American Society of Hematology living guidelines on use of anticoagulation for thromboprophylaxis for patients with COVID-19: executive summary

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CLINICAL GUIDELINES

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American Society of Hematology living guidelines on use of anticoagulation for thromboprophylaxis for patients with COVID-19: executive summary

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Background: COVID-19–related critical and acute illness is associated with an increased risk of venous thromboembolism (VTE). These evidence-based recommendations of the American Society of Hematology (ASH) are intended to support patients, clinicians, and other health care professionals in decisions about using anticoagulation for thromboprophylaxis for patients with COVID-19–related critical illness; patients with COVID-19–related acute illness; and those being discharged from the hospital, who do not have suspected or confirmed VTE.

Methods: ASH formed a multidisciplinary panel, including patient representatives. The Michael G. DeGroote Cochrane Canada and MacGRADE Centres at McMaster University supported guideline development, including performing systematic reviews (up to June 2023). The panel prioritized clinical questions and outcomes according to their importance for clinicians and patients. The panel used the

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

Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess certainty in the evidence and make recommendations.

Results: This is an executive summary of 3 updated recommendations that have been published, which concludes the living phase of the guidelines. For patients with COVID-19–related critical illness, the panel issued conditional recommendations suggesting (a) prophylactic-intensity over therapeutic-intensity anticoagulation and (b) prophylactic-intensity over intermediate-intensity anticoagulation. For patients with COVID-19–related acute illness, conditional recommendations were suggested (a) prophylactic-intensity over intermediate-intensity anticoagulation, and (b) therapeutic-intensity over prophylactic-intensity anticoagulation. The panel issued a conditional recommendation suggesting against the use of postdischarge anticoagulant thromboprophylaxis.

Conclusions: These conditional recommendations were made based on low or very low certainty in the evidence, underscoring the need for additional, high-quality, randomized controlled trials for patients with COVID-19.

Summary of recommendations

Background

Venous thromboembolism (VTE) is an important complication that occurs in patients who are acutely and critically ill with COVID-19 despite the use of standard thromboprophylaxis regimens.[1] Thrombosis of the microvascular circulation may also contribute to other complications of COVID-19, including respiratory failure.[2,3] Meanwhile, higher-intensity anticoagulation is associated with an increase in bleeding risk among hospitalized patients who have COVID-19.[4] Therefore, there has been broad interest in establishing how anticoagulant regimens may improve clinical outcomes both during hospitalization and after hospital discharge.

These guidelines address the use of anticoagulation for thromboprophylaxis as follows: (1) higher intensity anticoagulation (intermediate or therapeutic intensity) compared with standard prophylactic-intensity anticoagulation for patients with COVID-19–related critical illness, (2) higher intensity anticoagulation (intermediate or therapeutic intensity) compared with standard prophylactic-intensity anticoagulation for patients with COVID-19–related acute illness, and (3) prophylactic-intensity anticoagulation compared with no anticoagulation for patients discharged after hospitalization for COVID-19. These guidelines are based on systematic reviews of evidence conducted under the direction of the Michael G. DeGroote Cochrane Canada and MacGRADE Centres at McMaster University with international collaborators. The panel followed best practice for guideline development recommended by the Institute of Medicine and the Guidelines International Network.[5-7] The panel used the grading of recommendations assessment, development and evaluation approach to assess the certainty in the evidence and formulate recommendations.[8-14]

Recommendation 1a

The American Society of Hematology (ASH) guideline panel *suggests* using prophylactic-intensity over intermediate-intensity anticoagulation for patients with COVID-19–related critical illness who do not have suspected or confirmed VTE or another indication for anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Recommendation 1b

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

Remarks:

- 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) because of COVID-19. 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 (RAMs) to estimate thrombotic risk have been validated in hospitalized patients with COVID-19 (critically or noncritically ill), with modest prognostic performance. No RAMs for bleeding have been validated for patients with COVID-19. The panel acknowledges that higher-intensity anticoagulation may be preferred for patients judged to be at low bleeding risk and high thrombotic risk.
- 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] and unfractionated heparin [UFH]) may be based on availability, resources required, familiarity, the aim of minimizing the use of personal protective equipment or exposure to staff to patients with COVID-19, as well as patient-specific factors (eg, renal function, history of heparin-induced thrombocytopenia, and bleeding risk). LMWH and UFH were used in the identified studies and may be preferred because of a preponderance of evidence with these agents. There are no studies of intermediate- or therapeutic-intensity fondaparinux, argatroban, or bivalirudin in this population.
- These recommendations do not apply to patients who require anticoagulation to prevent thrombosis of extracorporeal circuits such as those on extracorporeal membrane oxygenation (ECMO) or continuous renal replacement therapy (CRRT).

Recommendation 2a

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

Recommendation 2b

The ASH guideline panel *suggests* using therapeutic-intensity over prophylactic-intensity anticoagulation for patients with COVID-19–related acute illness who do not have suspected or confirmed VTE or another indication for anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- Patients with COVID-19–related acute illness are defined as those with clinical features that would typically result in admission to an inpatient medical ward without requirement for intensive clinical support. Examples include patients with dyspnea or mild-to-moderate hypoxia.
- An individualized assessment of the patient's risk of thrombosis and bleeding is important when deciding on anticoagulation intensity. RAMs to estimate thrombotic risk have been validated in hospitalized patients with COVID-19 (critically or noncritically ill), with modest prognostic performance. No RAMs for bleeding have been validated for patients with COVID-19. The panel acknowledges that lower-intensity anticoagulation may be preferred for patients judged to be at high bleeding risk and low risk of thrombosis.
- At present, there is no direct high-certainty evidence comparing different types of anticoagulants for patients with COVID-19. LMWH or UFH may be preferred because of a preponderance of evidence with these agents. There are no studies of therapeutic-intensity fondaparinux, argatroban, or bivalirudin in this population.

