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RECOMMENDATIONS AND GUIDELINES

ISTH guidelines for antithrombotic treatment in COVID-19

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Abstract

Antithrombotic agents reduce risk of thromboembolism in severely ill patients. Patients with coronavirus disease 2019 (COVID-19) may realize additional benefits from heparins. Optimal dosing and timing of these treatments and benefits of other antithrombotic agents remain unclear. In October 2021, ISTH assembled an international panel of content experts, patient representatives, and a methodologist to

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develop recommendations on anticoagulants and antiplatelet agents for patients with COVID-19 in different clinical settings. We used the American College of Cardiology Foundation/American Heart Association methodology to assess level of evidence (LOE) and class of recommendation (COR). Only recommendations with LOE A or B were included. Panelists agreed on 12 recommendations: three for non-hospitalized, five for non–critically ill hospitalized, three for critically ill hospitalized, and one for post-discharge patients. Two recommendations were based on high-quality evidence, the remainder on moderate-quality evidence. Among non–critically ill patients hospitalized for COVID-19, the panel gave a strong recommendation (a) for use of prophylactic dose of low molecular weight heparin or unfractionated heparin (LMWH/UFH) (COR 1); (b) for select patients in this group, use of therapeutic dose LMWH/UFH in preference to prophylactic dose (COR 1); but (c) against the addition of an antiplatelet agent (COR 3). Weak recommendations favored (a) sulodexide in non-hospitalized patients, (b) adding an antiplatelet agent to prophylactic LMWH/UFH in select critically ill, and (c) prophylactic rivaroxaban for select patients after discharge (all COR 2b). Recommendations in this guideline are based on high-/moderate-quality evidence available through March 2022. Focused updates will incorporate future evidence supporting changes to these recommendations.

KEYWORDS
anticoagulants, COVID-19, critical illness, platelet aggregation inhibitors

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization on March 11, 2020.[1] The pandemic has since progressed through several waves, each with distinct transmission and virulence characteristics that have been driven in large part by the severe acute respiratory coronavirus 2 (SARS-CoV-2) variant, the availability of COVID-19 testing, and the extent of vaccination coverage in different populations. The pandemic continues to be fueled by reinfections, new variants, or subvariants of SARS-CoV-2 against which vaccines are less effective, and waning immunity from previous vaccination and infection. In many countries vaccination rates are very low. Taken together, these ongoing challenges point to the urgent need for clinical practice guidelines that inform on evidence-based management for COVID-19 patients in diverse clinical settings.

Numerous randomized controlled trials (RCTs) of various antithrombotic treatment regimens for patients with COVID-19 have been conducted and published within a relatively short time span. Based on this growing body of evidence, ISTH prioritized the transition of its previously published guidance documents[2,3] into a formal practice guideline using evidence from RCTs and well-designed observational studies with strong methodology.

To date, most RCTs and observational studies published have recruited patients during the first waves with the initial variants of SARS-CoV-2, and before vaccination was widely available. It is for this reason that future studies of antithrombotic treatment among patients with COVID-19 conducted during subsequent phases of the pandemic may yield different results than earlier ones that are synthesized in this guideline. Accordingly, planning for this guideline included strategies to facilitate the rapid development of focused updates as new evidence becomes available. The guideline focused on treatment questions for which high-quality evidence was available; questions for which limited or low quality level of evidence was available are addressed in the accompanying ISTH COVID-19 Antithrombotic Good Practice Statements.[4]

The targeted audience for this guideline includes clinicians in internal medicine, intensive care, infectious disease, hematology, and vascular medicine, as well as hospitalists, family practitioners, and other health-care providers who deliver inpatient or outpatient care to patients with COVID-19 or a COVID-19 diagnosis.

2 | METHODS

This guideline was developed using methods recommended by the American College of Cardiology Foundation and the American Heart Association (ACCF/AHA).[5,6]

2.1 | Panel selection and management of conflicts of interest

ISTH empaneled 13 clinicians with outstanding knowledge of antithrombotic therapy as well as two patient representatives. The

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guideline chairman extended invitations to potential panelists, who completed disclosures prior to being seated on the panel. Disclosures included information on relationships with industry and other potential conflicts of interest. Panelists were assigned to one of three working groups that correspond to the patient categories and care settings covered in this guideline: critically ill patients, non–critically ill patients, and outpatients (non-hospitalized and post-discharge). Critically ill and non–critically ill patients were defined based on criteria in each study. Please see evidence tables for more information on these definitions. Although definitions for levels of illness will vary among countries, health-care systems, stages of the COVID-19 pandemic, and so on, in general, patients not requiring mechanical ventilation or organ support other than low-flow supplemental oxygen are considered non–critically ill. Critical illness due to COVID-19 signifies a life-threatening condition requiring immediate organ support, such as invasive or non-invasive positive pressure ventilation, high-flow supplemental oxygen therapy, vasopressor or inotrope support, extracorporeal membrane oxygenation, or continuous renal replacement therapy, irrespective of patient location within a hospital.

The different dose levels of anticoagulants, that is, prophylactic, intermediate, or therapeutic, are described in Table 1.

2.2 | Search strategy and deployment

With input from the guideline panel, an experienced medical librarian drafted search algorithms (PubMed, Cochrane, EMBASE) for each of the 16 recommendations that were initially proposed for the guideline (see Appendix S1 in supporting information). Searches were executed in each database and de-duplicated files containing citations and abstracts were generated for each potential recommendation.

