10: Antithrombotic Therapy in Patients with COVID-19

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Summary Recommendations

Laboratory Testing

- In nonhospitalized patients with COVID-19, there are currently no data to support the measurement of coagulation markers (e.g., D-dimers, prothrombin time, platelet count, fibrinogen) **(AIII)**.
- In hospitalized patients with COVID-19, hematologic and coagulation parameters are commonly measured, although there are currently insufficient data to recommend either for or against using this data to guide management decisions.

Chronic Anticoagulant and Antiplatelet Therapy

- Patients who are receiving anticoagulant or antiplatelet therapies for underlying conditions should continue these medications if they receive a diagnosis of COVID-19 **(AIII)**.

Venous Thromboembolism Prophylaxis and Screening

- For nonhospitalized patients with COVID-19, anticoagulants and antiplatelet therapy should not be initiated for the prevention of venous thromboembolism (VTE) or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial **(AIII)**.
- Hospitalized nonpregnant adults with COVID-19 should receive prophylactic dose anticoagulation **(AIII)** (see the recommendations for pregnant individuals below). Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the usual standard of care for patients without COVID-19 **(AIII)**.
- There are currently insufficient data to recommend either for or against the use of thrombolytics or higher than the prophylactic dose of anticoagulation for VTE prophylaxis in hospitalized COVID-19 patients outside of a clinical trial.
- Hospitalized patients with COVID-19 should not routinely be discharged from the hospital while on VTE prophylaxis **(AIII)**. Continuing anticoagulation with a Food and Drug Administration-approved regimen for extended VTE prophylaxis after hospital discharge can be considered for patients who are at low risk for bleeding and high risk for VTE, as per the protocols for patients without COVID-19 (see details on defining at-risk patients below) **(BI)**.
- There are currently insufficient data to recommend either for or against routine deep vein thrombosis screening in COVID-19 patients without signs or symptoms of VTE, regardless of the status of their coagulation markers.
- For hospitalized COVID-19 patients who experience rapid deterioration of pulmonary, cardiac, or neurological function, or of sudden, localized loss of peripheral perfusion, the possibility of thromboembolic disease should be evaluated **(AIII**).

Hospitalized Children With COVID-19

- For hospitalized children with COVID-19, indications for VTE prophylaxis should be the same as those for children without COVID-19 **(BIII)**.

Treatment

- When diagnostic imaging is not possible, patients with COVID-19 who experience an incident thromboembolic event or who are highly suspected to have thromboembolic disease should be managed with therapeutic doses of anticoagulant therapy **(AIII)**.
- Patients with COVID-19 who require extracorporeal membrane oxygenation or continuous renal replacement therapy or who have thrombosis of catheters or extracorporeal filters should be treated with antithrombotic therapy as per the standard institutional protocols for those without COVID-19 **(AIII)**.

Special Considerations During Pregnancy and Lactation

- If antithrombotic therapy is prescribed during pregnancy prior to a diagnosis of COVID-19, this therapy should be continued **(AIII)**.
- For pregnant patients hospitalized for severe COVID-19, prophylactic dose anticoagulation is recommended unless contraindicated (see below) **(BIII)**.

- Like for nonpregnant patients, VTE prophylaxis after hospital discharge **is not recommended** for pregnant patients **(AIII)**. Decisions to continue VTE prophylaxis in the pregnant or postpartum patient after discharge should be individualized, considering concomitant VTE risk factors.
- Anticoagulation therapy use during labor and delivery requires specialized care and planning. It should be managed in pregnant patients with COVID-19 in a similar way as in pregnant patients with other conditions that require anticoagulation in pregnancy **(AIII)**.
- Unfractionated heparin, low molecular weight heparin, and warfarin do not accumulate in breast milk and do not induce an anticoagulant effect in the newborn; therefore, they can be used by breastfeeding individuals with or without COVID-19 who require VTE prophylaxis or treatment **(AIII)**. In contrast, use of direct-acting oral anticoagulants during pregnancy is not routinely recommended due to lack of safety data **(AIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Association Between COVID-19 and Thromboembolism

