Antithrombotic therapy in the management of hospitalised patients with COVID-19

Abstract

Hospitalised patients with coronavirus disease 2019 (COVID-19) are at a significantly higher risk of having thromboembolic events while in hospital and in the immediate post-hospital discharge period. Based on early data from observational studies, multiple high quality randomised controlled trials have been conducted worldwide to evaluate optimal thromboprophylaxis regimens to reduce thromboembolism and other COVID-19-related adverse outcomes in hospitalised patients. The International Society on Thrombosis and Haemostasis has published evidence-based guideline recommendations using established methodology for the management of antithrombotic therapy of COVID-19 patients, both in-hospital and in the immediate post-hospital discharge period. A good clinical practice statement supplemented these guidelines based on topics for which there was no or limited high-quality evidence. This review summarises the main recommendations of these documents to serve as a quick access tool for hospital doctors to use in their everyday practice when treating COVID-19 patients.

Key words: Anticoagulants; Antiplatelets; Arterial thromboembolism; Coronavirus disease 2019; Hospitalisation; ISTH guidelines; Venous thromboembolism

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Ioannis Koulas[1]

Mark Goldin[1,2]

Sam Schulman[3]

Alex C Spyropoulos[1,2,4]

Author details can be found at the end of this article

Correspondence to:
Alex C Spyropoulos
aspyropoul@northwell.edu

Introduction

Throughout the coronavirus 2019 (COVID-19) pandemic, one of the main indicators of poor prognosis was the occurrence of thromboembolic events, either venous or arterial thromboembolism (Klok et al, 2020). Patients with COVID-19 are at a significantly higher risk of having thromboembolic events at any stage of the disease, from pre-hospitalisation into the post-discharge period (Peacock et al, 2022; Spyropoulos et al, 2022b). In response to early reports of unusually high rates of thromboembolism, especially in critical care settings, several inpatient clinical trials were completed to try to identify optimal antithrombotic strategies (Tritschler et al, 2020) (Table 1). Despite reinfections and new variants, which may alter thrombogenic potential, as well as evolving hospital-based care and vaccination efforts, which may dampen rates of thrombosis, the need remained for antithrombotic clinical practice guidelines for hospitalised COVID-19 patients using established methodology.

Towards this aim, the International Society on Thrombosis and Haemostasis (ISTH) published recommendations based on evidence from randomised trials on the management of antithrombotic therapy in hospitalised COVID-19 patients using the American College of Cardiology Foundation/American Heart Association methodology to assess level of evidence and class of recommendation (Schulman et al, 2022) (Table 2). The guidelines provided recommendations when the level of evidence was A or B, ie randomised clinical trials or well-designed observational studies/registries. To address specific topics for which only lower quality evidence was available, members of the guideline committee also published good practice statements to accompany the guideline recommendations (Spyropoulos et al, 2022a).

This review provides hospital-based clinicians a practical overview of the ISTH guidelines and good practice statements for the management of antithrombotic therapy in hospitalised COVID-19 patients (Figure 1). In both documents non-critically ill are patients are defined as those not requiring mechanical ventilation or organ support other than low-flow supplemental oxygen, while critically ill patients are defined as those requiring immediate organ support, such as invasive or non-invasive positive pressure ventilation, high-flow supplemental oxygen therapy, vasopressor or inotrope support, extracorporeal membrane

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Table 1. Key randomised clinical trials on anticoagulation in hospitalised COVID-19 patients

