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Anticoagulation and Antiplatelet Therapy for Prevention of Venous and Arterial Thrombotic Events in Critically Ill Patients With COVID-19: COVID-PACT

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BACKGROUND: The efficacy and safety of prophylactic full-dose anticoagulation and antiplatelet therapy in critically ill COVID-19 patients remain uncertain.

METHODS: COVID-PACT (Prevention of Arteriovenous Thrombotic Events in Critically-ill COVID-19 Patients Trial) was a multicenter, 2×2 factorial, open-label, randomized-controlled trial with blinded end point adjudication in intensive care unit–level patients with COVID-19. Patients were randomly assigned to a strategy of full-dose anticoagulation or standard-dose prophylactic anticoagulation. Absent an indication for antiplatelet therapy, patients were additionally randomly assigned to either clopidogrel or no antiplatelet therapy. The primary efficacy outcome was the hierarchical composite of death attributable to venous or arterial thrombosis, pulmonary embolism, clinically evident deep venous thrombosis, type 1 myocardial infarction, ischemic stroke, systemic embolic event or acute limb ischemia, or clinically silent deep venous thrombosis, through hospital discharge or 28 days. The primary efficacy analyses included an unmatched win ratio and time-to-first event analysis while patients were on treatment. The primary safety outcome was fatal or life-threatening bleeding. The secondary safety outcome was moderate to severe bleeding. Recruitment was stopped early in March 2022 (≈50% planned recruitment) because of waning intensive care unit–level COVID-19 rates.

RESULTS: At 34 centers in the United States, 390 patients were randomly assigned between anticoagulation strategies and 292 between antiplatelet strategies (382 and 290 in the on-treatment analyses). At randomization, 99% of patients required advanced respiratory therapy, including 15% requiring invasive mechanical ventilation; 40% required invasive ventilation during hospitalization. Comparing anticoagulation strategies, a greater proportion of wins occurred with full-dose anticoagulation (12.3%) versus standard-dose prophylactic anticoagulation (6.4%; win ratio, 1.95 [95% CI, 1.08–3.55]; *P*=0.028). Results were consistent in time-to-event analysis for the primary efficacy end point (full-dose versus standard-dose incidence 19/191 [9.9%] versus 29/191 [15.2%]; hazard ratio, 0.56 [95% CI, 0.32–0.99]; *P*=0.046). The primary safety end point occurred in 4 (2.1%) on full dose and in 1 (0.5%) on standard dose (*P*=0.19); the secondary safety end point occurred in 15 (7.9%) versus 1 (0.5%; *P*=0.002). There was no difference in all-cause mortality (hazard ratio, 0.91

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[95% CI, 0.56–1.48]; *P*=0.70). There were no differences in the primary efficacy or safety end points with clopidogrel versus no antiplatelet therapy.

CONCLUSIONS: In critically ill patients with COVID-19, full-dose anticoagulation, but not clopidogrel, reduced thrombotic complications with an increase in bleeding, driven primarily by transfusions in hemodynamically stable patients, and no apparent excess in mortality.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT04409834.

Key Words: anticoagulants ■ clopidogrel ■ COVID-19 ■ hemorrhage ■ platelet aggregation inhibitors ■ thrombosis

Clinical Perspective

What Is New?

- COVID-PACT (Prevention of Arteriovenous Thrombotic Events in Critically-ill COVID-19 Patients Trial) was a 2×2 factorial, randomized-controlled trial in critically ill patients with COVID-19 of (1) full-dose anticoagulation versus standard-dose prophylactic anticoagulation and (2) clopidogrel versus no antiplatelet therapy for prevention of thrombotic events.
- Full-dose anticoagulation substantially reduced the proportion of patients experiencing a venous or arterial thrombotic event (9.9% versus 15.2%); there was no benefit from treatment with clopidogrel.
- Severe bleeding events were rare but were numerically increased in patients on full-dose versus standard-dose prophylactic anticoagulation (2.1% versus 0.5%) without any fatal bleeding events. Moderate to severe bleeding was significantly increased with full-dose anticoagulation, with no difference in all-cause mortality.

What Are the Clinical Implications?

- In a population of critically ill patients with COVID-19, a strategy of prophylaxis with full-dose versus standard-dose prophylactic anticoagulation, but not the addition of clopidogrel, reduced thrombotic complications with an increase in bleeding, driven primarily by transfusions in hemodynamically stable patients, and no apparent excess in mortality.
- COVID-PACT may be relevant when revisiting current consensus treatment guidelines, which suggest using standard-dose prophylactic-intensity anticoagulation over full-dose anticoagulation in the critically ill population with COVID-19.

Nonstandard Abbreviations and Acronyms

DVT	deep venous thrombosis
GUSTO	Global Use of Strategies to Open Occluded Coronary Arteries
ICU	intensive care unit
PROBE	prospective, randomized, open-label, blinded end-point adjudication
TIMI	Thrombolysis in Myocardial Infarction

Infection with the SARS-CoV2 virus carries a risk of venous and arterial thrombosis, and this risk is substantially higher in patients requiring critical care.[1–3] Possibly driven by the inflammatory response to infection, SARS-CoV2 infection results in activation of the coagulation cascade, systemic endothelial dysfunction, and a hyperreactive platelet response.[1,4,5]

Thromboprophylaxis with anticoagulant therapy is recommended in critically ill patients without COVID-19 on the basis of a significant reduction in venous thrombotic events.[6,7] Given the excess risk of thrombosis and the potential role of platelet aggregation and platelet-rich clot formation in the pathogenesis of COVID-19, multiple randomized trials have assessed the benefit of anticoagulant and antiplatelet treatment strategies in patients with COVID-19.[8–15] These studies have yielded varied primary results, perhaps because of differing study populations, designs, and end points. As such, the optimal pharmacologic thromboprophylaxis strategy, particularly in critically ill patients with COVID-19, has remained uncertain,[16,17] with a possible benefit for prevention of thrombotic events with increased intensity of antithrombotic prophylaxis.[18]

We conducted the COVID-PACT trial (Prevention of Arteriovenous Thrombotic Events in Critically-ill COVID-19 Patients Trial) as a 2×2 factorial, randomized-controlled trial in critically ill patients with COVID-19 to evaluate whether an increased intensity of prophylactic antithrombotic therapy prevents venous and arterial thrombotic complications associated with severe COVID-19 infection with an acceptable safety profile.

METHODS

Trial Design and Oversight

COVID-PACT was a multicenter, 2×2 factorial, randomized-controlled trial in critically ill patients with COVID-19, evaluating the efficacy and safety of: (1) full-dose anticoagulation for prophylaxis versus standard-dose prophylactic

anticoagulation, and (2) antiplatelet therapy with clopidogrel versus no antiplatelet therapy for the prevention of venous and arterial thrombotic events. The trial followed the principles of a prospective, randomized, open-label, blinded end-point adjudication (PROBE) design. This investigator-initiated trial was designed by its Steering Committee and coordinated by the Critical Care Cardiology Trials Network and the trial sponsor and funder, the TIMI Study Group, Brigham and Women's Hospital (Boston, MA).

