2020

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Received: 9 April 2020 | Revised: 22 April 2020 | Accepted: 23 April 2020

DOI: 10.1002/rth2.12358

FORUM

rpth research & practice in thrombosis & haemostasis

Emergence of institutional antithrombotic protocols for coronavirus 2019

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Handling Editor: Susan Kahn

Keywords: acute infectious disease, anticoagulant, antiplatelet, antithrombotic therapy, coronavirus, COVID-19, deep vein thrombosis, pulmonary embolism, pulmonary infection, SARS-CoV-2

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19), first identified in December 2019 in Wuhan, China, is a major public health crisis with new infections increasing exponentially worldwide.[1] COVID-19 is an acute infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) and has contributed to significant morbidity and mortality, including the development of coagulopathy.[2] Similar thrombotic and thromboembolic events have occurred during other viral outbreaks, including severe acute respiratory syndrome (SARS), Middle Eastern respiratory syndrome, and influenza A H1N1.[3–7]

Venous thromboembolism (VTE) (ie, deep vein thrombosis or pulmonary embolism [PE]) is a common complication of acute infectious diseases, which increase VTE risk 2-fold to 32-fold.[8–10] Survival among patients with incident and recurrent VTE is significantly reduced, especially after PE.[11] Hospitalized patients with acute medical illness, including infections such as pneumonia, are at increased risk of VTE, both in-hospital and for an extended period of time (up to 45 days) after hospital discharge.[8,9,12–16] Despite this well-established association,[8–10] there are few data specifically addressing VTE in patients recently hospitalized with COVID-19 infections.[17,18] Indeed, infection-associated VTE might account for a substantial burden of incident or recurrent VTE among those with COVID-19. In addition, small-vessel hyaline thrombus formation has been described in autopsies of patients with COVID pneumonia.[19] There is increasing concern that mortality seen across all age groups may be secondary to PE, as 31% incidence of thrombotic complications in ICU patients with COVID-19 infections is recently reported. PE was the most frequent thrombotic complication and contributed to 81% of thrombotic complications.[20] To improve outcomes, targeted prophylaxis efforts to improve coagulopathy and reduce incident VTE in patients with acute infectious diseases, specifically COVID-19, may be advantageous.

Currently, VTE prophylaxis duration is mainly limited to the period of hospitalization,[21] but most VTE events occur within the first month following hospital discharge.[22] Recent data support the finding that an elevated D-dimer (>2× upper limit of normal [ULN]) is an

important novel biomarker in identifying a high-VTE-risk population that would benefit from extended thromboprophylaxis, an observation that is especially important in the hospitalized COVD-19 population.[23] If all hospitalized patients received universally effective prophylaxis, one quarter of the VTE burden in the community would be prevented.[24] To further reduce the VTE burden, better prophylaxis strategies are needed, which include prolonging VTE prophylaxis beyond hospital dismissal.

There are several concerns linked to the VTE prevention in COVID-19 patients: How can we limit the risk of VTE among patients who are hospitalized? Do we use similar prophylaxis in the common medical ward and in the intensive care unit (ICU)? How do we manage patients with COVID-19 who are already taking oral anticoagulants or antiplatelets?

To address these concerns, several leading national and international health care institutions have developed protocols to help guide health care professionals on how to manage thrombotic and antithrombotic therapy related to COVID-19 during this pandemic. Currently, there is significant variability in expertise, as many of the existing protocols derived are from sporadic reports and small retrospective studies. Given the lack of large prospective cohorts, the current document represents an effort to provide several simple and easy-to-follow algorithms to be considered as an interim clinical guidance since the knowledge and therapeutics in managing COVID-19 is rapidly evolving. The aim of this document is to provide clinicians and hospital systems a template on safe and effective use of antithrombotic medications in health care systems affected by the COVID-19 pandemic from an institutional perspective, including post–hospital discharge prophylaxis.

1.1 | Role of COVID-19 and antithrombotic considerations

Patients with COVID-19 and underlying cardiovascular disease and comorbidities have greater morbidity and mortality from COVID-19.[25,26] Common laboratory abnormalities include lymphopenia and increase in lactate dehydrogenase and inflammatory markers such as C-reactive protein, D-dimer, ferritin, interleukin (IL)-6, and fibrinogen.[27,28] Thrombocytopenia[29] and increased D-dimer levels[30] are the most consistent laboratory abnormalities associated with a higher risk of developing severe COVID-19. Therefore, several protocols suggest measuring D-dimers, prothrombin time, and platelet counts to help assess COVID-19 severity. Whether the very elevated D-dimers seen in very sick COVID-19 patients represent severe coagulopathy or are markers of a severe inflammatory "cytokine storm" is not known.