Study	N	Setting	Intervention	Comparison	Main conclusions
HEP-COVID (Spyropoulos et al, 2021)	253	Non-intensive care unit and intensive care unit hospitalised patients, D-dimer >4 times upper limit of normal of local lab or sepsis-induced coagulopathy score ≥4; modified from initial >6x upper limit of normal	Therapeutic dose enoxaparin	Prophylactic or intermediate low-molecular weight heparin or unfractionated heparin	Improved clinical outcomes with therapeutic dose in non-intensive care unit patients, no benefit in intensive care unit patients
RAPID (Sholzberg et al, 2021b)	465	Non-intensive care unit patients with D-dimer above upper limit of normal of local hospital in presence of an oxygen saturation ≤93% on room air, or ≥2 times upper limit of normal irrespective of oxygen saturation	Therapeutic dose low-molecular weight heparin or unfractionated heparin	Prophylactic dose low-molecular weight heparin or unfractionated heparin	Mortality was lower in the intervention arm
Perepu et al (2021)	176	Intensive care unit admission and/or had laboratory evidence of coagulopathy	Intermediate dose enoxaparin	Prophylactic dose enoxaparin	No difference in preventing death or thrombosis at 30 days
X-COVID-19 (Morici et al, 2022)	183	Non-intensive care unit hospitalised patients	Intermediate dose enoxaparin	Prophylactic dose enoxaparin	Underpowered but fewer pulmonary embolisms with intermediate dose
ACTION (Lopes et al, 2021)	615	Hospitalised patients with elevated D-dimer defined as above upper limit of normal per local lab	Therapeutic dose rivaroxaban if clinically stable; if unstable, intravenous unfractionated heparin and transition to rivaroxaban, including post-discharge rivaroxaban	Prophylactic enoxaparin or unfractionated heparin	No significant difference in primary outcomes
INSPIRATION (Sadeghipour et al, 2021)	562	Intensive care unit hospitalised patients	Intermediate dose enoxaparin	Prophylactic dose enoxaparin	No difference in primary outcomes
HESACOVID (Lemos et al, 2020)	20	Intensive care unit hospitalised patients	Therapeutic dose enoxaparin	Prophylactic dose enoxaparin or unfractionated heparin	Improved oxygenation parameters with therapeutic dosing
Oliynyk et al (2021)	126	Intensive care unit hospitalised patients	Therapeutic dose enoxaparin or unfractionated heparin	Prophylactic dose enoxaparin	Downward trend in the number of intubations and mortality in patients receiving unfractionated heparin as compared to low-molecular weight heparin

Table 1. Key randomised clinical trials on anticoagulation in hospitalised COVID-19 patients (continued)

Study	N	Setting	Intervention	Comparison	Main conclusions
REMAP-CAP, ACTIV-4a, ATTACC critically ill (REMAP-CAP Investigators et al, 2021)	1098	Intensive care unit hospitalised patients	Therapeutic dose low-molecular weight heparin or unfractionated heparin	Prophylactic or intermediate dose low-molecular weight heparin or unfractionated heparin	No difference in primary outcomes
REMAP-CAP, ACTIV-4a, ATTACC non-critically ill (ATTACC Investigators et al, 2021)	2219	Non-intensive care unit hospitalised patients	Therapeutic dose low-molecular weight heparin or unfractionated heparin	Prophylactic or intermediate dose low-molecular weight heparin or unfractionated heparin	Higher probability of superiority of therapeutic doses for organ support-free days
COVID-HEP (Blondon et al, 2022)	159	Non-intensive care unit and intensive care unit hospitalised patients	Therapeutic dose enoxaparin or unfractionated heparin	Prophylactic or intermediate dose enoxaparin or unfractionated heparin	No difference in primary outcomes
BEMICOP (Marcos-Jubilar et al, 2022)	65	Non-intensive care unit hospitalised patients	Therapeutic dose bemiparin	Prophylactic dose bemiparin	No difference in primary outcomes

oxygenation, or continuous renal replacement therapy, irrespective of patient location within a hospital (Schulman et al, 2022).

Thromboprophylaxis for non-critically ill, hospitalised patients

Several observational studies have shown that low (prophylactic) dose low-molecular weight heparin or unfractionated heparin compared to no heparin leads to a reduction in mortality rates among patients hospitalised for COVID-19 with no significant increase in bleeding (Cohen et al, 2021; Di Castelnuovo et al, 2021; Ionescu et al, 2021; Pereyra et al, 2021; Rentsch et al, 2021; Spyropoulos et al, 2021; Battistoni et al, 2022; Poli et al, 2022; Shen et al, 2022).

