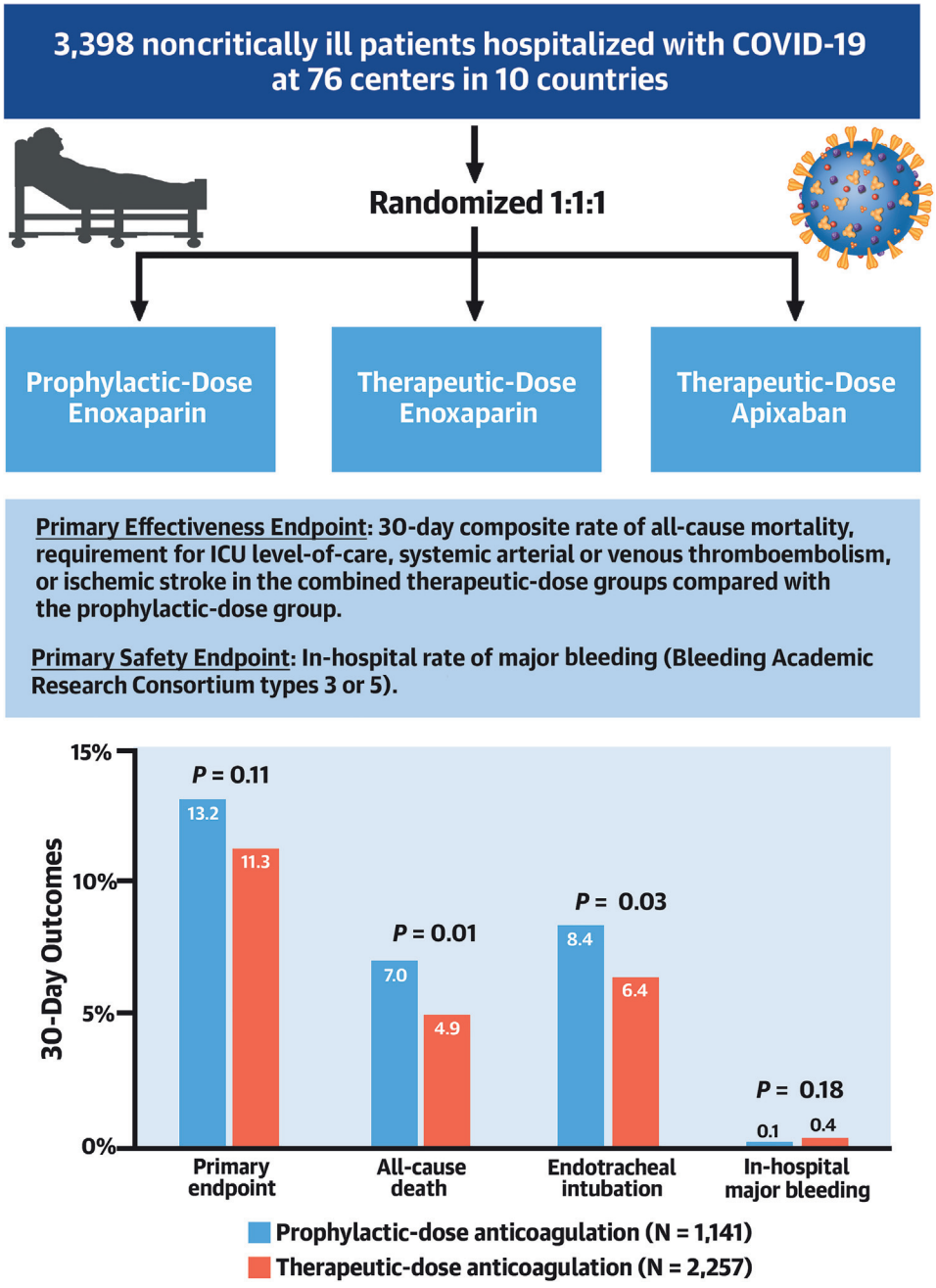
CENTRAL ILLUSTRATION **Major 30-Day Outcomes From the FREEDOM COVID-19 Anticoagulation Strategy Trial**



Stone GW, et al. J Am Coll Cardiol. 2023;81(18):1747-1762.

In this large-scale, international trial, the outcomes of therapeutic-dose anticoagulation with either subcutaneous enoxaparin or oral apixaban were compared with standard prophylactic-dose anticoagulation with subcutaneous enoxaparin in 3,398 patients hospitalized for COVID-19 who did not require intensive care unit (ICU) level of care at admission. Therapeutic-dose anticoagulation did not significantly reduce the 30-day composite primary endpoint, but it did reduce the rates of progressive pulmonary disease requiring endotracheal intubation with mechanical ventilation and all-cause mortality. Major bleeding was infrequent. Therapeutic-dose anticoagulation should thus be preferred in noncritically ill patients hospitalized with COVID-19, especially in those with higher-risk characteristics (eg, advanced age, bilateral pulmonary infiltrates) who do not yet require ICU level of care.

not require therapeutic-dose anticoagulation for another specific indication. However, this guidance is considered weak (strength of recommendation C) and based on moderate quality of evidence.[20]

