Accepted Manuscript

Submission Date: 2021-04-07
Accepted Date: 2021-04-15
Publication Date: **2021-04-17**

Thrombosis and Haemostasis

Intermediate vs Standard-dose Prophylactic Anticoagulation in Patients with COVID-19 Admitted to ICU: Ninety-day Results from the INSPIRATION Trial

Behnood Bikdeli, Azita H Talasaz, Farid Rashidi, Hooman Bakhshandeh, Farnaz Rafiee, Samira Matin, Elahe Baghizadeh, Parisa Rezaeifar, Sepehr Jamalkhani, Ooria Tahamtan, Babak Sharif-Kashani, Mohammad Taghi Beigmohammadi, Mohsen Farrokhpour, Seyed Hashem Sezavar, Pooya Payandemehr, Ali Dabbagh, Keivan Gohari Moghadam, Hossein Khalili, Mahdi Yadollahzadeh, Taghi Riahi, Atefeh Abedini, Somayeh Lookzadeh, Hamid Rahmani, Elnaz Zoghi, Keyhan Mohammadi, Pardis Sadeghipour, Homa Abri, Sanaz Tabrizi, Seyed Masoud Mousavian, Shaghayegh Shahmirzaei, Ahmad Amin, Bahram Mohebbi, Seyed Ehsan Parhizgar, Rasoul Aliannejad, Vahid Eslami, Alireza Kashefizadeh, Paul Dobesh, Hessam Kakavand, Seyed Hossein Hosseini, Shadi Shafaghi, Samrand Fattah Ghazi, Atabak Najafi, David Jiménez, Aakriti Gupta, Mahesh V Madhavan, Sanjum Sethi, Sahil A Parikh, Manuel Monreal, Naser Hadavand, Alireza Hajighasemi, Majid Maleki, Saeed Sadeghian, Gregory Piazza, Ajay J Kirtane, Benjamin W Van Tassell, Gregg W Stone, Gregory Y Lip, Harlan Krumholz, Samuel Z Goldhaber, Parham Sadeghipour.

Affiliations below.

DOI: 10.1055/a-1485-2372

Please cite this article as: Bikdeli B, Talasaz A H, Rashidi F et al. Intermediate vs Standard-dose Prophylactic Anticoagulation in Patients with COVID-19 Admitted to ICU: Ninety-day Results from the INSPIRATION Trial. Thromb Haemost 2021. doi: 10.1055/a-1485-2372

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 &amp; 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 healthcare 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 Squibb/Pfizer Alliance, Portola, and Janssen. He has received consulting fees from Amgen, Pfizer, Boston Scientific Corporation and Thrombolex. Dr. Kirtane reports Institutional funding to Columbia University and/or Cardiovascular Research Foundation from Medtronic, Boston Scientific, Abbott Vascular, Abiomed, CSI, CathWorks, Siemens, Philips, ReCor Medical. In addition to research grants, institutional funding includes fees paid to Columbia University and/or Cardiovascular Research Foundation for speaking engagements and/or consulting. Personal: Travel Expenses/Meals from Medtronic, Boston Scientific, Abbott Vascular, Abiomed, CSI, CathWorks, Siemens, Philips, ReCor Medical, Chiesi, OpSens, Zoll, and Regeneron. Dr. Van Tassell received the research support from Novartis, Swedish Orphan Biovitrum, Olatec Therapeutics, Serpin Pharm. He is a consultant of R-Pharm, Serpin Pharma. Dr. Stone has received speaker or other honoraria from Cook, Terumo, and Orchestra Biomed; served as a consultant to Valfix, TherOx, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, Miracor, Neovasc, V-Wave, Abiomed, Ancora, MAIA Pharmaceuticals, Vectorious, Reva, Matrizyme, Cardiomech; and has received equity or options from Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, MedFocus family of funds, and Valfix. Dr. Lip reports consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are received personally. Dr. Krumholz reports personal fees from UnitedHealth, personal fees from IBM Watson Health, personal fees from Element Science, personal fees from Aetna, personal fees from Facebook, personal fees from Siegfried &amp; Jensen Law Firm, personal fees from Arnold &amp; Porter Law Firm, personal fees from Ben C. Martin Law Firm, personal fees from National Center for Cardiovascular Diseases, Beijing, ownership of HugoHealth, ownership of Refactor Health, contracts from the Centers for Medicare &amp; Medicaid Services, grants from Medtronic and the Food and Drug Administration, grants from Medtronic and Johnson and Johnson, grants from Shenzhen Center for Health Information, and is a Venture Partner at FPrime. outside the submitted work. Dr. Bikdeli reports that he is a consulting expert,

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

This article is protected by copyright. All rights reserved.

Accepted Manuscript

on behalf of the plaintiff, for litigation related to two specific brand models of IVC filters. All other authors report no relevant Enoxaparin was provided through Alborz Darou, Pooyesh Darou and Caspian Pharmaceuticals companies, and atorvastatin and matching placebo was provided by Sobhan Darou. None of these companies were study sponsors and they had no other role and will not have a role in the design, conduct, analysis, or interpretation of the ongoing results or the decision to submit the resultant manuscript(s).

This study was supported by Rajaie Cardiovascular Medical and Research Center

Trial registration: NCT04486508, https://clinicaltrials.gov/ct2/show/NCT04486508, Randomized, Multi-Center Clinical Trials

Abstract:

Background: Thrombotic complications are considered among the main extrapulmonary manifestations of COVID-19. The optimal type and duration of prophylactic antithrombotic therapy in these patients remain unknown.
Methods: This manuscript 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). No significant differences were observed between the two groups for other efficacy outcomes, or in the landmark analysis from days 31-90. Overall, 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, P=0.33).
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.

Corresponding Author:
Behnood Bikdeli, Cardiovascular Research Foundation, New York, United States, Behnood.bikdeli@yale.edu

Affiliations:
Behnood Bikdeli, Cardiovascular Research Foundation, Cardiovascular Research Foundation, New York, United States
Behnood Bikdeli, Brigham and Women‘s Hospital, Cardiovascular Medicine Division, Boston, United States
Azita H Talasaz, Tehran Heart Center, Tehran Heart Center, Tehran, Iran (the Islamic Republic of)
[...]
Parham Sadeghipour, Rajaie Cardiovascular Medical and Research Center, Rajaie Cardiovascular Medical and Research Center, Tehran, Iran (the Islamic Republic of)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Visual Summary

