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Intermediate-Dose versus Standard-Dose Prophylactic Anticoagulation in Patients with COVID-19 Admitted to the Intensive Care Unit: 90-Day Results from the INSPIRATION Randomized Trial

Behnood Bikdeli[1,2,3,*] Azita H. Talasaz[4,*] Farid Rashidi[5] Hooman Bakhshandeh[6,7] Farnaz Rafiee[7] Parisa Rezaeifar[5] Elahe Baghizadeh[7] Samira Matin[5] Sepehr Jamalkhani[8] Ouria Tahamtan[5] Babak Sharif-Kashani[9,10] Mohammad Taghi Beigmohammadi[11] Mohsen Farrokhpour[12] Seyed Hashem Sezavar[13] Pooya Payandemehr[14] Ali Dabbagh[15] Keivan Gohari Moghadam[16] Hossein Khalili[17] Mahdi Yadollahzadeh[12] Taghi Riahi[18] Atefeh Abedini[19] Somayeh Lookzadeh[19] Hamid Rahmani[20] Elnaz Zoghi[21] Keyhan Mohammadi[21] Pardis Sadeghipour[12] Homa Abri[12] Sanaz Tabrizi[18] Seyed Masoud Mousavian[18] Shaghayegh Shahmirzaei[14] Ahmad Amin[7] Bahram Mohebbi[22] Seyed Ehsan Parhizgar[7] Rasoul Aliannejad[23,24] Vahid Eslami[25] Alireza Kashefizadeh[26] Paul P. Dobesh[27] Hessam Kakavand[21] Seyed Hossein Hosseini[21] Shadi Shafaghi[10] Samrand Fattah Ghazi[11] Atabak Najafi[14] David Jimenez[28,29,30] Aakriti Gupta[2,3,31] Mahesh V. Madhavan[3,31] Sanjum S. Sethi[3,31] Sahil A. Parikh[3,31] Manuel Monreal[32,33] Naser Hadavand[7] Alireza Hajighasemi[4] Majid Maleki[7] Saeed Sadeghian[4] Gregory Piazza[1] Ajay J. Kirtane[3,31] Benjamin W. Van Tassell[34,35] Gregg W. Stone[3,36] Gregory Y. H. Lip[37,38] Harlan M. Krumholz[2,39,40] Samuel Z. Goldhaber[1] Parham Sadeghipour[6,7,21]

[1] Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, United States
[2] Yale/YNHH Center for Outcomes Research and Evaluation, New Haven, Connecticut, United States
[3] Cardiovascular Research Foundation, New York, New York, United States
[4] Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran
[5] Tuberculosis and Lung Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[6] Clinical Trial Center, Rajaie Cardiovascular, Medical, and Research Center, Iran University of Medical Sciences, Tehran, Iran
[7] Rajaie Cardiovascular Medical and Research Center, Iran university of Medical Sciences, Tehran, Iran
[8] Student Research Committee, Iran University of Medical Sciences, Tehran, Iran
[9] Tobacoo Prevention and Control Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[10] Department of Cardiology, Lung Transplantation Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[11] Anesthesiology and Intensive Care, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
[12] Department of Internal Medicine, Firouzgar Hospital, Iran University of Medical Sciences, Tehran, Iran
[13] Research Center for Prevention of Cardiovascular Disease, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran
[14] Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran
[15] Department of Anesthesiology, School of Medicine Anesthesiology Research Center, Shahid Modarres Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[16] Department of Internal Medicine, School of Medicine, Shariati Hospital, Tehran, Iran
[17] Department of Pharmacotherapy, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
[18] Rasoul-e-Akram Hospital, Iran University of Medical Sciences, Tehran, Iran
[19] Chronic Respiratory Disease Research Center, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[20] Department of Pharmacotherapy, Faculty of Pharmacy, Kermanshah University of Medical Sciences, Kermanshah, Iran

Address for correspondence Behnood Bikdeli, MD, MS, Cardiovascular Medicine Division, Brigham and Women's Hospital, 75 Francis Street, Shapiro 5, Suite 5156, Boston, MA 02115, United States (e-mail: bbikdeli@bwh.harvard.edu; Behnood.bikdeli@yale.edu).

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* *Drs. Bikdeli and Talasaz contributed equally to this manuscript.*

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[21] School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[22] Cardiovascular Intervention Research Center, Rajaie Cardiovascular, Medical, and Research Center, Iran University of Medical Sciences, Tehran, Iran
[23] Department of Pulmonary and Critical Care, School of Medicine, Shariati Hospital, Tehran, Iran
[24] Advanced Thoracic Research Center, Tehran University of Medical Sciences, Tehran, Iran
[25] Cardiovascular Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[26] Shahid Dr. Labbafinejad Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[27] College of Pharmacy, University of Nebraska Medical Center, Omaha, Nebraska, United States
[28] Respiratory Department, Hospital Ramón y Cajal, Madrid, Spain
[29] Medicine Department, Universidad de Alcalá, Madrid, Spain
[30] CIBER Enfermedades Respiratorias, Madrid, Spain
[31] Division of Cardiology, Columbia University Irving Medical Center/NewYork-Presbyterian Hospital, New York, New York, United States
[32] Department of Internal Medicine, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain
[33] Universidad Católica de Murcia, Murcia, Spain
[34] Department of Pharmacotherapy and Outcome Science, School of Pharmacy, Virginia Commonwealth University, Richmond, Virginia, United States
[35] Division of Cardiology, Department of Internal Medicine, Pauley Heart Center, School of Pharmacy, Virginia Commonwealth University, Richmond, Virginia, United States
[36] The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York, United States
[37] Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart and Chest Hospital, Liverpool, United Kingdom
[38] Aalborg University, Aalborg, Denmark
[39] Section of Cardiovascular Medicine, Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut, United States
[40] Department of Health Policy and Administration, Yale School of Public Health, New Haven, Connecticut, United States

Abstract

Background Thrombotic complications are considered among the main extrapulmonary manifestations of coronavirus disease 2019 (COVID-19). The optimal type and duration of prophylactic antithrombotic therapy in these patients remain unknown.

