Antithrombotic Therapy in Patients With COVID-19

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Summary Recommendations

Chronic Anticoagulant and Antiplatelet Therapy

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends that patients with COVID-19 who are receiving anticoagulant or antiplatelet therapies for underlying conditions continue these medications unless significant bleeding develops or other contraindications are present (AIII).
- Before prescribing ritonavir-boosted nirmatrelvir (Paxlovid) to patients who are receiving anticoagulant or antiplatelet therapy, clinicians should carefully review the patient's concomitant medications to evaluate potential drug-drug interactions. It may be necessary to modify the dosage of the antithrombotic agent, switch to another antithrombotic agent, or prescribe an alternative COVID-19 therapy. See <u>Drug-Drug Interactions Between Ritonavir-Boosted</u> <u>Nirmatrelvir (Paxlovid) and Concomitant Medications</u> for more information.

Screening and Evaluation for Venous Thromboembolism

- There is insufficient evidence for the Panel to recommend either for or against routine screening for venous thromboembolism (VTE) in patients with COVID-19 who do not have signs or symptoms of VTE, regardless of the status of their coagulation markers.
- For hospitalized patients with COVID-19 who experience rapid deterioration of pulmonary, cardiac, or neurological function or sudden, localized loss of peripheral perfusion, the Panel recommends evaluating the patients for thromboembolic disease (AIII).

Antithrombotic Therapy for Nonhospitalized Adults Without Evidence of Venous Thromboembolism

• In nonhospitalized patients with COVID-19, the Panel **recommends against** the use of anticoagulant and antiplatelet therapy (i.e., **aspirin, P2Y12 inhibitors**) for the prevention of VTE or arterial thrombosis, except in a clinical trial **(Alla)**. This recommendation does not apply to patients with other indications for antithrombotic therapy.

Antithrombotic Therapy for Hospitalized, Nonpregnant Adults Without Evidence of Venous Thromboembolism

- The Panel **recommends against** using anticoagulant or antiplatelet therapy to prevent arterial thrombosis outside of the usual standard of care for patients without COVID-19 (AIII).
- In hospitalized patients, **low-molecular-weight heparin** (LMWH) or **unfractionated heparin** (UFH) is preferred over oral anticoagulants **(AIII)**. Because these types of heparin have shorter half-lives, their effects can be reversed quickly. They can also be administered intravenously or subcutaneously, and they have fewer drug-drug interactions than oral anticoagulants.
- · When heparin is used, LMWH is preferred over UFH.

For adults who require low-flow oxygen and do not require intensive care unit (ICU)-level care:

- The Panel recommends the use of a **therapeutic dose of heparin** for patients with D-dimer levels above the upper limit of normal who require low-flow oxygen and who do not have an increased risk of bleeding **(Clla)**.
 - Contraindications for the use of therapeutic anticoagulation in patients with COVID-19 include a platelet count <50,000 cells/µL, hemoglobin <8 g/dL, the need for dual antiplatelet therapy, bleeding within the past 30 days that required an emergency department visit or hospitalization, a history of a bleeding disorder, or an inherited or active acquired bleeding disorder. This list is based on the exclusion criteria from clinical trials; patients with these conditions have an increased risk of bleeding
- In patients without VTE who have started treatment with therapeutic doses of heparin, treatment should continue until 1 of the following occurs, whichever comes first:
 - The patient receives 14 days of treatment, at which time, they should be switched to prophylactic anticoagulation until hospital discharge;
 - The patient is transferred to the ICU, and prophylactic anticoagulation should be administered for the remainder of the hospitalization period; *or*

Summary Recommendations, continued

- The patient is discharged from the hospital.
- The Panel recommends the use of a **prophylactic dose of heparin** for patients who do not meet the criteria for receiving therapeutic heparin or are not receiving a therapeutic dose of heparin for other reasons, unless a contraindication exists **(AI)**.
- There is insufficient evidence for the Panel to recommend either for or against the use of a therapeutic dose of apixaban for VTE prophylaxis or the prevention of COVID-19 progression.
- The Panel **recommends against** the use of a **therapeutic dose of rivaroxaban** for VTE prophylaxis or the prevention of COVID-19 progression (Alla).
- The Panel **recommends against** the use of antiplatelet therapy to prevent COVID-19 progression or death in noncritically ill patients (**Blla**).