2.3 | Abstract review and identification of included studies

Results files for each search were loaded into Abstrackr, an online abstract review platform.[7] Abstracts were screened by two reviewers against a set of pre-specified criteria:

1. Date range: January 1, 2020–December 17, 2021
2. Human subjects aged 18+
3. Established COVID-19 diagnosis
4. Study designs: RCTs, prospective/retrospective cohort studies
5. Minimum follow-up: ≥7 days
6. RCT minimum sample size ≥100
7. Observational study minimum sample size ≥400

Conflicts that arose during abstract review were adjudicated by the guideline methodologist. Once potentially relevant studies were identified, full-text copies were provided to the appropriate working group for review. Each working group then proposed a set of included studies to the panel for discussion and approval. In some cases, included papers were relevant to more than one recommendation. Included papers and other guideline materials were maintained in shared, cloud-based files. Searches were rerun on March 6, 2022 to ensure that all relevant studies were incorporated into the recommendations immediately prior to submission for publication. A preprint of an RCT that was published on March 22, 2022 was available to the panel and included in the evidence base for this guideline.

2.4 | Assessment of bias and the strength and quality of evidence

Evidence tables were developed for each recommendation with data that described prespecified study characteristics and outcomes from included studies (Appendix S1). These tables contain information on potential biases for each included study, and panelists used this information in their assessment of available evidence for each recommendation. In addition to assessing biases recommended by Cochrane,[8] additional potential biases related to the COVID-19 pandemic were examined. These included, for example, if institutional anticoagulation protocols were introduced during a study's data collection period and when a study was conducted in relation to circulating COVID-19 variants and the availability of COVID-19 vaccine.

Panelists assessed the strength and quality of evidence for each recommendation using ACCF/AHA methods (Figure 1).[6] The class of recommendation (COR) indicates whether and to what degree panelists determined that available evidence reflects benefits or harms associated with a particular treatment; the level of evidence (LOE) reflects panelists' assessment of the quality of the studies that inform the recommendation, with RCTs providing higher quality evidence than observational studies. This guideline focuses on

TABLE 1 Dose levels of the anticoagulants used in the studies cited in the guideline

Drug	Prophylactic	Intermediate	Therapeutic
UFH	5000 U SQ BID or TID	7500 U SQ BID or TID	Intravenous, adjusted to APTT or anti-Xa
LMWH	Enoxaparin 40 mg SQ QD, dalteparin 5000 IU SQ QD, tinzaparin 4500 IU SQ QD, bemiparin 3500 IU SQ QD	Enoxaparin 40 mg SQ BID or 80 mg SQ QD, or 0.5 mg/kg SQ QD	Enoxaparin 1 mg/kg SQ BID, dalteparin 200 IU/kg SQ QD, tinzaparin 175 IU/kg SQ QD, bemiparin 115 IU/kg SQ QD
DOAC	Rivaroxaban 10 mg PO QD, apixaban 2.5 mg PO BID	Not applicable	Rivaroxaban 20 mg PO QD, apixaban 5 mg PO BID

Abbreviations: APTT, activated partial thromboplastin time; BID, twice daily; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; PO, orally; QD, once daily; SQ, subcutaneous; TID, three times daily; UFH, unfractionated heparin.

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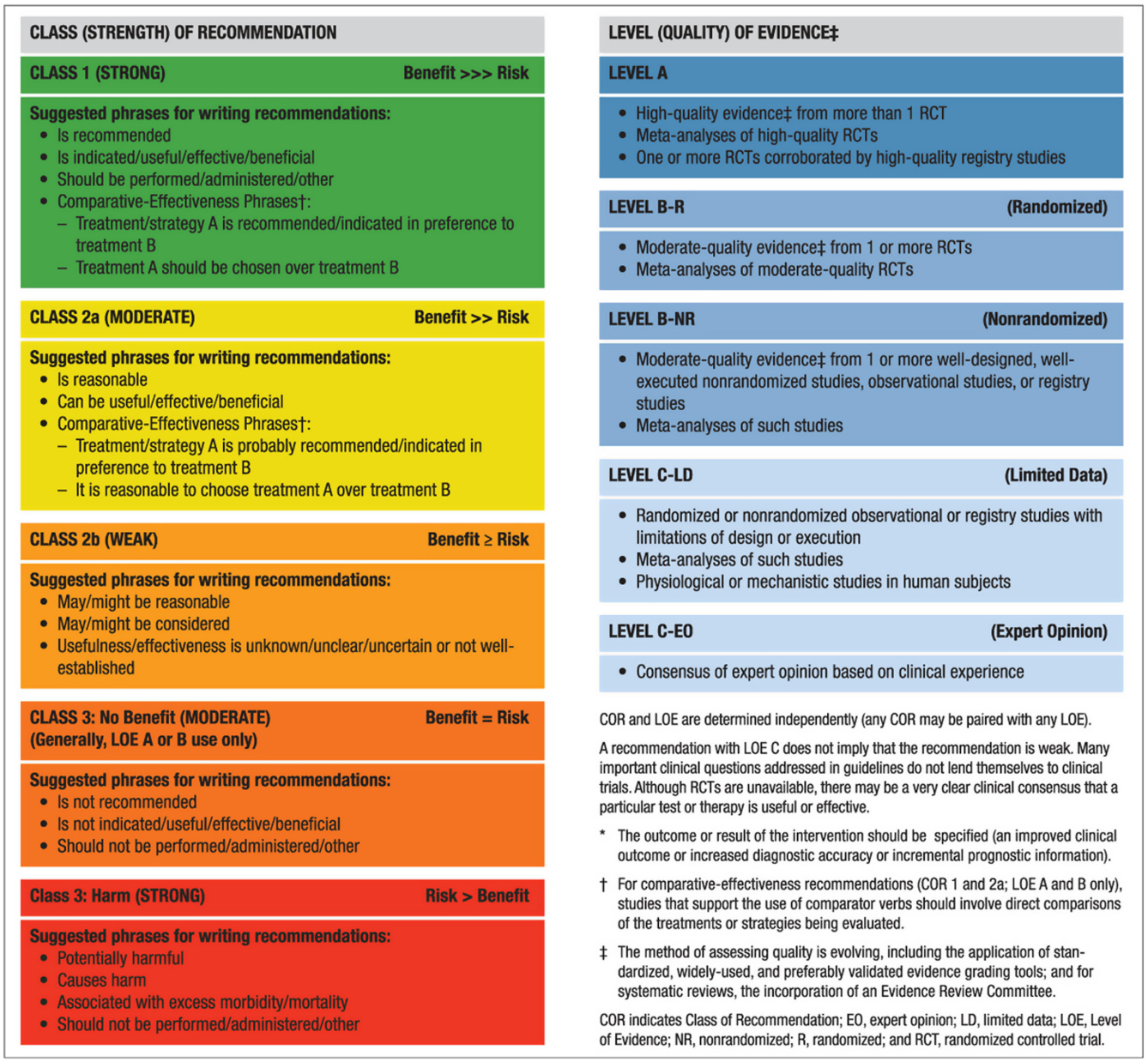

