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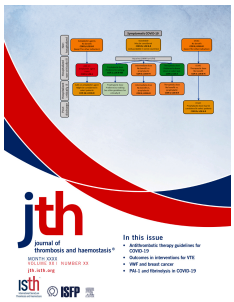

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2023 ISTH update of the 2022 ISTH guidelines for antithrombotic treatment in COVID-19

Sam Schulman[1,2] | Donald M. Arnold[1,3] | Charlotte A. Bradbury[4] | Lisa Broxmeyer | Jean Marie Connors[5] | Anna Falanga[6,7] | Toshiaki Iba[8] | Scott Kaatz[9] | Jerrold H. Levy[10] | Saskia Middeldorp[11] | Tracy Minichiello[12] | Ishac Nazy[1,3] | Eduardo Ramacciotti[13,14] | Helaine E. Resnick[15] | Charles Marc Samama[16] | Michelle Sholzberg[17] | Jecko Thachil[18] | Ryan Zarychanski[19] | Alex C. Spyropoulos[20,21] | on behalf of the International Society on Thrombosis and Haemostasis

1Department of Medicine, McMaster University, Hamilton, Ontario, Canada

2Department of Obstetrics and Gynecology and Perinatal Medicine, I.M. Sechenov First Moscow State Medical University, Moscow, Russia

3Michael G. DeGroote Centre for Transfusion Research, McMaster University, Hamilton, Ontario, Canada

4Faculty of Health Sciences, University of Bristol, Bristol, UK

5Division of Hematology, Brigham and Women's Hospital, Boston, Massachusetts, USA

6Department of Transfusion Medicine and Hematology, Hospital Papa Giovanni XXIII, Bergamo, Italy

7University of Milan Bicocca, Monza, Italy

8Department of Emergency and Disaster Medicine, Juntendo University, Tokyo, Japan

9Division of Hospital Medicine, Henry Ford Hospital, Detroit, Michigan, USA

10Departments of Anesthesiology, Critical Care, and Surgery (Cardiothoracic), Duke University School of Medicine, Durham, North Carolina, USA

11Department of Internal Medicine and Radboud Institute of Health Sciences, Radboud University Medical Centre, Nijmegen, the Netherlands

12Division of Hematology, San Francisco VA Medical Center, University of California, San Francisco, San Francisco, California, USA

13Science Valley Research Institute, São Paulo, Brazil

14Hospital e Maternidade Christóvão da Gama, Grupo Leforte, Santo André, São Paulo, Brazil

15Resnick, Chodorow & Associates, Silver Spring, Maryland, US

16Department of Anaesthesia, Intensive Care and Perioperative Medicine, GHU AP-HP Centre—Université Paris—Cité, Cochin Hospital, Paris, France

17Departments of Medicine, and Laboratory Medicine and Pathobiology, St Michael's Hospital, Li Ka Shing Knowledge Institute, University of Toronto, Toronto, Ontario, Canada

18Department of Haematology, Manchester University Hospitals, Manchester, UK

19Sections of Hematology/Oncology and Critical Care, University of Manitoba, Winnipeg, Manitoba, Canada

20Institute of Health System Science, Feinstein Institutes for Medical Research, Manhasset, New York, USA

21Department of Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York, USA

Correspondence: Sam Schulman, Thrombosis Service, HHS-General Hospital, 237 Barton Street East, Hamilton, ON L8L2X2, Canada

Email: schulms@mcmaster.ca

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Abstract

Based on emerging evidence from the corona virus 19 (COVID-19) pandemic, the ISTH guidelines for antithrombotic treatment in COVID-19 were published in 2022. Since then at least 16 new randomized controlled trials have contributed additional evidence, which necessitated a modification of most of the previous recommendations. We used again the American College of Cardiology Foundation/American Heart Association methodology for assessment of level of evidence (LOE) and class of recommendation (COR). Five recommendations had the LOE upgraded to A and 2 new recommendations on antithrombotic treatment for patients with COVID-19 were added. Furthermore, a section was added to answer questions about COVID-19 vaccination and vaccine-induced immune thrombotic thrombocytopenia (VITT), for which studies have provided some evidence. We only included recommendations with LOE A or B. Panelists agreed on 19 recommendations, four for non-hospitalized, five for non-critically ill hospitalized, three for critically ill hospitalized, and two for post-discharge patients, as well as 5 for vaccination and VITT.A strong recommendation (COR 1) was given for (a) use of prophylactic dose of low molecular weight heparin or unfractionated heparin (LMWH/UFH) in non-critically ill patients hospitalized for COVID-19, (b) 1); (b) for select patients in this group, use of therapeutic dose LMWH/UFH in preference to prophylactic dose, and (c) for use of anti-platelet factor 4 enzyme immunoassays for diagnosing VITT. A strong recommendation was given against (COR 3) the addition of an antiplatelet agent in hospitalized, non-critically ill patients. These international guidelines provide recommendations for countries with diverse health care resources and COVID-19 vaccine availability.

Key Words: Anticoagulants, COVID-19, COVID-19 vaccines, Critical Illness, Platelet Aggregation Inhibitors,

1 | PREAMBLE

The International Society on Thrombosis and Haemostasis (ISTH) has published evidence-based clinical practice guidelines since 2020 with recommendations that aim to improve global health. ISTH strives to promote increased adoption of evidence-based guidelines by increasing the speed, quality, access, and applicability of these resources. Guideline panel members volunteer their time to gather and evaluate published literature and to synthesize and classify evidence. Guidelines are official policy of the ISTH.

1.1 | Target audience

This guideline provides recommendations for clinicians in Internal Medicine, Intensive Care, Infectious Disease, Hematology, Vascular Medicine, as well as hospitalists, family practitioners and other health care providers who deliver inpatient or outpatient care to patients with COVID-19. Although guidelines endeavor to apply to a majority of patients, they can never be relevant to every individual and must be accompanied by good clinical judgement. The ultimate goal is to optimize quality of care while taking patient preferences into account. Clinical practice guidelines may also help inform decision-making among regulatory agencies and payers.

1.2 | Clinical implementation

Successful treatment is predicated on effective interactions between the clinical team and the patients they treat. One aspect of these interactions is communicating the value of clinical practice guidelines. Engagement and adherence to treatment are improved among patients who receive education on the evidence underpinning their recommended treatments and

among those who engage in shared decision-making with their care teams. Patient values and preferences are particularly important when the quality of the evidence and/or the strength of a recommendation is low.

2 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) was declared a pandemic on March 11, 2020 [1]. Although the World Health Organization downgraded COVID-19 from this level on May 5, 2023 because it no longer considered it a global emergency, COVID-19 remains prevalent across the globe, with new spikes in cases in 2023 [2]. COVID-19 has claimed almost seven million lives, yet as of March 2023 28% of the world population had not received any vaccination against COVID-19, with glaring disparities between highly developed and less developed countries[3]. Although new subvariants of the severe acute respiratory coronavirus 2 (SARS-CoV-2) omicron variant appear to cause less severe disease, they are more contagious than previous variants. Persistently high transmission rates, coupled with a large numbers of community-dwelling individuals at high risk of infection and complications suggests that clinicians must remain vigilant about COVID-19 and up-to-date on treatment recommendations.

2.1 | Purpose of the update

More than a dozen new randomized controlled trials (RCTs) have been published since the original ISTH guidelines for antithrombotic treatment in COVID-19 were published on line in July 2022 [4]. To ensure clinicians remain current on emerging evidence, the guideline panel proposed production of a focused update. This proposal was approved by ISTH in March 2023 with a request to add a section on vaccination against COVID-19 and vaccine-induced immune

thrombotic thrombocytopenia (VITT). However, during review of the new literature it became clear that most of the original recommendations required modifications linked to changes in the level of evidence and/or the class of recommendation. Furthermore, some questions that did not meet the pre-specified evidence threshold for inclusion in the original guideline were now sufficiently supported to warrant new recommendations. Based on these observations, the project shifted from a focused update to a general update of the entire guideline.