1.1.1 | In-hospital VTE prophylaxis

Hospitalized patients with acute medical illness, including COVID-19, should have an assessment of VTE versus bleeding risk. There are several risk stratification tools available (eg, the Caprini, IMPROVE [International Medical Prevention Registry on Venous Thromboembolism], and Padua models) to assist the health care provider in assessing VTE risk among hospitalized patients.[31–34] Regardless, the ISTH guidelines recommend prophylactic dose of low-molecular-weight heparin (LMWH) in all hospitalized COVID patients (including non-ICU) unless contraindicated.[35]

For parenteral anticoagulants, there is in vitro evidence that coronavirus may use the sulfated, negatively charged heparan sulfate as the initial receptor for target cells (even in the absence of angiotensin converting enzyme 2 [ACE2]).[36] ACE2 is an enzyme attached to the outer surface on cell membranes within the lungs, arteries, heart, kidney, and intestines and serves as the entry point into cells for some coronaviruses.[37–40] There is a suggestion from in vitro evidence that LMWH may competitively bind to coronavirus. Heparins as a class may suppress the cytokine storm induced by activated T cells, macrophages, and monocytes/neutrophils, all with increased IL expression (including IL-2R/6).[41] Empiric evidence supports use of treatment dose unfractionated heparin (UFH) as improving thrombosis-free survival in acute respiratory distress syndrome with influenza A H1N1 but not coronavirus.[42] There is also recent evidence that prophylactic doses of LMWH (namely, enoxaparin at 40-60 mg subcutaneous [s.c.] daily) or UFH (10 000-15 000 units/d) appears to be associated with better prognosis in COVID-19 patients with serious illness meeting sepsis-induced coagulopathy score of ≥4 or with markedly elevated D-dimer (>6× ULN) compared to non–heparin users.[43] The World Health Organization interim guidance statement as well as a recent guidance statement from ISTH recommends prophylactic use of daily LMWH over twice-daily subcutaneous UFH.[44,45]

Obese patients with body mass index (BMI) >30 kg/m^2 have increased risk of VTE,[46] recurrent VTE,[47] and postthrombotic syndrome[48]; however, prior studies have mainly focused VTE prophylaxis on extreme obesity defined by BMI >40 kg/m^2. As the distribution of LMWH is weight based, the efficacy of standard doses may be decreased due to the effects of plasma drug distribution and pharmacokinetics in obese individuals.[49] Furthermore, in a subgroup analysis of obese patients from the PREVENT (Prevention of Recurrent Thromboembolism) trial, dalteparin lost its thromboprophylactic benefit in patients with BMI >35 kg/m^2.[50] The ITOHENOX (Adjusted Value of Thromboprophylaxis in Hospitalized Obese Patients: A Comparative Study of Two Regimens of Enoxaparin) study shows in medically obese inpatients that thromboprophylaxis with enoxaparin 60 mg provides higher control of anti-Xa activity, without more bleeding complications than the standard enoxaparin regimen.[51]

Based on these observations and guidance, several of the protocol strategies suggest the use of thromboprophylaxis with LMWH at prophylactic or intermediate doses (ie, 40 mg s.c. daily or 40 mg s.c. twice daily, especially for BMI > 30 kg/m^2) as the preferred agent over UFH, unless patients have severe renal insufficiency (creatinine clearance [CrCl] < 30 mL/min or even 15 mL/min) (Table 1). This strategy avoids the increased health care worker exposure, use

TABLE 1 Comparisons of different institutional protocols proposed in United States and France in case of COVID-19