The trial was conducted in accordance with the principles of the Good Clinical Practice guidelines of the International Council for Harmonization. The protocol and amendments were approved by the relevant institutional review boards at each participating site, and at the coordinating center, as well. Written informed consent was obtained from each participant or legal authorized representative. The trial database was designed and maintained by the coordinating center. Safety was monitored by an independent Data Monitoring Committee. We encourage parties interested in collaboration and data sharing to contact the corresponding author.

Study Population

COVID-PACT randomly assigned patients at 34 sites in the United States (see Supplemental Material). Eligible patients were at least 18 years of age with an acute infection with SARS-CoV2 who were requiring intensive care unit (ICU) level of care, were at that level of care for ≤96 hours before randomization, and did not have an indication for full-dose anticoagulation. ICU level of care was defined as (1) being admitted to an ICU or (2) being cared for in a non-ICU room by an ICU team or requiring advanced respiratory support (ie, invasive mechanical ventilation, noninvasive positive pressure ventilation, or high-flow nasal canula for respiratory insufficiency), continuous vasopressor use, or mechanical circulatory support. Exclusion criteria included any ongoing or planned use of full-dose anticoagulation for any indication, ongoing or planned use of dual antiplatelet therapy, contraindication to antithrombotic therapy, high risk of bleeding (including fibrinogen <200 mg/dL), history of heparin-induced thrombocytopenia, or ischemic stroke within the past 2 weeks. Patients with ongoing or planned antiplatelet therapy, including aspirin monotherapy, were excluded from the second randomization to antiplatelet versus no antiplatelet therapy. Full eligibility criteria are provided in the Supplemental Material.

Trial recruitment was stopped early on March 2, 2022, because of the waning rates of ICU-level admissions for COVID-19 and consequent slow recruitment.

Randomization and Study Therapies

Enrolled patients were randomly assigned in a 1:1 ratio to a strategy of full-dose anticoagulation or standard-dose prophylactic anticoagulation until the end of the follow-up period, defined as the earliest of hospital discharge or day 28 (Supplemental Material). Randomization was stratified by eligibility for the 2nd level randomization to antiplatelet therapy. Patients eligible for the 2nd level randomization (ie, patients without ongoing or planned antiplatelet therapy) were randomly assigned in a 1:1 ratio to clopidogrel or no antiplatelet therapy to be given until the end of the follow-up period.

Treatment was open-label and hospital-supplied by the institutional pharmacy per standard practice using local, standard formulations and concentrations. Patients randomly assigned to antiplatelet therapy were administered clopidogrel 300 mg orally once on the day of randomization, followed by 75 mg orally once daily on subsequent days. Acceptable initial anticoagulation regimens included intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin for the full-dose anticoagulation strategy and subcutaneous heparin or low-molecular-weight heparin for the standard-dose prophylactic anticoagulation strategy. A full list of acceptable regimens by strategy are included in the Supplemental Material. Transitions between acceptable regimens within a randomized treatment strategy were allowed.

Temporary or permanent discontinuation of study-related antithrombotic therapy was recommended in the event of active, clinically significant bleeding, severe thrombocytopenia, or evidence of overt disseminated intravascular coagulation (see Supplemental Material).

Study Procedures

Study procedures included monitoring of anticoagulation per local practice, as well as following the international normalized ratio daily and fibrinogen at least every 3 days while receiving ICU-level of care. Patients were to have a single, screening bilateral lower extremity venous ultrasound 10 to 14 days after randomization, or earlier if prematurely discontinuing the randomized strategy (Supplemental Material). Additionally, patients were monitored for adverse events, leading to discontinuation of study-related antithrombotic therapy, and serious adverse events related to study medications.

End Points

The primary efficacy outcome was a hierarchical composite of venous and arterial thrombotic events, defined in the following order: death attributable to venous or arterial thrombosis, pulmonary embolism, clinically evident deep venous thrombosis (DVT), type 1 myocardial infarction, ischemic stroke, systemic embolic event or acute limb ischemia, and clinically silent DVT. The key secondary efficacy outcome of clinically evident venous and arterial thrombotic events contained the same elements with the exception of clinically silent DVT (ie, DVTs identified at the time of the screening ultrasound). The primary safety outcome was fatal or life-threatening bleeding, defined as a bleeding event that led to death or was intracranial, intrapericardial with tamponade, associated with hemodynamic instability requiring intervention, or resulted in transfusion of at least 4 units over 24 hours (Supplemental Material). A secondary safety outcome was Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) moderate or severe bleeding (Supplemental Material). Other prespecified outcomes, including all-cause mortality, are described in the Supplemental Material. A central clinical events adjudication committee, whose members were unaware of the randomized treatment strategy, adjudicated all key primary and secondary efficacy and safety outcomes.

Statistical Analysis

The efficacy of each factorial intervention was analyzed using an unmatched pair win ratio,[19] and time-to-first event analysis

(frequentist approach), with each comparison stratified by the other factorial randomization arm. The unmatched win ratio evaluated the key primary and secondary composite outcomes in a hierarchical manner (according to the order of the components listed above), with a win ratio >1 favoring the full-dose anticoagulation and antiplatelet arms, respectively. For the time-to-first event analysis, differences in clinical outcomes between the 2 treatment groups were assessed using the stratified Gray test for equality of cumulative incidence functions. Hazard ratios and 95% CIs were calculated using a Fine-Gray model to account for the competing risk of nonthrombotic death. Differences between treatment groups in all-cause mortality were assessed using the stratified log-rank test, with hazard ratios and 95% CIs calculated using a Cox model. The proportional hazards assumptions were verified as described in the Supplemental Material.

The primary efficacy and safety analyses were conducted using the on-treatment analysis population, consisting of all randomly assigned patients who received at least 1 dose of the randomly allocated study anticoagulant or antiplatelet strategy. The primary assessments were prespecified to be on-treatment comparisons, including events that occurred during therapy with the randomized treatment strategy or within 72 hours of the last dose of randomized treatment strategy. Additional supportive analyses were conducted according to the intention-to-treat principle. There was no interaction between the randomized anticoagulant and antiplatelet strategies; therefore, each of the randomized strategies is presented separately.

A prespecified Bayesian analysis of the primary efficacy end point and mortality was conducted as described (Supplemental Material).

