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.

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

TABLE 1] Selected Recommendations From CHEST Guidelines and Expert Panel Reports and Selected Exclusion Criteria of the Randomized Controlled Trials That Were Considered for These Recommendations[2,5]

CHEST recommendation	In patients with VTE, we recommend apixaban, dabigatran, edoxaban, or rivaroxaban over vitamin K agonist as treatment-phase anticoagulant therapy.	In patients with acute VTE in the setting of cancer, we recommend an oral Xa inhibitor over low-molecular-weight heparin for the initiation and treatment phases of therapy.	In patients with acute illness hospitalized with COVID-19 who have a low risk of bleeding, we suggest therapeutic dose heparin over current standard-dose anticoagulant thromboprophylaxis.
Exclusion criteria of pertinent randomized controlled trials	Active bleeding or high risk for bleeding	Active bleeding or high risk for bleeding	Contraindication to anticoagulation
	Anemia	Anemia	Anemia
	Thrombocytopenia	Thrombocytopenia	Thrombocytopenia
	Uncontrolled hypertension	Uncontrolled hypertension	Uncontrolled hypertension
	Recent major surgery	Recent brain, spinal, or ophthalmic surgery	Recent major surgery
	Recent stroke	Intracranial malignancy	Recent stroke
	Recent intracranial bleeding	Nonsteroidal antiinflammatory drug/antiplatelet drug other than acetylsalicylic acid ≤ 100 mg	History of intracranial bleeding
	Recent intracranial surgery	Creatinine clearance < 30 mL/min	Recent intracranial surgery
	Intracranial neoplasm, cerebral aneurysm, or arteriovenous malformation	Acute hepatitis, chronic active hepatitis, liver cirrhosis, or alanine aminotransferase or aspartate aminotransferase > 3 times upper limit of normal	Intracranial malignancy, cerebral aneurysm, mass lesions of the CNS, or history of arteriovenous malformation
	Nonsteroidal antiinflammatory drug/antiplatelet drug other than acetylsalicylic acid ≤ 100 mg	Total bilirubin > 2 times upper limit of normal	Dual antiplatelet therapy
	Recent GI bleeding	Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current episode of VTE	Recent GI bleeding
	Active peptic ulcer	Pregnancy or breastfeeding	History of bleeding diatheses (eg, hemophilia)
	Recent acute coronary syndrome	Eastern Cooperative Oncology Group performance status of 3 or 4	Thrombolysis within the previous 7 d
	Creatinine clearance < 25-30 mL/min	Life expectancy < 6 mo	Presence of an epidural or spinal catheter
	Alanine aminotransferase or aspartate aminotransferase > 2 times upper limit of normal	Patient considered unsuitable for inclusion	Pregnancy
	Total bilirubin > 1.5 times upper limit of normal	…	Imminent death
	Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current episode of VTE	…	…
	Pregnancy or breastfeeding	…	…
	Life expectancy < 6 mo	…	…
	Patient considered unsuitable for inclusion	…	…

similar for the use of therapeutic heparin in patients with acute illness who are hospitalized with COVID-19. RCTs provide the best experimental design to study interventions; it is common to select participants who may gain the greatest benefit from the intervention. RCTs aim to provide evidence for relative treatment effectiveness under optimal conditions.[3] Such relative effects can often be applied to other populations, but physicians are required to estimate absolute risk differences that are based on relative benefits (or harms) and absolute baseline risks of an individual patient.[3]

Some of the alleged limitations of RCTs evaluating therapeutic dose heparin in patients with acute illness with COVID-19 need to be addressed.[1] First, the fact that 20% of participants who were allocated to the therapeutic heparin arm in the multiplatform trial received less than therapeutic dose anticoagulation is not a reasonable concern. If anything, nonadherence to the study protocol would have diluted treatment effects and biased effect measures towards the null. The same is true for inclusion of participants up to 14 days after admission in the REMAP-CAP trial. Of note, only 13% of the acutely ill patient population of the multiplatform trial was enrolled in REMAP-CAP. Second, although potential interaction by co-treatment is a potential concern, Jimenez et al[1] use this argument one-sided: What if therapeutic heparin diminishes the efficacy of other established treatments that were studied in patients who did not receive therapeutic heparin? The urgency to find effective treatments for a novel disease left investigators no choice but to study interventions simultaneously. Third, the assumptions that patients were kept on organ support because of the open-label trial design are unfounded, speculative, and unlikely, given the shortage of ICU beds during the pandemic. Furthermore, Jimenez et al[1] criticize that none of the trials included VTE in the primary outcome, except for the HEP-COVID trial. Ascertainment bias of thrombotic events was the exact reason that trials did not include VTE in the primary outcome or, when they did, performed screening ultrasonography as in the HEP-COVID trial. Finally, requiring supplemental oxygen was not part of the definition of organ support in the multiplatform trial. Furthermore, and as outlined in our editorial,[4] physicians can define the most relevant threshold of organ support-free days based on their individual preference because treatment effect measures of the multiplatform trial can be applied to any threshold of cumulative probabilities on the scale.

As for any treatment of COVID-19, uncertainties remain, given the rapid evolution of the pandemic, novel virus variants, and new preventive and therapeutic options. However, best current evidence from four RCTs support the use of therapeutic heparin in hospitalized patients with acute illness who are not at high risk of bleeding.

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. Jimenez D, Rali P, Doerschug K. Point: Should therapeutic heparin be administered to acutely-ill hospitalized patients with COVID-19? No. *Chest*. 2022;161(6):1448-1453.
2. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic therapy for VTE disease: second update of the CHEST Guideline and Expert Panel Report. *Chest*. 2021;160(6):e545-e608.
3. Harrell FE. Randomized clinical trials do not mimic clinical practice, thank goodness. 2020. Accessed December 24, 2021. https://www.fharrell.com/post/rct-mimic
4. Tritschler T, Le Gal G, Brosnahan S, Carrier M. Point: Should therapeutic heparin be administered to acutely ill hospitalized patients with COVID-19? Yes. *Chest*. 2022;161(6):1446-1448.
5. 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*. https://doi.org/10.1016/j.chest.2022.02.006

Rebuttal From Dr David Jimenez et al

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

We thank our colleagues for their thoughtful insights in describing the potential role of therapeutic heparin in patients with COVID-19 who are not critically ill.[1]

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.2022.01.038