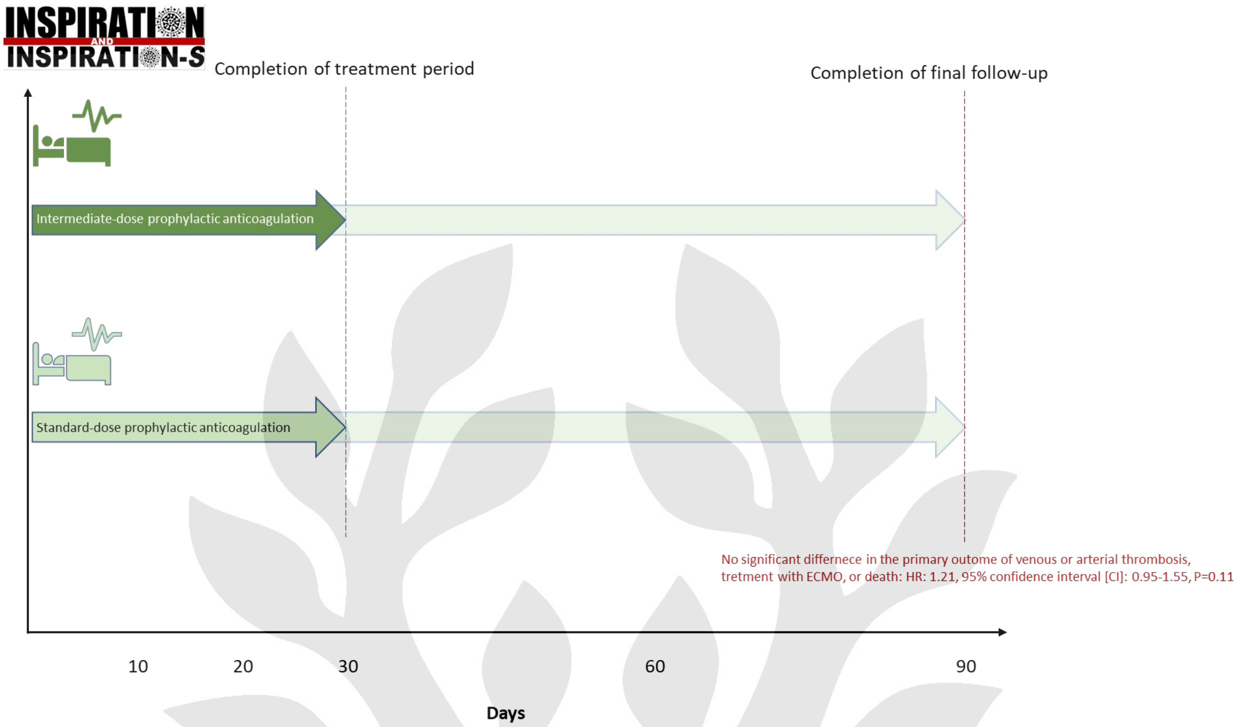
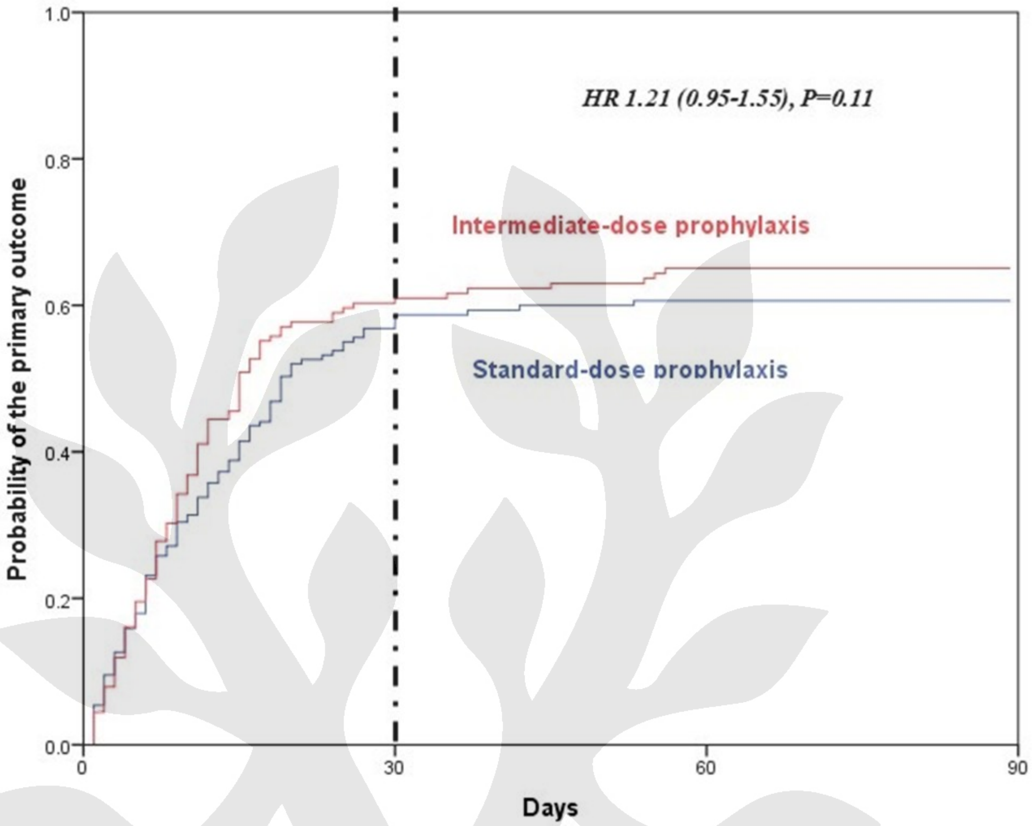

INSPIRATION
AND
INSPIRATION-S
Completion of treatment period
Completion of final follow-up
Intermediate-dose prophylactic anticoagulation
Standard-dose prophylactic anticoagulation
No significant differnece in the primary outome of venous or arterial thrombosis, tretment with ECMO, or death: HR: 1.21, 95% confidence interval [CI]: 0.95-1.55, P=0.11
10
20
30
60
90
Days

Figure 1.

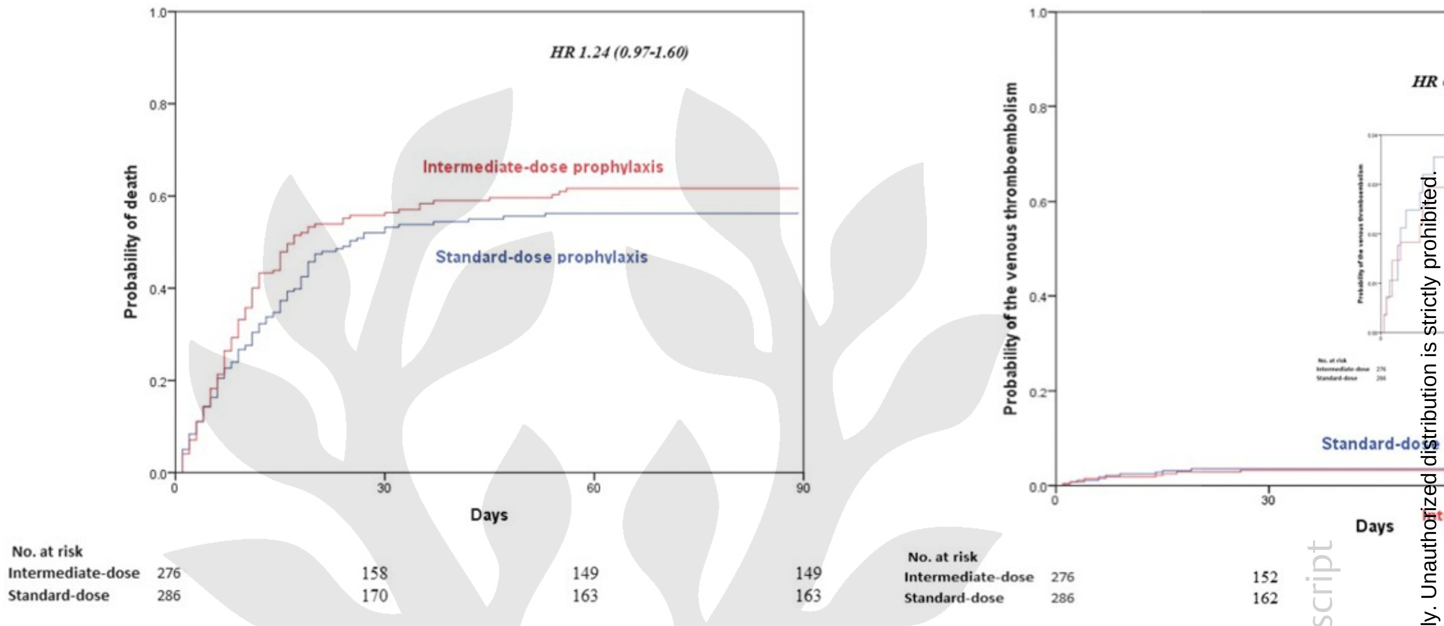


No. at risk				
Intermediate-dose	276	150	144	144
Standard-dose	286	160	156	156

Figure 2.

A

B



HR 1.24 (0.97-1.60)
Intermediate-dose prophylaxis
Standard-dose prophylaxis
Probability of death
1.0
0.8
0.6
0.4
0.2
0.0
0
30
60
90
Days
No. at risk
Intermediate-dose 276 158 149 149
Standard-dose 286 170 163 163
Probability of the venous thromboembolism
1.0
0.8
0.6
0.4
0.2
0.0
0
30
Days
HR
Standard-dose
No. at risk
Intermediate-dose 276 152
Standard-dose 286 162

Figure 3.