Three randomised trials compared therapeutic-dose heparin (either low-molecular weight heparin or unfractionated heparin) to standard-dose heparin. The large ATTACC/ACTIV-4a/REMAP-CAP multiplatform trial revealed an increase in organ support-free days with mostly therapeutic low-molecular weight heparin over prophylactic-to-intermediate dose heparin (ATTACC Investigators et al, 2021), the HEP-COVID trial demonstrated a 13.2% absolute risk reduction in major thromboembolism and mortality with therapeutic-dose heparin (mostly low-molecular weight heparin) over prophylactic to intermediate-doses of heparin (Spyropoulos et al, 2021), and the RAPID trial revealed an 5.8% absolute risk reduction in all-cause mortality as a secondary outcome with therapeutic low-molecular weight heparin or unfractionated heparin over prophylactic low-molecular weight heparin or unfractionated heparin (Sholzberg et al, 2021b). A small randomised trial did not show any difference between therapeutic vs prophylactic dose of the low-molecular weight heparin bemiparin in the composite outcome of death, intensive care unit admission, need for mechanical ventilation, development of moderate or severe acute respiratory distress, and venous or arterial thromboembolism, but the trial was severely underpowered to show treatment effects (Marcos-Jubilar et al, 2022).

Based on these data, the ISTH guidelines state that in non-critically ill patients hospitalised for COVID-19, low (prophylactic) dose low-molecular weight heparin or unfractionated heparin is recommended in preference to no low-molecular weight heparin or unfractionated heparin to reduce the risk of thromboembolism and possibly death (class of recommendation 1, level of evidence B-NR), and therapeutic-dose low-molecular weight heparin or unfractionated

Table 2. Summary of International Society on Thrombosis and Haemostasis guidelines for hospitalised patients with Coronavirus disease 2019

Group of patients	Class of recommendation	Level of evidence	Description
Non–critically ill, hospitalised patients	1	B-NR	In non-critically ill patients hospitalised for COVID-19, low (prophylactic) dose low-molecular weight heparin or unfractionated heparin is recommended in preference to no low-molecular weight heparin or unfractionated heparin to reduce risk of thromboembolism and possibly death
	1	A	In select non-critically ill patients hospitalised for COVID-19, therapeutic-dose low-molecular weight heparin or unfractionated heparin is beneficial in preference to low (prophylactic) or intermediate dose low-molecular weight heparin or unfractionated heparin to reduce risk of thromboembolism and end organ failure
	3: No benefit	B-R	In non-critically ill patients hospitalised for COVID-19, intermediate-dose low-molecular weight heparin or unfractionated heparin is not recommended in preference to low (prophylactic) dose low-molecular weight heparin or unfractionated heparin to reduce risk of thromboembolism and other adverse outcomes
	3: Harm	A	In non-critically ill patients hospitalised for COVID-19, add-on treatment with an antiplatelet agent is potentially harmful and should not be used
	3: No benefit	B-R	In non-critically ill patients hospitalised for COVID-19, therapeutic-dose direct oral anticoagulant is not effective to reduce risk of thromboembolism and other adverse outcomes
Critically ill, hospitalised patients	3: No benefit	B-R	In critically ill patients hospitalised for COVID-19, intermediate dose low-molecular weight heparin or unfractionated heparin is not recommended over prophylactic dose low-molecular weight heparin or unfractionated heparin to reduce risk of adverse events, including mortality and thromboembolism
	3: No benefit	B-R	In critically ill patients hospitalised for COVID-19, therapeutic dose low-molecular weight heparin or unfractionated heparin is not recommended over usual-care or prophylactic dose low-molecular weight heparin or unfractionated heparins
	2b	B-R	In select critically ill patients hospitalised for COVID-19, add on treatment with an antiplatelet agent to prophylactic dose low-molecular weight heparin or unfractionated heparin is not well established but might be considered to reduce mortality
Post-discharge phase	2b	B-R	In select patients who have been hospitalised for COVID-19, post-discharge treatment with prophylactic dose rivaroxaban for approximately 30 days may be considered to reduce risk of venous thromboembolism

From Schulman et al (2022)

heparin is beneficial in preference to low (prophylactic) or intermediate dose low-molecular weight heparin or unfractionated heparin to reduce risk of thromboembolism and end organ failure in select patients with risk factors for thromboembolism or organ failure (class of recommendation 1, level of evidence A) (Schulman et al, 2022). The good practice statements define these patients as those with low bleeding risk, and elevated D-dimer levels (≥2 times the upper limit of normal) or with need for supplemental oxygen or reduced oxygen saturation (≤93% room air) (Spyropoulos et al, 2022a) (Figure 1).

