

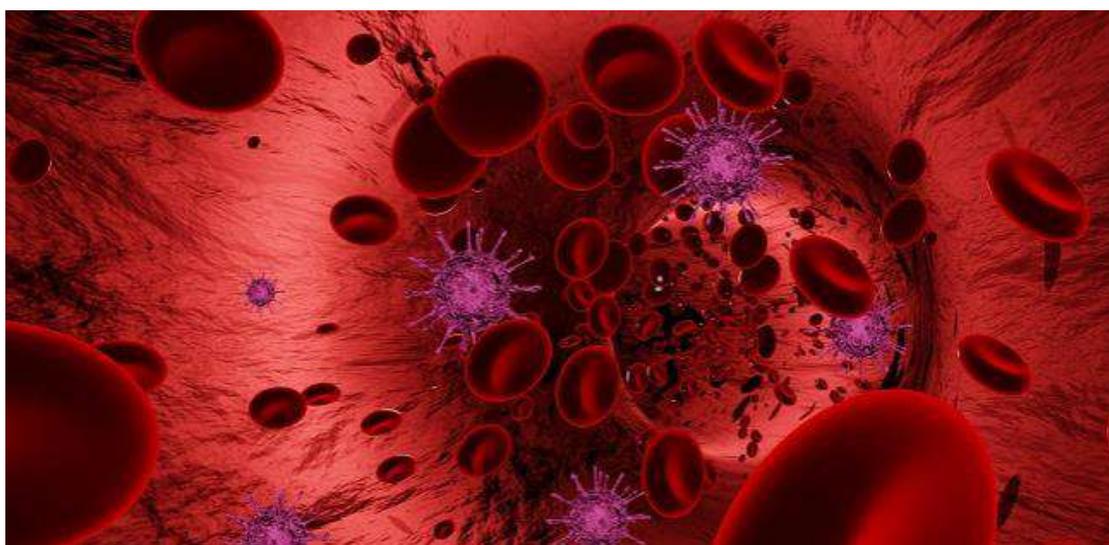
NEWS

How COVID-19 Promotes Thrombosis, Posing Problems for Drug-Drug Interactions

A new review explores the higher risk of thrombotic disease with this coronavirus, how to prevent and treat it, plus research gaps.



By **Michael O'Riordan** April 22, 2020



Solid data is lacking, but an emerging body of evidence suggests that COVID-19 may predispose patients to arterial and venous thrombotic disease, and that some of the therapies under investigation may pose distinct drug-drug interactions with common antithrombotic medications.

That's prompted a global effort to summarize what's known to date about preventing venous thromboembolism (VTE) in patients with COVID-19 during hospitalization and back at home, as well as the ideal management of COVID-19-positive patients with a VTE

diagnosis.

Behnood Bikdeli, MD (NewYork-Presbyterian Hospital/Columbia University Irving Medical Center, New York, NY, and Yale Center for Outcomes Research and Evaluation, New Haven, CT), who led an international collaboration to summarize the available data, said that despite uncertainties and limited evidence, the expert consensus is that COVID-19 is a prothrombotic disease. What's not known is the extent to which it promotes thrombosis and how to manage it.

“Speaking with colleagues around the world, before the pandemic really hit New York, they were seeing a number of thrombotic events in the venous and arterial system,” Bikdeli told TCTMD. “Of course, these were very sick people, and acute medical illness in and of itself predisposes people to stasis, inflammation, and many times endothelial dysfunction, among a host of other things, which predisposes them to blood clots. However, what they were seeing was an exaggerated response above and beyond just what you'd see with acute medical illness.”

When the pandemic struck New York City, Bikdeli and others saw similar cases in their hospital. Meanwhile others have shown that some COVID-19 patients develop hemostatic abnormalities such as elevated D-dimer and, in serious cases, disseminated intravascular coagulation. The disease is also marked by a severe inflammatory response and critical illness, not to mention traditional risk factors, such as older age and being immobile for extended stretches, all of which predispose patients to thrombosis.