For adults who require ICU-level care, including those receiving high-flow oxygen:

- The Panel recommends using a prophylactic dose of heparin as VTE prophylaxis, unless a contraindication exists (AI).
- The Panel recommends against the use of a therapeutic dose of anticoagulation for VTE prophylaxis (BI).
- For patients who start on a therapeutic dose of heparin in a non-ICU setting due to COVID-19 and then transfer to the ICU, the Panel recommends switching from the therapeutic dose to a **prophylactic dose of heparin**, unless VTE is confirmed **(BIII)**.
- There is insufficient evidence for the Panel to recommend either for or against the use of an intermediate dose of anticoagulation for VTE prophylaxis.
- There is insufficient evidence for the Panel to recommend either for or against the use of antiplatelet therapy in critically ill patients with COVID-19.

Antithrombotic Therapy for Patients Discharged From the Hospital

• The Panel **recommends against** routinely continuing VTE prophylaxis in patients with COVID-19 after hospital discharge unless they have another indication for anticoagulation (Alla).

Pregnant and Lactating Patients

- The Panel recommends that pregnant patients who are receiving anticoagulant or antiplatelet therapies for underlying conditions continue these medications after they receive a diagnosis of COVID-19 (AIII).
- The Panel recommends the use of a prophylactic dose of anticoagulation for pregnant patients who are hospitalized for manifestations of COVID-19, unless a contraindication exists (BIII).
- Because pregnant patients were not included in most of the clinical trials that evaluated the use of therapeutic
 anticoagulation in people with COVID-19, there is insufficient evidence for the Panel to recommend either for or against
 the use of therapeutic anticoagulation in pregnant patients with COVID-19 who do not have evidence of VTE.
- As in nonpregnant patients with COVID-19, VTE prophylaxis after hospital discharge is not routinely recommended for pregnant patients (BIII). Clinicians should consider an individual patient's VTE risk factors when making decisions about continuing VTE prophylaxis after discharge in pregnant or postpartum patients.
- The use of anticoagulant therapy during labor and delivery requires specialized care and planning. The management of anticoagulant therapy in pregnant patients with COVID-19 should be similar to the management used for pregnant patients with other conditions (AIII).
- UFH, LMWH, 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 who require VTE prophylaxis or treatment (AIII).

Children With COVID-19 or MIS-C

• For the Panel's recommendations on the use of antithrombotic therapy in children, see <u>Therapeutic Management</u> of <u>Hospitalized Children With COVID-19</u> and <u>Therapeutic Management of Hospitalized Children With MIS-C, Plus a</u> <u>Discussion on MIS-A</u>.

Each recommendation in the Guidelines receives a rating for the strength of the recommendation (A, B, or C) and a rating for the evidence that supports it (I, IIa, IIb, or III). See <u>Guidelines Development</u> for more information.

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Association Between COVID-19 and Thromboembolism

COVID-19 has been associated with inflammation and a prothrombotic state, with increases in levels of fibrin, fibrin degradation products, fibrinogen, and D-dimer.^{1,2} In some studies, elevations in these markers have been associated with worse clinical outcomes.^{3,4}

Studies have reported varying incidences of venous thromboembolism (VTE) in patients with COVID-19. A meta-analysis of studies of hospitalized patients with COVID-19 who received VTE prophylaxis 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 pandemic, the incidence of VTE in 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 In randomized trials, the VTE incidence among critically ill patients without COVID-19 who received a prophylactic dose of 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

Guidelines for the use of antithrombotic therapy in patients with COVID-19 have been released by multiple organizations, including the American College of Chest Physicians,¹³ the American Society of Hematology,¹⁴ the Anticoagulation Forum,¹⁵ the International Society on Thrombosis and Haemostasis,¹⁶ the Italian Society on Thrombosis and Haemostasis,¹⁷ the National Institute for Health and Care Excellence,¹⁸ and the Royal College of Physicians.¹⁹ The American College of Chest Physicians also has guidance on the use of antithrombotic therapy to treat arterial thrombosis in people with COVID-19.²⁰

The guidelines referenced above agree that hospitalized, nonpregnant patients with COVID-19 should receive, at a minimum, a prophylactic dose of anticoagulation to prevent VTE. The <u>National Institute</u> for Health and Care Excellence guidelines state: "Consider a treatment dose of a low-molecular-weight heparin (LMWH) for young people and adults with COVID-19 who need low-flow oxygen and who do not have an increased bleeding risk." Results from clinical trials have provided further information on the safety and efficacy of different antithrombotic strategies for patients with COVID-19.

Chronic Anticoagulant or Antiplatelet Therapy

The COVID-19 Treatment Guidelines Panel (the Panel) recommends that patients with COVID-19 who are receiving anticoagulant or antiplatelet therapies for underlying conditions continue these medications unless significant bleeding develops or other contraindications are present (AIII). Outpatients with COVID-19 who are receiving warfarin and are in isolation and unable to have international normalized ratio monitoring may be candidates for switching to direct oral anticoagulant therapy.²¹ Patients with a mechanical heart valve, a ventricular assist device, valvular atrial fibrillation, or antiphospholipid antibody syndrome and patients who are lactating should not discontinue treatment with warfarin (AIII).