Infection with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resulting syndrome, COVID-19, have been associated with inflammation and a prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen, and D-dimers.[1,2] In some studies, elevations in these markers have been associated with worse clinical outcomes.[3,4]

A number of studies have reported varying incidences of venous thromboembolism (VTE) in patients with COVID-19. A meta-analysis of studies in hospitalized patients with COVID-19 found an overall VTE prevalence of 14.1% (95% CI, 11.6–16.9).[5] The VTE prevalence was higher in studies that used ultrasound screening (40.3%; 95% CI, 27.0–54.3) than in studies that did not (9.5%; 95% CI, 7.5–11.7). In randomized controlled trials conducted prior to the COVID-19 pandemic, the incidence of VTE in non-COVID-19 hospitalized patients who received VTE prophylaxis ranged from 0.3% to 1% for symptomatic VTE and from 2.8% to 5.6% for VTE overall.[6-8] The VTE incidence in randomized trials in critically ill non-COVID-19 patients who received prophylactic dose anticoagulants ranged from 5% to 16%, and a prospective cohort study of critically ill patients with sepsis reported a VTE incidence of 37%.[9-12] VTE guidelines for non-COVID-19 patients have recommended against routine screening ultrasounds in critically ill patients because no study has shown that this strategy reduces the rate of subsequent symptomatic thromboembolic complications.[13] Although the incidence of thromboembolic events, especially pulmonary emboli, can be high among hospitalized patients with COVID-19, there are no published data demonstrating the clinical utility of routine surveillance for deep vein thrombosis using lower extremity ultrasound in this population.

A meta-analysis performed by an American Society of Hematology guidelines panel compared the odds of bleeding and thrombotic outcomes in patients with COVID-19 treated with prophylactic dose anticoagulation versus in those treated with intermediate or therapeutic dose anticoagulation.[14] Overall, the odds of VTE and mortality were not different between the patients treated with prophylactic dose anticoagulation and those treated with higher doses of anticoagulation. In critically ill patients, intermediate or therapeutic dose anticoagulation was associated with a lower odds of pulmonary embolism (OR 0.09; 95% CI, 0.02–0.57) but a higher odds of major bleeding (OR 3.84; 95% CI, 1.44–10.21). In studies in patients with COVID-19, incidences of symptomatic VTE between 0% to 0.6% at 30 to 42 days after hospital discharge have been reported.[15-17] Epidemiologic studies that control for clinical characteristics, underlying comorbidities, prophylactic anticoagulation, and COVID-19-related therapies are needed.

There are limited prospective data demonstrating the safety and efficacy of using therapeutic doses of anticoagulants to prevent VTE in patients with COVID-19. A retrospective analysis of 2,773

hospitalized COVID-19 patients from a single center in the United States reported in-hospital mortality in 22.5% of patients who received therapeutic anticoagulation and 22.8% of patients who did not receive anticoagulation. The study further reported that in a subset of 395 mechanically ventilated patients, 29.1% of the patients who received anticoagulation and 62.7% of those who did not receive anticoagulation died. The study had important limitations: it lacked details on patient characteristics, indications for anticoagulant initiation, and descriptions of other therapies that the patients received that may have influenced mortality. In addition, the authors did not discuss the potential impact of survival bias on the study results. For these reasons, the data are not sufficient to influence standard of care, and this study further emphasizes the need for prospective trials to define the risks and potential benefits of therapeutic anticoagulation in patients with COVID-19.[18] Three international trials (Antithrombotic Therapy to Ameliorate Complications of COVID-19 [ATTACC], Therapeutic Anticoagulation; Accelerating COVID-19 Therapeutic Interventions and Vaccines-4 [ACTIV-4], and the Randomized, Embedded, Multi-factorial Adaptive Platform Trial for Community-Acquired Pneumonia [REMAP-CAP]) compared the effectiveness of therapeutic dose anticoagulation and prophylactic dose anticoagulation in reducing the need for organ support over 21 days in moderately ill or critically ill adults hospitalized for COVID-19. The need for organ support was defined as requiring high-flow nasal oxygen, invasive or noninvasive mechanical ventilation, vasopressor therapy, or extracorporeal membrane oxygenation (ECMO). The trials paused enrollment of patients requiring intensive care unit (ICU)-level care after an interim pooled analysis demonstrated futility of therapeutic anticoagulation in improving organ support, and a concern for safety. The results of the interim analysis are available on the ATTACC website. Unblinded data and additional study outcomes, including the occurrence of thrombosis, are expected to be reported soon.[19]

