To Anticoagulate or Not to Anticoagulate in COVID-19: Lessons after 2 Years

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Abstract

A hypercoagulable state associated with coronavirus disease 2019 (COVID-19) has been well documented and is believed to be strongly supported by a proinflammatory state. The hypercoagulable state in turn results in increased incidence of arterial and venous thromboembolism (VTE) seen in hospitalized COVID-19 when compared with hospitalized non-COVID-19 patient cohorts. Moreover, patients with arterial or VTE and COVID-19 have higher mortality compared with COVID-19 patients without arterial or VTE. Prevention of arterial or VTE thus remains an essential question in the management of COVID-19 patients, especially because of high rates of reported microvascular and macrovascular thrombosis. This has prompted multiple randomized control trials (RCTs) evaluating different anticoagulation strategies in COVID-19 patients at various stages of the disease. Herein, we review findings from RCTs in the past 2 years of antithrombotic therapy in critically ill hospitalized patients, noncritically ill hospitalized patients, patients postdischarge from the hospital, and outpatients. RCTs in critically ill patients demonstrated therapeutic dose anticoagulation does not improve outcomes and has more bleeding than prophylaxis dose anticoagulant in these patients. Trials in noncritically ill hospitalized patients showed a therapeutic dose anticoagulation with a heparin formulation might improve clinical outcomes. Anticoagulation with a direct oral anticoagulant posthospital discharge may improve outcomes, although there is a large RCT in progress. Nonhospitalized COVID-19 patients have an insufficient burden of events to be candidates for antithrombotic therapy. Anticoagulation in pregnant and lactating patients with COVID-19, as well as antiplatelet therapy for COVID-19, is also reviewed.

Keywords
- COVID-19
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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has engrossed the entire scientific community and highlighted the need for consensus guidelines on how to treat various aspects of coronavirus disease 2019 (COVID-19). Although various studies on management of COVID-19 have been published, there is still significant uncertainty with respect to pharmacologic treatment and areas of supportive care.[1–4] One such area is the role of antithrombotic therapy. This article will aim to discuss the rationale for thromboprophylaxis in COVID-19 and review the relevant literature to base decisions on which patients would be more appropriate to initiate anticoagulation.

Initial reports out of Wuhan (China) were essential in describing the clinical course of disease and understanding the body's response to COVID-19.[5,6] From these studies, pooled analyses revealed that higher levels of D-dimer[5,7,8] were associated with increased odds of severe disease and death.[6] In severe COVID-19 disease, patients had elevated levels of white blood cell counts, lymphocyte counts, platelet counts, interleukin (IL)-6, lactate dehydrogenase, and serum ferritin.[7,9] Larger studies out of China reported thrombocytopenia in 36.2% of patients.[10,11] This trend of abnormal coagulation parameters was confirmed in other studies along with reports of prolonged prothrombin time (PT), decreased antithrombin activity, and fibrinogen, particularly among severe COVID patients.[7,12] Laboratory results thus primarily reflect thrombocytopenia, mildly elevated PT, and increased D-dimer. These laboratory findings suggested an important role of coagulopathy and inflammation among COVID-19-related deaths.

Indeed, COVID-associated coagulopathy seems to impact all facets of hemostasis, including primary hemostasis, secondary hemostasis, and fibrinolysis.[13–15] Moving beyond laboratory findings, reports of pulmonary embolism (PE) and deep vein thrombosis (DVT) were later described.[16,17] A case series described an increased incidence of PE at 20.6% compared with historical controls of intensive care unit (ICU) patients at 6.1%.[16] Following various published reports of venous thromboembolisms (VTEs), a systematic review and meta-analysis was conducted of 27 studies, totaling 3,342 patients with COVID-19, which reported a pooled incidence of 16.5% for PE and 14.8% for DVT; PE was more common among patients admitted to the ICU compared with those who were not (24.7% vs. 10.5%).[17] These findings brought awareness to the complication of VTE in COVID-19 and prioritized the need for effective anticoagulation strategies.

Pathophysiology of VTE

VTE occurs when the components of Virchow's triad are met and activates the coagulation cascade. Virchow's triad includes endothelial injury, hypercoagulability, and venous stasis.[18] Tissue factor expression via endothelial injury will activate the coagulation cascade via the extrinsic pathway, and subsequently the intrinsic pathway, which converge to activate the common pathway leading to thrombin generation.[19] Thrombin converts fibrinogen to fibrin, which supports clot stabilization. In addition, the inflammatory process increases the expression of $P2Y_{12}$ receptors and subsequently platelet aggregation.[20] Activated platelets provide a surface for mediators of the coagulation cascade to bind and shield coagulation proteins from inactivation.[21] Activated platelets will attract and bind neutrophils, which produce neutrophil extracellular traps (NETs), a web-like structure consisting of deoxyribonucleic acid, histones, and neutrophil granules.[22,23] Platelet aggregation is aided by histone and as the venous thrombus begins to form, red blood cells (RBCs) will also bind to this structure of platelets, neutrophils, and NETs. Venous thrombi consist of fibrin, RBCs, platelets, and neutrophils, which can continue to propagate in the setting of injury or infection in an environment surrounded by inflammatory cytokines.