Before prescribing ritonavir-boosted nirmatrelvir (Paxlovid) to patients who are receiving anticoagulant or antiplatelet therapy, clinicians should carefully review the patient's concomitant medications to evaluate potential drug-drug interactions. It may be necessary to modify the dosage of the antithrombotic agent, switch to another antithrombotic agent, or prescribe an alternative COVID-19 therapy. See Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications for more information.

Screening and Evaluation for Venous Thromboembolism

VTE guidelines for patients without COVID-19 have recommended against performing routine screening ultrasounds in critically ill patients because no study has shown that this strategy reduces

the rate of subsequent symptomatic thromboembolic complications.²² Although the incidence of thromboembolic events, especially pulmonary embolism, can be high among hospitalized patients with COVID-19, no published data demonstrate the clinical utility of using lower extremity ultrasounds as routine surveillance for deep vein thrombosis in this population.

There is insufficient evidence for the Panel to recommend either for or against routine screening for VTE in patients with COVID-19 who do not have signs or symptoms of VTE, regardless of the status of their coagulation markers. For hospitalized patients with COVID-19 who experience rapid deterioration of pulmonary, cardiac, or neurological function or sudden, localized loss of peripheral perfusion, the Panel recommends evaluating the patients for thromboembolic disease (AIII).

Selection of Anticoagulant or Antiplatelet Drugs

Whenever anticoagulant or antiplatelet therapy is used, potential drug-drug interactions with other concomitant medications must be considered. The <u>Liverpool COVID-19 Drug Interactions website</u> provides a list of drug-drug interactions. In hospitalized patients, **LMWH** or **unfractionated heparin** (UFH) is preferred over oral anticoagulants (**AIII**). Because these types of heparin have shorter half-lives, their effects can be reversed quickly. They can also be administered intravenously or subcutaneously (SUBQ), and they have fewer drug-drug interactions than oral anticoagulants.

Management of Nonhospitalized Adults

ACTIV-4b was a placebo-controlled, randomized trial that evaluated the efficacy of using aspirin or prophylactic doses (2.5 mg) or therapeutic doses (5 mg) of apixaban in outpatients with COVID-19 aged >40 years.²³ After 657 outpatients were randomized, the trial was stopped in June 2021 due to a low event rate for the composite outcome of thromboembolic events, hospitalization, or death (1 patient each in the placebo, aspirin, and apixaban 2.5 mg arms and 2 patients in the apixaban 5 mg arm). The median time from randomization to receipt of treatment was 3 days, and 22 patients were hospitalized for COVID-19 prior to initiation of the study drugs.

Two trials evaluated the use of LMWH and its impact on hospitalization and mortality in outpatients with COVID-19. The ETHIC trial was a multicenter, open-label randomized controlled trial of unvaccinated outpatients with COVID-19.²⁴ Adults with at least 1 risk factor for severe disease were randomized to receive enoxaparin 40 mg SUBQ once daily (if they weighed <100 kg) or enoxaparin 40 mg SUBQ twice daily (if they weighed >100 kg) for 21 days or standard of care. The study was terminated early due to a low event rate and slow accrual of participants. There was no difference between the arms in the number of patients who met the composite endpoint of all-cause mortality or all-cause hospitalization (12 of 105 patients [11%] in the enoxaparin arm vs. 12 of 114 patients [11%] in the standard of care arm). Four of the 12 patients in the enoxaparin arm who were admitted to the hospital required acute medical care or intensive care unit (ICU) admission (3 patients required mechanical ventilation or extracorporeal membrane oxygenation [ECMO]). There were no hospitalizations in the standard of care arm. Bleeding events occurred in 2 patients who received enoxaparin and in 1 patient who received standard of care.

The OVID trial was a multicenter, open-label randomized controlled trial of 472 outpatients with COVID-19 aged >50 years who were randomized to receive enoxaparin 40 mg SUBQ once daily for 14 days or standard of care.²⁵ The study was terminated after recruiting 50% of the planned number of participants due to a low probability that enoxaparin would be superior to standard of care for the primary outcome. There was no difference between the arms in the number of patients who met the primary composite endpoint of all-cause hospitalization or mortality (8 of 234 patients [3%] in the enoxaparin arm vs. 8 of 238 patients [3%] in the standard of care arm). No major bleeding events

occurred during the study.

The clinical data for these trials are summarized in Table 6a.

In nonhospitalized patients with COVID-19, the Panel **recommends against** the use of anticoagulant and antiplatelet therapy (i.e., **aspirin, P2Y12 inhibitors**) for the prevention of VTE or arterial thrombosis, except in a clinical trial **(AIIa)**. This recommendation does not apply to patients with other indications for antithrombotic therapy.

