

The Case for Therapeutic-Intensity Anticoagulation in Patients with COVID-19-Associated Moderate Illness

Adam Cuker, MD, MS¹

¹Department of Medicine and Department of Pathology & Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Address for correspondence Adam Cuker, MD, MS, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19014 (e-mail: adam.cuker@pennmedicine.upenn.edu).

Semin Thromb Hemost 2023;49:76–78.

Thrombosis is common in patients with coronavirus disease 2019 (COVID-19)-associated moderate illness. A systematic review and meta-analysis reported venous thromboembolism in 7.9% of such patients, often despite the use of standard thromboprophylaxis.¹ Microvascular thrombosis associated with COVID-19 may contribute to other complications including critical illness, respiratory failure, and death. At the same time, increasing the intensity of anticoagulation in hospitalized patients with COVID-19 comes at the cost of increased bleeding.² As such, there has been intense interest in establishing the optimal intensity of anticoagulation in patients with COVID-19-associated moderate illness.

Evidence

Several randomized controlled trials have compared therapeutic intensity with prophylactic-intensity anticoagulation in patients with COVID-19-associated moderate illness.^{3–7} The results of a meta-analysis of these trials, conducted as part of the American Society of Hematology (ASH) guideline on Anticoagulation in Patients with COVID-19, is summarized in ►Table 1.⁸ As the table shows, some outcomes are potentially improved (benefits) while others are worsened (harms) with therapeutic-intensity anticoagulation.

Benefits of Therapeutic-Intensity Anticoagulation

The point estimate of the absolute effect favors therapeutic intensity over prophylactic-intensity anticoagulation for several patient important outcomes (►Table 1). For example, therapeutic-intensity anticoagulation was associated

with an estimated 17 fewer (95% confidence interval [95% CI], 22 fewer to 9 fewer) patients with pulmonary embolism, four fewer (95% CI, seven fewer to four more) patients with deep vein thrombosis, 16 fewer (95% CI, 32 fewer to 11 more) patients requiring invasive mechanical ventilation, 15 fewer (95% CI, from 38 fewer to 17 more) patients requiring transfer to an intensive care unit, 26 fewer (95% CI, 48 fewer to 208 more) patients with multiorgan failure, and 20 fewer (95% CI, 52 fewer to 30 more) deaths per 1,000 patients.

Harms of Therapeutic-Intensity Anticoagulation

While the point estimate of absolute effect favors therapeutic-intensity anticoagulation for several outcomes, there is only one outcome (major bleeding) for which the point estimate favors prophylactic-intensity anticoagulation. Specifically, therapeutic-intensity anticoagulation was associated with nine more (95% CI, 0 to 26 more) major bleeds per 1,000 patients (►Table 1).

Balance of Benefits and Harms

The ASH guideline panel used prespecified decision thresholds to support judgments about the magnitude of an absolute effect estimate. Thresholds were based on outcome-specific utility values and results from a decision threshold survey. For example, the impact of an intervention on mortality was considered trivial, small, moderate, or large if the intervention resulted in <16, 16 to 30, 31 to 60, or >60 fewer deaths per 1,000 patients, respectively.⁸ The guideline panel's judgments about magnitude of effect for each outcome are provided in ►Table 1.

article published online
September 29, 2022

Issue Theme Maintaining Hemostasis and Preventing Thrombosis in COVID-19—Part IV; Guest Editors: Emmanuel J. Favaloro, PhD, FFSc (RCPA), Leonardo Pasalic, FRCPA, FRACP, PhD, and Giuseppe Lippi, MD

© 2022, Thieme. All rights reserved.
Thieme Medical Publishers, Inc.,
333 Seventh Avenue, 18th Floor,
New York, NY 10001, USA

DOI <https://doi.org/10.1055/s-0042-1756709>.
ISSN 0094-6176.