The target sample size was based on the log-rank test accounting for competing risk using the method of Pintilie,[20] which was expected to be conservative with respect to the win ratio analysis. We estimated that 170 primary end point events would be required to have 80% power to detect a 35% relative risk reduction with full-dose anticoagulation over standard-dose prophylactic anticoagulation with a 2-sided α of 0.05. Assuming an event rate of 40% in patients on standard-dose prophylactic anticoagulation and no antiplatelet therapy, a 10% competing risk of nonthrombotic death, and a 1% dropout rate, the target sample size was 750 patients. Assuming that 10% of patients would not be eligible for randomization to antiplatelet therapy, we anticipated a sample size of 675 patients for the comparison of antiplatelet versus no antiplatelet therapy, which would provide 70% power to detect a 35% relative risk reduction.

Incidence rates (n/N) are presented unless otherwise indicated. All reported *P* values are 2-sided, and a *P* value <0.05 was considered to signify nominal statistical significance with no adjustment for multiple comparisons. All analyses were conducted by the TIMI Study Group using SAS, version 9.4 (SAS Institute).

RESULTS

Study Population

From August 5, 2020, through March 2, 2022, a total of 390 patients were randomly assigned in the first factorial comparison of anticoagulation strategies, and 292 (75% of total) were randomly assigned in the second factorial comparison of antiplatelet strategies. Three hundred eighty-two and 290 were included in the on-treatment analyses, respectively. The median duration of follow-up was 13.0 days (25th, 75th percentiles, 8, 22 days) in the overall population, and in those randomly assigned to antiplatelet therapy versus not.

In general, the baseline characteristics were well balanced for both randomizations (Table 1). In the cohort treated in the anticoagulation strategy, the median age was 61 years (25th, 75th percentiles, 51, 69 years) and 41% of the patients were female (Table 1). Patients had high rates of hypertension, diabetes, and pulmonary disease, but relatively low rates of atherosclerotic cardiovascular disease and chronic kidney disease. Almost all patients (99%) required advanced respiratory therapy (ie, high-flow nasal canula or noninvasive or invasive mechanical ventilation) at the time of randomization (Table 1). Forty percent of patients required invasive mechanical ventilation during the trial follow-up period (Table S1).

Patients eligible and treated in the antiplatelet randomization strata were slightly younger than the overall cohort with a median age of 58 years (25th, 75th percentiles, 48, 67 years) and less comorbid atherosclerotic cardiovascular disease (Table 1). Baseline characteristics for the intention-to-treat population are provided in Table S2.

The median time from hospital admission to randomization was 2.1 days (25th, 75th percentiles, 1.5, 3.4 days). Most patients (97%) were receiving anticoagulation in the hospital before randomization, with the majority being either standard-dose (69%) or intermediate-dose prophylaxis (25%; Table S3). Twenty-five percent of the total population was receiving antiplatelet monotherapy in-hospital before randomization; only 2.4% of patients eligible for the antiplatelet randomization had received any antiplatelet therapy in-hospital before randomization (Table S3).

Study Therapy and Retention

Low-molecular-weight heparin was the most common regimen used (82%) as the initial anticoagulant in both randomized strategies (Table S4). Crossover to the alternative randomized therapy occurred more frequently from standard-dose prophylactic anticoagulation (34%) than with full-dose anticoagulation (17%; *P*=0.0002); overall rates of discontinuation or crossover were similar between the randomized anticoagulation arms (*P*=0.33; Table S5). Thirty-one percent of patients randomly assigned to clopidogrel discontinued therapy (Table S5). The reasons for discontinuation or crossover are presented in Table S5. The median duration of exposure to the randomized anticoagulation strategy was 9.9 days for full-dose anticoagulation and

Table 1. Baseline Characteristics in On-Treatment Population

Baseline characteristics	Total for anticoagulation randomization (n=382)		Total for antiplatelet randomization (n=290)	
	Full-dose anticoagulation (n=191)	Standard-dose prophylactic anticoagulation (n=191)	Clopidogrel (n=150)	No clopidogrel (n=140)
Demographics				
Age, y	59 (50, 70)	62 (51, 68)	58 (49, 67)	58 (47, 67)
>65	68 (36)	70 (37)	44 (29)	39 (28)
Female	73 (38)	83 (43)	58 (39)	60 (43)
White	134 (75)	139 (79)	115 (83)*	91 (71)*
Hispanic	30 (18)	27 (16)	28 (21)	25 (20)
Body mass index, kg/m^2	34 (29, 40)	34 (29, 41)	34 (29, 42)	34 (29, 40)
Body mass index ≥30	123 (65)	135 (71)	104 (69)	97 (70)
Medical history				
Hypertension	107 (56)	118 (62)	76 (51)	76 (54)
Diabetes	73 (38)*	49 (26)*	40 (27)	41 (29)
Atherosclerotic cardiovascular disease	28 (15)	25 (13)	10 (6.7)	9 (6.4)
Active cancer	10 (5.2)	7 (3.7)	8 (5.3)	5 (3.6)
Current or past smoking	82 (43)	73 (38)	56 (37)	49 (35)
Chronic kidney disease	20 (11)	20 (11)	10 (6.7)	11 (7.9)
Pulmonary disease	42 (22)	36 (19)	31 (21)	29 (21)
Status at randomization				
Time from admission to randomization, days	2.3 (1.5, 3.7)	2.1 (1.5, 3.3)	2.1 (1.6, 3.6)	2.1 (1.4, 3.2)
World Health Organization COVID-19 ordinal scale				
No oxygen therapy	0 (0)	0 (0)	0 (0)	0 (0)
Oxygen by mask or nasal canula	3 (1.6)	1 (0.5)	1 (0.7)	3 (2.1)
Noninvasive ventilation or high-flow nasal canula	151 (79)*	168 (88)*	128 (85)	115 (82)
Invasive ventilation	37 (19)*	22 (12)*	21 (14)	22 (16)
P/F ≥150	9 (4.7)	5 (2.6)	5 (3.3)	8 (5.7)
P/F <150 or vasopressor	25 (13.1)	14 (7.3)	14 (9.3)	11 (7.9)
P/F <150 and organ support†	3 (1.6)	3 (1.6)	2 (1.3)	3 (2.1)
Laboratories				
Estimated glomerular filtration rate; mL·min^{-1}·1.73 m^{-2}	88 (66, 102)	86 (65, 101)	90 (75, 107)	90 (69, 103)
Hemoglobin, g/dL	13.2 (11.9, 14.2)	13.0 (11.9, 14.3)	13.2 (12.2, 14.2)	13.3 (11.8, 14.3)
D-dimer, ng/mL	886 (610, 1718)	950 (546, 1790)	807 (500, 1550)	902 (551, 1440)
D-dimer >2× upper limit of normal	73 (40)	77 (45)	49 (36)	55 (43)

Counts (%) or median (25th, 75th percentile) presented. P/F indicates Pao_2 over fraction inspired oxygen.
*P value for comparison between arms within strategy <0.05 using the χ^2 test.
†Organ support refers to vasopressor, renal replacement therapy or extracorporeal membrane oxygenation.

