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August 2020 ~ Resource #360817

COVID-19 and Thromboembolism: FAQs

Patients with COVID-19, the disease caused by the SARS-CoV-2 virus, appear to have a higher thrombosis risk than other hospitalized or intensive care patients.[3] The chart below provides information or resources on thromboembolism pertinent to COVID-19 patients. The information is presented in an FAQ format, with an emphasis on thrombosis prevention and treatment. Keep in mind that although there is little information specific to COVID-19 thrombosis management, there are some special considerations that may affect treatment decisions, including risk of hospital staff exposure to infected patients.

Abbreviations: ACS = acute coronary syndrome; aPTT = activated partial thromboplastin time; CV = cardiovascular; DAPT = dual antiplatelet therapy; DIC = disseminated intravascular coagulation; DOAC = direct oral anticoagulant; DVT = deep venous thrombosis; IPC = intermittent pneumatic compression; IVC = inferior vena cava; PCI = percutaneous coronary intervention; PEEP = positive end-expiratory pressure; PT = prothrombin time; VTE = venous thromboembolism; LMWH = low molecular-weight heparin; PE = pulmonary embolism; UFH = unfractionated heparin; ULN = upper limit of normal

Clinical Question	Pertinent Information and Resources

What is the proposed pathophysiology of venous thromboembolism as a complication of COVID-19?	• COVID-19 triggers all three arms of Virchow's triad: endothelial injury, hypercoagulability, and blood flow stasis.[3]
	  • COVID-19 may increase levels of von Willebrand factor and Factor VIII via endothelial injury.[3]
	  • Release of inflammatory cytokines (cytokine storm) could activate the coagulation cascade.[2] Antiphospholipid antibodies may play a role.[2] On autopsy, megakaryocytes have been found in unusually high numbers outside the bone marrow (e.g., in the lungs and heart).[4]
	  • Immobility, and treatments used for seriously ill COVID-19 patients such as fluid restriction and high PEEP, may cause blood flow stasis and microthrombi.[3]
	• COVID-19-induced hypoxia facilities thrombus formation.[1]
	• Some drugs being investigated as treatments for COVID-19 may increase thrombosis risk directly (e.g., bevacizumab-induced CV events), or indirectly by reducing efficacy of antithrombotics (e.g., lopinavir/ritonavir may reduce clopidogrel conversion to its active metabolite).[2]
	• Severely ill COVID-19 patients may have non-COVID-19-specific contributors to VTE risk, such as central lines.[2]
	• DIC has been reported, but it is unclear if this is related to a specific effect of COVID-19, or a nonspecific complication of critical illness.[2] Contrary to what is usually seen in DIC, COVID-19 coagulopathy is characterized by normal or even increased fibrinogen.[10] Moreover, overt bleeding seems not to be common in COVID-19 patients.[2,10]

