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American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: January 2022 update on the use of therapeutic-intensity anticoagulation in acutely ill patients

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Abstract:

Background: COVID-19 related acute 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 decisions about the use of anticoagulation in patients with COVID-19. Methods: ASH formed a multidisciplinary guideline panel, including patient representatives, and applied strategies to minimize potential bias from conflicts of interest. The McMaster University GRADE Centre supported the guideline development process, including performing systematic evidence reviews (through November 2021). The panel prioritized clinical questions and outcomes according to their importance for clinicians and patients. The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess evidence and make recommendations, which were subject to public comment. This is an update to guidelines published in February 2021 as part of the living phase of these guidelines. Results: The panel made one additional recommendation. The panel issued a conditional recommendation in favor of therapeutic-intensity over prophylactic-intensity anticoagulation in patients with COVID-19-related acute illness who do not have suspected or confirmed VTE. The panel emphasized the need for an individualized assessment of thrombotic and bleeding risk. The panel also noted that heparin (unfractionated or low-molecular-weight) may be preferred because of a preponderance of evidence with this class of anticoagulants. Conclusions: This conditional recommendation was based on very low certainty in the evidence, underscoring the need for additional, high-quality, randomized controlled trials comparing different intensities of anticoagulation in patients with COVID-19-related acute illness.
**Conflict of interest:** COI declared - see note

**COI notes:** All authors were members of the guideline panel or members of the systematic review team or both. As such, they completed a disclosure of interest form, which was reviewed by ASH and is available as Supplements 4 and 5.

**Preprint server:** No;

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**Clinical trial registration information (if any):**
American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: January 2022 update on the use of therapeutic-intensity anticoagulation in acutely ill patients

Short title: ASH guidelines on anticoagulation in COVID-19

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Abstract

Background: COVID-19 related acute 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 decisions about the use of anticoagulation in patients with COVID-19.

Methods: ASH formed a multidisciplinary guideline panel, including patient representatives, and applied strategies to minimize potential bias from conflicts of interest. The McMaster University GRADE Centre supported the guideline development process, including performing systematic evidence reviews (through November 2021). The panel prioritized clinical questions and outcomes according to their importance for clinicians and patients. The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess evidence and make recommendations, which were subject to public comment. This is an update to guidelines published in February 2021 as part of the living phase of these guidelines.

Results: The panel made one additional recommendation. The panel issued a conditional recommendation in favor of therapeutic-intensity over prophylactic-intensity anticoagulation in patients with COVID-19-related acute illness who do not have suspected or confirmed VTE. The panel emphasized the need for an individualized assessment of thrombotic and bleeding risk. The panel also noted that heparin (unfractionated or low-molecular-weight) may be preferred because of a preponderance of evidence with this class of anticoagulants.

Conclusions: This conditional recommendation was based on very low certainty in the evidence, underscoring the need for additional, high-quality, randomized controlled trials comparing different intensities of anticoagulation in patients with COVID-19-related acute illness.

Keywords

COVID-19; anticoagulation; practice guidelines; thromboprophylaxis
Summary of recommendations

**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 a medicine inpatient 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. Risk-assessment models to estimate thrombotic risk in hospitalized patients have been validated in COVID-19 patients, with modest prognostic performance. No risk assessment models for bleeding have been validated in COVID-19 patients. The panel acknowledges that lower-intensity anticoagulation may be preferred for patients judged to be at high bleeding risk and low thrombotic risk.

- At present, there is no direct high-certainty evidence comparing different types of anticoagulants in patients with COVID-19. Unfractionated or low molecular weight heparin 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.

**Background**

There is a high incidence of thrombotic complications in acutely ill patients with COVID-19. Venous thromboembolism (VTE) has been reported in up to 7.9% of such patients despite the use of standard
Thrombosis of the microvasculature contributes to other complications of COVID-19 including respiratory failure and death. At the same time, higher-intensity anticoagulation is associated with an increased risk of bleeding among hospitalized COVID-19 patients. Consequently, there has been strong interest in establishing whether intensified anticoagulant regimens improve outcomes.