6.6 days for standard-dose prophylactic anticoagulation; however, the median duration of exposure to any anticoagulation was 10.6 days in both groups, reflecting the higher rate of crossover from standard-dose prophylactic anticoagulation to full-dose anticoagulation (Table S5). The median duration of exposure to clopidogrel was 8.6 days (Table S5). Study drug management in the intention-to-treat population is detailed in Table S6. All patients completed follow-up in the trial for both randomizations; overall, 30% of patients died during follow-up, 56% were discharged alive on or before day 28, and 14% remained hospitalized at the end of the 28-day follow-up (Figures S1 and S2).

Efficacy for Prevention of Venous and Arterial Thrombotic Events by Intensity of Anticoagulation

With use of the hierarchical, unmatched pair win ratio approach in the on-treatment analysis set, a greater proportion of wins occurred for the primary efficacy end point of venous or arterial thrombotic events in the full-dose

anticoagulation group (12.3%) versus in the standard-dose prophylactic anticoagulation group (6.4%; win ratio, 1.95 [95% CI, 1.08–3.55]; *P*=0.028; Table 2). For the key secondary end point of clinically evident venous or arterial thrombotic events, wins occurred in 10.0% in the full-dose anticoagulation group versus in 5.5% in the standard-dose prophylactic anticoagulation group (win ratio, 1.79 [95% CI, 0.92–3.47]; *P*=0.087; Table 2). An exploratory analysis in which all-cause mortality replaced deaths attributable to arterial or venous thrombotic events similarly demonstrated a greater proportion of wins with full-dose anticoagulation compared with standard-dose prophylactic anticoagulation for the primary and key secondary efficacy end points (Table S7).

Results were consistent for the primary and key secondary efficacy end points using time-to-first event analyses (Table 3 and Table S8). Nineteen patients (9.9%) experienced a primary end point event in the full-dose anticoagulation group and 29 (15.2%) in the standard-dose prophylactic anticoagulation group during the on-treatment window (stratified Gray test *P*=0.046), with a hazard ratio of 0.56 (95% CI, 0.32–0.99; Table 3 and Figure 1). Fourteen patients (7.3%) experienced a key secondary end point event in the full-dose anticoagulation group and 23 (12.0%) in the standard-dose prophylactic anticoagulation group (hazard ratio [HR], 0.55 [95% CI, 0.28–1.08]; Table 4 and Figure 1).

The individual components of the composite outcomes are shown in Table 3. Incidence rates of venous thrombotic events were lower in patients randomly assigned to full-dose anticoagulation versus standard-dose prophylactic anticoagulation (18 versus 28 events; 9.4% versus 14.7%; HR, 0.55 [95% CI, 0.31–0.99]; Table 3) with consistency across the components of pulmonary embolism (6 versus 7 events), clinically evident DVT (9 versus 16 events), and clinically silent DVT (5 versus 6 events). Rates of arterial thromboses were low (Table 3). There was no difference in all-cause mortality with full-dose anticoagulation versus standard-dose prophylactic anticoagulation (HR, 0.91 [95% CI, 0.56–1.48]; Table 3).

There was no heterogeneity in treatment benefit for the primary efficacy end point for full-dose anticoagulation versus standard-dose prophylactic anticoagulation across any of the prespecified subgroups, including by randomization to antiplatelet therapy or D-dimer concentration (Figure 2).

Additional analyses using the intention-to-treat principle with the win ratio (Table 2) and time-to-event (Table S9, Figures S3) approaches demonstrated an attenuated but directionally consistent treatment effect of full-dose anticoagulation versus standard-dose prophylactic anticoagulation, including for the primary (13.2% versus 16.6%; HR, 0.72 [95% CI, 0.43–1.19]) and key secondary end points (9.1% versus 13.0%; HR, 0.66 [95% CI, 0.36–1.20]). Rates of all-cause mortality were 27.9% in full-dose anticoagulation versus 32.1% in standard-dose prophylactic anticoagulation (HR, 0.80 [95% CI, 0.56–1.16]; Table S9).

A Bayesian approach to analysis of the primary efficacy end point and all-cause mortality yielded posterior estimates of the HRs and credible intervals that were highly consistent with the primary results from COVID-PACT (Supplemental Material).

Safety by Intensity of Anticoagulation

The primary safety end point, fatal or life-threatening bleeding, occurred in 4 (2.1%) patients in the full-dose anticoagulation group and in 1 (0.5%) patient in the standard-dose prophylactic anticoagulation group during the on-treatment window (*P*=0.19; Table 3), without any fatal bleeding events in either

Table 2. Primary and Key Secondary Efficacy Outcomes Using Win Ratio Approach

Outcomes	Anticoagulation strategy				Antiplatelet strategy			
	FDAC wins (%)	SDPAC wins (%)	Stratified win ratio (95% CI) (FDAC/SDPAC)	*P* value	Clopidogrel wins (%)	No clopidogrel wins (%)	Stratified win ratio (95% CI) (Clopi/no Clopi)	*P* value
On treatment								
Total comparisons	n=36 481				n=21 000			
Primary end point	4486 (12.3)	2351 (6.4)	1.95 (1.08–3.55)	0.028	2052 (9.8)	1994 (9.5)	1.04 (0.54–2.01)	0.90
Key secondary end point	3649 (10.0)	2021 (5.5)	1.79 (0.92–3.47)	0.087	1452 (6.9)	1900 (9.0)	0.79 (0.38–1.65)	0.53
Intention to treat								
Total comparisons	n=38 021				n=21 280			
Primary end point	5123 (13.5)	3212 (8.4)	1.64 (0.95–2.82)	0.074	2208 (10.4)	2342 (11.0)	0.93 (0.50–1.72)	0.82
Key secondary end point	4085 (10.7)	2492 (6.6)	1.65 (0.88–3.07)	0.12	1547 (7.3)	2068 (9.7)	0.75 (0.37–1.53)	0.44

Number of wins (%) presented. Primary end point is a hierarchical composite of venous and arterial thrombotic events in the following order: (1) death attributable to venous or arterial events, (2) pulmonary embolism, (3) clinically evident deep venous thrombosis, (4) type 1 myocardial infarction, (5) ischemic stroke, (6) systemic embolic event or acute limb ischemia, and (7) clinically silent deep venous thrombosis. Key secondary end point is a hierarchical composite of clinically evident venous and arterial thrombotic events, including the following events: (1) death attributable to venous or arterial events, (2) pulmonary embolism, (3) clinically evident deep venous thrombosis, (4) type 1 myocardial infarction, (5) ischemic stroke, and (6) systemic embolic event or acute limb ischemia. Clopi indicates clopidogrel; FDAC, full-dose anticoagulation; and SDPAC, standard-dose prophylactic anticoagulation.