Recommendation 3

The ASH guideline panel *suggests* against using post-discharge outpatient anticoagulant thromboprophylaxis for patients with COVID-19 who are being discharged from hospital and who do not have suspected or confirmed VTE or another indication for anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- An individualized assessment of the patient's risk of thrombosis and bleeding and shared decision-making are important when deciding on whether to use postdischarge thromboprophylaxis.
- The panel acknowledged that postdischarge thromboprophylaxis may be reasonable for patients judged to be at high thrombotic risk and low bleeding risk.

Values and preferences

Please refer to the full recommendation reports below and the online evidence-to-decision (EtD) frameworks for considerations regarding values and preferences.

Explanations and other considerations

Please refer to the full recommendation reports below and the online EtD frameworks for explanations and other considerations.

Interpretation of strong and conditional recommendations

The strength of a recommendation is expressed as either strong ("the guideline panel recommends…") or conditional ("the guideline panel suggests…") and has the following interpretation[15]:

Strong recommendation

- For patients: most individuals in this situation would want the recommended course of action, and only a small proportion would not.
- For clinicians: most individuals should follow the recommended course of action; formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.
- For policymakers: the recommendation can be adopted as policy in most situations; adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.
- For researchers: the recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations.

Conditional recommendation

- For patients: the majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
- For clinicians: recognize that different choices will be appropriate for individual patients and that the clinician must help each patient arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
- For policymakers: policy-making will require substantial debate and involvement of various stakeholders. Performance measures about the suggested course of action should focus on whether an appropriate decision-making process is duly documented.
- For researchers: this recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations)

that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

Introduction

Aims and specific objectives of these guidelines

The ASH guidelines on thromboprophylaxis for patients with COVID-19 were created as living guidelines that were updated through living systematic reviews, as new evidence emerged throughout the course of the global pandemic. More background on this methodology and approach can be found in the original ASH guideline on thromboprophylaxis for patients with COVID-19.[15]

Using living guideline methods, these recommendations were initially published individually as new evidence was published. The first guideline (recommendations 1 and 2, regarding patients who are critically or acutely ill with COVID-19) was published in February 2021. There have been 4 subsequent updates including the addition of recommendation 3 regarding postdischarge thromboprophylaxis.[16-19]

This article is an executive summary of all updated ASH guideline panel recommendations (summarized in Table 1) representing the conclusion of the living guideline phase. All recommendations and updates to these living guidelines are also accessible at the ASH COVID-19 anticoagulation webpage.[20]

Description of the health problem

The COVID-19 pandemic has had a significant public health impact, with substantial global morbidity and mortality.[21] Patients who develop COVID-19–related acute or critical illness may develop hypercoagulability, thrombosis, and coagulopathy, which is marked by elevated fibrinogen, D-dimer concentrations, and inflammatory markers.[22,23] Vascular endothelial dysfunction (endotheliopathy) may also occur, which can contribute to systemic hypercoagulability and microvascular thrombosis.[24]

Thrombosis is an important complication of patients hospitalized with COVID-19–related acute or critical illness. Early cohort studies in predominantly unvaccinated patients reported VTE in 7.9% and 22.7% of patients in these clinical contexts, respectively, despite the use of standard pharmacological thromboprophylaxis.[1]

Additionally, based on the high observed incidence of VTE during hospitalization for COVID-19, there is concern that patients with COVID-19 may have a higher risk of VTE after discharge than patients without COVID-19. However, estimates of postdischarge VTE in patients with COVID-19 generally range from 0.5% to 1.5%, comparable with the incidence of VTE after hospitalization for non-COVID-19 illnesses.[25-27] Nevertheless, there has been ongoing interest in establishing whether extended thromboprophylaxis is beneficial in these patients. There are no RAMs that