More of TCTMD's coverage on our COVID-19 hub.

“We're certainly seeing a number of thrombotic complications in our clinical practice in these patients,” said Mahesh Madhavan, MD (NewYork-Presbyterian Hospital/Columbia University Irving Medical Center), who worked with Bikdeli in pulling together the new review and consensus-based recommendations. “Many people weren't initially surprised to see here and there a clotted catheter or arterial line, which certainly happens in patients in our ICUs who don't have COVID-19. In routine practice, sometimes, we give patients anticoagulants or potentially have to replace lines, but in the first 1 to 2 weeks of this initial experience, we noted that the rate at which these complications were happening exceeded our initial expectations.”

What is the Ideal Anticoagulant Strategy and Dose?

Published April 15, 2020, in the *Journal of the American College of Cardiology*, the review highlights the “pathogenesis, epidemiology, treatment, and available outcome data” related to thrombotic disease in patients with COVID-19. Hemostatic abnormalities consistently seen in patients with COVID-19 include mild thrombocytopenia and increased D-dimer levels, both of which are associated with higher risk of needing mechanical ventilation, ICU admission, or death. The severity of COVID-19 is also linked with abnormalities in commonly assessed anticoagulation parameters, including prolonged prothrombin and thrombin times.

To TCTMD, Bikdeli said one of the biggest questions facing physicians is how to handle COVID-19 patients with coagulation and platelet abnormalities. One option is standard dosing of prophylactic anticoagulation, as would be the case with any medically ill patient. Another option would be to aggressively screen all COVID-19 patients for VTE. There is also the possibility of intensifying treatment to provide the intermediate or full dose of therapeutic anticoagulation in these patients.

“Truthfully, nobody knows what the best answer is right now, but running the issue by our panel the consensus was that most of these patients, especially those that are hospitalized in the ICU, need the preventive dose of blood thinners,” said Bikdeli. “Use of the higher doses is a little uncertain, but many clinicians, including some panel members use it in their practice.”

Finding the optimal anticoagulation regimen for VTE prophylaxis is one of the more pressing issues, agreed Madhavan. “We’re hearing about clinicians giving full-dose anticoagulation even without clear evidence of thrombotic disease in some of these patients, given their high risk for clotting events and oftentimes overall poor prognosis,” he said. “Certainly, some of the clinical and laboratory parameters might suggest a thrombotic event or that thromboembolism may have occurred in many circumstances, but full-dose anticoagulation also puts the patient at risk for hemorrhagic events or complications. So, we need to come up with strategies based on evidence.”

When considering the discharge of COVID-19 patients, physicians should assess thrombotic and hemorrhagic risk and consider extended VTE prophylaxis in selected patients at high risk for VTE, such as immobile patients, those with comorbidities, and possibly even those

with elevated D-dimer levels.

“There is evidence from prior studies of acutely ill patients showing that a select group may actually benefit from extended prophylaxis,” said Bikdeli. “When they get discharged home, they’d receive a short-term regimen of blood thinners that would be stopped after a few weeks. The same consideration is being made with COVID-19 patients.”

Treatment of VTE

In their review, endorsed by numerous organizations including the International Society on Thrombosis and Hemostasis, the experts note that therapeutic anticoagulation is the cornerstone of treatment of VTE, but say a diagnosis may be challenging in COVID-19-positive patients because there may be restricted access to necessary imaging given concerns about transmitting infection. These patients might also be unstable, and some might not be capable of being in a prone position due to profound hypoxemia, which limits the possibility for imaging studies to diagnose pulmonary embolism or deep vein thrombosis.

For the treatment of VTE, unfractionated heparin is typically preferred because it can be withheld (the parenteral agents have no known interaction with any of the investigational COVID-19 drugs). However, Madhavan noted that unfractionated heparin often requires frequent monitoring and one consideration might be to use longer-acting agents, such as low-molecular-weight heparin (LMWH), because it can be given subcutaneously one or two times per day and doesn’t require frequent monitoring to ensure it’s being effectively dosed.

