American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19

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CLINICAL GUIDELINES

blood advances

American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19

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Background: Coronavirus disease 2019 (COVID-19)–related critical illness and acute illness are associated with a 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 for thromboprophylaxis for patients with COVID-19–related critical illness and acute illness who do not have confirmed or suspected VTE.

Methods: ASH formed a multidisciplinary guideline panel and applied strict management strategies to minimize potential bias from conflicts of interest. The panel included 3 patient representatives. The McMaster University GRADE Centre supported the guideline-development process, including performing systematic evidence reviews (up to 19 August 2020). 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, including GRADE Evidence-to-Decision frameworks, to assess evidence and make recommendations, which were subject to public comment.

Results: The panel agreed on 2 recommendations. The panel issued conditional recommendations in favor of prophylactic-intensity anticoagulation over intermediate-intensity or therapeutic-intensity anticoagulation for patients with COVID-19–related critical illness or acute illness who do not have confirmed or suspected VTE.

Conclusions: These recommendations were based on very low certainty in the evidence, underscoring the need for high-quality, randomized controlled trials comparing different intensities of anticoagulation. They will be updated using a living recommendation approach as new evidence becomes available.

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

Summary of recommendations

Patients with COVID-19, which is caused by the novel severe acute respiratory distress syndrome coronavirus 2, may develop hemostatic abnormalities.[1-4] Early reports demonstrated high rates of VTE for patients who are acutely ill or hospitalized with COVID-19, including those receiving critical care.[5] The optimal strategy for thromboprophylaxis in these patients remains uncertain.

These guidelines are based on updated and original systematic reviews of evidence conducted under the direction of the McMaster University GRADE Centre with international collaborators. The panel followed best practices for guideline development recommended by the Institute of Medicine and the Guidelines International Network (GIN).[6-8] The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[9-15] to assess the certainty in the evidence and formulate recommendations. The recommendations are listed in Table 1.

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:

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 policy makers: 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.

Table 1. Recommendations

Recommendation	Remarks
Recommendation 1. The ASH guideline panel *suggests* using prophylactic-intensity over intermediate-intensity or 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 ⊕◯◯◯)	• Between the time this recommendation was published online (27 October 2020) and when it was published in *Blood Advances*, a press release (https://www.nih.gov/news-events/news-releases/nih-activ-trial-blood-thinners-pauses-enrollment-critically-ill-covid-19-patients) describing the results of a planned interim analysis of 3 randomized controlled trials, REMAP-CAP, ACTIV-4, and ATTACC (NCT 02735707, 04505774, and 04372589, respectively), was issued. In these trials, therapeutic-intensity anticoagulation was compared with prophylactic-intensity anticoagulation for patients with COVID-19–related critical illness. The ASH guideline panel plans to update this recommendation when the full results of REMAP-CAP, ACTIV-4, and ATTACC become available. Clinicians should weigh the potential benefits and harms based on the most up-to-date available evidence in caring for their patients. • Patients with COVID-19–related critical illness are defined as those suffering from an immediately life-threatening condition who would typically be admitted to an intensive care unit. Examples include patients requiring hemodynamic support, ventilatory support, and renal replacement therapy. • An individualized assessment of the patient's risk of thrombosis and bleeding is important when deciding on anticoagulation intensity; risk-assessment models to estimate thrombotic and bleeding risk are available, but they have not been validated for patients with COVID-19; the panel acknowledges that higher-intensity anticoagulation may be preferred for patients judged to be at high thrombotic risk and low bleeding 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, unfractionated heparin, etc) may be based on availability, resources required, familiarity, and the aim of minimizing PPE use or staff exposure to COVID-19–infected patients as well as patient-specific factors (eg, renal function, history of heparin-induced thrombocytopenia, concerns about gastrointestinal tract absorption) • This recommendation does not apply to patients who require anticoagulation to prevent thrombosis of extracorporeal circuits such as those on ECMO or CRRT
Recommendation 2. The ASH guideline panel *suggests* using prophylactic-intensity over intermediate-intensity or therapeutic-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 ⊕◯◯◯)	• Between the time this recommendation was published online (27 October 2020) and when it was published in *Blood Advances*, a press release (https://www.nih.gov/news-events/news-releases/full-dose-blood-thinners-decreased-need-life-support-improved-outcome-hospitalized-covid-19-patients) describing the results of a planned interim analysis of 3 randomized controlled trials, REMAP-CAP, ACTIV-4, and ATTACC (NCT 02735707, 04505774, and 04372589, respectively), was issued. In these trials, therapeutic-intensity anticoagulation was compared with prophylactic-intensity anticoagulation for moderately ill hospitalized patients with COVID-19. The ASH guideline panel plans to update this recommendation when the full results of REMAP-CAP, ACTIV-4, and ATTACC become available. Clinicians should weigh the potential benefits and harms based on the most up-to-date available evidence in caring for their patients. • 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 advanced 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 and bleeding risk are available, but they have not been validated for patients with COVID-19; the panel acknowledges that higher-intensity anticoagulation may be preferred for patients judged to be at high thrombotic risk and low bleeding 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, unfractionated heparin, etc) may be based on availability, resources required, familiarity, and the aim of minimizing PPE use or staff exposure to COVID-19–infected patients as well as patient-specific factors (eg, renal function, history of heparin-induced thrombocytopenia, concerns about gastrointestinal tract absorption)

- For clinicians: Recognize that different choices will be appropriate for individual patients and that you 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 policy makers: 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.

Recommendations

Recommendation 1. The American Society of Hematology (ASH) guideline panel *suggests* using prophylactic-intensity over intermediate-intensity or therapeutic-intensity anticoagulation for patients with coronavirus disease 2019 (COVID-19)–related critical illness who do not have suspected or confirmed venous thromboembolism (VTE) (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- Between the time this recommendation was published online (27 October 2020) and when it was published in *Blood Advances*, a press release (https://www.nih.gov/news-events/news-releases/nih-activ-trial-blood-thinners-pauses-enrollment-critically-ill-covid-19-patients) describing the results of a planned interim analysis of 3 randomized controlled trials, REMAP-CAP, ACTIV-4, and ATTACC (NCT 02735707, 04505774, and 04372589, respectively), was issued. In these trials, therapeutic-intensity anticoagulation was compared with prophylactic-intensity anticoagulation for patients with COVID-19–related critical illness. The ASH guideline panel plans to update this recommendation when the full results of REMAP-CAP, ACTIV-4, and ATTACC become available. Clinicians should weigh the potential benefits and harms based on the most up-to-date available evidence in caring for their patients.
- Patients with COVID-19–related critical illness are defined as those suffering from an immediately life-threatening condition who would typically be admitted to an intensive care unit (ICU). Examples include patients requiring hemodynamic support, ventilatory support, and renal-replacement therapy.
- An individualized assessment of the patient's risk of thrombosis and bleeding is important when deciding on anticoagulation intensity. Risk-assessment models to estimate thrombotic and bleeding risk in hospitalized patients are available, but they have not been validated for patients with COVID-19. The panel acknowledges that higher-intensity anticoagulation may be preferred for patients judged to be at high thrombotic risk and low bleeding 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, unfractionated heparin, etc) may be based on availability, resources required, familiarity, and the aim of minimizing personal protective equipment (PPE) use or staff exposure to COVID-19–infected patients as well as patient-specific factors (eg, renal function, history of heparin-induced thrombocytopenia, concerns about gastrointestinal tract absorption).
- This recommendation does not apply to patients who require anticoagulation to prevent thrombosis of extracorporeal circuits such as those on extracorporeal membrane oxygenation (ECMO) or continuous renal-replacement therapy (CRRT).

