CLINICAL GUIDELINES

blood advances

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

Objective: These evidence-based guidelines from the American Society of Hematology (ASH) are intended to support patients, clinicians, and other health care professionals in making decisions about the use of anticoagulation in patients with COVID-19.

Methods: ASH formed a multidisciplinary guideline panel that included patient representatives and applied strategies to minimize potential bias from conflicts of interest. The McMaster University GRADE Centre supported the guideline development process and performed 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

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

with COVID-19–related acute illness who do not have suspected or confirmed VTE. The panel emphasized the need for an individualized assessment of risk of thrombosis and bleeding. 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.

Conclusion: 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.

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 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. Risk assessment models for estimating risk of thrombosis in hospitalized patients have been validated in patients with COVID-19, with modest prognostic performance. No risk assessment models for bleeding have been validated in patients with COVID-19. The panel acknowledges that lower-intensity anticoagulation may be preferred for patients judged to be at high risk of bleeding and low risk of thrombosis.
- 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 thromboprophylaxis.[1] 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 patients who have COVID-19.[2] 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 of the previous American Society of Hematology (ASH) guideline published in February 2021,[3] and it focuses on the role of anticoagulation in patients with COVID-19–related acute illness. The panel followed best practices for guideline development recommended by the Institute of Medicine and the Guidelines International Network (GIN).[4-6] The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[7-13] to assess the certainty of the evidence and formulate recommendations. The recommendation is provided 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, admission to the intensive care unit (ICU), 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.[3]

Interpretation of strong and conditional recommendations

Please refer to the original ASH guideline on thromboprophylaxis in patients with COVID-19.[3]

Introduction

Aims of this guideline and specific objectives

Please refer to the original ASH guideline on thromboprophylaxis in patients with COVID-19.[3] All recommendations and updates to these living guidelines are accessible at the ASH COVID-19 anticoagulation webpage.[14]

Description of the health problem

The COVID-19 pandemic has had a significant impact on public health. As of 27 January 2022, more than 363 million cases and 5.6 million deaths had been attributed to COVID-19–related illness globally.[15] Thrombosis has emerged as an important complication of patients hospitalized with COVID-19–related acute illness, with VTEs occurring in up to 7.9% of such patients during hospitalization, often despite the use of standard thromboprophylaxis.[1] 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.[7] That recommendation was based on very low certainty evidence derived exclusively from observational studies. Since then, several randomized controlled trials (RCTs) have been reported that compared therapeutic-intensity with prophylactic-intensity anticoagulation in patients with COVID-19–related acute illness.[16-20] 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 obtaining new evidence and updating analyses in living systematic reviews, a living recommendation process to reconsider recommendations based on prespecified criteria regarding changes in the evidence, and a living guideline panel that is continuously available to reconvene when needed (see supplement 2). The ASH guideline panel generated Recommendation 2b on 30 November 2021, before soliciting public comments. We followed the same methods as those published in the initial guideline,[3] 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 that contain details on financial and nonfinancial interests, as well as the ASH conflict-of-interest policies agreed to by each individual. Supplement 5 provides the updated complete "Participant Information Forms" for researchers on the methods and systematic review teams who contributed to these guidelines.

Formulating specific clinical questions and determining outcomes of interest

This updated manuscript focuses on 1 question: In patients with COVID-19–related acute illness who do not have confirmed or suspected VTE, 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.[21]

Evidence review and development of recommendations

A new Evidence-to-Decision (EtD) framework was created for Recommendation 2b (see "Recommendations") using any applicable evidence and information from the EtD framework for the initial Recommendation 2,[7] and it was updated with new evidence and

Table 1. Recommendation

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 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. Risk assessment models for estimating risk of thrombosis in hospitalized patients have been validated in patients with COVID-19, with modest prognostic performance. No risk assessment models f or bleeding have been validated in patients with COVID-19. The panel acknowledges that lower-intensity anticoagulation may be preferred for patients judged to be at high risk of bleeding and low risk of thrombosis. • 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 medical ward, without intensive clinical support (ie, not to the ICU), 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 and had fewer than 20% in the ICU without separating their outcomes. Such populations were labeled as acutely ill.

considerations specifically for Recommendation 2b. The systematic review for identifying comparative antithrombotic studies for the entire guideline was updated until 28 November 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 29 March 2021, and prophylactic-intensity anticoagulation event rates from RCTs were updated until 28 November 2021. The up-to-date protocols and search strategies for both systematic reviews are provided in supplements 6 to 9. The decision to create this updated guideline recommendation was based on publication of several RCTs,[16-20] some of which were not already included from the systematic literature searches but were identified by expert panel members, were critically assessed by the evidence synthesis team, and were 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 by 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 1 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 for the Evidence Profile).