With 3,398 randomized patients, the present trial is the largest to date to examine the safety and effectiveness of different anticoagulant dosing regimens in noncritically ill patients hospitalized with COVID-19. Although the incidence rate of the 30-day primary outcome, a composite of events that may be influenced by anticoagulation, was lower in patients treated with therapeutic-dose anticoagulation (11.3%) than with prophylactic-dose anticoagulation (13.2%), a 15% relative reduction, this difference did not reach statistical significance. Such a finding precludes formal hypothesis testing of additional outcomes. However, all-cause death within 30 days occurred in 7.0% of patients treated with prophylactic-dose anticoagulation and 4.9% of patients with therapeutic-dose anticoagulation ($P = 0.01$), a 30% relative reduction (48 patients needed-to-treat to prevent 1 death). Therapeutic dose anticoagulation also reduced the 30-day composite rate of all-cause death, systemic arterial or venous thromboembolism, or ischemic stroke, an alternative endpoint endorsed by the U.S. Food and Drug Administration in COVID-19 trials.[26] Although a chance finding cannot be excluded, a careful consideration of the validity of these observations is warranted. In this regard, our prespecified primary endpoint was dominated by the need for ICU level of care in all 3 treatment groups; among the 386 patients reaching a primary endpoint, 320 (83.4%) required ICU level of care. Since most deaths occur after entering the ICU, the influence of treatment on mortality was obscured in the time to first event primary analysis. Furthermore, many of the deaths prevented by therapeutic-dose anticoagulation were adjudicated to be of primary pulmonary cause, and therapeutic-dose anticoagulation also reduced the need for endotracheal intubation by 25%. As the pathophysiology of COVID-19 involves a hypercoagulable state with pulmonary vascular macrothrombosis and microthrombosis, these findings are consistent with the hypothesized mechanistic benefits of therapeutic-dose anticoagulation.[1-6] Moreover, as previously reported, the presence of ARDS on the admission chest x-ray or computed tomography (albeit not so severe as to require ICU level of care at study entry) in the present study identified patients with a marked increase in symptomatic progression and mortality within 30 days, and those in whom therapeutic-dose anticoagulation was most likely to improve survival.[27] That the survival benefit of therapeutic-dose anticoagulation was greatest in patients with radiologic evidence of ARDS lends further support to the hypothesis that therapeutic-dose anticoagulation may mitigate the pulmonary consequences of severe acute respiratory syndrome coronavirus 2 infection by preventing progressive vascular thrombosis.

The extent to which the prognosis in noncritically ill patients hospitalized with COVID-19 was improved in this study by the effects of therapeutic-dose anticoagulation on preventing or treating venous thromboembolism versus in situ pulmonary thrombosis is unknown. Venous thromboembolism (especially pulmonary emboli) was diagnosed infrequently in the present study. However, in the absence of routine screening the rate of venous thromboembolism was likely underestimated given the reluctance to image deteriorating patients with COVID-19, especially as all patients were receiving at least prophylactic-dose anticoagulation. Moreover, no tests are pathognomonic for in situ pulmonary thrombosis. Further study is warranted to elucidate the mechanism(s) underlying the benefits of therapeutic-dose anticoagulation in selected noncritically ill patients with COVID-19.

STUDY LIMITATIONS. Study drug use was open-label, introducing the potential for bias. This risk was mitigated by on-site monitoring and event adjudication by an independent committee masked to treatment assignment. The lower rates with therapeutic-dose anticoagulation of all-cause mortality and endotracheal intubation, 2 endpoints with a low risk of indication or ascertainment bias, further reinforces the reliability of the results. In this regard the discordance in statistical significance between our chosen primary endpoint (numerically but nonsignificantly lower with therapeutic-dose anticoagulation) and death and intubation (both significantly reduced) also emphasizes the fundamental importance of selection of a primary endpoint specific to the effects of the therapy. The number of observed events was lower than anticipated (reducing study power), largely because of the low event rate from India. These results emphasize that varying country-specific thresholds for hospitalization may affect patient prognosis and the potential utility of advanced therapies. ARDS in the present study was site-defined according to radiologic criteria (eg, bilateral opacities on the admission chest x-ray or computed tomography not explained by cardiac failure) and did not require the full Berlin criteria to be present.[28] Further studies are required to determine whether additional variables (eg, D-dimer levels, supplemental oxygen requirements, etc) can discriminate patients with and without radiologic ARDS who might benefit from therapeutic-dose anticoagulation. Additional analysis

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is also required to examine whether use of adjunctive therapies (eg, steroids, remdesivir, and antiplatelet agents) moderated the present results. These analyses may be useful to generate a COVID-19 risk score to better inform prognosis and anticoagulant regimen selection for noncritically ill patients hospitalized with COVID-19. Finally, we cannot exclude an interaction between specific COVID-19 variants and anticoagulation effectiveness. Such an analysis is precluded by the lack of genomic sequencing in individual patients, and the differing per-country timing and rate of enrollment and patient risk-profiles.

