February 2022 ~ Resource #380218

COVID-19 and Thromboembolism

Patients with COVID-19 appear to have a higher thrombosis risk than otherwise similar hospitalized or intensive care patients.[3,5] The FAQ below provides information on thromboembolism pertinent to COVID-19 patients with an emphasis on thrombosis prevention and treatment. There are some special considerations that may affect treatment decisions, including risk of hospital staff exposure to infected patients.

Question	Answer/Pertinent Information

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 facilitates thrombus formation.[1]
	• Some drugs being used as treatments for COVID-19 may increase thrombosis risk directly (e.g., baricitinib), or indirectly by reducing efficacy of antithrombotics (e.g., tocilizumab could potentially speed metabolism of oral anticoagulants).[2,13,14]
	• 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.[10]

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]

Question	Answer/Pertinent Information
Which COVID-19 **inpatients** should receive VTE prophylaxis?	• **All** hospitalized COVID-19 patients should receive VTE prophylaxis.[6,19] • Use LMWH (or fondaparinux for patients with HIT) for most patients.[6] • IPC is an alternative if an anticoagulant cannot be used, but combining mechanical and pharmacologic prophylaxis is generally not recommended.[3,6]
Should higher-than-usual anticoagulant **doses** be used for VTE prophylaxis in **critically ill** COVID-19 patients?	• Current data support starting with **standard-dose** VTE prophylaxis in **critically ill** COVID-19 patients.[19] • In critically ill COVID-19 patients, a full-dose heparin (mostly enoxaparin) or intermediate-dose LMWH (enoxaparin 1 mg/kg/day) does not improve outcomes (e.g., thrombosis, mortality, need for organ support) vs usual-dose prophylaxis (e.g., enoxaparin 40 mg once daily) [Evidence level B-1].[5,9,12] • 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 (i.e., full or intermediate dose) if bleeding risk allows.[6]

Should higher than usual anticoagulant doses be used for VTE prophylaxis in **moderately ill hospitalized** COVID-19 patients?	• Current data suggest that VTE prophylaxis using **full-dose** anticoagulation (preferably LWWH) can benefit moderately ill, **select patients** (e.g., elevated D-dimer, requiring only low-flow oxygen, non-pregnant), without **increased bleeding risk** (e.g., platelets <50 x 10^9/L, hemoglobin <8 g/dL, DAPT, hospital visit for bleeding within the past 30 days, bleeding disorder) [Evidence level B-1].[5,15,16,19]
	  • In a multiplatform adaptive-design trial (MPT) hospitalized patients not needing high-flow oxygen, noninvasive or invasive mechanical ventilation, or vasopressors, full-dose anticoagulation with a heparin (mostly enoxaparin) started within 72 hours of admission or positive in-hospital COVID-19 test increased days free of cardiovascular or respiratory support vs usual-dose VTE prophylaxis.[15] Major bleeding occurred in 1.9% of the full-dose anticoagulation patients vs 0.9% of the usual-dose prophylaxis patients (not a statistically significant difference).
	  • In the RAPID trial, non-ICU patients with elevated D-dimer (n=465) were randomized to a full-dose or prophylactic-dose heparin (mostly enoxaparin).[16] Although there were fewer VTEs among patients who received full-dose anticoagulation (0.9% vs 2.5%; OR 0.34, 95% CI 0.07 to 1.71, p=0.19), there was no significant difference in occurrence of the primary composite outcome (need for non-invasive or invasive mechanical ventilation, ICU admission, or death). Major bleeding occurred in 1.7% of the full-dose anticoagulation patients vs 0.9% of the usual-dose prophylaxis patients (not a statistically significant difference). Mortality at 28 days was lower in the full-dose arm (OR 0.22 [95% CI 0.07 to 0.65, p=0.006).
	  • In the HEP-COVID study (n=257), patients with D-dimer >4 times ULN or sepsis-induced coagulopathy score ≥4 were randomized to full-dose enoxaparin or a prophylactic/intermediate-dose heparin (mostly enoxaparin).[5] The primary composite outcome was VTE, arterial thromboembolism, or death. Almost all patients were enrolled based on their D-dimer level. About 2/3 of the study patients were non-ICU patients. Only non-ICU patients benefited from full-dose enoxaparin, driven by reduced thrombosis (NNT = 5 to prevent one thrombotic

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Question	Answer/Pertinent Information
Anticoagulant dosing in moderately ill hospitalized COVID-19 patients, continued	event). Major bleeding occurred in 2.4% of the non-ICU patients treated with full-dose enoxaparin, vs 2.3% in the prophylactic/intermediate-dose group. • Patients in MPT and RAPID were relatively young (mean age ~60 years[15,16]). Patients with high bleeding risk or dual antiplatelet therapy were excluded from all three studies.[5,15,16] In MPT and RAPID, few included patients were taking a single antiplatelet (~12%), and only about 7% had chronic kidney disease.[15,16] In HEP-COVID, <4% of patients had chronic kidney disease.[5]