In the setting of COVID-19, there are various postulated mechanisms for development of VTEs. One component of Virchow's triad that is influenced by COVID is endothelial injury mediated by angiotensin-converting enzyme 2 (ACE2) entry of SARS-CoV-2 through its spike protein.[24] ACE2 is a component of the renin–angiotensin–aldosterone system (RAAS), this system has the potential to contribute to clot formation via various mechanisms.[25] Angiotensin II (AngII) binds to AngII receptor type I (AT1), which mediates vasoconstrictive, proinflammatory, and pro-oxidative effects. Plasminogen activator inhibitor-1 (PAI-1) release is stimulated via AngII, which inhibits tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA). Increased production of PAI-1 shifts the balance between PAI-1 and tPA/uPA toward a hypofibrinolytic state, preventing degradation of clots.[26] Moving beyond the RAAS, declines in oxygen saturation, which is frequently present with a COVID infection, can affect thrombus formation via hypoxia-inducible transcription factors leading to a prothrombotic state.[27] Host responses against viral infections are mediated by type 1 interferons (IFNs), IFNα and IFNβ. SARS-CoV-1 has been demonstrated to inhibit the production of these types of IFNs and it is postulated that SARS-CoV-2 works similarly leading to a delayed and persistent type 1 response.[28,29] This dysregulated IFN response leads to the recruitment of macrophages and neutrophils, which produce proinflammatory cytokines, as evidenced by increased levels of IL-1β, IL-6, and tumor necrosis factor α. This hyperinflammatory state as explained above will contribute toward the developments of thrombi. In addition, critically ill patients with severe COVID-19 requiring ICU admission and ventilator supports are at risk for venous stasis due to immobilization from paralytics, which further increases risk of thrombosis.[30]

Autoantibodies directed at phospholipids and phospholipid-binding proteins, including lupus anticoagulant, antibodies against cardiolipin, and antibodies against the cardiolipin-binding proteins phosphatidylserine/prothrombin (Factor 2) and β-2 glycoprotein I (β2GPI), are commonly identified in COVID-19 patients affected by coagulopathies but infrequently in mild cases.[31,32] These antibodies are also transiently present in many COVID-19 patients who do not develop coagulopathies, which casts doubt on this association.

Clinical Trials of Anticoagulation in COVID-19 Patients

Since the phenomenon of increased thrombosis in COVID-19 patients was first determined, clinical trials, both observational and randomized, were quickly designed and implemented. A summary of these studies is provided in ►**Table 1**, and a summary of recommendations at different stages of the disease is illustrated in ►**Fig. 1**. These studies will be further described below by the stage of disease in which the patient was studied.

ICU Patients

The relative risk (RR) of developing VTE in critically ill COVID-19 patients was found to range between 16 and 69% in several observational studies.[16,33,34] Early in the pandemic, anticoagulation irrespective of dose used showed benefit in mortality in ICU COVID-19 patients over no anticoagulation

Table 1 Summary of randomized controlled trial results evaluating anticoagulation in different COVID-19 patient populations