Ideally, studies published since mid-2022 would provide COVID-19 variant specific results, but this was rarely the case. New studies were initiated early in the pandemic and enrolled patients with predominantly or only early variants, or they enrolled patients over several years but did not specify outcomes by COVID-19 variant. Accordingly, it was not possible to report variant-specific recommendations. It could also be argued that the recommendations should be tailored to patients' vaccination status. Again, available data from the RCTs are not sufficiently detailed to inform of differences in management according to patients' vaccination status. Although most patients with recent vaccination will have no or mild symptoms, it is more relevant to tailor treatment recommendations to severity of the illness.

3 | METHODS

Consistent with the original guideline, ISTH used methods recommended by the American College of Cardiology Foundation and the American Heart Association (ACCF/AHA) [5, 6]. These methods keep the guideline short and user friendly by presenting each set of recommendations in tabular format, followed by a brief synopsis and recommendation-specific supportive text. Due to the temporal proximity of this update to the original guideline, we do not repeat

recommendation-specific supportive text if there was no change in level of evidence, class of recommendation, or outcomes. For those recommendations, readers are referred to the original version of the guideline.

3.1 | Panel selection and management of conflicts of interest

The guideline Chairman, 13 content expert panel members and two patient representatives (L.B. and S.K.) from the original version of the guidelines participated in this update. Two additional content experts were invited to lead the new section on vaccination and VITT. All members completed disclosures including information on relationships with industry and other potential conflicts of interest. Panelists remained in their previously-assigned sections (outpatients [non-hospitalized and post-discharge] [J.T., T.I., and T.A.M.], non-critically ill patients [A.C.S., S.M., C.A.B., and E.R.], and critically ill patients [R.Z., C.M.S., and J.H.L.]) except three who were assigned to the new vaccine and VITT section (M.S., J.M.C., A.F. and the content experts D.M.A. and I.N.). Critically ill and non-critically ill patients were defined based on criteria in each included study, and details are available in the evidence tables. Generally, patients not requiring organ support or mechanical ventilation other than low-flow supplemental oxygen were considered non-critically ill. Although there are relatively few patients with critical illness due to COVID-19, some patients require immediate organ support, such as invasive or non-invasive positive pressure ventilation, high-flow supplemental oxygen therapy, extracorporeal membrane oxygenation, continuous renal replacement therapy, vasopressor or inotrope support.

3.2 | Search strategy and deployment

The literature search algorithm for the recommendations in the 2022 ISTH guidelines for antithrombotic treatment in COVID-19 were used again but with the time period changed from 2020/01/01 - 2022/03/06 to 2022/03/01 - 2023/03/31. However, for the section on vaccines and VITT the search, based on extensive input from the guideline panel, included the period 2020/06/11 - 2023/08/03 (PubMed, Cochrane, EMBASE) and was performed by an experienced medical librarian.

3.3 | Abstract review and identification of included studies

For the original recommendations, which with one exception were based on data from RCTs, the working groups only selected and reviewed abstracts from new RCTs or meta-analyses. Pre-specified criteria included: the updated date range, human subjects aged 18+, established COVID-19 diagnosis, RCT design, minimum follow-up 7 days, minimum sample size 100 subjects. For the recommendation on vaccination against COVID-19 (Recommendation 15), the additional criterion retrospective cohort studies with at least 400 cases was also included.

VITT context experts initially proposed eight “patient, intervention, comparator, outcome” (PICO) questions. Of these, four were excluded due to lack of evidence. For the remaining VITT-related PICOs, only non-randomized studies on intervention effects were available. Producing recommendations for interventions based on non-randomized studies is challenging because of the greater risk of bias compared to RCTs. Nonetheless, panelists agreed that because VITT is a rare disease, it was important to include all available evidence that met inclusion criteria for this condition.

Accordingly, pre-specified criteria for inclusion of studies on VITT (laboratory diagnosis, heparin versus non-heparin, and intravenous gammaglobulin [IVIG]) were: date range 2020/06/11 - 2023/08/03, human subjects any age, established VITT (for treatment-related questions) suspected VITT (for diagnosis-related questions), cohort or case-control design, specification of a gold standard comparison for diagnostic accuracy studies, and minimum sample size 30 subjects.

As with the original version of the guideline, results files for the vaccine/VITT literature searches were loaded into an online abstract review platform [7]. Two reviewers screened abstracts against the pre-specified inclusion criteria, and the guideline methodologist adjudicated any conflicts that arose during abstract review. Full text copies of potentially relevant studies were provided to members of the vaccine/ VITT working group. The working group, guideline Chairman, and methodologist reviewed all papers, and together determined which met inclusion criteria.

Studies published after the literature search end dates and up to October 31, 2023 were eligible for inclusion if they met relevant criteria and had the potential to change the recommendations. Panel members did not become aware of any such studies after the close of the searches.

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

Evidence tables describing characteristics and outcomes of included studies are available in the online Supplement. Development of written recommendations followed ACCF/AHA methods (Figure 1), with the class of recommendation (COR) indicating whether and to what degree

panelists determined that available evidence reflects benefits or harms associated with a particular treatment, and the level of evidence (LOE) reflecting panelists' assessment of the quality of the studies that inform the recommendation. Only PICO questions represented by studies fulfilling LOE A or B were included in this guideline. Vaccine/VITT evidence table development and bias assessment followed the same methodology as the original version of the guidelines [4]. For the PICO questions on treatment of VITT the available studies only fulfilled LOE C-LD, but this information should be important for providers and patients. It is very unlikely that new studies with higher quality of evidence on treatment of VITT will become available, and therefore the panel decided to include Recommendations 18 and 19 in the guidelines. In addition, for questions related to diagnostic accuracy of VITT, sensitivity, specificity, and positive and negative predictive values were calculated when data were available, and the Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2) was used [8]. The latter method assesses four risk of bias domains in diagnostic accuracy studies, with each domain consisting of several questions. These domains are: patient selection, index test, reference standard, and flow and timing. The first 3 domains are also assessed in terms of concerns regarding applicability. In assessing risk of bias for a given domain, if answers to all domain-specific questions are judged as "yes" then risk of bias for that domain can be judged as low. If any questions are judged as "no" then potential for bias exists. A similar approach applies for judgement of applicability, with reviewers rating how well the study matches the review question.

3.5 | Debate and voting

Each working group presented assessments of quality of evidence and strength of recommendations for the recommendations in its section. Panel members received section-specific materials in advance of virtual meetings, all could contribute to the discussion and prepare recommendations for voting. Panel discussions were recorded and members had an opportunity to review the recordings and make additional comments. Discussions were aimed at reaching consensus among the panelists. Voting for all recommendations was conducted using a confidential ISTH website and was based on methods outlined by ACCF/AHA, with recusals as appropriate. Intellectual conflict of interest did not disqualify from voting. Recommendations were approved by 94%-100% of panel members, with at least 51% required for approval.

3.6 | Public review and comment

The final draft of these guidelines were posted on the ISTH website and made available for organizations with different stakeholders, including patients, for public review during 2 weeks, and comments were invited. The guideline Chairman reviewed all comments, consulted with the appropriate working group if needed, and responded. Recommendation-specific supportive texts were revised as required by the public comments.

4 | TREATMENT RECOMMENDATIONS

Introductory Text

Each of the four sections starts with a synopsis, which may comment on terminology used and on what is new in the section. The synopsis may also briefly mention new studies with a closely

related topic but with insufficient evidence to qualify for a recommendation. Thereafter, the recommendations are listed, each one with a brief comment below if the recommendation is new or has been modified. Unchanged recommendations from the 2022 ISTH guidelines do not have any comment or recommendation-specific supportive text. The reader is referred for that to the respective section in the 2022 ISTH guidelines [4]. Sequencing of the list of recommendation-specific supportive text within the body of the article is aligned with the numbering of recommendations used in the tables.

