

Finding the Optimal Thromboprophylaxis Dose in Patients With COVID-19

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From the early days of the COVID-19 pandemic, a distinct coagulation disturbance of SARS-CoV-2 infection has been recognized. This thrombo-inflammatory phenotype, characterized by endotheliopathy, hypercoagulability, and coagulation activation, results in an increased risk of thromboembolic events.¹⁻³ Initial observational cohort studies described high rates of venous thromboembolism (VTE) in critically ill patients with COVID-19, despite consistent use of standard prophylactic doses of heparin-based anticoagulants.⁴ Additionally, published autopsy series described microthrombosis in multiple organs.⁵ These reports led to the rapid publication of expert guidance statements that advocated consideration of escalated thromboprophylaxis doses in critically ill patients with COVID-19,^{6,7} pending the results of randomized clinical trials evaluating different doses. Escalated thromboprophylaxis can take the form of empirical therapeutic-dose anticoagulation or, alternatively, intermediate-dose anticoagulation (generally 0.5 mg/kg of enoxaparin twice daily or 1 mg/kg of enoxaparin once daily [or an equivalent]) in an attempt to better balance thrombotic and bleeding risks. Although major bleeding is less common in patients with COVID-19, it has been associated with substantial morbidity.⁸

In this issue of *JAMA*, Sadeghipour and colleagues⁹ report the results of a multicenter randomized clinical trial of intermediate-dose vs standard-dose heparin-based thromboprophylaxis in critically ill patients with COVID-19. Among 562 patients included in the primary analysis, the authors found no significant difference in the primary efficacy outcome (a composite of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality within 30 days of enrollment) or in the main safety outcomes (major bleeding and severe thrombocytopenia) between the 2 groups. The primary efficacy outcome occurred in 126 patients (45.7%) in the intermediate-dose group and 126 patients (44.1%) in the standard-dose prophylaxis group, death occurred in 43.1% of patients vs 40.9% of patients, VTE occurred in 3.3% of patients vs 3.5% of patients, and major bleeding occurred in 2.5% of patients vs 1.4% of patients. Severe thrombocytopenia, defined as a platelet count less than $20 \times 10^3/\mu\text{L}$, occurred in 6 patients in the intermediate-dose group vs 0 patients in the standard-dose group. In addition, there was no benefit of intermediate-dose thromboprophylaxis in any of the prespecified subgroups.

Notably, the trial, which employed a 2×2 factorial design, also evaluated the effect of statin therapy in addition to thromboprophylaxis dose. The authors reported that there was

no interaction between anticoagulation intensity and statin use for the primary outcomes, and therefore present the results of testing the anticoagulation hypothesis independently of the statin hypothesis.

When considering these important findings, which challenge many current expert guidance statements, several issues are worthy of discussion. One issue is the overall low thrombotic event rate reported in both study groups, raising the possibility of a significant number of uncaptured events. VTE rates reported in clinical COVID-19 studies have varied considerably, with higher rates generally reported in early investigations and in studies that used universal VTE screening and lower rates reported in more recent investigations and in studies that did not screen for VTE. Although the relevance of clinically occult VTE in these patients is not known, the trial by Sadeghipour et al⁹ did not use universal screening for VTE.

As an example of how important the difference in rates of reported thrombotic events might be, 2 small studies that used universal deep vein thrombosis screening with lower extremity ultrasonography found deep vein thrombosis rates approaching 70% to 80% in critically ill patients with COVID-19,^{10,11} compared with the 2.1% deep vein thrombosis event rate reported in the trial by Sadeghipour et al.⁹ The arterial thrombotic event rate was similarly low; there were no type I myocardial infarctions or peripheral arterial thrombotic events in any study participants and only 1 ischemic stroke event in each study group. Despite these low thrombotic event rates, the composite primary outcome measure, which was driven primarily by all-cause mortality, found no difference between the 2 groups. The possibility for missed thrombotic events notwithstanding, there did not appear to be any effect of higher-dose anticoagulation on the mechanisms leading to death in these patients.