These guidelines are based on systematic reviews of evidence conducted under the direction of the McMaster University GRADE Centre with international collaborators. This is an update on the previous American Society of Hematology (ASH) guideline published in February 2021, and focuses on the role of anticoagulation in patients with COVID-19-related acute illness. The panel followed best practice for guideline development recommended by the Institute of Medicine and the Guidelines International Network (GIN). The panel used the GRADE approach to assess the certainty of the evidence and formulate recommendations. The recommendation is listed in Table 1.

**Values and preferences**

- The guideline panel identified all-cause mortality, pulmonary embolism (PE), deep vein thrombosis (DVT), major bleeding, intracranial hemorrhage, ischemic stroke, ST-elevation myocardial infarction, multiple organ failure, limb amputation, invasive mechanical ventilation, intensive care unit (ICU) admission, and length of hospitalization 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.

**Explanations and other considerations**

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

**Interpretation of strong and conditional recommendations**

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

Aims of these guidelines and specific objectives

Please refer to the original ASH guideline on thromboprophylaxis in patients with COVID-19. All recommendations and updates to these living guidelines are accessible at the ASH COVID-19 anticoagulation webpage.

Description of the health problem

The COVID-19 pandemic has had a significant public health impact. As of January 27, 2022, over 363 million cases and 5.6 million deaths had been attributed to COVID-19-related illness globally. Thrombosis has emerged as an important complication of patients hospitalized with COVID-19-related acute illness, with VTE occurring in up to 7.9% of such patients during hospital admission, often despite the use of standard thromboprophylaxis. Moreover, microvascular thrombosis associated with COVID-19 may contribute to other adverse outcomes including respiratory failure and death.

Previously published ASH guidelines issued a conditional recommendation in favor of prophylactic-intensity rather than higher-intensity anticoagulation in patients with COVID-19-related acute illness without suspected or confirmed VTE. That recommendation was based on very low certainty evidence derived exclusively from observational studies. Since then, several randomized controlled trials (RCTs) comparing therapeutic-intensity vs. prophylactic-intensity anticoagulation in patients with COVID-19-related acute illness have been reported. This living guideline update incorporates evidence from these RCTs to address the role of therapeutic-intensity vs. prophylactic-intensity anticoagulation in patients with COVID-19-related acute illness.

Description of the target populations

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

This updated guideline recommendation on the use of therapeutic-intensity anticoagulation in acutely ill patients was developed in the living phase of the ASH living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19 and is reported following the RIGHT checklist (Supplement 1). Living guidelines use continuous screening for new evidence and updating analyses in living systematic reviews, a living recommendation process to reconsider recommendations based on pre-specified criteria regarding changes in the evidence, and a living guideline panel which is continuously available to reconvene when needed (see Supplement 2). The ASH guideline panel generated recommendation 2b on November 30, 2021 before soliciting public comments.

We followed the same methods as published in the initial guideline, with the following important updates and differences for the recommendation reported here:

- Guideline funding and management of conflicts of interest: Supplement 3 lists all members of the guideline panel, methods team, and systematic review team who contributed to this recommendation. Supplement 4 provides updated “Participant Information Forms” for all panel members, detailing financial and non-financial interests, as well as the ASH conflict of interest policies agreed to by each individual. Supplement 5 provides the updated complete “Participant Information Forms” of researchers on the methods and systematic review teams who contributed to these guidelines.

- Formulating specific clinical questions and determining outcomes of interest: This updated manuscript focuses on one question: In patients with COVID-19-related acute illness who do not have confirmed or suspected venous thromboembolism, should we use direct oral anticoagulants, low molecular weight heparin, unfractionated heparin, fondaparinux, argatroban, or bivalirudin at therapeutic-intensity vs. prophylactic-intensity? There were no changes in the definitions for population (Table 2), anticoagulation intensity, or outcomes.

