

American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: May 2021 update on the use of intermediate-intensity anticoagulation in critically ill patients.

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26 10 2021 14 10 2021 5 20 403792 3951 3959 09 6 2021 09 8 2021 2 9 2021 14 10 2021 07 09 2021 12 02 2025 8416320 10.1182/bloodadvances.2021005493 1 04 09 2021 8945625 10.1182/bloodadvances.2021005493 2 14 10 2021 © 2021 by The American Society of Hematology. Licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) , permitting only noncommercial, nonderivative use with attribution. All other rights reserved. 2021 <https://creativecommons.org/licenses/by-nc-nd/4.0/> Cuker A, Tseng EK, Nieuwlaar R, et al. American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: May 2021 update on the use of intermediate-intensity anticoagulation in critically ill patients. *Blood Adv.* 2021;5(20):3951-3959. 7 5 10 3 2023 811 811 Blood Advances PMC9999174 36867457 Visual Abstract

Background: COVID-19–related critical illness is associated with an increased risk of venous thromboembolism (VTE).

Objective: These evidence-based guidelines of the American Society of Hematology (ASH) are intended to support patients, clinicians, and other health care professionals in making decisions about the use of anticoagulation for thromboprophylaxis in patients with COVID-19–related critical illness who do not have confirmed or suspected VTE.

Methods: ASH formed a multidisciplinary guideline panel that included 3 patient representatives and applied strategies to minimize potential bias from conflicts of interest. The McMaster University

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Centre supported the guideline development process by performing systematic evidence reviews (up to 5 March 2021). The panel prioritized clinical questions and outcomes according to their importance for clinicians and patients. The panel used the GRADE approach to assess evidence and make recommendations, which were subject to public comment. This is an update on guidelines published in February 2021.

Results: The panel agreed on 1 additional recommendation. The panel issued a conditional recommendation in favor of prophylactic-intensity over intermediate-intensity anticoagulation in patients with COVID-19–related critical illness who do not have confirmed or suspected VTE.

Conclusions: This recommendation was based on low certainty in the evidence, which underscores the need for additional high-quality, randomized, controlled trials comparing different intensities of anticoagulation in critically ill patients. Other key research priorities include better evidence regarding predictors of thrombosis and bleeding risk in critically ill patients with COVID-19 and the impact of nonanticoagulant therapies (eg, antiviral agents, corticosteroids) on thrombotic risk.

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Remarks: The ASH guideline panel plans to continue to update this recommendation when the full results of other trials become available. Clinicians should weigh the benefits and harms based on the most up-to-date evidence in caring for their patients.

A now-expired recommendation published on 27 October 2020 compared therapeutic-intensity or intermediate-intensity with prophylactic-intensity anticoagulation in patients with COVID-19–related critical illness. With the emergence of new evidence, this recommendation has now been split into 2 recommendations: a recommendation comparing intermediate-intensity with prophylactic-intensity anticoagulation (Recommendation 1a) and a separate recommendation comparing therapeutic-intensity with prophylactic-intensity anticoagulation (Recommendation 1b), whereby the latter remains unchanged for now, but, as with other recommendations in this guideline, is subject to review and revision as new evidence becomes available that meets prespecified criteria for updating.

Patients with COVID-19–related critical illness are defined as those suffering from an immediately life-threatening condition who would typically be admitted to an intensive care unit (ICU). Examples include patients requiring hemodynamic support, ventilatory support, and renal replacement therapy.

An individualized assessment of the patient's risk of thrombosis and bleeding is important when deciding on anticoagulation intensity. Risk assessment models to estimate thrombotic and bleeding risk in hospitalized patients are available, but they have not been prospectively validated in patients with COVID-19.

At present, there is no direct high-certainty evidence comparing different types of anticoagulants. The selection of a specific agent (eg, low molecular weight heparin [LMWH], unfractionated heparin [UFH]) may be based on availability, resources required, familiarity, and the aim of minimizing the

use of personal protective equipment or exposure of staff to COVID-19–infected patients as well as patient-specific factors (eg, renal function, history of heparin-induced thrombocytopenia, concerns about gastrointestinal tract absorption).