Table 1. Recommendations

Recommendation	Remarks
Recommendation 1a: the ASH guideline panel *suggests* using prophylactic-intensity over intermediate-intensity anticoagulation for patients with COVID-19–related critical illness who do not have suspected or confirmed VTE (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯). Recommendation 1b: the ASH guideline panel *suggests* using prophylactic-intensity over therapeutic-intensity anticoagulation for patients with COVID-19–related critical illness who do not have suspected or confirmed VTE (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).	• 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 ICU due to COVID-19. Examples include patients requiring hemodynamic support, ventilatory support, and renal replacement therapy. This does not include patients admitted to the ICU for other reasons who incidentally test positive for COVID-19. • An individualized assessment of the patient's risk of thrombosis and bleeding is important when deciding on anticoagulation intensity. RAMs to estimate thrombotic risk have been validated in hospitalized patients with COVID-19 (critically or noncritically ill), with modest prognostic performance. No RAMs for bleeding have been validated for patients with COVID-19. The panel acknowledges that higher-intensity anticoagulation may be preferred for patients judged to be at low bleeding risk and high thrombotic risk. • At present, there is no direct high-certainty evidence comparing different types of anticoagulants. The selection of a specific agent (eg, LMWH and UFH) may be based on availability, resources required, familiarity, the aim of minimizing the use of personal protective equipment or exposure to staff to patients with COVID-19, as well as patient-specific factors (eg, renal function, history of heparin-induced thrombocytopenia, and concerns about gastrointestinal tract absorption). LMWH and UFH were used in the identified studies and may be preferred because of a preponderance of evidence with these agents. There are no studies of intermediate- or therapeutic-intensity fondaparinux, argatroban, or bivalirudin in this population. • These recommendations do not apply to patients who require anticoagulation to prevent thrombosis of extracorporeal circuits such as those on ECMO or CRRT.
Recommendation 2a: the ASH guideline panel *suggests* using prophylactic-intensity over intermediate-intensity anticoagulation for patients with COVID-19–related acute illness who do not have suspected or confirmed VTE (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯). Recommendation 2a: the ASH guideline panel *suggests* using therapeutic-intensity over prophylactic-intensity anticoagulation for patients with COVID-19–related acute illness who do not have suspected or confirmed VTE (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).	• Patients with COVID-19–related acute illness are defined as those with clinical features that would typically result in admission to an inpatient medical ward without requirement for intensive clinical support. Examples include patients with dyspnea or mild-to-moderate hypoxia. • An individualized assessment of the patient's risk of thrombosis and bleeding is important when deciding on anticoagulation intensity. RAMs to estimate thrombotic risk have been validated in hospitalized patients with COVID-19 (critically or noncritically ill), with modest prognostic performance. No RAMs for bleeding have been validated for patients with COVID-19. The panel acknowledges that lower-intensity anticoagulation may be preferred for patients judged to be at high bleeding risk and low risk of thrombosis. • At present, there is no direct high-certainty evidence comparing different types of anticoagulants for patients with COVID-19. LMWH or UFH may be preferred because of a preponderance of evidence with these agents. There are no studies of therapeutic-intensity fondaparinux, argatroban, or bivalirudin in this population.
Recommendation 3: the ASH guideline panel *suggests* against using postdischarge outpatient anticoagulant thromboprophylaxis for patients with COVID-19 who are being discharged from hospital and who do not have suspected or confirmed VTE or another indication for anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).	• An individualized assessment of the patient's risk of thrombosis and bleeding and shared decision-making are important when deciding on whether to use postdischarge thromboprophylaxis. • The panel acknowledged that postdischarge thromboprophylaxis may be reasonable for patients judged to be at high thrombotic risk and low bleeding risk.

Table 2. Descriptions of target populations

Target population	Definition
Critically ill	Patients with COVID-19 who develop respiratory or cardiovascular failure normally requiring advanced clinical support in the ICU or critical care unit (CCU) but could include admission to another department if the ICU/CCU was over capacity. ICU/CCU capacity and admission criteria could vary according to the specific setting. This does not include patients admitted to the ICU for other reasons who incidentally test positive for COVID-19.
Acutely ill	Patients with COVID-19 who require hospital admission, generally to an inpatient medical ward, without intensive clinical support (ie, not in the ICU/CCU) but may be treated in other settings if the hospital is over capacity. Hospital capacity and admission criteria may vary according to the specific setting. Some observational studies informing the baseline risk of critical outcomes reported on all patients hospitalized with COVID-19 in aggregate had <20% in the ICU without separating their outcomes. Such patients were characterized as being acutely ill.
Postdischarge	Patients discharged from an acute care hospital after COVID-19–related critical illness or acute illness.

have been specifically derived and prospectively validated in patients with COVID-19, although non-COVID RAMs such as International Medical Prevention Registry on Venous Thromboembolism D-dimer (IMPROVE-DD) have been externally validated in retrospective cohorts of hospitalized patients with COVID-19, and the COVID-TE score was derived specifically in patients with COVID-19 with concomitant malignancy.[28-30]

This article is an executive summary encompassing 3 updated recommendations on the use of anticoagulant therapy for patients admitted with COVID-19–related critical illness, patients admitted with COVID-19–related acute illness, and patients discharged from hospital that concludes the living phase of the guidelines.

Description of the target populations

The target populations in this guideline include patients with COVID-19 with critical illness, those with acute illness, and those discharged from acute care hospitals. These groups are described in Table 2.

Methods

This updated executive summary includes 3 recommendations, which were developed as part of ASH's living guidelines effort regarding the use of anticoagulant thromboprophylaxis in hospitalized patients with COVID-19 (Table 3). These recommendations have been previously published separately as stand-alone recommendations or updates.[16-19] The living phase (ie, continuous review and updating) is concluded. Going forward, ASH will maintain these guidelines through regular review and scheduled revision. For all recommendations, we followed the same methods as reported in publications to date, and important methodological aspects and updates are highlighted below.

The initial and updated recommendations were created and updated as shown in Table 3.

This executive summary includes final versions of all recommendations as approved by the ASH Guideline Oversight Subcommittee and the ASH Committee on Quality in April 2024. For the executive summary we have applied the following important aspects:

- Guideline funding and management of conflicts of interest: supplemental File 1 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. supplemental File 2 provides the updated complete participant information forms of researchers on the systematic review team who contributed to these guidelines.
- Evidence review and development of recommendation: new EtD frameworks were created for all recommendations including new evidence and considerations. The systematic review to identify comparative anticoagulation studies for the entire guideline was updated until June 2023. During the project, the initial guideline's literature search strategy (supplemental File 3) was modified to add search terms for antiplatelet agents for the guideline question on postdischarge anticoagulation, and the protocol (supplemental File 4) was modified to focus on inclusion of only randomized controlled trials. The systematic review to identify baseline risk studies for important outcomes for all guideline questions was updated until June 2023 and the methods remained the same throughout the project (search strategy and protocol previously published[15]).
- Criteria to update living systematic reviews and recommendations: due to the rapid emergence of a wealth of research studies related to this topic, the systematic reviews were periodically updated and recommendations were reconsidered if new evidence could potentially lead to important changes in baseline risk estimates, intervention effect estimates, certainty in the evidence, or to ensure face validity especially to include important trials.