Trial	COVID-19 patient population	Size of trial (*N*)	Anticoagulant dose comparisons (LMWH)	Main results
Perepu et al[40]	ICU and/or had laboratory evidence of coagulopathy (high D-dimer)	176	Intermediate versus prophylactic	No difference. All-cause mortality (OR, 0.66; 95% CI, 0.30–1.45; $p = 0.31$)
INSPIRATION[39]	ICU patients	562	Intermediate versus prophylactic	No difference. Thrombosis, use of ECMO, or mortality (HR 1.06; 95% CI 0.83 to 1.36)
Multiplatform RCT[38]	ICU patients	1,098	Therapeutic versus prophylactic or intermediate	Prophylactic dose better. Survival to hospital discharge (65 vs. 63%; odds ratio [OR] 0.84, 95% CI 0.64–1.11). Bleeding (3.8 vs. 2.3%; OR 1.48, 95% CI 0.75–3.04). Organ support-free days (OR 0.83, 95% CI 0.67–1.03)
Multiplatform RCT[44]	Non-ICU patients	2,219	Therapeutic versus prophylactic or intermediate	Therapeutic dose better. Organ support-free days with therapeutic dosing (80 vs. 76%; OR 1.27, 95% CI 1.03–1.58)
ACTION[45]	Non-ICU patients with high D-dimers	615	Therapeutic versus prophylactic (DOAC)	No difference. Time to death, duration of hospitalization, or duration of supplemental oxygen to day 30 (win ratio 0.86 [95% CI 0.59–1.22; $p = 0.4$])
HEP-COVID[41]	Non-ICU patients with high D-dimers	257	Therapeutic versus prophylactic or intermediate	Therapeutic dose better. Death, VTE, or arterial thromboembolism (RR 0.68; 95% CI, 0.49–0.96; $p = 0.03$)
RAPID[43]	Non-ICU with high D-dimers	465	Therapeutic versus prophylactic	Therapeutic dose better. Death, ICU admission, or mechanical ventilation at 28 days (OR 0.69; 95% CI 0.43–1.10; $p = 0.12$)
ACTIV-4B[53]	Outpatients	657	Aspirin (81 mg orally once daily), prophylactic dose apixaban (2.5 mg orally twice daily), therapeutic dose apixaban (5 mg orally twice daily), or placebo	No difference compared with placebo. All-cause mortality, symptomatic venous or arterial thromboembolism, myocardial infarction, stroke, or hospitalization for cardiovascular or pulmonary cause (0.0% [95% CI not calculable] in the aspirin group, 0.7% [95% CI, −2.1% to 4.1%] in the 2.5 mg apixaban group, and 1.4% [95% CI, −1.5% to 5.0%] in the 5-mg apixaban group)
Ananworanich et al[54]	Outpatients	497	Prophylactic versus placebo (DOAC)	No difference compared with placebo. Disease progression (risk difference −1.0, 95% CI, −6.4 to 8.4; $p = 0.78$)
MICHELLE[51]	Postdischarge at high risk	320	Prophylactic versus placebo (DOAC)	Prophylactic better. VTE, symptomatic arterial thromboembolism, or any fatal cardiovascular event (RR, 0.33, 95% CI 0.12–0.90).

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019, DOAC, direct oral anticoagulant; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; ICU, intensive care unit; LMWH, low-molecular-weight heparin; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; VTE, venous thromboembolism.

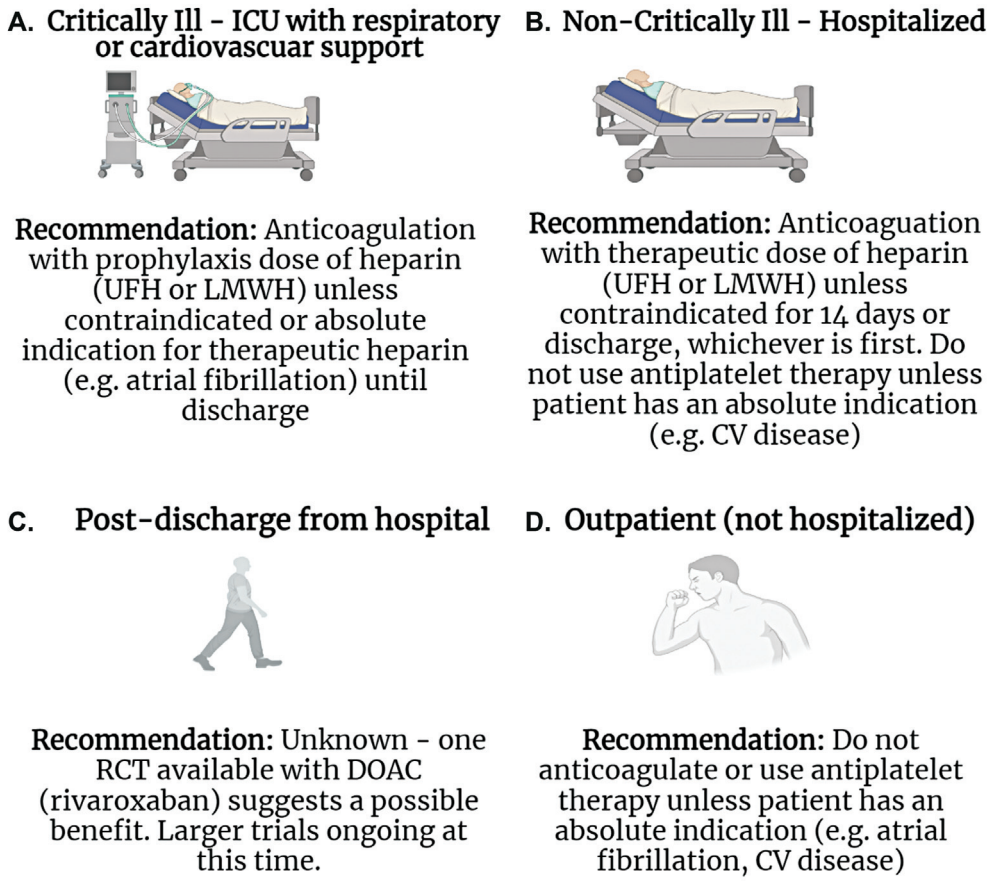

Fig. 1 (**A–D**) Summary of recommendations according to results of randomized clinical trials for different stages of disease in patients with COVID-19. CV, cardiovascular; DOAC, direct oral anticoagulant; ICU, intensive care unit; UFH, unfractionated heparin; LMWH, low molecular weight heparin.