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Clinical Question	Pertinent Information and Resources
How does COVID-19-associated thromboembolism present clinically?	• In a German cohort of 12 autopsied patients (52 to 87 years of age) who died with a confirmed case of COVID-19, **microthrombi** were common in the lungs. Seven patients had **DVT** that had not been suspected before death. For four patients, **PE** was the cause of death.[1] • These findings suggest that clinicians should maintain a high index of suspicion for VTE in COVID-19 patients.[1] • Patients with severe COVID-19 may have **myocardial injury** (e.g., elevated troponin, electrocardiogram signs), which may be thrombotic ACS or myocarditis.[2] • Hemostasis lab abnormalities seen in COVID-19 patients include elevated D-dimer, low platelets, prolonged PT, and shortened aPTT.[2]
For which COVID-19 patients should thromboembolism **prophylaxis** be considered, and how should it be provided? *Continued…*	• Experts advocate prophylaxis for all COVID-19 patients.[3,5,6] For patients with contraindications to anticoagulants such as active bleeding or platelets <25,000/mm^3, use IPC.[2,3,5] Some experts feel it is reasonable to combine anticoagulants with IPC in critically ill COVID-19 patients, although benefit has not been demonstrated for non-COVID-19 patients.[3,11] • In general, use the same VTE prophylaxis regimens as for non-COVID patients.[8] Consider LMWH for most patients, even those with DIC but without overt bleeding; it may decrease thrombin.[2] Fondaparinux is a choice for patients with heparin-induced thrombocytopenia.[6] As for other acutely ill hospitalized patients, avoid prophylaxis with DOACs due to higher bleeding risk.[3] • See our charts, *Venous Thromboembolism Prophylaxis*, *Cancer-Associated Thrombosis FAQs*, and *LMWH Dosing in Special Populations* (e.g., obesity) for prophylaxis options and dosing used in **non-COVID** patients. COVID-19 patients seem to have a higher risk of VTE than other critically ill patients, even with appropriate prophylaxis.[12] Therefore, some experts are using anticoagulant doses higher than those normally used for prophylaxis, such as twice-daily dosing of LMWH (e.g., enoxaparin 40 mg twice daily), or dosing as for VTE treatment, particularly in patients that seem to have higher thrombosis risk, such as those with D-dimer >6 x ULN, depending on bleeding risk, and stepping-down once the patient transfers out of intensive care.[6,8,9,11] If feasible, reserve higher doses for clinical trials[6] (see www.clinicaltrials.gov). If, despite prophylactic anticoagulation, COVID-19 patients develop clots in vascular access devices or extracorporeal circuits, consider trying a different anticoagulant, or increasing the dose if bleeding risk allows.[6] • Extrapolating from other populations, antiplatelets (e.g., aspirin) are likely inferior to anticoagulants for VTE prophylaxis in COVID-19 patients needing hospitalization.[3] • Whether COVID-19 patients discharged from the hospital should continue thromboprophylaxis at home is unclear.[6] Based on data from non-COVID medical patients, prophylactic anticoagulation could be considered for patients with low bleeding risk with VTE risks such as restricted mobility and active cancer, age ≥75 years, or D-dimer >2 ULN.[2,6,7] However, studies of extended-duration VTE prophylaxis in non-COVID medical patients don't clearly show that VTE reduction outweighs bleeding risk.[7] Consider extended prophylaxis for patients similar to those in clinical trials of extended VTE prophylaxis in medical patients, using an agent (rivaroxaban, betrixaban), dose, and duration used in