Table 3. Initial and updated recommendations

Recommendation	Population	Anticoagulation intensities being compared	First version*	Update*	Update for executive summary*
1a	Patients with COVID-19 who are critically ill	Prophylactic vs intermediate	October 2020	June 2021	April 2024
1b	Patients with COVID-19 who are critically ill	Prophylactic vs therapeutic	October 2020	April 2022	April 2024
2a	Patients with COVID-19 who are acutely ill	Prophylactic vs intermediate	October 2020	July 2022†	April 2024
2b	Patients with COVID-19 who are acutely ill	Prophylactic vs therapeutic	October 2020	March 2022	April 2024
3	Patients with COVID-19 being discharged	Prophylactic vs none	August 2021	August 2022	April 2024

*Dates on which the recommendations were approved by the ASH Guideline Oversight Subcommittee and the ASH Committee on Quality.
†Date when public commenting was closed on the ASH website.

- Decision thresholds: to support judgments about whether the magnitude of an effect estimate was trivial, small, moderate, or large, as well as for determining imprecision of effect estimates, we used decision thresholds for all outcomes considered in the final reported recommendations in the executive summary. Thresholds were calculated using the outcome-specific utility value and results from a decision threshold survey that included the members of the panel. The decision threshold values that were used for each recommendation are reported in the footnotes of the online evidence profiles.
- Document review: draft recommendations were reviewed by all members of the panel, and made available online from 1 December 2023 to 22 December 2023 for external review by stakeholders including allied organizations, other medical professionals, patients, and the public. One individual submitted a response that did not require changes to the recommendations. In April 2024, the ASH Guideline Oversight Subcommittee and the ASH Committee on Quality approved that the defined guideline development process was followed, and in May 2024, the officers of the ASH executive committee approved submission of the executive summary manuscript for publication under the imprimatur of ASH.

For more information on how these guidelines should be used by patients, clinicians, policymakers, and researchers, we refer readers to the description in the initial guideline publication from February 2021,[15] as well as the user guide to ASH clinical practice guidelines.[31]

Recommendations

Patients with COVID-19–related critical illness

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

Recommendation 1a

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

Recommendation 1b

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

Remarks:

- Patients with COVID-19–related critical illness are defined as those suffering from an immediately life–threatening condition due to COVID-19 who would typically be admitted to an 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. RAMs to estimate thrombotic risk have been validated in hospitalized patients with COVID-19 (critically or noncritically ill), with modest prognostic performance. No RAMs for bleeding have been validated for patients with COVID-19. The panel acknowledges that higher-intensity anticoagulation may be preferred for patients judged to be at low bleeding risk and high thrombotic risk.
- 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, the aim of minimizing the use of personal protective equipment or exposure to staff to patients with COVID-19, as well as patient-specific factors (eg, renal function, history of heparin-induced thrombocytopenia, and bleeding risk). LMWH and UFH were used in the identified studies. LMWH or UFH may be preferred because of a preponderance of evidence with these agents. There are no studies of intermediate- or therapeutic-intensity fondaparinux, argatroban, or bivalirudin in this population.
- These recommendations do not apply to patients who require anticoagulation to prevent thrombosis of extracorporeal circuits such as those on ECMO or CRRT.

Summary of the evidence. The now-expired, first iteration of recommendation 1 published in February 2021 compared therapeutic-intensity or intermediate-intensity with prophylactic-intensity anticoagulation for patients with COVID-19–related critical illness. However, with the publication of new evidence this recommendation was split into 2 recommendations comparing intermediate-intensity vs prophylactic-intensity anticoagulation (recommendation 1a, first published in October 2021) and a separate recommendation comparing therapeutic-intensity vs prophylactic-intensity anticoagulation (recommendation 1b, first published in September 2022).

Recommendation 1a

The EtD framework for recommendation 1a was updated as of November 2023. Three randomized controlled trials were identified that provided evidence related to this question regarding the effects of intermediate-intensity compared with prophylactic-intensity anticoagulation on multiple critical outcomes among all-cause mortality, pulmonary embolism (PE), deep venous thrombosis (DVT), ischemic stroke, major bleeding, intracranial hemorrhage (ICH), multiple organ failure, ST-elevation myocardial infarction (STEMI), limb amputation, invasive mechanical ventilation (IMV), length of hospital admission, and length of ICU admission.[32-34] Two of the trial groups provided unpublished data on request for selected outcomes. The overall certainty in the evidence of effects was very low. Depending on the outcome, this was primarily because of extremely serious imprecision and/or serious risk of bias (see evidence profile and EtD framework online at https://guidelines.ash.gradepro.org/profile/blz3F6oWNWs).

Based on the panel's thresholds for effect sizes, intermediate-intensity anticoagulation may reduce all-cause mortality (odds ratio [OR], 0.92; 95% confidence interval [CI], 0.62-1.37; corresponding to 16 fewer [from 85 fewer to 67 more] deaths per 1000 patients), and may reduce PE (OR, 0.55; 95% CI, 0.12-2.62; corresponding to 34 fewer [from 68 fewer to 103 more] PEs per 1000 patients), but the evidence was very uncertain. Intermediate-intensity anticoagulation likely results in little to no effect on length of hospital admission (mean difference: 0.39 days fewer [from 1.82 days fewer to 1.04 days more]) and may not reduce length of ICU admission (mean difference: 0.09 days fewer [from 1.83 days fewer to 1.65 days more]). Intermediate-intensity anticoagulation may have little to no effect on DVT (OR, 0.93; 95% CI, 0.23-3.80; corresponding to 3 fewer [from 31 fewer to 99 more] DVTs per 1000 patients), but the evidence was very uncertain. In terms of potential harms, intermediate-intensity anticoagulation may result in little to no difference in major bleeding (OR, 1.50; 95% CI, 0.63-3.58; corresponding to 16 more [from 12 fewer to 78 more] major bleeding events per 1000 patients), but the evidence was very uncertain. Intermediate-intensity anticoagulation may have little to no effect on all other critical outcomes, but the evidence was very uncertain. No effects could be determined for multiple organ failure and limb amputation.