in multiple observation studies.[35,36] However, most subsequent randomized trials have failed to show any benefit of both therapeutic and intermediate dose anticoagulation beyond that offered by prophylactic dose anticoagulation alone in ICU patients. The only randomized study to show any benefit of therapeutic anticoagulation in ICU COVID-19 patients involved only 20 patients requiring mechanical ventilation. These patients were assigned to either therapeutic enoxaparin or prophylactic anticoagulation. Therapeutic anticoagulation group improved gas exchange as measured by arterial oxygen partial pressure to fractional inspired oxygen (PaO2/FiO2), had more ventilator-free days, and higher ratio of successful liberation from mechanical ventilation.[37]

In the summer of 2020, three independent groups (ATTACC, ACTIV-4a, REMAP-CAP) running randomized trials of therapeutic dose anticoagulation with heparin (unfractionated heparin [UFH] or low-molecular-weight heparin [LMWH]), compared with thromboprophylaxis doses joined forces by harmonizing their protocols and endpoints. The Multiplatform Randomized Clinical Trial group (mpRCT) studied 1,098 patients with severe COVID-19 infection admitted to the ICU randomized to either therapeutic dose anticoagulation or usual-care thromboprophylaxis. Therapeutic dose anticoagulation consisted of doses used for treatment for acute VTE according to local site protocols for up to 14 days or until recovery. Usual-care thromboprophylaxis was determined according to the local practice and included either standard low-dose or enhanced intermediate-dose thromboprophylaxis. Therapeutic dose anticoagulation failed to show an increase in probability of survival to hospital discharge or number of days free of cardiovascular (CV) or respiratory organ support. Major bleeding occurred more frequently in the therapeutic dose anticoagulation group (3.8% vs. 2.3% in the usual-care thromboprophylaxis group), whereas major thrombotic events were less frequent (6.4% vs. 10.4% in the usual-care thromboprophylaxis group).[38]

The INSPIRATION study evaluated intermediate dose anticoagulation in a multicenter randomized control trial (RCT) of 562 COVID-19 patients admitted to ICU where LMWH (enoxaparin 1 mg/kg daily), was compared with standard

prophylactic anticoagulation (enoxaparin 40 mg daily). At 30 days there was no statistically significant difference in primary outcome of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality within 30 days. Both major and clinically relevant nonmajor bleeding events were more frequent in the intermediate dose group, but this outcome was not statistically significant.[39] In another RCT of 176 patients, all-cause mortality at 30 days did not differ between prophylactic and intermediate dose enoxaparin in patients with COVID-19 admitted to ICU and/or laboratory evidence of coagulopathy.[40]

Additionally, in the HEP-COVID study,[41] 257 patients with COVID-19 and D-dimer levels > 4 times the upper limit of normal (ULN) or sepsis-induced coagulopathy score of 4 or greater were randomized to either standard prophylactic or intermediate dose LMWH or UFH versus therapeutic dose LMWH throughout hospitalization. As with other trials, the 72 patients in the ICU stratum did not have any benefit from therapeutic anticoagulation (RR [95% confidence interval [CI]] 0.89 [0.60–1.33]; $p = 0.56$) while there was a very large (but not statistically significant) increase in major bleeding (RR 7.63 [0.43–136.69]; $p = 0.12$).

Non-ICU Hospitalized Patients

Data on use of more than prophylactic dose anticoagulation in moderately ill COVID-19 patients requiring hospitalization but not ICU level care is more promising. A large observational study evaluated use of apixaban in prophylactic (2.5 mg twice daily) and therapeutic (5 mg twice daily) doses as well as thromboprophylaxis and therapeutic doses of heparin (LMWH or UFH) at the beginning of the pandemic. Less than 10% of the patients were either in the ICU or receiving mechanical ventilation for the first 48 hours of their admission. When compared with patients not on anticoagulation, there was a significant decrease in mortality associated with apixaban, but not with LMWH or UFH. However, when stratified by D-dimer level, there was no benefit of apixaban if D-dimer level was < 1 µg/mL (fibrinogen-equivalent units [FEU]) or between 3 and < 10 µg/mL. Apixaban, both therapeutic and prophylactic dose, reduced mortality with D-dimer between > 1 and 3 µg/mL and at > 10 µg/mL as did prophylaxis doses of enoxaparin.[42]

In the HEP-COVID study,[41] 257 patients with COVID-19 and D-dimer levels > 4 times the ULN or sepsis-induced coagulopathy score of 4 or greater were randomized to either standard prophylactic or intermediate dose LMWH or UFH versus therapeutic dose LMWH throughout hospitalization. Therapeutic dose LMWH resulted in reduction in primary efficacy outcome of VTE, arterial thromboembolism, or death from any cause in non-ICU patients. There was no significant difference in major bleeding events between the two groups, although CIs were wide.

