

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

### Screening and Evaluation for Venous Thromboembolism

- There is currently insufficient evidence to recommend either for or against routine screening for deep vein thrombosis in patients with COVID-19 who do not have signs or symptoms of venous thromboembolism (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**).

### Anticoagulant Treatment for Thrombosis

- The Panel recommends that 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 be managed with therapeutic anticoagulation (**AIII**).
- The Panel recommends that patients with COVID-19 who require extracorporeal membrane oxygenation or continuous renal replacement therapy or who have thrombosis related to catheters or extracorporeal filters be treated with antithrombotic therapy as per the standard institutional protocols for those without COVID-19 (**AIII**).

### Antithrombotic Therapy for Nonhospitalized Patients Without Evidence of Venous Thromboembolism

- The Panel **recommends against** the use of anticoagulants and antiplatelet therapy for the prevention of VTE or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial (**AIIa**).
- The Panel **recommends against** routinely continuing VTE prophylaxis after hospital discharge, except in a clinical trial (**AIII**). For patients who are at high risk for VTE and at low risk of bleeding, extended VTE prophylaxis can be considered, as per the protocol for patients without COVID-19 (**BI**).

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

- The Panel **recommends against** the use of aspirin to prevent mortality or the need for organ support (**AI**).
- The Panel recommends that anticoagulant or antiplatelet therapy not be used 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, because these 2 types of heparin have shorter half-lives and the effect can be reversed quickly, can be administered intravenously or subcutaneously, and have fewer drug-drug interactions (**AIII**).
- 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 bleeding risk (**CIIa**).
  - Contraindications for the use of therapeutic anticoagulation in patients with COVID-19 are a platelet count  $<50 \times 10^9/L$ , hemoglobin  $<8$  g/dL, the need for dual antiplatelet therapy, bleeding within the past 30 days that required an emergency department visit or hospitalization, 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 begun a therapeutic dose of heparin, treatment should continue for 14 days or until hospital discharge, whichever comes first.
- The Panel recommends the use of a **prophylactic dose** of heparin for patients who are not receiving a therapeutic dose of heparin, unless a contraindication exists (**AIIb**).

- The Panel **recommends against** the use of a **therapeutic dose** of oral anticoagulants for VTE prophylaxis or prevention of COVID-19 progression, except in a clinical trial (**AIIa**).
- There is currently insufficient evidence to recommend either for or against the use of thrombolytics for COVID-19.

*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 an **intermediate dose** (e.g., **enoxaparin 1 mg/kg once daily**) or a **therapeutic dose** of anticoagulation for VTE prophylaxis, except in a clinical trial (**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**).

### **Hospitalized Children**

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

### **Special Considerations During Pregnancy and Lactation**

- 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 hospitalized for manifestations of COVID-19, unless otherwise contraindicated (**BIII**).
- Because pregnant patients have not been included in most clinical trials evaluating therapeutic anticoagulation in the setting of COVID-19, there is currently insufficient evidence to recommend either for or against therapeutic anticoagulation for pregnant patients with COVID-19 without evidence of VTE.
- Like for nonpregnant patients, VTE prophylaxis after hospital discharge is not routinely recommended for pregnant patients (**BIII**). Decisions to continue VTE prophylaxis in the pregnant or postpartum patient after discharge should be individualized, with consideration of 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 (**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**).

**Rating of Recommendations:** A = Strong; B = Moderate; C = Weak

**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**

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

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 treated with VTE prophylaxis found an overall VTE prevalence of 14.1% (95% CI, 11.6–16.9).<sup>5</sup> 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 without COVID-19 who received VTE prophylaxis ranged from 0.3% to 1% for symptomatic VTE and from 2.8% to 5.6% for VTE overall.<sup>6-8</sup> The VTE incidence in randomized trials in 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%.<sup>9-12</sup>

Guidelines about coagulopathy and the prevention and management of VTE in patients with COVID-19 have been released by multiple organizations, including the American College of Chest Physicians,<sup>13</sup> American Society of Hematology,<sup>14</sup> Anticoagulation Forum,<sup>15</sup> International Society on Thrombosis and Haemostasis,<sup>16</sup> Italian Society for Haemostasis and Thrombosis,<sup>17</sup> National Institute for Health and Care Excellence (NICE),<sup>18</sup> and Royal College of Physicians.<sup>19</sup>

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 [NICE guideline](#) recommendation states: “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 that assess the safety and efficacy of different anticoagulant doses and strategies have provided further information on antithrombotic strategies for patients with COVID-19.