Should VTE prophylaxis be considered for **outpatients**?	• It is generally recommended that VTE prophylaxis be discontinued at discharge.[6,19]
	  • Post-discharge, VTE risk is low and comparable to the risk of other medical conditions.[6] However, COVID-19 patients discharged early to free up hospital beds may need an assessment of their VTE risk.[6]
	  • In a large, placebo controlled study in **non**-COVID-19 discharged medical patients (MARINER), extended duration VTE prophylaxis with rivaroxaban did not provide net benefit [Evidence level A-1].[18] NNT to prevent one symptomatic VTE was 430. Major or clinically important bleeding (e.g., requiring discontinuation or medical contact) occurred in 1.7% of rivaroxaban patients vs 0.7% of placebo patients (NNH = 143).
	  • **In COVID-19 patients**, one study (MICHELLE) suggests benefit of post-discharge VTE prophylaxis.[7] **However**, findings are limited by open-label design, small sample size (n=320), and inclusion of patients with low bleeding risk (e.g., mean age 57.1 years, 95% not taking an antiplatelet, no severe renal disease).[7] In MICHELLE, rivaroxaban 10 mg/day for 35 days post-discharge prevented a symptomatic or fatal VTE in 1 in 23 COVID-19 patients with high thrombosis risk (IMPROVE score ≥4, or 2-3 with D-dimer >500 ng/mL).[7] Major bleeding did not occur.[7]
	• At discharge, educate COVID-19 patients to seek help for symptoms of VTE.[6]
	• For patients with mild COVID-19 who are isolating at home, advise keeping active.[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] • Consider using anti-factor Xa levels to monitor UFH due to aPTT abnormalities in these patients.[11] • 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]

Question	Answer/Pertinent Information
What are some **general considerations for antithrombotic use** of special relevance to COVID-19?	• Extrapolating from other populations, antiplatelets (e.g., aspirin) are likely inferior to anticoagulants for VTE prophylaxis in COVID-19 patients needing hospitalization.[3] • 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 hospitalized COVID-19 patients 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] • Educate outpatients taking antithrombotics to discern clinically important bleeding from nuisance bleeding to reduce unnecessary emergency room visits.[2] • Be alert for **drug interactions** between antithrombotics and drugs used to treat COVID-19. Select drug interactions are covered in the next section.
What are some **select drug interactions** between anticoagulants and drugs used treat COVID-19? *Continued…*	• **Dexamethasone** (high dose): increased warfarin effect.[14] Dexamethasone is a CYP3A4 inducer, but whether it significantly reduces DOAC efficacy is unknown.[6] • **Methylprednisolone** (high dose): increased warfarin effect.[14] • ***Paxlovid*** (nirmatrelvir/ritonavir): increased rivaroxaban effect; avoid.[17] Monitor INR closely in patients taking warfarin (may increase or decrease).[17] • **Sarilumab**: may increase CYP450 activity, potentially decreasing efficacy of warfarin, apixaban, and rivaroxaban.[14] • **Tocilizumab**: may increase CYP450 activity, potentially decreasing efficacy of warfarin, apixaban, and rivaroxaban.[14]

Question	Answer/Pertinent Information
Drug interactions with COVID-19 drugs, continued	• See the Liverpool COVID-19 Drug Interaction website: https://www.covid19-druginteractions.org to screen for more drug interactions.

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; ECMO = extracorporeal membrane oxygenation; HIT = heparin-induced thrombocytopenia; ICU = intensive care unit; IMPROVE = International Medical Prevention Registry on Venous Thromboembolism; 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

Levels of Evidence

In accordance with our goal of providing Evidence-Based information, we are citing the **LEVEL OF EVIDENCE** for the clinical recommendations we publish.

Level	Definition	Study Quality
A	Good-quality patient-oriented evidence.*****	1. High-quality randomized controlled trial (RCT) 2. Systematic review (SR)/Meta-analysis of RCTs with consistent findings 3. All-or-none study
B	Inconsistent or limited-quality patient-oriented evidence.*****	1. Lower-quality RCT 2. SR/Meta-analysis with low-quality clinical trials or of studies with inconsistent findings 3. Cohort study 4. Case control study
C	Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints); case series for studies of diagnosis, treatment, prevention, or screening.	

***Outcomes that matter to patients** (e.g., morbidity, mortality, symptom improvement, quality of life).

[Adapted from Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *Am Fam Physician* 2004;69:548-56. https://www.aafp.org/afp/2004/0201/p548.pdf.]

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Cite this document as follows: **Clinical Resource,** ***COVID-19 and Thromboembolism. Pharmacist's Letter/Prescriber's Letter.*** **February 2022. [380218]**