A

B

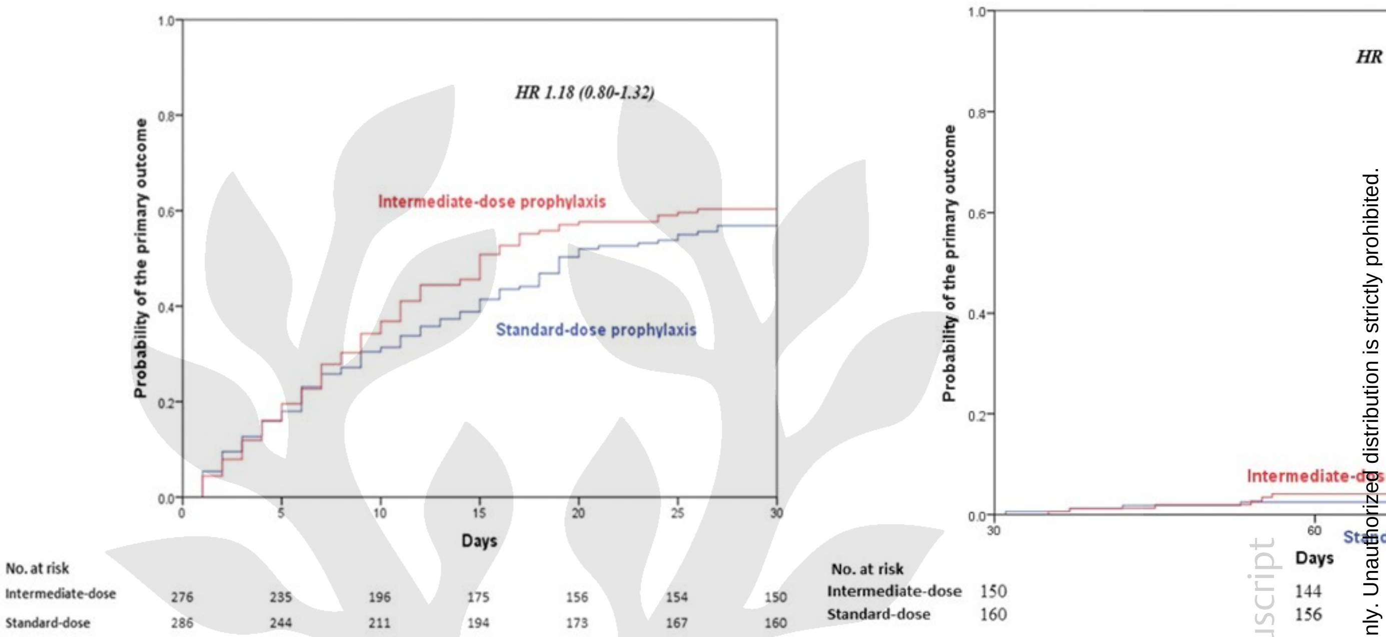
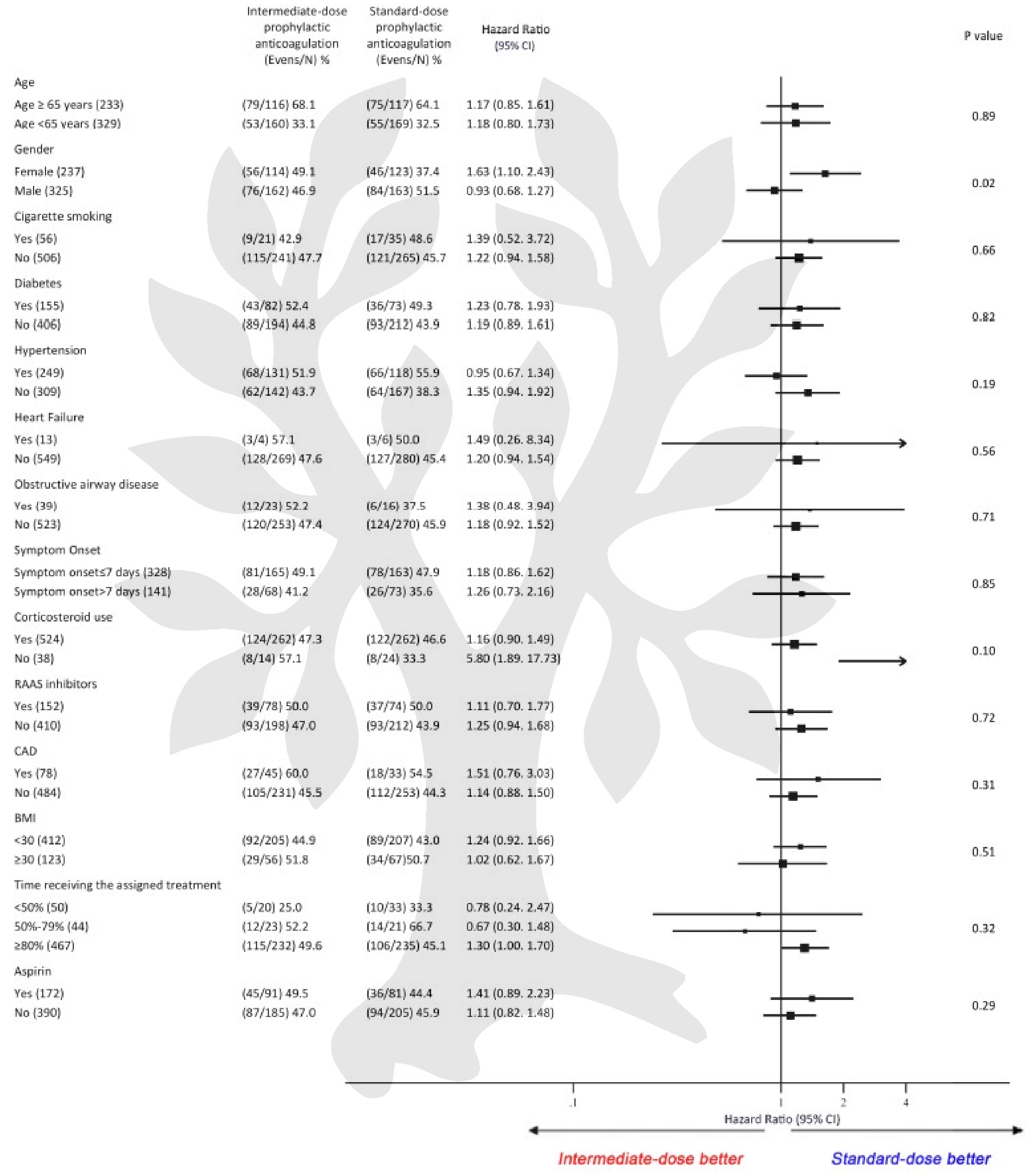

1.0
0.8
0.6
0.4
0.2
0.0
Probability of the primary outcome
HR 1.18 (0.80-1.32)
Intermediate-dose prophylaxis
Standard-dose prophylaxis
0
5
10
15
20
25
30
Days
No. at risk
Intermediate-dose 276 235 196 175 156 154 150
Standard-dose 286 244 211 194 173 167 160
1.0
0.8
0.6
0.4
0.2
0.0
Probability of the primary outcome
HR
Intermediate-dos
Stand
30
60
Days
No. at risk
Intermediate-dose 150 144
Standard-dose 160 156

Figure 4.



	Intermediate-dose prophylactic anticoagulation (Evens/N) %	Standard-dose prophylactic anticoagulation (Evens/N) %	Hazard Ratio (95% CI)	P value
Age				
Age ≥ 65 years (233)	(79/116) 68.1	(75/117) 64.1	1.17 (0.85. 1.61)	0.89
Age <65 years (329)	(53/160) 33.1	(55/169) 32.5	1.18 (0.80. 1.73)	
Gender				
Female (237)	(56/114) 49.1	(46/123) 37.4	1.63 (1.10. 2.43)	0.02
Male (325)	(76/162) 46.9	(84/163) 51.5	0.93 (0.68. 1.27)	
Cigarette smoking				
Yes (56)	(9/21) 42.9	(17/35) 48.6	1.39 (0.52. 3.72)	0.66
No (506)	(115/241) 47.7	(121/265) 45.7	1.22 (0.94. 1.58)	
Diabetes				
Yes (155)	(43/82) 52.4	(36/73) 49.3	1.23 (0.78. 1.93)	0.82
No (406)	(89/194) 44.8	(93/212) 43.9	1.19 (0.89. 1.61)	
Hypertension				
Yes (249)	(68/131) 51.9	(66/118) 55.9	0.95 (0.67. 1.34)	0.19
No (309)	(62/142) 43.7	(64/167) 38.3	1.35 (0.94. 1.92)	
Heart Failure				
Yes (13)	(3/4) 57.1	(3/6) 50.0	1.49 (0.26. 8.34)	0.56
No (549)	(128/269) 47.6	(127/280) 45.4	1.20 (0.94. 1.54)	
Obstructive airway disease				
Yes (39)	(12/23) 52.2	(6/16) 37.5	1.38 (0.48. 3.94)	0.71
No (523)	(120/253) 47.4	(124/270) 45.9	1.18 (0.92. 1.52)	
Symptom Onset				
Symptom onset≤7 days (328)	(81/165) 49.1	(78/163) 47.9	1.18 (0.86. 1.62)	0.85
Symptom onset>7 days (141)	(28/68) 41.2	(26/73) 35.6	1.26 (0.73. 2.16)	
Corticosteroid use				
Yes (524)	(124/262) 47.3	(122/262) 46.6	1.16 (0.90. 1.49)	0.10
No (38)	(8/14) 57.1	(8/24) 33.3	5.80 (1.89. 17.73)	
RAAS inhibitors				
Yes (152)	(39/78) 50.0	(37/74) 50.0	1.11 (0.70. 1.77)	0.72
No (410)	(93/198) 47.0	(93/212) 43.9	1.25 (0.94. 1.68)	
CAD				
Yes (78)	(27/45) 60.0	(18/33) 54.5	1.51 (0.76. 3.03)	0.31
No (484)	(105/231) 45.5	(112/253) 44.3	1.14 (0.88. 1.50)	
BMI				
<30 (412)	(92/205) 44.9	(89/207) 43.0	1.24 (0.92. 1.66)	0.51
≥30 (123)	(29/56) 51.8	(34/67)50.7	1.02 (0.62. 1.67)	
Time receiving the assigned treatment				
<50% (50)	(5/20) 25.0	(10/33) 33.3	0.78 (0.24. 2.47)	0.32
50%-79% (44)	(12/23) 52.2	(14/21) 66.7	0.67 (0.30. 1.48)	
≥80% (467)	(115/232) 49.6	(106/235) 45.1	1.30 (1.00. 1.70)	
Aspirin				
Yes (172)	(45/91) 49.5	(36/81) 44.4	1.41 (0.89. 2.23)	0.29
No (390)	(87/185) 47.0	(94/205) 45.9	1.11 (0.82. 1.48)	