Recommendation 1b

The EtD framework for recommendation 1b was last updated as of September 2023. Seven randomized controlled trials were identified that provided evidence related to this question regarding the effects of therapeutic-intensity compared with prophylactic-intensity anticoagulation on the same multiple critical outcomes.[33,35-40] Unpublished data were provided on request for selected outcomes by 2 trial groups. The overall certainty in the evidence of effects was very low. Depending on the outcome, this was primarily because of very serious imprecision, serious risk of bias, and/or serious indirectness (see evidence profile and EtD framework online at https://guidelines.ash.gradepro.org/profile/lHYtm7MSFLE).

Based on the panel's thresholds for effect sizes, therapeutic-intensity anticoagulation may reduce all-cause mortality (OR, 0.90; 95% CI, 0.70-1.17; corresponding to 21 fewer [from 66 fewer to 33 more] deaths per 1000 patients), PE (OR, 0.40; 95% CI, 0.26-0.61; corresponding to 45 fewer [from 56 fewer to 29 fewer] PEs per 1000 patients), and invasive mechanical ventilation (OR, 0.82; 95% CI, 0.57-1.20; corresponding to 33 fewer [from 84 fewer to 34 more] IMV per 1000 patients), but the evidence was very uncertain. Therapeutic-intensity anticoagulation may result in little to no difference in ischemic stroke (OR, 0.75; 95% CI, 0.32-1.77; corresponding to 5 fewer [from 14 fewer to 15 more] ischemic strokes per 1000 patients) and STEMI (OR, 0.83; 95% CI, 0.33-2.10; corresponding to 2 fewer [from 6 fewer to 10 more] STEMIs per 1000 patients). Therapeutic-intensity anticoagulation may have little to no effect on DVT (OR, 0.73; 95% CI, 0.42-1.24; corresponding to 11 fewer [from 23 fewer to 9 more] DVTs per 1000 patients), but the evidence was very uncertain. In terms of potential harms, therapeutic-intensity anticoagulation may increase major bleeding (OR, 1.78; 95% CI, 1.00-3.18; corresponding to 25 more [from 0 to 67 more] major bleedings per 1000 patients), may result in little to no difference in length of hospital admission (mean difference: 1.32 days more [from 0.02 days more to 2.61 days more]), but the evidence for the latter was very uncertain. Therapeutic-intensity anticoagulation may have little to no effect on all other critical outcomes, but the evidence was very uncertain. No effects could be determined for ICH.

Conclusions for this recommendation. Regarding intermediate-intensity anticoagulation, although the panel judged the overall certainty of evidence to be very low for both desirable and undesirable effects, the panel judged that the trivial-to-small benefits do not outweigh the trivial harms of intermediate-intensity anticoagulation. Regarding therapeutic-intensity anticoagulation, although the panel judged the overall certainty of evidence to be very low for both desirable and undesirable effects, the panel judged that the small-to-moderate harms would outweigh the small benefits of therapeutic-intensity anticoagulation. Other factors considered in the EtD framework did not importantly affect this assessment for the recommendations. The panel therefore suggested prophylactic-intensity rather than intermediate-intensity and therapeutic-intensity anticoagulation for patients with COVID-19–related critical illness, as used in those with critical illness not related to COVID-19.[41-45] This guideline did not address the use of therapeutic- vs intermediate-intensity anticoagulation for patients with COVID-19–related critical illness because this clinical question was not prioritized by the panel.

The panel noted that for both recommendations 1a and 1b 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.[46-50] This recommendation does not apply to thrombotic complications related to extracorporeal circuits. Although high rates of circuit-related thrombosis during ECMO and CRRT have been reported in patients with COVID-19, this outcome was not prioritized as critical for this question.[51]

Patients with COVID-19–related acute illness

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

Recommendation 2a

The ASH guideline panel *suggests* using prophylactic-intensity over intermediate-intensity anticoagulation for patients with COVID-19–related acute illness who do not

have suspected or confirmed VTE or another indication for anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Recommendation 2b

The ASH guideline panel *suggests* using therapeutic-intensity over prophylactic-intensity anticoagulation for patients with COVID-19–related acute illness who do not have suspected or confirmed VTE or another indication for anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- Patients with COVID-19–related acute illness are defined as those with clinical features that would typically result in admission to an inpatient medical ward without requirement for intensive clinical support. Examples include patients with dyspnea or mild-to-moderate hypoxia.
- An individualized assessment of the patient's risk of thrombosis and bleeding is important when deciding on anticoagulation intensity. RAMs to estimate thrombotic risk have been validated in hospitalized patients with COVID-19 (critically or noncritically ill), with modest prognostic performance. No RAMs for bleeding have been validated for patients with COVID-19. The panel acknowledges that lower-intensity anticoagulation may be preferred for patients judged to be at high bleeding risk and low risk of thrombosis.
- At present, there is no direct high-certainty evidence comparing different types of anticoagulants in patients with COVID-19. LMWH or UFH may be preferred because of a preponderance of evidence with these agents. There are no studies of therapeutic-intensity fondaparinux, argatroban, or bivalirudin in this population.