No trial has shown reduced need for mechanical ventilation or all-cause mortality with intermediate dose low-molecular weight heparin or unfractionated heparin compared with prophylactic dose heparin in non-critically ill COVID-19 patients, including the X-COVID trial (Morici et al, 2022) and the PROTHROMCOVID trial (Muñoz-Rivas et al, 2022). The ISTH guidelines state that in non-critically ill patients hospitalised for COVID-19, intermediate-dose low-molecular weight heparin or unfractionated heparin is not recommended in preference to low (prophylactic) dose low-molecular weight

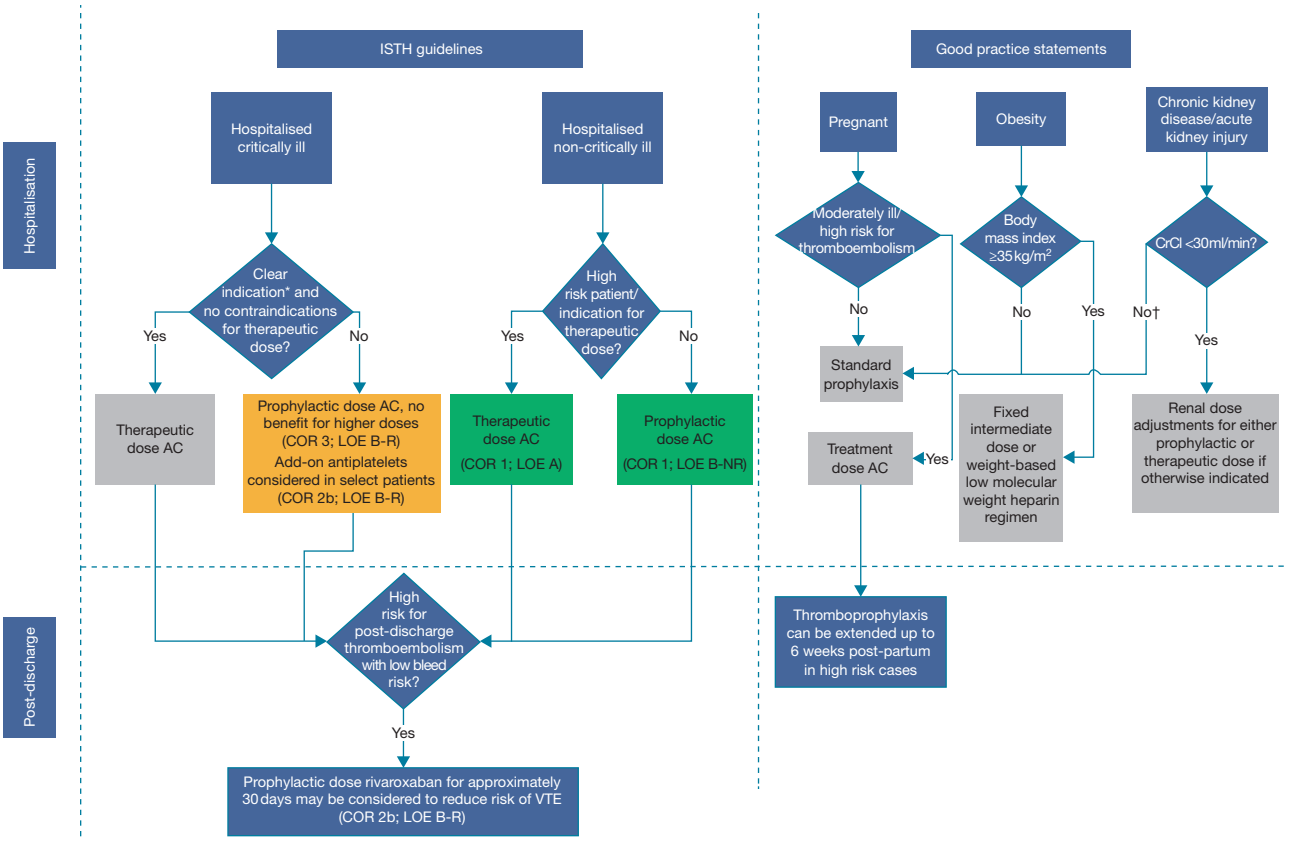

Figure 1. Flowchart of the 2022 International Society on Thrombosis and Haemostasis (ISTH) guidelines (Schulman et al, 2022) and good practice statements (Spyropoulos et al, 2022a) for antithrombotic treatment of hospitalised patients with Coronavirus disease 2019. The colour coding from the guidelines is based on the American Heart Association formats for level of evidence (LOE) and class of recommendation (COR). AC = anticoagulation; CrCl = creatinine clearance; VTE = venous thromboembolism. *New or recent VTE, atrial fibrillation, mechanical heart valves; † Therapeutic doses can be used for CrCl >30 ml/min if indicated.

heparin or unfractionated heparin to reduce the risk of thromboembolism or other adverse outcomes (class of recommendation 3 (no benefit), level of evidence B-R). Last, based on the results of the ACTION trial, which showed no benefit of in-hospital and extended duration rivaroxaban 20 mg daily vs standard in-hospital heparin, therapeutic-dose direct oral anticoagulants are not effective to reduce risk of thromboembolism and other adverse outcomes (class of recommendation 3 (no benefit), level of evidence B-R) (Lopes et al, 2021; Marcos-Jubilar et al, 2022; Schulman et al, 2022) (Figure 1).

Use of antiplatelets in hospitalised ward patients