Recommendation 2. The ASH guideline panel *suggests* using prophylactic-intensity over intermediate-intensity or therapeutic-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 ⊕◯◯◯).

Remarks:

- Between the time this recommendation was published online (27 October 2020) and when it was published in *Blood Advances*, a press release (https://www.nih.gov/news-events/news-releases/full-dose-blood-thinners-decreased-need-life-support-improved-outcome-hospitalized-covid-19-patients) describing the results of a planned interim analysis of 3 randomized controlled trials, REMAP-CAP, ACTIV-4, and ATTACC (NCT 02735707, 04505774, and 04372589, respectively), was issued. In these trials, therapeutic-intensity anticoagulation was compared with prophylactic-intensity anticoagulation in moderately ill hospitalized patients with COVID-19. The ASH guideline panel plans to update this recommendation when the full results of REMAP-CAP, ACTIV-4, and ATTACC become available. Clinicians should weigh the potential benefits and harms based on the most up-to-date available evidence in caring for their patients.
- 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 advanced 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 and bleeding risk in hospitalized patients are available, but they have not been validated for patients with COVID-19. The panel acknowledges that higher-intensity anticoagulation may be preferred for patients judged to be at high thrombotic risk and low bleeding 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, unfractionated heparin, etc) may be based on availability, resources required, familiarity, and the aim of minimizing PPE use or staff exposure to COVID-19–infected patients as well as patient-specific factors (eg, renal function, history of heparin-induced thrombocytopenia, concerns about gastrointestinal tract absorption).

Values and preferences

The guideline panel identified all-cause mortality, pulmonary embolism (PE), deep vein thrombosis (DVT), and major bleeding as critical outcomes, and placed a high value on avoiding these outcomes with the interventions assessed. Multiple organ failure, severe ischemic stroke, intracranial hemorrhage, invasive ventilation, limb amputation, ICU/critical care unit (CCU) hospitalization, and ST-elevation myocardial infarction were also judged to be critical

outcomes but could not be assessed as there was no direct evidence available. 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

These recommendations take into consideration cost, impact on equity, acceptability, and feasibility. Although the cost of intermediate- or therapeutic-intensity anticoagulation may be higher than prophylactic-intensity anticoagulation, the panel determined that the incremental cost of higher-intensity anticoagulation was negligible relative to the total costs of care for hospitalized patients with COVID-19. ASH will develop tools to facilitate the dissemination and implementation of the recommendations including a pocket guide, mobile application, and educational slide set.

Introduction

Aims of these guidelines and specific objectives

The purpose of these guidelines is to provide evidence-based recommendations on the use of anticoagulation for patients with COVID-19–related acute and critical illness who do not have suspected or confirmed VTE. Through improved provider and patient education of the available evidence and evidence-based recommendations, these guidelines aim to provide clinical decision support for shared decision-making with the goal of improved patient outcomes.

The target audience includes patients, hematologists, general practitioners, hospitalists, internists, intensivists, other clinicians, and decision-makers. Policy makers interested in these guidelines include those involved in developing local, national, or international plans aiming to prevent the development of VTE for patients with COVID-19–related illness. This document may also serve as the basis for adaptation by local, regional, or national guideline panels.

Description of the health problem

The COVID-19 pandemic has had a significant public health impact. As of 28 October 2020, over 44 million cases and 1.1 million deaths had been attributed to COVID-19–related illness globally.[16] COVID-19–related respiratory illness has led to a substantial burden of hospitalization. It is estimated that 5% to 20% of infected patients require hospital admission, of whom 5% to 15% may develop critical illness requiring intensive care support.[17-19]

VTE has emerged as an important complication for patients hospitalized with COVID-19. Early reports documented high rates of VTE (and, in particular, PE) for patients hospitalized with COVID-19–related acute illness and critical illness despite pharmacological thromboprophylaxis.[20-25] In addition, arterial thrombotic complications including stroke have been noted in early case series.[26,27] Microvascular thrombosis, which may involve the pulmonary vasculature and other organs, has been reported in autopsy studies, although its impact on the development of respiratory and multiorgan failure remains unclear.[28,29] Imaging studies have confirmed that the radiological appearance of PE differs in COVID-19 compared with non–COVID-19 patients, with more peripheral localization of thrombi and generally lower clot burden.[30,31] These observations may support the hypothesis that for patients with COVID-19, PE may result from in situ immunothrombosis rather than from embolization from lower-extremity DVT. In this report, the term PE is used to collectively refer to both embolus and in situ thrombus of the pulmonary arteries.

The mechanisms of hypercoagulability in COVID-19 have yet to be fully elucidated. Characteristic hemostatic abnormalities including elevations in factor VIII, von Willebrand factor, fibrinogen, and D-dimer concentration have been described.[2,4,32] Endotheliopathy, due either to direct viral invasion or immune-mediated endothelial injury, may also play an important role.[33,34]

The optimal thromboprophylaxis strategy for patients hospitalized with COVID-19–related illness remains uncertain.[21-23,35] Several laboratory predictors of VTE in hospitalized patients with COVID-19 have been reported including elevated D-dimer, C-reactive protein, erythrocyte sedimentation rate, and platelet count.[36,37] In addition, clinical risk factors for VTE in COVID-19 have been identified including the development of acute respiratory distress syndrome[20] and older age.[23] However, it remains unclear whether these or other parameters should be used to stratify patients for risk of thrombotic complications, or influence decisions about thromboprophylaxis intensity. Although COVID-19–associated coagulopathy appears to be marked primarily by thrombotic complications, patients may develop major bleeding complications on anticoagulation therapy, which can impact the safety of intensified thromboprophylaxis regimens.[36,38]

Description of the target populations

For this guideline, the panel separately considered 2 groups of patients: those with COVID-19–related acute illness and critical illness. These patient populations are typically defined by the setting of hospital admission (medical ward and ICU/CCU, respectively) as an indication of illness severity.[39] However, the panel acknowledged that during the COVID-19 pandemic, such patients may not be admitted to the hospital or ICU owing to limitations in hospital capacity and health care resources, despite meeting traditional criteria for provision of care in these settings. The panel also acknowledged that criteria for admission to the hospital or ICU/CCU may vary by institution or region. Therefore, the panel defined COVID-19–related acute illness and critical illness based on clinical features rather than the type of unit to which the patient was admitted (Table 2).[39-43]

The panel defined patients with COVID-19–related critical illness as those suffering from an immediately life-threatening condition who would typically be admitted to an ICU/CCU for advanced clinical support.[39] Examples include patients requiring hemodynamic support, ventilatory support including mechanical ventilation, and renal-replacement therapy.[42] Patients with critical illness in the absence of COVID-19 may be at increased thrombotic risk due to a variety of risk factors including advanced age, immobility, infection, central venous catheterization, and other comorbid illness.[43]

The panel defined patients with COVID-19–related acute illness as those with clinical features that would typically result in admission to a medicine inpatient ward without requirement for advanced