Management of Hospitalized Adults

Several studies have evaluated the risks and benefits of using prophylactic or therapeutic doses of anticoagulants in patients with COVID-19. Observational studies and clinical trials have examined the effects of anticoagulation on mortality, progression of COVID-19, thrombosis, and bleeding. Some of these studies are outlined below. Observational studies are included here only when evidence from clinical trials is not available. The clinical data for these trials are summarized in <u>Table 6a</u>.

Prophylactic Dose of Anticoagulation Versus No Anticoagulation

An observational study of 4,297 veterans hospitalized with COVID-19 evaluated the use of prophylactic anticoagulation.²⁶ A prophylactic dose of anticoagulation was administered to 3,627 patients with COVID-19 within 24 hours of hospital admission. An inverse probability of treatment weighted analysis showed a cumulative 30-day mortality of 14% among patients who received prophylactic anticoagulation and 19% among patients who were not treated with anticoagulation (HR 0.73; 95% CI, 0.66–0.81). Patients treated with the prophylactic dose did not have a significant difference in the risk of bleeding that required transfusion when compared with patients who were not treated with anticoagulation (HR 0.87; 95% CI, 0.71–1.05). Overall, the study demonstrated that patients with COVID-19 may benefit from a prophylactic dose of anticoagulation.

Therapeutic Versus Prophylactic Doses of Heparin in Hospitalized Patients Who Do Not Require Intensive Care Unit-Level Care

Four open-label randomized controlled trials (the large ATTACC/ACTIV-4a/REMAP-CAP multiplatform trial and the FREEDOM trial, and the smaller RAPID and HEP-COVID trials) compared therapeutic doses of heparin to prophylactic or intermediate doses of the anticoagulant in selected hospitalized patients who did not require intensive care. The inclusion and exclusion criteria for these studies varied, but most of the studies included patients who required supplemental oxygen and had no risk of a major bleeding event. In the larger multiplatform trial, therapeutic doses of heparin increased the number of organ support-free days but did not significantly affect mortality or length of hospitalization when compared with prophylactic doses of heparin.²⁷ In the FREEDOM trial, there was no difference between the therapeutic and prophylactic anticoagulation arms in the occurrence of the 30-day primary composite outcome of all-cause mortality, need for ICU-level care, systemic thromboembolism, or ischemic stroke. In a secondary analysis, 30-day mortality was significantly lower in patients who received therapeutic enoxaparin than in patients who received prophylactic enoxaparin.²⁸ However, only a small proportion of patients received concomitant corticosteroids or remdesivir as standard of care, and the trial was stopped early due to slow recruitment.

The RAPID trial enrolled patients with elevated D-dimer levels and hypoxemia.²⁹ The patients were randomized to receive therapeutic or prophylactic doses of heparin. There was no statistically significant difference between the arms for the primary endpoint, which was a composite of ICU admission, noninvasive ventilation (NIV) or mechanical ventilation, or death by Day 28. However, the therapeutic dose of heparin reduced the risk of all-cause death, a secondary outcome.

The HEP-COVID trial enrolled patients who required supplemental oxygen and had a D-dimer value >4 times the upper limit of normal (ULN) or a sepsis-induced coagulopathy score of \geq 4.³⁰ There were significantly fewer occurrences of the primary endpoint of VTE, arterial thromboembolism, or all-cause death within 32 days of randomization in the therapeutic LMWH arm than in the prophylactic LMWH arm, but there was no difference between arms for the outcome of death within 32 days.

Given the results of the ATTACC/ACTIV-4a/REMAP-CAP, FREEDOM, RAPID, and HEP-COVID trials, for hospitalized, nonpregnant adults with COVID-19 who do not require ICU-level care and have no evidence of VTE:

- The Panel recommends the use of a **therapeutic dose of heparin** for patients with D-dimer levels above the ULN who require low-flow oxygen and who do not have an increased risk of bleeding **(CIIa)**.
 - Contraindications for the use of therapeutic anticoagulation in patients with COVID-19 include a platelet count <50,000 cells/ μ L, hemoglobin <8 g/dL, the need for dual antiplatelet therapy, bleeding within the past 30 days that required an emergency department visit or hospitalization, a history of a bleeding disorder, or an inherited or active acquired bleeding disorder. This list is based on the exclusion criteria from clinical trials; patients with these conditions have an increased risk of bleeding.
- LMWH is preferred over UFH because of its ease of administration and because LMWH was the predominant form of heparin used in the clinical trials for COVID-19.
- In patients without VTE who have started treatment with therapeutic doses of heparin, treatment should continue until 1 of the following occurs, whichever comes first:
 - The patient receives 14 days of treatment, at which time, they should be switched to prophylactic anticoagulation until hospital discharge;
 - The patient is transferred to the ICU, and prophylactic anticoagulation should be administered for the remainder of the hospitalization period; *or*
 - The patient is discharged from the hospital.
- Patients with predicted hospitalizations of <72 hours were excluded from the multiplatform ATTACC/ACTIV-4a/REMAP-CAP trial. It is currently unknown whether the benefits of using therapeutic doses of anticoagulation for short hospital stays outweigh the risks.
- The Panel recommends the use of a **prophylactic dose of heparin** for patients who do not meet the criteria for receiving therapeutic heparin or are not receiving a therapeutic dose of heparin for other reasons, unless a contraindication exists (AI).

Prophylactic Versus Intermediate or Therapeutic Doses of Heparin in Hospitalized Patients Who Require Intensive Care Unit-Level Care

Several randomized controlled trials have evaluated the role of therapeutic doses of heparin in reducing the incidence of VTE events or death in patients in the ICU setting. The clinical data for these trials are summarized in <u>Table 6a</u>.

The INSPIRATION trial compared the use of an intermediate dose of enoxaparin (1 mg/kg SUBQ once daily) to a prophylactic dose of enoxaparin (40 mg/kg SUBQ once daily) in patients with COVID-19 who were in the ICU.³¹ The study reported no difference between the arms in the occurrence of the composite endpoint of adjudicated VTE, arterial thrombosis, ECMO, or all-cause mortality. Major bleeding occurred in 2.5% of patients in the intermediate-dose anticoagulation arm and in 1.4% of patients who received the prophylactic dose. Overall, there was no significant benefit of receiving an

intermediate dose of anticoagulation for patients with COVID-19 who were in the ICU.

The ANTICOVID trial was an open-label study of hospitalized patients with COVID-19 who required oxygen therapy.³² Patients were randomized to receive a prophylactic dose of LMWH (n = 114), an intermediate dose of LWMH (n = 110), or a therapeutic dose of LMWH (n = 110). Patients in the study received either enoxaparin or tinzaparin. Patients underwent a computed tomography scan at baseline to ensure they did not have a pulmonary embolism. The study excluded patients weighing <40 kg or >100 kg.

The primary hierarchical outcome for this study was all-cause mortality or time to clinical improvement by Day 28. There was no difference between the arms for this outcome. The study also evaluated net clinical outcome, which was defined as a composite of venous and arterial thrombosis, major bleeding events (as defined by the International Society on Thrombosis and Haemostasis), or all-cause mortality by Day 28. A smaller percentage of patients who received the intermediate dose of anticoagulation met the net clinical outcome criteria compared with those who received the prophylactic dose of anticoagulation (16.4% vs. 29.8%; absolute difference -13.5%; P = 0.02). There was no statistically significant difference in the occurrence of the net clinical outcome between the therapeutic-dose anticoagulation arm and the prophylactic-dose or intermediate-dose arms. No difference in the occurrence of major bleeding events was seen among the study arms.

Tinzaparin is not available in the United States. This lack of availability, combined with the conflicting results of the INSPIRATION and ANTICOVID trials, has led the Panel to conclude that there is insufficient evidence to recommend either for or against the use of an intermediate dose of anticoagulation for VTE prophylaxis.

The multiplatform ATTACC/ACTIV-4a/REMAP-CAP trial compared the effectiveness of a therapeutic dose of heparin or LMWH with usual care in reducing the number of organ support-free days among critically ill patients with COVID-19.²⁷ All 3 trials were stopped for futility. The doses of heparin that were administered to patients in the usual care arm varied. The median number of organ support-free days and likelihood of survival to hospital discharge did not differ between the arms. Major bleeding occurred in 4% of patients who received therapeutic anticoagulation and in 2% of patients who received usual care. Therapeutic doses of heparin showed no significant benefit in patients with COVID-19 who were admitted to the ICU.

The COVID-PACT trial was a multicenter trial with a 2 x 2 factorial design.³³ Critically ill patients with COVID-19 were randomized to receive a therapeutic dose or a prophylactic dose of anticoagulation. They were also randomized to receive either clopidogrel or no antiplatelet therapy. The trial was stopped early because the decreasing number of ICU admissions for patients with COVID-19 made recruitment difficult. There was no difference between the arms in the occurrence of the primary endpoint (a composite of VTE or arterial thrombotic events at hospital discharge or Day 28). More moderate to severe bleeding events occurred among patients who were treated with therapeutic anticoagulation than among those who received prophylactic anticoagulation.

