Coronavirus disease 2019 (COVID-19) infection is associated with an increased risk of veno-thromboembolism (VTE). In the microcirculation, this occurs as a consequence of pulmonary vascular endotheliitis. In the macrocirculation, this occurs as a consequence of systemic inflammation and pro-thrombotic state, with pulmonary embolism and deep vein thrombosis as well as various types of arterial thrombosis. The incidence of VTE is higher in hospitalized patients and the highest in patients admitted to the intensive care unit (ICU) despite a high utilization rate of thromboprophylaxis. In one meta-analysis, the overall incidence of VTE was 24% in patients admitted to the ICU with a predominance of pulmonary embolism (19%) and 9% in patients admitted to the ward. Coronavirus disease 2019 triggers an inflammatory response with cytokine activation, complement activation, immunosuppression, and activation of the coagulation cascade with predominance of the hypercoagulable state that includes increase in D-dimer and fibrin/fibrinogen degradation products. The presence of VTE is by itself a risk factor for worse clinical outcome with increased morbidity and mortality. A high incidence of VTE has been described in the initial reports coming from China, Europe, and New York. The incidence of VTE was higher when routine screening was applied. The benefit of an augmented dose of prophylactic anticoagulation (intermediate or enhanced prophylaxis) to prevent VTE remains uncertain. National guidelines continue to recommend a standard prophylactic dose of anticoagulation in hospitalized patients and maybe intermediate dose in patients in the ICU. A full dose of anticoagulation has presented no benefit in terms of reducing the need for organ support and potential for harm with higher hemorrhagic complications in patients in the ICU. There is still no convincing evidence that full anticoagulation prevents the occurrence of VTE upon discharge after the initial hospitalization.

In this issue of Mayo Clinic Proceedings, Chaudhary et al present a retrospective observational study of 3790 adult patients hospitalized with COVID-19 test results in 19 medical centers of the Mayo Clinic enterprise around the country from January 1, to May 8, 2020. Their goal was to evaluate the incidence of VTE in patients hospitalized for COVID-19 infection during the initial months of the pandemic. They compared the incidence of VTE in 102 patients hospitalized with positive COVID-19 test results with that in 3688 patients hospitalized during the same period for reasons other than COVID-19 infection and who tested negative for COVID-19. A majority of COVID-19–positive patients (57.1%) were in the ICU. They found that (1) the incidence of VTE overall was low and similar in both COVID-19–positive and COVID-19–negative groups (2.9% vs 4.6%) and (2) neither a positive COVID-19 test result nor the presence of VTE was associated with 30-day mortality. The lower-than-previously reported incidence may be surprising at first but has already been reported by others and in prospective registries, with an overall rate of VTE of 3% in studies that included 400 patients or more. Previous higher incidence rate might have been attributed to bias related to the smaller sample size in earlier studies. With only 102 patients in the study by Chaudhary et al, what other reason(s) could explain this low rate of VTE? The first reason is hospital capacity. When the disease spread throughout the United States, it initially remained confined to, albeit rapidly overwhelming, the northeast. Meanwhile, this delay in propagating to other states bought
some time for the remaining of the country to anticipate and prepare for a large influx of patients. Unlike New York or some places in Europe such as Lombardy in Italy, most centers never reached capacity, a key feature associated with the outcome. Centers that remained at or below capacity may have been more adhered to the best clinical practices recommended by international societies early by the end of March 2020. A center effect is a key feature linked to outcome. Mayo Clinic has a unique model of care that has been associated with a low mortality rate of COVID-19 infection for about that same initial period. The second reason is VTE prophylaxis. In their study, only 3% of patients did not receive anticoagulation therapy whereas 97% received either thromboprophylaxis or therapeutic anticoagulation for a preexisting condition. The third reason is timing. The first reports of COVID-19–positive patients began at the end of March and the study, which started on January 2020, continued until the beginning of May 2020. This represents a brief 6-week study period for patients who tested positive for COVID-19. Moreover, this study reported cases during their first hospitalization only. Venothromboembolic may occur later in the course of the disease and require (re-)hospitalization, but, by design, patients who were rehospitalized for any reasons were excluded from the present analysis. Finally, this study reported cases only during the first wave of the pandemic; since then, the United States has endured 4 waves and phenotypes of the disease may have changed over time. The fourth reason is diagnosis. As the authors rightly pointed out, there was no systematic screening for VTE by Doppler ultrasound and subclinical cases may have been missed. In the COVID-19–positive group, only a few patients underwent screening: 3.9% underwent lower extremity Duplex ultrasound, 21% underwent upper extremity Duplex ultrasound, and 27% underwent chest computed tomography angiography. By its retrospective character, this study may also have missed asymptomatic cases of VTE, although the authors meticulously reviewed the electronic medical record by using artificial extracting tools to assert the completeness of their search of symptomatic cases of VTE. The fifth reason is race and underlying conditions. The findings from a predominant white population may not extrapolate to other races. Overall, age and the burden of comorbidities were lower than reported in previous studies and therefore the risk of VTE may be lower than that in an older population or with a higher burden of comorbid conditions. The sixth reason is COVID-19–directed therapy. The reduction in viral load expected with antiviral agents, and the modulation of the exuberant inflammatory response with corticosteroids, could eventually lead to the reduction in prothrombotic phase and thus decrease in the risk of VTE. In this study, the details on COVID-19–directed therapies were not provided, although corticosteroids may have been used liberally early.

Coronavirus disease 2019 infection has generated myths relative to its pathophysiology. Like the cytokine storm that is not as prevalent as is commonly assumed, the hypercoagulable state may have been exaggerated because it was initially underrecognized and therefore underestimated. This may have been true elsewhere in medical centers submerged by patients, particularly in the ICU with a high incidence of invasive mechanical ventilation, deep and prolonged sedation, higher frequency of central vein catheter use, and higher rate of secondary infections—all risk factors for VTE. Still, the abnormal incidence of VTE reported by others, including some unusual forms of the prothrombotic state, such as cerebral sinus vein thrombosis or arterial thrombosis, suggests that COVID-19 infection is likely associated with an increased risk of VTE depending on the conditions, which may include high viral load, delay in treatment and hospitalization, and the strain on the health care system. Coronavirus disease 2019 infection deserves a special attention for VTEs, maybe with the application of enriched techniques (eg, thromboprophylaxis based on D-dimer, fibrinogen, and
platelet count) and adherence to the best clinical practice to reduce VTE occurrence and its inherent complications.

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REFERENCES