- Evidence review and development of recommendations: A new evidence-to-decision framework was created for recommendation 2b (see Recommendations) using any applicable evidence and information from the Evidence-to-Decision (EtD) framework for the initial recommendation 2, and updated with new evidence and considerations specifically for recommendation 2b. The systematic review to identify comparative antithrombotic studies for the entire guideline was updated until November 28, 2021, the literature search strategy was modified only to add search
terms for antiplatelet agents for another guideline question, and the protocol was modified to focus on inclusion of only RCTs for the guideline after the initial phase. Baseline risk estimates for outcomes in patients with COVID-19 related acute illness were updated with observational evidence until March 29, 2021 and prophylactic-intensity anticoagulation event rates from RCTs until November 28, 2021. The up-to-date protocols and search strategies for both systematic reviews are provided in Supplements 6-9. The decision to create this updated guideline recommendation was based on publication of several RCTs,16–20 of which some were not yet included from the systematic literature searches but were 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. Decision thresholds were obtained for each critical outcome (Table 3) to support judgments about whether the magnitude of an effect estimate was trivial, small, moderate, or large, as well as for determining imprecision of the effect estimate. Thresholds were calculated using the outcome-specific utility value and results from a decision threshold survey that included the members of this panel.

In case of a statistically significant difference in effects among prespecified subgroups, the Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN) for meta-analysis of RCTs was completed independently by two or more evidence synthesis team members with expertise in anticoagulation to assess whether the credibility of the subgroup effect was high, moderate, low, or very low.22 Finally, for all outcomes we report pooled effect estimates based on unadjusted effects from all trials. Because one adaptive multiplatform trial reported adjusted effect estimates for certain outcomes,18 we performed sensitivity analyses by pooling their adjusted effects with the unadjusted effects of the remaining trials to determine whether the results remained similar (see the footnotes of the Evidence Profile).

- Document review: An initial draft recommendation was reviewed by all members of the panel, and made available online from October 8 to October 15, 2021 for external review by stakeholders including allied organizations, other medical professionals, patients, and the public. As part of the public comment, there were 68 views; 7 individuals or organizations submitted responses. Based on the public comments and the very low certainty of the evidence, the panel decided to review the evidence and EtD framework judgments and draft a revised recommendation with the new use of decision thresholds (see explanation above). The revised draft recommendation was generated on November 30, 2021, and made available online from December 20, 2021 to January 3, 2022 for external review by stakeholders including allied organizations, other medical
professionals, patients, and the public. As part of the public comment, there were 320 views; 15 individuals or organizations submitted responses. On March 7, 2022 the ASH Guideline Oversight Subcommittee and the ASH Committee on Quality approved that the defined guideline development process was followed, and on March 11, 2022, 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, as well as the user guide to ASH clinical practice guidelines.

**Recommendations**

**Recommendation 2b**

*Should direct oral anticoagulants, low molecular weight heparin, unfractionated heparin, fondaparinux, argatroban, or bivalirudin be prescribed at therapeutic-intensity or prophylactic-intensity in patients with COVID-19-related acute illness who do not have suspected or confirmed VTE or another indication for anticoagulation?*

**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 a medicine inpatient 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. Risk-assessment models to estimate thrombotic risk in hospitalized patients have been validated in COVID-19 patients, with modest prognostic performance. No risk assessment models for bleeding have been validated in COVID-19 patients. The panel acknowledges that lower-intensity anticoagulation may be preferred for patients judged to be at high bleeding risk and low thrombotic risk.