Intermediate-dose versus Standard-dose Prophylactic Anticoagulation in Patients with COVID-19 Admitted to the Intensive Care Unit: Ninety-day Results from the INSPIRATION Randomized Trial

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

[1]Cardiovascular Medicine Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA. [2]Yale/YNHH Center for Outcomes Research & Evaluation (CORE), New Haven, CT, USA. [3]Cardiovascular Research Foundation (CRF), New York, NY, USA. [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 (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran. [10]Lung Transplantation Research Center, Department of Cardiology, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), 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]Firouzgar hospital, Department of internal medicine, Iran University of Medical Sciences, Tehran, Iran. [13]Research Center for Prevention of Cardiovascular Disease, Institute of Endocrinology & 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. [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, USA. [28]Respiratory Department, Hospital Ramón y Cajal (IRYCIS), Madrid, Spain. [29]Medicine Department, Universidad de Alcalá (IRYCIS), Madrid, Spain. [30]CIBER Enfermedades Respiratorias (CIBERES), Madrid, Spain. [31]Division of Cardiology, Columbia University Irving Medical Center / NewYork-Presbyterian Hospital, New York, NY, USA. [32]Department of Internal Medicine, Hospital Germans Trias i Pujol, Badalona, Barcelona, Universidad Católica de Murcia, Murcia, Spain. [33]Department of Pharmacotherapy and Outcome Science, School of Pharmacy, Virginia Commonwealth University, Richmond, VA, USA. [34]Pauley Heart Center, Division of Cardiology, Department of Internal Medicine, School of Pharmacy, Virginia Commonwealth University, Richmond, VA, USA; [35]The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [36]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom, [37]Aalborg University, Aalborg, Denmark. [38]Section of Cardiovascular Medicine, Department of Internal Medicine, Yale School of Medicine, New Haven, CT, USA. [39]Department of Health Policy and Administration, Yale School of Public Health, New Haven, CT, USA.

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

Correspondence:

Dr. Bikdeli, Cardiovascular Medicine Division, Brigham and Women's Hospital, 75Francis Street, Shapiro 5, Suite 5156. Boston, MA 02115; Email: bbikdeli@bwh.harvard.edu, Behnood.bikdeli@yale.edu

Dr. Sadeghipour, Cardiovascular Intervention Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Vali-Asr Ave, Niyayesh Blvd, Tehran 1996911101, Iran; psadeghipour@hotmail.com

ABSTRACT

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

Methods: This manuscript 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 31-90 (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 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 post-acute 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 manuscript summarizes the final results of the INSPIRATION trial, that includes 90-day follow-up for the study participants.

METHODS

The trial design has been described previously.(18) Briefly, INSPIRATION and INSPIRATION-statin (INSPIRATION-S) is a trial with 2x2 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 pre-specified 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 40mg once daily. In both arms, dose adjustment was pre-specified according to body weight and renal function(18, 21) (Supplemental Tables 1 and 2). 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. Post-discharge 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 non-major 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 (mITT) 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% confidence interval 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 pre-specified to be performed via mixed effects models accounting for the enrolling site as a random effect, and hazard ratio as the main effect measure. For the assessment of non-mortality 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 2x2 factorial design (second active intervention being atorvastatin 20mg once daily versus 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 pre-specified. Therefore, assessment of the 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/).

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) (Supplemental Figure 1). 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 was 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, co-morbidities, 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 (Supplemental Table 3).

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 a and efficacy or major safety event requiring a change. Supplemental Table 4 summarizes the information related to treatment adherence in both groups in the post-discharge and 30-day follow up states.

Efficacy outcomes

Ninety-day outcomes data was 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 (hazard ratio [HR]: 1.21; 95% confidence interval [CI]: 0.95-1.55, P=0.11) (Figure 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) (Figure 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) (Figure 2, Panel 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 non-major 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 3 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% 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 Supplemental Table 5.

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 (Supplemental Table 6).

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 31-90. 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 31-90 (HR: 1.59, 95% CI: 0.45-5.06,) (Figure 3). Findings were similar in a landmark analysis for mortality (Supplemental Figure 2).

Subgroup analysis

In assessment of the pre-specified subgroups, no specific group was identified in whom a potentially beneficial effect from intermediate-dose prophylactic anticoagulation was identified (Figure 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 versus HR: 0.93, 95% CI: 0.68-1.27, $P_{interaction}$ =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 31-90, unlike initial concerns for post-discharge heightened risk of adverse events,(3, 15) indicated very few additional efficacy vents without a significant difference between the group. Fatal bleeding and severe thrombocytopenia were rare but numerically more frequent with intermediate-dose prophylactic anticoagulation.

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 pre-print 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 post-discharge setting occurs in the first 3 weeks post-discharge.(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 post-discharge (days 31-90). Some studies suggest that patients with COVID-19 have a relatively low rate of post-discharge VTE(29-32). Further, a recent study did not identify a significantly increased risk of post-discharge VTE in patients with SARS-CoV-2 infection compared with non-infected 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 pre-specified 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 RCTs 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 need 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 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 healthcare 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 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 studies have suggested that many VTE events in COVID-19 are distal deep vein thrombosis or sub-segmental 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 warrants 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 post-discharge 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 post-discharge extended prophylaxis 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 grorps. 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.

Summary Table

What is known on 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 this paper adds 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 30-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.

Acknowledgements

The authors would like to extend their sincere appreciation to study participants, and to healthcare workers, all around the world, whose generous efforts would be unforgettable during this pandemic. The authors would like to also thank the member of the Data Safety and Monitoring Board, Saeideh Mazloomzadeh, MD, PhD, Shiva Khaleghparast, PhD, Behshid Ghadrdoost, PhD, Mostafa Mousavizadeh, MD, Mohammad Reza Baay, MD; and Feridoun Noohi, MD, Hamidreza Sharifnia, MD, Sasan Tavana, MD, Arezoo Ahmadi, MD, Nasser Malekpour Alamdari, MD, Mohammad Fathi, MD, Mahshid Soleimanzadeh, MD, Mostafa Mohammadi, MD, Navid Davoody, MD, Maryam Zarinsadaf, Sara Tayyebi, MS, Fahimeh Farrokhzadeh, MS, Faeze Nezamabadi, MS, and Esmaeil Soomari, MS for their support and contribution.