Summary of the evidence. The now-expired, first iteration of recommendation 2 published in February 2021 compared therapeutic-intensity or intermediate-intensity with prophylactic-intensity anticoagulation for patients with COVID-19–related acute illness. However, with the publication of new evidence this recommendation was split into 2 recommendations comparing intermediate-intensity vs prophylactic-intensity anticoagulation (recommendation 2a) and a separate recommendation comparing therapeutic-intensity vs prophylactic-intensity anticoagulation (recommendation 2b**,** first published in September 2022).

Recommendation 2a

The EtD framework for recommendation 2a was updated as of November 2023. Three randomized controlled trials were identified that provided evidence related to this question regarding the effects of intermediate-intensity compared with prophylactic-intensity anticoagulation on multiple critical outcomes among all-cause mortality, PE, DVT, ischemic stroke, major bleeding, ICH, multiple organ failure, STEMI, limb amputation, IMV, and ICU admission.[32,52,53] One of the trial groups provided unpublished data on request for selected outcomes. The overall certainty in the evidence of effects was very low. This was primarily because of extremely serious imprecision and for some outcomes risk of bias (see evidence profile and EtD framework online at https://guidelines.ash.gradepro.org/profile/cZ63B6hzUMI).

Based on the panel's thresholds for effect size, intermediate-intensity anticoagulation may increase all-cause mortality (OR, 1.49; 95% CI, 0.82-2.72; corresponding to 41 more [from 16 fewer to 129 more] deaths per 1000 patients) and multiple organ failure (OR, 1.53; 95% CI, 0.25-9.40; corresponding to 24 more [from 36 fewer to 277 more] deaths per 1000 patients), but the evidence is very uncertain. Intermediate-intensity anticoagulation may have little to no effect on all other critical outcomes, including major bleeding, but the evidence was very uncertain. No effects could be determined for DVT, ICH, and limb amputation.

Recommendation 2b

The EtD framework for recommendation 2b was updated as of September 2023. Nine randomized controlled trials were identified that provided evidence related to this question regarding the effects of therapeutic-intensity compared with prophylactic-intensity anticoagulation on the same multiple critical outcomes.[35,52,54-60] Three of the trial groups provided unpublished data on request for selected outcomes. The overall certainty in the evidence of effects was low. This was primarily because of imprecision and risk of bias (see evidence profile and EtD framework online at https://guidelines.ash.gradepro.org/profile/nolMdHDZo6Y.

Based on the panel's thresholds for effect sizes, therapeutic-intensity anticoagulation may reduce all-cause mortality (OR, 0.80; 95% CI, 0.55-1.16; corresponding to 26 fewer [from 41 fewer to 16 more] deaths per 1000 patients) and probably results in little difference (low absolute risk reduction) in PE (OR, 0.53; 95% CI, 0.33-0.83; corresponding to 12 fewer [from 17 fewer to 4 fewer] PEs per 1000 patients), DVT (OR, 0.58; 95% CI, 0.30-1.08; corresponding to 3 fewer [from 6 fewer to 1 more] DVTs per 1000 patients), and IMV (OR, 0.76; 95% CI, 0.59-0.96; corresponding to 15 fewer [from 26 fewer to 3 fewer] IMV per 1000 patients). Therapeutic-intensity anticoagulation may not reduce ICU hospitalization and STEMI and may have little to no effect on ischemic stroke, multiple organ failure, and limb amputation, but the evidence was very uncertain.

In terms of potential harms, therapeutic-intensity anticoagulation probably results in little difference in major bleeding (OR, 1.92; 95% CI, 1.10 to 3.36; corresponding to 1 more [from 12 more to 29 more] major bleedings per 1000 patients) and may have little to no effect on ICH (OR, 2.12; 95% CI, 0.22 to 20.37; corresponding to 1 more [from 1 fewer to 19 more] ICH per 1000 patients), although the evidence was very uncertain for the latter.

Conclusions for this recommendation. Regarding recommendation 2a, the panel judged that the balance of effects probably favors the comparison (prophylactic-intensity anticoagulation)

based on the trivial desirable effects, trivial undesirable effects, possibly important uncertainty or variability in how much people value the outcomes, and the overall very low certainty of the available data. Other factors considered in the EtD framework did not importantly affect this assessment for the recommendations.

Regarding recommendation 2b, the panel judged that the balance of effects probably favors the intervention (therapeutic-intensity anticoagulation) based on the small desirable effects, owing to additive trivial effects on multiple independent outcomes, trivial undesirable effects, possibly important uncertainty or variability in how much people value the outcomes, and the overall low certainty of the available data. Other factors considered in the EtD framework did not importantly affect this assessment for the recommendations.

The panel noted that for both recommendations 2a and 2b 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.[46-50] This guideline did not address the use of therapeutic- vs intermediate-intensity anticoagulation for patients with COVID-19–related acute illness because this clinical question was not prioritized by the panel.

Patients being discharged from hospital after COVID-19

Should prophylactic-intensity direct oral anticoagulants, LMWH, UFH, or fondaparinux vs no anticoagulation be used for post-discharge outpatient thromboprophylaxis for patients with COVID-19 who are being discharged from the hospital and who do not have suspected or confirmed VTE or another indication for anticoagulation?

Recommendation 3

The ASH guideline panel *suggests* against using post-discharge outpatient anticoagulant thromboprophylaxis for patients with COVID-19 who are being discharged from the hospital and who do not have suspected or confirmed VTE or another indication for anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- An individualized assessment of the patient's risk of thrombosis and bleeding and shared decision-making are important when deciding on whether to use postdischarge thromboprophylaxis.
- The panel acknowledged that postdischarge thromboprophylaxis may be reasonable for patients judged to be at high thrombotic risk and low bleeding risk.