FIGURE 1 Classification of recommendations and level of evidence. Reprinted with permission, Stroke.2021;52:e364-e467 ©2021 American Heart Association, Inc.[60]

recommendations with LOE levels A and B. It presents three recommendations for non-hospitalized patients with COVID-19; five recommendations for hospitalized, non–critically ill patients; three recommendations for hospitalized, critically ill patients; and one recommendation for post-discharge patients.

2.5 | Debate and voting

Working groups drafted initial recommendations that were presented to the full panel in a series of meetings in February and March 2022. Discussions were directed toward establishing consensus among panelists and ensuring that the ACCF/AHA framework was applied uniformly for all recommendations. Voting was conducted for each recommendation based on methods outlined by ACCF/AHA, including appropriate recusals. Repeat voting after revision aimed at reaching consensus. Intellectual conflict of interest was not an exclusion criterion for voting. Recommendations were approved by 93%–100% of panel members, with 51% defined as the threshold for approval. The panel met again to approve responses to the reviewers selected by the journal editor, to hold a final round of voting for these recommendations to ensure the guideline methodology remained robust.

2.6 | Public review and comment

This document was posted on the website of ISTH and of other organizations for different stakeholders, including patients, for

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2 weeks during which public review and comment were invited. All comments were reviewed by the guideline chairman and, if needed, by the appropriate working group. Supportive text was amended as required in response to the public comment period.

3 | TREATMENT RECOMMENDATIONS

3.1 | Antithrombotic therapy for non-hospitalized patients (Table 2)

3.1.1 | Synopsis

In this section of the guideline, the term "non-hospitalized" refers to adults with COVID-19 who reside in the community and have no history of hospitalization for COVID-19. Studies that support recommendations in this section examined treatments that these patients received in relation to outcomes such as subsequent hospitalization and mortality. The traditional outcome in studies on anticoagulants—venous or arterial thromboembolic events—is rare in non-hospitalized patients.[13] One RCT and two cohort studies on antiplatelet agents and oral anticoagulants did not demonstrate any benefit of prescribing these agents after diagnosis of COVID-19.[9–11] A single study that used a randomized control design, showed that the glycosaminoglycan oral drug sulodexide may reduce risk of hospitalization and possibly also the need for oxygen supplementation.[12] These results need to be confirmed in future studies.

TABLE 2 Recommendations for antithrombotic therapy for non-hospitalized patients

COR	LOE	
3: No Benefit	B-R	1. In non-hospitalized patients with symptomatic COVID-19, initiation of antiplatelet therapy is not effective to reduce risk of hospitalization, arterial or venous thrombosis, or mortality.[9]
3: No Benefit	B-R	2. In non-hospitalized patients with symptomatic COVID-19, initiation of direct oral anticoagulant (DOAC) therapy is not effective to reduce risk of hospitalization, arterial or venous thrombosis, or mortality.[9–11]
2b	B-R	3. In non-hospitalized patients with COVID-19 at higher risk of disease progression, initiation of oral sulodexide therapy within 3 days of symptom onset may be considered to reduce risk of hospitalization.[12]

Note: Evidence from referenced studies that support recommendations are summarized in Evidence Tables S10 and S11 in supporting information.

Abbreviations: COR, class of recommendation; COVID-19, coronavirus disease 2019; DOAC, direct oral anticoagulant; LOE, level of evidence.