Methods This article reports the final (90-day) results of the Intermediate versus Standard-dose Prophylactic anticoagulation In cRitically-ill pATIents with COVID-19: An opeN label randomized controlled trial (INSPIRATION) study. Patients with COVID-19 admitted to intensive care were randomized to intermediate-dose versus standard-dose prophylactic anticoagulation for 30 days, irrespective of hospital discharge status. The primary efficacy outcome was a composite of adjudicated venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation (ECMO), or all-cause death. The main safety outcome was major bleeding.

Results Of 600 randomized patients, 562 entered the modified intention-to-treat analysis (median age [Q1, Q3]: 62 [50, 71] years; 237 [42.2%] women), of whom 336 (59.8%) survived to hospital discharge. The primary outcome occurred in 132 (47.8%) of patients assigned to intermediate dose and 130 (45.4%) patients assigned to standard-dose prophylactic anticoagulation (hazard ratio [HR]: 1.21, 95% confidence interval [CI]: 0.95–1.55, $p = 0.11$). Findings were similar for other efficacy outcomes, and in the landmark analysis from days 31 to 90 (HR: 1.59, 95% CI: 0.45–5.06). There were 7 (2.5%) major bleeding events in the intermediate-dose group (including 3 fatal events) and 4 (1.4%) major bleeding events in the standard-dose group (none fatal) (HR: 1.82, 95% CI: 0.53–6.24).

Conclusion Intermediate-dose compared with standard-dose prophylactic anticoagulation did not reduce a composite of death, treatment with ECMO, or venous or arterial thrombosis at 90-day follow-up.

Keywords
- anticoagulation
- heparin
- enoxaparin
- COVID-19
- trial

Introduction

Besides pulmonary parenchymal involvement, coronavirus disease-2019 (COVID-19) has important extrapulmonary manifestations during[1,2] and after the acute phase.[3] These include thrombotic and thromboembolic complications,[4–7] which may be due to endothelial injury,[8] unhinged immune response and a hypercoagulable state,[4,9] and bedridden state leading into stasis.[4] The majority of thrombotic events is thought to be venous thromboembolism (VTE), which has higher rates in critically ill patients. Although the event rates are variable based on the routine use of screening for VTE (such as serial ultrasound studies), and the type of prophylactic antithrombotic regimens,[5,10–12] a systematic review suggested that up to 28% of critically ill patients with COVID-19 may have VTE.[13]

In this setting, clinicians, health systems, and consensus statements provided a variety of prophylactic recommendations to prevent venous and arterial thrombosis in COVID-19.[4,14–16] However, the evidence base remains limited[17] with dozens of ongoing randomized trials.[18–20] Recently, we reported the short-term (30-day) results from the Intermediate versus

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Standard-dose Prophylactic anticoagulation In cRitically-ill pATIents with COVID-19: An opeN label randomized controlled trial (INSPIRATION) study.[21] The trial did not show a reduction in 30-day rates of a composite of venous or arterial thrombosis, treatment with extracorporeal oxygenation, or mortality in patients with COVID-19 admitted to the intensive care unit (ICU) (odds ratio: 1.06; 95% confidence interval [CI]: 0.76–1.48; $p = 0.70$).

With greater appreciation of postacute COVID-19 manifestations,[3] there is concern that the risk of adverse events including thrombotic events or mortality may extend beyond the initial hospital stay or the first few weeks.[9,14,22] To address this issue, the current article summarizes the final results of the INSPIRATION trial, which includes 90-day follow-up for the study participants.

Methods

The trial design has been described previously.[18] Briefly, INSPIRATION/INSPIRATION-statin (INSPIRATION-S) is a trial with 2×2 factorial design in patients with COVID-19 admitted to the ICU. This manuscript summarizes the final (90-day) follow-up results for the anticoagulation hypothesis. According to the prespecified study design, enrollment for the statin hypothesis remains ongoing.[18]

Study Patients

Patients with COVID-19, confirmed by polymerase chain reaction and admitted to the ICU within 7 days of initial hospitalization—with expected survival of at least 24 hours at the discretion of the enrolling clinician—were considered for inclusion. Main exclusion criteria consisted of an indication for therapeutic anticoagulation, overt bleeding or platelet count <50,000/fL, recent surgery or major bleeding, and pregnancy. The full list of eligibility criteria has been described previously.[18,21]

Intervention and Control

The study intervention was intermediate-dose prophylactic anticoagulation with heparin-based regimens. For patients who weighed <120 kg and had a creatinine clearance >30 mL/min, enoxaparin 1 mg/kg once daily constituted the intermediate-dose prophylactic regimen. The comparator was enoxaparin 40 mg once daily. In both arms, dose adjustment was prespecified according to body weight and renal function[18,21] (►**Supplementary Tables S1–S3**, available in the online version). The study intervention or control was planned to be continued until 30 days from randomization or death or a thrombotic or hemorrhagic event, irrespective of hospital stay status. In those discharged prior to 30 days, a supply of the study drugs was provided to patients. Patients or their caregivers were educated about the appropriate dose and technique for injection. Postdischarge adherence was monitored via periodic phone and video interviews.

Study Outcomes

For this final follow-up study, the primary outcome was a composite of adjudicated objectively confirmed VTE, arterial thrombosis, treatment with extracorporeal membrane oxygenation (ECMO), or all-cause mortality at 90 days from enrollment. Other efficacy outcomes included the 90-day occurrence of individual components of the primary outcome, the rates of new renal replacement therapy, and incident atrial fibrillation. VTE included lower or upper extremity deep vein thrombosis or pulmonary embolism diagnosed by objective imaging tests based on clinical suspicion. Routine screening was not part of the study protocol. More details about the study outcomes have been described previously.[18]

The main safety outcome was major bleeding, defined according to the Bleeding Academic Research Consortium type 3 or 5 definition[23] (bleeding events leading to a decrease in the hemoglobin of >3 g per deciliter, transfusion, cardiac tamponade, or intracranial or ocular involvement; or death) assessed by 90 days from randomization. Other safety outcomes included clinically relevant nonmajor bleeding and severe thrombocytopenia (platelet count <20,000/fL). All study outcomes were adjudicated by a clinical events committee blinded to treatment assignment.