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Clinical Question	Pertinent Information and Resources
Thromboembolism **prophylaxis**, continued	clinical trials.[11] Ensure that the dose, purpose, and duration of VTE prophylaxis is clearly communicated to the outpatient prescriber.[11] • For patients with mild COVID-19 who are isolating at home, advise keeping active.[2] Pharmacologic prophylaxis may be considered for very high-risk patients (e.g., immobility, history of VTE, active cancer) without high bleeding risk.[2]
How is thromboembolism in COVID-19 patients **treated**?	• Anticoagulation, for at least three months, is the mainstay of treatment.[2,3] Initiate treatment with a parenteral agent in critically ill patients.[3] • For patients with recurrent VTE despite appropriate anticoagulation, consider switching from oral therapy to LMWH, or increasing the LMWH dose by 25% to 30% in patients failing standard-dose LMWH, based on low-quality evidence in other populations.[3] • Catheter-directed therapy or systemic thrombolysis should be reserved for the most serious cases.[2,3] See our chart, *Pulmonary Embolism: Focus on Thrombolytics*, for more information. • Reserve IVC filters for recurrent PE despite appropriate anticoagulation, or clinically important VTE with absolute contraindications to anticoagulation.[2]
What are some general considerations for antithrombotic use of special relevance to COVID-19? *Continued…*	• For patients who might need procedures, consider parenteral antithrombotics over oral antithrombotics due to shorter duration of action.[2] • DOACs may be difficult to manage in this patient population due to clinical instability resulting in impaired oral drug absorption or deterioration of renal function, and drug interactions with COVID-19 treatments.[3] • In the hospital, consider fondaparinux (not for intensive care patients) or LMWH over UFH to reduce caregiver viral exposure and to reduce the risk of missed doses; fondaparinux and LMWH require less frequent blood draws for monitoring and fewer daily doses.[2,3] However, UFH might be preferred for patients with hemodynamic instability or renal insufficiency due to quicker offset.[3] • In patients with ACS and elevated bleeding risk (e.g., due to DIC), consider clopidogrel over other antiplatelets.[2] • In patients taking antithrombotics chronically who develop known or suspected DIC without overt bleeding, consider risk/benefit of reducing the intensity of therapy or discontinuation. For example, in patients taking DAPT, consider risk/benefit of continuing DAPT if platelets ≥50,000/mm^3, switching to a single antiplatelet if platelets are ≥25,000 to <50,000/mm^3, or discontinuing if platelets <25,000/mm^3.[2] • In outpatients, consider a DOAC or LMWH over warfarin if home or drive-in INR monitoring is not available, assuming use is feasible given cost, indication (e.g., prosthetic heart valve), comorbidities (e.g., pregnancy), etc.[2,8] • Outpatients with COVID-19 and previously diagnosed thrombotic or CV disease should generally continue their usual antithrombotic regimen (e.g., aspirin, anticoagulant).[2] But for patients taking warfarin, consider transitioning to a DOAC or LMWH.[2] • Educate outpatients taking antithrombotics to discern clinically important bleeding from nuisance bleeding to reduce unnecessary emergency room visits.[2]

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Clinical Question	**Pertinent Information and Resources**
General considerations for antithrombotic use, continued	• Be alert for **drug interactions** between antithrombotics and drugs used to treat COVID-19. Select drug interactions are covered in the next section. Consider using injectable antithrombotics when drug interactions are a concern.[2]

What are some **select drug interactions** between antithrombotics and drugs being investigated to treat COVID-19?	• **Warfarin**: Monitor INR and adjust dose as appropriate (e.g., with methylprednisolone, azithromycin, lopinavir/ritonavir, interferon, ribavirin, sarilumab, tocilizumab)[2,6]
	• **DOACs**:
	  • Apixaban: reduce apixaban dose by 50% with lopinavir/ritonavir (avoid if initial apixaban dose is 2.5 mg twice daily).[2]
	  • Rivaroxaban: avoid with lopinavir/ritonavir.[2]
	  • Edoxaban: avoid with lopinavir/ritonavir. Limit edoxaban dose to 30 mg once daily for VTE treatment with azithromycin.[2]
	  • Betrixaban: reduce dose to 80 mg x 1, then 40 mg once daily with lopinavir/ritonavir or azithromycin.[2]
	  • Dexamethasone is a CYP3A4 inducer, but whether it significantly reduces DOAC efficacy is unknown.[6]
	• **Antiplatelets**:[2]
	  • Clopidogrel: lopinavir/ritonavir may decrease efficacy via CYP3A4 inhibition of formation of active metabolite. Switch to prasugrel with caution, or use P2Y12 platelet function assay to monitor efficacy.
	  • Ticagrelor: lopinavir/ritonavir may increase effects via CYP3A4 inhibition. Consider prasugrel (with caution), reduce dose (not commonly done), or use P2Y12 platelet function assay to monitor effect.
	  • Cilostazol (U.S.): lopinavir/ritonavir may increase effect via CYP3A4 inhibition. Limit dose to 50 mg twice daily.
	• See www.covid19-druginteractions.org for more interactions.

Users of this resource are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

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Cite this document as follows: **Clinical Resource,** ***COVID-19 and Thromboembolism: FAQs. Hospital Pharmacist's Letter/Prescriber's Letter.*** **August 2020.**

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