3.1.2 | Recommendation-specific supportive text

1. A placebo-controlled trial of non-hospitalized, non-pregnant patients with COVID-19 aged 40 to 80 at low risk of bleeding who were randomized to 81 mg of aspirin daily or placebo showed lack of benefit for aspirin treatment.[9] The composite primary outcome included all-cause mortality, symptomatic thrombosis, or hospitalization for cardiovascular or pulmonary cause. The trial was terminated early due to low event rates and small increases in both minor and clinically relevant non-major bleeding (CRNMB)[9,14] in the aspirin arm. A large cohort study of outpatients with COVID-19 compared those who were prescribed aspirin for cardiovascular disease to those who were not, and showed decreased risk of all-cause mortality both in- and out of the hospital among those on aspirin.[15] The study did not adjust for inpatient treatments, nor did it report bleeding events. Another population-based, outpatient cohort study found a small increase in mortality among those on pre-existing anti-platelet therapy. However, there was no adjustment for in-hospital treatments or adjustment for antithrombotic regimen modification.[16] Although current data do not support initiation of aspirin therapy among outpatients with COVID-19,[9] there is also no clear evidence supporting cessation of aspirin in outpatients with COVID-19 and a prior cardiovascular indication for antiplatelet therapy.
2. A placebo-controlled trial that randomized non-hospitalized, non-pregnant patients with COVID-19 aged 40 to 80 at low risk of bleeding to 2.5 mg or 5 mg of apixaban twice daily showed lack of benefit for both doses of apixaban.[9] The composite primary outcome included all-cause mortality, symptomatic thrombosis, or hospitalization for cardiovascular or pulmonary cause. The trial was terminated early due to low event rates and small increases in minor and CRNMB.[14] A large cohort study of outpatients aged 65 and older showed that oral anticoagulation at the time of positive SARS-CoV-2 test was associated with reduced mortality risk or hospitalization among men.[17] Two large cohort studies of outpatients with cardiovascular disease, who were mostly on direct oral anticoagulants (DOACs), did not show reduced risk of hospitalization, death, or thrombosis.[10,11] However, in the larger of the two studies, no minimum exposure to outpatient oral anticoagulation was required, nor was there adjustment for in-hospital treatments.[10] A population-based outpatient cohort study found a small increase in mortality risk among those on pre-existing oral anticoagulation, but there was no adjustment for in-hospital treatments or antithrombotic regimen modification.[16]Another cohort study that evaluated a similar outpatient population demonstrated decreased hospitalization risk in the small subset of patients that was on anticoagulation for a cardiovascular indication prior to hospitalization.[18] Only one cohort study reported bleeding events, showing an infrequent, but statistically significantly increased risk of bleeding in anticoagulated patients.[10,11,16–18] Although current evidence does not support initiation of DOACs among outpatients with COVID-19, there is also no evidence to support cessation of DOACs in outpatients with COVID-19 and a prior cardiovascular indication for oral anticoagulation.[18]

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3. In a single-center placebo-controlled trial, 243 non-hospitalized, non-pregnant patients aged 40 and older with COVID-19 were randomized to oral sulodexide 500 lipase-releasing units twice daily or placebo.[12] Sulodexide is a compound of two glycosaminoglycans, a fast-moving heparin fraction (80%) and dermatan sulfate (20%) that is used in parts of Europe, South America, and Asia but does not have regulatory approval in other countries. Patients were included in this trial if they were at higher risk of COVID-19 progression, as defined by the COVID-19 Health Complications (C19HC) calculator, which takes age, body mass index, smoking status, and chronic comorbidities into consideration.[19] The study medication was started within 3 days from onset of symptoms and continued for 21 days. The trial showed a statistically significant decrease in risk of hospitalization with an absolute risk reduction (ARR) of 11.7%, a borderline significant reduction in oxygen supplementation, a non-significant decrease in all-cause mortality, and no indication of harm associated with treatment. The trial did not demonstrate decreased risk of thrombotic events. Overall, the trial supports the effectiveness and safety of sulodexide in outpatients with COVID-19.[12]

3.2 | Antithrombotic therapy for non–critically ill, hospitalized patients (Table 3)

3.2.1 | Synopsis

In this and the following section, data were examined for "non-critically ill" and "critically ill" patients as defined by the selection criteria in each included study (see "Study Characteristics" in the accompanying evidence tables). The variability across studies in these definitions was considered by panelists during the evidence review. Seven observational studies in non–critically ill patients hospitalized for COVID-19 demonstrated reduced mortality risk with prophylactic dose low molecular weight heparin or unfractionated heparin (LMWH/UFH) compared to no prophylaxis.[20–26] Despite these consistent findings, the potential for bias and residual confounding in observational studies led the panel to use the term "possibly" when describing reduced mortality risk in recommendation #4. None of the studies ascertained thromboembolism, but in view of the high risk of thromboembolism in this population and a wealth of indirect data from well-designed trials, the panel recommended using these agents to reduce the thromboembolism risk. However, for patients with a low risk of bleeding and with indicators—which varied across studies—of increased risk of adverse events, therapeutic dose LMWH/UFH was more effective than lower doses of LMWH/UFH to reduce the thromboembolism and end-organ failure risk.[27–30] Conversely, intermediate dose LMWH/UFH,[20,31–34] or therapeutic dose of a DOAC[37] did not appear to provide any benefit compared to prophylactic dose LMWH/UFH, and addition of an antiplatelet agent to LMWH/UFH increased risk of major bleeding without any countervailing benefits.[35,36]

[Correction added on 11th September 2022, after first online publication: Sequencing of the list within the body of the article is corrected to align with the numbering used in the tables.]