• At present, there is no direct high-certainty evidence comparing different types of anticoagulants in patients with COVID-19. Unfractionated or low molecular weight heparin 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

We rated the certainty in the evidence as moderate for the outcome of pulmonary embolism due to serious risk of bias, moderate for major bleeding due to serious imprecision, low for the outcomes of deep venous thrombosis, invasive mechanical ventilation and ICU admission due to serious risk of bias and serious imprecision, and as very low for all other outcomes, mainly owing to very serious imprecision (see Evidence Profile and Evidence to Decision [EtD] framework online at: https://guidelines.ash.gradepro.org/profile/YmZiP8YDDNA).

We found several systematic reviews of randomized controlled trials that addressed this question, either specifically or as part of a larger systematic review on anticoagulation in COVID-19 patients. None of these systematic reviews reported a Summary of Findings table or Evidence Profile, with certainty of the evidence assessment, for all critical outcomes prioritized for this recommendation. The living systematic reviews informing all recommendations for the ASH living guidelines since June 2020 provided the
Five RCTs reported the effect of therapeutic-intensity anticoagulation in acutely ill COVID-19 patients. In the publication, or by providing unpublished data, all five trials reported results for all-cause mortality, PE, DVT, major bleeding, ischemic stroke, intracranial hemorrhage, and ST-elevation myocardial infarction. Four trials provided results for limb amputation. Three trials provided results for multiple organ failure, invasive mechanical ventilation, and ICU admission (see Evidence Profile). Three RCTs provided unpublished data for non-ICU patients separately and/or for additional outcomes. In accordance with the GRADE approach, the overall certainty of the evidence of effects was very low based on the lowest certainty among critical outcome.

Benefits

Based on the panel’s thresholds for effect sizes (Table 3), therapeutic-intensity anticoagulation probably results in little to no difference in PE with 17 fewer (from 22 fewer to 9 fewer) PE’s per 1,000 patients (OR: 0.42, 95% CI: 0.25 to 0.71); moderate certainty. Therapeutic-intensity anticoagulation may result in little to no difference in DVT with 4 fewer (from 7 fewer to 4 more) DVT’s per 1,000 patients (OR: 0.56, 95% CI: 0.22 to 1.41); low certainty. Therapeutic-intensity anticoagulation may result in little to no difference in invasive mechanical ventilation with 16 fewer (from 32 fewer to 11 more) cases of invasive mechanical ventilation per 1,000 patients (OR: 0.69, 95% CI: 0.39 to 1.22); low certainty. Therapeutic-intensity anticoagulation may result in little to no difference in ICU admission with 15 fewer (from 38 fewer to 17 more) cases of invasive mechanical ventilation per 1,000 patients (OR: 0.80, 95% CI: 0.52 to 1.23); low certainty.

Therapeutic-intensity anticoagulation may reduce all-cause mortality with 20 fewer (from 52 fewer to 33 more) deaths per 1,000 patients (OR: 0.78, 95% CI: 0.43 to 1.40), but the evidence is very uncertain (very low certainty). We investigated whether a subgroup effect was present for the type of anticoagulant, i.e. low molecular weight heparin/unfractionated heparin versus direct oral anticoagulant (DOAC), for the outcome of all-cause mortality using the ICEMAN instrument. We found low credibility for a subgroup effect and therefore the overall effect estimate was used, but there is remaining uncertainty. Sensitivity analysis including only the trials testing low molecular weight heparin/unfractionated heparin showed a
pooled OR of 0.60, 95% CI: 0.29 to 1.22, which corresponds to 36 fewer (from 66 fewer to 19 more) deaths per 1,000 patients; very low certainty.