This recommendation does not apply to patients who require anticoagulation to prevent thrombosis of extracorporeal circuits such as those on extracorporeal membrane oxygenation or continuous renal replacement therapy.

There is a high incidence of thrombotic complications in critically ill patients with COVID-19. 1 VTE is the most common thrombotic complication and has been reported in up to 23% of critically ill patients with COVID-19. 2 Consequently, there has been intense clinical and research interest in establishing whether intensified thromboprophylaxis regimens are needed in this population. 3 However, critically ill patients may be at increased risk for bleeding complications, which may also occur in patients with COVID-19–related critical illness. 4-8 The optimal strategy for thromboprophylaxis that balances these thrombosis and bleeding risks remains uncertain.

These guidelines are based on updated and original systematic reviews of evidence conducted under the direction of the McMaster University Grading of Recommendations Assessment, Development and Evaluation (GRADE) Centre with international collaborators. This is an update of the previous ASH guideline published in February 2021, 9 and it focuses on intermediate-intensity vs prophylactic-intensity anticoagulation. The panel followed best practices for guideline development recommended by the Institute of Medicine and the Guidelines International Network. 10-12 The panel used the GRADE approach 13-19 to assess the certainty of the evidence and formulate recommendations. The recommendation is listed in Table 1 .

The guideline panel identified all-cause mortality, pulmonary embolism (PE), deep vein thrombosis (DVT), and major bleeding as critical outcomes and placed a high value on avoiding these outcomes with the interventions assessed.

Panel members noted that there was possible uncertainty and variability in the relative value that patients place on avoiding major bleeding events compared with reducing thrombotic events.

Please refer to the original ASH guideline on thromboprophylaxis in patients with COVID-19. 9

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The COVID-19 pandemic has had a significant public health impact. As of 2 May 2021, more than 152 million cases and 3.2 million deaths had been attributed to COVID-19–related illness globally. 20 It is estimated that 5% to 20% of infected patients require hospital admission, of whom 5% to 15% may develop critical illness requiring intensive care support. 21-23

Patients with critical illness resulting from COVID-19 may develop a severe inflammatory response and endothelial dysfunction, which may result in platelet activation, activation of the coagulation cascade, and a hypercoagulable state. 24 Several laboratory predictors of thrombosis in hospitalized patients with COVID-19 have been reported, including elevated D-dimer, C-reactive protein, and erythrocyte sedimentation rate. 5,25 VTE has emerged as an important complication in critically ill patients with COVID-19, occurring in up to 23% of such patients. 2 This was observed in the very early days of the pandemic, but it remains an important issue, even with the introduction of improved treatments in subsequent waves of the pandemic. 26,27 In addition, arterial thrombotic complications including stroke have been noted. 28,29 Microvascular thrombosis, which may involve the pulmonary vasculature and other organs, has been reported in autopsy studies, although its impact on the development of respiratory and multiorgan failure remains unclear. 30,31 Patients who are critically ill may also be at increased bleeding risk, which may be a result of

platelet dysfunction, thrombocytopenia, organ dysfunction, or consumptive coagulopathy. 4,5

The optimal thromboprophylaxis strategy that balances thrombotic and bleeding risk in critically ill patients with COVID-19 remains uncertain. 32-35 This uncertainty has led to variability in clinical practice regarding empiric thromboprophylaxis regimens, and several randomized trials are in progress. 36,37 Although COVID-19–associated coagulopathy seems to be marked primarily by thrombotic complications, patients may develop major bleeding complications when receiving anticoagulation therapy, which can have an impact on the safety of intensified thromboprophylaxis regimens. 5,8,38 In this living guideline update, the role of intermediate- vs prophylactic-intensity anticoagulation in critically ill patients with COVID-19 is addressed.