Table 2. Definitions 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 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
Acutely ill	• Patients with COVID-19 who require hospital admission without advanced clinical support (ie, not to the ICU/CCU), but could include treatment in other settings if the hospital was over capacity • Hospital capacity and admission criteria could vary according to the specific setting

clinical support. Examples include patients with dyspnea or mild to moderate hypoxia. Patients with acute illness in the absence of COVID-19 are at increased risk for VTE due to a variety of risk factors including reduced mobility, age, organ dysfunction, and other comorbid illness.[40,41]

Risk-assessment models have been developed to assess bleeding and thrombosis risk in hospitalized medical patients, but these tools remain to be validated and have not been well studied for patients hospitalized with COVID-19.[40,44-46]

Methods

We developed and will maintain these "living" guideline recommendations in 2 phases. During the first phase, we used methodology for guideline development consistent with the ASH guidelines for management of VTE, but with a condensed timeline.[47] This was a rapid guideline-development process, with systematic review searches being conducted on 19 July and 19 August 2020, followed by the drafting of recommendations on 29 September 2020. Panel and Methods team members also suggested additional important eligible studies until 29 September 2020. During the second phase, using a living guideline approach (supplemental File 1), we aim to provide updates using the living recommendations approach that we previously conceptualized based on living systematic reviews (https://community.cochrane.org/sites/default/files/uploads/inline-files/Transform/201912_LSR_Revised_Guidance.pdf).[48-51]

To assess the certainty in the body of evidence and develop recommendations, we followed the GRADE approach.[9-12,15,48,52] The overall guideline-development process, including funding of the work, panel formation, management of conflicts of interest, internal and external review, and organizational approval, was guided by ASH policies and procedures derived from the GIN-McMaster Guideline Development Checklist (http://cebgrade.mcmaster.ca/guidecheck.html)[53] intended to meet recommendations for trustworthy guidelines by the Institute of Medicine and GIN.[6-8] We report the guideline following the RIGHT checklist (supplemental File 2).[54]

Organization, panel composition, planning, and coordination

The work of this panel was coordinated by ASH and the McMaster University GRADE Center (funded by ASH under a paid agreement). Project oversight was provided by the ASH Guideline Oversight Subcommittee, which reported to the ASH Committee on Quality. ASH vetted and appointed individuals to the guideline panel. The McMaster University GRADE Centre vetted and retained researchers to conduct systematic reviews of evidence and coordinate the guideline-development process including the use of the GRADE approach. The membership of the panels and the systematic review team are described in supplemental File 3.

The panel included adult and pediatric hematologists, internists, intensivists, an infectious disease specialist, a nephrologist, and an anticoagulation pharmacist with expertise on the guideline topic, and 3 patient representatives. The panel was chaired by 1 clinical co-chair (A.C.) and 2 guideline methodology co-chairs (H.J.S., R.A.M.).

In addition to synthesizing evidence systematically, the McMaster University GRADE Centre supported the guideline-development process, including determining methods, preparing meeting materials, and facilitating panel discussions. The panel's work was done using Web-based tools (www.surveymonkey.com and www.gradepro.org) and online meetings.

In the living phase, we will apply and enhance these processes of guideline development in the following ways. We aim to retain the composition of panel members throughout the development of the living recommendations unless conflicts of interest emerge that could lead to exclusion of panel members or members decide to leave the panel for other reasons. All panel members will be apprised of potential changes to the evidence and engaged for reassessment of new evidence. If dictated by the emergence of new evidence, they will support the updating of living recommendations based on explicit criteria.

Guideline funding and management of conflicts of interest

Development of these guidelines was wholly funded by ASH, a nonprofit medical specialty society that represents hematologists. Direct funding by for-profit companies was not accepted. ASH staff supported panel appointments and coordinated meetings but had no role in choosing the guideline questions or determining the recommendations.

Through funding by ASH to the McMaster University GRADE Centre, some of the researchers who contributed to the systematic evidence reviews received salary or grant support. Other researchers participated to fulfill requirements of an academic degree or program. The guideline panel received no payments or reimbursements from ASH for their work on these guidelines.

Conflicts of interest of all participants were managed according to ASH policies based on recommendations of the Institute of Medicine[55] and GIN.[7] Participants disclosed all financial and nonfinancial interests relevant to the guideline topic. ASH staff and the ASH Guideline Oversight Subcommittee reviewed the disclosures and composed the guideline panel to include a diversity of expertise and perspectives and to avoid a majority of the panel having the same or similar conflicts. Greatest attention was given to conflicts from direct financial interests in for-profit companies that could be affected by the guidelines. During the guideline-development process, all members of the guideline panel and all members of the systematic review team avoided direct financial interests in for-profit health care companies more than $5000 per year regardless of relevance to the guideline topic.

Supplemental File 4 provides "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