A small, single-center randomized trial (n = 20) compared therapeutic and prophylactic anticoagulation in mechanically ventilated patients with D-dimers >1,000 µg/L (as measured by the VIDAS D-dimer Exclusion II assay). Only the patients treated with therapeutic anticoagulation showed improvement in the ratio of arterial oxygen partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2). The number of ventilator-free days was higher in the therapeutic anticoagulation arm than in the prophylactic anticoagulation arm (15 days [IQR 6–16] vs. 0 days [IQR 0–11]; $P = 0.028$). There was no difference between the arms in in-hospital or 28-day mortality. Two patients treated with therapeutic anticoagulation had minor bleeding, and two patients in each arm experienced thrombosis.[20] Additional evidence from large, multicenter trials is needed, and the trial results are expected soon.

Several randomized controlled trials have been developed to evaluate the risks and benefits of anticoagulation in patients with COVID-19 (visit *ClinicalTrials.gov* for the current list of trials). Guidelines about coagulopathy and prevention and management of VTE in patients with COVID-19 have been released by multiple organizations, including the Anticoagulation Forum,[21] the American College of Chest Physicians,[22] the American Society of Hematology,[23] the International Society of Thrombosis and Haemostasis (ISTH),[24] the Italian Society on Thrombosis and Haemostasis,[25] and the Royal College of Physicians.[26] In addition, a paper that outlines issues related to thrombotic disease with implications for prevention and therapy has been endorsed by the ISTH, the North American Thrombosis Forum, the European Society of Vascular Medicine, and the International Union of Angiology.[27]

All of the guidelines referenced above agree that hospitalized patients with COVID-19 should receive prophylactic dose anticoagulation for VTE. Some guidelines note that intermediate dose anticoagulation can be considered for critically ill patients.[21,23,26,28] Given the variation in VTE incidence and the unknown risk of bleeding in critically ill patients with COVID-19, the COVID-19 Treatment Guidelines Panel and guideline panels of the American Society of Hematology and the American College of Chest Physician recommend treating all hospitalized patients with COVID-19, including critically ill patients, with prophylactic dose anticoagulation.[22,29] Results from clinical trials that assess the safety and efficacy

of different anticoagulant doses will provide further information on the best prophylactic strategies for patients with COVID-19.

Monitoring Coagulation Markers in Patients With COVID-19

In nonhospitalized patients with COVID-19, markers of coagulopathy, such as D-dimer level, prothrombin time, fibrinogen level, and platelet count, should not routinely be obtained **(AIII)**. Although abnormalities in these coagulation markers have been associated with worse outcomes, prospective data demonstrating that the markers can be used to predict the risk of VTE in those who are asymptomatic or who have mild SARS-CoV-2 infection is lacking.

In hospitalized patients with COVID-19, hematologic and coagulation parameters are commonly measured; however, there are currently insufficient data to recommend either for or against using such data to guide management decisions.