The target population, patients with COVID-19–related critical illness, is described in Table 2 .

This updated guideline recommendation on the use of intermediate-intensity anticoagulation in critically ill patients was developed in the living phase of the ASH 2021 living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. The ASH guideline panel generated Recommendation 1a on 30 March 2021 before asking for public comments.

We followed the same methods as published in the initial guideline, 9 with the following important updates and differences for the recommendation reported here: Organization, panel composition, planning, and coordination: With one exception, we retained the same panel members because no conflicts of interest emerged that would require exclusion of panel members.

Guideline funding and management of conflicts of interest: Supplement 4 provides updated “Participant Information Forms” for all panel members, detailing financial and nonfinancial interests, as well as the ASH conflict-of-interest policies agreed to by each individual. Supplement 5 provides the updated complete Participant Information Forms for researchers on the Systematic Review Team who contributed to these guidelines.

Formulating specific clinical questions and determining outcomes of interest: This updated manuscript focuses on 1 question: In patients with COVID-19–related critical illness who do not have confirmed or suspected VTE, should we use direct oral anticoagulants, LMWH, UFH, fondaparinux, argatroban, or bivalirudin at intermediate intensity or prophylactic intensity? There were no changes in the definitions for population (Table 2), anticoagulation intensity, or outcomes. 9

Evidence review and development of recommendations: A new evidence-to-decision (EtD) framework was created for Recommendation 1a (see Recommendations) that uses any applicable evidence and information from the EtD framework for the initial Recommendation 1, and it will be updated with new evidence and considerations specifically for Recommendation 1a. The systematic review to identify comparative antithrombotic studies for the entire guideline was updated until 5 March 2021, the literature search strategy (Supplement 6) was modified only to add search terms for antiplatelet agents for another guideline question, and the protocol (Supplement 9) was modified to focus on inclusion of only randomized controlled trials for the guideline after the initial phase. Baseline risk estimates for outcomes in patients with COVID-19–related critical illness were not updated. The decision to create this updated guideline recommendation was based on publication of the INSPIRATION trial, 39 which was not yet included in the systematic literature searches but was identified by expert panel members, critically assessed by the evidence synthesis team, and determined to increase the certainty of the evidence for several critical outcomes.

Document review: The draft recommendation was reviewed by all members of the panel, revised, and then made available online from 21 to 28 April 2021 for external review by stakeholders, including allied organizations, other medical professionals, patients, and the public. Two individuals or organizations submitted responses that did not require changes to the document. On 1 June 2021, the ASH Guideline Oversight Subcommittee and the ASH Committee on Quality verified that

the defined guideline development process was followed, and on 3 June 2021, the officers of the ASH Executive Committee approved submission of the updated guideline manuscript for publication under the imprimatur of ASH. The updated guideline manuscript was then subjected to peer review by Blood Advances .

How to use these guidelines: We refer readers to the description in the initial guideline publication from February 2021, 9 as well as the user guide for the ASH clinical practice guidelines. 40

Should direct oral anticoagulants, LMWH, UFH, fondaparinux, argatroban, or bivalirudin at intermediate-intensity vs prophylactic-intensity be used for patients with COVID-19–related critical illness who do not have suspected or confirmed VTE?

The ASH guideline panel suggests using prophylactic-intensity over intermediate-intensity anticoagulation in patients with COVID-19–related critical illness who do not have suspected or confirmed VTE (conditional recommendation based on low certainty in the evidence about effects ■■■■).

Remarks: The ASH guideline panel plans to continue to update this recommendation when the full results of other trials become available. Clinicians should weigh the benefits and harms based on the most up-to-date evidence in caring for their patients.

A now-expired recommendation published on 27 October 2020 compared therapeutic-intensity or intermediate-intensity with prophylactic-intensity anticoagulation in patients with COVID-19–related critical illness. With the emergence of new evidence, this recommendation has now been split into 2 recommendations: a recommendation comparing intermediate-intensity with prophylactic-intensity anticoagulation (Recommendation 1a) and a separate recommendation comparing therapeutic-intensity with prophylactic-intensity anticoagulation (Recommendation 1b), whereby the latter remains unchanged for now but, as with other recommendations in this guideline, is subject to review and revision as new evidence becomes available that meets prespecified criteria for updating.