CONCLUSIONS

Among noncritically ill patients hospitalized with COVID-19, the difference in the 30-day primary composite outcome with therapeutic-dose anticoagulation compared with prophylactic-dose anticoagulation did not reach statistical significance. However, fewer patients treated with therapeutic-dose anticoagulation required endotracheal intubation and fewer died within 30 days. Outcomes with therapeutic-dose enoxaparin and apixaban were similar, and bleeding was infrequent with all 3 anticoagulation regimens. Based on these findings and the results from prior studies, the use of therapeutic-dose anticoagulation may improve outcomes in noncritically ill patients hospitalized with COVID-19, especially in higher-risk patients such as those who are older or have radiologic evidence of ARDS but do not yet require ICU level of care.

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Dr Stone has received speaker honoraria from Medtronic, Pulnovo, Infraredx, Abiomed, and Abbott; has served as a consultant to Daiichi-Sankyo, Valfix, TherOx, Robocath, HeartFlow, Ablative Solutions, Vectorious, Miracor, Neovasc, Ancora, Elucid Bio, Occlutech, CorFlow, Apollo Therapeutics, Impulse Dynamics, Cardiomech, Gore, Amgen, Adona Medical, and Millennia Biopharma; and has equity/options from Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, Valfix, and Xenter; his daughter is an employee at IQVIA; and his employer, Mount Sinai Hospital, receives research support from Abbott, Abiomed, Bioventrix, Cardiovascular Systems Inc, Phillips, Biosense-Webster, Shockwave, Vascular Dynamics, Pulnovo, and V-wave. Dr Farkouh has received institutional research grants from Amgen, AstraZeneca, Novo Nordisk, and Novartis; has received consulting fees from Otitopic; and has received honoraria from Novo Nordisk. Dr Lala has received consulting fees from Merck and Bioventrix; has received honoraria from Zoll Medical and Novartis; has served on an advisory board for Sequana Medical; and is the Deputy Editor for the *Journal of Cardiac Failure*. Dr Moreno has received honoraria from Amgen, Cuquerela Medical, and Gafney; has received payment for expert testimony from Koskoff, Koskoff & Dominus, Dallas W. Hartman, and Riscassi & Davis PC; and has stock options in Provisio. Dr Goodman has received institutional research grants from Bristol Myers Squibb/Pfizer Alliance, Bayer, and Boehringer Ingelheim; has received consulting fees from Amgen, Anthos Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CSL Behring, Ferring Pharmaceuticals, HLS Therapeutics, Novartis, Pendopharm/Pharmascience, Pfizer, Regeneron, and Sanofi; has received honoraria from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Ferring Pharmaceuticals, HLS Therapeutics, JAMP Pharma, Merck, Novartis, Pendopharm/Pharmascience, Pfizer, Regeneron, Sanofi, and Servier; has served on Data Safety and Monitoring boards for Daiichi-Sankyo/American Regent and Novo Nordisk A/C; has served on advisory boards for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CSL Behring, Eli Lilly, Ferring Pharmaceuticals, HLS Therapeutics, JAMP Pharma, Merck, Novartis, Pendopharm/Pharmascience, Pfizer, Regeneron, Sanofi, Servier, and Tolmar Pharmaceuticals; has a leadership role in the Novartis Council for Heart Health (unpaid); and otherwise has received salary support or honoraria from the Heart and Stroke Foundation of Ontario/University of Toronto (Polo) Chair, Canadian Heart Failure Society, Canadian Heart Research Centre and MD Primer, Canadian VIGOUR Centre, Cleveland Clinic Coordinating Centre for Clinical Research, Duke Clinical Research Institute, New York University Clinical Coordinating Centre, PERFUSE Research Institute, and the TIMI Study Group (Brigham Health). 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Dr Nadkarni has received consulting fees from Renalytix, Variant Bio, Qiming Capital, Menarini Health, Daiichi-Sankyo, BioVie, and Cambridge Health; has received honoraria from Daiichi-Sankyo and Menarini Health; has patents for automatic disease diagnoses using longitudinal medical record data, methods, and apparatus for diagnosis of progressive kidney function decline using a machine learning model, electronic phenotyping technique for diagnosing chronic kidney disease, deep learning to identify biventricular structure and function, fusion models for identification of pulmonary embolism, and SparTeN: a novel spatio-temporal deep learning model; has served on a Data Safety and Monitoring Board for CRIC OSMB; has leadership roles for Renalytix scientific advisory board, Pensive Health scientific advisory board, and ASN Augmented Intelligence and Digital Health Committee; has ownership interests in Renalytix, Data2Wisdom LLC, Verici Dx, Nexus I Connect, and Pensieve Health; and his institution receives royalties from Renalytix. 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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Therapeutic-dose anticoagulation does not decrease the 30-day composite outcome in noncritically ill patients hospitalized with COVID-19, but high-dose anticoagulated patients are less likely to require endotracheal intubation or die.

TRANSLATIONAL OUTLOOK: Additional analyses are needed to determine whether the benefit of therapeutic-dose anticoagulation differs across virus variants or is influenced by vaccination or adjunctive therapies.

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APPENDIX For supplemental text, tables, and figures, please see the online version of this paper.