Disclosures

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 healthcare 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 Squibb/Pfizer Alliance, Portola, and Janssen. He has received consulting fees from Amgen, Pfizer, Boston Scientific Corporation and Thrombolex. Dr. Kirtane reports Institutional funding to Columbia University and/or Cardiovascular Research Foundation from Medtronic, Boston Scientific, Abbott Vascular, Abiomed, CSI, CathWorks, Siemens, Philips, ReCor Medical. In addition to research grants, institutional funding includes fees paid to Columbia University and/or Cardiovascular Research Foundation for speaking engagements and/or consulting. Personal: Travel Expenses/Meals from Medtronic, Boston Scientific, Abbott Vascular, Abiomed, CSI, CathWorks, Siemens, Philips, ReCor Medical, Chiesi, OpSens, Zoll, and Regeneron. Dr. Van Tassell received the research support from Novartis, Swedish Orphan Biovitrum, Olatec Therapeutics, Serpin Pharm. He is a consultant of R-Pharm, Serpin Pharma. Dr. Stone has received speaker or other honoraria from Cook, Terumo, and Orchestra Biomed; served as a consultant to Valfix, TherOx, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, Miracor, Neovasc, V-Wave, Abiomed, Ancora, MAIA Pharmaceuticals, Vectorious, Reva, Matrizyme, Cardiomech; and has received equity or options from Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, MedFocus family of funds, and Valfix. Dr. Lip reports consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are received personally. Dr. Krumholz reports personal fees from UnitedHealth, personal fees from IBM Watson Health, personal fees from Element Science, personal fees from Aetna, personal fees from Facebook, personal fees from Siegfried & Jensen Law Firm, personal fees from Arnold & Porter Law Firm, personal fees from Ben C. Martin Law Firm, personal fees from National Center for Cardiovascular Diseases, Beijing, ownership of HugoHealth, ownership of Refactor Health, contracts from the Centers for Medicare & Medicaid Services, grants from Medtronic and the Food and Drug Administration, grants from Medtronic and Johnson and Johnson, grants from Shenzhen Center for Health Information, and is a Venture Partner at FPrime. outside the submitted work. Dr. Bikdeli reports that he is a consulting expert, on behalf of the plaintiff, for litigation related to two specific brand models of IVC filters. All other authors report no relevant Enoxaparin was provided through Alborz Darou, Pooyesh Darou and Caspian Pharmaceuticals companies, and atorvastatin and matching placebo was provided by Sobhan Darou. None of these companies were study sponsors and they had no other role and will not have a role in the design, conduct, analysis, or interpretation of the ongoing results or the decision to submit the resultant manuscript(s).

REFERENCES

1. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. Nat Med 2020; 26(7): 1017-32.
2. Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the COVID-19 Pandemic. J Am Coll Cardiol 2020; 75(18): 2352-71.
3. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. Nat Med 2021.
4. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. J Am Coll Cardiol 2020; 75(23): 2950-73.
5. Fauvel C, Weizman O, Trimaille A, et al. Pulmonary embolism in COVID-19 patients: a French multicentre cohort study. Eur Heart J 2020; 41(32): 3058-68.
6. Klok FA, Kruip M, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. Thromb Res 2020; 191: 148-50.
7. Torbicki A. COVID-19 and pulmonary embolism: an unwanted alliance. Eur Heart J 2020; 41(32): 3069-71.
8. Libby P, Lüscher T. COVID-19 is, in the end, an endothelial disease. Eur Heart J 2020; 41(32): 3038-44.
9. Bikdeli B, Madhavan MV, Gupta A, et al. Pharmacological Agents Targeting Thromboinflammation in COVID-19: Review and Implications for Future Research. Thromb Haemost 2020.
10. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost 2020; 18(8): 1995-2002.
11. Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood 2020; 136(4): 489-500.
12. Hendren NS, de Lemos JA, Ayers C, et al. Association of Body Mass Index and Age With Morbidity and Mortality in Patients Hospitalized With COVID-19: Results From the American Heart Association COVID-19 Cardiovascular Disease Registry. Circulation 2021; 143(2): 135-44.
13. Jiménez D, García-Sanchez A, Rali P, et al. Incidence of VTE and Bleeding Among Hospitalized Patients With Coronavirus Disease 2019: A Systematic Review and Meta-analysis. Chest 2020.

14. Spyropoulos AC, Levy JH, Ageno W, et al. Scientific and Standardization Committee communication: Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost 2020; 18(8): 1859-65.
15. Gerotziafas GT, Catalano M, Colgan MP, et al. Guidance for the Management of Patients with Vascular Disease or Cardiovascular Risk Factors and COVID-19: Position Paper from VAS-European Independent Foundation in Angiology/Vascular Medicine. Thromb Haemost 2020; 120(12): 1597-628.
16. The European Society for Cardiology. ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic. https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance. (Last update: 10 June 2020), Date last accessed: March 12, 2021.
17. Bikdeli B. Anticoagulation in COVID-19: Randomized trials should set the balance between excitement and evidence. Thromb Res 2020; 196: 638-40.
18. Bikdeli B, Talasaz AH, Rashidi F, et al. Intermediate versus standard-dose prophylactic anticoagulation and statin therapy versus placebo in critically-ill patients with COVID-19: Rationale and design of the INSPIRATION/INSPIRATION-S studies. Thromb Res 2020; 196: 382-94.
19. Tritschler T, Mathieu ME, Skeith L, et al. Anticoagulant interventions in hospitalized patients with COVID-19: A scoping review of randomized controlled trials and call for international collaboration. J Thromb Haemost 2020; 18(11): 2958-67.
20. Talasaz AH, Sadeghipour P, Kakavand H, et al. Recent Randomized Trials of Antithrombotic Therapy for Patients With COVID-19. J Am Coll Cardiol. 2021, J Am Coll Cardiol. 2021; 77(15):1903-1921.
21. Sadeghipour P, Talasaz AH, Rashidi F, et al. Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial. JAMA. 2021, ePub Ahead of Print, doi: 10.1001/jama.2021.4152.
22. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19: Multiorgan Sequelae and Management Considerations. Nat Med. 2021, ePub Ahead of Print, doi: 10.1038/s41591-021-01283-z.
23. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011; 123(23): 2736-47.
24. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. J Am Stat Assoc 1999; 94(446): 496-509.
25. Moores LK, Tritschler T, Brosnahan S, et al. Prevention, Diagnosis, and Treatment of VTE in Patients With Coronavirus Disease 2019: CHEST Guideline and Expert Panel Report. Chest 2020; 158(3): 1143-63.
26. Cuker A, Tseng EK, Nieuwlaat R, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. Blood Adv 2021; 5(3): 872-88.
27. Zarychanski R. Therapeutic Anticoagulation in Critically Ill Patients with Covid-19 – Preliminary Report. medRxiv 2021: 2021.03.10.21252749.
28. Picariello C, Caravita S, Vatrano M, et al. [ANMCO Position paper: Pulmonary circulation diseases and COVID-19]. G Ital Cardiol (Rome) 2020; 21(8): 575-83.
29. Hill JB, Garcia D, Crowther M, et al. Frequency of venous thromboembolism in 6513 patients with COVID-19: a retrospective study. Blood Adv 2020; 4(21): 5373-7.
30. Rashidi F, Barco S, Kamangar F, et al. Incidence of symptomatic venous thromboembolism following hospitalization for coronavirus disease 2019: Prospective results from a multi-center study. Thromb Res 2021; 198: 135-8.
31. Salisbury R, Iotchkova V, Jaafar S, et al. Incidence of symptomatic, image-confirmed venous thromboembolism following hospitalization for COVID-19 with 90-day follow-up. Blood Adv 2020; 4(24): 6230-9.

32. Venturelli S, Benatti SV, Casati M, et al. Surviving COVID-19 in Bergamo province: a post-acute outpatient re-evaluation. Epidemiol Infect 2021; 149: e32.
33. Roubinian NH, Dusendang JR, Mark DG, et al. Incidence of 30-Day Venous Thromboembolism in Adults Tested for SARS-CoV-2 Infection in an Integrated Health Care System in Northern California. JAMA Intern Med. 2021, ePub Ahead of Print, doi: 10.1001/jamainternmed.2021.0488.
34. Piazza G, Campia U, Hurwitz S, et al. Registry of Arterial and Venous Thromboembolic Complications in Patients With COVID-19. J Am Coll Cardiol 2020; 76(18): 2060-72.
35. Regitz-Zagrosek V, Kararigas G. Mechanistic Pathways of Sex Differences in Cardiovascular Disease. Physiological reviews 2017; 97(1): 1-37.
36. Gallastegui N, Zhou JY, Drygalski AV, et al. Pulmonary Embolism Does Not Have an Unusually High Incidence Among Hospitalized COVID19 Patients. Clin Appl Thromb Hemost 2021; 27: 1076029621996471.
37. Al-Samkari H, Gupta S, Leaf RK, et al. Thrombosis, Bleeding, and the Observational Effect of Early Therapeutic Anticoagulation on Survival in Critically Ill Patients With COVID-19. Ann Intern Med. 2021, ePub Ahead of Print, doi: 10.7326/M20-6739.

Figure 1. Primary composite outcome in the prespecified primary cohort
Panel A. 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 dash 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 ratio were calculated with a random effect for enrolling centers.

Figure 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 ratio were calculated with a random effect for enrolling centers. For panel B, competing risks of mortality was addressed.

Figure 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 ratio were calculated with a random effect for enrolling centers.

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

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 to 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 non-major 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 non-major 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) %		

BARC, denotes 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 Supplement).

[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 followings; 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 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 electrocardiographic 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 Bleeding Academic Research Consortium (BARC) Type 3 and 5, which defines as Type 3a for overt bleeding plus hemoglobin drop of 3 to 5 g/dL) or any transfusion with overt bleeding; Type 3b for overt bleeding plus hemoglobin drop 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

Supplemental Appendix

Intermediate versus Standard-dose Prophylactic anticoagulation In cRitically-ill pATIents with COVID-19: An opeN label randomized controlled trial

Table of contents

Investigators and Committees ....