In the RAPID trial,[43] 465 moderately ill COVID-19 patients were randomized to therapeutic or prophylactic dose anticoagulation with UFH or LMWH. Moderately ill patients were defined as not requiring ICU or mechanical ventilation and with elevated D-dimer levels. At 28 days, primary composite outcome of admission to ICU, invasive and noninvasive mechanical ventilation, or death was not different between the two groups, but odds of death were decreased with therapeutic dose anticoagulation, and there was no increase in major bleeding compared with prophylactic anticoagulation.

In the mpRCT of 2,219 noncritically ill patients (defined as not needing respiratory or CV support in an ICU) hospitalized with COVID-19,[44] an initial strategy of therapeutic dose anticoagulation with LMWH or UFH increased the probability of survival to hospital discharge with reduced use of organ support when compared with thromboprophylaxis. Therapeutic dose anticoagulation was beneficial irrespective of baseline D-dimer values. Major bleeding occurred in 1.9 and 0.9% of patients in the therapeutic and thromboprophylaxis group, respectively. A major thrombotic event or in-hospital death occurred in 8% of the therapeutic dose anticoagulation group compared with 9.9% in the thromboprophylaxis group. Stratification by D-dimer level did not affect the results of the study.

The ACTION study,[45] a multicenter open-label trial that assigned 615 hospitalized patients with elevated D-dimer concentration to either prophylactic or therapeutic dose anticoagulation, failed to show any benefit of therapeutic anticoagulation over prophylactic anticoagulation in moderately ill COVID-19 patients. The former study group received prophylactic dose enoxaparin or UFH and the latter group anticoagulation regimen included oral rivaroxaban (20 mg daily or 15 mg daily) for stable patients, or therapeutic dose enoxaparin or UFH for unstable patients followed by rivaroxaban to day 30. There was no difference in primary efficacy outcome of time to death, duration of hospitalization, or supplemental oxygen to day 30. There was a statistically significant increased bleeding seen in the therapeutic anticoagulation group. A possible explanation for lack of benefit seen in this trial with therapeutic anticoagulation using rivaroxaban is absence of heparin's pleiotropic effects (e.g., prevention of viral adhesion, anti-inflammatory activity[46]). This will be further elucidated, as at the time of this writing there is an ongoing clinical trial (FREEDOM COVID) comparing enoxaparin with apixaban in this patient population (NCT04512079).

Posthospital Discharge

In high VTE risk non-COVID-19 patients, the risk of VTE extends up to 6 weeks posthospital discharge with at least 60% of all VTE occurring in posthospital discharge patients.[47,48] Observational studies have shown generally low risk of VTE in posthospital discharge COVID-19 patients with significant association seen with advanced age, prior VTE, ICU stay, chronic kidney disease, peripheral arterial disease, carotid occlusive disease, IMPROVE-DD score ≥ 4, and coronary artery disease.[49] A quality improvement study at Kings College London based on 1,877 hospital discharges reported a postdischarge VTE rate of 4.8/1,000, compared with a postdischarge VTE rate of 3.1/1,000 after 18,159 non-COVID discharges in 2019, which is consistent with a 60% higher risk of thrombosis (odds ratio 1.6; 95% CI, 0.77–3.1).[50]

More recently, the MICHELLE trial,[51] a 320-patient open-label multicenter RCT, showed that extended anticoagulation with low-dose rivaroxaban (10 mg/day for 35 days) after hospitalization for COVID-19 reduces the odds of VTE without increasing the risk of bleeding in high-risk VTE patients. The primary efficacy outcome (a composite of symptomatic or fatal VTE, asymptomatic VTE, symptomatic arterial thromboembolism, and CV death at day 35) occurred in 3 and 9% of patients assigned to rivaroxaban and no anticoagulation, respectively (RR, 0.33; 95% CI, 0.13–0.90; $p = 0.029$). There were no major bleeding events defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria in either cohort. Clinically relevant nonmajor bleeding, a secondary safety endpoint, was also very low and did not differ between the two cohorts. At the time of writing, a much larger trial with apixaban (ACTIV-4c – 5,300 patients) is currently enrolling. The result of this study should provide greater clarity on the use of anticoagulation in postdischarge patients (NCT04650087).

Outpatients with COVID-19

Outpatients comprise the largest population of individuals infected with SARS-CoV-2. A retrospective cohort study from the beginning of the pandemic published by Piazza et al[52] did not find any case of symptomatic VTE in COVID-19 outpatients, compared with 27 and 2.2% in the intensive care and hospitalized nonintensive care cohorts, respectively.

