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CHEST

POINT:
Should Therapeutic Heparin Be Administered to Acutely Ill Hospitalized Patients With COVID-19? Yes

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

Many factors contribute to increased mortality rates from COVID-19, including coagulopathy and thrombosis.[1] It has been hypothesized therefore that the administration of therapeutic anticoagulation, particularly therapeutic heparin that potentially has pleiotropic effects, may improve outcomes in patients with COVID-19. To date, four randomized controlled trials (RCT) have assessed the efficacy and safety of therapeutic anticoagulation compared with thromboprophylaxis in hospitalized patients with COVID-19.[2-6] Combined findings from these RCTs indicate that, in acutely ill hospitalized patients with COVID-19, therapeutic heparin (unfractionated heparin [UFH] or low-molecular-weight heparin [LMWH]) increases organ support-free days (OSFD), and reduces the probability of VTE and 28-day mortality or the need for respiratory support or invasive mechanical ventilation, at the cost of an increased risk of major bleeding. However, the absolute risks of major bleeding in patients who received therapeutic anticoagulation were low (ie, 1% to 2%), and most adjudications for major bleeding events were based on requirement for RBC transfusion only.[2-4] This benefit of therapeutic heparin was not found in critically ill patients or those patients who were treated with non-heparin anticoagulants.[5,6] In this issue of *CHEST*, an updated evidence-based expert panel guidance statement suggests therapeutic heparin (UFH or LMWH) over current standard-dose thromboprophylaxis in acutely ill hospitalized patients with COVID-19 who have a low risk of bleeding.[7] Although several trials are ongoing and uncertainties remain, we believe that the available evidence supports this recommendation for several reasons.

Although developed as an anticoagulant, negatively charged heparin binds close to 250 proteins other than antithrombin and can modulate their biologic properties.[8] These pleiotropic effects must be considered when an effort is made to interpret the results of RCTs that evaluate anticoagulant interventions in acutely ill hospitalized patients with COVID-19. Potential effects include antiinflammatory and antiviral effects. In SARS-CoV-2, heparin binding results in a conformational change within the viral spike protein, which alters the virus's ability to enter host cells through the angiotensin-converting enzyme 2 receptor.[9] Heparin binds chemokines, cytokines, and complement factors and thereby prevents these factors from exhibiting their proinflammatory effects.[10] It also appears to reduce the production of cytokines and adhesion molecules by blocking nuclear transcription factor-κB.[10,11] Furthermore, heparin may interfere with leukocyte adhesion to endothelial cells and, consequently, may

ABBREVIATIONS: LMWH = low-molecular-weight heparin; RCT = randomized controlled trial; OSFD = organ support-free days; UFH = unfractionated heparin

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.

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

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reduce endothelial dysfunction and vascular injury.[10,11] Finally, heparin inhibits thrombin formation; thrombin is proinflammatory and increases endothelial permeability.[11] Although the specific impact of these mechanisms in acutely ill hospitalized patients with COVID-19 must be better understood, it would not be the first time that findings from clinical trials advance our understanding of pathophysiologic and pharmacologic mechanisms.

COVID-19 is not the first inflammatory disease whose outcome is improved by heparin. Most notably, evidence suggests that heparin may reduce mortality rates in sepsis. A meta-analysis of six RCTs showed that heparin at different doses, compared with placebo or usual care, was associated with a 12% relative risk reduction of death (risk ratio, 0.88; 95% CI, 0.77 to 1.00; I^2, 0%).[12] These findings are supported by a retrospective propensity-score matched study of 695 patients with septic shock.[13] Compared with a control group in which 74% of patients received thromboprophylaxis, early IV therapeutic heparin appeared to be associated with lower 28-day mortality rate (hazard ratio, 0.85; 95% CI, 0.73 to 1.00). These findings highlight the potential benefits of therapeutic heparin in patients with infectious diseases that are associated with significant inflammatory states.

In the pre-COVID era, most trials and clinical practice guidelines focused on anticoagulants for the prevention of VTE and balanced potential benefits with the increased risk of bleeding. Several trials that evaluated anticoagulation in patients with COVID-19 went beyond these traditional aims of the prevention of macro vessel thromboembolism, and incorporated outcomes that are reflective of disease severity or progression, such as OSFD or organ support as a component of the primary composite outcome. These outcomes are not only relevant to patients but also to health care systems, particularly during a pandemic when the availability of ICU beds is limited. In contrast to organ support (days), the choice of OSFD or organ support combined with death allows trialists to account for death as a competing event. However, understanding of outcomes like OSFD can be challenging. OSFD is evaluated on an ordinal scale according to the number of days free from organ support, in which death is assigned the worst score (eg, -1). Each category of the scale has an individual (eg, OSFD = 5) and cumulative (eg, OSFD ≥5) probability. The primary effect measure in the multiplatform RCT was the OR of a cumulative probability in the intervention group compared with the control group (eg, cumulative probability of OSFD ≥5 is higher for therapeutic heparin than usual-care or thromboprophylaxis). Because it has been proven statistically that the same effect applied to the cumulative probabilities on every level (eg, the OR for OSFD ≥5 was the same as the OR for OSFD ≥15), an OR for the entire scale could be computed that can be applied to any threshold of cumulative probabilities on the scale. To support understanding of their findings with the use of a more clinician-intuitive outcome, prespecified analyses were conducted for survival without organ support. Results were near identical when this dichotomous outcome was used (adjusted OR, 1.27 vs 1.30).[2] The RAPID trial that evaluated therapeutic heparin in acutely ill hospitalized patients with COVID-19 also reported a very similar treatment effect for the composite of organ support or death,[3] which strongly supports the conclusion that therapeutic heparin reduces mortality rates or the need for organ support.

To design a meaningful study successfully, several elements (such as, anticipated recruitment rate, outcome rate, and treatment effect size) need to be considered. However, at the beginning of the pandemic, trialists were faced with many uncertainties. Although some have used more traditional designs with a frequentist approach to statistical inference and prespecified sample sizes, others have used innovative designs that included Bayesian adaptive trials. The latter provided the needed flexibility to function in a rapidly evolving pandemic and addressed many of the problematic uncertainties. However, clinicians are now also confronted with the challenge of understanding this more complex method to incorporate trial findings confidently into clinical practice. We highlight two features of the multiplatform RCT that are crucial to understand the choice for specific design elements and their implications. First, an adaptive trial design permits enrollment of participants until a prespecified conclusion is reached. Unlike premature termination in trials with traditional design, stopping the trial when reaching a prespecified threshold for either superiority or futility is an indispensable component of the trial and prevents over- or underpowering. Second, response-adaptive randomization alters the randomization allocation ratio to favor beneficial interventions that are based on the results of adaptive interim analysis. Benefits of response-adaptive randomization are to provide not only a potentially beneficial treatment to a higher proportion of patients but also to increase acceptance of the study by both patients and clinicians. However, without appropriate

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.

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