TABLE 3 Recommendations for antithrombotic therapy for non–critically ill, hospitalized patients

COR	LOE	
1	B-NR	4. In non-critically ill patients hospitalized for COVID-19, low (prophylactic) dose LMWH or UFH is recommended in preference to no LMWH or UFH to reduce risk of thromboembolism and possibly death.[20–26]
1	A	5. In select non-critically ill patients hospitalized for COVID-19, therapeutic-dose LMWH or UFH is beneficial in preference to low (prophylactic) or intermediate dose LMWH or UFH to reduce risk of thromboembolism and end organ failure.[27–30]
3: No Benefit	B-R	6. In non-critically ill patients hospitalized for COVID-19, intermediate-dose LMWH or UFH is not recommended in preference to low (prophylactic) dose LMWH or UFH to reduce risk of thromboembolism and other adverse outcomes.[20,31–34]
3: Harm	A	7. In non-critically ill patients hospitalized for COVID-19, add-on treatment with an antiplatelet agent is potentially harmful and should not be used.[35,36]
3: No Benefit	B-R	8. In non-critically ill patients hospitalized for COVID-19, therapeutic-dose DOAC is not effective to reduce risk of thromboembolism and other adverse outcomes.[37]

Note: Evidence from referenced studies that support recommendations are summarized in Evidence Tables S1–S5 in supporting information.

Abbreviations: COR, class of recommendation; COVID-19, coronavirus disease 2019; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; LOE, level of evidence; UFH, unfractionated heparin.

3.2.2 | Recommendation-specific supportive text

4. Seven observational studies revealed that among patients hospitalized for COVID-19, low (prophylactic) dose LMWH/UFH compared to no LMWH/UFH reduced mortality by 24% to 82%,[20,22–26,38] and one observational study showed an ARR of 11.4% in thromboembolic events or mortality with prophylactic heparin over no anticoagulation.[21] There was no significant increase in bleeding events in these studies. The risk of bias in these observational studies was generally low, with the possible exception for performance biases. Risk of venous thromboembolism (VTE) in non–critically ill patients hospitalized for COVID-19 is approximately 3-fold higher overall than among medically ill patients who were hospitalized in the pre-COVID era with acute infection or pneumonia.[21,39] Indirect evidence from RCTs reveals that LMWH-based thromboprophylaxis is beneficial over no thromboprophylaxis in hospitalized medically ill patients, including those with acute infection.[40,41] Due to acute infection, immobilization, respiratory failure, and elevated

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D-dimer, patients who are hospitalized for COVID-19 score sufficiently high on commonly used risk assessment models, to qualify as at a high risk for VTE and therefore to warrant thromboprophylaxis.[42–44]

5. Three randomized trials demonstrated benefits of therapeutic-dose LMWH/UFH over low- to intermediate-dose heparins in non–critically ill, non-pregnant patients hospitalized for COVID-19.[27–29] A large multiplatform trial ($N = 2219$) revealed an increase in organ support–free days (days alive and free of intensive care unit (ICU)-based respiratory or cardiovascular organ support),[29] and another RCT revealed an ARR of 13.2% in major thromboembolism and mortality with therapeutic-dose LMWH or UFH over low- to intermediate-dose LMWH or UFH in non–critically ill patient groups.[28] A third RCT did not find a significant difference in the primary outcome but revealed an ARR of 5.8% in all-cause mortality as a secondary outcome with therapeutic LMWH/UFH over prophylactic LMWH/UFH.[27] A meta-analysis of four RCTs showed an ARR of 1.2% in major thromboembolism with therapeutic LMWH/UFH over up to intermediate-dose LMWH/UFH without a statistically significant increase in major bleeding.[30] Patients with low bleed risk criteria were selected across trials, and selection criteria for two of the trials specified patients with elevated D-dimer and increased oxygen requirements.[27,28] Therefore, in patients at low risk of bleeding and with risk factors for thromboembolism or organ failure, such as elevated D-dimer or increased oxygen requirements, therapeutic dose LMWH/UFH should be considered.
6. One small, randomized trial with important methodological limitations, including small sample size and a large number of protocol violations, compared intermediate dose LMWH/UFH versus standard dose LMWH/UFH in non–critically ill patients hospitalized for COVID-19 and showed no difference in need for mechanical ventilation or all-cause mortality.[33] Four observational studies yielded inconsistent results concerning the benefits of intermediate dose LMWH/UFH over low (prophylactic) dose LMWH/UFH.[20,31,32,34]
7. Two RCTs (including the large RECOVERY trial, $N = 14892$)[36] revealed no mortality benefit of antiplatelet therapy (including aspirin and P2Y12 inhibitors) as add-on therapy among non–critically ill patients hospitalized for COVID-19.[35,36] These trials also indicated evidence of harm with increased major bleeding events in patients on antiplatelet therapy. In one trial the use of study antiplatelet therapy was given on top of therapeutic-dose heparin.[35,36] However, among patients who are already on antiplatelet therapy with clear indications, good clinical practice suggests continuation of antiplatelet therapy if a patient is hospitalized for COVID-19.[4]

   (One panel member voted for COR 3: No Benefit.)
8. One moderate-size RCT of patients hospitalized for COVID-19 showed no benefit of the DOAC rivaroxaban at a therapeutic dose, 20 mg daily, neither during hospitalization nor post-discharge, over inpatient low (prophylactic) dose LMWH or UFH.[37] For patients hospitalized for COVID-19 and already on a DOAC for clear indications, good clinical practice suggests to continue DOAC therapy or, if clinically unstable, to be switched to a parenteral anticoagulant (LMWH or UFH).[4]

3.3 | Antithrombotic therapy for critically ill, hospitalized patients (Table 4)

Note that the recommendation does not apply to patients who otherwise have a clinical indication for therapeutic anticoagulation.