### Chronic Anticoagulant or Antiplatelet Therapy

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](#). Patients with a mechanical heart valve, ventricular assist device, valvular atrial fibrillation, or antiphospholipid antibody syndrome or who are lactating should not discontinue treatment with warfarin (**AIII**). The COVID-19 Treatment Guidelines Panel (the Panel) recommends that hospitalized patients with COVID-19 who are receiving anticoagulant or antiplatelet therapy for underlying medical conditions continue this treatment unless significant bleeding develops or other contraindications are present (**AIII**).

### Screening and Evaluation for Venous Thromboembolism

VTE guidelines for patients without COVID-19 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.<sup>20</sup> Although the incidence of thromboembolic events, especially pulmonary emboli, can be high among hospitalized patients with COVID-19, no published data demonstrate the clinical utility of using lower extremity ultrasound as routine surveillance for deep vein thrombosis in this population.

- There is currently insufficient evidence to recommend either for or against routine screening for deep vein thrombosis 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**).

### Managing Antithrombotic Therapy in Patients With COVID-19

The Panel recommends that 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 be managed with therapeutic anticoagulation (**AIII**).

The Panel recommends that patients with COVID-19 who require extracorporeal membrane oxygenation (ECMO) or continuous renal replacement therapy or who have thrombosis related to catheters or extracorporeal filters be treated with antithrombotic therapy as per the standard institutional protocols for those without COVID-19 (**AIII**).

## ***Selection of Anticoagulant or Antiplatelet Drugs***

Whenever anticoagulant or antiplatelet therapy is used, potential drug-drug interactions with other concomitant drugs must be considered. The University of Liverpool has collated a list of [drug interactions](#). In hospitalized, critically ill patients, LMWH or unfractionated heparin (UFH) is preferred over oral anticoagulants, because these 2 types of heparin have shorter half-lives and the effect can be reversed quickly, can be administered intravenously or subcutaneously, and have fewer drug-drug interactions (AIII).

## ***Management of Nonhospitalized Patients***

The ACTIV-4b placebo-controlled, randomized trial evaluated the efficacy of aspirin versus prophylactic (2.5 mg) or therapeutic (5 mg) doses of apixaban to prevent thromboembolic events, hospitalization, and mortality in outpatients >40 years with COVID-19. The trial was stopped in June 2021 due to a low event rate (1 patient each in the placebo, aspirin, and apixaban 2.5 mg arms and 2 patients in the apixaban 5 mg arm) after randomization of 657 symptomatic outpatients. The median time from randomization to study treatment was 3 days, and 22 participants were hospitalized for COVID-19 prior to initiation of study drug.<sup>21</sup> It is not known whether patients with previous VTE events or inherited thrombophilias were included in this trial. For nonhospitalized patients with COVID-19, the Panel **recommends against** the use of anticoagulants and antiplatelet therapy for the prevention of VTE or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial (AIIa).

## ***Management of Hospitalized Patients***

Several studies have evaluated the risks and benefits of prophylactic and 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 (visit [ClinicalTrials.gov](#) for a current list of trials). Observational studies are included here only when evidence from clinical trials is not available.

### **Prophylactic-Dose of Anticoagulation Versus No Anticoagulation—Observational Cohort**

An observational study of 4,297 veterans hospitalized with COVID-19 evaluated the benefit of prophylactic anticoagulation. 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 veterans who received prophylactic anticoagulation and 19% among patients who were not treated with anticoagulation (HR 0.73; 95% CI, 0.66–0.81). Participants treated with the prophylactic dose did not have a significant difference in risk of bleeding that required transfusion when compared with participants who were not treated (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.<sup>22</sup>

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

Several randomized controlled trials have evaluated the role of therapeutic doses of heparin in reducing VTE events or mortality in patients hospitalized for COVID-19.