Document review

An initial draft recommendation was reviewed by all members of the panel and made available online from 8 October to 15 October 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. The revised draft recommendation was generated on 30 November 2021, and made available online from 20 December 2021 to 3 January 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 7 March 2022, the ASH Guideline Oversight Subcommittee and the ASH Committee on Quality verified that the defined guideline development process was followed, and on 11 March 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,[3] and to the user guide to ASH clinical practice guidelines.[23]

Recommendation

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

Table 3. Decision thresholds per critical outcome

Outcome	Mean utility value (SD)*	Decision thresholds for No. of events per 1000 patients (95% CI)†		
		Trivial/small	Small/moderate	Moderate/large
Mortality	0	16 (9-22)	31 (22-39)	60 (46-73)
Moderate PE	0.42 (0.15)	27 (15-38)	53 (38-68)	103 (80-125)
Moderate proximal DVT	0.58 (0.14)	37 (21-53)	73 (53-94)	142 (110-173)
Major bleeding	0.33 (0.23)	23 (13-33)	46 (33-59)	89 (69-109)
Severe ischemic stroke	0.14 (0.10)	18 (10-26)	36 (26-46)	69 (54-85)
Intracranial hemorrhage	0.12 (0.10)	18 (10-25)	35 (25-45)	68 (53-83)
Multiple organ failure	0.15 (0.14)	18 (10-26)	36 (26-46)	70 (54-86)
STEMI	0.31 (0.19)	23 (13-32)	44 (32-57)	86 (67-105)
Limb amputation	0.26 (0.16)	21 (12-30)	41 (30-53)	80 (63-98)
ICU hospitalization	0.38 (0.16)	25 (14-36)	50 (36-63)	96 (75-117)
Long-term invasive ventilation	0.20 (0.12)	20 (11-28)	38 (28-49)	74 (58-91)

SD, standard deviation; STEMI, ST-elevation myocardial infarction.

*Health utility values indicate how patients would value their health state when experiencing the outcome of interest; 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 VTE.

†A survey was administered to 151 panel members from various ASH guidelines related to the management of VTE and COVID-19, using various 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 a utility value of 0, and the thresholds for other outcomes were determined on the basis of their utility value relative to mortality.

of serious risk of bias, moderate for major bleeding because of serious imprecision, low for the outcomes of DVT, invasive mechanical ventilation and admission to the ICU because of serious risk of bias and serious imprecision, and as very low for all other outcomes, mainly because of very serious imprecision (see Evidence Profile and 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 patients with COVID-19.[24-27] 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 evidence for the Evidence Profile and EtD framework. Supplement 10 presents the characteristics of the included studies.

Five RCTs reported the effects of therapeutic-intensity anticoagulation in patients who were with COVID-19–related acute illness.[16-20] In the publications, or by providing unpublished data, all 5 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 patients who were not admitted to the ICU 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 outcomes.

Benefits. Based on the panel's thresholds for effect sizes (Table 3), therapeutic-intensity anticoagulation probably results in little to no difference in PEs with 17 fewer (from 22 fewer to 9 fewer) PEs per 1000 patients (odds ratio [OR], 0.42; 95% confidence interval [CI], 0.25-0.71) (moderate certainty). Therapeutic-intensity anticoagulation may result in little to no difference in DVTs with 4 fewer (from 7 fewer to 4 more) DVTs per 1000 patients (OR, 0.56; 95% CI, 0.22-1.41) (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 1000 patients (OR, 0.69; 95% CI, 0.39-1.22) (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 1000 patients (OR, 0.80; 95% CI, 0.52-1.23) (low certainty).

Therapeutic-intensity anticoagulation may reduce all-cause mortality with 20 fewer (from 52 fewer to 33 more) deaths per 1000 patients (OR, 0.78; 95% CI, 0.43-1.40), but the evidence is very uncertain (very low certainty). We investigated whether a subgroup effect was present for the type of anticoagulant (ie, low molecular weight heparin/unfractionated heparin vs direct oral anticoagulant) 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 or unfractionated heparin showed a pooled OR of 0.60 (95% CI, 0.29-1.22), which corresponds to 36 fewer (from 66 fewer to 19 more) deaths per 1000 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 1000 patients (OR, 0.46; 95% CI, 0.03-6.59), 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 1000 patients (OR, 0.92; 95% CI, 0.19-4.48), 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 1000 patients (OR, 0.33; 95% CI, 0.01-8.03), 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 1000 patients (OR, 0.65; 95% CI, 0.14-2.97), but the evidence is very uncertain (very low certainty).