Managing Antithrombotic Therapy in Patients With COVID-19

Selection of Anticoagulant or Antiplatelet Drugs for Patients With COVID-19

Whenever anticoagulant or antiplatelet therapy is used, potential drug-drug interactions with other concomitant drugs must be considered **(AIII)**. The University of Liverpool has collated a list of drug interactions. In hospitalized, critically ill patients, low molecular weight heparin or unfractionated heparin is preferred over oral anticoagulants because the two types of heparin have shorter half-lives, can be administered intravenously or subcutaneously, and have fewer drug-drug interactions **(AIII)**.

Chronic Anticoagulant or Antiplatelet Therapy

COVID-19 outpatients receiving warfarin who are in isolation and thus unable to have international normalized ratio monitoring may be candidates for switching to direct oral anticoagulant therapy. Patients receiving warfarin who have a mechanical heart valve, ventricular assist device, valvular atrial fibrillation, or antiphospholipid antibody syndrome or who are lactating should continue treatment with warfarin **(AIII)**. Hospitalized patients with COVID-19 who are taking anticoagulant or antiplatelet therapy for underlying medical conditions should continue this treatment unless significant bleeding develops, or other contraindications are present **(AIII)**.

Patients with COVID-19 Who Are Managed as Outpatients

For nonhospitalized patients with COVID-19, anticoagulants and antiplatelet therapy should not be initiated for the prevention of VTE or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial **(AIII)**.

Hospitalized Patients With COVID-19

For hospitalized patients with COVID-19, prophylactic dose anticoagulation should be prescribed unless contraindicated (e.g., a patient has active hemorrhage or severe thrombocytopenia) **(AIII)**. Although data supporting this recommendation are limited, a retrospective study showed reduced mortality in patients who received prophylactic anticoagulation, particularly if the patient had a sepsis-induced coagulopathy score ≥ 4.[4] For those without COVID-19, anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the standard of care **(AIII)**. Anticoagulation is routinely used to prevent arterial thromboembolism in patients with heart arrhythmias. Although there are reports of strokes and myocardial infarction in patients with COVID-19, the incidence of these events is unknown.

When imaging is not possible, patients with COVID-19 who experience an incident thromboembolic event or who are highly suspected to have thromboembolic disease should be managed with therapeutic doses of anticoagulant therapy as per the standard of care for patients without COVID-19 **(AIII)**.

There are currently insufficient data to recommend either for or against the use of thrombolytic agents or higher than the prophylactic dose of anticoagulation for VTE prophylaxis for hospitalized patients with COVID-19 outside of a clinical trial. Three international trials (ACTIV-4, REMAP-CAP, and ATTACC) compared the effectiveness of therapeutic dose anticoagulation and prophylactic dose anticoagulation in reducing the need for organ support over 21 days in moderately ill or critically ill adults hospitalized for COVID-19. The need for organ support was defined as requiring high-flow nasal oxygen, invasive or noninvasive mechanical ventilation, vasopressor therapy, or ECMO. The trials paused enrollment of patients requiring ICU-level care at enrollment after an interim pooled analysis demonstrated futility of therapeutic anticoagulation in reducing the need for organ support and a concern for safety. The results of the interim analysis are available on the ATTACC website. Unblinded data and additional study outcomes, including the occurrence of thrombosis, are expected to be reported soon.[19]

Although there is evidence that multi-organ failure is more likely in patients with sepsis who develop coagulopathy,[30] there is no convincing evidence to show that any specific antithrombotic treatment will influence outcomes in those with or without COVID-19. Participation in randomized trials is encouraged.

Patients with COVID-19 who require ECMO or continuous renal replacement therapy or who have thrombosis of catheters or extracorporeal filters should be treated as per the standard institutional protocols for those without COVID-19 **(AIII)**.

Hospitalized Children With COVID-19

A recent meta-analysis of publications on COVID-19 in children did not discuss VTE.[31] Indications for VTE prophylaxis in hospitalized children with COVID-19 should be the same as those for hospitalized children without COVID-19 **(BIII)**.