3.3.1 | Synopsis

For a description of the term "critically ill," see the previous Synopsis. Use of prophylactic dose LMWH/UFH to prevent VTE in critically ill patients without active or high risk of bleeding is well established and recommended.[51,52] In the setting of COVID-19, available evidence included only cohort studies with low-quality evidence for the comparison of prophylactic dose LMWH/UFH versus control in critically ill patients. As a result, the panel refrained from making a recommendation regarding this regimen. Two RCTs in critically ill patients hospitalized for COVID-19 failed to show any benefit of intermediate dose LMWH/UFH versus prophylactic dose.[46,47] Two RCTs did not show any benefit of therapeutic dose LMWH/UFH versus lower doses to reduce mortality or need for organ support.[28,48] In these trials, there were inconsistent results regarding reduction of thromboembolic events and a potential risk of increased major bleeding, despite exclusion of patients at high risk of bleeding, which led the panel to not recommend therapeutic dose of these agents.

TABLE 4 Recommendations for antithrombotic therapy for critically ill, hospitalized patients

COR	LOE	
3: No Benefit	B-R	9. In critically ill patients hospitalized for COVID-19, intermediate dose LMWH/UFH is not recommended over prophylactic dose LMWH/UFH to reduce risk of adverse events, including mortality and thromboembolism.[45–47]
3: No Benefit	B-R	10. In critically ill patients hospitalized for COVID-19, therapeutic dose LMWH/UFH is not recommended over usual-care or prophylactic dose LMWH/UFHs.[28,48,49]*
2b	B-R	11. In select critically ill patients hospitalized for COVID-19, add on treatment with an antiplatelet agent to prophylactic dose LMWH/UFH is not well established but might be considered to reduce mortality.[36,50]

Note: Evidence from referenced studies that support recommendations are summarized in Evidence Tables S7, S8 and S9b in supporting information.

Abbreviations: COR, class of recommendation; COVID-19, coronavirus disease 2019; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; LOE, level of evidence; UFH, unfractionated heparin.

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Addition of an antiplatelet agent to treatment with LMWH/UFH was examined in one RCT that included both non–critically and critically ill patients. In this trial, the combined regimen was not effective in reducing mortality in either subgroup and there was increased risk of bleeding events.[36] In another RCT, addition of an antiplatelet agent to prophylactic dose LMWH/UFH reduced mortality until discharge. Reduced mortality had reached even higher probability by day 90, but this benefit was accompanied by increased risk of bleeding.[50] Key differences in design between the two trials, as described below (supportive text for Recommendation 11) may explain the inconsistent results concerning the role of antiplatelet agents in mortality risk.

3.3.2 | Recommendation-specific supportive text

9. Two RCTs comparing intermediate versus low (prophylactic) dose LMWH/UFH in critically ill adults were identified.[45–47] In one trial (INSPIRATION; *N* = 562) results were available in two publications: one reporting on 30 days of follow-up,[47] and the other on 90 days.[45] The primary outcome, which was a composite of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, and all-cause mortality, did not differ across treatment arms, a null finding similar to other outcomes that were assessed in this trial. In the second RCT (*N* = 176) prophylactic versus intermediate-dose LMWH were compared in patients admitted to the ICU and/or showed laboratory evidence of coagulopathy.[46] The primary outcome, 30-day all-cause mortality, was 15% in the intermediate and 21% in the prophylactic LMWH dose groups, a difference that was not statistically significant. Neither trial showed differences in venous or arterial event rates or major bleeding.
10. A large multiplatform RCT (*N* = 1098) in critically ill patients hospitalized for COVID-19 was halted for futility to demonstrate a difference in the primary outcome of organ support-free days between therapeutic dose of LMWH/UFH and lower doses of LMWH/UFH.[48] However, the trial showed a 4% ARR in major thromboembolic events without significant differences in either mortality or major bleeding in the therapeutic LMWH/UFH group versus usual care thromboprophylaxis. Another RCT that included 83 critically ill patients hospitalized for COVID-19 did not show significant differences in any outcomes between therapeutic dose of LMWH/UFH and lower doses of LMWH/UFH.[28] A meta-analysis of three RCTs[28,48,53] demonstrated among the critically ill patients a significant reduction in major thrombotic events (ARR 4.1%) with therapeutic dose LMWH/UFH, as well as a non-significant increase in risk of major bleeding and a decrease in organ support–free days.[30] However, the weighted results of the meta-analysis are dominated by findings from the multiplatform RCT.[48] Although these results do not support escalation of LMWH/UFH to therapeutic dose, patients with a clear indication—new or recent VTE, atrial fibrillation, mechanical heart valves—should be offered therapeutic dose LMWH/UFH unless contraindicated.
11. In a large RCT (REMAP-CAP; *N* = 1549) critically ill patients hospitalized for COVID-19 received aspirin 75–100 mg daily, a P2Y12 inhibitor (mainly clopidogrel at 75 mg daily without loading dose), or no antiplatelet therapy.[50] Most patients (90%) also received LMWH, and 72% of VTE prophylaxis was at low (prophylactic) or intermediate dose. The trial was stopped for futility to demonstrate a difference in the primary outcome, which was organ support–free days. Because results from the two antiplatelet groups were similar, they were pooled and compared to control. The adjusted absolute difference between groups in survival until discharge was 5% (95% confidence interval, −0.2, 9.5) with 97% posterior probability of efficacy with antiplatelet therapy. The adjusted absolute difference in survival until 90 days was also 5% with 99.7% posterior probability of efficacy with antiplatelet therapy. However, the risk of major bleeding[50,54] increased with antiplatelet therapy, with an adjusted absolute risk increase of 0.8% with 99.4% probability of harm. Post hoc analyses indicated increased risk of bleeding when antiplatelet therapy was combined with therapeutic dose anticoagulation. A very large RCT (RECOVERY), randomized 14 892 adults with COVID-19 to aspirin 150 mg daily or usual care.[36] Among patients receiving non-invasive or invasive ventilation (*N* = 4920) there was no reduction in mortality risk at 28 days with aspirin compared to control. It is important to note that in the REMAP-CAP trial, divergence in cumulative mortality risk occurred between day 28 and day 90, aspirin dose was lower than in the RECOVERY trial, and risk of bleeding was likely mitigated by enrolling patients at low risk of bleeding and by recommending gastric acid suppression.[50] The combination of antiplatelet agents with therapeutic dose anticoagulation is probably harmful in critically ill patients with COVID-19.

