Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

adjustment, it can lead to between-group imbalances in baseline co-variates and in therapeutic strategies. Therefore, the multiplatform RCT adjusted analyses for age, sex, trial site, D-dimer levels, and enrollment period which is not typically performed in traditional RCTs. These design choices, although complex to use, are not limitations of the study but demonstrate great adaptation to the challenges investigators faced when conducting trials early in the pandemic and provides reassurance on the validity of the results.

Heparin is inexpensive and widely available and has a high probability of improving outcomes and reducing strain on health care systems when given to hospitalized patients with COVID-19 who are note critically ill. Available evidence from approximately 3,000 patients who were enrolled in RCTs that indicate a benefit of therapeutic heparin (UFH or LMWH) in acutely ill hospitalized patients with COVID-19 cannot be discounted by clinicians committed to the practice of evidence-based medicine. Admittedly, uncertainties remain; however, several trials and collaborative efforts, such as the prospective meta-analysis by the World Health Organization and an individual participant data network meta-analysis, are ongoing and will further enhance our understanding of the optimal anticoagulant intervention in hospitalized patients with COVID-19.

Acknowledgments

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

References

1. Leentjens J, van Haaps TF, Wessels PF, Schutgens REG, Middeldorp S. COVID-19-associated coagulopathy and antithrombotic agents-lessons after 1 year. *Lancet Haematol*. 2021;8(7):e524-e533.
2. Lawler PR, Goligher EC, Berger JS, et al; ATTACC Investigators, ACTIV-4a Investigators, REMAP-CAP Investigators, et al. Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. *N Engl J Med*. 2021;385(9):790-802.
3. Sholzberg M, Tang GH, Rahhal H, et al; RAPID trial investigators. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with covid-19 admitted to hospital: RAPID randomised clinical trial. *BMJ*. 2021;375:n2400.
4. Spyropoulos AC, Goldin M, Giannis D, et al; HEP-COVID Investigators. Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: the HEP-COVID randomized clinical trial. *JAMA Intern Med*. 2021;181(12):1612-1620.
5. Goligher EC, Bradbury CA, McVerry BJ, et al; REMAP-CAP Investigators, ACTIV-4a Investigators, ATTACC Investigators, et al. Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. *N Engl J Med*. 2021;385(9):777-789.
6. Lopes RD, de Barros ESPGM, Furtado RHM, et al; ACTION Coalition COVID-19 Brazil IV Investigators. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. *Lancet*. 2021;397(10291):2253-2263.
7. Moores LK, Tritschler T, Brosnahan S, et al. Thromboprophylaxis in patients with COVID-19. A brief update to the CHEST guideline and expert panel report [published online ahead of print February 12, 2022]. *Chest*. 2022. https://doi.org/10.1016/j.chest.2022.02.006
8. Beurskens DMH, Huckriede JP, Schrijver R, Hemker HC, Reutelingsperger CP, Nicolaes GAF. The anticoagulant and nonanticoagulant properties of heparin. *Thromb Haemost*. 2020;120(10):1371-1383.
9. Clausen TM, Sandoval DR, Spliid CB, et al. SARS-CoV-2 infection depends on cellular heparan sulfate and ACE2. *Cell*. 2020;183(4):1043-1057.e15.
10. Young E. The anti-inflammatory effects of heparin and related compounds. *Thromb Res*. 2008;122(6):743-752.
11. Cornet AD, Smit EG, Beishuizen A, Groeneveld ABJ. The role of heparin and allied compounds in the treatment of sepsis. *Thromb Haemost*. 2007;98(3):579-586.
12. Zarychanski R, Abou-Setta AM, Kanji S, et al; Canadian Critical Care Trials Group. The efficacy and safety of heparin in patients with sepsis: a systematic review and metaanalysis. *Crit Care Med*. 2015;43(3):511-518.
13. Zarychanski R, Doucette S, Fergusson D, et al. Early intravenous unfractionated heparin and mortality in septic shock. *Crit Care Med*. 2008;36(11):2973-2979.

COUNTERPOINT:

Should Therapeutic Heparin Be Administered to Acutely Ill Hospitalized Patients With COVID-19? No

David Jimenez, MD
Madrid, Spain
Parth Rali, MD
Philadelphia, PA
Kevin Doerschug, MD
Iowa City, IA

SARS-CoV-2 causes a systemic illness that is unique from other respiratory viruses. Chief among the differences compared with other viruses is the

AFFILIATIONS: From Respiratory Medicine (D. Jimenez), Ramón y Cajal Hospital (IRYCIS), and CIBER Enfermedades Respiratorias (CIBERES); the Department of Thoracic Medicine and Surgery (P. Rali), Lewis Katz School of Medicine, Temple University; and Pulmonary, Critical Care, and Occupational Medicine (K. Doerschug), University of Iowa.