Patients with COVID-19–related critical illness are defined as those suffering from an immediately life-threatening condition who would typically be admitted to an intensive care unit. Examples include patients requiring hemodynamic support, ventilatory support, and renal replacement therapy.

An individualized assessment of the patient's risk of thrombosis and bleeding is important when deciding on anticoagulation intensity. Risk assessment models to estimate thrombotic and bleeding risk in hospitalized patients are available, but they have not been prospectively validated in patients with COVID-19.

At present, there is no direct high-certainty evidence comparing different types of anticoagulants. The selection of a specific agent (eg, LMWH or UFH) may be based on availability, resources required, familiarity, and the aim of minimizing the use of personal protective equipment or staff exposure to COVID-19–infected patients as well as patient-specific factors (eg, renal function, history of heparin-induced thrombocytopenia, concerns about gastrointestinal tract absorption).

This recommendation does not apply to patients who require anticoagulation to prevent thrombosis of extracorporeal circuits such as those on extracorporeal membrane oxygenation or continuous renal replacement therapy.

We rated the certainty in the evidence as moderate for the outcomes of ventilator-free days and length of ICU stay owing to serious imprecision, and as low for all other outcomes owing to very serious imprecision (see evidence profile and EtD online at <https://guidelines.ash.gradepro.org/profile/iqf3QTWtZt0>). We found no systematic reviews that

addressed this question. There was 1 randomized controlled trial that provided evidence related to this question. 39 Supplement 10 presents the characteristics of the included study.

One randomized controlled trial reported the effect of intermediate-intensity anticoagulation on all-cause mortality, PE, DVT, VTE, major bleeding, renal replacement therapy, ischemic stroke, intracranial hemorrhage, ventilator-free days, length of ICU stay, and myocardial infarction. 39 No studies reported the effect of intermediate-intensity anticoagulation on multiorgan failure or limb amputation.

Intermediate-intensity anticoagulation may reduce the risk of PE but the evidence is uncertain (odds ratio [OR], 0.41; 95% confidence interval [CI], 0.08-2.13); this corresponds to 55 fewer (from 89 fewer to 90 more) PEs per 1000 patients; low certainty. 39 Taking PE and DVT together, intermediate-intensity anticoagulation may reduce the risk of VTE, but the evidence is uncertain (OR, 0.93; 95% CI, 0.37-2.32); this corresponds to 8 fewer (from 78 fewer to 127 more) VTE events per 1000 patients; low certainty. Intermediate-intensity anticoagulation may reduce the length of ICU stay, but the evidence is uncertain (mean difference, 1 day fewer; 95% CI, 4 days fewer to 3 days more); moderate certainty. Intermediate-intensity anticoagulation had no effect on ventilator-free days, but the evidence is uncertain (mean difference, 0 days; 95% CI, 0-0 days); moderate certainty.

Intermediate-intensity anticoagulation may increase the risk of all-cause mortality, but the evidence is uncertain (OR, 1.09; 95% CI, 0.78-1.53); this corresponds to 16 more (from 42 fewer to 85 more) deaths per 1000 patients; low certainty. 39 Intermediate-intensity anticoagulation may increase the risk of DVT, but the evidence is uncertain (OR, 1.46; 95% CI, 0.46-4.66); this corresponds to 42 more (from 54 fewer to 250 more) DVTs per 1000 patients; low certainty. Intermediate-intensity anticoagulation may increase the risk of major bleeding, but the evidence is uncertain (OR, 1.83; 95% CI, 0.53-5.93); this corresponds to 60 more (from 38 fewer to 268 more) major bleeding events per 1000 patients; low certainty. Intermediate-intensity anticoagulation may increase the use of renal replacement therapy, but the evidence is uncertain (OR, 1.49; 95% CI, 0.58-3.86); this corresponds to 125 more (from 48 fewer to 230 more) uses of renal replacement therapy per 1000 patients; low certainty. The effect of intermediate-intensity anticoagulation on the outcomes of ischemic stroke, intracranial hemorrhage, and myocardial infarction was very uncertain because only 1 ischemic stroke, 1 intracranial hemorrhage, and no myocardial infarctions occurred in the trial.