Two randomised controlled trials, including the large RECOVERY trial, have shown no reduction in death or need for organ support with the use of aspirin or P2Y12 inhibitors as add-on therapy in non-critically ill hospitalised patients with COVID-19; moreover, this strategy has shown increased frequency of major bleeding events (Berger et al, 2022; RECOVERY Collaborative Group, 2022). As such, ISTH guidelines state that in non-critically ill patients hospitalised for COVID-19, add-on therapies with antiplatelet agents are potentially harmful and should not be used (class of recommendation 3 (harm), level of evidence A) (Figure 1).

Good practice statements for hospitalised patients

Pregnancy

Standard thromboprophylaxis, preferentially with low-molecular weight heparin, is recommended for all hospitalised antepartum patients admitted primarily for COVID-19 pneumonia and without bleeding risk or anticipated delivery within 12 hours. In patients with

elevated peripartum bleeding risk, intravenous unfractionated heparin can be used instead. For moderately ill patients, treatment dose low-molecular weight heparin can be used on a case-by-case basis. Thromboprophylaxis can be extended up to 6 weeks postpartum in high-risk cases, such as patients with high International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) scores and/or elevated D-dimer levels with low bleeding risk (D'Souza et al, 2020; Spyropoulos et al, 2022a) (Figure 1).

Paediatric population

Based on the COVAC-TP trial (Sochet et al, 2022), use of weight-based enoxaparin at half the treatment dose (0.5 mg/kg subcutaneously twice daily, maximum 60 mg/dose) should be considered for primary thromboprophylaxis in children hospitalised for COVID-19 with or without paediatric multisystem inflammatory syndrome, with intravenous unfractionated heparin preferred in clinically unstable patients or those with severe renal impairment (Spyropoulos et al, 2022a).