Table 3. Classification of anticoagulant regimens by intensity

Regimen
Prophylactic*
Apixaban 2.5 mg, PO BID (with intent for VTE prophylaxis)
Bemiparin 3500 U, SC OD
Betrixaban 80 mg, PO OD
Betrixaban 160 mg, PO OD
Dabigatran 220 mg, PO OD
Dalteparin 5000 U, SC OD
Enoxaparin 30 mg (3000 U), SC OD (for GFR 15-30)
Enoxaparin 30 mg (3000 U), SC BID (for BMI ≥40 kg/m^2)
Enoxaparin 40 mg (4000 U), SC OD
Enoxaparin 40 mg (4000 U), SC BID (for BMI ≥40 kg/m^2)
Fondaparinux 2.5 mg, SC OD
Unfractionated heparin 5000 U, SC BID
Unfractionated heparin 5000 U, SC TID
Unfractionated heparin 7500 U, SC BID (for BMI ≥40 kg/m^2)
Nadroparin 2850 U, SC q24h (post-op general surgery)
Nadroparin 5700 U, SC q24h (high-risk medical patients >70 kg)
Nadroparin 3800 U, SC q24h (high-risk medical patients ≤70 kg or post-op hip replacement surgery)
Rivaroxaban 10 mg, PO OD
Tinzaparin 3500 U, SC OD
Tinzaparin 4500 U, SC OD
Tinzaparin 75 U/kg, SC OD
Intermediate*
Enoxaparin 0.5 mg/kg (50 U/kg), SC BID (if CrCl >30 mL/min)
Enoxaparin 0.5 mg/kg (50 U/kg), SC OD (if CrCl <30 mL/min)
Enoxaparin 30 mg (3000 U), SC BID (for BMI <40 kg/m^2)
Enoxaparin 40 mg (4000 U), SC BID (for CrCl >30 mL/min and BMI <40 kg/m^2)
Enoxaparin 60 mg (6000 U), SC BID (for CrCl >30 mL/min and BMI >40 kg/m^2)
Unfractionated heparin 7500 U, SC TID
Dalteparin 5000 U, SC BID
Therapeutic*
Acenocoumarol, PO (target INR 2.0-3.0 or greater)
Apixaban 5 mg, PO BID
Apixaban 10 mg, PO BID
Argatroban, IV to target aPTT therapeutic range as per institutional guidelines
Bemiparin 5000 U, SC OD (if weight ≤50 kg and CrCl >30 mL/min)
Bemiparin 7500 U, SC OD (if weight 50-70 kg and CrCl >30 mL/min)
Bemiparin 10000 U, SC OD (if weight 70-100 kg and CrCl >30 mL/min)
Bemiparin 115 U/kg, SC OD (if weight >100 kg and CrCl >30 mL/min)
Bivalirudin, IV to target aPTT therapeutic range as per institutional guidelines
Dabigatran 75 mg, PO BID (if CrCl 15-30 mL/min)
Dabigatran 110 mg, PO BID (AF: age ≥80 y, or >75 y and 1 or more risk factors for bleeding)
Dabigatran 150 mg, PO BID (if CrCl >30 mL/min)
Dalteparin 100 U/kg, SC BID
Dalteparin 150 U/kg, SC OD
Dalteparin 200 U/kg, SC OD
Edoxaban 30 mg, PO OD (≤60 kg, CrCl 15-50 mL/min)
Edoxaban 60 mg, PO OD (weight ≥60 kg and CrCl >50 mL/min)
Enoxaparin 0.8 mg/kg, SC BID (for BMI >40 and CrCl >30 mL/min)
Enoxaparin 1 mg/kg (100 U/kg), SC BID (for CrCl >30 mL/min)
Enoxaparin 1.5 mg/kg (150 U/kg), SC OD (for CrCl >30 mL/min)
Enoxaparin 1 mg/kg (100 U/kg), SC OD (for CrCl <30 mL/min)
Tinzaparin 175 U/kg, SC OD
Fluindione, PO (target INR 2.0-3.0 or greater)
Fondaparinux 5 mg, SC OD (if weight <50 and CrCl >50 mL/min
Fondaparinux 5 mg, SC OD (if weight 50-100 kg and CrCl 30-50 mL/min)
Fondaparinux 7.5 mg, SC OD (if weight 50-100 kg and CrCl >50 mL/min
Fondaparinux 7.5 mg, SC OD (if weight >100 kg and CrCl 30-50 mL/min)
Fondaparinux 10 mg, SC OD (if weight >100 kg and CrCl >30 mL/min)
Unfractionated heparin, IV to target aPTT therapeutic range as per institutional guidelines or anti-Xa activity 0.3-0.7 IU/mL
Unfractionated heparin 250 U/kg, SC q12h
Nadroparin 86 U/kg, SC q12h (for acute coronary syndrome)
Nadroparin 171 U/kg, q24h (for DVT treatment)
Phenprocoumon, PO (target INR 2.0-3.0 or greater)
Rivaroxaban 15 mg, PO BID
Rivaroxaban 15 mg, PO OD (for GFR 15-50 in AF patients)
Rivaroxaban 20 mg, PO OD
Warfarin, PO (target INR 2.0-3.0 or greater)

AF, atrial fibrillation; aPTT, activated partial thromboplastin time; BID, twice daily; BMI, body mass index; CrCl, creatinine clearance; GFR, glomerular filtration rate; INR, international normalized ratio; OD, once a day; PO, oral; post-op, postoperative; q12h, every 12 hours; q24h, every 24 hours; SC, subcutaneous; TID, 3 times a day.
*Intensity of anticoagulation.

individual. Supplemental File 5 provides the complete Participant Information Forms of researchers on the systematic review team who contributed to these guidelines.

Formulating specific clinical questions and determining outcomes of interest

The panel used the GRADEpro Guideline Development Tool (www.gradepro.org)[56] and SurveyMonkey (www.surveymonkey.com) to brainstorm and then prioritize the questions. The aim was to develop a "small informative recommendation unit" that would create focused clinical questions that could be answered in a timely manner, and then clearly and feasibly implemented by clinicians.[57] The prioritized questions were:

1. For patients with COVID-19–related critical 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 intermediate intensity or therapeutic intensity vs prophylactic intensity?
2. For 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 intermediate intensity or therapeutic intensity vs prophylactic intensity?

Definitions

We defined COVID-19 according to the World Health Organization (WHO) criteria (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/laboratory-guidance) including suspected, probable, and confirmed cases. All included studies enrolled, exclusively or largely, laboratory-confirmed COVID-19 patients.

We used the following definition for critical illness related to COVID-19 (Table 2): respiratory or cardiovascular failure normally requiring advanced clinical support in the ICU or 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.

We applied the following definition to acute illness related to COVID-19 (Table 2): normally requiring hospital admission without advanced clinical support (ie, not to the ICU/CCU), but could include treatment in other clinical settings if the hospital was over capacity. Hospital capacity and admission criteria could vary according to the specific setting. Some studies reported on all hospitalized COVID-19 patients and had <20% in the ICU/CCU without separating their outcomes, and such populations were labeled as acutely ill.

A guideline panel working group predefined prophylactic-, intermediate-, and therapeutic-intensity anticoagulation, and the overall panel approved these definitions (Table 3). Interventions reported in included studies were categorized according to these definitions. Studies not providing sufficient details to categorize the intensities according to our definitions were labeled according to the authors' definition of the intensity.

The panel selected outcomes of interest for each prioritized question a priori, following the approach described in detail elsewhere.[47] In brief, we used the outcomes that the ASH management of VTE guideline panels prioritized as our initial candidate outcomes using health outcome descriptors (https://ms.gradepro.org).[39,58-64] We then asked for additional outcomes that may be important or critical for decision-making in COVID-19–related illness. The panel considered the following outcomes as critical for clinical decision-making: all-cause mortality, PE, DVT of the upper leg, VTE (including DVT or PE), major bleeding, multiple organ failure, severe ischemic stroke, intracranial hemorrhage, invasive ventilation, limb amputation, ICU hospitalization, and ST-elevation myocardial infarction.

Typically, included studies reported venous thromboembolic outcomes as any PE, any DVT, or any VTE, without further specification. Some studies did not distinguish asymptomatic thromboembolic events that were detected by the routine performance of sensitive screening studies for VTE from symptomatic thromboembolic events where patients developed overt signs or symptoms that were subsequently confirmed by objective testing to be associated with VTE. Reporting of symptomatic thromboembolic events was inconsistent across studies.

Where available, we included evidence from studies that reported symptomatic thromboembolic events. As the ratio of screening-detected and symptomatic thromboembolic events is not yet established in COVID-19 patients, we made no assumptions about the distribution of asymptomatic vs symptomatic outcomes.

We used evidence for major bleeding as labeled by the study authors, as outcome definitions were not always provided.

The duration of follow-up for the prioritized outcomes was captured, and outcome rates at 14- to 35-day follow-up were used when data were available. The evidence for prioritized outcomes other than mortality, VTE, and major bleeding, and details on their reported definitions, will be provided in the living phase for these recommendations.

We do not expect changes to the questions, outcomes, and definitions during the living phase, but will reconsider them if deemed necessary by the panel based on new insights.