Table 3. Efficacy and Safety Outcomes Using Time-to-Event Approach in On-Treatment Analysis Set

Outcomes	Total for anticoagulation randomization (n=382)				Total for antiplatelet randomization (n=290)			
	FDAC (n=191)	SDPAC (n=191)	Hazard ratio (95% CI)	*P* value	Clopidogrel (n=150)	No clopidogrel (n=140)	Hazard ratio (95% CI)	*P* value
Efficacy end points								
Primary efficacy	19 (9.9)	29 (15.2)	0.56 (0.32–0.99)	0.046	17 (11.3)	21 (15.0)	0.90 (0.48–1.69)	0.75
Key secondary efficacy	14 (7.3)	23 (12.0)	0.55 (0.28–1.08)	0.076	16 (10.7)	13 (9.3)	1.29 (0.62–2.66)	0.49
Efficacy end point components								
Venous thrombotic events	18	28	0.55 (0.31–0.99)	–	17	21	0.90 (0.48–1.69)	–
Arterial thrombotic events	1	2	0.49 (0.04–5.73)	–	1	0	–	–
Pulmonary embolism	6	7	0.78 (0.26–2.34)	–	6	6	1.03 (0.33–3.19)	–
Clinically evident DVT	9	16	0.51 (0.23–1.16)	–	11	9	1.29 (0.53–3.15)	–
Clinically silent DVT	5	6	0.59 (0.20–1.77)	–	1	8	0.17 (0.02–1.44)	–
Death attributable to venous thrombotic or arterial thrombotic events	1	1	–	–	1	0	–	–
Type 1 MI	1	0	–	–	0	0	–	–
Ischemic stroke	0	0	–	–	0	0	–	–
SEE or ALI	0	2	–	–	1	0	–	–
All-cause mortality	36 (18.8)	32 (16.8)	0.91 (0.56–1.48)	0.70	24 (16.0)	34 (24.3)	1.15 (0.67–1.98)	0.60
Safety end points								
Primary safety	4 (2.1)	1 (0.5)	3.86 (0.44–34.28)	0.19	2 (1.3)	2 (1.4)	1.00 (0.14–7.18)	1.00
Fatal bleeding	0	0	–	–	0	0	–	–
Life-threatening bleeding	4	1	–	–	2	2	–	–
Secondary safety	15 (7.9)	1 (0.5)	12.30 (1.64–92.08)	0.002	6 (4.0)	9 (6.4)	0.87 (0.30–2.55)	0.83
GUSTO severe bleeding	4	1	–	–	2	2	–	–
GUSTO moderate bleeding	11	0	–	–	4	7	–	–

Number of events ± n/N rate presented. On-treatment analysis set used with events included that occurred while on randomized treatment strategy or within 72 hours of last dose of randomized treatment strategy. Primary efficacy end point is a composite of venous and arterial thrombotic events (death attributable to venous or arterial events, pulmonary embolism, clinically evident DVT, type 1 MI, ischemic stroke, SEE or ALI, and clinically silent DVT). Key secondary efficacy end points are a composite of clinically evident venous and arterial thrombotic events (death attributable to venous or arterial events, pulmonary embolism, clinically evident DVT, type 1 MI, ischemic stroke, SEE or ALI). Venous thrombotic events include pulmonary embolism and any DVT (clinically evident and clinically silent). Arterial thrombotic events include ischemic stroke, SEE, ALI, or type 1 MI. The primary safety end point is a composite of fatal or life-threatening bleeding. The secondary safety end point is a composite of GUSTO moderate or severe bleeding. Hazard ratio and 95% CIs are from Fine and Gray subdistribution regression accounting for any nonthrombotic death as a competing event with stratification by randomization stratification factors. *P* values are from the stratified Gray test for equality of cumulative incidence functions. All-cause mortality analysis used Cox proportional hazards regression with stratification by randomization stratification factors; *P* values are from the stratified log-rank test. ALI indicates acute limb ischemia; DVT, deep venous thrombosis; FDAC, full-dose anticoagulation; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; MI, myocardial infarction; SDPAC, standard-dose prophylactic anticoagulation; and SEE, systemic embolic event.

group. GUSTO moderate or severe bleeding occurred in 15 (7.9%) patients in the full-dose anticoagulation group and 1 (0.5%) patient in the standard-dose prophylactic anticoagulation group during the on-treatment window (*P*=0.002; Table 3 and Figure S4), with the majority of events being moderate in severity. There was no difference in the rates of any adverse events, adverse events leading to discontinuation of antithrombotic therapy, or serious adverse events between the full-dose anticoagulation and standard-dose prophylactic anticoagulation groups (Table S10). There were 4 serious adverse events not attributable to bleeding thought to be related to study medications with full-dose anticoagulation versus 1 such serious adverse event with standard-dose prophylactic anticoagulation (Table S10).

Efficacy for Prevention of Venous and Arterial Thrombotic Events by Antiplatelet Versus No Antiplatelet Therapy

With the use of the hierarchical, unmatched pair win ratio approach, wins occurred in 9.8% in the clopidogrel group for the primary efficacy end point versus 9.5% in the no antiplatelet group in the on-treatment window (win ratio, 1.04 [95% CI, 0.54–2.01]; *P*=0.90; Table 2). Wins occurred in 6.9% in the clopidogrel group for the key secondary end point versus 9.0% in the no antiplatelet group (win ratio, 0.79 [95% CI, 0.38–1.65]; *P*=0.53; Table 2). Results were consistent with no treatment effect observed for the primary and key secondary efficacy end points using time-to-event analyses (Table 3 and Figure 1).