The guideline panel noted that there was possible uncertainty and variability in the relative value patients place on reducing thrombotic events compared with avoiding major bleeding events. The panel agreed that the use of intermediate-intensity anticoagulation would be acceptable to patients and health care providers. However, given the low certainty in the evidence, there may be regional variation in the acceptability of intermediate-intensity anticoagulation, particularly in regions where baseline VTE risk may be lower (eg, Asian populations). 41,42

The panel recognized that COVID-19 disproportionately affects certain racial and ethnic groups, including Black and Hispanic individuals. However, the use of intermediate-intensity anticoagulation was judged to probably not have a differential impact on health equity relative to the use of prophylactic-intensity anticoagulation. Although intermediate-intensity anticoagulation would result in a higher cost for drugs, the panel judged this difference to be negligible relative to the total costs of providing critical care.

The panel judged that there was low certainty evidence in the desirable and undesirable effects of intermediate-intensity anticoagulation in patients with COVID-19–related critical illness. There was a suggestion of a reduction in PE with intermediate-intensity anticoagulation, but the opposite was observed for DVT, and the evidence for both outcomes was of low certainty.

Meanwhile, there was less uncertainty in the potential undesirable effects of intermediate-intensity anticoagulation with respect to increased risk of major bleeding complications. The panel considered that there was higher-quality indirect evidence from critically ill patients who did not have COVID-19 for a dose-dependent increase in the risk of major bleeding with anticoagulation, although the magnitude of this effect was of low certainty in the population who did have COVID-19. 8,43 - 46 Given that there was low certainty for potential benefit to offset the moderate risk of major bleeding complications, the usual practice of prophylactic-intensity anticoagulation, as used in critically ill patients who did not have COVID-19, was suggested. 47

However, the panel noted that an individualized decision is important for each patient based on an assessment of thrombosis and bleeding risk. Dose adjustment of prophylactic-intensity anticoagulation for extremes of body weight or renal impairment may also be considered. 48-52

This recommendation does not apply to thrombotic complications related to extracorporeal circuits. Although high rates of circuit-related thrombosis during extracorporeal membrane oxygenation and continuous renal replacement therapy have been reported in patients with COVID-19, this outcome was not prioritized by the guideline panel as part of its systematic review of the evidence. 53

There are multiple other guidance documents on the use of anticoagulation in patients with COVID-19. These include the 2020 CHEST COVID-19 Guidelines, the Anticoagulation (AC) Forum interim clinical guidance, the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee (SSC) COVID-19 clinical guidance, the National Institutes of Health (NIH) COVID-19 treatment guidelines, and the American College of Cardiology (ACC) clinical guidance. 54-58

Major differences between the current ASH guidelines and these other documents include use of high-quality systematic reviews and EtD frameworks, which increase transparency, along with use of marker states to estimate the relative importance to patients as key outcomes of treatment. This ASH guideline is also unique in its “living” format, which enables the inclusion of the recently published INSPIRATION clinical trial 39 to inform the current recommendation (most other guidance documents were published before this trial's results were made available; they may be revised as new evidence becomes available).