Statistical Analysis

The main analyses were performed in the modified intention-to-treat cohort, consisting of randomized patients who did not meet the exclusion criteria, did not withdraw consent, and received at least 1 dose of the assigned treatment. In a sensitivity analyses, results were repeated among all non-duplicated randomized patients who agreed for their data to be included.

Categorical variables were reported as percentages with 95% CI estimates, where needed. Continuous variables were reported as mean and standard error, or median with Q1/Q3 interquartile ranges (if not normally distributed).

The association between the assigned treatment and the 90-day primary outcome was prespecified to be performed via mixed effects models accounting for the enrolling site as a random effect, and hazard ratio (HR) as the main effect measure. For the assessment of nonmortality outcomes, the competing risk of death was also considered.[24] Time to event was visually displayed using Kaplan–Meier curves. Since INSPIRATION/INSPIRATION-S had a 2×2 factorial design (second active intervention being atorvastatin 20 mg once daily vs. placebo), a test of interaction between the two interventions was performed. As there was no significant interaction between the assigned prophylactic anticoagulant regimen and the assigned statin regimen for the 90-day primary efficacy ($p = 0.75$) or the main safety outcome ($p = 0.27$), results of the anticoagulation hypothesis are presented independently.

A p-value <0.05 was considered significant for the primary outcome. No adjustment for multiplicity of comparisons was prespecified. Therefore, assessment of the outcomes within subgroups should be considered exploratory. Statistical analyses were performed via R statistical software package (R 4.0.3 for Mac OS, R Core Team, Vienna, Austria, URL: https://www.R-project.org/).

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Results

A total of 600 patients were randomized between July 29, 2020 and November 19, 2020. After excluding the duplicate entries and ineligible patients, 562 patients entered the primary analysis population (276 randomized to intermediate-dose and 286 randomized to standard-dose prophylactic anticoagulation) (►**Supplementary Fig. S1**, available in the online version). Baseline patient characteristics of the cohort have been described previously.[21] Briefly, the median (Q1, Q3) age in the intermediate-dose and standard-dose prophylactic anticoagulation groups were 62 (51, 71) and 61 (47, 71) years, respectively. Women constituted 41.3% versus 43.0% of study participants in each group. Other baseline characteristics, comorbidities, and background therapies were comparable in both groups, except for current smoking status, reported in 12.7% and 7.3% of the participants in each group, respectively (►**Supplementary Table S4**, available in the online version).

The duration of receiving the assigned anticoagulation regimen was comparable between the two groups: 19 [Q1, Q3: 7–30] days in patients randomized to intermediate-dose and 20 [Q1, Q3: 7–30] days in those randomized to standard-dose prophylactic anticoagulation. Overall, 336 patients were discharged alive before completion of the active intervention period (i.e., day 30). Of those 336 patients, 123 (75.0%) randomized to intermediate-dose and 126 (73.2%) randomized to standard-dose prophylactic anticoagulation received the assigned treatment until the end of day 30 or having an efficacy or major safety event requiring a change. ►**Supplementary Table S5** (available in the online version) summarizes the information related to treatment adherence in both groups in the postdischarge and 30-day follow-up states.

Efficacy Outcomes

Ninety-day outcome data were available for all 562 participants. By 90-day follow-up, the primary efficacy outcome occurred in 132 (47.8%) patients assigned to intermediate-dose prophylactic anticoagulation and 130 (45.4%) patients assigned to standard-dose prophylactic anticoagulation (HR: 1.21; 95% CI: 0.95–1.55, $p = 0.11$) (►**Fig. 1**). Ninety-day all-cause mortality was adjudicated in 127 (46.0%) and 123 (43.0%) of patients, respectively (HR: 1.24; 95% CI: 0.97–1.60) (►**Fig. 2**, panel A).

Adjudicated VTE events occurred in 9 (3.3%) patients assigned to intermediate-dose prophylactic anticoagulation and 10 (3.5%) patients assigned to standard-dose prophylactic anticoagulation (HR: 0.93; 95% CI: 0.48–1.76) (►**Fig. 2**, panel