Harms and burdens. 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 1000 patients (OR, 1.79; 95% CI, 1.00-3.21) (moderate certainty). The evidence is very uncertain about the effect of therapeutic-intensity anticoagulation on intracranial hemorrhage (OR, 2.95; 95% CI, 0.12-72.74) as well as the pooled mean baseline risk (0%); this corresponds to 0 more (from 0 to 0 more) intracranial hemorrhages per 1000 patients (very low certainty).

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 health care 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 risk of VTE may be lower (eg, Asian populations).[28] In addition, the panel noted possible racial and ethnic disparity in clinical trial enrollment.[16-20]

Conclusions. 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. On the basis of 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[29]; 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 because 4 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 because of the exclusion of patients at high risk of bleeding 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 noted 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[30] and the European Respiratory Society living guidelines[31] recommend anticoagulation in patients with COVID-19–related acute illness, but they do not specify an intensity. Italian and French guidelines suggest prophylactic-intensity anticoagulation, although the Italian guideline notes that therapeutic-intensity anticoagulation may be considered in patients deemed to be at high risk of thrombosis.[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 level above the upper limit of normal, require low-flow oxygen, and have no increased risk of bleeding.[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 this guideline

The limitations of this guideline 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 (eg, 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.

Revision or adaptation of the guideline

Plans for updating the guideline

Our recommendations will continue to be updated on the basis of 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 risk of VTE, risk of major bleeding, 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 (eg, vaccines, corticosteroids, antiviral therapies, anticytokine therapies, monoclonal antibody therapies) on risk of thrombosis
- Studies examining the impact of different viral variants on risk of thrombosis
- 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 and ethnicity
- Studies comparing mortality, thrombosis, bleeding, and functional outcomes with different anticoagulant agents and different dose intensities
- Studies estimating the relative disutility of thrombotic and bleeding outcomes in patients with COVID-19–related acute illness

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Authorship

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References

1. Nopp S, Moik F, Jilma B, Pabinger I, Ay C. Risk of venous thromboembolism in patients with COVID-19: a systematic review and meta-analysis. *Res Pract Thromb Haemost.* 2020;4(7):1178-1191.
2. Jiménez D, García-Sanchez A, Rali P, et al. Incidence of VTE and bleeding among hospitalized patients with coronavirus disease 2019: a systematic review and meta-analysis. *Chest.* 2021;159(3):1182-1196.
3. Cuker A, Tseng EK, Nieuwlaat R, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. *Blood Adv.* 2021;5(3):872-888.
4. Institute of Medicine. Clinical Practice Guidelines We Can Trust. Washington, DC: National Academic Press; 2011.
5. Schünemann HJ, Al-Ansary LA, Forland F, et al; Board of Trustees of the Guidelines International Network. Guidelines International Network: principles for disclosure of interests and management of conflicts in guidelines. *Ann Intern Med.* 2015;163(7):548-553.
6. Qaseem A, Forland F, Macbeth F, Ollenschläger G, Phillips S, van der Wees P; Board of Trustees of the Guidelines International Network. Guidelines International Network: toward international standards for clinical practice guidelines. *Ann Intern Med.* 2012;156(7):525-531.