Whenever the type of heparin was defined in a study as unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), this is specified in the text. In some studies the type was either not defined or the results provided with the UFH and LMWH together, which is referred to as "heparins" in the text. The prophylactic, intermediate and therapeutic dose levels of UFH, LMWH and direct oral anticoagulants (DOACs) included in these guidelines were presented in Table 1 in the 2022 ISTH guidelines [4].

The definition of "non-critically-ill" and "critically ill" varies between studies. We examined data for these patient categories as defined by the inclusion criteria in each study and details are available in the accompanying evidence tables under "Study Characteristics".

4.1 | Antithrombotic therapy for non-hospitalized patients (Table 1)

4.1.1 | Synopsis

The term "non-hospitalized" refers to patients with COVID-19, residing in the community and without recent hospitalization for COVID-19. The treatments evaluated in this section were

evaluated for outcomes such as thromboembolism, subsequent hospitalization or mortality. Three new RCTs provided additional evidence to forego treatment with a DOAC to reduce the risk for adverse outcomes in this patient population. A new recommendation was generated as the result of two recent trials evaluating LMWH at a prophylactic dose in non-hospitalized patients, both with negative results. In the vast majority of patients with COVID-19 and mild-moderate symptoms the incidence of thromboembolism, hospitalization or death appears to be so low that no antithrombotic therapy is required, unless indicated by other pre-existing disease.

4.1.2 | Recommendation-specific supportive text

2. Three additional RCTs have been published comparing prophylactic dose of the DOAC rivaroxaban with placebo [10, 12] or usual care [11] for 14 to 35 days in non-hospitalized patients with suspected COVID-19 or a positive SARs-CoV-2 polymerase chain reaction (PCR) test. Patients had risk factors for thrombosis and/or clinical deterioration. Risk of bias was generally low. There was no significant difference between treatment groups for composite outcomes – venous thromboembolism (VTE), need for mechanical ventilation, acute myocardial infarction, stroke, acute limb ischemia, and death not attributed to major injury [11], or major venous and arterial thrombotic events [12], or separately for thromboembolism, myocardial infarction, death, or bleeding. Together with the previously published RCT [9], these four studies with 3,098 patients and consistently negative results justified a change of the LOE from B-R to A.

4. In two RCTs a prophylactic dose of the LMWH enoxaparin was compared with usual care for 14-21 days in non-hospitalized patients with symptomatic COVID-19 and positive SARS-CoV-2 PCR test plus at least one risk factor for severe disease [15], or body temperature higher than 37·5°C [14]. The two studies enrolled 689 patients and both were discontinued because of slow recruitment/futility. There was no significant difference between the treatment groups for the composite outcome of all-cause death and all-cause admission to hospital at 21 days after randomization [15], or any unplanned hospitalization and all-cause mortality within 30 days [14], or for the individual outcomes of hospitalization, thromboembolism, death or major bleeding.

4.2 | Antithrombotic therapy for non-critically ill, hospitalized patients (Table 2)

4.2.1 | Synopsis

Three new RCTs comparing therapeutic dose with intermediate or prophylactic dose LMWH have been published, but only one had adequate sample size to evaluate outcomes [29]. This together with a new meta-analysis [30] provided support for adding “reduced risk of death” to the outcomes listed in the recommendation for therapeutic dose heparin LMWH or UFH. Two new RCTs evaluated intermediate dose LMWH versus other dose regimens [28, 32]. The results were mixed with reduced incidence of thromboembolism in one and increased risk of bleeding in the other study. Together with the inconsistent results from previous observational studies and one RCT, there is no evidence to support use of intermediate dose heparins in this setting. One new, large RCT added to the evidence from previous trials that anti-platelet agents do not reduce the risk for adverse outcomes in non-critically ill, hospitalized patients [35]. Another

new, large RCT (FREEDOM COVID) compared the effect of therapeutic dose of the DOAC apixaban with therapeutic dose LMWH and with prophylactic dose LMWH [29]. The results were similar for apixaban and therapeutic dose LMWH, both demonstrating reduced mortality compared to prophylactic dose. Although this was not the primary endpoint, it can be argued that death is a hard endpoint that is difficult to neglect. However, the results contradicted those of a smaller RCT (ACTION) with a different DOAC (rivaroxaban). For this reason, the recommendation informs that it is “not well established”.

Lastly, a small RCT comparing prophylactic to intermediate doses of rivaroxaban versus enoxaparin in hospitalized, non-critically ill patients found superiority of the former using a composite of multiple efficacy and safety endpoints. The panel did not include it in this guideline as it had several methodological limitations [36]. One registry study in 1,500 patients compared UFH with LMWH in hospitalized patients with COVID-19, using propensity score analysis [37]. The need for organ failure support and mortality were higher among those treated with UFH, but there was no information on the doses used with UFH and LMWH, and therefore the data are inconclusive and do not qualify for a recommendation.

4.2.2 | Recommendation-specific supportive text

6. The FREEDOM COVID trial randomized 3,398 non-critically ill patients with COVID-19 to prophylactic-dose enoxaparin, therapeutic-dose enoxaparin, or therapeutic dose apixaban [29]. All-cause mortality occurred in 7.0% of patients treated with prophylactic-dose enoxaparin and 4.9% of patients treated with therapeutic-dose anticoagulation, and intubation was required in 8.4% vs 6.4% of patients, respectively; both differences were statistically significant. Two

smaller trials that randomized 159 [27] and 315 [28] non-critically ill hospitalized COVID-19 patients, respectively, to therapeutic versus low or intermediate dose LMWH suggested lack of benefit of therapeutic anticoagulation but these findings were too imprecise for definitive conclusions. An updated meta-analysis of high quality studies of hospitalized, non-critically-ill patients with COVID-19 found that therapeutic dose anticoagulation with UFH or LMWH reduced all-cause mortality and major thromboembolism compared with prophylactic or intermediate-dose heparins, without a significant difference in major bleeding [30]. The recommendation was therefore modified to include reduced mortality risk. An exploratory analysis of a large multiplatform adaptive randomized trial [38] found that therapeutic-dose heparins increased organ support free days in hospitalized patients with COVID-19 who were not severely ill at presentation or had low body mass index [39].

7. The PROTHROMCOVID trial randomized 311 non-critically ill patients with COVID-19 to tinzaparin at prophylactic (4500 IU), intermediate (100 IU/kg) or therapeutic (175 IU/kg) doses given once daily during hospitalization and followed by seven days prophylaxis after discharge [28]. There was no significant difference among treatment groups for the composite outcome of symptomatic thrombotic event, need for non-invasive or invasive ventilation, or death within 30 days and there were no major bleeding events. The trial was stopped early based on futility analysis. The COVIDOSE trial randomized hospitalized patients with COVID-19 (n=1005, 80.1% non-critically ill and 19.9% critically ill) to weight-adjusted intermediate dose or fixed-dose thromboprophylaxis with LMWH [32]. The observed rate of symptomatic VTE was lower than expected and occurred in 1.2% of patients in the weight adjusted intermediate dose group versus 2.1% in the fixed-dose prophylaxis group. This difference was not statistically significant,

but there was a significant, two-fold increase in major bleeding in the weight-adjusted intermediate dose LMWH group. Taken together, these results do not support use of intermediate dose LMWH in non-critically ill patients with COVID-19.