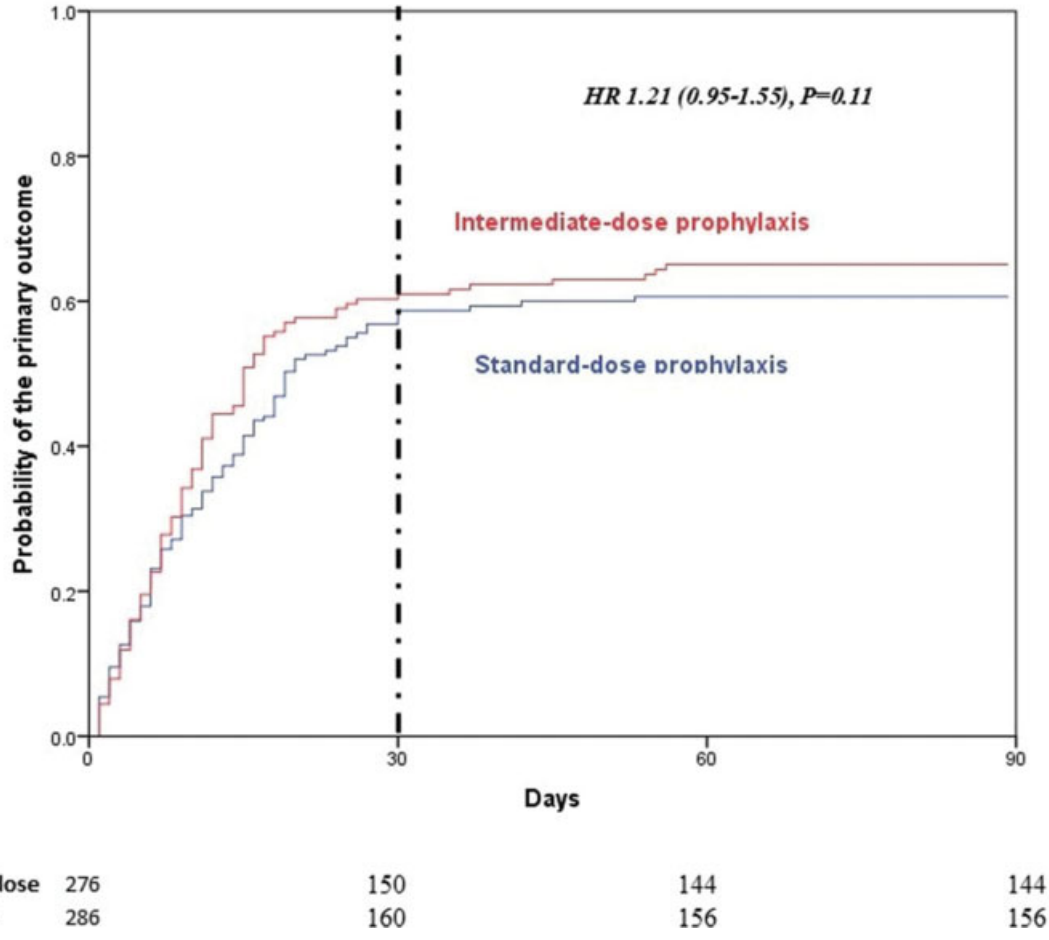

Fig. 1 Primary composite outcome in the prespecified primary cohort. The primary outcome was a composite of adjudicated acute arterial thrombosis, venous thromboembolism, extracorporeal membrane oxygenation, or all-cause mortality during 90 days from enrollment. Completion of the assigned treatment is marked with a dashed line at 30 days. The prespecified primary cohort consisted of patients who received at least one dose of the study drugs, were not excluded, and did not withdraw consent. Hazard ratios were calculated with a random effect for enrolling centers.

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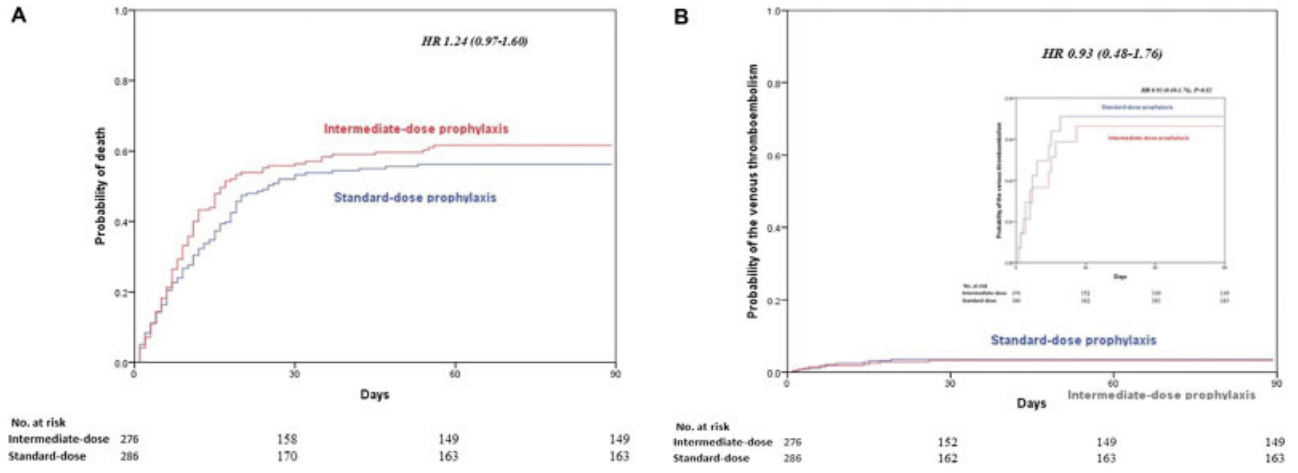

Fig. 2 Kaplan–Meier curve for all-cause mortality (**A**) and venous thromboembolism (**B**) in the prespecified primary cohort during 90 days from enrollment. The prespecified primary cohort consisted of patients who received at least one dose of the study drugs, were not excluded, and did not withdraw consent. Hazard ratios (HRs) were calculated with a random effect for enrolling centers. For panel (B), competing risks of mortality was addressed.

B). There were no cases of objectively confirmed adjudicated type I myocardial infarction. New atrial fibrillation was diagnosed in 3 (1.0%) and 6 (2.1%) patients in each group (HR: 0.51; 95% CI: 0.12–2.05). One patient in each group developed ischemic stroke. New renal replacement therapy at 90-day follow-up occurred in 10 (3.6%) patients assigned to intermediate-dose prophylactic anticoagulation and 7 (2.4%) patients assigned to standard-dose prophylactic anticoagulation (HR: 1.53; 95% CI: 0.58–4.05).

Safety Outcomes

By 90-day follow-up, major bleeding occurred in 7 (2.5%) of patients assigned to intermediate-dose prophylactic anticoagulation compared with 4 (1.4%) in the standard prophylactic anticoagulation group (HR: 1.82, 95% CI: 0.53–6.24). A composite of major or clinically relevant nonmajor bleeding occurred in 17 (6.2%) versus 10 (3.4%) patients, respectively (HR: 1.70, 95% CI: 0.77–3.77). Fatal bleeding occurred in three patients randomized to intermediate-dose prophylactic anticoagulation (risk difference: 1.0%, 95% CI: −0.1 to 2.3%). In addition, severe thrombocytopenia (platelet count < 20,000/ fL) occurred in 6 (2.2%) patients assigned to intermediate-dose anticoagulation (risk difference: 2.2%, 95% CI: 0.4–3.8%). Results for the efficacy and safety outcomes are summarized in ►**Table 1**. Use of diagnostic tests for confirming thrombotic events is summarized in ►**Supplementary Table S6** (available in the online version).