Three open-label randomized controlled trials (the large ATTACC/ACTIV-4a/REMAP-CAP multiplatform 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. Clinical data for these trials are summarized in [Table 5](#). The inclusion and exclusion criteria for these studies varied, but most included a need for supplemental oxygen and no risk

of a major bleeding event. In the larger multiplatform trial, therapeutic doses of heparin increased organ support-free days but did not significantly affect mortality or length of hospitalization when compared with prophylactic doses of heparin.<sup>23</sup>

The RAPID trial enrolled patients with elevated D-dimer levels and hypoxemia. 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 intensive care unit (ICU) admission, noninvasive or mechanical ventilation, or death by Day 28. However, the therapeutic dose of heparin reduced all-cause death, a secondary outcome.<sup>24</sup>

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  $\geq 4$ . 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.<sup>25</sup> Results from smaller randomized trials, single-center studies, and observational studies have also been published.

Given the results of the ATTACC/ACTIV-4a/REMAP-CAP, RAPID, and HEP-COVID trials conducted among hospitalized, nonpregnant adults with COVID-19 who did not require ICU-level care and without 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 bleeding risk (**CIIa**).
  - Based on clinical trial exclusion criteria, contraindications for use of therapeutic anticoagulation for patients with COVID-19 are a platelet count  $< 50 \times 10^9/L$ , hemoglobin  $< 8$  g/dL, the need for dual antiplatelet therapy, bleeding within the past 30 days that required an emergency department visit or hospitalization, history of a bleeding disorder, or an inherited or active, acquired bleeding disorder.
- LMWH is preferred over UFH because of its decreased administrative burden and because LMWH was the predominant form of heparin used in the clinical trials for COVID-19.
- In patients without VTE who have begun a therapeutic dose of heparin, treatment should continue for 14 days or until hospital discharge, whichever comes first.
- Patients with predicted hospitalizations of  $< 72$  hours were excluded from the multiplatform trial. The risk/benefit ratio of therapeutic doses of anticoagulation for short hospital stays is not known.
- 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 (**AIIb**).
- The Panel **recommends against** the use of a **therapeutic dose** of oral anticoagulants for VTE prophylaxis or prevention of COVID-19 progression, except in a clinical trial (**AIIa**).
- There is currently insufficient evidence to recommend either for or against the use of thrombolytics for COVID-19.

### **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 VTE events or mortality in patients in the ICU setting. Clinical data for these trials are summarized in [Table 5](#).

For the composite endpoint of adjudicated VTE, arterial thrombosis, ECMO, or all-cause mortality, the INSPIRATION trial found no difference between patients in the ICU treated with an intermediate dose of anticoagulation (enoxaparin 1 mg/kg daily) and those who received a prophylactic dose (45.7% vs. 44.1%; OR 1.06; 95% CI, 0.76–1.48). Major bleeding occurred in 2.5% of patients in the intermediate-dose anticoagulation arm compared with 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 in the ICU.<sup>26</sup>

A multiplatform randomized control trial (REMAP-CAP/ACTIV-4a/ATTACC) 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.<sup>27</sup> All 3 trials were stopped for futility. Heparin doses in the usual care arm varied. The median number of organ support-free days was 3 days (IQR -1 to 16) for patients who received a therapeutic dose of anticoagulation and 4 days (IQR -1 to 16) for patients who received usual care. The likelihood of survival to hospital discharge did not differ between arms (63% therapeutic arm vs. 65% usual care arm; aOR 0.84; 95% CrI, 0.64–1.11). Major bleeding occurred in 4% of participants receiving therapeutic anticoagulation and in 2% of participants receiving usual care. Therapeutic doses of heparin showed no significant benefit for patients with COVID-19 admitted to the ICU.

Given the results of these trials, 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**).
- 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**).
- The Panel **recommends against** the use of an **intermediate dose** (e.g., **enoxaparin** 1 mg/kg daily) or a **therapeutic dose** of anticoagulation for VTE prophylaxis, except in a clinical trial (**BI**).

#### **Rivaroxaban Versus Usual Care in Hospitalized Patients With Elevated D-Dimer Levels**

The ACTION trial randomized adults hospitalized with COVID-19 and elevated D-dimer levels (defined as above the laboratory ULN) to receive rivaroxaban 20 mg daily for 30 days or usual care<sup>28</sup> (see [Table 5](#) for a summary of clinical data for this trial). No statistical difference was found for the composite endpoint of time to death, hospitalization duration, and oxygen use duration (hierarchical analysis; win ratio 0.86; 95% CI, 0.59–1.22) or for the individual components. The probability of clinically relevant nonmajor bleeding was greater with rivaroxaban (5% rivaroxaban arm vs. 1% usual care arm; relative risk 5.23; 95% CI, 1.54–17.77), but for major bleeding events the difference between arms was not significant (3% rivaroxaban arm vs. 1% 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 anticoagulation for VTE prophylaxis and prevention of COVID-19 progression, except in a clinical trial (**BI**).