8. The ACT trial used a multifactorial design to randomize 2,119 patients to aspirin (100 mg/day) plus rivaroxaban (2.5 mg twice daily) or usual care (and to colchicine or usual care) [35]. There were no significant differences between the combined antithrombotic treatment and usual care groups for the composite outcome of major thrombosis (myocardial infarction, stroke, acute limb ischemia, or pulmonary embolism), the need for high-flow oxygen, mechanical ventilation, death, or serious bleeding. The large RECOVERY trial (n=14,892) [34] and a third RCT [33] revealed no mortality benefit for aspirin or a P2Y12 inhibitor, respectively, as add-on therapy among non-critically ill patients hospitalized for COVID-19. The RECOVERY trial indicated evidence of harm with significantly increased risk for major bleeding among patients on antiplatelet therapy [34]. A fourth RCT that compared interventions including aspirin, clopidogrel, low-dose rivaroxaban, atorvastatin, and omeprazole to standard care was not included in this guideline due to the complexity of the intervention and because 36% of patients in the control group received at least one antiplatelet agent [40]. However, among patients who are already on antiplatelet therapy with clear indications, good clinical practice suggests continuing antiplatelet therapy among patients hospitalized for COVID-19 [41].

9. The FREEDOM trial randomized 3,398 non-critically ill patients hospitalized with COVID-19, 1:1:1 to prophylactic-dose enoxaparin (40 mg once daily), therapeutic-dose enoxaparin (1 mg/Kg twice daily) or therapeutic-dose apixaban (5 mg twice daily) [29]. The primary outcome was a 30-day composite of all-cause mortality, requirement for intensive care unit–level of

care, systemic thromboembolism, or ischemic stroke assessed in the combined therapeutic-dose groups compared with the prophylactic-dose group. There was no significant difference in the primary outcome between the treatment groups. All-cause mortality was reduced significantly from 7.0% among patients treated with prophylactic-dose enoxaparin to 4.9% of patients treated with therapeutic-dose anticoagulation. Similar results were observed for apixaban and LMWH, and major bleeding was infrequent in all three groups. Furthermore, fewer patients who were treated with therapeutic-dose anticoagulation required intubation.

4.3 | Antithrombotic therapy for critically ill, hospitalized patients (Table 3)

4.3.1 | Synopsis

With the current, less aggressive SARS-CoV-2 variants and with increasing immunity in the population from vaccination and previous COVID-19 episodes, the number of patients hospitalized for COVID-19 and requiring organ support has diminished. Persons without such immunity are still susceptible for severe COVID-19 and they occasionally require treatment in an intensive care unit. Two new RCTs addressed the value of intermediate dose regimen of LMWH in critical care. One study demonstrated a reduction of new thromboembolism compared to standard prophylactic dose [44], whereas the other study showed a significant increase in bleeding with intermediate dose [32]. Likewise, the 3 new RCTs that compared therapeutic dose heparins with lower doses provided mixed results with reduction of thromboembolism in 2 trials [44, 46] but increased severe and moderate bleeding [46]. The balance between efficacy and safety is obviously difficult in these very ill patients. Another RCT explored the transition of patients from non-critically ill to critically ill and enrolled from the

subset of patients in the REMAP-CAP RCT that had been allocated to treatment dose heparin [50]. The patients were then re-randomized to continued treatment dose or to intermediate or standard prophylactic dose heparin in the ICU. The therapeutic dose arm was prematurely discontinued by the data safety monitoring board when 75 patients had been randomized, for futility to demonstrate any advantage of continuing therapeutic dose heparin. This small study did not qualify for a recommendation in the guideline.

Two new RCTs compared platelet inhibition with clopidogrel or ticagrelor versus usual care and there was no evidence of efficacy benefit [46, 48]. In the 2022 ISTH guidelines, the addition of antiplatelet agent to prophylactic dose heparin was given a very guarded positive suggestion, but with all 4 RCT results taken together now there is no support for a net benefit.

4.3.2 | Recommendation-specific supportive text

10. The COVI-DOSE study was a multicenter, open-label, phase 4, superiority trial with blinded outcome adjudication that randomized 1000 adult inpatients presenting with acute respiratory SARS-CoV-2 into two treatment groups: intermediate weight-adjusted prophylactic dose LMWH or a fixed-dose of subcutaneous LMWH [32]. The observed rate of thromboembolic events was lower than expected in both groups. There was a statistically significant, twofold increased risk of major or clinically relevant non-major bleeding in the weight-adjusted dose group compared to the fixed-dose group, and no significant difference in thromboembolism or mortality. Similar in design to COVI-DOSE, the ANTICOVID study randomized 339 patients with hypoxemic COVID-19 pneumonia, of whom 90% were in an intensive care unit at randomization [44]. Patients were assigned in equal numbers to standard prophylactic dose, high prophylactic dose or

treatment dose LMWH. Compared with standard prophylactic dose, neither high prophylactic dose nor treatment dose heparin improved the primary outcome of all-cause mortality or time to clinical improvement; however, the high prophylactic dose resulted in significantly better net clinical by decreasing the risk of venous or arterial thrombosis without increased risk of bleeding. Taken together with two previous trials with negative findings [42, 43], these results do not suggest any advantage of intermediate or high prophylactic dose LMWH compared to standard dose LMWH among critically ill patients. A variety of factors may have contributed the differences in outcome in the critically ill, compared to the non-critically ill patients. A great variability in exposure to LMWH has been demonstrated in critically ill patients [51], but there is no evidence yet to support that adjustment of dose according to Xa-monitoring will lead to improved clinical outcomes.

11. The ANTICOVID randomized, open-label trial included 339 patients with hypoxemic COVID-19 pneumonia requiring supplemental oxygen and compared therapeutic anticoagulation or high-dose prophylactic anticoagulation with standard-dose prophylactic anticoagulation, and with 90% of the patients in an intensive care unit at randomization [44]. The patients were assigned in equal numbers to standard prophylactic dose, high prophylactic dose or treatment dose LMWH. Compared with standard prophylactic dose, neither high prophylactic dose nor treatment dose heparin improved the primary hierarchical outcome of all-cause mortality or time to clinical improvement in patients with hypoxemic COVID-19 pneumonia; however, the high prophylactic dose resulted in significantly better net clinical outcome by decreasing the risk of venous or arterial thrombosis without increased risk of bleeding. In the COVID-PACT study, patients were randomized to full-dose anticoagulation or standard-dose prophylactic

anticoagulation (n=390) [46] and patients with no indication for antiplatelet therapy were randomized to either clopidogrel or no antiplatelet therapy (n=292). In critically ill patients with COVID-19, full-dose anticoagulation, but not clopidogrel, significantly reduced thrombotic complications but with an increase in severe or moderate bleeding (Global Use of Strategies to Open Occluded Arteries = GUSTO-definition) [52] that was driven primarily by transfusions in hemodynamically stable patients. No difference in mortality was observed between groups. In the smaller COVID-HEP trial 159 patients with acute severe COVID-19 were randomized within 48 h of hospital admission to therapeutic dose LMWH or UFH versus intermediate or prophylactic dose LMWH or UFH [27]. However, only 88 patients were in the ICU, and there were no differences in thromboembolism, mortality, or major bleeding between groups. Taken together with the large, negative, multiplatform RCT (REMAP-CAP, ACTIV-4a, and ATTACC)[38] and the secondary analysis, which showed that heparin was more likely to cause harm in the more severely ill patients [39], the results of these trials do not suggest any advantage of therapeutic dose heparin compared to lower doses among critically ill patients.