Sensitivity Analysis

In a sensitivity analysis of all unique patients who allowed their data to be incorporated ($N = 590$), the results were similar to the main analyses: the primary efficacy outcome occurred in 137 (46.2%) of patients randomized to intermediate-dose and 130 (44.2%) of patients randomized to standard-dose prophylactic anticoagulation (HR: 1.18; 95% CI: 0.93–1.150). Results for other outcomes were also similar to the main analyses (►**Supplementary Table S7**, available in the online version).

In a landmark analysis, the majority of adverse events in both groups occurred in the first 30 days. However, clinical outcomes were comparable in the two groups for the first 30 days and days 31 to 90. During the first 30 days, there was no significant difference in the primary outcome among patients randomized to intermediate-dose versus standard-dose prophylactic anticoagulation (HR: 1.18, 95% CI: 0.80–1.32). Results were similar for days 31 to 90 (HR: 1.59, 95% CI: 0.45–5.06; ►**Fig. 3**). Findings were similar in a landmark analysis for mortality (►**Supplementary Fig. S2**, available in the online version).

Subgroup Analysis

In assessment of the prespecified subgroups, no specific group was identified in whom a potentially beneficial effect from intermediate-dose prophylactic anticoagulation was identified (►**Fig. 4**). Women tended to show an undesirable treatment effect for the primary composite outcome, compared with men (HR: 1.63, 95% CI: 1.10–2.43 vs. HR: 0.93, 95% CI: 0.68–1.27, $p_{\text{interaction}} = 0.02$), although the results were not adjusted for multiplicity.

Discussion

In this study, intermediate-dose versus standard-dose prophylactic anticoagulation with heparin-based regimens was not associated with a reduction in the 90-day composite of all-cause death, treatment with ECMO, or venous or arterial thrombosis. No reduction was observed in the individual components of the primary outcome. Findings were consistent across subgroups and in sensitivity analyses. A landmark analysis that reported new follow-up information from days 31 to 90, unlike initial concerns for postdischarge heightened risk of adverse events,[3,15] indicated very few additional efficacy events without a significant difference between the groups. Fatal bleeding and severe thrombocytopenia were rare but numerically more frequent with intermediate-dose prophylactic anticoagulation.

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Table 1 Primary, secondary, and exploratory outcomes within 90 days from enrollment in the prespecified primary analysis

Outcome	Intermediate-dose prophylactic anticoagulation ($n = 276$)	Standard-dose prophylactic anticoagulation ($n = 286$)	Absolute difference (95% CI)	Hazard ratio (95% CI)
Primary outcome, no./total no. of patients (%) Composite of adjudicated acute venous thromboembolism[a], arterial thrombosis[b], treatment with extracorporeal membrane oxygenation[c], or all-cause mortality	132 (47.8)	130 (45.4)	2 (−5.8–10.6) %	1.21 (0.95–1.55)
Secondary outcomes				
All-cause mortality, no./total no. of patients (%)	127 (46.0)	123 (43.0)	3.0 (−5.2–11.2) %	1.24 (0.97–1.60)
Adjudicated venous thromboembolism, no./total no. of patients (%)	9 (3.3)	10 (3.5)	−0.2 (−3.2–2.7) %	0.93 (0.48–1.76)
Exploratory outcomes				
Objectively clinically diagnosed type I acute myocardial infarction, no./total no. of patients (%)[d]	0	0		
Objectively clinically diagnosed stroke, no./total no. of patients (%)	1 (0.4)	1 (0.3)	0.1 (−0.9–0.9) %	1.03 (0.06–16.56)
Objectively clinically diagnosed acute peripheral arterial thrombosis, no./total no. of patients (%)	0	0		
Incident atrial fibrillation, no./total no. of patients (%)	3 (1.0)	6 (2.1)	−1.0 (−3.0–1.0) %	0.51 (0.12–2.05)
Undergoing new renal replacement therapy, no./total no. of patients (%)	10 (3.6)	7(2.4)	1.1 (−1.6–4.0) %	1.53 (0.58–4.05)
Safety outcomes, no./total no. of patients (%)				
Major bleeding[e]	7 (2.5)	4 (1.4)	1.1 (−1.1–3.4) %	1.82 (0.53–6.24)
BARC Type 3a: hemoglobin drop of 3–5 g/dL or any transfusion	3 (1.1)	4 (1.4)	−0.3 (−2.1–1.5) %	0.77 (0.17–3.45)
BARC Type 3b: hemoglobin drop >5 g/dL	1 (0.4%)	0[f]	0.3 (−0.3–1.0) %	
BARC Type 3c: intracranial hemorrhage	1 (0.4%)	0[f]	0.3 (−0.3–1.0) %	
BARC Type 5: fatal bleeding	3 (1.0)	0[f]	1.0 (−0.1–2.3) %	
Clinically relevant nonmajor bleeding[g] (BARC 2)	12 (4.3)	6 (2.0)	2.2 (−0.6–5.1) %	1.94 (0.71–5.24)
Composite of major and nonmajor bleeding	17 (6.2)	10 (3.4)	3.0 (−0.4–6.4) %	1.70 (0.77–3.77)
Severe thrombocytopenia[h]	6 (2.2)	0[f]	2.2 (0.4–3.8) %	

Abbreviations: BARC, Bleeding Academic Research Consortium; CI, confidence interval; ICU, intensive care unit.

[a]All the venous thromboembolism events were adjudicated by the online clinical event committee. Each event was only confirmed by presenting a guideline-recommended imaging test (see Supplementary Material).

[b]Acute arterial thrombosis defined as type I acute myocardial infarction, ischemic stroke, and acute peripheral arterial thrombosis.

[c]No patients received extracorporeal membrane oxygenation.