FINANCIAL/NONFINANCIAL DISCLOSURES: The authors have reported to *CHEST* the following: D. J. has served as an advisor/consultant for Sanofi. None declared (P. R., K. D.).

CORRESPONDENCE TO: Parth Rali, MD; email: parth.rali@tuhs.temple.edu

DOI: https://doi.org/10.1016/j.chest.2022.01.037

propensity to activate clotting cascade within afflicted patients. Specifically, initial reports identified VTE in as many as 35% of patients with COVID-19.[1,2] Lung specimens from autopsies of patients with COVID-19 demonstrate widespread thrombosis with capillary microthrombi nine times more prevalent compared with autopsy specimens from patients with severe influenza A.[3] Anticoagulation potentially could decrease thrombotic events. Further, heparins (both unfractionated and low-molecular-weight) have some antiviral properties by binding to receptor binding domain spike protein of SARS-CoV-2.[4] This, in turn, may prevent organ injury from SARS-CoV-2.

For critically ill patients with COVID-19, the INSPIRATION trial and a multiplatform randomized control trial (RCT) failed to demonstrate a net clinical benefit for heparin-based intermediate-dose thromboprophylaxis or therapeutic anticoagulation, respectively.[5,6] These study findings are in accordance with a previously published *CHEST* guideline and expert panel report that recommended standard-dose VTE prophylaxis in critically ill populations.[7] This leads many clinicians to ask: "Should patients with COVID-19 who are hospitalized in a ward (not ICU) setting receive therapeutic anticoagulation?"

Four open-label multicenter RCTs attempt to provide an answer to this question.[8-11] The study designs and characteristics of these trials are described in Table 1.

Only two of these trials achieved their primary efficacy end points. The multiplatform trial (Randomized Embedded Multifactoral Adaptive Platform Trial for Community-Acquired Pneumonia [REMAP-CAP], Acute Inpatient Anti-Thrombotic Study [ACTIV-4a, and Anti-Thrombotic Therapy To Ameliorate Complications of COVID-19 [ATTACC]) investigated a novel primary end point of organ support free days (OSFD). It reached primary efficacy end point with OR of 1.27 (95% credible interval, 1.03 to 1.58) in favor of heparin-based anticoagulation.[9] The HEP-COVID trial diverted attention to the combined primary end point of thrombosis events (arterial and/or venous) and/or death. The HEP-COVID trial demonstrated benefit from therapeutic heparin-based anticoagulation with relative risk of 0.46 (95% CI, 0.27-0.81) in patients who were not critically ill with elevated D-dimers.[11] However, the between-group difference in combined end points was driven primarily by venous thrombotic events, not by mortality rate. In contrast to these "positive" trials, the Randomized Clinical Trial To Evaluate a Routine Full Anticoagulation Strategy in Patients with Coronavirus (COVID-19): COALIZAO ACTION trial investigated full-dose rivaroxaban vs standard-dose thromboprophylaxis and failed to meet its primary efficacy end point (time to death, duration of hospitalization, or duration of oxygen use) with a win ratio of 0.86 (95% CI, 0.59-1.22).[8] The Asessing Point-of-Care Influenza and Other Respiratory

TABLE 1] Antithrombotic Trials for Hospitalized Patients With COVID-19 Who Are Not Critically Ill

Trial	Elevated D-Dimer as Inclusion Criterion	Intervention and Duration	Primary Efficacy Outcome	Safety Outcome (ISTH)
ACTION[8] (N = 615; 576 not critically ill)	Yes (above the local ULN)	Therapeutic rivaroxaban for 30 days	Win ratio for death, duration of hospitalization, or oxygen use for first 30 days	Major or clinically relevant nonmajor bleeding (ISTH criteria)
Multiplatform randomized controlled trial[9] (N = 2,219 not critically ill)	No	Therapeutic LMWH for 14 days or recovery	Survival to hospital discharge and days free of organ support through first 21 days	Major bleeding (ISTH criteria)
RAPID[10] (N = 465)	Yes (above the local ULN)	Therapeutic heparin until 28 days or discharge or death	Composite of death or noninvasive mechanical ventilation or ICU admission.	Major bleeding (ISTH criteria)
HEP-COVID[11] (N = 253; 170 not critically ill)	Yes (> 4 times the ULN) or sepsis-induced coagulopathy ≥ 4	Therapeutic LMWH until hospital discharge	VTE or arterial thromboembolism or death in first 30 days	Major bleeding (ISTH criteria)

ISTH = International Society of Thrombosis and Haemostasis; LMWH = low-molecular-weight heparin; ULN = upper limit of normal.