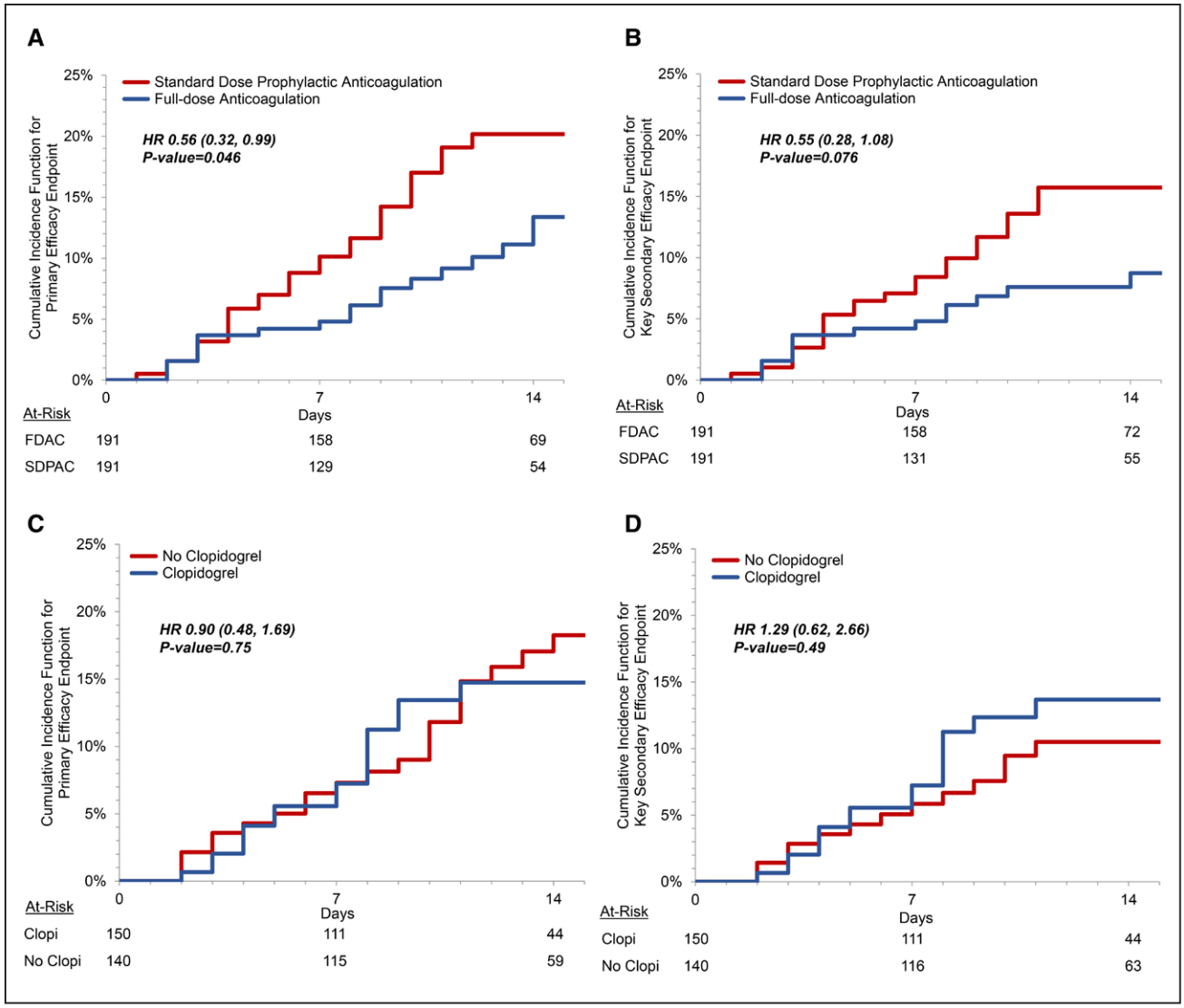


Figure 1. Cumulative incidence function curves for primary efficacy end point for anticoagulation and antiplatelet randomizations in on-treatment analysis set.

Cumulative incidence function curves accounting for competing nonthrombotic deaths in the on-treatment analysis set. Primary efficacy end point (**A**) and key secondary efficacy end point (**B**) for full-dose anticoagulation (FDAC) versus standard-dose prophylactic anticoagulation (SDPAC). Primary efficacy end point (**C**) and key secondary efficacy endpoint (**D**) for clopidogrel (Clopi) versus no clopidogrel. HR indicates hazard ratio.

Results were consistently neutral for the individual components of the composite outcomes (Table 3), in prespecified subgroups (Figure 2), and in supportive additional analyses (Table 2, Table S9, and Figure S3).

Safety of Antiplatelet Therapy

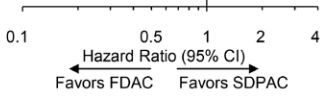
The primary safety end point, fatal or life-threatening bleeding, occurred in 2 (1.3%) patients in the clopidogrel group and in 2 (1.4%) patients in the no antiplatelet group during the on-treatment window (P=1.00; Table 3). GUSTO moderate or severe bleeding occurred in 6 (4.0%) patients in the clopidogrel group and in 9 (6.4%) patients in the no antiplatelet group (P=0.83; Table 3).

DISCUSSION

In this 2×2 factorial, randomized-controlled trial in critically ill patients with COVID-19, full-dose anticoagulation, compared with standard-dose prophylactic anticoagulation, substantially reduced the proportion of patients experiencing a venous or arterial thrombotic event (9.9% versus 15.2%), whereas there was no benefit from treatment with clopidogrel. Severe bleeding events were rare but were numerically increased in patients on full-dose anticoagulation compared with standard-dose prophylactic anticoagulation (2.1% versus 0.5%) without any fatal bleeding events. GUSTO moderate or severe bleeding was significantly increased with full-dose anticoagulation, with no difference in all-cause mortality. The results of COVID-PACT support the efficacy of full-dose

A

Subgroups	Total Patients	FDAC (n/N%)	SDPAC (n/N%)	PEP Hazard Ratio (95% CI)	P-int
Overall	382	9.9	15.2	0.56 (0.32, 0.99)	
AP Therapy	152	8.1	14.1	0.53 (0.20, 1.42)	0.73
No AP Therapy	136	13.0	13.4	0.73 (0.30, 1.80)	
Not Eligible for AP Rando	94	8.3	19.6	0.41 (0.12, 1.33)	
Age ≥ 65	149	6.8	17.3	0.33 (0.12, 0.95)	0.21
Age < 65	233	12.0	13.8	0.75 (0.37, 1.49)	
Male	226	10.2	17.6	0.48 (0.23, 0.97)	0.50
Female	156	9.6	12.0	0.72 (0.28, 1.82)	
BMI ≥ 35	174	11.9	15.6	0.67 (0.30, 1.48)	0.58
BMI < 35	207	8.5	14.9	0.48 (0.21, 1.09)	
DM	122	15.1	16.3	0.80 (0.33, 1.96)	0.26
No DM	260	6.8	14.8	0.40 (0.18, 0.90)	
D-dimer ≥ median	174	16.1	18.4	0.78 (0.38, 1.63)	0.29
D-dimer < median	178	4.3	9.5	0.37 (0.12, 1.19)	
hsCRP ≥ median	178	9.8	15.1	0.59 (0.25, 1.39)	0.98
hsCRP < median	175	11.0	15.5	0.60 (0.27, 1.35)	
No ASCVD	329	11.0	14.5	0.65 (0.36, 1.19)	0.22
ASCVD	53	3.6	20.0	0.16 (0.02, 1.39)	
No mechanical ventilation	323	8.4	15.4	0.46 (0.24, 0.90)	0.20
Mechanical ventilation	59	16.2	13.6	1.19 (0.32, 4.44)	