The ACTIV-4B Outpatient Thrombosis Prevention Trial,[53] aimed at evaluating the effects of antithrombotic therapy in outpatients with COVID-19, was a randomized, adaptive, double-blind, placebo-controlled trial that randomly assigned outpatients with COVID-19 in a 1:1:1:1 ratio to receive aspirin (81 mg orally once daily), prophylactic dose apixaban (2.5 mg orally twice daily), therapeutic dose apixaban (5 mg orally twice daily), or matching placebo for 45 days. The primary adjudicated outcome was a composite of all-cause mortality, symptomatic VTE or arterial thromboembolism, myocardial infarction, stroke, or hospitalization for CV or pulmonary causes. The study was terminated after enrollment of 9% of participants because of a primary event rate lower than anticipated, similar to the Piazza et al study. Treatment with aspirin or apixaban compared with placebo did not reduce the rate of composite clinical outcome; the absolute risk reductions compared with placebo for the primary outcome were 0.0% (95% CI not calculable) in the aspirin group, 0.7% (95% CI, –2.1 to 4.1%) in the prophylactic dose apixaban group, and 1.4% (95% CI, –1.5 to 5%) in the therapeutic dose apixaban group, respectively. No major bleeding events were reported, although there was a small, nonsignificant increase in clinically relevant nonmajor bleeding with apixaban at either dose, but not with aspirin.

A phase 2b placebo-controlled randomized study of rivaroxaban 10 mg once daily in patients with COVID-19 not currently hospitalized or under immediate consideration for hospitalization, was terminated after almost 500 of the target 600 participants were enrolled because a prespecified interim analysis of the first 200 participants in the intent-to-treat population demonstrated it would be futile to meet the primary efficacy endpoint.[54] Disease progression rates with rivaroxaban was 20.7 versus 19.8% in placebo groups, with a risk difference of –1.0 (95% CI, −6.4 to 8.4%; $p = 0.78$). There were no major bleeds in either cohort, although there was a nonsignificant increase in clinically relevant nonmajor bleeding with rivaroxaban compared with placebo (2.3% vs. 0.9%). At the time of this writing, there is an ongoing large (∼400 patients) randomized trial, PREVENT-HD, comparing rivaroxaban 10 mg once daily with placebo in outpatients with COVID-19.[55]

Thus, the use of antiplatelet or antithrombotic therapy for the management of outpatients with COVID-19 cannot be recommended at this time. Despite these findings, risk stratification based on comorbidities, including obesity, sedentary lifestyle, past/family history of VTE, or thrombophilia, may be helpful in guiding thromboprophylaxis use in these patients.[56]

Pregnancy and Lactation

Pregnancy is a hypercoagulable state; however, VTE has not been reported as a complication in pregnancy and COVID-19, even in cases of severe infection.[57–60] Randomized data are lacking with respect to thromboprophylaxis in pregnant and lactating patients with COVID-19 as these patients were excluded from the current clinical trials due to the unknown risks of the intervention arm on the fetus. Current society guidelines recommend thromboprophylaxis for COVID-19 pregnant patients if there are no contraindications and potential benefits outweigh the risks of bleeding.[61] LMWH is the recommended anticoagulant rather than UFH due to reliability and ease of administration.[62] Due to lack of safety data, direct-acting oral anticoagulants (DOACs) are not recommended in this setting.[63,64] Warfarin should be avoided especially in the first trimester due to risk of teratogenicity.[63] Breastfeeding women hospitalized with COVID-19 infection should receive thromboprophylaxis with LMWH, UFH, or coumadin.[63]

Antiplatelet Agents

The role of aspirin was studied in a large RCT that enrolled 14,892 patients to receive either aspirin 150 mg daily or usual care. At 28 days, there was no reduction in mortality or the risk of progressing to invasive mechanical ventilation or death. However, there was a small increase in the rate of being discharged alive within 28 days (75% vs. 74%; rate ratio 1.06, 95% CI, 1.02–1.10; $p = 0.0062$). There was also a reduction in thrombotic events (4.6% vs. 5.3%) but an increase in major bleeding events (1.6% vs. 1%) in the aspirin group.[65] Whether the use of aspirin in the early stages of COVID-19, where thromboxane levels are not high, is beneficial, remains a matter of study,[66] and findings from a meta-analysis suggests that antiplatelet agents, especially aspirin, may have favorable effects by lowering the risk of death,[67] even in the prehospital setting.[68] However, as seen above, aspirin did not provide any benefit in the outpatient RCT ACTIV-4B.