12. In the ACTIV-4a trial which included 943 critically ill participants hospitalized for COVID-19, 14-day treatment with a P2Y12 inhibitor compared to usual care did not improve the number of days alive and free of cardiovascular or respiratory organ support nor did it increase risk of major bleeding [48]. In the COVID-PACT multifactorial RCT, 290 critically ill patients with COVID-19 were randomized to clopidogrel versus usual care until hospital discharge or day 28 [46]. There were no significant differences in efficacy outcomes or bleeding between the two groups. Updated data of the REMAP-CAP trial have been published with follow-up through 180 days for 895 patients in the platelet domain (initial publication was up to 90 days) [49]. Among critically

ill patients with COVID-19 in this study who were randomized to receive one or more therapeutic interventions, treatment with an antiplatelet had a 95.0% probability of improved 180-day mortality compared with control; the posterior probability of superiority was not statistically significant. Taken together with negative findings from the RECOVERY trial, these data do not support routine use of an antiplatelet agent, and specifically not a P2Y12 inhibitor in critically ill patients hospitalized for COVID-19. For patients who are already on an antiplatelet agent with clear indications, good clinical practice suggests continuation of antiplatelet therapy if a patient is hospitalized for COVID-19 [41].

4.4 | Antithrombotic therapy for patients discharged from hospital (Table 4)

4.4.1 | Synopsis

In the 2022 ISTH guidelines [4] a single RCT was available for evaluating post-discharge prophylaxis – rivaroxaban for 30 days reduced the risk for thromboembolism in the MICHELLE trial [55]. Since then another RCT (ACTIV-4C) compared prophylactic dose apixaban versus placebo without any apparent differences between the groups [53]. The study was stopped for low event rate and declining accrual rate. An important difference between the two studies is the selected high-risk population in the Michelle trial versus the broad patient population in ACTIV-4C. Although the ACTIV-4C was inconclusive, together with data from a number of observational studies (Table 5), it demonstrated that the adverse event rate after discharge is declining and currently so low that for the vast majority of patients there is no benefit from post-discharge prophylaxis with anticoagulants. A small subset of patients at high risk for thromboembolism, based on previous medical history or elevated D-dimer or a high score in

IMPROVE VTE risk assessment model [56], should still be considered for post-discharge prophylaxis. The recommendation was therefore split in two – the first for patients in general and no need for prophylaxis, and the second for a highly selected subset of patient at high risk for thromboembolism to consider rivaroxaban at a dose of 10 mg daily. (Table 5)

4.4.2 | Recommendation-specific supportive text

13. The ACTIV-4c randomized, double-blind trial compared apixaban at a prophylactic dose (2.5 mg twice daily) with placebo for 30 days in 1,217 patients discharged after hospitalization for COVID-19 [53]. Recruitment spanned the period of February 2021 to June 2022, covering the Delta and early Omicron variant waves. Both event- and recruitment rates were lower than expected, prompting early discontinuation of the trial. Due to low incidence of the composite endpoint of death or any thromboembolism (apixaban 2.1%, placebo 2.3%) results were imprecise. In an observational study using linked databases, rates of serious clinical outcomes in 77,347 patients discharged after hospitalization for COVID-19 during 2020-2021 were compared with patients discharged after pre-pandemic pneumonia and with controls [60]. The risk of deep vein thrombosis during the following five months was comparable for COVID-19 and non-COVID pneumonia and risk for pulmonary embolism was slightly higher for COVID-19. The trend of decreasing risk of thromboembolism or death among patients without thromboprophylaxis post-discharge is shown in Table 5. Routine post-discharge thromboprophylaxis is not recommended for patients hospitalized for non-COVID-pneumonia.

14. As the incidence of thromboembolic events in post-discharge patients has decreased since the onset of COVID-19 pandemic, need for post discharge prophylactic anticoagulation is reduced and should be reserved for those at highest risk [55].

4.5 | COVID-19 vaccination and VITT (Table 6) (New)

4.5.1 | Synopsis (New)

There has been substantial hesitance and even resistance against COVID-19 vaccination in many populations, partly fueled by the occurrence of very rare side effects, including VITT and myocarditis. VITT was recognized as a new syndrome following the use of adenoviral vector-based vaccines for COVID-19. Because of the similarities between VITT and severe forms of heparin-induced thrombocytopenia (HIT), treatments that are used to treat severe HIT and prevent thromboembolism were adopted for VITT including anticoagulants and intravenous immune globulin (IVIG).

We acknowledge that the AHA rubric that is being applied to evaluate the level (quality) of evidence was not designed for the evaluation of diagnostic tests. The use of VITT-associated vaccines has diminished in high income countries; however, VITT continues to be an important consideration for low-to-middle income countries and remains an issue of health equity [71]. Important knowledge gaps remain and there is an ongoing need for additional research including comparison of multiple assays to clarify the optimal diagnostic approach. Where resources to perform these assays are unavailable, the diagnosis of VITT can be established

based on a high degree of suspicion (e.g. probable VITT), defined as a high D-dimer and thrombocytopenia (<150,000/μL) and thrombosis occurring 5-30 days after vaccination with adenoviral vector-based vaccine for COVID-19.

Patients with a history of thromboembolism have been naturally concerned about the risk of recurrent thrombosis after vaccination. A large observational study in patients with a diagnosed thrombophilia defect did not show increased risk for thrombosis during 3 months after almost exclusive use of the m-RNA vaccines [61].

The treatment of VITT is complex, which makes the interpretation of studies that focus on a single agent challenging. Furthermore, as information about VITT rapidly accumulated, the diagnosis was made sooner and the management of the disease changed. There is thus important confounding in the studies on treatment of VITT. The use of heparins to treat the thrombotic events in VITT was of potential concern due to similarities between VITT and heparin-induced thrombocytopenia. In countries with limited resources the more expensive non-heparin anticoagulants are not available. The panel identified 3 studies comparing heparins with non-heparin agents [68-70], and one meta-analysis [67] that rendered support for the safe use of heparins, although non-heparin anticoagulants might still be preferred.

For the use of intravenous immune globulin (IVIG), 3 studies with more than 30 patients were identified, with two demonstrating reduced mortality compared to usual care [69, 70], whereas the largest study did not find a difference [68]. Therefore, only weak support for the use of IVIG was given in the recommendation.

4.5.2 | Recommendation-specific supportive text (New)

15. Based on electronic medical records across the Mayo Clinic enterprise, a cohort study of 6,067 adults with inherited or acquired thrombophilia who were vaccinated for COVID-19 examined acute VTE occurrence in the 90 days before and after the first vaccine dose [61]. There were 51 and 39 VTE events before and after vaccination, with no statistically significant difference. No differences were found when the data were analyzed by thrombophilia type (i.e., factor V Leiden or prothrombin gene mutation, or antiphospholipid syndrome). No data were presented on the proportion of patients on antithrombotic treatment. The annualized thrombotic event rate during the 90 days before vaccination was 3.3%, which can be compared with literature data. Systematic reviews and meta-analyses including studies of patients with unprovoked VTE with a high risk of recurrence (similar to those with thrombophilia and VTE) have shown that with long-term anticoagulation the incidence of VTE recurrence is 1.4%/year [72], and after stopping anticoagulation, VTE recurrence is 3.6%/year [73]. Data from this cohort study suggest that the majority of patients were not on anticoagulation at the time of VTE recurrence or vaccination.

16. Six studies were eligible for evaluation of performance characteristics [62-66, 74]. Anti-PF4 enzyme immunoassays (EIA) have excellent diagnostic accuracy for the diagnosis of VITT. Prevalence impacts both negative predictive value (NPV) and positive predictive value (PPV). Based on eligible studies, median NPV of EIA is 1.0 (range 0.76, 1.0) and median PPV of EIA is 0.86 (range 0.51, 1.0) (see Table 7). Therefore, a negative EIA essentially rules out the diagnosis of VITT unless high clinical suspicion remains [63]. In cases where there is high clinical suspicion of VITT and EIA testing is negative, testing using another EIA assay and VITT-modified functional testing for PF4-related platelet activation is suggested. A positive EIA correlates well with the

presence of PF4-platelet activating antibodies [62, 64-66, 74], thus a positive EIA essentially rules-in VITT when there is substantial clinical suspicion.