Given the results from the studies discussed above, for hospitalized, nonpregnant adults with COVID-19 who require ICU-level care and who do not have documented or suspected VTE:

- The Panel recommends using a **prophylactic dose of heparin** as VTE prophylaxis, unless a contraindication exists **(AI)**.
- The Panel **recommends against** the use of a therapeutic dose of anticoagulation for VTE prophylaxis **(BI)**.
- For patients who start on a therapeutic dose of heparin in a non-ICU setting due to COVID-19

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and then transfer to the ICU, the Panel recommends switching from the therapeutic dose to a **prophylactic dose of heparin**, unless VTE is confirmed **(BIII)**.

• There is insufficient evidence for the Panel to recommend either for or against the use of an intermediate dose of anticoagulation for VTE prophylaxis.

Apixaban or Rivaroxaban in Hospitalized Patients

The FREEDOM trial randomized patients 1:1:1 to receive a therapeutic dose of apixaban, a therapeutic dose of enoxaparin, or a prophylactic dose of enoxaparin.²⁸ The trial showed no difference in the occurrence of the primary composite endpoint between the therapeutic and prophylactic anticoagulation arms. In a secondary analysis, fewer deaths were reported at 30 days among patients who were treated with a therapeutic dose of apixaban than among those who received prophylactic enoxaparin (5% vs. 7%; HR 0.7; 95% CI, 0.49–0.99). Only a small proportion of patients were treated with dexamethasone or remdesivir as part of usual care; both of these drugs have been shown to have a benefit in this population. This open-label trial was also stopped early due to slow recruitment.

The FREEDOM trial is the only study that has evaluated the use of therapeutic apixaban in patients with COVID-19; in contrast, 4 trials have evaluated the use of therapeutic heparin. Additionally, oral anticoagulants have the potential for drug-drug interactions and present unique challenges for managing hemorrhages. Due to these limitations, there is insufficient evidence for the Panel to recommend either for or against the use of a therapeutic dose of apixaban for VTE prophylaxis or the prevention of COVID-19 progression.

The ACTION trial randomized adults who were hospitalized with COVID-19 and elevated D-dimer levels (defined as levels that were above the laboratory ULN) to receive rivaroxaban 20 mg once daily for 30 days (n = 311) or usual care (n = 304).³⁴ A heterogenous population was included; 25% of patients did not require oxygen, 60% were treated with low-flow oxygen, and 15% needed high-flow oxygen, NIV, or mechanical ventilation. No statistical difference was found between the arms for the composite endpoint of time to death, hospitalization duration, or oxygen use duration (hierarchical analysis; win ratio 0.86; 95% CI, 0.59–1.22) or for the individual components of the composite endpoint. The probability of clinically relevant, nonmajor bleeding was greater in the rivaroxaban arm (5% in the rivaroxaban arm vs. 1% in the usual care arm; relative risk 5.23; 95% CI, 1.54–17.77), but for major bleeding events, the difference in probability between the arms was not significant (3% in the rivaroxaban arm vs. 1% in the usual care arm; relative risk 2.45; 95% CI, 0.78–7.73). Given the lack of benefit and the increased risk of bleeding events, the Panel **recommends against** the use of a **therapeutic dose of rivaroxaban** for VTE prophylaxis or the prevention of COVID-19 progression (AIIa).

Antiplatelet Therapy Versus Usual Care in Hospitalized Patients

The RECOVERY trial randomized hospitalized adults with COVID-19 to receive usual care plus aspirin 150 mg once daily (n = 7,351) or usual care only (n = 7,541).³⁵ At enrollment, 38% of the patients required NIV or mechanical ventilation. Mortality at 28 days was 17% in both arms (rate ratio 0.96; 95% CI, 0.89–1.04). Among patients who were not receiving mechanical ventilation at baseline, there was no difference between the arms in the proportion of patients who progressed to requiring mechanical ventilation or who died (21% in the aspirin arm vs. 22% in the usual care arm; rate ratio 0.96; 95% CI, 0.90–1.03). Among those treated with aspirin, the incidence of thrombotic events was lower (4.6% vs. 5.3%; absolute difference 0.6%; SE 0.4%), and the incidence of major bleeding events was higher (1.6% vs. 1.0%; absolute difference 0.6%; SE 0.2%). Overall, the use of aspirin was associated with an increase in the incidence of major bleeding events and did not reduce the risk of death.

The ACTIV-4a trial compared the use of P2Y12 inhibitor therapy plus a therapeutic dose of heparin to a therapeutic dose of heparin alone in hospitalized patients with COVID-19.³⁶ In this study, enrollment of noncritically ill patients was stopped early due to futility; the combination therapy did not increase the number of organ support-free days. The limitations of this study include the open-label design, the use of different P2Y12 inhibitors, and the small sample size.