Chronic kidney disease, acute kidney injury and renal replacement therapy

Observational studies and clinical trials in patients without COVID-19 support the use of standard prophylactic doses of low-molecular weight heparin (eg enoxaparin 40 mg subcutaneously daily) or unfractionated heparin (5000 IU subcutaneously twice or thrice daily) down to a creatinine clearance of 30 ml/min (Spyropoulos et al, 2022a) (Figure 1). When indicated, therapeutic dose low-molecular weight heparin may be used down to a creatinine clearance of 30 ml/min, whereas for creatinine clearance of 15–29 ml/min a renal dose adjustment of low-molecular weight heparin would be needed for both prophylaxis (eg enoxaparin 30 mg subcutaneously daily) or treatment (eg enoxaparin 1 mg/kg subcutaneously every 24 hours or 0.5 mg/kg subcutaneously twice daily). For creatinine clearance <15 ml/min unfractionated heparin should be used for both prophylactic (unfractionated heparin 5000 IU subcutaneously twice daily) and standard therapeutic doses (80 IU/kg bolus intravenously followed by 18 IU/kg/hr infusion), ideally with monitoring via heparin anti-Xa levels or the activated partial thromboplastin time. For patients on continuous renal replacement therapy, standard-dose thromboprophylaxis should be used. In all cases fondaparinux should be avoided because of its dependence on renal clearance, especially in patients with fluctuating renal function or with a creatinine clearance <30 ml/min (Spyropoulos et al, 2022a).

Obese patients

In hospitalised COVID-19 patients with class I obesity (body mass index 30–35 kg/m^2) thromboprophylaxis dosing mirrors that for non-obese patients – low (prophylactic) dose low-molecular weight heparin (eg enoxaparin 40 mg subcutaneously daily) or unfractionated heparin (eg 5000 IU subcutaneously twice or thrice daily). For patients with class II or greater obesity (body mass index ≥35 kg/m^2) who do not meet criteria for therapeutic-dose heparin, a fixed intermediate dose low-molecular weight heparin (eg enoxaparin 40 mg subcutaneously twice daily) or a weight-based low-molecular weight heparin regimen (eg enoxaparin 0.5 mg/kg subcutaneous twice daily) can be used (Spyropoulos et al, 2022a) (Figure 1).

Patients taking oral anticoagulants pre-hospital

It is reasonable for patients taking direct oral anticoagulants to switch to low-molecular weight heparin or unfractionated heparin during hospitalisation if they concurrently receive medications that affect CYP3A4 liver enzymes, such as the antiviral nirmatrelvir/ritonavir (Spyropoulos et al, 2022a). Patients on vitamin K antagonists can continue these drugs in-hospital at the prescribed target international normalised ratio range with frequent monitoring; instability of the international normalised ratio or invasive procedures may prompt switching to low-molecular weight or unfractionated heparin (Spyropoulos et al, 2022a).

Management of patients with indications for therapeutic-dose anticoagulants

Based on the ISTH guidelines all patients with new or recent venous thromboembolism, atrial fibrillation or mechanical heart valves should be placed on therapeutic dose low-molecular

weight heparin or unfractionated heparin unless otherwise contraindicated (Schulman et al, 2022). For patients hospitalised for COVID-19 with acute venous thromboembolism, the use of low-molecular weight or unfractionated heparin should be considered over a direct oral anticoagulant, preferably weight-based therapeutic-dose low-molecular weight heparin at twice-daily dosing (Spyropoulos et al, 2022a). For patients with high body mass index, weight-adjusted low-molecular weight heparin with anti-Xa trough and peak levels can be used to assess adequate anticoagulation on one occasion after 48 hours. For patients on intravenous unfractionated heparin, weight-adjusted and nomogram-based monitoring with anti-Xa levels are preferred over activated partial thromboplastin time monitoring.

Use of antiplatelet treatments

For patients who were previously on antiplatelet therapy, the decision to continue or interrupt such treatment during anticoagulant therapy should be based on an individual assessment of risk factors for thrombosis and bleeding. Continuation would be acceptable in patients with clear indications, such as recent acute coronary syndrome or those with a coronary stent (Spyropoulos et al, 2022a).

Thromboprophylaxis on transfer from hospital ward to intensive care unit

The good practice statements recommended that hospital ward patients initially meeting criteria for therapeutic dose thromboprophylaxis who develop severe illness and require transfer to the intensive care unit should be de-escalated from therapeutic dose unfractionated or low-molecular weight heparin to prophylactic dose heparin, except in cases of confirmed thrombosis, atrial fibrillation, or other clear indications for therapeutic anticoagulation (Spyropoulos et al, 2022a). As for add-on antiplatelet therapies, select critically ill patients at low bleeding risk who are not on therapeutic anticoagulation and who receive gastric acid suppression may be considered for add-on therapy with low-dose aspirin or a P2Y12 inhibitor in addition to standard low-dose heparin thromboprophylaxis (Spyropoulos et al, 2022a).