17. Only one cohort study in 34 patients with suspected VITT was eligible for inclusion [66]. A rapid assay for heparin-induced thrombocytopenia (HIT), particle gel immunoassay (PaGIA), was compared with a modified heparin-induced platelet aggregation assay as the reference standard. Sensitivity, specificity, PPV and NPV for PaGIA were 0.54, 0.67, 0.54 and 0.61, respectively. Despite limited evidence comparing rapid HIT assays to the gold standard (VITT-modified functional testing for PF4-related platelet activation), indirect evidence demonstrating poor correlation between rapid HIT assay and EIA results supports the recommendation against the use of rapid HIT assays for VITT diagnosis. Rapid HIT assays are not sensitive for VITT and are likely to yield false negative results [66]. VITT antibodies bind to PF4 alone with variable reactivity against the PF4-heparin complex. The reduced sensitivity of the rapid assays for VITT compared with HIT may be due to competition between heparin and VITT antibodies for the heparin binding site on PF4, or the lack of competition between KKO and VITT antibodies which is essential for proper assay functioning in the case of latex-enhanced immunoturbidimetric assay (LIA). Thus, rapid HIT assays are not useful for VITT diagnosis and are potentially harmful when used as a stand-alone diagnostic test for VITT because they may delay initiation of treatment for this life-threatening condition. However, the evidence for harm is indirect and of low quality in the absence of reliable clinical data.

18. An international prospective registry of patients with definite VITT and cerebral vein thrombosis compared treatment with non-heparin anticoagulants (n=51) with heparin (n=35) [70]. There was no difference in mortality or new VTE between groups. In a prospective cohort

study of 170 cases of definite VITT and 50 cases of probable VITT, 150 patients were treated with non-heparin anticoagulants and 50 received a heparin at some point during their hospital admission [68]. Mortality was numerically higher in patients who received heparin but the difference was not statistically significant. In a multicenter, retrospective analysis of patients with cerebral venous thrombosis and definite or probable VITT, data on clinical characteristics, laboratory results, treatments and outcomes were collected [69]. Death or dependence (modified Rankin score 3-6) occurred in 8 of 16 treated with unfractionated heparin or LMWH, in 18 of 50 with a non-heparin anticoagulant and four of 22 treated with a DOAC, with none of the differences being statistically significant. A meta-analysis including two of the above-mentioned studies [68, 69], and an additional study showed no difference in mortality between patients treated with heparin and those receiving a non-heparin anticoagulant (19% vs. 17%) [67]. Given the small number of total patients, non-randomized use of anticoagulants, confounding by use of other treatments, and change in mortality over time with the evolution in understanding and treatment of VITT, use of a heparin anticoagulant is reasonable if non-heparin anticoagulants are unavailable.

19. An international prospective registry of patients with definite VITT and cerebral vein thrombosis compared treatment with immunomodulation (n=65) with no immunomodulation (n=34) [70]. Immunomodulation was used in 94% of cases with IVIG. Mortality was significantly lower with immunomodulation, but there was no difference in risk of new VTE between the treatment groups. In a prospective cohort study of 170 cases of definite VITT and 50 cases of probable VITT, 159 were treated with IVIG and 61 were not; overall 72% of these 220 patients were treated with IVIG [68]. Mortality was similar in the two groups. In a multicenter,

retrospective analysis of patients with cerebral venous thrombosis and VITT, data on clinical characteristics, laboratory results, treatments and outcomes were collected [69]. Death or dependence (modified Rankin score 3-6) occurred in 22 of 55 treated with IVIG, and in 11 of 15 not treated with IVIG. Although authors of some of these studies noted that patients treated with IVIG had a trend towards fewer deaths compared to those not treated with IVIG, sample sizes were too small for robust comparisons. Based on the small number of patients, non-randomized administration of IVIG, and confounding by simultaneous use of anticoagulation, use of high-dose IVIG may be considered in the treatment of VITT.

5 | DISCUSSION

During the four years of the COVID-pandemic the disease panorama has changed substantially, due to the emergence of new, dominant virus variants with differences in transmissibility and severity of disease, and improved herd immunity. Many patients are now hospitalized for other reasons and have concomitant COVID-19 or contract it during the hospitalization. Our recommendations may not be generalizable for such cases, since the studies mainly included patients hospitalized for COVID-19. Although more than 16 new RCTs on antithrombotic treatment for patients with COVID-19 were published since the 2022 ISTH guidelines, it is important to note that several of them were discontinued prematurely due to accrual problems. Nevertheless, the totality of evidence rendered support for an upgrade of LOE for five recommendations. Two recommendations were added for the non-hospitalized and post-discharge patients. For the vaccine and VITT section of the initially raised questions, two were combined (anticoagulation prophylaxis for patients with thrombophilia and antiplatelet

prophylaxis for the same group), one was considered already answered (anticoagulation prophylaxis for the general population – since not needed in persons with thrombophilia), and two had insufficient or low-quality evidence (use of plasma exchange, rituximab or other agents for severe VITT, subsequent mRNA vaccine for patients that had VITT). Any of these questions might be addressed in a future ISTH Guidance document. Two recommendations discuss use of specific DOACs (recommendation 9 – apixaban and recommendation 14 – rivaroxaban), as no data for other DOAC were available demonstrating a favorable risk/benefit ratio for the respective indication. Differences in properties between DOACs, such as protein binding, metabolism, renal elimination, drug interactions, dosing regimens, and possibly bleeding risk, preclude generalization of these recommendations to include all DOACs. As opposed to the 2022 ISTH guidelines, there are no accompanying Good Practice Statements, since very little has changed in that part.

5 | CONCLUSION

The treatment recommendations for COVID-19 are summarized in Figure 2. The recommendations for vaccination and VITT are summarized in Figure 3

AUTHOR CONTRIBUTIONS

Sam Schulman planned and organized the guideline work; Helaine Resnick led the literature search, created the evidence tables for the vaccine and VITT section, 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; served on data safety monitoring boards for Alexion, Bayer, Boehringer-Ingelheim, and Sanofi; served on event adjudication for Daiichi-Sankyo; and served on an advisory board for Servier. Dr. Arnold received research grants from Rigel Pharmaceuticals and Public Health Agency of Canada (PHAC) and a consultant for Amgen, Paradigm, Sobi, Alpine, Novartis, Argenx. Dr. Bradbury has received research grant from Amgen; honoraria from BMS-Pfizer, Janssen, Sanofi; and served on advisory board for Novartis. Ms. Broxmeyer currently owns a stock portfolio with Johnson & Johnson and Pfizer. Dr. Connors has received research grant from CSL Behring and has served on scientific advisory boards for Abbott, Anthos, Bristol Myers Squibb, Pfizer, and Werfen. Dr. Falanga has received honoraria from Kedrion and Rovi and served on an advisory board for Sanofi. Dr. Kaatz has received research grants from Bayer and a consultant for Inari and Janssen. Dr. Levy has served on a data safety monitoring board with Merck, a research study steering committee with Octapharma, and served on advisory board for Werfen. Dr. Middeldorp has received research grants from Bayer, Abbvie, Hemab, Viatris and Sanofi and received honoraria from AstraZeneca, Norgine, and Alveron. Dr. Nazy has received research grants from Paradigm Pharmaceuticals, Janssen/Johnson & Johnson, UCB Biopharma, AstraZeneca, and Public Health Agency of Canada and is a consultant for Paradigm Pharmaceuticals, Janssen/Johnson & Johnson, UCB Biopharma, and AstraZeneca. Dr. Ramacciotti has received research grants from Bayer, Pfizer, and Novartis; and honoraria from Sanofi, Bayer, Ache, Daiichi Sankyo, and Pfizer. Dr. Samama served on an advisory board for Norgine Pharma. Dr. Sholzberg has received research grant from Pfizer, Amgen, and Sanofi; and received honoraria from Pfizer, Octapharma, Amgen, Novartis; served on advisory boards for Amgen and Novartis. Dr. Spyropoulos has received research grant from AstraZeneca and honoraria from

Janssen, Regeneron, and AstraZeneca. Dr. Thachil received honoraria from Bristol Myers Squibb, Pfizer, and Daiichi Sankyo. Dr. Zarychanski has received research grants from Canadian Institute of Health Research, LifeArc, Nation Institute of Health, Research Manitoba, Cancercare Manitoba Foundation, Peter Munk Cardiac Centre, Thistledown Foundation, and Manitoba Medical Services Foundation. The remaining authors have no conflicts of interest to declare.