Evidence review and development of recommendations

For each guideline question, the McMaster University GRADE Centre prepared a GRADE "Evidence-to-Decision" (EtD) framework, using the GRADEpro Guideline Development Tool (www.gradepro.org).[9,10,52] The EtD table summarized the results of systematic reviews of the literature that were updated or performed for this guideline. The EtD table addressed the baseline risk for critical outcomes, effects of interventions, resource utilization (cost and cost-effectiveness), values and preferences (relative importance of outcomes), equity, acceptability, and feasibility. The guideline panel reviewed draft EtD tables before, during, and after the guideline panel meeting, made suggestions for corrections, and identified missing evidence. To ensure that we did not miss recent studies in preparation for voting on the recommendations, we asked panel members to suggest any studies that may have been published after the most recent systematic review search dates (19 July 2020 for the baseline risk review and 19 August 2020 for review of the anticoagulation-intensity effect) and fulfilled the inclusion criteria for the individual questions (see supplemental Files 6 and 7 for the search strategies per targeted database).

Under the direction of the McMaster University GRADE Centre, researchers followed the general methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (handbook.cochrane.org) and Cochrane guidance for conducting living systematic reviews of intervention effects[49-51,65] (see supplemental Files 8 and 9 for detailed protocols for the reviews of the baseline risk and anticoagulation-intensity effect). For new reviews, risk of bias was assessed at the health outcome level using the Cochrane Collaboration's risk-of-bias tool for randomized trials of interventions, or ROBINS-I for nonrandomized studies of interventions, or the Newcastle-Ottawa Scale for case-control studies with anticoagulation intensity as exposure. In addition to conducting systematic reviews of intervention effects, the researchers searched for evidence related to baseline risks, values, preferences, and costs, and summarized findings within the EtD frameworks.[9,10,52] Subsequently, we assessed the certainty in the body of evidence (also known as quality of the evidence or confidence in the estimated effects) for each effect estimate of the outcomes of interest following the GRADE approach based on the following domains: risk of bias, precision, consistency and magnitude of the estimates of effects, directness of the evidence, risk of publication bias, presence of large effects, dose-response relationship, and an assessment of the effect of residual, opposing confounding. The certainty was categorized into 4 levels ranging from very low to

high.[11,15,48] Within this report, these categories are represented by symbols, as follows:

⊕⊕⊕⊕ High certainty in the evidence about effects

⊕⊕⊕◯ Moderate certainty in the evidence about effects

⊕⊕◯◯ Low certainty in the evidence about effects

⊕◯◯◯ Very low certainty in the evidence about effects

Interested readers may find more explanation about the GRADE approach to assessing and rating certainty in a body of evidence in other publications.[11,15,48]

We conducted new systematic reviews to establish the base recommendation in our first phase. We will use existing systematic reviews to supplement our ongoing living reviews. The panel decided not to use indirect evidence from non–COVID-19 patients for baseline risk or the effects of interventions. However, as we identified no COVID-19–specific evidence for other EtD domains including patients' values and preferences, resource use, acceptability, and feasibility, we used the evidence from the ASH guidelines on management of VTE regarding prophylaxis for hospitalized medical patients for these EtD criteria.[39]

Using weekly conference calls, online communication, and GRADEpro software, the panel developed clinical recommendations based on the evidence summarized in the EtD tables. For each recommendation, the panel took a population perspective and came to consensus on the following: the certainty in the evidence, the balance of benefits and harms of the compared management options, and the assumptions about the values and preferences associated with the decision. The guideline panel also explicitly took into account the extent of resource use associated with alternative management options.

The panel agreed on the recommendations (including direction and strength), remarks, and qualifications by consensus based on the balance of all desirable and undesirable consequences. With regard to arriving at recommendations, panel members reviewed the identified evidence, which was synthesized and provided to them along with the individual studies. Multiple rounds of feedback on this research evidence was sought both electronically and during virtual panel meetings. Anonymous prevoting on individual criteria of the EtD was conducted to identify areas requiring more discussion (eg, understanding a study's intervention effects). In using the EtD frameworks, voting was only to be used if consensus did not emerge on a criterion or for the recommendation and final dissents were to be noted. Because consensus was achieved on all judgments, voting was not necessary and no dissents were registered. The final guidelines, including recommendations, were reviewed and approved by all panel members and all meetings were video-recorded to document the process.

In the living phase, we will update systematic reviews on a monthly basis and, when meeting explicit criteria, conduct new meta-analyses to incorporate changes (see supplemental Files 1 and 9 for details).[48] We will deploy machine learning to facilitate screening the large volume of research evidence and conduct network meta-analysis if possible. We will inform the "living" guideline panel about changes in the evidence and will determine whether the published recommendations will need to be reassessed, according to explicit criteria. These criteria include:

- New information on a critical outcome that previously had no included studies
- Changes to the magnitude of the absolute effect for at least 1 critical outcome
- Changes to the certainty in the evidence for absolute effect for at least 1 critical outcome (eg, from very low/low to moderate/high)
- Potential change in the judgments regarding any other criteria (costs, feasibility, acceptability, equity) that has an important bearing on the recommendation

We will develop the living recommendations using the GRADEpro EtD to make judgments about all evidence, following the same processes we used for our original recommendations. After reassessment of a recommendation, whether the recommendation changes or not, we will highlight in the EtDs when the recommendation was reassessed and the reasons for reassessment, and we will describe the rationale for any changes or the lack of changes.

Interpretation of strong and conditional recommendations

The recommendations are labeled as either "strong" or "conditional" according to the GRADE approach. The words "the guideline panel *recommends*" are used for strong recommendations, and "the guideline panel *suggests*" for conditional recommendations. Table 4 provides GRADE's interpretation of strong and conditional recommendations by patients, clinicians, health care policy makers, and researchers.[38]

Document review

Draft recommendations were reviewed by all members of the panel, revised, and then made available online on 8 October 2020 for external review by stakeholders including allied organizations, other medical professionals, patients, and the public. Two individuals or organizations submitted comments. The document was revised to address pertinent comments, but no changes were made to recommendations. On 26 October 2020, the ASH Guideline Oversight Subcommittee and the ASH Committee on Quality approved that the defined guideline-development process was followed, and on 2 November 2020 the officers of the ASH Executive Committee approved submission of the guidelines for publication under the imprimatur of ASH. The guidelines were then subjected to peer review by *Blood Advances*.

How to use these guidelines

ASH guidelines are primarily intended to help clinicians make decisions about diagnostic and treatment alternatives. Other purposes are to inform policy, education, and advocacy, and to state future research needs. They may also be used by patients. These guidelines are not intended to serve or be construed as a standard of care. Clinicians must make decisions on the basis of the clinical presentation of each individual patient, ideally through a shared process that considers the patient's values and preferences with respect to the anticipated outcomes of the chosen option. Decisions may be constrained by the realities of a specific clinical setting and local resources, including but not limited to institutional policies, time limitations, or availability of treatments. These guidelines may not include all appropriate methods of care for the clinical scenarios described. As science advances and new evidence becomes

available, recommendations may become outdated. Following these guidelines cannot guarantee successful outcomes. ASH does not warrant or guarantee any products described in these guidelines.

Statements about the underlying values and preferences as well as qualifying remarks accompanying each recommendation are its integral parts and serve to facilitate more accurate interpretation. They should never be omitted when quoting or translating recommendations from these guidelines. The use of these guidelines is also facilitated by the links to the EtD frameworks and interactive summary-of-findings tables in each section. The ASH users' guide to recommendations provides additional insights into how to use the recommendations.[66] Guideline users need to be aware that the guideline recommendations may change in the living phase as new evidence becomes available. ASH will publish and alert readers to such updates, but guideline users are responsible for being informed about changes.