Summary of the evidence. The now-expired first iteration of recommendation 3 published in January 2022 compared post-discharge outpatient prophylactic-intensity anticoagulation with no anticoagulation in patients being discharged after hospitalization for COVID-19–related illness.

The EtD framework for recommendation 3 was updated as of June 2023. Two randomized controlled trials were identified that provided evidence related to this question regarding the effects of postdischarge outpatient prophylactic-intensity anticoagulation compared with no anticoagulation on multiple critical outcomes among all-cause mortality, PE, DVT, ischemic stroke, major bleeding, STEMI, and readmission.[61,62] One of the trial groups provided unpublished data on request for selected outcomes. The overall certainty in the evidence of effects was low. This was primarily because of extremely serious imprecision and, for some outcomes, risk of bias (see evidence profile and EtD framework online at https://guidelines.ash.gradepro.org/profile/hzJoT4NBkkk).

Based on the panel's thresholds for effect sizes, postdischarge outpatient prophylactic-intensity anticoagulation probably results in little to no difference for DVT (OR, 0.51; 95% CI, 0.08-3.29; corresponding to 1 fewer [from 3 fewer to 7 more] DVTs per 1000 patients), and may result in little to no difference for all-cause mortality (OR, 0.84; 95% CI, 0.37-1.89; corresponding to 3 fewer [12 fewer to 16 more] deaths per 1000 patients), PE (OR, 0.66; 95% CI, 0.08-5.44; corresponding to 2 fewer [6 fewer to 30 more] PEs per 1000 patients), STEMI (OR, 0.14; 95% CI, 0.01-2.74; corresponding to 5 fewer [from 6 fewer to 10 more] STEMIs per 1000 patients), and readmission (OR, 0.20; 95% CI, 0.01-4.15; corresponding to 25 fewer [31 fewer to 86 more] readmissions per 1000 patients). Postdischarge anticoagulation may have little to effect on ischemic stroke (OR, 2.99; 95% CI, 0.12-73.55; corresponding to 4 more [from 2 fewer to 126 more] ischemic strokes per 1000 patients), but the evidence is very uncertain.

In terms of potential harms, postdischarge anticoagulation may have little to no effect on major bleeding in patients with COVID-19 (OR, 1.99; 95% CI, 0.18-22.04; corresponding to 3 more [from 2 fewer to 59 more] major bleeds per 1000 patients) and probably has little to effect on major bleeding in other patients being discharged (indirect evidence: OR, 2.09; 95% CI, 1.33-3.27; corresponding to 4 more [from 2 fewer to 125 more] per 1000 patients).

Conclusions for this recommendation. The panel judged the benefits of postdischarge outpatient thromboprophylaxis to be trivial in terms of absolute effects on all critical outcomes. This judgment was based primarily on the low baseline risk estimates for thrombotic events after hospital discharge. Meanwhile, the risk of major bleeding was also judged to be of trivial magnitude, based on low baseline risk estimates along with indirect evidence from patient without COVID-19.[63-65] Of note, patients with high bleed risk characteristics were excluded from the Medically Ill Hospitalized Patients for COVID–Thrombosis Extended Prophylaxis with Rivaroxaban Therapy (MICHELLE) trial (eg, recent bleeding, recent major surgery, known coagulopathy or bleeding diathesis, prior ICH, recent gastroduodenal ulcer, and thrombocytopenia active cancer) and the ACTIV-4c trial (eg, recent intracranial bleed, stroke or neurosurgery, recent major surgery, inherited or acquired bleeding disorder, and thrombocytopenia).

On balance, the panel judged that the undesirable potential major bleeding complications outweighed the potential benefits, particularly considering the low baseline risk of postdischarge VTE. The panel emphasized the importance of an individualized decision for each patient based on an assessment of thrombosis and bleeding

risk. This thrombosis risk assessment may include the use of externally validated RAMs such as the IMPROVE-DD risk score, which was used in the MICHELLE trial to identify patients at potentially higher thrombotic risk for study inclusion.[28,60] No RAMs for bleeding have been validated in patients with COVID-19.

Conclusions: what others are saying and where we go from here

At the onset of the COVID-19 pandemic, the ASH living guidelines were created to answer urgent questions in a time of rapidly evolving evidence and clinical experience. The living phase (ie, continuous review and updating) is concluded. Going forward, ASH will maintain these guidelines through regular review and scheduled revision. It was noted by the panel that the included trials primarily enrolled patients early in the COVID-19 pandemic and that the applicability of these results to the current phase of the pandemic are unclear because of potential differences in the patient population, baseline rates of VTE, and illness severity related to evolution of viral variants, prior infection, and use of nonanticoagulant therapies (corticosteroids, vaccination, antiviral therapies, and monoclonal antibodies), which have contributed to improvements in the burden and severity of COVID-19 disease.

Other guidance

Four years after the onset of the pandemic, multiple guideline documents on the use of anticoagulation for patients with COVID-19 are available. These other guidance documents include the 2022 CHEST (American College of Chest Physicians) COVID-19 guidelines update, the 2024 International Society on Thrombosis and Haemostasis (ISTH) 2023 ISTH update of the 2022 ISTH guidelines for antithrombotic treatment in COVID-19, National Institutes of Health (NIH) COVID-19 treatment guidelines, and the European Society of Cardiology guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic.[66-69]

Major methodologic 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 and decision thresholds to estimate the relative importance to patients as key outcomes of treatment. The present ASH guideline is also unique in its "living" format, although other guidance documents may also be updated.

