The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 has taken the world by storm. As of May 4, 2020, there are >1.2 million confirmed cases in the United States and >66,000 deaths. Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is common in seriously ill patients with infection. Early reports suggested a VTE rate of approximately 27% in critically ill patients hospitalized with COVID-19. This high rate of VTE, and, in particular, PE, is consistent with what has been reported in critically ill patients with pneumonias caused by other viruses, including H1N1 pneumonia and severe acute respiratory syndrome.

Key markers of inflammation and coagulopathy have been associated with morbidity and increased mortality in hospitalized patients with COVID-19, suggesting that either the severe acute respiratory syndrome coronavirus 2 infection itself or the cytokine storm produced by the hyperinflammatory state induces a prothrombotic state. COVID-19 is associated with a coagulopathy characterized by mild thrombocytopenia, high levels of d-dimer and fibrin(ogen) degradation products, slight prolongation of the prothrombin time, and elevated levels of fibrinogen and factor VIII. Although the drivers of this coagulopathy are uncertain, overexpression of tissue factor, endothelial dysfunction, and activation of the contact and complement systems are potential candidates. In patients dying of COVID-19, multiple thrombi are found in the vessels of the lungs, and those of the liver, heart, and kidneys. This hypercoagulable state may explain the high rate of VTE reported in patients with COVID-19 despite anticoagulant thromboprophylaxis, and the acute kidney injury, myocardial infarction, ischemic stroke, and arterial occlusion, as well, that have been described in these patients.

In this issue of Circulation, case series of hospitalized patients with COVID-19 reported from China by Zhang et al and Ren et al and from France by Poissy et al highlight the high prevalence of VTE in this population. Consistent with earlier reports of high VTE rates in critically ill patients with COVID-19, the prevalence of PE in 107 consecutive patients in the intensive care unit was 20.6% in the study by Poissy et al. Of the 22 patients with documented PE, 20 were receiving anticoagulant thromboprophylaxis at the time of PE diagnosis. When 48 patients in an intensive care unit with documented COVID-19 were screened with compression ultrasonography of the lower extremities, Ren et al reported a prevalence of asymptomatic DVT of 85.4%, with 75% localized to the calf veins. In the patients with DVT, all but 1 were receiving low-molecular-weight heparin thromboprophylaxis. Likewise, with compression ultrasound screening of 143 hospitalized patients with COVID-19 on medical wards, Zhang et al found DVT in 46.1% overall, of which the location is...
Ren et al.\textsuperscript{9} also suggests that emboli from lower extremity DVT also contribute to the burden of PE. This concept of an in situ thrombosis is supported by a recent case series of autopsy reports from patients who have severe acute respiratory syndrome coronavirus 2 in the United States, which found an unusually high degree of microthrombi in the lung arteries, suggesting that a thrombotic microangiopathic process may also contribute to coagulopathy associated with COVID-19.\textsuperscript{14} Nonetheless, the high prevalence of asymptomatic DVT in hospitalized patients with COVID-19 reported by Zhang et al.\textsuperscript{8} and Ren et al.\textsuperscript{8} also suggests that emboli from lower extremity DVT also contribute to the burden of PE.

Third, the high rates of VTE events in hospitalized patients with COVID-19, especially in studies of critically ill patients, occur despite standard anticoagulant thromboprophylaxis with unfractionated heparin or low-molecular-weight heparin (47/48 in the study of Poissy et al.\textsuperscript{10}) and need for hospitalization or advanced care. The most pressing clinical question is whether escalated doses of unfractionated heparin or low-molecular-weight heparin (including intermediate to treatment doses) offer benefits over prophylactic doses in reducing the morbidity and mortality in hospitalized patients with COVID-19, in particular, those who are critically ill. To address this question, several randomized trials have been recently initiated. These trials are comparing the effect of either intermediate or treatment doses of unfractionated heparin or low-molecular-weight heparin with the standard prophylactic dose of heparin on mortality and the rates of thromboembolic events in hospitalized patients with COVID-19. Such trials include COVID-HEP (Preventing COVID-19 Complications With Low- and High-Dose Anticoagulation; URL: http://www.clinicaltrials.gov. Unique identifier: NCT04345848), IMPROVE (Intermediate or Prophylactic-Dose Anticoagulation for Venous or Arterial Thromboembolism in Severe COVID-19; URL: http://www.clinicaltrials.gov. Unique identifier: NCT04367831), COVI-DOSE (Weight-Adjusted Venous or Arterial Thromboembolism in Severe COVID-19; URL: http://www.clinicaltrials.gov. Unique identifier: NCT04373707), X-Covid 19 (Comparison of Two Doses of Enoxaparin for Thromboprophylaxis in Hospitalized COVID-19 Patients; URL: http://www.clinicaltrials.gov. Unique identifier: NCT04366960), and HEP-COVID (Full Dose Heparin vs Prophylactic Or Intermediate Dose Heparin in High Risk COVID-19 Patients; URL: https://www.clinicaltrials.gov. Unique identifier: NCT04401293).

What does the future hold for understanding the coagulopathy, and, in particular, the VTE, associated with COVID-19? With the growing burden of the COVID-19 pandemic, a better understanding of the coagulopathy, and new approaches to its management are required. Better estimates of the prevalence, predictors, and outcomes of VTE in hospitalized patients with COVID-19 are needed using high-quality patient-level data, preferably from multiple institutions. Such data can be used to create a risk prediction model for VTE in hospitalized patients with COVID-19 using clinical and laboratory-based variables. Also needed are estimates of the thrombotic risk in the immediate period after patients with COVID-19 are discharged from the hospital. Such information will help to determine whether extended thromboprophylaxis should be prescribed at the time of hospital discharge, especially because there are data to suggest that elevated d-dimers, which remain a key component in predicting poor outcomes in these patients, have previously been shown to predict a high VTE risk population of medically ill patients that benefit from extended thromboprophylaxis with a direct oral anticoagulant.\textsuperscript{15} Information on the thrombotic risk in the prehospitalization period, in particular, in high-risk groups such as those who are elderly with immobility and known cardiovascular disease, will help to inform whether primary thromboprophylaxis in outpatients with severe COVID-19 may reduce the thrombotic burden and need for hospitalization or advanced care.
in COVID-19. Inflammation and coagulation are intimately linked. Consequently, the suppression of inflammation with inhibitors of interleukin-1 or interleukin-6, use of interferon-γ or administration of modulators of the janus kinase, and signal transducers and activators of the transcription pathway may downregulate clotting. The contact system provides another link between coagulation and inflammation, so inhibitors of factor XII or factor XI have the potential to attenuate both pathways. The thrombi in the vessels of patients dying of COVID-19 are composed of platelets and fibrin. Therefore, advantages to dual-pathway inhibition with a low dose of an anticoagulant plus an antiplatelet agent may be more effective than strategies that target only a single pathway. Last, if endothelial dysfunction and complement activation drive the coagulopathy, soluble thrombomodulin or inhibitors of complement may be useful agents.

The coagulopathy of COVID-19 represents the perfect storm of immune-, cytokine-, and coagulation-driven processes that conspire to create a hypercoagulable state. Although the peak of the initial wave of the pandemic has eased in some areas, the resurgence of COVID-19 and its associated coagulopathy remain a risk until a vaccine becomes available. Ongoing studies are evaluating many novel approaches in the management of the coagulopathy, and, in particular, the risk of VTE, associated with COVID-19. These studies should provide new insights into the pathogenesis of the hypercoagulable state associated with COVID-19. Such information is essential to optimize prevention and treatment of the thrombotic complications of this disease so as to reduce death and disability.

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