INTELLECTUAL CONFLICTS OF INTEREST

Dr. Schulman has been primary author and co-author on review articles on COVID-19. Dr. Arnold has been co-author and senior author on articles on diagnosis and treatment of VITT. Dr. Bradbury has been primary author and co-author on articles on heparins and antiplatelet agents for treatment of COVID-19. Dr. Connors has been primary author and co-author on articles on antiplatelet agents, apixaban and heparin for treatment of COVID-19. Dr. Falanga has been co-author on review articles on treatment of COVID-19, including with heparin. Dr. Iba has been primary author and co-author on articles on coagulopathy in COVID-19 and in VITT. Dr. Kaatz has been co-author on articles on heparin and antiplatelet agents for treatment of COVID-19. Dr. Levy has been primary author and co-author on articles on coagulopathy in COVID-19 and in VITT and on heparin for treatment of COVID-19. Dr. Middeldorp has been co-author on articles on heparin and oral anticoagulants for the treatment of COVID-19. Dr. Nazy has been primary author, senior author and co-author on articles on coagulopathy and laboratory diagnosis in VITT and COVID-19. Dr. Samama has been co-author on articles on coagulopathy in COVID-19. Dr. Sholzberg has been primary author on articles on heparin for treatment of COVID-19. Dr. Spyropoulos has been primary author and senior author on articles on heparin and co-author on articles on rivaroxaban for treatment of COVID-19. Dr. Thachil has been primary author and co-author on articles on coagulopathy in in COVID-19. Dr. Zarychanski has been primary author and co-

author on articles on heparin and antiplatelet agents, respectively, for treatment of COVID-19. The remaining authors have no intellectual conflicts of interest.

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Legends to Figures

Fig. 1. Classification of recommendations and level of evidence. Reprinted with permission, Stroke.2022;53:e282-e361 ©2022 American Heart Association, INC [75].

Fig. 2. Summary of the recommendations 1 to 14 on symptomatic COVID-19. Color coding refers to the COR. For further details, see Recommendation-specific supportive texts and Evidence tables (in the Appendix S1). COR, class or recommendation; DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; LOE, level of evidence; UFH, unfractionated heparin.

Fig. 3. Summary of the recommendations 15-19 on vaccination and VITT. Color coding refers to the COR. For further details, see Recommendation-specific supportive texts and Evidence tables (in the Appendix S1). COR, class or recommendation; HIT, heparin-induced thrombocytopenia; LMWH, low-molecular-weight heparin; LOE, level of evidence; UFH, unfractionated heparin; VITT, vaccine-induced immune thrombotic thrombocytopenia.

	Table 1. Recommendations for antithrombotic therapy for non-hospitalized patients Evidence from referenced studies that support recommendations are summarized in online data supplement Evidence tables 1-4.	
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 thromboembolism, or mortality [9]. MODIFIED: "thrombosis" was changed to "thromboembolism". (Section 3.1 in the 2022 ISTH COVID Guideline)
3: No Benefit	**A**	2. In non-hospitalized patients with symptomatic COVID-19, initiation of DOAC therapy is not effective to reduce risk of hospitalization, arterial or venous thromboembolism, or mortality [9-12]. MODIFIED: "thrombosis" was changed to "thromboembolism". New evidence was added, LOE was updated from B-R to A. (Section 3.1 in the 2022 ISTH COVID Guideline)
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 [13].
3: No Benefit	**B-R**	4. In non-hospitalized patients with symptomatic COVID-19, thromboprophylaxis with LMWH is not effective to reduce the risk of disease progression [14, 15]. NEW: New evidence has been published to support a LOE B-R recommendation

	Table 2. Recommendations for antithrombotic therapy for non-critically ill, hospitalized patients Evidence from referenced studies that support recommendations are summarized in online data supplement Evidence tables 5-9.	
COR	**LOE**	
1	**B-NR**	5. 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 [16-22].
1	**A**	6. 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, end organ failure, and death [23-30]. MODIFIED: The outcome "death" was added because of new evidence. (Section 3.2. in the 2022 ISTH COVID Guideline)
3: No Benefit	**A**	7. 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 [28, 31, 32]. MODIFIED: New evidence has been added. LOE was updated from B-R to A. (Section 3.2. in the 2022 ISTH COVID Guideline)
3: Harm	**A**	8. In non-critically ill patients hospitalized for COVID-19, add-on treatment with an antiplatelet agent is potentially harmful and should not be used [33-35]. MODIFIED: New information is included in the supportive text.
2b	**B-R**	9. In non-critically ill patients hospitalized for COVID-19, therapeutic-dose apixaban is not well established but might be considered to reduce end organ failure and death [29]. MODIFIED: New evidence has been published about therapeutic dose apixaban. (Section 3.2. in the 2022 ISTH COVID Guideline)

	Table 3. Recommendations for antithrombotic therapy for critically ill, hospitalized patients Evidence from referenced studies that support recommendations are summarized in online data supplement Evidence tables 10-12.	
COR	**LOE**	
3: No Benefit	**A**	10. In critically ill patients hospitalized for COVID-19, intermediate dose LMWH or UFH is not recommended over prophylactic dose LMWH or UFH to reduce risk of adverse events, including mortality [32, 42-44]. MODIFIED: New studies have been added and LOE has therefore been updated from B-R to A for mortality; "thromboembolism" has been removed, due to discrepant results. (Section 3.3. in the 2022 ISTH COVID Guideline)
3: No Benefit	**A**	11. In critically ill patients hospitalized for COVID-19, therapeutic dose LMWH or UFH is not recommended over usual-care or prophylactic dose LMWH or UFH [24, 27, 38, 44-46]. MODIFIED: New studies have been added and LOE has therefore been updated from B-R to A. (Section 3.3. in the 2022 ISTH COVID Guideline)
3: No Benefit	**A**	12. In critically ill patients hospitalized for COVID-19, add on treatment with an antiplatelet agent to prophylactic dose LMWH/UFH is not recommended to reduce adverse events [34, 46-49]. MODIFIED: New studies have been added and LOE has therefore been updated from B-R to A. There is overall limited evidence for reduced mortality balanced by increased risk of bleeding and COR has therefore been updated from 2b to 3:NB. (Section 3.3. in the 2022 ISTH COVID Guideline)

	Table 4. Recommendation for patients discharged from hospital Evidence from referenced studies that support recommendations are summarized in online data supplement Evidence table 13+14	
COR	**LOE**	
3: No Benefit	**A**	13. In patients who have been hospitalized for COVID-19 and are not deemed at high-risk for complications, routine post-discharge prophylactic dose DOAC is not recommended to reduce the risk of death or thromboembolism [53]. NEW: A new RCT together with observational studies demonstrating a trend to decreasing severity of COVID-19 support a LOE A recommendation. (Section 3.4. in the 2022 ISTH COVID Guideline)
2b	**B-R**	14. In select high-risk 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 major thromboembolism [54, 55]. MODIFIED: "high-risk" has been added to point out the difference from recommendation 13. (Section 3.4. in the 2022 ISTH COVID Guideline)