Eligibility criteria ....

Definitions of Outcome Events ....

Supplemental Figure 1. Enrollment and randomization
Supplemental Figure 2. Landmark Analysis for All-cause Mortality
Supplemental Table 1. Intervention and comparator dosing considerations for the anticoagulation hypothesis
Supplemental Table 2a. Detailed dosing recommendations for intermediate-dose prophylactic anticoagulation

Supplemental Table 2b. Detailed dosing recommendations for standard-dose prophylactic anticoagulation
Supplemental Table 3. Baseline Characteristics
Supplemental Table 4. Post-discharge and 30-day follow up treatment status
Supplemental Table 5. Summary of venous thromboembolism diagnostic tests performed by enrolling centers
Supplemental Table 6. Primary, Secondary and exploratory outcomes within 90 days from enrollment in the total study population who allowed their data to contribute to the final results

Investigators and Committees

Steering Committee: P. Sadeghipour (Co-Chair), B. Bikdeli (Co-Chair), A. H. Talasaz

Advisory Committee: F. Rashidi, B. Sharif-Kashani, MT, Beigmohammadi, M. Farrokhpour, H. Sezavar, P. Payandemehr, A. Dabbagh, MD, K. Gohari Moghadam, V. Eslami, A. Amin, D.Jimenez, A.Gupta, M. Madhavan, S. Sethi, S Parikh, M. Monreal, G. Piazza, A. Kirtane, P. Dobesh, G. W. Stone, G.Y.H. Lip, H. M. Krumholz, S. Z. Goldhaber

Clinical Event Committee: A. Amin (Chair), P. Sadeghipour, A. H. Talasaz, B. Mohebbi, B. Bikdeli, A. Dabbagh

Data and Safety Monitoring Board (DSMB): S. Mazloomzadeh (Chair), S. Khaleghparast, B. Ghadrdoost, M. Mousavizadeh, MR Baay

Study Statisticians & Programmer: H. Bakhshandeh

Project Office Study Staff: S. Tayyebi, M. Zarin-Sadaf, F. Nezamabadi, S. Soomary

Site Principal and Co-Investigators:

N=number of participants randomized

Imam Reza Hospital, Tabriz, Iran N=155, F. Rashidi, P. Rezaeifar, O. Tahamtan, S. Matin, L. Asgharpour,

Masih Daneshvari Hospital, Tehran, Iran N=109, B. Sharif-Kashani, A. Abedini, S. Lookzadeh, S. Shafaghi, F. Karimi

Imam Khomeini Hospital, Tehran, Iran N= 96, MT. Beigmohammadi, H. Khalili, H. Rahmani, E. Zoghi, K. Mohammadi, S. Fattah Ghazi

Firoozgar General Hospital, Tehran, Iran N=65, M. Farrokhpour, M. Yadollahzadeh, P. Sadeghipour, H. Abri

Hazrate Rasool-e Akram General Hospital, Tehran, Iran N=55, H. Sezavar, T. Riahi, S. Tabrizi, SM. Mousavian

Sina Hospital, Tehran, Iran N=39, P. Payandemehr, S. Shahmirzaei, A. Ahmadi

Modarres Hospital, Tehran, Iran N=34, A. Dabbagh, M. Soleimanzadeh

Shariati Hospital, Tehran, Iran N= 25, K. Gohari Moghadam, R. Aliannejad, S. Hossein Hosseini

Shahid Dr. Labbafinejad Hospital, Tehran, Iran N=17, V. Eslami, A. Kashefizadeh,

Tehran Heart Center, Tehran, Iran N=5, AH. Talasaz, H. Kakavand

Coordinator sites:

Rajaie Cardiovascular Medical and Research Center, Tehran, Iran: P. Sadeghipour, S. Jamalkhani, F. Rafiee, SE. Parhizgar, E. Baghizadeh, MD, M. Maleki, N. Hadavand, S. Tayyebi, M. Zarin-Sadaf, F. Nezamabadi, S. Soomary

Tehran Heart Center, Tehran, Iran: AH. Talasaz, A. Hajighasemi, S. Sadeghian

Eligibility criteria:

Inclusion Criteria for Anticoagulation Hypothesis

- Adult patients (≥18 years), with PCR-confirmed COVID-19[1]admitted to ICU within 7 days of initial hospitalization[2], who do not have another firm indication for anticoagulation (such as mechanical valve, high-risk AF, VTE, or left ventricular thrombus), who are not enrolled in another blinded randomized trial, and are willing to participate in the study and provide informed consent[3].
- Estimated survival of at least 24 hours at the discretion of enrolling physician

Exclusion Criteria for Anticoagulation Hypothesis

- Weight <40Kg
- Use of systemic anticoagulation for another indication (mechanical valve, ECMO, AF, left ventricular thrombus, or diagnosed VTE(1))
- Overt bleeding at the day of enrollment
- Known major bleeding within 30 days (according to the Bleeding Academic Research Consortium (BARC) definition)
- Platelet count <50,000/Fl
- Pregnancy (as confirmed by beta-HCG testing among female patients <50 years)
- History of heparin induced thrombocytopenia or immune thrombocytopenia
- Ischemic stroke within the past 2 weeks
- Major head or spinal trauma in the past 30 days
- Craniotomy/major neurosurgery within the past 3 months

---

[1] COVID-19 will be defined by positive RT-PCR test plus either pulmonary infiltrates in radiography (chest X-ray or chest CT), and/or abnormal results for at least one of the following biomarkers: ESR, CRP, D-dimer, ferritin, LDH

[2] If patients are transferred across facilities, we will set time zero (for 7 days) as date of presentation to the first medical facility.

[3] For critically ill patients who are not able to participate in informed decision-making for participation in the study (e.g., due to sedation and mechanical ventilation), their healthcare proxy will be contacted for the possibility of enrollment and informed consent.

- Known brain metastases or vascular malformations (aneurysm)
- Presence of an epidural, spinal or pericardial catheter
- Major surgery other than neurosurgery within 14 days prior to enrollment
- Coexistence of severe obesity (weight >120Kg or BMI>35Kg/M^2 along with severe renal insufficiency defined as CrCl<30 mL/min)
- Allergic reaction to study medications
- Lack or withdrawal of informed consent

Definitions of Outcome Events

All-cause death

Death due to any causes within the first 30 days. Considering the inaccuracies with adjudication of the cause of death in critically-ill patients with COVID-19 in the absence of systematic autopsy, the steering committee made the decision not to adjudicate the cause of death.

Venous Thromboembolism

Deep venous thrombosis

Any deep vein thrombosis diagnosed in the upper (internal jugular, subclavian, axillary/brachial), or lower extremity (iliac, femoral/popliteal, gastrocnemius, peroneal, posterior tibial) or the inferior vena cava or deep splanchnic veins based on ultrasonography, or contrast-enhanced vascular imaging, including computed tomography or angiography; or vascular magnetic resonance imaging.

Pulmonary embolism

Any pulmonary embolism diagnosed on CT angiography, V/Q scan, invasive pulmonary angiography, echocardiography (thrombus visualized in the main pulmonary artery), or at autopsy.

Undergoing ECMO

Use of veno-venous or veno-arterial extracorporeal membrane oxygenation

Acute arterial thrombosis

Type 1 myocardial infarction (T1MI)

Rise and/or fall in cardiac troponin values with at least on value above the 99th percentile upper reference limits with at least one of the followings; symptoms of ischemia, or new or presumed new ischemic 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 ischemic etiology; confirmed by coronary angiography, intravascular imaging or autopsy

Ischemic stroke

An acute episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction and verified by dedicated brain imaging and confirmed by neurology consultation.

Acute limb ischemia

Sudden decrease in limb perfusion that threatens limb viability with confirmed arterial obstruction based on duplex ultrasonography or contrast-enhanced vascular imaging, including computed tomography or angiography; or vascular magnetic resonance imaging.