Table 1 Effect of therapeutic-intensity compared with prophylactic-intensity anticoagulation on key outcomes in patients with COVID-19-associated moderate illness

Outcome	Relative effect of therapeutic-intensity anticoagulation, OR (95% CI)	Absolute effect of therapeutic-intensity anticoagulation (95% CI)	Magnitude of effect ^a	Certainty of evidence ^b
Benefits				
Pulmonary embolism	0.42 (0.25–0.71)	17 fewer per 1,000 patients (from 22 fewer to nine fewer)	Trivial	Moderate
Deep vein thrombosis	0.56 (0.22–1.41)	Four fewer per 1,000 patients (from seven fewer to four more)	Trivial	Low
Invasive mechanical ventilation	0.69 (0.39–1.22)	16 fewer per 1,000 patients (from 32 fewer to 11 more)	Trivial	Low
ICU admission	0.80 (0.52–1.23)	15 fewer per 1,000 patients (from 38 fewer to 17 more)	Trivial	Low
Multiorgan failure	0.46 (0.03–6.59)	26 fewer per 1,000 patients (from 48 fewer to 208 more)	Small	Very low
Mortality	0.78 (0.43–1.40)	20 fewer per 1,000 patients (from 52 fewer to 30 more)	Small	Very low
Harms				
Major bleeding	1.79 (1.00–3.21)	Nine more per 1,000 patients (from 0 to 26 more)	Trivial	Moderate

Abbreviations: 95% CI, 95% confidence interval; ICU, intensive care unit; OR, odds ratio; STEMI, ST-elevation myocardial infarction.

Note: Evidence is derived from the American Society of Hematology guidelines.⁸ Outcomes for which the point estimate favors therapeutic-intensity anticoagulation are shown and those for which the point estimate favors prophylactic-intensity anticoagulation are also shown.

^aEffects were judged to be trivial, small, moderate, or large based on prespecified decision thresholds.

^bCertainty of evidence was rated according to GRADE criteria.

Aided by the use of decision thresholds, the harms of therapeutic-intensity anticoagulation were judged by the ASH guideline panel to be trivial, driven by a trivial increase in major bleeding. The benefits of therapeutic-intensity anticoagulation were judged to be small, driven by small effects on mortality and multiorgan failure and additive trivial effects on pulmonary embolism, deep vein thrombosis, invasive mechanical ventilation, and admission to the intensive care unit, though it should be acknowledged that at least some of these outcomes (e.g., invasive mechanical ventilation, admission to the intensive care unit, mortality) are likely to be overlapping. Overall, the guideline panel judged the benefits of therapeutic-intensity anticoagulation to outweigh the harms.⁸

Recommendation

Based on the balance of benefits and harms, I agree with the ASH guideline panel’s conditional (weak) recommendation in favor of therapeutic intensity over prophylactic-intensity anticoagulation in patients with COVID-19-associated moderate illness.⁸ By definition, a “conditional” recommendation applies to a majority of patients, but acknowledges that the intervention may not be appropriate in a substantial minority.⁹ An individualized risk assessment is therefore paramount. While therapeutic-intensity anticoagulation is appropriate for most patients with COVID-19-associated moderate illness, lower-intensity therapy may be preferred in patients judged to be at low thrombotic risk and/or high bleeding risk.

Other organizations have issued similar guidance. The U.S. National Institutes of Health COVID-19 Treatment Guideline panel recommends therapeutic-intensity heparin in patients with COVID-19-related moderate illness who have a D-dimer above the upper limit of normal, require low-flow oxygen, and have no increased bleeding risk.¹⁰ Draft guidelines of the International Society on Thrombosis and Haemostasis note that therapeutic-dose heparin is preferred over lower-intensity anticoagulation in select patients with COVID-19-associated moderate illness.¹¹ Updated guidance from the Anticoagulation Forum suggests therapeutic-intensity heparin in patients with COVID-19-associated moderate illness who are at increased risk of disease progression or thromboembolism and who are not at high risk for bleeding.¹²

Limitations

Several limitations and caveats to my argument require acknowledgment. First, my recommendation applies only to the management of patients with COVID-19-associated moderate illness during hospitalization. It is not intended to apply to patients with COVID-19-associated critical illness, ambulatory outpatients with COVID-19, patients with COVID-19 who have been discharged from the hospital, or patients hospitalized for a different reason who incidentally test positive for SARS-CoV2 infection. Second, despite the availability of data from several randomized controlled trials, there remains significant uncertainty in the evidence