The ACTIV-4a trial compared the addition of a $P2Y_{12}$ inhibitor for 35 days to therapeutic heparin with therapeutic

heparin alone in noncritically ill patients hospitalized for COVID-19.[69] Enrollment was discontinued after 562 noncritically ill patients were enrolled when a planned adaptive analysis demonstrated that the statistical criterion for futility was met. The choice of which $P2Y_{12}$ inhibitor was left to the investigator and ticagrelor was used in 63% of the patients and clopidogrel was used in 37% of the patients. The primary endpoint was the median number of organ support-free days which was 21 days in both groups.

Other antiplatelet agents have yet to be evaluated in randomized trials. COVID-PACT is a multicenter randomized 2×2 factorial design trial that will be evaluating risk of venous and arterial thrombotic events in ICU patients with full dose anticoagulation versus standard dose prophylactic anticoagulation and antiplatelet therapy (clopidogrel) versus no antiplatelet therapy (NCT04409834). At this time, society guidelines recommend against use of antiplatelet agents for purposes of thromboprophylaxis.[70]

Sulodexide

Sulodexide is a natural glycosaminoglycan with antithrombotic and profibrinolytic activities.[71] It has a weaker effect on hemostasis than heparin, with a very low risk of bleeding.[72] In a RCT[71,72] evaluating the use of sulodexide in 243 ambulant patients with COVID-19 at high risk of severe clinical progression due to the presence of chronic comorbidities, 22/124 (17.7%) required hospital admission at 21 days' follow-up in the sulodexide group compared with 35/119 (29.4%) in the placebo group, thus compounding a nearly 40% risk reduction (RR 0.6; 95% CI, 0.37–0.96). However, sulodexide did not provide significant reduced mortality.

Society Guidelines

Many organizations have established guidelines related to anticoagulation in COVID-19 patients. It should be noted that the guideline recommendations subsequently listed in this section were predominantly created prior to publication of the results of the RCTs discussed earlier in the article (►**Table 2**), although the National Institutes of Health (NIH) guidelines[63] released in January 2022, appear to be updated based on the results of many of the studies cited here. Ongoing discussions on updating societal guidelines are occurring. However, as stated earlier, this has been a quickly moving field with new information being added frequently to the literature.

ICU Patients

Based on the above data, there is a general consensus among society guidelines about the use of only standard prophylactic dose of anticoagulation in critically ill patients

Table 2 Current societal recommendations for thromboprophylaxis in COVID-19 patients

Society/expert group	Outpatient	Hospitalized, non-ICU	Hospitalized, ICU	Postdischarge
National Institutes of Health (January 2022)[63]	Not recommended, unless the patient has other indications or is participating in a clinical trial	Therapeutic dose heparin for patients who have a D-dimer above the ULN, require low-flow oxygen, and have no increased bleeding risk. LMWH preferred over unfractionated heparin	Prophylactic dose heparin unless a contraindication exists	VTE prophylaxis after hospital discharge is not recommended, unless patient is at high-VTE risk
International Society on Thrombosis and Haemostasis (August 2022)[83]	Patients should be evaluated regularly, measure D-dimers; if $>$ 1,500 ng/mL, LMWH may be considered	Routine thromboprophylaxis	Increased intensity thromboprophylaxis	Recommended in patients with immobility, high inflammatory activity, or other risk factors, or both
American Society of Hematology (ASH) (July, 2021)[84]	Not mentioned	Prophylactic-intensity over intermediate-intensity anticoagulation	Therapeutic-intensity over prophylactic-intensity anticoagulation	Not recommended
The American College of Chest Physicians (CHEST) guideline and expert panel report (June, 2020)[70]	Not mentioned	Anticoagulant thromboprophylaxis over no anticoagulant thromboprophylaxis	Anticoagulant thromboprophylaxis over no anticoagulant thromboprophylaxis	No routine prophylaxis; anticoagulant thromboprophylaxis considered in high-risk patients with low risk of bleeding
World Health Organization (November, 2021)[85]	Not recommended	Routine thromboprophylaxis	Routine thromboprophylaxis	Not recommended

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; LMWH, low-molecular-weight heparin; ULN, upper limit of normal; VTE, venous thromboembolism.

admitted to ICU with COVID-19 disease unless absolutely contraindicated due to high bleeding risk.[63,70,73–75] LMWH is recommended over UFH because of less frequent patient interaction for dosing.[70] DOAC use is discouraged because of the interaction with nonanticoagulant medications (e.g., remdesivir) which can cause increased bleeding and likelihood of renal dysfunction which will reduce clearance of DOACs.[70] There is some evidence of more potent antiviral activity against SARS-CoV-2 with UFH compared with LMWH, but how this translates into clinical benefit has yet to be demonstrated.[76] The ISTH does recommend consideration of intermediate dose LMWH in high-risk patients. High risk features are not specified in their guideline document.[75] However, these guidelines were drafted prior to the results of the RCTs discussed here. It should also be noted that patients in the ICU with conditions warranting the use of therapeutic anticoagulation (e.g., atrial fibrillation or known VTE event) were excluded from these trials and should be treated with therapeutic anticoagulation as indicated.