[d]Type I myocardial infarction was defined as rise and/or fall in cardiac troponin values with at least one value above the 99th percentile upper reference limits with at least one of the following: symptoms of ischemia, or new or presumed new ischemic electrocardiographic (ECG) change, or development of pathologic Q waves on the ECG, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with ischemic etiology, confirmed by coronary angiography, intravascular imaging, or autopsy. Myocardial injury was noted in six patients with a combination of cardiac biomarker rise and ECG changes, coronary angiography was only pursued in one patient (with normal coronary vasculature) and thus type I myocardial infarction was not adjudicated in any participants.

[e]Major bleeding consisted of BARC Type 3 and 5, which defines as Type 3a for overt bleeding plus hemoglobin drop of 3–5 g/dL or any transfusion with overt bleeding; Type 3b for overt bleeding plus hemoglobin drop of 5 g/dL, cardiac tamponade, or bleeding requiring surgical intervention for control, Type 3c for intracranial hemorrhage, and Type 5 for fatal bleeding.[23]

[f]For events with zero incidence in one group, only absolute risk difference was reported.

[g]Clinically significant bleeding that warranted attention from the medical personnel, but not fulfilling criteria for major bleeding.

[h]Severe thrombocytopenia defined as platelet count less than 20,000/fL.

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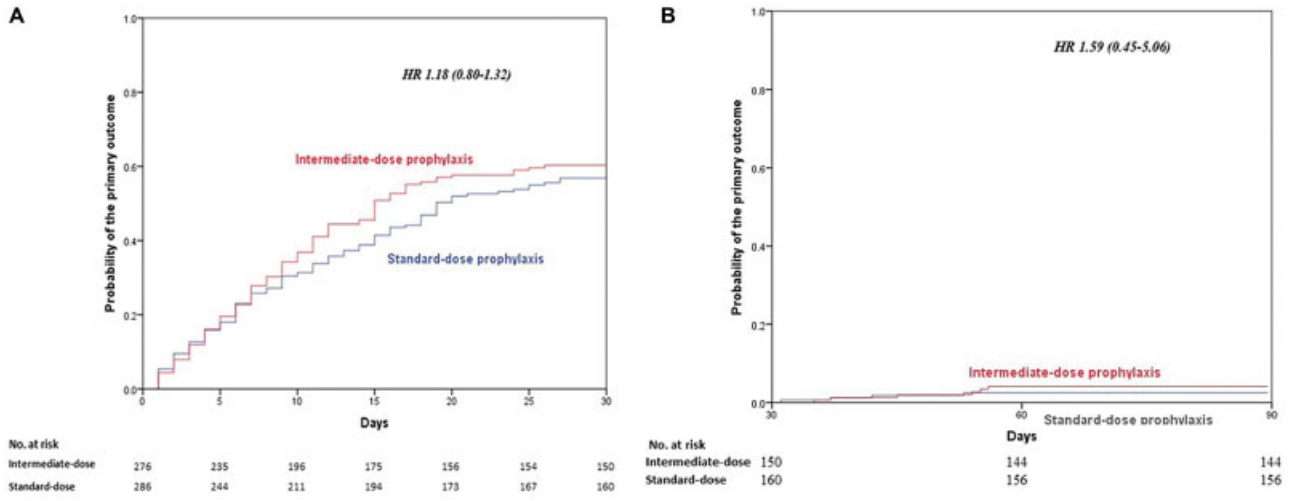

Fig. 3 Kaplan–Meier curve for the landmark analysis showing the primary composite outcome in the first 30 days (**A**) and from days 31 to 90 in the prespecified primary cohort. The prespecified primary cohort consisted of patients who received at least one dose of the study drugs, were not excluded, and did not withdraw consent. Hazard ratios (HRs) were calculated with a random effect for enrolling centers.

These findings from the final 90-day follow-up of the study participants build on and are consistent with the short-term 30-day results of the INSPIRATION trial.[21] The results are also aligned with consensus recommendations that encouraged standard-dose prophylaxis during the period of hospitalization.[4,25,26] In addition, a preprint report from the multiplatform trial (including REMAP CAP, ACTIV4, and ATTACC) of fully therapeutic anticoagulation versus standard-dose prophylaxis in critically ill patients with COVID-19[27] did not suggest a reduction in mortality or the need for organ support with therapeutic anticoagulation. However, these results collectively are in contrast to recommendations from other consensus recommendations for empiric escalated-dose prophylaxis.[14,15,28] Multiple ongoing randomized studies are assessing other therapeutic targets, including antiplatelet agents, oral anticoagulants, or even fibrinolytic therapy.[19,20] The results from these studies can inform whether any of these regimens confer benefit in patients with COVID-19.

We identified very few additional efficacy events after the first 30 days, mostly in the form of mortality. The greatest risk of VTE in the postdischarge setting occurs in the first 3 weeks postdischarge.[14] In this study, results from the landmark analysis do not indicate a different treatment effect in the early period (30 days) versus the durable follow-up period in which the vast majority of survivors were postdischarge (days 31–90). Some studies suggest that patients with COVID-19 have a relatively low rate of postdischarge VTE.[29–32] Further, a recent study did not identify a significantly increased risk of postdischarge VTE in patients with SARS-CoV-2 infection compared with noninfected individuals.[33] The current study did not include a "no anticoagulation" group upon hospital discharge. Therefore, findings from multicenter observational studies, including CORONA-VTE,[34] will further elucidate the risk of events. Results from ongoing randomized trials, including ACTIV4c (NCT04498273), will be enlightening to understand the tradeoffs of empiric extended prophylaxis.

In the assessment of the outcomes across the prespecified subgroups, a treatment interaction was noted by sex, with women having worse outcomes with intermediate-dose anticoagulation. Sex differences in clinical presentation, treatment, response to therapies, and outcomes of cardiovascular diseases in women and men have been under investigation.[35] However, considering the lack of adjustment for multiplicity, this analysis should be considered hypothesis-generating. Subgroup-specific results from the multiplatform trials and other randomized controlled trials will provide further clarity in future.