Ventilator free days

Difference between total number of days alive post-enrollment and total number of days on invasive mechanical ventilation

Atrial fibrillation

New incident atrial fibrillation identified on electrocardiogram, or telemetry monitoring

Renal replacement therapy

Undergoing venovenous hemofiltration, hemodialysis, or peritoneal dialysis in patients without prior history of dialysis

ICU length of stay

Total number of days spent in the ICU

Discharge from ICU

Alive discharge from the ICU

Major bleeding (1)

BARC Type 3

Type 3a: Overt bleeding plus hemoglobin drop of 3 to 5 g/dL (provided hemoglobin drop is related to bleed) Any transfusion with overt bleeding

Type 3b: Overt bleeding plus hemoglobin drop 5 g/dL (provided hemoglobin drop is related to bleed) Cardiac tamponade Bleeding requiring surgical intervention for control (excluding dental/ nasal/skin/hemorrhoid) Bleeding requiring intravenous vasoactive agents

Type 3c: Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal) Subcategories confirmed by autopsy or imaging or lumbar puncture Intraocular bleed compromising vision

BARC Type 5: Fatal bleeding

Type 5a: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

Type 5b: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

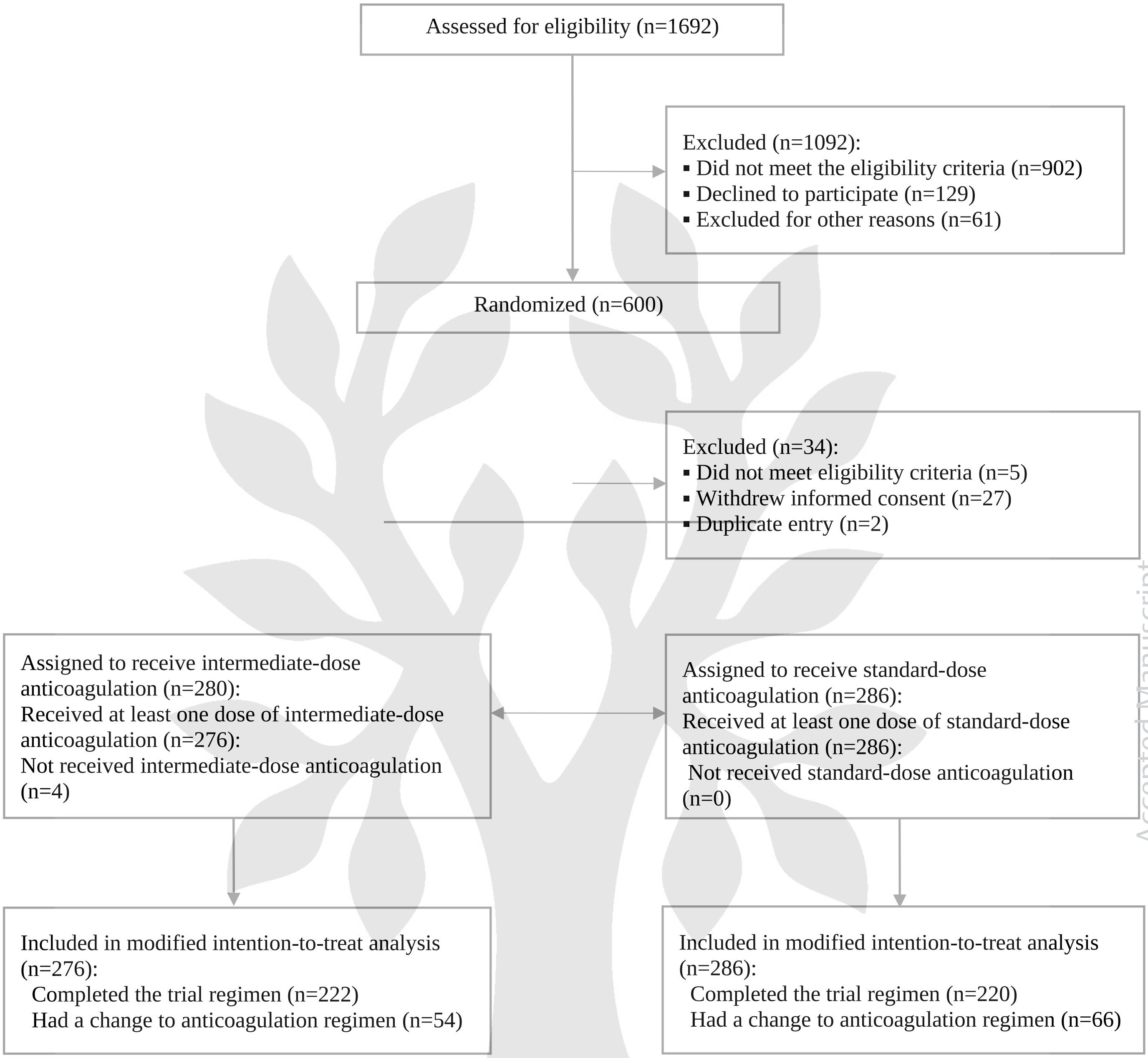
Clinically-relevant non-major bleeding

Clinically-significant bleeding that warranted attention from the medical personnel, but not fulfilling criteria for major bleeding

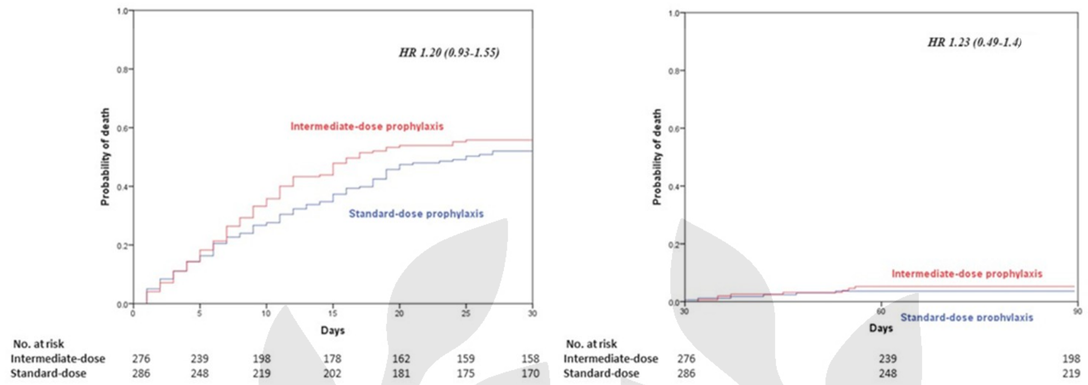
Severe thrombocytopenia

Incident thrombocytopenia with platelet count < 20,000/fL

Supplemental Figure 1. Enrollment and randomization


Assessed for eligibility (n=1692)
Excluded (n=1092):
▪ Did not meet the eligibility criteria (n=902)
▪ Declined to participate (n=129)
▪ Excluded for other reasons (n=61)
Randomized (n=600)
Excluded (n=34):
▪ Did not meet eligibility criteria (n=5)
▪ Withdrew informed consent (n=27)
▪ Duplicate entry (n=2)
Assigned to receive intermediate-dose anticoagulation (n=280):
Received at least one dose of intermediate-dose anticoagulation (n=276):
Not received intermediate-dose anticoagulation (n=4)
Assigned to receive standard-dose anticoagulation (n=286):
Received at least one dose of standard-dose anticoagulation (n=286):
Not received standard-dose anticoagulation (n=0)
Included in modified intention-to-treat analysis (n=276):
Completed the trial regimen (n=222)
Had a change to anticoagulation regimen (n=54)
Included in modified intention-to-treat analysis (n=286):
Completed the trial regimen (n=220)
Had a change to anticoagulation regimen (n=66)

Supplemental Figure 2. Landmark Analysis for All-cause Mortality



Supplemental Table 1. Intervention and comparator dosing considerations for the anticoagulation hypothesis

Intervention group	Routine Protocol
CrCl[1] ≥30 mL/min	CrCl ≥30 mL/min
Enoxaparin 1 mg/kg SC Daily[2]	Enoxaparin 40 mg SC Daily
Obesity and CrCl ≥30 mL/min (weight ≥120 kg or BMI ≥35 kg/m^2)	Obesity and CrCl ≥30 mL/min (weight ≥120 kg or BMI ≥35 kg/m^2)
Enoxaparin 0.6 mg/kg SC twice daily (TBW)[2]	Enoxaparin 40 mg SC twice daily
15< CrCl <30 mL/min	15< CrCl <30 mL/min
Enoxaparin 0.5 mg/kg SC Daily[2] (At least 40 mg)	Enoxaparin 30 mg SC Daily
CrCl ≤15 mL/min	CrCl ≤15 mL/min
UFH 10000 units SC twice daily	UFH 5000 units SC twice daily

[1]Creatinine clearance will be calculated according to Cockcroft-Gault Formula using total body weights. [2]Doses rounded up to nearest above 10 mg;

BMI, body mass index, CrCl, creatinine clearance, TBW, totally body weight, UFH, unfractionated heparin.

Please see the approximation tables for pragmatic dose assignment.