	Froedtert Health & The Medical College of Wisconsin, USA	Northwell Health, USA	Northshore University Health System, USA
Which patients?	In- and outpatients	Inpatients	In- and outpatients
Thrombotic risk assessment	Yes	Yes	Yes
Criteria for VTE risk	Use of Wells' Criteria IMPROVE VTE score D-dimer	Use of ISTH DIC score IMPROVE VTE score D-dimer	Use of ISTH DIC score
Hemostasis surveillance	Not mentioned	Not mentioned	Yes
Assessment of bleeding risk	Yes	Yes	Not mentioned
Proposed prophylactic treatments	Patients hospitalized with suspected or confirmed COVID-19, VTE prophylaxis with enoxaparin at prophylactic or intermediate doses (ie, 40 mg s.c. daily or 40 mg s.c. twice daily, especially for BMI > 40 kg/m^2) as the preferred agent over UFH, unless patients have acute renal failure or chronic kidney disease (CrCl < 15 mL/min); if CrCl < 15 mL/min, then UFH 5000 IU s.c. 3 times daily for BMI < 40 kg/m^2 or 7500 IU s.c. twice daily for BMI > 40 kg/m^2	Suggestion of the use of thromboprophylaxis with enoxaparin at prophylactic or intermediate doses (ie, 40 mg s.c. daily or 40 mg s.c. twice daily, especially for BMI > 30 kg/m^2) as the preferred agent over UFH, unless patients have severe renal insufficiency (CrCl < 15 mL/min); if CrCl < 15 mL/min, then UFH 5000 IU s.c. 3 times daily for BMI < 30 kg/m^2 or 7500 IU s.c. 3 times daily for BMI > 30 kg/m^2	For moderate to severe with DIC and no overt bleed, consider intermediate dose of LMWH
		Multimodal thromboprophylaxis with pharmacologic + mechanical compression should be used in ICU settings	VTE prophylaxis with daily LMWH, or twice daily subcutaneous UFH is strongly recommended (LMWH may be advantageous to reduce PPE use and provider exposure)
	Extended VTE prophylaxis with rivaroxaban 10 mg p.o. daily for 30 d should be considered at hospital discharge, without bleeding risk factors; if D-dimer is > 2× ULN during the hospitalization and Previous VTE or ≥2 of the following characteristics are met: Age > 60, ICU stay, current lower limb paralysis or paresis, current cancer, known thrombophilia	Patients hospitalized with COVID-19, especially those with an IMPROVE VTE score of ≥4 or over 60 y and with elevated D-dimers and without bleeding risk factors, should be strongly considered for extended thromboprophylaxis up to 39 d after hospital discharge with either enoxaparin 40 mg s.c. daily or rivaroxaban 10 mg p.o. daily	Continue postdischarge prophylaxis to all patients with COVID-19 over 50 y old; consider extending prophylaxis to 6 wk rivaroxaban or betrixaban in patients with any additional risk factor: prior history of thrombosis, ICU stay, cancer, thrombophilia, paralysis
	Patients with a CrCl <30 mL/min were excluded from the clinical trials of extended prophylaxis; therefore, the risk and benefit in this patient population is not known and extended prophylaxis is not recommended		For outpatients diagnosed with mild or moderate COVID-19 and low risk of bleeding, consider VTE prophylaxis as above
Patients with long-term anticoagulation	Assuming no contraindications, DOACs are considered first line for anticoagulation for most patients and preferred to coumadin. Alternatively, dose-adjusted warfarin with extended INR monitoring should be an option	If possible, patients may be switched to dabigatran as the DOAC of choice; alternatively, dose-adjusted warfarin with extended INR monitoring should be an option	Assuming no contraindications, DOACs preferred to coumadin for chronically anticoagulated COVID-19 outpatients
Lower limb ultrasound exam	As usual; not systematic	Not mentioned	Not mentioned

BMI, body mass index; COVID-19, coronavirus disease 2019; CrCl, creatinine clearance; DIC, disseminated intravascular coagulation; DOAC, direct oral anticoagulant; GFR, glomerular filtration rate; ICU, intensive care unit; INR, International Normalized Ratio; LMWH, low-molecular-weight heparin; NA, not available; PPE, personal protective equipment; s.c., subcutaneous; UFH, unfractioned heparin; IU, international units; ULN, upper limit normal; VKA, vitamin K antagonist; VTE, venous thromboembolism.