Therapeutic-intensity anticoagulation may reduce multiple organ failure with 26 fewer (from 48 fewer to 208 more) cases of multiple organ failure per 1,000 patients (OR: 0.46, 95% CI: 0.03 to 6.59), but the evidence is very uncertain (very low certainty). Therapeutic-intensity anticoagulation may have trivial to no effect on ischemic stroke with 0 fewer (from 3 fewer to 14 more) ischemic strokes per 1,000 patients (OR: 0.92, 95% CI: 0.19 to 4.48), but the evidence is very uncertain (very low certainty). Therapeutic-intensity anticoagulation may have trivial to no effect on limb amputation with 1 fewer (from 2 fewer to 14 more) limb amputations per 1,000 patients (OR: 0.33, 95% CI: 0.01 to 8.03), but the evidence is very uncertain (very low certainty). Therapeutic-intensity anticoagulation may have trivial to no effect on ST-elevation myocardial infarction with 1 fewer (from 3 fewer to 8 more) ST-elevation myocardial infarctions per 1,000 patients (OR: 0.65, 95% CI: 0.14 to 2.97), but the evidence is very uncertain (very low certainty).

**Harms and burden**

In accordance with the panel’s thresholds for effect sizes (Table 3), therapeutic-intensity anticoagulation probably results in little to no difference in major bleeding with 9 more (from 0 to 26 more) major bleeding events per 1,000 patients (OR: 1.79, 95% CI: 1.00 to 3.21); moderate certainty. The evidence is very uncertain about the effect of therapeutic-intensity anticoagulation on intracranial hemorrhage (OR: 2.95, 95% CI: 0.12 to 72.74) as well as the pooled mean baseline risk (0%); this corresponds to 0 more (from 0 to 0 more) intracranial hemorrhages per 1,000 patients; very low certainty.

**Other EtD criteria and considerations**

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 therapeutic-intensity anticoagulation would be acceptable to patients and healthcare providers. However, given the low certainty in the evidence for some outcomes, there may be regional variation in the acceptability of therapeutic-intensity anticoagulation, particularly in regions where baseline VTE risk may be lower (e.g., Asian populations). In addition, the panel noted possible racial and ethnic disparity in clinical trial enrollment.
Conclusions for this recommendation

The use of decision thresholds (Table 3) allowed the panel to quantify the magnitude of effect per outcome to come to an overall judgment on the balance of health effects. The undesirable effects of the intervention were considered trivial, driven by a trivial effect on major bleeding. The desirable effects of the intervention were considered small, driven by small effects on mortality and multiorgan failure and additive trivial effects on PE, DVT, invasive mechanical ventilation, and ICU admission. Based on these judgments, the panel made a conditional recommendation for therapeutic-intensity anticoagulation over prophylactic-intensity anticoagulation in acutely ill medical patients with COVID-19 while acknowledging that individualized decision-making is required. The predictive value of risk assessment models to estimate thrombotic risk in hospitalized patients with COVID-19 has been validated; no risk assessment models for bleeding have been validated in this population. Although the panel did not identify credible evidence of a differential effect among types of anticoagulants, they noted that unfractionated or low molecular weight heparin may be preferred as 4 out of 5 included trials used these agents.

The panel’s recommendation was not unanimous: 8 panelists voted for a conditional recommendation in favor of therapeutic-intensity anticoagulation, 4 panelists voted for a conditional recommendation in favor of prophylactic-intensity anticoagulation, 4 panelists voted for a conditional recommendation in favor of either therapeutic- or prophylactic-intensity anticoagulation, and 3 panelists abstained, underscoring the uncertainty in the evidence. Among panelists who voted for a conditional recommendation in favor of prophylactic-intensity anticoagulation, concerns were expressed about the potential morbidity of anticoagulant-associated major bleeding events and possible underestimation of the absolute risk of major bleeding due to exclusion of patients at high bleeding risk from some clinical trials. In addition, baseline risks for thrombosis-related events were largely based on evidence collected earlier in the pandemic and it was expressed that these risks may be lower in the current phase of the pandemic.
What are others saying and what is new in these guidelines?