The lack of benefit on efficacy outcomes in short-term or 90-day follow-up should raise concern for the routine use of intermediate-dose prophylactic anticoagulation in ICU patients with COVID-19. Safety events were relatively rare in the study. The rate of adverse events such as major bleeding and severe thrombocytopenia with intermediate-dose prophylaxis needs further investigation and results from other ongoing trials and routine practice registries with these regimens will be enlightening. In addition, the impact of escalated-dose anticoagulation regimens in patients with less severe forms of the disease should be further elucidated, with preliminary reports from the multiplatform trials (including REMAP CAP, ACTIV4, and ATTACC) suggesting a reduction in thrombotic events and the need for organ support in hospitalized non-ICU patients.

This study has several limitations. First, the rate of thrombotic events reported in this study is lower than those of several others in the literature. This issue may be multifactorial. Missing thrombotic events is possible, particularly in the setting of resource limitations and concern for excessive exposure of health care workers. Routine screening was not part of the study protocol and diagnostic tests were ordered based on the clinicians' suspicion for thrombosis. Among patients who had diagnostic tests for thrombotic evens, only 19 (21.5%) yielded positive results. A recent systematic review suggested that larger studies have reported a markedly lower rate of VTE compared with small or single-institution studies.[36] In addition, findings from two large-scale multicenter studies report lower rates of thrombotic events than initially anticipated.[12,37] Other

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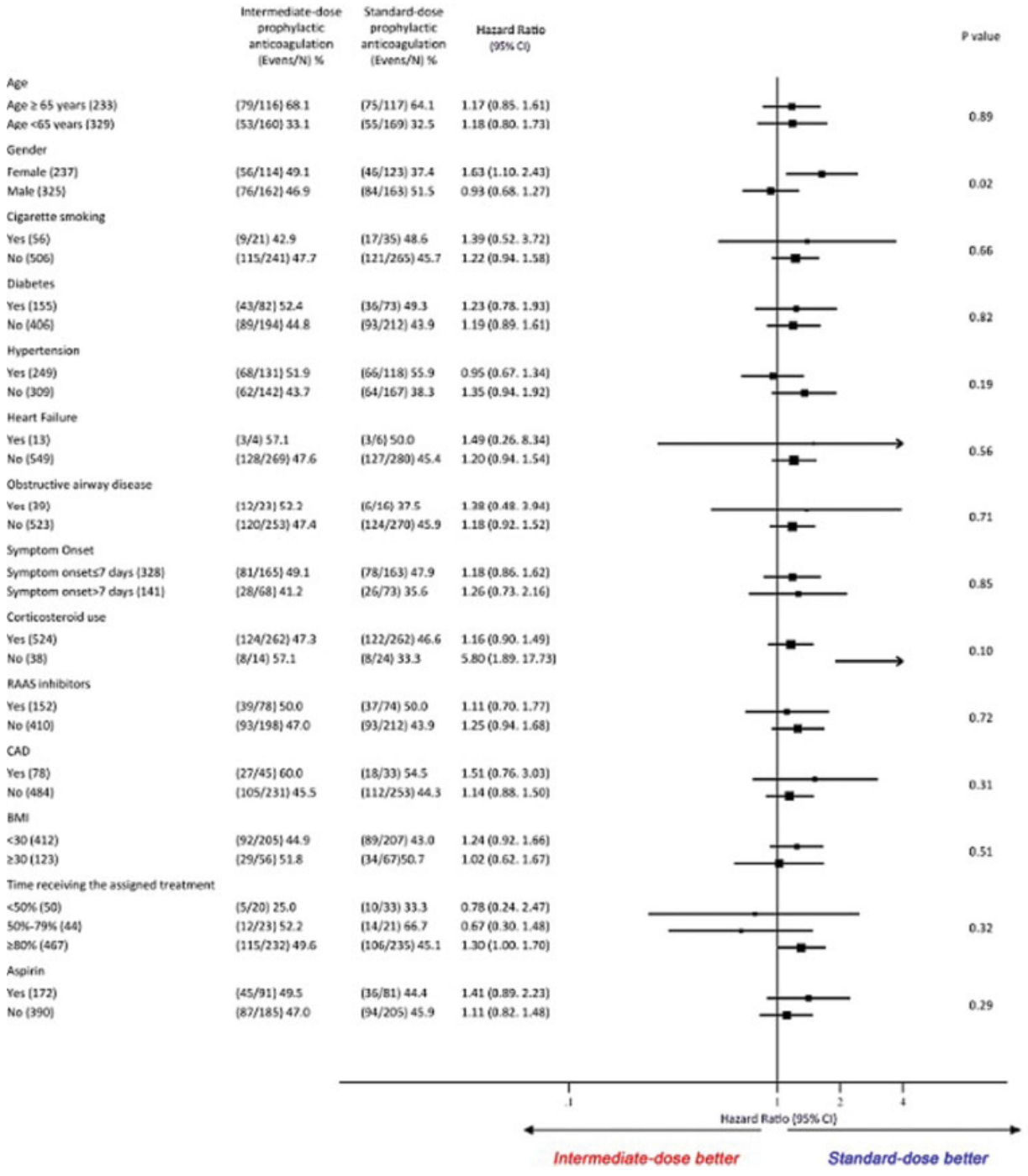

Fig. 4 Subgroup analysis for the primary composite outcome. The point estimates and confidence intervals are reported as hazard ratio, the *x*-axis, itself is transformed into the log scale. BMI, body mass index; CAD, coronary artery diseases; RAAS, renin–angiotensin–aldosterone system.

studies have suggested that many VTE events in COVID-19 are distal deep vein thrombosis or subsegmental pulmonary embolism,[13,34] which are less likely to impact mortality. Of note, we did not notice a difference in the rate of all-cause mortality in the two study groups. Second, INSPIRATION, by design, focused on the intensity of prophylactic anticoagulation and did not include patients with COVID-19 who had a confirmed thrombotic event prior to enrollment. Third, findings related to subgroups, including a potential detrimental treatment interaction in women, warrant further attention for analyses in other trials. However, caution should be exercised since this finding was not adjusted for multiplicity. Fourth, although we did not identify a benefit with heparin-based intermediate-dose anticoagulant therapy in patients with COVID-19 admitted to the ICU, it is possible that heparin-based regimens are beneficial at earlier stages of the disease. In turn, in ICU patients, other alternative therapeutic options may be shown to confer benefit.[20] Finally, although we noted a low rate of postdischarge VTE events and mortality in this study, both groups were assigned to continue their anticoagulant regimen until day 30, including in the outpatient setting. Therefore, pros and cons of postdischarge extended prophylaxis