Recommendations

Patients with COVID-19–related critical illness

Should direct oral anticoagulants, low-molecular-weight heparin, unfractionated heparin, 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?

Recommendation 1

The ASH guideline panel *suggests* using prophylactic-intensity over intermediate-intensity or 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 ⊕◯◯◯).

Remarks:

- Between the time this recommendation was published online (27 October 2020) and when it was published in *Blood Advances*, a press release (https://www.nih.gov/news-events/news-releases/nih-activ-trial-blood-thinners-pauses-enrollment-critically-ill-covid-19-patients) describing the results of a planned interim analysis of 3 randomized controlled trials, REMAP-CAP, ACTIV-4, and ATTACC (NCT 02735707, 04505774, and 04372589, respectively), was issued. In these trials, therapeutic-intensity anticoagulation was compared with prophylactic-intensity anticoagulation for patients with COVID-19–related critical illness. The ASH guideline panel plans to update this recommendation when the full results of REMAP-CAP, ACTIV-4, and ATTACC become available. Clinicians should weigh the potential benefits and harms based on the most up-to-date available evidence in caring for their patients.
- 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. Examples include patients requiring hemodynamic support, ventilatory support, and renal-replacement therapy.
- An individualized assessment of the patient's risk of thrombosis and bleeding is important when deciding on anticoagulation intensity. Risk-assessment models to estimate thrombotic and bleeding risk in hospitalized patients are available, but they have not been validated for patients with COVID-19. The panel acknowledges that higher-intensity anticoagulation may be preferred for patients judged to be at high thrombotic risk and low bleeding 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, unfractionated heparin, etc) may be based on availability, resources required, familiarity, and the aim of minimizing PPE use or staff exposure to COVID-19–infected patients as well as patient-specific factors (eg, renal function, history of heparin-induced thrombocytopenia, concerns about gastrointestinal tract absorption).
- This recommendation does not apply to patients who require anticoagulation to prevent thrombosis of extracorporeal circuits such as those on ECMO or CRRT.

Summary of the evidence. For all outcomes, we rated the certainty in the evidence as very low owing to serious or very serious risk of bias and imprecision of the estimates (see evidence profile and EtD online at: https://guidelines.ash.gradepro.org/profile/3CQ7J0SWt58). We found no systematic reviews that addressed this question. Altogether, there were 5 observational studies that provided evidence related to this question.[25,67-70] All studies exclusively or largely included patients with laboratory-confirmed COVID-19 who were categorized as critically ill or admitted to the ICU. Supplemental File 10 presents the characteristics of all included studies.

One study reported the effect of therapeutic-intensity anticoagulation on all-cause mortality and major bleeding,[67] 1 study reported the effect of intermediate-intensity anticoagulation on the development of PE,[70] 1 study reported the effect of intermediate-intensity anticoagulation on the development of DVT,[69] and 2 studies reported the effect of therapeutic-intensity anticoagulation on the development of VTE (either DVT or PE).[25,68] No studies reported the effect of therapeutic- or intermediate-intensity anticoagulation on multiple organ failure, severe ischemic stroke, intracranial hemorrhage, invasive ventilation, limb amputation, or ST-elevation myocardial infarction.

Benefits. Therapeutic-intensity anticoagulation may reduce the risk of all-cause mortality but the evidence is very uncertain (adjusted odds ratio [OR], 0.73; 95% confidence interval [CI], 0.33-1.76); this corresponds to 52 fewer (from 143 fewer to 116 more) deaths per 1000 patients (very low certainty).[67] Intermediate-intensity anticoagulation may reduce the risk of PE but the evidence is very uncertain (adjusted OR, 0.09; 95% CI, 0.02-0.57); this corresponds to 88 fewer (from 96 to 40 fewer) PEs per 1000 patients (very low certainty).[70] Intermediate-intensity anticoagulation may reduce the risk of DVT but the evidence is very uncertain (OR, 0.35; 95% CI, 0.06-2.02); this corresponds to 66 fewer (from 99 fewer to 87 more) DVTs per 1000 patients (very low certainty).[69] Studies assessing the effect of

Table 4. Interpretation of strong and conditional recommendations

Implications for	Strong recommendation	Conditional recommendation
Patients	• Most individuals in this situation would want the recommended course of action, and only a small proportion would not	• 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
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	• Recognize that different choices will be appropriate for individual patients and that you 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
Policy makers	• 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	• Policymaking will require substantial debate and involvement of various stakeholders • Performance measures should assess whether decision-making is appropriate
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	• The 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

therapeutic-intensity anticoagulation on VTE found that it may result in a small difference but the evidence is very uncertain (pooled OR, 0.87; 95% CI, 0.45-1.67); this corresponds to 15 fewer (from 67 fewer to 70 more) VTE per 1000 patients (very low certainty).[25,68]

Harms and burden. Therapeutic-intensity anticoagulation may increase the risk of major bleeding but the direct evidence in critically ill COVID-19 patients is uncertain (OR, 3.84; 95% CI, 1.44-10.21); this corresponds to 176 more (from 33 to 400 more) major bleeding events per 1000 patients (very low certainty due to risk of bias and imprecision).[67] However, the panel also considered a plethora of indirect evidence in non–COVID-19 critically ill patients demonstrating a dose-dependent effect of anticoagulation on bleeding risk.[71-74]

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 intermediate-intensity or therapeutic-intensity anticoagulation would be acceptable to patients and health care providers. However, given the very low certainty in the evidence there may be regional variation in the acceptability of higher-intensity anticoagulation, particularly in regions where baseline VTE risk may be lower (eg, Asian populations).[75,76]

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

Conclusions for this recommendation. The panel judged that there was very low–certainty evidence in the desirable and undesirable effects of intermediate-intensity or therapeutic-intensity anticoagulation for patients with COVID-19–related critical illness. There was a suggestion of mortality benefit and reduction in VTE with intermediate-intensity or therapeutic-intensity anticoagulation, but this evidence was of very low certainty.

Meanwhile, there was less uncertainty in the potential undesirable effects of intermediate-intensity or therapeutic-intensity anticoagulation in increasing the risk of major bleeding complications. The panel considered that there was higher-quality indirect evidence from non–COVID-19 critically ill patients for a dose-dependent increase in the risk of major bleeding with anticoagulation, although the magnitude of this effect was uncertain in the COVID-19 population.[71-74] Given that there was very low certainty for benefit to offset the moderate risk of major bleeding complications, the usual practice of prophylactic-intensity anticoagulation, as used in critically ill non–COVID-19 patients, was suggested.[39]

The panel, however, recognized the potential for benefit and noted that an individualized decision is important for each patient based on an assessment of thrombosis and bleeding risk. For patients judged to be at high thrombotic risk and low bleeding risk, panel members acknowledged that higher-intensity anticoagulation could be considered. Dose adjustment of prophylactic-intensity anticoagulation for extremes of body weight or renal impairment may also be considered.[77-81]

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 for patients with COVID-19, this outcome was not prioritized by the guideline panel as part of its systematic review of the evidence.[20]

Patients with COVID-19–related acute illness

Should direct oral anticoagulants, low-molecular-weight heparin, unfractionated heparin, 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?