#### **Aspirin Versus Usual Care in Hospitalized Patients**

The RECOVERY trial randomized 7,351 hospitalized adults with COVID-19 to usual care plus aspirin 150 mg per day and 7,541 patients to usual care only.<sup>29</sup> Mortality at 28 days was 17% in both arms (rate ratio 0.96; 95% CI, 0.89–1.04). Results were similar in all prespecified subgroups, including when restricted to patients with polymerase chain reaction–documented SARS-CoV-2 infection. Among participants not receiving mechanical ventilation at baseline, there was no difference in progression

to mechanical ventilation or death (21% aspirin arm vs. 22% 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%). Given the large trial size, lack of mortality benefit, and increase in bleeding events, the Panel **recommends against** the use of aspirin to prevent mortality or the need for organ support in hospitalized patients with COVID-19 (**AI**).

### **P2Y12 Inhibitor Versus Usual Care in Hospitalized Patients**

The ACTIV-4a trial evaluated P2Y12 inhibitor therapy plus a therapeutic dose of heparin versus therapeutic heparin alone in noncritically ill, hospitalized patients with COVID-19. In this study, enrollment in the cohort that did not receive intensive care was stopped due to futility because the combination therapy did not improve the number of organ support-free days.<sup>30</sup>

### ***Thrombolytic Therapy***

Clinical trials are evaluating the use of thrombolysis on mortality and the progression of COVID-19 illness. There is currently insufficient evidence to recommend either for or against the use of thrombolytic agents for VTE prophylaxis for hospitalized patients with COVID-19 outside of a clinical trial.

### ***Hospitalized Children***

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

### ***Patients Discharged From the Hospital***

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.<sup>32,33</sup> Inclusion criteria for the trials that studied post-discharge VTE prophylaxis included:

- A VTE risk score of  $\geq 4$  on the modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) tool,<sup>34</sup> *or*
- A VTE risk score  $\geq 2$  on the modified IMPROVE tool<sup>35</sup> and a D-dimer level  $> 2$  times ULN.<sup>32</sup>

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, bleeding risks, and feasibility. The MICHELLE trial of post-discharge prophylaxis in patients with COVID-19 was recently published and is being reviewed by the Panel.<sup>36</sup> 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.<sup>37</sup> 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.<sup>38-40</sup> 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 individuals hospitalized with COVID-19, particularly for those who have severe

disease.<sup>41</sup> If there are no contraindications to use, the Society for Maternal-Fetal Medicine recommends prophylactic heparin or LMWH in critically ill or mechanically ventilated pregnant patients.<sup>42</sup> 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.<sup>43,44</sup> If delivery is imminent, or if there are other risks for bleeding, the risk of bleeding may outweigh the potential benefit of VTE prophylaxis in pregnancy.

Outside of pregnancy, 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 during pregnancy in the setting of COVID-19.<sup>45-47</sup>

In general, the preferred anticoagulants for use during pregnancy are heparin compounds. Because of its reliability and ease of administration, LMWH is recommended rather than UFH for the prevention and treatment of VTE in pregnancy.<sup>44</sup> Direct-acting anticoagulants are not routinely recommended during pregnancy because of a lack of safety data for pregnant individuals.<sup>43</sup> 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 hospitalized for manifestations of COVID-19, unless otherwise contraindicated (**BIII**).
- Because pregnant patients have not been included in most clinical trials evaluating therapeutic anticoagulation in the setting of COVID-19, there is currently insufficient evidence to recommend either for or against therapeutic anticoagulation for pregnant patients with COVID-19 without evidence of VTE.
- Like for nonpregnant patients, VTE prophylaxis after hospital discharge is not routinely recommended for pregnant patients (**BIII**). Decisions to continue VTE prophylaxis in the pregnant or postpartum patient after discharge should be individualized, with consideration of 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 (**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**).

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