Thromboprophylaxis of critically ill hospitalised patients

Two randomised controlled trials compared intermediate low-molecular weight heparin vs low (prophylactic) dose low-molecular weight heparin or unfractionated heparin in critically ill COVID-19 patients (Perepu et al, 2021; Sadeghipour et al, 2021; Bikdeli et al, 2022). The INSPIRATION trial found no difference across treatment arms for the primary outcome, a composite of venous or arterial thromboembolism, treatment with extracorporeal membrane oxygenation, and all-cause mortality (Sadeghipour et al, 2021; Bikdeli et al, 2022). A second trial comparing intermediate-dose low-molecular weight heparin with prophylactic dose heparin in intensive care unit patients with or without positive laboratory markers of coagulopathy revealed no difference in the primary outcome of 30-day all-cause mortality (Perepu et al, 2021).

The REMAP-CAP/ACTIV-4a/ATTACC multiplatform trial did not reveal any difference in the primary outcome of organ support-free days (REMAP-CAP Investigators et al, 2021), and the critically ill patient subgroup of the HEP-COVID trial did not reveal significant differences in outcomes with therapeutic dose low-molecular weight heparin or unfractionated heparin vs standard prophylactic or intermediate dose low-molecular weight heparin or unfractionated heparin (Spyropoulos et al, 2021). Another smaller trial, COVID-HEP, also did not show a statistically significant difference in reducing mortality or thrombotic outcomes in critically ill patients (Blondon et al, 2022). A meta-analysis of three randomised controlled trials in critically-ill COVID-19 patients (Lemos et al, 2020; REMAP-CAP Investigators et al, 2021; Spyropoulos et al, 2021) demonstrated mixed results with therapeutic dose low-molecular weight heparin or unfractionated heparin, showing a significant reduction in major thrombotic events (absolute risk reduction 4.1%), a non-significant increase in the risk of major bleeding and a decrease in organ support-free days (Sholzberg et al, 2021a). Thus, ISTH guidelines do not recommend intermediate or

therapeutic dose low-molecular weight or unfractionated heparin over prophylactic dose low-molecular weight or unfractionated heparin to reduce risk of adverse events, including mortality and thromboembolism, in critically ill patients hospitalised for COVID-19 (class of recommendation 3 (no benefit), level of evidence B-R for both intermediate and therapeutic-dose heparins) (Schulman et al, 2022) (Figure 1).

Use of antiplatelets in critical care settings

In the RECOVERY trial, there was no reduction in mortality risk at 28 days with aspirin 150 mg daily vs control among patients receiving non-invasive or invasive ventilation (RECOVERY Collaborative Group, 2022). In the REMAP-CAP trial, in which critically ill COVID-19 patients received aspirin 75–100 mg daily, a P2Y12 inhibitor or no antiplatelet therapy, the adjusted absolute difference in survival until 90 days was 5% with 99.7% posterior probability of efficacy in the group with antiplatelets, but the risk of major bleeding was increased (adjusted absolute risk increase 0.8%) (REMAP-CAP Writing Committee for the REMAP-CAP Investigators et al, 2022). Based on these results, ISTH guidelines state that in select critically ill patients hospitalised for COVID-19, add-on treatment with an antiplatelet agent to prophylactic dose low-molecular weight or unfractionated heparin is not well established but might be considered to reduce mortality (class of recommendation 2b, level of evidence B-R) (Schulman et al, 2022). The good practice statements defined select critically ill populations as those at low bleeding risk, not on therapeutic anticoagulation and receiving gastric acid suppression (Spyropoulos et al, 2022a) (Figure 1).