Virus Diagnostics (RAPID) trial not only compared heparin-based full-dose anticoagulation with standard-dose thromboprophylaxis but also failed to achieve the primary composite end point of death, invasive mechanical ventilation, or admission to ICU with an OR of 0.69 (95% CI, 0.43-1.10).[10] To summarize these results, a recently conducted meta-analysis of RCTs with 3,305 patients who were not critically ill showed that, compared with standard-dose thromboprophylaxis, therapeutic anticoagulation was associated with significantly lower rates of VTE (risk ratio, 0.53; 95% CI, 0.34-0.83), significantly higher rates of any bleeding (risk ratio, 3.92; 95% CI, 1.92-8.00), major bleeding (risk ratio, 1.86; 95% CI, 1.04-3.33), and minor bleeding (risk ratio, 5.23; 95% CI, 1.54-17.77), and no significant reduction in all-cause death (risk ratio, 0.80; 95% CI, 0.40-1.61).[12]

There were several general limitations among these RCTs. Therapeutic anticoagulation regimens varied not only in terms of agents used (rivaroxaban, unfractionated, or low-molecular-weight) but also in total duration (2 weeks, 4 weeks, or until hospital discharge/death).[8-11] All the trials were open-label in design, which means that clinicians might have provided other aspects of background care differently in the control vs active treatment groups. These trial designs are also prone to confirmation bias, as clinicians might have been more inclined to order diagnostic tests in search for VTE [11] or provide organ support for patients in the control group.[9] The definition of critically ill vs not critically ill was not consistent among the trials.[8-11] Given the nature of the interventions, all RCTs had extensive exclusion criterion (60% to 98% of the screened patients were excluded), which makes it very hard to apply therapeutic benefit to a general non-ICU population without risking harm from full-dose anticoagulation. [8-11] Notably, despite very high rates of thrombosis in COVID-19, none of the RCTs beyond the HEP-COVID trial included VTE as a primary end point (Table 1).[13]

One of the largest RCTs that exclusively looked at noncritically ill patients is the multiplatform trial (ATTACC, ACTIV-4a, and REMAP-CAP). Although we recognize the efforts to conduct such a large-scale study during the pandemic, we have several reservations about the trial.[9] Authors postulate that potential benefits of therapeutic anticoagulation in patients who are not critically ill act early during the disease, but the REMAP-CAP trial included patients up to 14 days. Approximately 20% of patients who were in the therapeutic anticoagulation arm were not actually receiving therapeutic anticoagulation. There was an exhaustive list of exclusion criterion based on bleeding risk profile (even varied among three trial platforms: ATTACC, ACTIV-4a, and REMAP-CAP) further diminishing generalizability (ie, how well the outcomes can be expected to apply to other settings) to general ward populations. Only 62% and 36% of the patients in the multiplatform trials received steroids and remdesivir. One must consider whether the antiinflammatory effects of heparins might be less beneficial when this now current standard of care is provided. Primary outcome was OSFDs, evaluated on an ordinal scale that combined in-hospital death and the number of days free of cardiovascular or respiratory organ support up to day 21 among patients who survived to hospital discharge. Because most of the patients in the two treatment groups survived until hospital discharge without receipt of critical care-level organ support, the median value for OSFDs was 22 in both groups, and the study had to report the proportion of patients in each treatment group who survived until hospital discharge without receipt of organ support. In addition, organ support is a subjective, potentially problematic outcome. Each step on the scale is not necessarily of equivalent clinical significance. For example, moving from the clinical state of "low-flow oxygen" to "high-flow supplemental oxygen" is less important than moving to "requiring mechanical ventilation."

Similarly, the HEP-COVID trial has its own shortcomings. In the HEP-COVID trial, the absolute risk of VTE, arterial thrombosis, or death was very high (36%) in the control group.[11] Complication rates (mainly bleeding) were much lower than in routine practice, which generates consequent doubts about external validity.[11] Hence, the current results might not be applied to patients who are thought to be at lower risk for VTE or higher risk for bleeding.

In summary, after review of the literature: (1) Therapeutic anticoagulation significantly decreases rates of VTE during COVID, although its effects might be exaggerated because of confirmation bias in these open-labeled studies. (2) Although the trials enrolled COVID-19 at a very low risk for bleeding and were underpowered for safety, therapeutic anticoagulation significantly increases rates of major bleeding. (3) Current standards of care, including steroids/antiviral

therapies, were not used consistently in some studies, which raises concerns for external validity.

As a whole, the best evidence to date suggests that therapeutic anticoagulation likely benefits some patients who are moderately ill with COVID-19, but the concerns listed earlier urge us to avoid blindly following the guidelines and instead to consider carefully the risks and benefits for each individual patient.