University hospital of Amiens, FRA	University hospital of Montpellier, FRA	University Hospital of Rennes, FRA	University Hospital of Saint-Etienne, FRA
Outpatients	In- and outpatients	Inpatients and elderly in establishment	ICU patients
Yes	Yes	Not mentioned	Not mentioned
Immobilization > 48 h, cancer, recent surgery, personal history of VTE, BMI > 30 kg/m^2, age > 70 y old	Thrombotic risk and ISTH DIC score	NA	NA
Not mentioned	Yes	Yes	Yes
Not mentioned	Yes	Yes	Not mentioned
Patients with COVID-19 with at least 1 VTE risk factor will receive thrombosis prophylaxis with LMWH for at least 10 d (auto-injection should be preferred)	For all inpatients: enoxaparin 4000 IU/d for at least 14 d	For all hospitalized patients except with bleeding syndrome and BMI < 30 kg/m^2: enoxaparin 4000 IU/d	If BMI > 30 kg/m^2 or severe inflammatory syndrome or femoral venous catheter: Enoxaparin 6000 IU/d
	For outpatients with elevated D-dimers (>2 N) or with VTE risk factors (personal history of VTE, known thrombophilia, lower limb paralysis, active cancer, immobilization > 7 d, age > 60 y old): enoxaparin 4000 IU/d for at least 14 d	For all hospitalized patients except with bleeding syndrome and BMI 30-40 kg/m^2: enoxaparin 6000 IU/d	If BMI > 40 kg/m^2: enoxaparin 4000 IU × 2/d
	If GFR < 30 mL/min (Cockroft): UFH 5000 IU × 2/d	For all hospitalized patients except with bleeding syndrome and BMI > 40 kg/m^2: enoxaparin BMI × 2/d (eg BMI = 42 kg/m^2), then enoxaparin 4000 IU × 2/d	If CrCl < 30 mL/min: calciparin 0.2 mL × 3/d
	If BMI ≥ 40 kg/m^2: Enoxaparin 4000 IU × 2/d	For all hospitalized patients except with bleeding syndrome and GFR < 15 mL/min: tinzaparin 3500 IU/d (we do not suggest use of calciparin 0.2 mL × 3/d to avoid accumulation	
	If high bleeding risk: discuss preventive anticoagulation; if hospitalized patients: compression bands (BIFLEX) if no peripheral artery disease; in ICU patients: intermittent pneumatic compression	In ICU patients: proceed as for hospitalized patients	
		In elderly patients in establishment: enoxaparin 4000 IU/d	
Not mentioned	In hospitalized patients: replace by LWMH (in the absence of contraindication)	Not mentioned	Not mentioned
Not mentioned	As usual; not systematic	As usual; not systematic	Fast (4 points): • Systematic at days 7, 14, and 21 • Earlier if patient gets worse without any evident cause • Earlier if femoral venous catheter • Before first chair setting

of limited resources such as personal protective equipment for frequent blood draws, and the time needed to achieve therapeutic activated partial thromboplastin times. There are randomized trials that are being initiated studying intermediate to high doses of LMWH in the management of patients with COVID-19 with severe illness.

1.1.2 | Antithrombotic use with antivirals

It is important to recognize the interactions that may occur between COVID-19 investigational therapies and antithrombotic use. If new medications are added to treat COVID-19 or other conditions, drug interaction checking should be completed due to the risk of interaction with antithrombotic medications through P-glycoprotein (P-gp) or the cytochrome 450 (CYP) system in the liver (especially CYP3A4). Several protocol strategies take into consideration the concomitant use of antithrombotic with antiviral therapies (especially with the antivirals liponavir and ritonavir), as this can affect choice and/or dosage of antiplatelet and anticoagulants. For antiplatelet agents, certain antivirals, especially lopinavir/ritonavir, may potentiate CYP3A4 or P-gp inhibition, and as such there may be reduction in clopidogrel effects and increased effects of ticagrelor.[52,53] Therefore, these agents should be switched over to prasugrel if possible (unless there are contraindications such as prior stroke or transient ischemic attack).[53] Alternatively, platelet function studies (P2Y12 monitoring) may also be considered.

For oral anticoagulants (OACs), drug interactions should be considered with direct oral anticoagulants (DOACs (P-gp or moderate to strong CYP3A4, either inhibitors or inducers). Apixaban and rivaroxaban have CYP3A4 and P-gp inhibition while dabigatran and edoxaban have only P-gp inhibition. Betrixaban has P-gp and ATP-binding cassette subfamily B member 1 inhibition.[54] Dose adjustments may be required if using vitamin K antagonists (VKAs), apixaban, or betrixaban, while adjustments are not needed for edoxaban and rivaroxaban. Parenteral anticoagulants, including UFH or LMWH, are non-CYP metabolized and do not interact with investigational agents, while edoxaban and rivaroxaban should not be coadministered with lopinavir/ritonavir. Currently, patients with COVID-19 treated with IL-6 inhibitors, such as tocilizumab, do not need dose adjustments at this time. If possible, patients may be switched to dabigatran, edoxaban, or betrixaban as the DOAC of choice if combined therapy with CYP3A4 inhibitor is prescribed.[54] Alternatively, dose-adjusted VKAs with frequent International Normalized Ratio (INR) monitoring or parenteral anticoagulants may be a good option.