Patients With COVID-19 Who Are Discharged from the Hospital

VTE prophylaxis after hospital discharge **is not recommended** for patients with COVID-19 **(AIII)**. For certain high-VTE risk patients without COVID-19, post-discharge prophylaxis has been shown to be beneficial. The Food and Drug Administration approved the use of rivaroxaban 10 mg daily for 31 to 39 days in these patients.[32,33] Inclusion criteria for the trials that studied post-discharge VTE prophylaxis included:

- Modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) VTE risk score ≥4; *or*
- Modified IMPROVE VTE risk score ≥2 and D-dimer level >2 times the upper limit of normal.[32]

Any decision to use post-discharge VTE prophylaxis for patients with COVID-19 should include consideration of the individual patient's risk factors for VTE, including reduced mobility, bleeding risks, and feasibility. Participation in clinical trials is encouraged.

Special Considerations During Pregnancy and Lactation

Because pregnancy is a hypercoagulable state, the risk of thromboembolism is greater in pregnant individuals than in nonpregnant individuals.[34] It is not yet known whether COVID-19 increases this risk. In several cohort studies of pregnant women with COVID-19 in the United States and Europe,

VTE was not reported as a complication even among women with severe disease, although the receipt of prophylactic or therapeutic anticoagulation varied across the studies.[35-37] The American College of Obstetricians and Gynecologists (ACOG) advises that, although there are no data for or against thromboprophylaxis in the setting of COVID-19 in pregnancy, VTE prophylaxis can reasonably be considered for pregnant women hospitalized with COVID-19, particularly for those who have severe disease.[38] If there are no contraindications to use, the Society of Maternal Fetal Medicine recommends prophylactic heparin or low molecular weight heparin in critically ill or mechanically ventilated pregnant patients.[39] Several professional societies, including the American Society of Hematology and ACOG, have guidelines that specifically address the management of VTE in the context of pregnancy.[40,41] If delivery is threatened, or if there are other risks for bleeding, the risk of bleeding may outweigh the potential benefit of VTE prophylaxis in pregnancy.

There are no data on the use of scoring systems to predict VTE risk in pregnant individuals. Additionally, during pregnancy, the D-dimer level may not be a reliable predictor of VTE because there is a physiologic increase of D-dimer levels throughout gestation.[42-44]

In general, the preferred anticoagulants during pregnancy are heparin compounds. Because of its reliability and ease of administration, low-molecular weight heparin is recommended, rather than unfractionated heparin, for the prevention and treatment of VTE in pregnancy.[41]

Direct-acting anticoagulants are not routinely used during pregnancy due to the lack of safety data in pregnant individuals.[40] The use of warfarin to prevent or treat VTE should be avoided in pregnant individuals, regardless of their COVID-19 status, and especially during the first trimester due to the concern for teratogenicity.

Specific recommendations for pregnant or lactating individuals with COVID-19 include:

- If antithrombotic therapy is prescribed during pregnancy prior to a diagnosis of COVID-19, this therapy should be continued **(AIII)**.
- For pregnant patients hospitalized for severe COVID-19, prophylactic dose anticoagulation is recommended unless contraindicated **(BIII)**.
- Like for nonpregnant patients, VTE prophylaxis after hospital discharge **is not recommended** for pregnant patients **(AIII)**. Decisions to continue VTE prophylaxis in the pregnant or postpartum patient should be individualized, considering concomitant VTE risk factors.
- Anticoagulation therapy use during labor and delivery requires specialized care and planning. It should be managed in pregnant patients with COVID-19 in a similar way as in pregnant patients with other conditions that require anticoagulation in pregnancy **(AIII)**.
- Unfractionated heparin, low molecular weight heparin, and warfarin do not accumulate in breast milk and do not induce an anticoagulant effect in the newborn; therefore, they can be used by breastfeeding women with or without COVID-19 who require VTE prophylaxis or treatment **(AIII)**. In contrast, use of direct-acting oral anticoagulants during pregnancy is not routinely recommended due to lack of safety data **(AIII)**.[40]

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