3.4 | Antithrombotic therapy for patients discharged from hospital (Table 5)

3.4.1 | Synopsis

Patients with COVID-19, who survive until discharge from the hospital, may still be at increased risk of adverse outcomes. Some patients demonstrate biomarkers for residual hypercoagulability (high D-dimer),[55] and elevated inflammatory response (high C-reactive

TABLE 5 Recommendation for patients discharged from hospital

COR	LOE	
2b	B-R	12. In select patients who have been hospitalized for COVID-19, post-discharge treatment with prophylactic dose rivaroxaban for approximately 30 days may be considered to reduce risk of VTE.[55,56]

Note: Evidence from referenced studies that support recommendations are summarized in Evidence Table S14 in supporting information.

Abbreviations: COR, class of recommendation; COVID-19, coronavirus disease 2019; LOE, level of evidence; VTE, venous thromboembolism.

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protein),[57] which might increase post-discharge risk of thromboembolic events and death in the convalescence. One RCT showed that prophylactic dose of a DOAC (rivaroxaban) compared to no anticoagulation reduced risk of non-fatal or fatal VTE without a significant increase in bleeding risk.[56] Data from a large registry study supported findings from this trial.[55]

3.4.2 | Recommendation-specific supportive text

12. In an open-label, multicenter RCT of non-pregnant adults with increased risk of thrombosis, who were hospitalized for a minimum of 3 days for COVID-19, post-discharge treatment with rivaroxaban 10 mg per day for 35 days was compared to no anticoagulation.[56] Increased risk of thrombosis was defined as an elevated modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) VTE-score of 2–3 with D-dimer level more than two times the upper limit of normal at discharge or an IMPROVE VTE score of 4 or greater irrespective of the D-dimer level at discharge.[58] Enrolled patients had bilateral lower limb venous Doppler ultrasound and computed tomography pulmonary angiograms performed on day 35 post-randomization. Rivaroxaban 10 mg daily was associated with decreased risk of symptomatic or fatal VTE, but there was no difference in risk of death or arterial thrombosis. Results showed low risk of CRNMB and no increased risk of major bleeding.[14,54] These findings are supported by results from a registry on patients post–COVID-19 hospital discharge early on in the pandemic.[55] Therefore, in patients with persistent risk factors for VTE that may include an IMPROVE score of ≥4 or 2–3 with a D-dimer above the upper limit of normal, and without contraindication (e.g., high risk of bleeding, pregnancy, lactation), post-discharge treatment with 10 mg of rivaroxaban daily may be considered. Results from studies with other DOACs are not yet available. (One panel member voted for COR 2a.)

4 | DISCUSSION

The guideline panel identified during the project new published data that potentially could generate additional recommendations (Evidence Tables S9b and S11b) in supporting information. The first one concerned the question whether treatment with an antiplatelet agent in critically ill patients with COVID 19 is beneficial, which yielded Recommendation 11. The second question was related to the original question whether oral anticoagulants in non-hospitalized patients with COVID-19 is beneficial but specifically addressing DOACs versus vitamin K antagonists. This was prompted by the identification in the first literature search of a retrospective cohort study with more than 300 000 patients.[59] The study showed a significant reduction in mortality among patients on warfarin compared to DOACs. Due to potential risk of selection bias, performance