B

Subgroups	Total Patients	Clopi (n/N%)	No Clopi (n/N%)	PEP Hazard Ratio (95% CI)	P-int
Overall	290	11.3	15.0	0.90 (0.48, 1.69)	
SDPAC	145	14.1	14.9	1.04 (0.45, 2.42)	0.60
FDAC	145	8.3	15.1	0.73 (0.27, 1.98)	
Age ≥ 65	92	14.3	7.0	2.48 (0.63, 9.76)	0.08
Age < 65	198	9.9	18.6	0.63 (0.30, 1.34)	
Male	172	12.0	18.8	0.82 (0.38, 1.78)	0.67
Female	118	10.3	10.0	1.09 (0.36, 3.30)	
BMI ≥ 35	133	9.7	21.3	0.47 (0.19, 1.15)	0.05
BMI < 35	156	12.8	10.3	1.70 (0.67, 4.30)	
DM	81	12.5	22.0	0.70 (0.24, 2.03)	0.56
No DM	209	10.9	12.1	1.04 (0.47, 2.31)	
D-dimer ≥ median	120	15.5	22.6	0.82 (0.35, 1.96)	0.79
D-dimer < median	144	6.4	7.6	1.01 (0.31, 3.33)	
hsCRP ≥ median	135	11.0	14.5	0.96 (0.37, 2.51)	0.91
hsCRP < median	134	12.3	15.9	0.90 (0.37, 2.17)	
No ASCVD	271	11.4	15.3	0.88 (0.46, 1.69)	0.83
ASCVD	19	10.0	11.1	1.19 (0.08, 18.64)	
No mechanical ventilation	247	11.6	13.6	1.02 (0.51, 2.06)	0.39
Mechanical ventilation	43	9.5	22.7	0.47 (0.09, 2.41)	

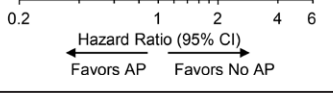


Figure 2. Primary efficacy in key subgroups.
Prespecified subgroups for primary efficacy end point (PEP) for full-dose anticoagulation (FDAC) versus standard-dose prophylactic anticoagulation (SDPAC; **A**) and clopidogrel vs no clopidogrel (**B**). Analysis uses Fine and Gray subdistribution hazard regression accounting for any nonthrombotic death as a competing event with stratification by randomization stratification factors (status of receiving or planned to receive antiplatelet therapy at screening and status of randomized to antiplatelet therapy). $P_{interaction}$ (*P*-int) for subgroup by randomized treatment shown. Mechanical ventilation refers to the requirement for invasive mechanical ventilation at the time of randomization. AP indicates antiplatelet; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; DM, diabetes; hs-CRP, high sensitivity C-reactive protein; and Rando, randomization.

anticoagulation versus standard-dose prophylactic anticoagulation, but not of the addition of clopidogrel, for prophylaxis against venous and arterial thrombotic complications in appropriately selected, critically ill patients with COVID-19.

Landscape of Trials of Prophylactic Anticoagulation in Critically Ill Patients With COVID-19

Previous trials of prophylactic anticoagulant strategies in patients with COVID-19 have varied in their principal hypothesis, patient populations, and primary results. Before COVID-PACT, a total of 6 trials of anticoagulation strategies included critically ill patients[12–15,21,22]; 4 evaluated a strategy of full-dose anticoagulation compared with usual care (defined as low±intermediate) dose prophylactic anticoagulation, and 2 others focused on intermediate-intensity anticoagulation versus low-dose prophylactic anticoagulation.

The largest of these studies, which included 1098 critically ill patients with COVID-19, tested the hypothesis that, compared with low- or intermediate-dose prophylactic anticoagulation, full-dose anticoagulation would prevent overall progression of COVID-19 as assessed by a primary end point of number of days alive without organ support at 21 days in the intention-to-treat population.[12] The trial was stopped for futility for the primary end point and demonstrated a numeric excess of major bleeding, numerically lower rates of thrombotic events (7.2% versus 11.1%), and no difference in all-cause mortality (37.3% versus 35.5%). Of note, 22% of patients assigned to full-dose anticoagulation were not on randomly assigned therapy 1 day after randomization, and in those on usual care, the majority (52%) were on intermediate dose, both of which may have diminished any observed treatment effect. In contrast, in the noncritically ill cohort among whom crossover rates were lower, full-dose anticoagulation increased the number of days alive without organ support, with an associated increase in major bleeding (1.9% versus 0.9%) and a lower rate of major thrombotic events or death (8.0% versus 9.9%).[11]

In the HEP-COVID trial (Full Dose Heparin Vs. Prophylactic or Intermediate Dose Heparin in High Risk COVID-19 Patients), among a selected population (n=257) based on D-dimer, full-dose anticoagulation reduced the primary end point of thrombotic events or all-cause mortality (relative risk, 0.68 [95% CI, 0.49–0.96]).[15] This benefit appeared to be limited to noncritically ill patients; however, there were few critically ill patients (n=83) in the study. The ACTION trial (Anticoagulation Coronavirus) comparing full-dose anticoagulation versus standard-dose prophylactic anticoagulation in 615 hospitalized but mostly stable patients did not meet the primary end point of prevention of thrombotic events (relative risk, 0.75 [95% CI, 0.45–1.26]).[14] The HESA-COVID trial (Therapeutic Versus Prophylactic Anticoagualtion for Severe COVID-19) included only 20 critically ill patients with COVID-19.[13]

It is important to note that, although the largest of the trials did not focus on thrombotic events as a primary end point, a meta-analysis of available data has suggested a reduction in thrombotic (particularly venous) events in critically ill patients, and in noncritically ill hospitalized patients, as well.[18] Nevertheless, in the absence of benefit on the primary end point of disease progression for the trial that focused on critically ill patients and an increased risk of bleeding, several guidelines have recommended against higher-intensity anticoagulation for prophylaxis in critically ill patients with COVID-19 while acknowledging very low certainty in the evidence.[16,17]

Potential Implications of COVID-PACT

The COVID-PACT trial was designed to evaluate the efficacy and safety of higher-intensity antithrombotic prophylaxis with respect to thrombotic events. The majority of the patients in the study required advanced, noninvasive, respiratory therapies at the time of randomization: a high-risk, critically ill population of patients in whom one could hypothesize there would still be the opportunity to modify outcomes. The results demonstrate a significant reduction in a hierarchical composite of venous or arterial events with prophylaxis with full-dose anticoagulation versus standard-dose prophylactic anticoagulation. The majority of thrombotic events were venous in origin. Findings were qualitatively consistent with a variety of additional analytical approaches, including a significant 44% to 45% reduction in the risk of the primary end point in both the time-to-first event and Bayesian approaches in the on-treatment analyses.

