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

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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. 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. 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. 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. 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. The guideline panel's judgments about magnitude of effect for each outcome are provided in Table 1.
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.  

**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. By definition, a "conditional" recommendation applies to a majority of patients, but acknowledges that the intervention may not be appropriate in a substantial minority. 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. 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. 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.

**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.
associated critical illness. Anticoagulation in two clinical trials that enrolled hospitalized patients with COVID-19-associated critical illness was not superior to prophylactic-intensity anticoagulation in patients with COVID-19. There is a paucity of evidence on the use of intermediate-intensity anticoagulation in patients with 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