Recommendation 2

The ASH guideline panel *suggests* using prophylactic-intensity over intermediate-intensity or therapeutic-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 ⊕◯◯◯).

Remarks:

- Between the time this recommendation was published online (27 October 2020) and when it was published in *Blood Advances*, a press release (https://www.nih.gov/news-events/news-releases/full-dose-blood-thinners-decreased-need-life-support-improved-outcome-hospitalized-covid-19-patients) describing the results of a planned interim analysis of 3 randomized controlled trials, REMAP-CAP, ACTIV-4, and ATTACC (NCT 02735707, 04505774, and 04372589, respectively), was issued. In these trials, therapeutic-intensity anticoagulation was compared with prophylactic-intensity anticoagulation for moderately ill hospitalized patients with COVID-19. The ASH guideline panel plans to update this recommendation when the full results of REMAP-CAP, ACTIV-4, and ATTACC become available. Clinicians should weigh the potential benefits and harms based on the most up-to-date available evidence in caring for their patients.
- 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 advanced 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 and bleeding risk in hospitalized patients are available, but they have not been validated for patients with COVID-19. The panel acknowledges that higher-intensity anticoagulation may be preferred for patients judged to be at high thrombotic risk and low bleeding 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, unfractionated heparin, etc) may be based on availability, resources required, familiarity, and the aim of minimizing PPE use or staff exposure to COVID-19–infected patients as well as patient-specific factors (eg, renal function, history of heparin-induced thrombocytopenia, concerns about gastrointestinal tract absorption).

Summary of the evidence. For all outcomes, we rated the certainty in the evidence as very low owing to serious or very serious risk of bias and imprecision of the estimates (see evidence profile and EtD online at: https://guidelines.ash.gradepro.org/profile/phJkOBz3-JEQ). We found no systematic reviews that addressed this question. Altogether, there were 5 observational studies that provided evidence related to this question.[69,70,82-84] Three studies exclusively or largely included patients with laboratory-confirmed COVID-19 who were categorized as severely or moderately ill or hospitalized in a ward other than the ICU. Two studies included patients with laboratory-confirmed COVID-19 who were categorized as critically ill or admitted to the ICU, as no reliable evidence was identified for PE and DVT in acutely ill patients. Supplemental File 11 presents the characteristics of all included studies.

One study reported the effect of therapeutic-intensity anticoagulation on all-cause mortality,[84] 1 study reported the effect of intermediate-intensity anticoagulation on the development of PE in critically ill patients,[70] 1 study reported the effect of intermediate-intensity anticoagulation on the development of DVT in critically ill patients,[69] and 2 studies reported the effect of therapeutic-intensity anticoagulation on major bleeding.[82,83] No studies reported the effect of therapeutic- or intermediate-intensity anticoagulation on multiple organ failure, severe ischemic stroke, intracranial hemorrhage, invasive ventilation, limb amputation, or ST-elevation myocardial infarction.

Benefits. Therapeutic-intensity anticoagulation may reduce the risk of all-cause mortality but the evidence is very uncertain (adjusted OR, 0.86; 95% CI, 0.73-1.02); this corresponds to 19 fewer (from 38 fewer to 3 more) deaths per 1000 patients (very low certainty).[84] Intermediate-intensity anticoagulation may reduce the risk of PE in critically ill patients but the evidence is very uncertain (adjusted OR, 0.09; 95% CI, 0.02-0.57); this corresponds to 15 fewer (from 16 fewer to 7 fewer) PEs per 1000 patients (very low certainty).[70] Intermediate-intensity anticoagulation may reduce the risk of DVT in critically ill patients but the evidence is very uncertain (OR, 0.35; 95% CI, 0.06-2.02); this corresponds to 13 fewer (from 18 fewer to 19 more) DVTs per 1000 patients (very low certainty).[69]

Harms and burden. One cohort study showed that therapeutic-intensity anticoagulation may increase the risk of major bleeding (adjusted hazard ratio, 3.89; 95% CI, 1.90-7.97),[83] and 1 matched case-control study reported a higher use of therapeutic-intensity anticoagulation in the groups with upper gastrointestinal bleeding (OR, 1.84; 95% CI, 0.49-6.98) and lower gastrointestinal bleeding (OR, 1.42; 95% CI, 0.14-15.02),[82] but the evidence from both studies was very uncertain. Taking the range of point estimates, this translates into 7 to 46 more major bleeding events per 1000 patients (very low certainty due to risk of bias and imprecision). However, the panel also considered a plethora of indirect evidence in non–COVID-19 acutely ill patients demonstrating a dose-dependent effect of anticoagulation on bleeding risk.[71-74]

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 intermediate-intensity or therapeutic-intensity anticoagulation would be acceptable to patients and health care providers. However, given the very low certainty in the evidence, there may be regional variation in the acceptability of higher-dose anticoagulation, particularly in regions where baseline VTE risk may be lower (eg, Asian populations).[75,76]

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

Conclusions for this recommendation. The panel judged that there was very low–certainty evidence in the desirable and undesirable effects of intermediate-intensity or therapeutic-intensity

anticoagulation for patients with COVID-19–related acute illness. The baseline risk of mortality, VTE, and major bleeding for patients with COVID-19–related acute illness receiving prophylactic-intensity anticoagulation was relatively low, leading to small absolute-risk differences for patients receiving intermediate-intensity or therapeutic-intensity compared with those receiving prophylactic-intensity anticoagulation.

There was a suggestion of mortality benefit and reduction in VTE with intermediate-intensity or therapeutic-intensity anticoagulation, but this evidence was of very low certainty. Meanwhile, there was less uncertainty in the potential undesirable effects of intermediate-intensity or therapeutic-intensity anticoagulation in increasing the risk of major bleeding complications. The panel considered that there was higher-quality indirect evidence from non–COVID-19 acutely ill patients for a dose-dependent increase in the risk of major bleeding with anticoagulation, although the magnitude of this effect was uncertain in the COVID-19 population.[71-74] Given that there was very low certainty for benefit to offset the moderate risk of major bleeding complications, the usual practice of prophylactic-intensity anticoagulation in acutely ill non–COVID-19 patients was suggested.[39]

The panel, however, recognized the potential for benefit and noted that an individualized decision is important for each patient based on an assessment of thrombosis and bleeding risk. Risk-assessment models have been developed for hospitalized patients without COVID-19 for estimation of thrombosis and bleeding risk, but these models have not been validated in the hospitalized COVID-19 population.[40,44,45] For patients judged to be at high thrombotic risk with low bleeding risk, panel members acknowledged that higher-intensity anticoagulation could be considered. Dose adjustment of prophylactic-intensity anticoagulation for extremes of body weight or renal impairment may also be considered.

What are others saying and what is new in these guidelines?

There are several recently published guidance documents that focus primarily on the use of anticoagulation for patients with COVID-19. These include the 2020 CHEST COVID-19 Guidelines, the Anticoagulation (AC) Forum interim clinical guidance, the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee (SSC) COVID-19 clinical guidance, and the American College of Cardiology (ACC) clinical guidance.[85-88] Major differences between the current ASH guidelines and these other documents include use of high-quality systematic reviews and EtD frameworks, which increase transparency, along with use of marker states to estimate the relative importance to patients as key outcomes of treatment. In addition, although the current ASH guidelines focused on only 2 clinical questions, the other 4 guidelines were broader in the clinical questions that were addressed.