Another issue is the use of a standardized low-molecular-weight heparin (LMWH) thromboprophylaxis dosing protocol adjusted for weight and creatinine clearance (detailed in eTables 1-3 of Supplement 3 in the article by Sadeghipour et al⁹). Obesity is one of the strongest predictors of severe disease and mortality in COVID-19¹² and is a well-known risk factor for thromboembolic complications generally.¹³ Although it is standard care to adjust LMWH doses for reduced kidney function, dose adjustment for weight (both in patients with and without COVID-19) is variably instituted from one center to another and remains controversial.¹⁴ The authors escalated the enoxaparin dose for patients who weighed at least 120 kg or who had a body mass index of at least 35 to 0.6 mg/kg twice daily in the intermediate-dose group and 40 mg twice daily in

the standard-dose group. Therefore, describing the trial as a comparison between intermediate-dose and standard-dose thromboprophylaxis is somewhat of an oversimplification; the authors actually compared 2 weight-based LMWH thromboprophylaxis dosing protocols. For the clinician practicing at a center that does not routinely use weight-based thromboprophylaxis dosing, this is a critical distinction.

The findings of this trial add to the growing body of evidence against dose-escalated thromboprophylaxis in critically ill patients with COVID-19. A 2021 large observational cohort study of 2809 critically ill patients with COVID-19 from 67 centers in the US found no benefit of therapeutic-dose anticoagulation initiated within 2 days of intensive care unit (ICU) admission compared with standard-dose thromboprophylaxis.⁸ A multiplatform randomized clinical trial, a collaboration between 3 independent international trial platforms (ATTACC, REMAP-CAP, and ACTIV-4) evaluating the safety and efficacy of therapeutic-dose vs standard-dose thromboprophylaxis in hospitalized patients with COVID-19, recently reported interim results (available from a National Heart, Lung, and Blood Institute website¹⁵). Among patients with severe illness (ie, those admitted to an ICU and receiving organ support, such as invasive medical ventilation or vasopressors), enrollment was halted for futility in December 2020 by the 3 trial data and safety monitoring boards after 1123 patients had been enrolled. An interim analysis in this group showed no improvement in organ support-free days in patients treated with therapeutic-dose anticoagulation and a high probability for harm with this intervention.

Conversely, enrollment of patients with moderately severe illness (hospitalized but not initially requiring ICU care or organ support) was halted in January 2021 after 1772 patients had been enrolled after an interim analysis found that therapeutic-dose anticoagulation was more effective than standard thromboprophylaxis with regard to organ support-free

days, regardless of baseline D-dimer level.¹⁵ However, the final analysis from this multiplatform randomized trial is needed to confirm these interim findings and to consider their potential influence on clinical practice. Evaluation of prespecified subgroup analyses in the final results will be important to know whether the findings in certain populations differ from the full study population, insofar as this is still possible given a lower-than-anticipated number of total enrolled patients due to premature halting of the study.

Although expert guidance to date has focused on dose escalation of thromboprophylaxis in critically ill patients, perhaps paradoxically, moderately ill patients could be the population most likely to benefit, such as those patients admitted to the hospital but not requiring ICU-level care or organ support. Substantial organ damage has already occurred by the time organ support is required, and therefore heparin-based anticoagulation during an earlier phase of the disease could mitigate microthrombotic and macrothrombotic complications before they occur or potentially exert a meaningful protective anti-inflammatory effect.¹⁶

Therefore, with an important contribution from the trial performed by Sadeghipour and colleagues,⁹ the preponderance of high-quality evidence at this time supports use of standard-dose thromboprophylaxis, not dose escalation, in critically ill patients with COVID-19. However, pending the publication of final results from the ATTACC, REMAP-CAP, and ACTIV-4a multiplatform trial confirming the interim report, escalated thromboprophylaxis could be appropriate in moderately ill hospitalized patients with COVID-19 while balancing known comorbidities and bleeding risks. Additional important questions pertaining to thromboprophylaxis in COVID-19 remain under active investigation, including the utility of postdischarge thromboprophylaxis and the effect of outpatient thromboprophylaxis for patients with mild COVID-19 not requiring hospital admission.

ARTICLE INFORMATION

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