7. Alonso-Coello P, Schünemann HJ, Moberg J, et al; GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: introduction. *BMJ.* 2016;353:i2016.
8. Alonso-Coello P, Oxman AD, Moberg J, et al; GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: clinical practice guidelines. *BMJ.* 2016;353:i2089.
9. Atkins D, Eccles M, Flottorp S, et al; GRADE Working Group. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. *BMC Health Serv Res.* 2004;4(1):38.
10. Schünemann HJ, Best D, Vist G, Oxman AD; GRADE Working Group. Letters, numbers, symbols and words: how to communicate grades of evidence and recommendations. *CMAJ.* 2003;169(7):677-680.
11. Schünemann HJ, Wiercioch W, Brozek J, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. *J Clin Epidemiol.* 2017;81:101-110.
12. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol.* 2011; 64(4):395-400.
13. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336(7650):924-926.
14. American Society of Hematology. ASH Guidelines on the Use of Anticoagulation in Patients With COVID-19. Available at: https://www.hematology.org/education/clinicians/guidelines-and-quality-care/clinical-practice-guidelines/venous-thromboembolism-guidelines/ash-guidelines-on-use-of-anticoagulation-in-patients-with-covid-19. Accessed 16 January 2022.
15. Johns Hopkins University of Medicine, Coronavirus Resource Center. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). Available at: https://coronavirus.jhu.edu/map.html. Accessed 16 January 2022.
16. Marcos-Jubilar M, Carmona-Torre F, Vidal R, et al. Therapeutic versus prophylactic bemiparin in hospitalized patients with nonsevere COVID-19 pneumonia (BEMICOP study): an open-label, multicenter, randomized, controlled trial. *Thromb Haemost.* 2022;122(2):295-299.
17. Sholzberg M, Tang GH, Rahhal H, et al; RAPID trial investigators. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with covid-19 admitted to hospital: RAPID randomised clinical trial. *BMJ.* 2021;375(2400):n2400.
18. Lawler PR, Goligher EC, Berger JS, et al; ATTACC Investigators; ACTIV-4a Investigators; REMAP-CAP Investigators. Therapeutic anticoagulation with heparin in noncritically ill patients with COVID-19. *N Engl J Med.* 2021;385(9):790-802.
19. Spyropoulos AC, Goldin M, Giannis D, et al; HEP-COVID Investigators. Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: the HEP-COVID randomized clinical trial. *JAMA Intern Med.* 2021;181(12):1612-1620.
20. Lopes RD, de Barros E Silva PGM, Furtado RHM, et al; ACTION Coalition COVID-19 Brazil IV Investigators. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. *Lancet.* 2021;397(10291):2253-2263.
21. Cuker A, Tseng EK, Nieuwlaat R, et al. American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: May 2021 update on the use of intermediate-intensity anticoagulation in critically ill patients. *Blood Adv.* 2021;5(20): 3951-3959.
22. Schandelmaier S, Briel M, Varadhan R, et al. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. *CMAJ.* 2020;192(32):E901-E906.
23. Izcovich A, Cuker A, Kunkle R, et al. A user guide to the American Society of Hematology clinical practice guidelines. *Blood Adv.* 2020;4(9): 2095-2110.
24. Sholzberg M, da Costa BR, Tang GH, et al; RAPID Trial Investigators. Randomized trials of therapeutic heparin for COVID-19: a meta-analysis. *Res Pract Thromb Haemost.* 2021;5(8):e12638.
25. Ortega-Paz L, Galli M, Capodanno D, et al. Safety and efficacy of different prophylactic anticoagulation dosing regimens in critically and non-critically ill patients with COVID-19: a systematic review and meta-analysis of randomized controlled trials. *Eur Heart J Cardiovasc Pharmacother.* 2021;pvab070.
26. Jorda A, Siller-Matula JM, Zeitlinger M, Jilma B, Gelbenegger G. Anticoagulant treatment regimens in patients with COVID-19: a meta-analysis. *Clin Pharmacol Ther.* 2022;111(3):614-623.
27. Kow CS, Ramachandram DS, Hasan SS. The effect of higher-intensity dosing of anticoagulation on the clinical outcomes in hospitalized patients with COVID-19: a meta-analysis of randomized controlled trials. *J Infect Chemother.* 2022;28(2):257-265.
28. Tran HN, Klatsky AL. Lower risk of venous thromboembolism in multiple Asian ethnic groups. *Prev Med Rep.* 2019;13:268-269.
29. Spyropoulos AC, Cohen SL, Gianos E, et al; COVID-19 Consortium Group. Validation of the IMPROVE-DD risk assessment model for venous thromboembolism among hospitalized patients with COVID-19. *Res Pract Thromb Haemost.* 2021;5(2):296-300.
30. Yamakawa K, Yamamoto R, Terayama T, et al; Special Committee of the Japanese Clinical Practice Guidelines for the Management of Sepsis and Septic Shock 2020 (J-SSCG 2020), the COVID-19 Task Force. Japanese rapid/living recommendations on drug management for COVID-19: updated guidelines (September 2021). *Acute Med Surg.* 2021;8(1):e706.

31. Chalmers JD, Crichton ML, Goeminne PC, et al. Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline. *Eur Respir J.* 2021;57(4):2100048.

32. Bassetti M, Giacobbe DR, Bruzzi P, et al; Italian Society of Anti-infective Therapy (SITA) and the Italian Society of Pulmonology (SIP). Clinical management of adult patients with COVID-19 outside intensive care units: guidelines from the Italian Society of Anti-Infective Therapy (SITA) and the Italian Society of Pulmonology (SIP). *Infect Dis Ther.* 2021;10(4):1837-1885.

33. Godon A, Tacquard CA, Mansour A, et al; Gihp, the GFHT. Prevention of venous thromboembolism and haemostasis monitoring in patients with COVID-19: updated proposals (April 2021): from the French working group on perioperative haemostasis (GIHP) and the French study group on thrombosis and haemostasis (GFHT), in collaboration with the French Society of Anaesthesia and Intensive Care (SFAR). *Anaesth Crit Care Pain Med.* 2021;40(4):100919.

34. National Institutes of Health, COVID-19 Treatment Guidelines. Antithrombotic Therapy in Patients With COVID-19. Available at: https://www.covid19treatmentguidelines.nih.gov/therapies/antithrombotic-therapy/. Accessed 16 January 2022.