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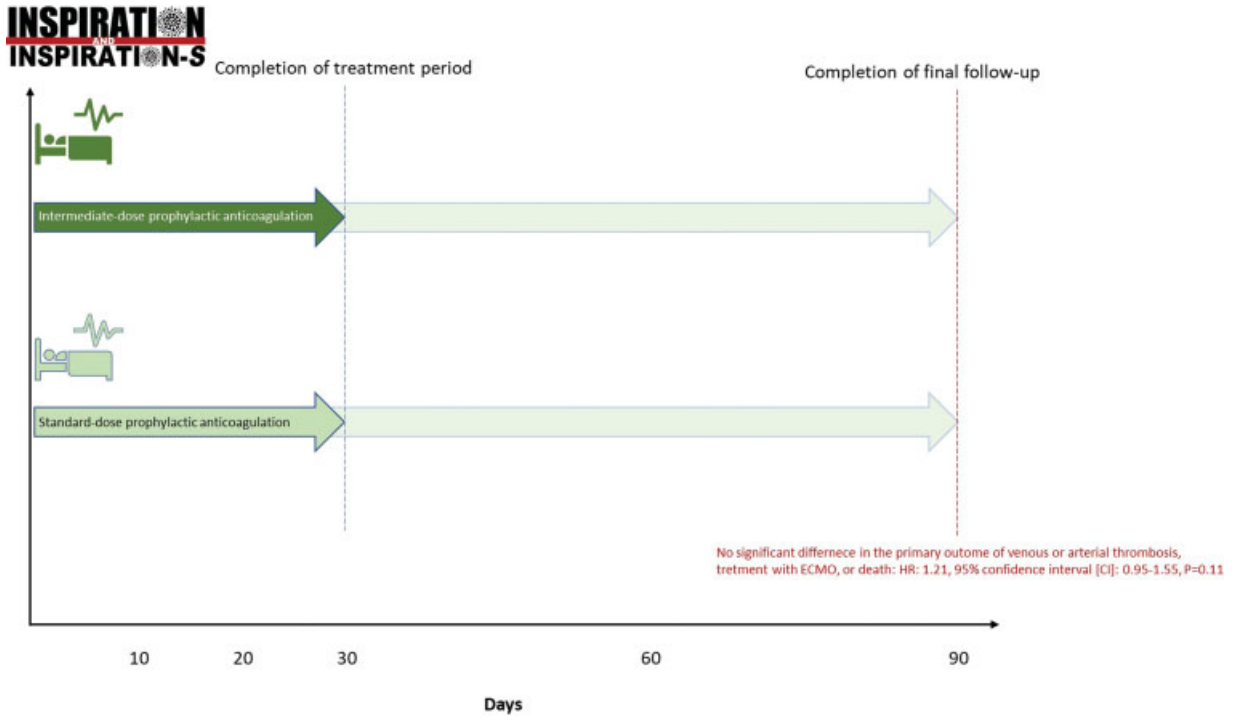

Fig. 5 Graphical summary of treatment assignment and the main findings. Note that the assigned treatments were continued until day 30 or reaching the primary outcome.

should be elucidated in future studies, including ACTIV4c (NCT04650087) and MICHELLE (NCT04662684).[20]

In conclusion, in the final (90-day) follow-up analysis of participants in a multicenter randomized trial, use of intermediate-dose versus standard-dose prophylactic anticoagulation in patients with COVID-19 admitted to the ICU did not result in reduction in a composite of adjudicated venous or arterial thrombosis, treatment with ECMO, or all-cause mortality. The individual components of the primary outcome were comparable in the two groups. Although adverse events were rare, fatal bleeding and severe thrombocytopenia occurred only in those assigned to intermediate-dose anticoagulation. Collectively, these findings do not support the routine use of intermediate-dose prophylactic anticoagulation in ICU patients with COVID-19 or its continuation after hospital discharge.

What is known about this topic?

- In the INSPIRATION randomized clinical trial, intermediate-dose compared with standard-dose prophylactic anticoagulation did not result in a reduction in the 30-day composite of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or all-cause mortality in ICU patients with COVID-19.

What does this paper add?

- This study summarizes the final follow-up for study participants in the INSPIRATION trial.
- By the end of 90-day clinical follow-up, intermediate-dose prophylactic anticoagulation compared with standard-dose prophylactic anticoagulation did not result in a reduction in the 90-day composite of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or all-cause mortality.
- Collectively, these findings do not support the routine use of intermediate-dose prophylactic anticoagulation in ICU patients with COVID-19.

Conflict of Interest

Dr. Parikh reports being on the Advisory Board for Abbott, Boston Scientific, Medtronic, CSI, Philips, Janssen; research grants: Abbott, Boston Scientific, Surmodics, TriReme Medical, Shockwave Medical; and receiving consulting fees from Terumo and Abiomed. Dr. Gupta received payment from the Arnold & Porter Law Firm for work related to the Sanofi clopidogrel litigation and from the Ben C. Martin Law Firm for work related to the Cook inferior vena cava filter litigation. Dr. Gupta holds equity in a health care telecardiology startup, Heartbeat Health, Inc. and received consulting fees from Edwards LifeSciences. Dr. Madhavan has received support from an institutional grant by the National Institutes of Health/National Heart, Lung, and Blood Institute to Columbia University Irving Medical Center (T32 HL007854). Dr. Sethi reports honoraria from Janssen and Chiesi and research grant support from the American Heart Association. Dr. Piazza has received research grant support to Brigham and Women's Hospital from EKOS, a BTG International Group company, Bayer, the Bristol Myers

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