Among patients who are critically ill, the guidance documents from ASH, the American College of Chest Physicians, ISTH, and NIH uniformly suggest prophylactic-intensity anticoagulation (as opposed to intermediate- or therapeutic-dose anticoagulation) for patients without suspected or confirmed VTE.

Meanwhile, for patients with COVID-19–related acute illness, most guidance documents suggest or recommend that therapeutic-intensity anticoagulation be considered in preference to prophylactic-intensity anticoagulation. The NIH is more specific in recommending that therapeutic-dose heparin be used for patients who have an elevated D-dimer, who are on low-flow oxygen, and who have low bleeding risk. The ISTH guidelines recommend that therapeutic LMWH or UFH is beneficial in preference to intermediate- or prophylactic-dose LMWH or UFH in select patients who are not critically ill.[66] European Society of Cardiology guidance endorses anticoagulation at standard-dose prophylactic doses for hospitalized patients with COVID-19.[69]

Finally, regarding postdischarge thromboprophylaxis, these other guidance documents also do not recommend the routine use of postdischarge pharmacological thromboprophylaxis. However, in the absence of high-quality evidence, they generally suggest that an individualized decision be made, balancing the patient's thrombosis and bleeding risk factors at the time of discharge, and that thromboprophylaxis may be considered for select patients. The CHEST 2020 guideline suggests that postdischarge thromboprophylaxis would only result in net clinical benefit if the risk of symptomatic VTE were found to be >1.8% within 35 to 42 days after release from the hospital,[67] whereas the updated 2022 CHEST guideline did not comment specifically on postdischarge thromboprophylaxis.[70] The 2023 ISTH guideline suggests that postdischarge thromboprophylaxis with prophylactic dose rivaroxaban may be considered for ~30 days to reduce the risk of VTE after hospitalization for COVID-19, particularly for patients with persistent VTE risk factors that may include a high IMPROVE risk score, or high D-dimer.[66]

There are several ongoing trials in a variety of settings that may have implications for patients with COVID-19.[71] These include studies of primary thromboprophylaxis with direct oral anticoagulants in nonhospitalized outpatients (eg, PREVENT-HD [ClinicalTrials.gov identifier: NCT04508023] and HERO-19 [ClinicalTrials.gov identifier: NCT04359246]), and anticoagulation in hospitalized non-ICU patients (eg, XACT [ClinicalTrials.gov identifier: NCT04640181] and FREEDOM COVID-19 [ClinicalTrials.gov identifier: NCT04512079]). Ongoing studies with patients with COVID-19 who are critically ill also include novel therapeutic approaches including the use of nebulized heparin (eg, CHARTER-MT [ClinicalTrials.gov identifier: NCT04397510]) and fibrinolytics for acute respiratory distress syndrome (eg, STARS [ClinicalTrials.gov identifier: NCT04357730]) and TRISTARDS [ClinicalTrials.gov identifier: NCT04640194]).

Future research priorities

Based on gaps in evidence identified during the guideline development process, the panel identified the following research priorities in this patient population:

- Large, high-quality, randomized controlled trials to increase the certainty in the evidence on health effects.
- Studies examining the impact of nonanticoagulant interventions (eg, vaccines, corticosteroids, antiviral therapies, antiplatelet therapies, anticytokine therapies, and monoclonal antibody therapies) on thrombotic risk.
- Studies examining the impact of different viral variants on thrombotic risk.
- Further development and validation of RAMs for thrombosis and bleeding in prospective cohorts of patients with COVID-19 during and after hospitalization.
- Studies examining the impact of anticoagulant therapy on thrombosis and bleeding according to social determinants of health.

Limitations of these guidelines

The limitations of these guidelines are inherent in the low to very low certainty in the evidence we identified for the research questions. This relates to risk of bias, as well as imprecision, which may also relate to heterogeneity in study designs, patient characteristics, and outcome measurements used.

In addition, nonanticoagulant treatments administered to hospitalized patients with COVID-19 (eg, corticosteroids, anticytokine therapies, and ventilatory support), patient characteristics, viral variants, and immunity have changed over the course of the pandemic. It remains uncertain how advancements in clinical care may affect the baseline risk of VTE in-hospital and after hospital discharge. 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 thromboprophylaxis in the current phase of the pandemic, because of the impact of vaccination, prior infection, viral variants, and other nonantithrombotic therapies on COVID-19 disease course and severity, and baseline VTE risk.

Updating or adapting recommendations locally

Adaptation of these guidelines will be necessary in many circumstances. These adaptations should be based on the associated EtD frameworks.[12]

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Authorship

Contribution: D.M.S., E.K.T., and R.N. wrote the manuscript; the remaining authors contributed to critical revisions of the manuscript; members of the knowledge synthesis team (R.N., R.A.J., Y.A.J., L.E.C.-L., K.D., A.J.D., S.G.K., G.P.M., R.Z.M., B.A.P., Y.R.B., K.S., and W.W.) searched the literature, extracted data from eligible studies, analyzed the data, and prepared evidence summaries and evidence to decision tables; panel members (D.M.S., E.K.T., H.J.S., P.A., A.C., K.D., M.T.D., D.D., D.O.G., F.A.K., A.I.L., I.N., A.P., M.R., K.M.S., D.R.T., R.A.M., and R.N.) assessed the evidence, voted, and made judgments within the EtD framework, and discussed and issued the recommendations; the methods leadership team (R.N., R.B.-P., K.D., A.S., K.S., A.C., E.A.A., W.W., R.A.M., and H.J.S.) developed the methods and provided guidance to the knowledge synthesis team and guideline panel; D.M.S., R.A.M., and R.N. were the co-chairs of the panel and led panel meetings; and all authors approved of the content of the manuscript.

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