The group also provides a list of all potential drug-drug interactions between investigational COVID-19 therapies and oral anticoagulants, including warfarin, the direct thrombin inhibitor dabigatran, and the factor Xa inhibitors apixaban, rivaroxaban, edoxaban, and betrixaban. Warfarin used outside the hospital can be tricky since it requires frequent international normalized ratio (INR) monitoring, the experts point out, something that isn’t ideal given social distancing mandates. At-home INR monitoring machines and drive-thru INR monitoring have been deployed to limit exposure to patients and staff, but depending on the patient’s condition, as well as insurance status, switching to a direct oral anticoagulant or LMWH may be preferred.

The authors also highlight the potential interactions between the

COVID-19 therapies and antiplatelet agents, including clopidogrel, prasugrel, ticagrelor, and cilostazol. The protease inhibitor lopinavir/ritonavir, for example, inhibits CYP3A4 metabolism, which may reduce the effectiveness of clopidogrel. At present, though, the experts do not recommend making any dose adjustments to oral antiplatelet medications in COVID-19-positive patients.

With respect to COVID-19 and acute coronary syndromes, the group point to the now-established phenomenon of elevated cardiac troponin levels in patients with severe COVID-19, elevations that do not always correspond to plaque rupture. They point to recent guidance from the American College of Cardiology and **Society for Cardiovascular Angiography and Interventions** stating it is reasonable to defer nonurgent cardiac procedures, and while they note that **fibrinolytic therapy for STEMI** has been adopted by some centers in China, they urge caution with this strategy given that COVID-19 can mimic ACS.

Regular Care of Patients With Thromboembolic Disease

In addition to all of these concerns and questions, another pertinent issue is the management of patients without COVID-19 who have a diagnosis of thromboembolic disease. In general, pharmacotherapy should follow a similar pattern prior to the epidemic. In contrast with a recent document from the Centers for Disease Control and Prevention, which lists people taking blood thinners as being at **higher risk of a serious infection**, the writing committee found no evidence that taking antiplatelet or anticoagulant agents, per se, increase the risk of contracting COVID-19 or developing severe COVID-19. Bikdeli noted that patients receiving these agents might be at higher risk not because of the drugs but rather due to some of their underlying health conditions.

“There is a lot of attention with COVID-19 and how it’s causing devastation, which is very true,” said Bikdeli. “The other piece is what’s happening to patients with new or known thrombotic disease and who need to receive care in the face of this unprecedented pandemic. The healthcare system isn’t fully prepared to be facing something like this. Early preliminary results are suggesting **lower rates of admission to the hospital for MIs**, stroke, and other conditions. These events haven’t gone away, but some of these patients might be scared of coming to the healthcare system because of the social distancing measures.”

Madhavan made a similar point, noting that multidisciplinary pulmonary embolism response teams (PERTs) are observing a decline in the number of catheter-based interventions for patients with VTE. In an attempt to limit the spread of infection and exposure, these procedures should be limited to the most critical patients during the outbreak, say the experts. Depending on the severity of disease and patient symptoms, this might mean medical therapy for some, said Madhavan.

Finally, the review concludes by proposing several areas for future research in COVID-19 positive patients. In the inpatient and outpatient setting, including patients diagnosed with disseminated intravascular coagulation, there are more than a dozen areas of research, they say, that require further investigation.

Sources

Bikdeli B, Madhavan MV, Jimenez D, et al. [COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up](#). *J Am Coll Cardiol*. 2020;Epub ahead of print.

Disclosures

Bikdeli reports serving as a consulting expert on behalf of plaintiffs for litigation related to a specific type of IVC filters.

Madhavan reports institutional grant support from the National Institutes of Health/National Heart, Lung, and Blood Institute.

TCTMD is produced by the Cardiovascular Research Foundation (CRF). CRF is committed to igniting the next wave of innovation in research and education that will help doctors save and improve the quality of their patients' lives. For more information, visit <http://www.crf.org>.

This website uses cookies to ensure you get the best experience on our website. [Read More](#)

GOT IT