(► **Table 1**), owing primarily to risk of bias and imprecision (as evidenced by the wide 95% CIs in ► **Table 1**). Any clinical recommendation on this question is subject to the limitations inherent in the underlying evidence. Third, major bleeding may be underestimated in the clinical trials due to exclusion of patients at high bleeding risk. Fourth, for simplicity, I limited my argument to the comparison between prophylactic and therapeutic-intensity anticoagulation, and did not discuss intermediate-intensity therapy. There is a paucity of evidence on the use of intermediate-intensity anticoagulation in patients with COVID-19-associated moderate illness. However, intermediate-intensity anticoagulation was not superior to prophylactic-intensity anticoagulation in two clinical trials that enrolled hospitalized patients with COVID-19, most of whom had COVID-19-associated critical illness.^{13,14} Fifth, and perhaps most importantly, there have been dramatic changes in circulating viral variants, the affected patient population, and non-anticoagulant therapies for prevention and treatment of COVID-19 over the course of pandemic. Much of the evidence summarized in ► **Table 1** was collected during earlier phases of the pandemic and the extent to which it is applicable to current practice is unknown.

Conclusion

Despite the aforementioned limitations, the evidence summarized in ► **Table 1** represents the best evidence available and suggests that the benefits of therapeutic-intensity anticoagulation outweigh the harms for most patients with COVID-19-associated moderate illness.

Conflict of Interest

A.C. has served as a consultant for Synergy and the New York Blood Center and has received authorship royalties from UpToDate. He is a member and former chair of the American Society of Hematology guideline panel on anticoagulation in patients with COVID-19.

References

- Nopp S, Moik F, Jilma B, Pabinger I, Ay C. Risk of venous thromboembolism in patients with COVID-19: a systematic review and meta-analysis. *Res Pract Thromb Haemost* 2020;4(07):1178–1191
- Jiménez D, García-Sánchez 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(03):1182–1196
- Marcos-Jubilar M, Carmona-Torre F, Vidal R, et al; BEMICOP Investigators. Therapeutic versus prophylactic bempiparin in hospitalized patients with nonsevere COVID-19 pneumonia (BEMICOP study): an open-label, multicenter, randomized, controlled trial. *Thromb Haemost* 2022;122(02):295–299
- 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(2400):n2400
- Lawler PR, Goligher EC, Berger JS, et al; ATTACC Investigators ACTIV-4a Investigators REMAP-CAP Investigators. Therapeutic anticoagulation with heparin in noncritically ill patients with COVID-19. *N Engl J Med* 2021;385(09):790–802
- 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
- Lopes RD, de Barros E Silva PGM, 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
- Cuker A, Tseng EK, Nieuwlaat R, et al. American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: January 2022 update on the use of therapeutic-intensity anticoagulation in acutely ill patients. *Blood Adv* 2022;bloodadvances.2022007561
- 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(03):872–888
- National Institutes of Health. The COVID-19 Treatment Guidelines Panel's statement on anticoagulation in hospitalized patients with COVID-19; 2022. Accessed 31 May 2022 at: <https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-anticoagulation-in-hospitalized-patients/>
- ISTH draft guidelines for antithrombotic treatment in COVID-19. Accessed 31 May 2022 at: https://cdn.ymaws.com/www.isth.org/resource/resmgr/guidance_and_guidelines/covid19/covid-19-draft_for_comment.pdf
- Barnes GD, Burnett A, Allen A, et al. Thromboembolic prevention and anticoagulant therapy during the COVID-19 pandemic: updated clinical guidance from the anticoagulation forum. *J Thromb Thrombolysis* 2022;54(02):197–210
- 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;325(16):1620–1630
- Perepu US, Chambers I, Wahab A, et al. Standard prophylactic versus intermediate dose enoxaparin in adults with severe COVID-19: A multi-center, open-label, randomized controlled trial. *J Thromb Haemost* 2021;19(09):2225–2234