It is worthwhile to note that, although nearly all patients received at least 1 dose of randomly assigned therapy, over the entire duration of follow-up, 17% of those randomly assigned to full-dose anticoagulation and 34% on standard-dose prophylactic anticoagulation crossed over to the alternative treatment strategy. The duration of use of the anticoagulation strategy was lower in the standard-dose prophylactic group, but the total duration of any anticoagulation was the same between arms, reflecting the higher rate of crossover from standard-dose prophylaxis to full-dose anticoagulation. In this context, the results of the intention-to-treat analyses for the primary efficacy end point are consistent but attenuated relative to the on-treatment analysis. Recognition of significant crossover is important when considering neutral results of other trials evaluating anticoagulation strategies in acutely ill patients with COVID-19.

With respect to the risk of increased intensity anticoagulation, the rates of the primary safety end point, fatal or life-threatening bleeding, were low with a nonsignificant, numeric excess of life-threatening bleeding with full-dose anticoagulation. There was a significant

excess of GUSTO moderate to severe bleeding, dominantly driven by higher rates of moderate bleeding, defined as clinically overt bleeding requiring transfusion without hemodynamic compromise. In this context, there was no apparent excess in mortality with full-dose anticoagulation.

In this trial specifically designed to assess thrombotic events in critically ill patients with COVID-19, full-dose anticoagulation was shown to be beneficial for this outcome at the cost of an increase in the risk of moderate to severe but not fatal bleeding. Although a previous trial focused on and showed no improvement in overall organ dysfunction in COVID-19, prevention of thrombotic complications in COVID-19, balanced against the risk of bleeding, may be a more appropriate primary focus of antithrombotic strategies as a preventive intervention. These outcomes, rather than organ failure or mortality, are, in fact, the basis for the positive recommendations for routine use of anticoagulants for prophylaxis against thrombotic complications in general ICU populations without COVID-19.[6,7] In these populations, data suggest a benefit for increased intensity of anticoagulation (prophylaxis versus none) for prevention of venous thrombotic complications with an increase in bleeding and no apparent difference in mortality, paralleling the findings of COVID-PACT.[6,7] As such, the findings from COVID-PACT may be relevant when revisiting current consensus treatment guidelines that suggest using standard-dose prophylactic intensity anticoagulation over full-dose anticoagulation in the critically ill population with COVID-19, including patients managed with advanced, noninvasive respiratory support. Analogous to management of the general ICU population, the individual bleeding risk of patients across the spectrum of severity of potential bleeding should be considered when weighing the risk/benefit of higher-intensity prophylactic anticoagulation in critically ill patients with COVID-19.

Prophylactic Antiplatelet Therapy in Patients With COVID-19

The RECOVERY trial (Randomized Evaluation of COVID-19 Therapy), which randomly assigned 14 892 hospitalized patients with COVID-19 (≈32% critically ill) to aspirin versus standard of care, found no difference in the primary end point of 28-day mortality, a nonsignificant trend toward a reduction in thrombotic events (4.6% versus 5.3%), and a significant increase in major bleeding (1.6% versus 1.0%).[10] The multiplatform trial, which randomly assigned 562 noncritically ill hospitalized patients with COVID-19 to P2Y12 inhibitor versus no antiplatelet therapy on a background of full-dose anticoagulation, was terminated early for futility for the primary end point of days alive without organ support and did not observe a difference in thrombotic events.[8] The critically ill arm of the trial randomly assigned patients to aspirin or P2Y12 inhibitor versus no antiplatelet therapy on a background of standard-dose prophylactic anticoagulation and observed no difference in the primary end point of days alive without organ support, a significant reduction in the secondary end point of thrombotic event or death (35.1% versus 40.7%; odds ratio, 0.70 [95% CI, 0.54–0.90]), and an increase in major bleeding (2.1% versus 0.4%).[9] ACTIV-4b trial (COVID-19 Outpatient Thrombosis Prevention Trial), which included 657 symptomatic outpatients randomly assigned to aspirin versus placebo was stopped early because of low event rates.[23] In COVID-PACT, we did not observe a signal of benefit or harm with the addition of clopidogrel versus no antiplatelet therapy.

Limitations

Several limitations warrant consideration. This pragmatic trial had an open-label design given the clear differences of the 2 anticoagulation regimens; however, adjudication was blinded. Slow recruitment during the pandemic may reflect patient selection that could affect the generalizability of the results. In addition, the trial was terminated early because of slow recruitment and waning rates of ICU admissions with COVID-19. However, sample size calculations were initially conservative, on the basis of a treatment effect of only 35% and determined for the time-to-event analyses, which would be expected to be underpowered relative to the primary win ratio analyses. To assess the effect of the intensity of antithrombotic therapy without the confounding effect of crossovers, the primary analyses of efficacy and safety were prespecified to be on-treatment. The possibility of informative censoring is a limitation of an on-treatment approach. Therefore, the results of the intention-to-treat analyses are also presented and were attenuated but qualitatively consistent for all end points. As in other trials of prophylactic anticoagulation strategies, the rates of crossover from the randomized strategy were high; however, there was a greater proportion who crossed over from standard-dose prophylactic anticoagulation to full-dose anticoagulation, which may have weakened the estimated treatment effect of full-dose anticoagulation in the intention-to-treat analyses. Both the on-treatment and intention-to-treat effect estimates should be considered when comparing results across clinical trials assessing similar end points. Clinically silent DVT (or DVT identified on surveillance imaging) was included in the primary efficacy composite end point, the clinical relevance of which may differ from clinically evident venous thrombotic events in this setting. However, clinically silent DVT accounted for a minority of venous thrombotic events, and the results for the key secondary composite end point, which excluded these events, were directionally consistent. The primary safety end point of fatal and life-threatening bleeding was infrequent, limiting the ability to precisely estimate

the hazard. The broader secondary safety end point of GUSTO moderate or severe bleeding was included to more fully evaluate the risk/benefit of anticoagulation intensification. Because of the challenges of adjudicating the immediate cause of death in this patient population, we did not adjudicate the cause of death beyond those preceded by thrombotic events. As such, we are not able to provide additional details around the mode of death in this study.

Conclusions

In a population of critically ill patients with COVID-19, most of whom were managed with advanced forms of noninvasive respiratory support, a strategy of prophylaxis with full-dose versus standard-dose prophylactic anticoagulation, but not the addition of clopidogrel, reduced thrombotic complications with an increase in bleeding, driven primarily by transfusions in hemodynamically stable patients, and no apparent excess in mortality.

ARTICLE INFORMATION

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Supplemental Material

Supplemental Methods
Supplemental Data
Figures S1–S4
Tables S1–S10

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