Antithrombotic therapy in the immediate hospital post-discharge phase

The MICHELLE trial compared post-discharge treatment with rivaroxaban 10 mg per day vs placebo for 35 days in patients hospitalised for COVID-19 at high risk of thrombosis, based on an IMPROVE plus D-dimer (IMPROVE-DD) score of 4 or higher at discharge (Ramacciotti et al, 2022). Post-discharge prophylaxis with rivaroxaban decreased the risk of major and fatal thromboembolism and cardiovascular death with no major bleeding. The ACTIV-IVc trial has recently been completed, comparing apixaban 2.5 mg twice daily vs placebo for 30 days post-discharge in hospitalised COVID-19 patients (https://clinicaltrials.gov/ct2/show/NCT04650087?term=apixaban&cond=COVID-19&draw=2&rank=3). However, the trial is not using enrichment criteria to define high-risk subgroups and thus has a low probability of success. ISTH guidelines recommend that in select patients hospitalised for COVID-19, post-discharge treatment with prophylactic dose rivaroxaban for approximately 30 days may be considered to reduce risk of venous thromboembolism (class of recommendation 2b, level of evidence B-R) (Schulman et al, 2022) (Figure 1). The good practice statements defined patients at high risk for venous thromboembolism as those with an IMPROVE score of ≥ 4 or 2–3 with a D-dimer level twice the upper limit of normal and without high risk of bleeding (Spyropoulos et al, 2020; Ramacciotti et al, 2022; Schulman et al, 2022).

Conclusions

The ISTH guidelines and related good practice statements for antithrombotic management in patients hospitalised for COVID-19 provide concise recommendations using established methodology regarding the thromboprophylaxis and antithrombotic treatment of COVID-19 patients in non-critical care, critical care and immediate post-hospital discharge settings, based on the best available evidence from published clinical trials and observational studies. With the emergence of new variants with lower pathogenicity of the severe acute respiratory coronavirus 2 (SARS-CoV-2), and with expanded use of vaccinations against the virus as well as improved hospital care with targeted anti-inflammatory and antiviral therapies, some of the recommendations and good practice statements may have to be modified depending upon new evidence from further studies. As these guidelines represent a ‘living document’, they will be updated with the addition of new high-quality evidence in the rapidly evolving field of antithrombotic therapy in the management of COVID-19 patients.

Key points

- In non-critically ill patients hospitalised for COVID-19, low (prophylactic) dose low molecular weight heparin or unfractionated heparin is recommended in preference to no low-molecular weight heparin or unfractionated heparin to reduce risk of thromboembolism and possibly death.
- In select non-critically ill patients hospitalised for COVID-19, therapeutic-dose low-molecular weight heparin or unfractionated heparin is beneficial in preference to low (prophylactic) or intermediate dose low-molecular weight heparin or unfractionated heparin to reduce risk of thromboembolism and end organ failure.
- In non-critically ill patients hospitalised for COVID-19, intermediate-dose low-molecular weight heparin or unfractionated heparin is not recommended in preference to low (prophylactic) dose low-molecular weight heparin or unfractionated heparin to reduce risk of thromboembolism and other adverse outcomes.
- In non-critically ill patients hospitalised for COVID-19, add-on treatment with an antiplatelet agent is potentially harmful and should not be used.
- In critically ill patients hospitalised for COVID-19, intermediate or therapeutic dose low-molecular weight heparin/unfractionated heparin is not recommended over prophylactic dose.
- In select patients who have been hospitalised for COVID-19, post-discharge treatment with prophylactic dose rivaroxaban for approximately 30 days may be considered to reduce risk of venous thromboembolism.

Author details

[1]Institute of Health System Science, Feinstein Institutes for Medical Research, Northwell Health, Manhasset, NY, USA

[2]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA

[3]Department of Medicine, Thrombosis and Atherosclerosis Research Institute, McMaster University, Hamilton, ON, Canada

[4]Department of Medicine, Anticoagulation and Clinical Thrombosis Services, Northwell Health at Lenox Hill Hospital, New York, NY, USA

Conflicts of interest

ACS has received research grants from Boehringer Ingelheim and Consultation fees from Janssen, Bristol Meyers Squibb, Portola, Boehringer Ingelheim, Bayer, the ATLAS group. SS 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. MG has received research grant support and honoraria from Janssen. IK has no conflicts of interest to declare.

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