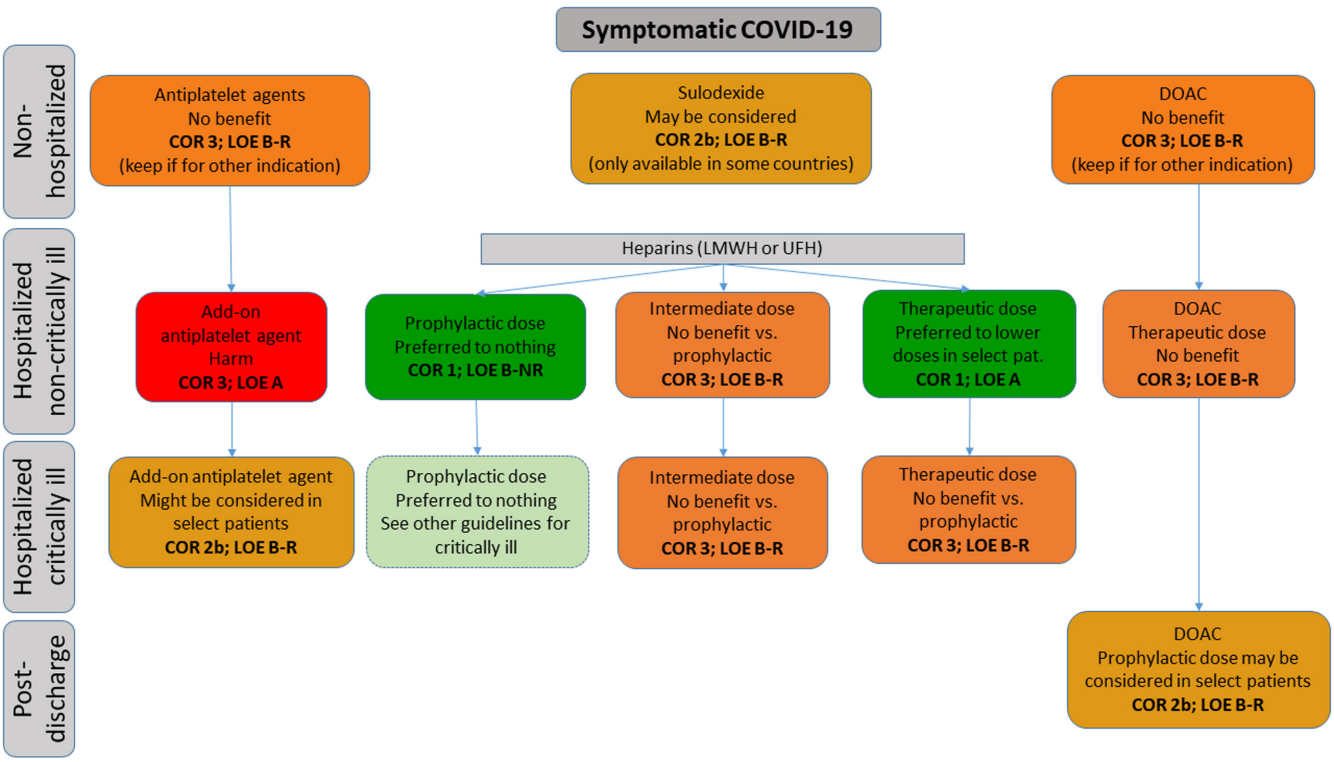

FIGURE 2 Summary of the recommendations. Color coding refers to the COR. For further details, see Recommendation-specific supportive texts and evidence tables (in the Appendix S1). COR, class of recommendation; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; LOE, level of evidence; UFH, unfractionated heparin.

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bias, prescription of anticoagulants several months before the infection, and missing key variables, the level of evidence was lower than B and no recommendation was made. Furthermore, of the 15 initially raised questions, 2 had no available evidence (prophylactic LMWH/UFH in non-hospitalized patients; change of heparin dose on transfer of hospitalized patients to ICU), and 3 had insufficient or low-quality evidence and were deemed to better fit for the ISTH COVID-19 Antithrombotic Good Practice Statements (prophylactic LMWH/UFH versus no prophylaxis for critically ill patients; prophylactic LMWH/UFH post-discharge; antiplatelet agents post-discharge; Evidence Tables S6, S13, and S15 in supporting information).[4]

5 | CONCLUSION

The recommendations are summarized in Figure 2. Questions that are not covered by these recommendations are likely to be addressed in the ISTH COVID-19 Antithrombotic Good Practice Statements.[4]

AUTHOR CONTRIBUTIONS

Sam Schulman planned and organized the guideline work; Helaine Resnick led the literature search, created the evidence tables, and provided methodological guidance. All authors analyzed the data and contributed to the text and tables.

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CONFLICTS OF INTEREST

Dr. Schulman has received research grant from Octapharma and honoraria for work in study committees from Daiichi-Sankyo, Boehringer-Ingelheim, Bayer, and Sanofi and for lectures from Servier and Bristol-Myers Squibb. He divested from equity interest in Pfizer in July 2021. Dr. Sholzberg has received research grants from Pfizer and Octapharma. Dr. Spyropoulos has received research grant from Janssen and honoraria from Janssen, Sanofi, and Alexion. Dr. Zarychanski has received research grants from CIHR, LifeArc, NIH, Research Manitoba, Cancercare Manitoba Foundation, Peter Munk Cardiac Centre, Thistledown Foundation, Manitoba Medical Services Foundation. Dr. Bradbury has received honoraria from Lilly, BMS-Pfizer, Bayer, Amgen, Novartis, Janssen, Portola, Ablynx, and Grifols. Dr. Connors has received research grant from CSL Behring and has served on scientific advisory boards and as a consultant for Abbott, Anthos, Alnylam, Bristol Myers Squibb, Pfizer, Five Prime Therapeutics, Pfizer, Roche, Sanofi, and Takeda. Dr. Falanga has received honoraria from Bayer, Bristol-Myers Squibb, Leo Pharma, Roche, and Sanofi. Dr. Iba has received a research grant from Japan Blood Products Organization. Dr. Kaatz has received research grants from Bristol-Myers Squibb, Janssen, NIH, and Osmosis Research and honoraria from Alexion/Astra-Zeneca, Bristol-Myers Squibb/Pfizer, Boston Scientific, Gilead, Janssen, and Phase Bio. Dr. Levy has received honoraria from Instrumentation Labs, Leading Bioscience, Merck, and Octapharma. Dr. Middeldorp has received research grants from Bayer, Bristol Myers Squibb/Pfizer, Boehringer-Ingelheim, and Portola. Dr. Minichiello has received honoraria from Bristol Myers Squibb. Dr. Ramacciotti has received research grants from Bayer, Brazilian Ministry of Science and Technology, and Pfizer, and honoraria from Aspen Pharma, Bayer, Biomm Pharma, Daiichi-Sankyo, Janssen, and Pfizer. The remaining authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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