After reviewing the results of the ACTIV-4a and RECOVERY trials, the Panel **recommends against** the use of antiplatelet therapy to prevent COVID-19 progression or death in noncritically ill patients (**BIIa**).

The REMAP-CAP study team randomized critically ill patients with COVID-19 to receive aspirin (n = 565), a P2Y12 inhibitor (n = 455), or no antiplatelet therapy (n = 529).³⁷ Treatment continued for 14 days or until hospital discharge, whichever came first. The aspirin and P2Y12 inhibitor arms were pooled for analysis because the criteria for equivalence were met. The trial was stopped early due to futility, as the median number of organ support-free days did not differ between the pooled antiplatelet arm and the control arm (7 days; IQR 1–16 days; 95.7% posterior probability of futility). There was no statistically significant difference between the arms in the number of patients who survived to hospital discharge (723 of 1,011 patients [71.5%] in the pooled antiplatelet arm vs. 354 of 521 patients [67.9%] in the control arm; median-adjusted OR 1.27; 95% CrI, 0.99–1.62). The pooled antiplatelet arm had improved survival by 90 days (median aHR 1.22; 95% CrI, 1.06–1.40). The use of antiplatelet therapy was associated with an increased incidence of major bleeding (2.1% in the pooled antiplatelet arm vs. 0.4% in the control arm; aOR 2.97; 95% CrI, 1.23–8.28; adjusted absolute risk difference of 0.8%; 95% CrI, 0.1% to 2.7%).

In the RECOVERY trial, the use of aspirin therapy was not associated with a reduction in mortality at 28 days in the subgroups of patients who required NIV or mechanical ventilation at baseline. In the REMAP-CAP trial, administering antiplatelet therapy to critically ill patients with COVID-19 improved 90-day survival but did not increase the number of organ support-free days. In both studies, the use of antiplatelet therapy was associated with an increased risk of bleeding. The COVID-PACT trial randomized 292 adult patients with COVID-19 who required ICU-level care to receive either clopidogrel or no antiplatelet therapy.³³ There was no difference between the arms in the incidence of VTE, arterial thrombotic events, or bleeding.

Given the inconsistent results of these trials, there is insufficient evidence for the Panel to recommend either for or against the use of antiplatelet therapy in critically ill patients with COVID-19. Eligible patients should be encouraged to participate in clinical trials that are evaluating the use of antiplatelet therapy.

The clinical data for the trials discussed above are summarized in Table 6b.

Patients Discharged From the Hospital

For patients with a high risk of VTE who do not have COVID-19, post-discharge prophylaxis has been shown to be beneficial. The Food and Drug Administration approved the use of rivaroxaban 10 mg once daily for 31 to 39 days in these patients.³⁸ Inclusion criteria for the trials^{39,40} that studied post-discharge VTE prophylaxis included:

- A VTE risk score of ≥4 on the modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) tool;⁴¹ or
- A VTE risk score ≥ 2 on the modified IMPROVE tool⁴² and a D-dimer level > 2 times ULN.³⁹

The MICHELLE trial randomized 320 patients with COVID-19 and an IMPROVE score of \geq 4 or an IMPROVE score of 2 to 3 with a D-dimer level >500 ng/mL to receive rivaroxaban 10 mg orally

once daily or no anticoagulation for 35 days.⁴³ The primary outcome was a composite of symptomatic VTE, fatal pulmonary embolism, symptomatic arterial thromboembolism, cardiovascular death, or asymptomatic VTE detected on screening imaging at Day 35. Five patients (3%) who were treated with rivaroxaban and 15 patients (9%) who did not receive anticoagulation experienced a thrombotic event (relative risk 0.33; 95% CI, 0.13–0.9). One patient who received rivaroxaban and 10 patients who did not receive anticoagulation experienced symptomatic events. No major bleeding events occurred, and 2 patients in each arm had clinically relevant, nonmajor bleeding. The open-label design and the inclusion of asymptomatic events that were detected on screening ultrasounds and computed tomography scans may have biased the results. Additionally, two-thirds of the screened patients did not meet the eligibility criteria for the trial, which limits the generalizability of the results.

The ACTIV-4c trial randomized 1,217 patients who were hospitalized for symptomatic COVID-19 for >48 hours to receive apixaban 2.5 mg orally twice daily or placebo at hospital discharge.⁴⁴ The 30-day composite endpoint of all-cause mortality, venous thrombosis, or arterial thrombosis occurred in 2.13% of patients in the apixaban arm and in 2.31% of patients in the placebo arm. Major bleeding events were infrequent, occurring in 2 patients (0.4%) in the apixaban arm and in 1 patient (0.2%) in the placebo arm. The trial's leadership and sponsors stopped the trial early because the event rate for the composite endpoint was lower than expected, and the decreasing number of hospitalizations for people with COVID-19 made recruitment difficult.