Supplemental Table 2a. Detailed dosing recommendations for intermediate-dose prophylactic anticoagulation

Weight[1] (kg)	CrCl[2]>30 Enoxaparin	15< CrCl≤30 Enoxaparin	CrCl≤15 UFH
41-50	50 mg Daily	40mg Daily	10000 U SC Bid
51-60	60mg Daily	40mg Daily	10000 U SC Bid
61-70	70mg Daily	40mg Daily	10000 U SC Bid
71-80	80mg Daily	40mg Daily	10000 U SC Bid
81-90	90mg Daily	50mg Daily	10000 U SC Bid
91-100	100mg Daily	50mg Daily	10000 U SC Bid
101-110	110mg Daily	60mg Daily	10000 U SC Bid
111-120	120mg Daily	60mg Daily	10000 U SC Bid
121-130	80 mg Bid	**Excluded**	
131-140	90 mg Bid		
141-150	90 mg Bid		
151-160	100 mg Bid		
161-170	100 mg Bid		
171-180	110 mg Bid		

[1] Total body weight

[2] Creatinine clearance will be calculated according to Cockcroft-Gault Formula using total body weight.

CrCl, creatinine clearance, UFH, unfractionated heparin.

Supplemental Table 2b. Detailed dosing recommendations for standard-dose prophylactic anticoagulation

Weight [1] (kg)	CrCl [2] >30 mL/min Enoxaparin	15< CrCl ≤30 mL/min Enoxaparin	CrCl ≤15 mL/min UFH
41-50	40mg Daily	30 mg Daily	5000 U SC Bid
51-60	40mg Daily	30 mg Daily	5000 U SC Bid
61-70	40mg Daily	30 mg Daily	5000 U SC Bid
71-80	40 mg Daily	30 mg Daily	5000 U SC Bid
81-90	40 mg Daily	30 mg Daily	5000 U SC Bid
91-100	40 mg Daily	30 mg Daily	5000 U SC Bid
101-110	40 mg Daily	30 mg Daily	5000 U SC Bid
111-120	40 mg Daily	30 mg Daily	5000 U SC Bid
121-130	40 mg Bid	**Excluded**	
131-140	40 mg Bid		
141-150	40 mg Bid		
151-160	40 mg Bid		
161-170	40 mg Bid		
171-180	40 mg Bid		

[1] Total body weight

[2] Creatinine clearance will be calculated according to Cockcroft-Gault Formula using total body weight

CrCl, creatinine clearance, UFH, unfractionated heparin.

Supplemental Table 3. Baseline Characteristics		
	Intermediate-dose prophylactic anticoagulation (n=276)	Standard-dose prophylactic anticoagulation (n=286)
Demographics		
Age— years	62 (51, 70.7)	61 (47, 71)
Sex		
Women — no. (%)	114 (41.3)	123 (43.0)
Current smokers— no. (%)	35 (12.7)	21 (7.3)
Coexisting Conditions— no. (%)		
Hypertension	131 (48.0)	118 (41.2)
Diabetes	82 (29.7)	73 (25.6)
Coronary artery disease	45 (16.3)	33 (11.5)
Obstructive airway disease	23 (8.3)	16 (5.6)
Heart failure	7 (2.5)	6 (2.1)
Ischemic cerebrovascular accidents	6 (2.2)	11 (3.8)
Markers of Clinical Severity		
Systolic blood pressure <100mmHg at the time of randomization — no. (%)	25 (9.0)	33 (11.5)
Vasopressor use wihin 72 hours of enrollment— no. (%)	63 (22.8)	64 (22.3)
Fraction of inspired oxygen>50% at the time of randomization — no. (%)	112 (40.5)	122 (42.6)
Mode of respiratory Support no. (%)		
Nasal cannula	10 (3.6)	14 (4.9)
Face mask	33 (12.0)	27 (9.4)
Reservoir mask	76 (27.5)	96 (33.6)
High flow nasal cannula	9 (3.3)	6 (2.1)
Non-invasive positive pressure ventilation	93 (33.7)	85 (29.7)
Invasive positive pressure ventilation (endotracheal intubation)	55 (19.9)	58(20.3)
Coexisting Treatments		
Remdesivir	168 (60.9)	170 (59.4)
Favipiravir	52 (18.8)	43 (15.0)
Lopinavir/Ritonavir	3 (1.1)	3 (1.0)
Atazanavir/Ritonavir	27 (9.8)	19 (6.6)
Corticosteroid use	262 (94.9)	262 (91.6)
Tocilizumab	34 (12.3)	40 (14.0)
Convalescent plasma	0	0
Neutralizing antibody	0	0

Supplemental Table 4. Post-discharge and 30-day follow up treatment status

	Intermediate-dose prophylactic anticoagulation	**Standard-dose prophylactic anticoagulation**
Median duration of 30-day follow-up (days)	30 (8-30)	30 (8-30)
Median duration of 30-day time on assigned treatment (days)	19 (7-30)	20 (7-30)
Median duration of post discharge follow-up	23 (16-26)	23 (16-26)
Median duration of post discharge time on assigned treatment	20 (4-25)	20 (4-25)

Supplemental Table 5.
Summary of venous thromboembolism diagnostic tests performed by enrolling centers

	N	**Intermediate-dose prophylactic anticoagulation**	**Standard-dose prophylactic anticoagulation**
Venous doppler ultrasound performed	66	34	32
Confirmed deep venous thrombosis	12	7	5
CT pulmonary angiogram performed	22	11	11
Confirmed pulmonary emboli[a]	7	2	5

[a] One pulmonary emboli event was diagnosed by transthoracic echocardiography in which free floating right heart thrombosis along thrombosis in the main pulmonary artery trunk were detected. Patient's unstable hemodynamic prohibited CT pulmonary angiography

Supplemental Table 6. Primary, Secondary and exploratory outcomes within 90 days from enrollment in the total study population who allowed their data to contribute to the final results [a]

Outcome	Intermediate-dose prophylactic anticoagulation (n=296)	Standard-dose prophylactic anticoagulation (n=294)	Absolute Difference (95% CI)	Hazard ratio (95% CI)	P value
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	137 (46.2)	130 (44.2)	2.0 (-5.9-10.0) %	1.18 (0.93-1.50)	0.16
Secondary outcomes					
All-cause mortality—no./total no. of patients (%)	132 (44.5)	123 (41.8)	2.7 (-5.2-10.7) %	1.22 (0.95-1.56)	0.10
Adjudicated venous thromboembolism—no./total no. of patients (%)	9 (3.0)	10 (3.4)	-0.3 (-3.2-2.4) %	0.89 (0.47-1.66)	0.71
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 (0.3)	1 (0.3)	0 (-0.9-0.9) %	0.99 (0.06-15.87)	0.99
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 (2.0)	-1.0 (-3.0-0.9) %	0.49 (0.12-1.96)	0.31
Undergoing new renal replacement therapy—no./total no. of patients (%)	10 (3.3)	7(2.3)	0.9 (-1.6-3.6) %	1.46 (0.55-3.86)	0.43
Safety outcomes—no./total no. of patients (%)					
Major bleeding[e]	7 (2.3)	4 (1.3)	1.1 (-1.1-3.4) %	2.00 (0.60-6.66)	0.25
BARC Type 3a- hemoglobin drop of 3 to 5 g/dL or any transfusion	3 (1.0)	4 (1.3)	-0.3 (-2.0-1.4) %	0.74 (0.16-3.31)	0.69
BARC Type 3b- hemoglobin drop> 5 g/dL	1 (0.3%)	0[f]	0.3 (-0.3-0.9) %		0.31
BARC Type 3c- intracranial hemorrhage	1 (0.3%)	0[f]	0.3 (-0.3-0.9) %		0.31
BARC Type 5- Fatal bleeding	3 (1.0)	0[f]	1.0 (-0.1-2.1) %		0.08
Clinically-relevant non-major bleeding[g] (BARC 2)	14 (4.7)	6 (2.0)	2.6 (-0.2-5.5) %	2.20 (0.83-5.80)	0.10
Composite of major and non-major bleeding	21 (7.0)	10 (3.4)	3.3 (-0.1-6.8) %	1.98 (0.92-4.27)	0.08
Severe thrombocytopenia[h]	6 (2.2)	0[f]	2.2 (0.4-3.6) %		0.01

BARC, denotes 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.

[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 followings; 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 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 electrocardiographic 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 Bleeding Academic Research Consortium (BARC) Type 3 and 5, which defines as Type 3a for overt bleeding plus hemoglobin drop of 3 to 5 g/dL) or any transfusion with overt bleeding; Type 3b for overt bleeding plus hemoglobin drop 5 g/dL, cardiac tamponade or bleeding requiring surgical intervention for control, Type 3c for intracranial hemorrhage and Type 5 for fatal bleeding(1).

[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

References

1. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;123(23):2736-47.