Numerous national and international organizations have published clinical practice guidelines or guidance documents on the role of anticoagulation in hospitalized COVID-19 patients. Among those published or updated since 2021, the year that RCTs comparing different intensities of anticoagulation were first published, both the Japanese living guidelines on drug management for COVID-19\(^\text{30}\) and the European Respiratory Society living guidelines\(^\text{31}\) recommend anticoagulation in patients with COVID-19-related acute illness, but do not specify an intensity. Italian and French guidelines suggest prophylactic-intensity anticoagulation, though the Italian guideline notes that therapeutic-intensity anticoagulation may be considered in patients deemed to be at high risk of thrombosis.\(^\text{32,33}\) The US National Institutes of Health COVID-19 Treatment Guideline panel recommends therapeutic-intensity heparin in patients with COVID-19-related acute illness who have a D-dimer above the upper limit of normal, require low-flow oxygen, and have no increased bleeding risk.\(^\text{34}\)

Major differences between the ASH guidelines and these other documents include use of high-quality systematic reviews and EtD frameworks, marker states to estimate the relative importance of key outcomes to patients, and decision thresholds to facilitate judgments about the magnitude of desirable and undesirable effects.

Limitations of these guidelines

The limitations of these guidelines are inherent in the low certainty of the evidence we identified for the research question. In addition, dramatic changes have occurred over the course of the pandemic with respect to circulating viral variants, the affected patient population, and the use of treatments other than anticoagulants for management of COVID-19-related acute illness (e.g., antiviral agents, corticosteroids, Janus kinase inhibitors, interleukin-6 inhibitors). Much of the evidence included in our systematic review was collected earlier in the pandemic and may not fully reflect baseline risk or the impact of different intensities of anticoagulation in the current phase of the pandemic.
Plans for updating these guidelines

Our recommendations will continue to be updated based on living reviews of evolving evidence. Our methods of living systematic reviews and recommendations, including criteria for deciding when to reassess and update recommendations, are described elsewhere.\(^3\)

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.\(^11\)

Priorities for research

On the basis of gaps in evidence identified during the guideline development process, the panel identified the following research priorities:

- Studies assessing baseline VTE risk, major bleeding risk, and mortality in acutely ill patients receiving prophylactic-intensity anticoagulation therapy and how these risks have varied over the course of the pandemic
- Studies examining the impact of non-anticoagulant interventions (e.g., vaccines, corticosteroids, antiviral therapies, anticytokine therapies, monoclonal antibody therapies) on thrombotic risk
- Studies examining the impact of different viral variants on thrombotic risk
- Development and validation of risk assessment models for thrombosis and bleeding in patients with COVID-19-related acute illness
- Studies examining the impact of anticoagulant therapy on thrombosis and bleeding outcomes in patients of differing race/ethnicity
• Studies comparing mortality, thrombosis, bleeding, and functional outcomes with different available anticoagulant agents and intensities
• Studies estimating the relative disutility of thrombotic and bleeding outcomes in patients with COVID-19-related acute illness

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Authorship contributions

A.C., R.N., R.A.M., and H.J.S. wrote the manuscript. All other authors contributed to critical revisions of the manuscript. All authors approved of the content. Members of the knowledge synthesis team (R.N., R.A.J., Y.A.J., A.M.B., A.B., M.B., R.B.P., R.C., L.E.C.L., K.D., A.J.D., H.H., S.G.K., R.M., G.P.M., R.Z.M., G.M.S., M.N., B.A.P., Y.Q., Y.R., A.S., K.S., W.W.) searched the literature, extracted data from eligible studies, analyzed the data, and prepared evidence summaries and evidence to decision tables. Panel members (A.C., E.K.T., P.A., C.B., K.D., J.D., M.T.D., D.D., D.O.G., S.R.K., F.A.K., A.I.L., I.N., A.P., M.R., K.M.S., D.M.S., M.S., D.R.T., K.T., R.A.M., H.J.S.) assessed the evidence, voted and made judgments within the evidence to decision 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. W.W., R.A.M., H.J.S.) developed the methods and provided guidance to the knowledge synthesis team and guideline panel. A.C., R.A.M., and H.J.S. were the co-chairs of the panel and led panel meetings.
Disclosures of conflicts of interest

