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RECOMMENDATIONS AND GUIDELINES

Good practice statements for antithrombotic therapy in the management of COVID-19: Guidance from the SSC of the ISTH

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Abstract

Despite the emergence of high quality randomized trial data with the use of antithrombotic agents to reduce the risk of thromboembolism, end-organ failure, and possibly mortality in patients with coronavirus disease 2019 (COVID-19), questions still remain as to optimal patient selection for these strategies, the use of antithrombotics in outpatient settings and in-hospital settings (including critical care units), thromboprophylaxis in special patient populations, and the management of acute thrombosis in hospitalized COVID-19 patients. In October 2021, the International Society on Thrombosis and Haemostasis (ISTH) formed a multidisciplinary and international panel of content experts, two patient representatives, and a methodologist to develop recommendations on treatment with anticoagulants and antiplatelet agents for COVID-19 patients. The ISTH Guideline panel discussed additional topics to be well suited to a non-Grading of Recommendations Assessment, Development, and Evaluation (GRADE) for Good Practice Statements (GPS) to support good clinical care in the antithrombotic management of COVID-19 patients in various clinical settings. The GPS panel agreed on 17 GPS: 3 in the outpatient (pre-hospital) setting, 12 in the hospital setting both in non-critical care (ward) as well as intensive care unit settings, and 2 in the immediate post-hospital discharge setting based on limited evidence or expert opinion that supports net clinical benefit in enacting the statements provided. The antithrombotic therapies discussed in these GPS should be available in low- and middle-income countries.

KEYWORDS
anticoagulant, antiplatelet, antithrombotic therapy, coronavirus disease 2019, hospitalization, severe acute respiratory syndrome coronavirus 2

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1 | METHODS

After finalizing the Population, Intervention, Comparison, and Outcome (PICO) questions for the International Society on Thrombosis and Haemostasis (ISTH) Guidelines on antithrombotic management of COVID-19, several topics were identified by the Guidelines panel to be well suited to a non-Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) for Good Practice Statements (GPS). The ISTH Guideline panel discussed these topics to support good clinical care in the antithrombotic management of coronavirus disease 2019 (COVID-19) patients and drafted an initial set of statements for distribution to the panelists of the GPS. The GPS panel constructed additional statements in pre-hospital (outpatient), in-hospital, and immediate post-hospital discharge settings and reviewed all statements for relevance and accuracy. The GPS were revised based on panelist feedback. The final GPS were redistributed for further revisions, which were approved by all panelists.

2 | COMMENT

The GPS are not based on a systematic search or formal review of the evidence and are intended to provide expert-based opinion on various aspects of antithrombotic management of COVID-19 patients that are considered clinically important. Moreover, they address topics for which there is either no or very limited high-certainty evidence, yet there is a body of direct or indirect evidence or clinical experience that supports the premise of net clinical benefit in enacting the statements provided. The following GPS are intended to assist health-care providers in antithrombotic management of COVID-19 patients and should be considered with caution, given this limited evidence base. As always, the unique clinical circumstances of individual patients, the provider's clinical judgment, and the patient's values and preferences should all be considered in clinical management decisions. Last, the antithrombotic therapies discussed in these GPS, including antiplatelet agents such as aspirin and heparins (including unfractionated heparin [UFH] and low molecular weight heparin [LMWH]), should be available in low- and middle-income countries.

3 | OUTPATIENT (PRE-HOSPITALIZATION) PERIOD

Retrospective studies and clinical trials suggest that patients with COVID-19 who do not require hospital-based care have an overall low rate (~1.0%) of major thromboembolism and mortality.[1] In general, two patient types with COVID-19 have been described in this outpatient (non-hospitalized) period: those with mild-severity disease, who are hemodynamically stable and have a resting room air oxygen saturation ≥ 94%, or those with moderate-severity disease who are hemodynamically stable, but have a resting room air oxygen saturation 90%–94% and require advanced care such as a "hospital-at-home" program, especially when hospitals are over capacity.[2–4] One placebo-controlled randomized trial—the ACTIV 4b trial—that compared usual care to treatment with the direct oral anticoagulant (DOAC) apixaban at therapeutic (5 mg twice daily) and prophylactic (2.5 mg twice daily) doses or 81 mg of aspirin daily, in addition to unadjusted cohort studies, has not shown benefit of initiating antithrombotic therapy during the outpatient period in COVID-19.[2] However, the results of other large placebo-controlled randomized trials in COVID-19 outpatients with similar inclusion criteria (including advanced age and cardiovascular risk factors) using LMWH and the DOAC rivaroxaban, respectively, are still pending.[5–9] Observational data suggest that COVID-19 outpatients with clinical indications for antiplatelet or oral anticoagulant therapy should continue such therapy.[1,10]

3.1 | The use of DOACs versus vitamin K antagonists in the outpatient (pre-hospitalization) period