Four of the 5 other guidance documents (NIH, ISTH, ACC, and CHEST) suggest that prophylactic-dose heparin (either UFH or LMWH) be used for thromboprophylaxis in critically ill patients with COVID-19 over higher-intensity anticoagulation. They acknowledge that although there is an increased risk of VTE in hospitalized patients with COVID-19, there is insufficient randomized data at this time to recommend increased-intensity anticoagulation. The ISTH guidance document suggests that intermediate-dose LMWH could be considered in high-risk patients, and that patients with obesity could be considered for a 50% empiric dose increase for thromboprophylaxis. The ISTH document also suggests that multimodal prophylaxis with mechanical methods should be considered. This is notable because current guidelines in critically ill patients who do not have COVID-19 suggest using pharmacologic prophylaxis alone over combined pharmacologic and mechanical prophylaxis. 47,59

Meanwhile, the guidance document from the AC Forum suggests that in critically ill patients with COVID-19, intermediate or increased intensities of thromboprophylaxis could be used. 55 The authors acknowledge that this was based on expert opinion, and this was published before the results of the INSPIRATION randomized trial were made available. 39

At the time of this writing, there has been only 1 small published randomized trial in critically ill patients with COVID-19 that compares therapeutic-dose and prophylactic-dose anticoagulation. 60 Although this trial demonstrated improvements in gas exchange (PaO₂ :FiO₂ ratio) with therapeutic anticoagulation, definitive conclusions cannot be drawn because only 20 patients were enrolled. A second randomized trial, the ACTION trial, compared therapeutic-intensity vs

prophylactic-intensity anticoagulation in hospitalized patients with COVID-19 and elevated D-dimer. Most of the patients did not have critical illness. Therapeutic-intensity anticoagulation did not improve clinical outcomes and was associated with increased bleeding. 61 A multiplatform study (ACTIV-4/REMAP-CAP/ATTACC) in critically ill patients with COVID-19 comparing therapeutic- with prophylactic-intensity anticoagulation has also recently been conducted. This study was stopped early because therapeutic anticoagulation met the predefined criteria for futility in the primary outcome of organ support–free days. 62 The preprint article for this study suggested that therapeutic anticoagulation did not improve hospital survival or days free of organ support, and a potential for harm could not be excluded. When the results of this study are published, the ASH guidelines will be updated accordingly.

The limitations of these guidelines are inherent in the low certainty of the evidence we identified for the research questions. There were 2 outcomes that were identified as critical for decision making by the guideline panel for which no direct evidence was available (multiple organ failure and limb amputation).

In addition, the use of treatments other than anticoagulants for management of COVID-19–related critical illness (eg, corticosteroids, anticytokine therapies, ventilatory support) as well as the emergence of different viral variants has changed over the course of the pandemic. These changes may impact the baseline risk of VTE. Evidence collected earlier in the pandemic and included in our systematic reviews may not fully reflect the baseline risk of VTE or the effect of different intensities of anticoagulation in the current state of the pandemic.

The reported recommendation is the first living update of recommendations from the initial guideline publication that will be maintained by ASH through surveillance for new evidence, ongoing review by experts, and regular revisions. See the initial guideline publication for methods of living systematic reviews and recommendations, including considerations for deciding when to reassess and update recommendations. 9

Adaptation of these guidelines will be necessary in many circumstances. These adaptations should be based on the associated EtD frameworks. 17

On the basis of gaps in evidence identified during the guideline development process, the panel identified the following urgent research priorities in this patient population: Studies assessing baseline VTE risk in critically ill patients receiving prophylactic-intensity anticoagulation therapy

Randomized controlled trials comparing anticoagulation at differing intensities (prophylactic vs intermediate vs therapeutic)

Studies examining the impact of nonanticoagulant interventions (eg, anticomplement therapy, corticosteroids, antiviral therapies, anticytokine therapies, antiplatelet therapies, monoclonal antibody therapy, convalescent plasma) on thrombotic risk

Development or validation of risk assessment models for thrombosis and bleeding in patients with COVID-19–related critical illness

Studies examining the impact of anticoagulant therapy on thrombosis and bleeding outcomes in critically ill patients of differing race and ethnicity

Studies comparing mortality, thrombosis, bleeding, and functional outcomes with different available anticoagulant agents in critically ill patients

The full-text version of this article contains a data supplement.

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