1.1.3 | Extended out-of-hospital VTE prophylaxis

Of all VTEs occurring in the community, at least half are related to current or recent hospitalization for surgery or medical illness.[55] Thus, hospitalization of acutely ill patients is associated with an 8-fold increase in VTE risk.[55] Studies of medically ill patients have shown the benefit of extended VTE prophylaxis in high-risk patient groups. Patients hospitalized for COVID-19 would meet criteria similar to these trials as an infectious disease. There is recent evidence that an IMPROVE score of ≥4 (Table 2) ± elevated D-dimer (>2× ULN) identifies a >3-fold higher VTE risk population that significantly benefit from extended out-of-hospital thromboprophylaxis up to 39 days or more with rivaroxaban without an increase in major bleeding.[12,23,34] There are also data with betrixaban that reveal net clinical benefit from extended thromboprophlaxis for up to 42 days in hospitalized medically ill patients, including those with severe infection.[56] Further, prolonged rivaroxaban prophylaxis reduced the incidence of VTE in patients hospitalized for acute infectious diseases, particularly those involving the lungs. Efficacy benefits were, in part, offset by bleeding outcomes.[57] Identification of independent VTE risk factors and estimating the magnitude of the associated risk may be helpful when strategies for prophylaxis delivery are devised. Alternatively, consider risk-benefit evaluation for extended enoxaparin in selected patients.[58] Protocols suggest patients hospitalized with COVID-19, especially those with an IMPROVE VTE score of ≥4, elevated D-dimer (>2× ULN), and ≥2 of the following characteristics are met: age > 60, previous VTE, current cancer, or known thrombophilia, should be strongly considered for extended thromboprophylaxis up to 39-45 days after hospital discharge with either lovenox 40 mg s.c. daily or rivaroxaban 10 mg p.o. daily and low risk of bleeding.[23,58] Insurance coverage investigation should be started early during acute hospital stay to ensure patient affordability. Consideration for prophylaxis should also include high-risk patients with COVID-19, including those with limited mobility, history of prior VTE, active malignancy, and BMI > 30 kg/m^2 requiring supplemental oxygen or recent stay in the ICU. All individuals are advised to stay active, if able, during times of quarantine.

1.1.4 | Continuation of home antithrombotic medications or need of chronic antithrombotic use

Evaluating choice of anticoagulant is always important to ensure that the patient is on optimal therapy. Several protocol strategies suggest that patients on chronic antithrombotics (antiplatelets or chronic OACs should be kept on their therapy unless there are absolute contraindications (such as active bleeding, severe thrombocytopenia, planned procedure, or significant new drug interaction or other contraindications). To reduce new patient contacts within the anticoagulation clinic, it is important that all pharmacists review the indication for anticoagulation and determine if a DOAC treatment could be clinically appropriate. Patients with long-term anticoagulation receiving a VKA should be considered for alternative therapies, such as DOACs or LMWH, or increasing the interval of INR monitoring to 12 weeks in stable patients on warfarin.[59] Patients who are breastfeeding or who have mechanical valves, ventricular assist devices, renal failure with a creatinine clearance <15 mL/min or rapidly worsening renal function, weight over 120 kg, gastric malabsorption disorders, or antiphospholipid antibody syndrome should be treated with warfarin.

TABLE 2 The 7-factor IMPROVE VTE RAM[a] (12)

VTE risk factor	Points for the risk score
Previous VTE	3
Thrombophilia[b]	2
Current lower limb paralysis or paresis[c]	2
Cancer[d]	2
Immobilization[e]	1
ICU/CCU stay	1
Age > 60 y	1

Note: The interpretation of the score predicts VTE risk through 3 mo as follows: score 0 = 0.4%; score 1 = 0.6%; score 2 = 1%; score 3 = 1.7%; score 4 = 2.9%; score ≥ 5=7.2%.

CCU, coronary care unit; ICU, intensive care unit; RAM, risk assessment model; VTE, venous thromboembolism.

[a]A score of 0-1 constitutes low VTE risk; A score of 2-3 constitutes moderate VTE risk; A score of ≥4 constitutes high VTE risk.

[b]A congenital or acquired condition leading to an excess risk of thrombosis.

[c]Leg falls to bed by 5 s, but has some effort against gravity (from National Institutes of Health stroke scale).