Non-ICU Patients

Current society guidelines recommend hospitalized moderately ill COVID-19 patients not requiring ICU should receive at least prophylactic dose anticoagulation unless absolutely contraindicated.[63,70,75] LMWH is preferred over UFH.[73,75] In the setting of heparin-induced thrombocytopenia, fondaparinux is recommended.[73,77] The American College of Chest Physicians also recommends fondaparinux over UFH.[70]

The American Society of Hematology recommends consideration of therapeutic dose anticoagulation in these patients after careful risk–benefit assessment and using D-dimer levels to aid in decision making.[73] ISTH similarly recommends use of intermediate dose LMWH in high-risk individuals.[75]

Posthospital Discharge Patients

Current society guidelines recommend against routine VTE prophylaxis after hospital discharge,[63,70,73] whereas postdischarge thromboprophylaxis for 7 to 45 days in recovered COVID-19 patients deemed at higher risk of developing postdischarge VTE may be warranted.[73] A risk assessment using the risk scores such as IMPROVE or modified IMPROVE with elevated D-dimer greater than two times the ULN is recommended to determine which individuals may benefit from postdischarge thromboprophylaxis.[63,73,75,78] This recommendation is based on the benefit of extended-duration thromboprophylaxis with prophylactic dose LMWH or a DOAC seen in posthospital discharge patients without COVID-19 at high risk of VTE but low risk of bleeding.[78–80]

Outpatients

In patients who do not require hospitalization, the NIH currently recommends against the initiation of anticoagulants and antiplatelet therapy for prevention of VTE or arterial thrombosis unless there are other indications (A III: Strong expert opinion).[63]

Limitations of Studies Used in This Review

The criteria used to classify patients into critically ill or noncritically ill differed across the studies. While individual components of the composite outcomes overlapped between many of the studies, the composite primary outcomes differed. Additionally, the cutoff for an elevated D-dimer level varied between the studies; some studies used values above the ULN while others used D-dimer levels that were >4 times the ULN. Most studies also did not specify whether D-dimer values were reported as D-dimer units or FEU.

Conclusion

Through the efficient dissemination of literature describing the clinical course of the COVID-19 and its sequalae, the scientific community was able to identify VTEs as a serious complication of COVID-19. The risk of VTE is higher in COVID-19 patients than in individuals vaccinated with adenoviral vaccines.[81,82] Various mechanisms for COVID-19-induced thrombosis have been postulated and each pathway presents an opportunity to intervene and reduce the risk of clot formation. Once the need for thromboprophylaxis was highlighted, it became essential to determine which agents are best indicated and at what dose, and which patients stand to benefit the most from the use of these anticoagulants. Again, the scientific community came together to publish their experiences with different strategies and have allowed organizations to develop consensus guidelines as summarized in ►**Table 2**.[63,70,83–85] However, because of the efficiency of implementing clinical trials in COVID-19, and unfortunately the large number of patients available to go into the clinical trials, many of these guidelines are out of date and do not correspond to the data that has been generated.

Findings from these studies support that therapeutic anticoagulation with LMWH or UFH is associated with improved outcomes in noncritically ill hospitalized patients with COVID-19, particularly those patients with elevated D-dimer levels. Patients who are critically ill do not seem to benefit from therapeutic anticoagulation and may experience increased risk of bleeding compared with patients receiving prophylactic dose anticoagulation. The beneficial effect of therapeutic anticoagulation appears to be diminished in the more advanced stages of disease, as the damage from thrombosis, particularly microvascular thrombosis,[86] and marked pulmonary inflammation[39] may be irreversible at the time of initiation of therapeutic heparin. Meanwhile the risk of hemorrhage tends to increase, in part due to hyperinflammation, endothelial disruption, platelet activation, and coagulopathy. The use of intermediate dose anticoagulation does not appear to be of benefit in either ICU or non-ICU patients.

Use of anticoagulation with DOACs may be useful in patients for a month postdischarge,[69] but another ongoing clinical trial will better define their use in this patient population (NCT04650087). Because of the very low rate of thrombotic complications in patients not needing

hospitalization for COVID-19, antiplatelet and antithrombotic therapy has thus far shown no benefit.[54,55]

When determining whether or not to initiate anticoagulation in COVID-19 positive patients, it is essential to consider their severity of illness as disease progresses, comorbidities, drug interactions, and any pertinent laboratory values that can help weigh the risks and benefits of whether or not to anticoagulate. However, patients with COVID-19 and a clear indication for anticoagulation (e.g., atrial fibrillation, PE, etc.) should be fully anticoagulated in the absence of contraindications, regardless of which stage of disease they may be.

Conflict of Interest

Dr. Effron has equity in and receives a pension from Eli Lilly and Company.

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