Invited Commentary

Anticoagulant Therapy in Patients Hospitalized With COVID-19

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Since the early days of the COVID-19 pandemic, clinicians have reported altered coagulation in hospitalized patients, with both thrombotic as well as hemorrhagic events. Several mechanisms for the increased thrombotic risk have been identified, but many patients who are hospitalized with SARS-CoV-2 infection appear to develop a cytokine storm, leading to hyperinflammation, endothelial disruption, platelet activation, and a coagulopathy, contributing to the hemostatic and thrombotic complications.[1] Early reports also suggested that standard prophylactic doses of anticoagulant therapy appeared to be inadequate for preventing thrombotic events in hospitalized patients.[2] Data from several large trials recently published give us more insight into treatment strategies for hospitalized patients with COVID-19.[3-7] In this issue of *JAMA Internal Medicine*, data from the HEP-COVID study[8] contribute additional evidence in the role of therapeutic vs prophylactic heparin dosing for thromboprophylaxis in patients hospitalized for COVID-19–related illnesses.

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The HEP-COVID study[8] randomized hospitalized adult patients with COVID-19 and evidence of coagulopathy, defined as a D-dimer level greater than 4 times the upper limit of normal or a sepsis-induced coagulopathy score of 4 or higher, to (1) standard prophylactic or intermediate-dose low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) or (2) therapeutic-dose LMWH throughout hospitalization. They found that the primary efficacy outcome of venous thromboembolism (VTE), arterial thromboembolism (ATE), or all-cause mortality was significantly reduced with therapeutic-dose anticoagulation in the non–intensive care unit (ICU) patients, but this benefit was not observed in the ICU patients. There was no significant difference in major bleeding between groups in either the non-ICU or ICU strata, although confidence intervals were wide.

This study confirms and builds on the observations recently reported by the ATTACC, ACTIV-4a, and REMAP-CAP Investigators in 2 studies investigating therapeutic-dose anticoagulation compared with "usual-care" thromboprophylaxis in hospitalized patients with COVID-19.[5,6] The primary outcome in these 2 studies was defined as organ-support-free days, defined by an ordinal scale combining in-hospital death and the number of days free of cardiovascular or respiratory organ support. In noncritically ill patients, defined as not needing respiratory or cardiovascular support in an ICU (oxygen delivered by high-flow nasal cannula, noninvasive or invasive mechanical ventilation, or the use of vasopressors or inotropes), therapeutic dosing increased the probability of survival to hospital discharge and reduced the use of cardiovascular or respiratory organ support compared with usual-care thromboprophylaxis.[5] Similar to the observation by the HEP-COVID Investigators, therapeutic-dose heparin was found to have no benefit in patients with severe COVID-19, defined as needing at least 1 of the measures stated above, and was associated with a higher incidence of bleeding.[6]

In contrast, the RAPID Trial Investigators[7] found that therapeutic-dose anticoagulation with LMWH or UFH in moderately ill hospitalized patients with COVID-19 and an elevated D-dimer level did not significantly reduce the primary outcome of ICU admission, noninvasive or invasive mechanical ventilation, or death up to 28 days compared with a prophylactic dose of LWMH or UFH. However, therapeutic-dose anticoagulation was associated with a decrease in the secondary outcome of death at 28 days in this study, and there was no increase in major bleeding compared with prophylactic anticoagulation.[7] In the ICU patient population, the INSPIRATION Investigators[3] reported that an intermediate dose of LMWH provided no benefit over standard prophylactic-dose anticoagulation in the prevention of the composite outcome of VTE, ATE, treatment with extracorporeal membrane oxygenation, or mortality within 30 days.

The beneficial effect of therapeutic anticoagulation in hospitalized patients with COVID-19 using heparin does not appear to extend to other classes of anticoagulant therapy. The ACTION study[4] demonstrated that hospitalized patients with COVID-19 who received therapeutic anticoagulation with rivaroxaban (clinically stable patients) or enoxaparin (unstable patients) compared with prophylactic anticoagulation with LMWH or UFH did not improve the primary efficacy outcome of a hierarchical analysis of time to death, duration of hospitalization, or duration of supplemental oxygen to day 30. Therapeutic anticoagulation was associated with increased bleeding in both clinically stable and clinically unstable patients.

While there are a number of similarities across these studies, there are differences that need to be taken into consideration. The criteria for who was considered to be noncritically ill (also referred to as moderately ill, or non-ICU setting) in contrast to critically ill (severely ill, or ICU setting) differed across the studies. The composite primary outcomes also differed across the studies, although the individual components of the composite outcomes frequently overlapped. All of the studies included an elevated D-dimer level as either part of the inclusion criteria for participation in the study or in the final analysis of the outcome data, although the cutoff for an elevated D-dimer level varied between the studies (from above the upper limit of the normal range to greater than 4 times the upper limit).

Despite the methodological differences, these studies help us draw 3 important conclusions concerning the efficacy and safety of anticoagulant therapy in hospitalized patients with COVID-19. First, the data support that therapeutic anticoagulation with LMWH or UFH is associated with improved outcomes in hospitalized patients with COVID-19 who are not critically ill or in the ICU setting, particularly those patients with

elevated D-dimer levels. Second, the data also indicate that patients who are critically ill and/or in the ICU do not benefit from therapeutic anticoagulation and manifest an increased risk for bleeding compared with patients receiving prophylactic-dose anticoagulation. The beneficial effect of therapeutic anticoagulation is diminished and the risk of hemorrhage is increased in patients with progressively more severe disease, potentially related to hyperinflammation, endothelial disruption, platelet activation, and coagulopathy. Third, none of the studies would support the use of an anticoagulant administered at a dose between prophylactic and therapeutic, whether for ICU or non-ICU patients.

The research community has quickly developed and modified guidelines for anticoagulation in patients hospitalized with COVID-19 based on the data. However, these studies highlight areas where more investigation is needed. The role of antiplatelet therapy remains to be determined as well as other therapies that might modulate the prothrombotic characteristics of SARS-CoV-2 in hospitalized patients. The distinction between moderate and severe disease can be better defined, specifically when it comes to oxygen requirement. In addition, the transition of patients between the ICU and non-ICU settings represents a time when the intensity of anticoagulant therapy needs to be revisited. Lastly, whether a course of extended anticoagulation following discharge from the hospital, particularly for patients who were hospitalized with a more severe clinical course of COVID-19, or who have persistently elevated D-dimer levels, remains to be determined.

ARTICLE INFORMATION

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