All authors were members of the guideline panel or members of the systematic review team or both. As such, they completed a disclosure of interest form, which was reviewed by ASH and is available as Supplements 4 and 5.
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Table 1. Recommendations.

| **Recommendation** | **Remarks** |
|--------------------|-------------|
| **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 certainty (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 a medicine inpatient 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. Risk-assessment models to estimate thrombotic risk in hospitalized patients have been validated in COVID-19 patients, with modest prognostic performance. No risk assessment models for bleeding have been validated in COVID-19 patients. The panel acknowledges that lower-intensity anticoagulation may be preferred for patients judged to be at high bleeding risk and low thrombotic risk.
• At present, there is no direct high-certainty evidence comparing different types of anticoagulants in patients with COVID-19. Unfractionated or low molecular weight heparin 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. |
### Table 2. Definition of target population.

| Target population | Definition                                                                                                                                 |
|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Acutely ill       | Patients with COVID-19 who require hospital admission, generally to an inpatient medicine ward, without intensive clinical support (i.e., not to the intensive care unit), but may include treatment 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 hospitalized COVID-19 patients in aggregate and had fewer than 20% in the intensive care unit without separating their outcomes. Such populations were labeled as acutely ill. |
Table 3. Decision thresholds per critical outcome.

| Outcome                        | Utility Valuea | Decision Thresholdsb |
|--------------------------------|----------------|---------------------|
|                                | Mean (SD)      | Trivial/Small       | Small/Moderate | Moderate/Large |
| Mortality                      | 0              | 16 (9 to 22)        | 31 (22 to 39) | 60 (46 to 73) |
| PE – Moderate                  | 0.42 (0.15)    | 27 (15 to 38)       | 53 (38 to 68) | 103 (80 to 125) |
| Proximal DVT – Moderate        | 0.58 (0.14)    | 37 (21 to 53)       | 73 (53 to 94) | 142 (110 to 173) |
| Major Bleeding                 | 0.33 (0.23)    | 23 (13 to 33)       | 46 (33 to 59) | 89 (69 to 109) |
| Ischemic Stroke - Severe       | 0.14 (0.10)    | 18 (10 to 26)       | 36 (26 to 46) | 69 (54 to 85) |
| Intracranial Hemorrhage        | 0.12 (0.10)    | 18 (10 to 25)       | 35 (25 to 45) | 68 (53 to 83) |
| Multiple Organ Failure         | 0.15 (0.14)    | 18 (10 to 26)       | 36 (26 to 46) | 70 (54 to 86) |
| ST Elevation MI (STEMI)        | 0.31 (0.19)    | 23 (13 to 32)       | 44 (32 to 57) | 86 (67 to 105) |
| Limb Amputation                | 0.26 (0.16)    | 21 (12 to 30)       | 41 (30 to 53) | 80 (63 to 98) |
| ICU Hospitalization            | 0.38 (0.16)    | 25 (14 to 36)       | 50 (36 to 63) | 96 (75 to 117) |
| Long-Term Invasive Ventilation | 0.20 (0.12)    | 20 (11 to 28)       | 38 (28 to 49) | 74 (58 to 91) |

aHealth utility values indicate how patients would value their health state when experiencing the outcome of interest, whereby 1.00 indicates perfect health and 0 equals death. Values were obtained from 70 panel members from various ASH guidelines related to the management of venous thromboembolism.
bA survey among 151 panel members from various ASH guidelines related to the management of venous thromboembolism and COVID-19 was administered, using varying clinical outcome scenarios with standardized outcome descriptors (marker states), to determine thresholds between trivial, small, moderate, and large effects for the different critical outcomes. Mortality was used as the anchor with utility value 0, and the thresholds for other outcomes were determined based on their utility value relative to mortality.