Table 5. Rates of thromboembolism and death without thromboprophylaxis during different periods of the COVID-19 pandemic

Author	Study type	Study period	Follow-up	N	VTE	ATE	Death
Giannis*[54]	Registry	March – May 2020	3 months	4313	1.55%	1.72%	4.83%
Courtney[57]	Observational	March – October 2020	35 days	1039	1.3%	–	–
Li**[58]	Observational	March – November 2020	3 months	2116	1.6%	0.5%	3.8%
Arachchillage[59]	Observational	April 2020- December 2021	3 months	971	0.9%	–	–
Wang[53]	Randomized controlled trial	February 2021 – June 2022	30 days***	607	0.82%	0.49%	1.48%

*89% did not receive prophylaxis

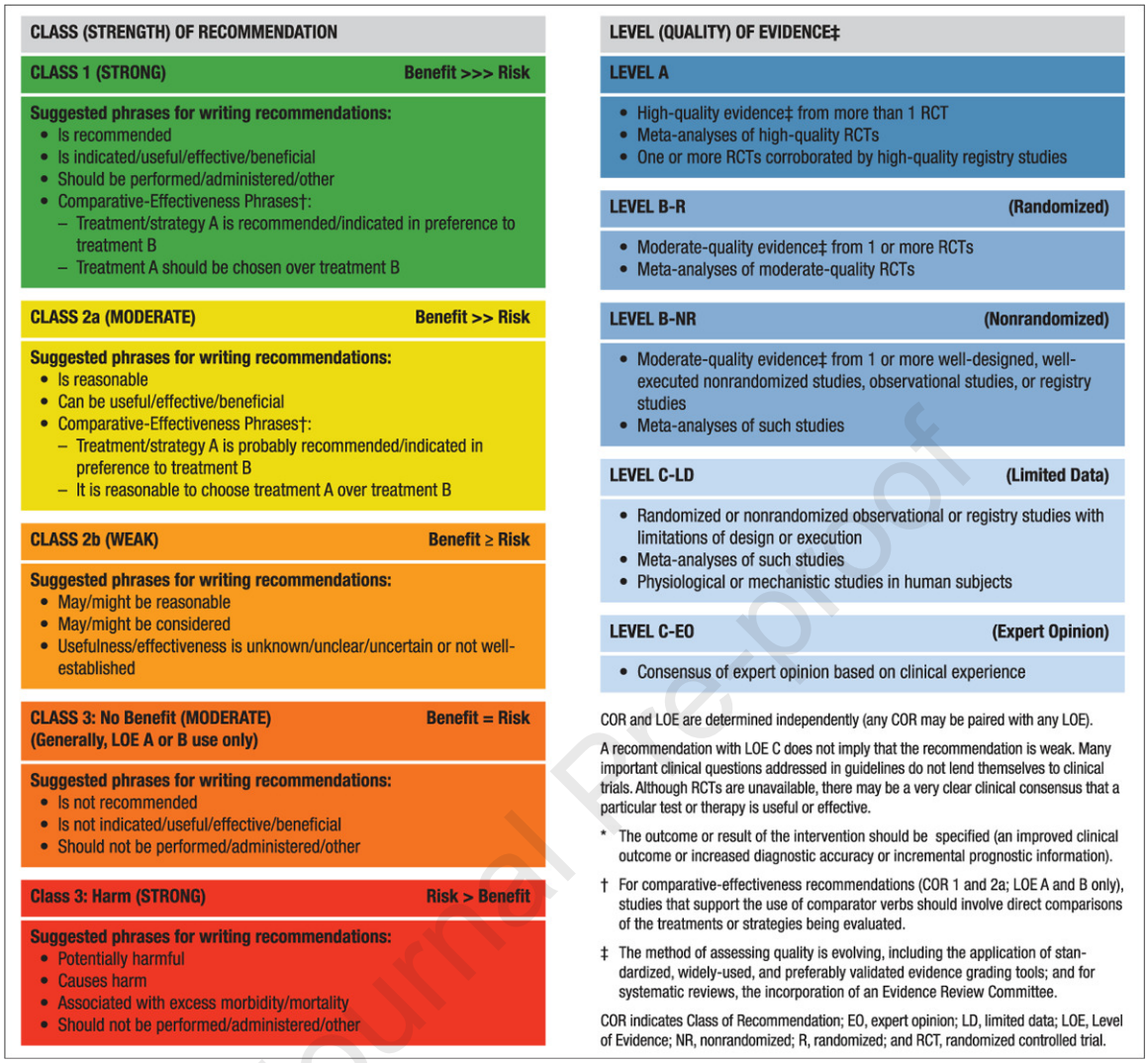
** The result for VTE is in patients without post-discharge anticoagulation (76% of entire population), whereas results for ATE and death are for the whole study population.

***The primary outcome was the event rate at 30 days. By 3 months the composite outcome of thromboembolism and death had increased from 2.3% to 2.8%.

		Table 6. Recommendation for patients with COVID-19 vaccination or with VITT Evidence from referenced studies that support recommendations are summarized in online data supplement Evidence tables 15-19
COR	**LOE**	
3: No Benefit	**B-NR**	15. For non-hospitalized patients with thrombophilia who receive a COVID-19 vaccine, prophylaxis with anticoagulants or an anti-platelet agent is not recommended for reducing risk of adverse outcomes [61].
1	**B-NR**	16. For diagnosing patients with suspected vaccine-induced thrombotic thrombocytopenia (VITT), use of anti-platelet factor 4 (PF4) enzyme immunoassays (EIA) is recommended [58, 62-66].
3: No Benefit	**B-NR**	17. For diagnosing patients with suspected VITT, use of rapid HIT assays such as particle gel immunoassay (PaGIA), lateral-flow assay (LFA), latex-enhanced immunoturbidimetric assay (LIA), or chemiluminescence immunoassay (CLIA) is not recommended [66].
2a	**C-LD**	18. For patients with VITT, when a non-heparin anticoagulant is unavailable, treatment with UFH or LMWH is reasonable for reducing risk of adverse outcomes [67-70].
2b	**C-LD**	19. For patients with VITT, treatment with intravenous immune globulin (IVIG) may be considered for reducing risk of death [68-70].

Table 7: Performance Characteristics of EIA for VITT

Author	EIA Test	Sensitivity	Specificity	NPV	PPV
Bissola [62]	Lifecodes: IgG/A/M-EIA In-house: PF4 EIA In-house: PF4/Hep-EIA	1.0 1.0 1.0	0.96 0.97 0.97	1.0 1.0 1.0	0.90 0.92 0.94
Mouta Nunes de Oliveira [64]	PF4/heparin IgG ELISA	1.0	1.0	1.0	1.0
Favaloro [63]	Asserachrom HPIA IgG ELISA	0.67 0.64 0.85	0.82 0.76 0.65	0.76 0.82 0.91	0.74 0.55 0.51
Lee [74]	PF4/heparin IgG ELISA	1.0	0.83	1.0	0.85
Thiele [65]	Anti-PF4/heparin IgG ELISA	1.0	0.80	1.0	0.95
Uzun [66]	Zymutest HIA IgG	1.0	0.87	1.0	0.90



CLASS (STRENGTH) OF RECOMMENDATION

CLASS 1 (STRONG) — **Benefit >>> Risk**

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS 2a (MODERATE) — **Benefit >> Risk**

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS 2b (WEAK) — **Benefit ≥ Risk**

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well-established

CLASS 3: No Benefit (MODERATE) — **Benefit = Risk**
(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

Class 3: Harm (STRONG) — **Risk > Benefit**

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R — **(Randomized)**
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL B-NR — **(Nonrandomized)**
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C-LD — **(Limited Data)**
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

LEVEL C-EO — **(Expert Opinion)**
- Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.