The CHEST guidelines are similar to the current ASH guidelines in that they recommend standard prophylactic-intensity anticoagulation over higher-intensity for both acutely ill and critically ill patients with COVID-19. However, although the current ASH guidelines do not suggest 1 specific anticoagulant over another due to lack of direct evidence, the CHEST guidelines favor low-molecular-weight heparin over unfractionated heparin in order to limit staff exposure to patients with COVID-19 (although the ASH panel acknowledges the importance of limiting staff exposure when selecting an anticoagulant). The CHEST guidelines also caution against the use of direct oral anticoagulants for patients hospitalized with COVID-19 due to concerns about possible drug interactions with other adjunctive therapies, and the risk of rapid clinical deterioration, which may impact on bleeding risk. The CHEST guidelines also explicitly recommend against the routine use of systemic thrombolysis for patients with COVID-19 who develop PE without hemodynamic compromise.[89] The current ASH guideline does not address the question of systemic thrombolysis in this context, nor was this question prioritized by the guideline panel. Other areas addressed by the CHEST guidelines that were not specifically addressed by the ASH guideline panel include postdischarge thromboprophylaxis and the role of screening ultrasound in asymptomatic patients with COVID-19.

The AC Forum interim clinical guidance recommends that acutely ill patients receive standard prophylactic-intensity anticoagulation, with dose adjustments according to the patient's age and renal function. However, in contrast to the current ASH COVID-19 guideline, the AC Forum suggests that critically ill patients should receive increased doses of VTE prophylaxis (intermediate-intensity) based largely on expert opinion, along with extrapolation from indirect evidence for efficacy and safety of such regimens in bariatric surgery, trauma, and influenza-related critical illness.[90-92] The AC Forum document includes suggestions on thromboprophylaxis in the setting of pregnancy, monitoring strategies for parenteral anticoagulation therapy, and thrombolytic therapy for acute respiratory distress syndrome. The AC Forum also recommends against serial monitoring of D-dimers, and recommends against intensification of anticoagulant dosing based on D-dimer concentration. The D-dimer as a prognostic factor for thrombotic risk and mortality is not addressed in the present ASH guideline.

The ISTH-SSC interim guidance in hospitalized patients with COVID-19 also suggests that acutely ill and critically ill patients should receive standard prophylaxis doses of low-molecular-weight heparin or unfractionated heparin, although intermediate-intensity low-molecular-weight heparin may be considered for patients judged to be at high VTE risk. The ISTH-SSC also explicitly suggests against the use of therapeutic-intensity anticoagulation until data are available from randomized trials that are currently being conducted. In addition, the ISTH-SSC document also suggests that multimodal thromboprophylaxis, including mechanical methods (ie, intermittent pneumatic compression), should be considered in conjunction with anticoagulation therapy in critically ill patients with COVID-19. This is notable as current guidelines in critically ill non–COVID-19 patients suggest using pharmacological prophylaxis alone over combined pharmacological and mechanical prophylaxis, which is also reflected in a recent large randomized trial.[39,93] These differences speak to the urgent need for more high-quality data on baseline thrombosis risk in COVID-19–related critical illness.

Finally, the ACC guidance document also suggests that hospitalized patients with COVID-19 should receive prophylactic-intensity anticoagulation. This recommendation applies to patients who do not have disseminated intravascular coagulation (DIC), and to those with DIC who do not have evidence of bleeding. The current ASH guidelines do not make recommendations based on specific thrombotic or bleeding risk factors such as DIC, as it remains unclear whether these factors are predictive of clinical outcomes in COVID-19. Although early observational studies were suggestive of clinical benefit

when heparin was given to patients with COVID-19 who had an elevated D-dimer or sepsis-induced coagulopathy,[94] there remain no high-quality randomized data addressing this question. The ACC document also contains recommendations on management of COVID-19 and acute coronary syndrome and post-discharge thromboprophylaxis, which are not addressed in the current ASH guideline.

Limitations of these guidelines

The limitations of these guidelines are inherent in the very low–certainty in the evidence we identified for the research questions. In addition, there were several outcomes that were identified as critical for decision-making by the guideline panel for which no direct evidence was available. This limited the breadth of outcomes that were available to panel members to inform their judgments and recommendations. These outcomes included multiple organ failure, ischemic stroke, intracranial hemorrhage, invasive mechanical ventilation, limb amputation, ICU hospitalization (duration), and ST-elevation myocardial infarction.

Revision or adaptation of the guidelines

Plans for updating these guidelines

After publication of these guidelines, ASH will maintain them through surveillance for new evidence, ongoing review by experts, and regular revisions. These recommendations will be updated based on a living review of evolving evidence, including data from randomized trials that have recently been published[95] or are actively recruiting patients at the time of this manuscript. Systematic reviews will be updated on a monthly basis, and new meta-analyses will be conducted when explicit criteria are met. The living guideline panel will be informed about whether published recommendations should be reassessed based on changes that occur in the balance of benefits and harms, the quality of evidence available, or other factors (eg, costs, feasibility, acceptability, equity) (supplemental File 1). These living recommendations will be developed using the GRADEpro EtD to make judgments on the evidence.

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.[13]

Priorities for research

On the basis of gaps in evidence identified during the guideline-development process, the panel identified the following urgent research priorities in this patient population:

- studies assessing baseline VTE risk in critically ill and acutely ill patients on prophylactic-intensity anticoagulation therapy;
- randomized controlled trials comparing anticoagulation at differing intensities (prophylactic vs intermediate vs therapeutic);
- studies examining the impact of nonanticoagulant interventions (eg, anticomplement therapy, corticosteroids, antiviral therapies, anticytokine therapies, antiplatelet therapies, monoclonal antibody therapy, convalescent plasma) on thrombotic risk;
- development or validation of risk-assessment models for thrombosis and bleeding for patients with COVID-19–related critical illness and acute illness;
- studies examining the impact of anticoagulant therapy on thrombosis and bleeding outcomes for patients of differing race/ethnicity;
- studies examining the impact of anticoagulant therapy on thrombosis and bleeding outcomes in pediatric and pregnant patients; and
- studies comparing mortality, thrombosis, bleeding, and functional outcomes with different available anticoagulant agents.

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Authorship

Contribution: E.K.T., R.N., A.C., R.A.M., and H.J.S. wrote the manuscript, and all other authors contributed to critical revisions of the manuscript; members of the knowledge synthesis team (R.N., I.B.A., M.B., R.B.-P., R.C., M.C., K. Dearness, A.J.D., P.K., L.E.C.-L., R.M., G.P.M., R.Z.M., A.N., T.P., Y.Q., Y.R., F.S., A.S., K.S., M.V., and W.W.) searched the literature, extracted data from eligible studies, analyzed the data, and prepared evidence summaries and EtD tables; panel members (A.C., E.K.T., P.A., C.B., K. Dane, J.D., M.T.D., D.D., D.O.G., S.R.K., F.A.K., A.I.L., I.N., A.P., M.P., M.R., K.M.S., D.S., M.S., K.T., R.A.M., and H.J.S.) 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. Dearness, 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; A.C., R.A.M., and H.J.S. were the co-chairs of the panel and led panel meetings; and all authors approved of the content.

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