After reviewing the results of the MICHELLE and ACTIV-4c trials, the Panel **recommends against** routinely continuing VTE prophylaxis in patients with COVID-19 after hospital discharge unless they have another indication for anticoagulation (AIIa).

Although there is no clear benefit of administering anticoagulation after hospital discharge in all patients with COVID-19, results from the MICHELLE trial, which evaluated patients with COVID-19, and the MARINER trial, which evaluated patients who were hospitalized for other conditions and who had risk factors for VTE, suggest a possible benefit of using anticoagulation after discharge in patients who are at high risk of VTE. The need for VTE prophylaxis after a COVID-19–related hospital discharge should be assessed on a case-by-case basis. The criteria for assessing the risk of VTE in these patients are the same as the criteria used for patients who are hospitalized for other acute illnesses.

Pregnant and Lactating Patients

Because pregnancy is a hypercoagulable state, the risk of thromboembolism is greater in pregnant individuals.⁴⁵ It is not yet known whether COVID-19 increases this risk, though some data do suggest that there is an increased risk. A cohort study in California compared perinatal outcomes among almost 44,000 pregnant people with and without COVID-19.⁴⁶ After adjusting for demographic factors and comorbidities, those with COVID-19 had a higher risk of severe maternal morbidity, preterm birth, and VTE.

In several other 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.⁴⁷⁻⁴⁹ Although there are currently not enough data to recommend either for or against the use of VTE prophylaxis, the <u>American College of Obstetricians and Gynecologists</u> notes that VTE prophylaxis can reasonably be considered for pregnant individuals who are hospitalized with COVID-19, particularly those who have severe disease. If there are no contraindications, the Society for Maternal-Fetal Medicine recommends using heparin or LMWH in pregnant patients who are critically ill or receiving mechanical ventilation.⁵⁰ Several professional societies, including the American Society of Hematology and the American College of Obstetricians and Gynecologists, have guidelines that specifically address the management of VTE in the context of pregnancy.^{51,52} If delivery is imminent, or if there are other risks for bleeding, the risk of bleeding may

outweigh the potential benefit of using VTE prophylaxis in pregnant individuals.

In nonpregnant people, D-dimer levels have been used to stratify VTE risk. However, physiologic increases in D-dimer levels may occur during pregnancy, making elevated D-dimer values an unreliable predictor that should not be used to evaluate VTE risk in pregnant people with COVID-19.⁵³⁻⁵⁵

In general, heparin compounds are the preferred anticoagulants to use during pregnancy. Because of its reliability and ease of administration, LMWH is recommended rather than UFH for the prevention and treatment of VTE in pregnant people.⁵² Direct-acting anticoagulants are not routinely recommended for use during pregnancy because of a lack of safety data for pregnant individuals.⁵¹ The use of warfarin to prevent or treat VTE should be avoided in pregnant individuals regardless of their COVID-19 status, especially during the first trimester, due to the concern for teratogenicity.

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

- The Panel recommends that pregnant patients who are receiving anticoagulant or antiplatelet therapies for underlying conditions continue these medications after they receive a diagnosis of COVID-19 (AIII).
- The Panel recommends the use of a prophylactic dose of anticoagulation for pregnant patients who are hospitalized for manifestations of COVID-19, unless a contraindication exists (**BIII**).
- Because pregnant patients were not included in most of the clinical trials that evaluated the use of therapeutic anticoagulation in people with COVID-19, there is insufficient evidence for the Panel to recommend either for or against the use of therapeutic anticoagulation in pregnant patients with COVID-19 who do not have evidence of VTE.
- As in nonpregnant patients with COVID-19, VTE prophylaxis after hospital discharge is not routinely recommended for pregnant patients (BIII). Clinicians should consider an individual patient's VTE risk factors when making decisions about continuing VTE prophylaxis after discharge in pregnant or postpartum patients.
- The use of anticoagulant therapy during labor and delivery requires specialized care and planning. The management of anticoagulant therapy in pregnant patients with COVID-19 should be similar to the management used for pregnant patients with other conditions (AIII).
- UFH, LMWH, 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 who require VTE prophylaxis or treatment (AIII).

Children With COVID-19 or MIS-C

For the Panel's recommendations on the use of antithrombotic therapy in children, see <u>Therapeutic</u> <u>Management of Hospitalized Children With COVID-19</u> and <u>Therapeutic Management of Hospitalized</u> <u>Children With MIS-C, Plus a Discussion on MIS-A</u>.

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