References

1. Scardapane A, Villani L, Bavaro DF, et al. Pulmonary artery filling defects in COVID-19 patients revealed using CT pulmonary angiography: a predictable complication? *Biomed Res Int*. 2021;2021:8851736.
2. Scarduelli C, Inglese F, Beccaria M, et al. Pulmonary embolism in patients with severe COVID-19 treated with intermediate- to full-dose enoxaparin: a retrospective study. *Monaldi Arch Chest Dis*. 2021;91(3):10.
3. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in covid-19. *N Engl J Med*. 2020;383(2):120-128.
4. Tree JA, Turnbull JE, Buttigieg KR, et al. Unfractionated heparin inhibits live wild type SARS-CoV-2 cell infectivity at therapeutically relevant concentrations. *Br J Pharmacol*. 2021;178(3):626-635.
5. REMAP-CAP Investigators, ACTIV-4a Investigators, ATTACC Investigators, et al. Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. *N Engl J Med*. 2021;385(9):777-789.
6. INSPIRATION Investigators, Sadeghipour P, Talasaz AH, 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;325(16):1620-1630.
7. 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):1143-1163.
8. Lopes RD, de Barros E Silva PGM, Furtado RHM, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. *Lancet*. 2021;397(10291):2253-2263.
9. ATTACC Investigators, ACTIV-4a Investigators, REMAP-CAP Investigators, et al. Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. *N Engl J Med*. 2021;385(9):790-802.
10. Sholzberg M, Tang GH, Rahhal H, et al. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with covid-19 admitted to hospital: RAPID randomised clinical trial. *BMJ*. 2021;375:n2400.
11. Spyropoulos AC, Goldin M, Giannis D, et al. Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: the HEP-COVID randomized clinical trial. *JAMA Intern Med*. 2021;181(12):1612-1620.
12. Ortega-Paz L, Galli M, Capodanno D, et al. Safety and efficacy of different prophylactic anticoagulation dosing regimens in critically and non-critically ill patients with COVID-19: a systematic review and meta-analysis of randomized controlled trials. *Eur Heart J Cardiovasc Pharmacother*. 2021 Sept 14:vab070.
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*. 2021;159(3):1182-1196.

Rebuttal From Dr Tritschler et al

Tobias Tritschler, MD
Bern, Switzerland
Grégoire Le Gal, MD, PhD
Ottawa, ON, Canada
Shari Brosnahan, MD
New York, NY
Marc Carrier, MD
Ottawa, ON, Canada

We agree with the point made by Jimenez et al[1] that consideration of bleeding risk is essential when evaluating administration of therapeutic anticoagulation. However, although well-intended, "first do not harm" is not an appropriate argument. If taken literally, anticoagulation could never be administered because it is well-known that anticoagulation increases the risk of bleeding. Instead, physicians must balance benefits with potential risks. Their assertion that therapeutic dose heparin should not be implemented for any patient because some patients that do not meet the eligibility criteria of randomized controlled trials (RCT) may not benefit is hard to follow. In fact, current clinical practice guideline recommendations on the use of therapeutic dose anticoagulation in different patient populations are based on RCTs that all used stringent eligibility criteria (Table 1).[2] These eligibility criteria are

AFFILIATIONS: From the Department of General Internal Medicine (T. Tritschler), Inselspital, Bern University Hospital, University of Bern; the Department of Medicine (G. Le Gal and M. Carrier), Ottawa Hospital Research Institute, University of Ottawa; and the Division of Pulmonary, Critical Care, and Sleep Medicine (S. Brosnahan), New York University Langone Health System.

FINANCIAL/NONFINANCIAL DISCLOSURES: The authors have reported to *CHEST* the following: G. Le Gal has received honoraria from Aspen Pharma, Bristol-Myers Squibb, Pfizer, and Sanofi that go directly to his institutional research fund. M. Carrier has received research funding from Bristol-Myers Squibb, LEO Pharma, and Pfizer and honoraria for advisory board meetings from Bayer, Sanofi, Pfizer, LEO Pharma, Bristol-Myers Squibb, and Servier that that go directly to his institutional research fund. None declared (T. Tritschler and S. Brosnahan).

FUNDING/SUPPORT: T. T., G. L., and M. C. are investigators of the CanVECTOR Network; the Network receives grant funding from the Canadian Institutes of Health Research (Funding Reference: CDT-142654). G. L. and M. C. hold a Clinical Research Chair from the Department and Faculty of Medicine of the University of Ottawa. G. L. holds a Clinician-Scientist Award from the Heart and Stroke Foundation of Canada.

CORRESPONDENCE TO: Tobias Tritschler, MD; email: tobias.tritschler@insel.ch

DOI: https://doi.org/10.1016/j.chest.2022.01.039