[d]May include active cancer (excluding nonmelanoma skin cancer) or a history of cancer within 5 y.

[e]Strict definition is complete immobilization confined to bed or chair ≥ 7 d; modified definition is complete immobilization with or without bathroom privileges ≥ 1 d.

1.2 | Summary of key recommendations from institutional protocols

These interim institutional protocols are not intended to replace clinical judgment and may not apply to all patients or clinical situations where antithrombotic therapy is needed.

1. Medical floor COVID-19–positive patients: LMWH at prophylactic or intermediate doses (ie, 40 mg s.c. daily or 40 mg s.c. twice daily, especially for BMI > 30 kg/m^2) as the preferred agent over UFH, unless patients have severe renal insufficiency (CrCl < 30 or 15 mL/min). In patients with acute renal failure or chronic kidney disease with CrCl <15 mL/min or on dialysis, UFH 5000 units 3 times daily or 7500 units 3 times daily if BMI > 40 kg/m^2 is recommended. We acknowledge the data are not as robust for a BMI > 30 kg/m^2 cutoff relative to 40 kg/m^2 BMI.
2. Patients with severe COVID-19 requiring high-flow oxygen or ventilator: LMWH at prophylactic or intermediate doses (ie, 40 mg s.c. daily or 40 mg s.c. twice daily, especially for BMI > 30 kg/m^2) as the preferred agent over UFH, should be utilized in ICU settings, with serious illness meeting sepsis-induced coagulopathy score of ≥4 or with markedly elevated D-dimer (>6× ULN). UFH 7500 3 times daily should be used in patients with acute renal failure or chronic kidney disease with CrCl <15 mL/min or on dialysis.
3. Extended thromboprophylaxis: Patients hospitalized with COVID-19, especially those with an IMPROVE VTE score of ≥4, elevated D-dimer (>2× ULN), or over 60 years and without bleeding risk factors, or recent ICU stay should be strongly considered for extended thromboprophylaxis up to 40 days after hospital discharge with either lovenox 40 mg s.c. daily, rivaroxaban 10 mg p.o. daily, or betrixaban 80 mg p.o. daily.
4. Routine empiric therapeutic dose of intravenous UFH or systemic tissue plasminogen activator or routine use of inferior vena cava filters: No current supporting evidence for its use without absolute indications.
5. Continuation of home antithrombotic medications or need of chronic antithrombotics: Patients on antiplatelets or OACs should be kept on their therapy unless there are absolute contraindications (such as active bleeding, severe thrombocytopenia, planned procedure, or significant new drug interaction or other contraindications). DOACs are preferred over warfarin for treatment of VTE or atrial fibrillation due to decreased need for monitoring. Patients with mechanical valves, ventricular assist devices, or antiphospholipid antibody syndrome should be treated with warfarin, with extended periods for INR monitoring or drive-through monitoring.
6. Patients on antiviral therapy, such as lopinavir/ritonavir: For antiplatelet agents, certain antivirals, especially lopinavir/ritonavir, may potentiate CYP3A4 or P-gp inhibition, and as such there may be reduction in clopidogrel effects and increased effects of ticagrelor. Therefore, patients on these agents should have them switched over to prasugrel if possible (unless contraindications such as prior stroke or transient ischemic attack). Alternatively, platelet function studies (P2Y12 monitoring) may also be considered. For OACs, if possible, patients may be switched to dabigatran, edoxaban, or betrixaban from apixaban and rivaroxaban as the DOACs of choice if combined therapy with CYP3A4 inhibitor is prescribed. Alternatively, dose-adjusted warfarin with frequent INR monitoring should be a good option.

RELATIONSHIP DISCLOSURE

KPC reports nothing to disclose. GM reports nonfinancial support from Aspen, personal fees from BMS/Pfizer, personal fees and nonfinancial support from Bayer, and personal fees from LEO pharma, outside the submitted work. AJT reports an educational grant from Janssen and research support from Janssen, BMS, Idorsia, and Daiichi Sankyo; and consulting for Recovery Force. ACS reports consulting fees from Bayer, BMS, Janssen, Boehringer Ingelheim, Portola, and ATLAS group; and research grants from Janssen and Boehringer Ingelheim.

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How to cite this article: Cohoon KP, Mahé G, Tafur AJ, Spyropoulos AC. Emergence of institutional antithrombotic protocols for coronavirus 2019. *Res Pract Thromb Haemost*. 2020;4:510–517. https://doi.org/10.1002/rth2.12358