3.1.1 | Statement 1

In non-hospitalized patients with clinical indications for anticoagulant therapy and eligible to receive certain anti-viral COVID-19 medications (e.g., nirmatrelvir/ritonavir [Paxlovid]), there is potential for important drug–drug interactions, particularly with oral direct factor Xa inhibitors (apixaban, rivaroxaban, edoxaban) that may increase the bioavailability of these anticoagulants and, in turn, may increase patients' risk for bleeding.[11,12] In the case of Paxlovid, the ritonavir component creates the potential drug–drug interaction because it competes with DOACs for cytochrome P450 (CYP) 3A4 metabolic elimination. Alternatives to drugs such as Paxlovid include the antiviral remdesivir or the monoclonal antibody sotrovimab in patients at high risk for hospitalization (e.g., immunocompromised), and fluvoxamine or inhaled budesonide in patients at low risk for hospitalization, although available monoclonal antibodies may have decreased efficacy against emerging COVID-19 variants. Although patients who are taking a DOAC could be switched to a vitamin K antagonist (VKA) such as warfarin, which would allow monitoring of the anticoagulant effect with international normalized ratio (INR) testing, this approach is problematic because of increased variability of INR in patients with newly diagnosed COVID-19 pneumonia, coupled with the short 5-day treatment duration of anti-viral drugs such as Paxlovid, especially as inhibition resolves approximately 3 days after Paxlovid is discontinued.[13] Unless otherwise stated, potentially interacting medications should be managed (held/dose-reduced/monitored closely) for at least 7 days from the time of Paxlovid initiation. Temporary use of LMWH is also a potential option for some. It is suggested to take an individualized approach with consideration of patient preference of oral anticoagulants during the period of antiviral COVID-19 treatment; however, oral anticoagulants should be

continued whenever possible.[14] The current revised product label (April 8, 2022) states the following about oral anticoagulants and use of Paxlovid: closely monitor the INR with warfarin and either avoid concomitant use with rivaroxaban and dabigatran, or depending upon dabigatran indication and renal function, reduce the dose of dabigatran (DDI Recommendations_v005.pdf; pfizerpro.com). Further guidance on use with medications that have potential drug–drug interactions can be found in the Paxlovid package insert at Paxlovid HCP FS 04142022 (fda.gov) and the Paxlovid patient eligibility checklist at PAXLOVID Patient Eligibility Screening Checklist and Drug Interaction Tool for Prescribers (fda.gov).

3.2 | LMWH and other heparins versus no heparin in the outpatient (pre-hospitalization) period

3.2.1 | Statement 2

A cohort study that evaluated patients (n = 5597) with COVID-19 demonstrated a decreased risk of hospitalization among the 2.9% (n = 160) of those on anticoagulation for cardiovascular indications prior to hospitalization.[10] Of those on anticoagulants, 82 patients were on DOACs, 67 on warfarin, and 11 on the LMWH enoxaparin. These findings suggest that anticoagulation may be of benefit among those with pre-existing cardiovascular disease. Expert opinion suggests continuation of heparin-specific anticoagulation in patients with prior indications.[10] Two ongoing trials with LMWH should provide guidance on whether its initiation in outpatients with COVID-19 will improve clinical outcomes.[9,15] Given the lack of evidence to date, heparin agents including LMWH should not be initiated in outpatients with COVID-19. Patients in "hospital-at-home" programs with the need for supplemental oxygen of at least 2 L/min and immobility may be considered for primary thromboprophylaxis (e.g., enoxaparin 40 mg subcutaneously daily) if determined to have the same risk as hospitalized patients with moderate-severity disease. Outpatients with COVID-19 with an ongoing clinical indication for UFH/LMWH therapy (e.g., cancer-associated thrombosis or thromboprophylaxis during pregnancy) should continue their heparin therapy during this period.

3.3 | Antiplatelets during the outpatient (pre-hospitalization) period

3.3.1 | Statement 3

A large retrospective cohort study suggested that prior antiplatelet use in patients who developed COVID-19 was associated with a decreased risk of venous thromboembolism (VTE) or mortality.[1] The previously described ACTIV-4b trial did not show benefit of daily low dose aspirin initiated in outpatients with COVID-19.[5] As such, antiplatelet therapy should be continued in outpatients with COVID-19 if there is a clinical indication, but as per the ISTH COVID-19 Antithrombotic Guidelines, antiplatelet therapy, including aspirin, should not be initiated in non-hospitalized patients with COVID-19.

4 | HOSPITALIZATION PERIOD

4.1 | Hospitalized non–critically ill COVID-19 populations

Hospitalization criteria for non–critically ill patients with COVID-19 have varied across countries, health systems, and phases of the pandemic.[16–18] Definitions of non–critically ill patients have also varied across randomized trials in hospitalized patients for COVID-19.[19] In general terms, patients hospitalized for COVID-19 not requiring mechanical ventilation or organ support other than low-flow supplemental oxygen are considered non–critically ill.

4.1.1 | Patient selection for therapeutic-dose heparin thromboprophylaxis in ward settings

Statement 4

There have been approximately 20 trials assessing optimal thromboprophylaxis dosing in hospitalized COVID-19 patients, comparing therapeutic-dose heparins (mostly LMWH) to either prophylactic-dose or up to intermediate-dose heparins including LMWH and UFH.[19] Inclusion criteria for moderately ill patients in non–critical care settings included those with an elevated D dimer (Dd), an elevated sepsis induced coagulopathy score, and increased oxygen requirements not requiring mechanical ventilation.[19] All trials selected patients at low bleeding risk, with key exclusionary criteria consisting of receipt of dual antiplatelet therapy, bleeding within the past month, active cancer (especially gastrointestinal or intracranial cancer), bronchiectasis or pulmonary cavitation, hepatic dysfunction with a baseline INR>1.5, creatinine clearance (CrCl) less than 15 ml/min/1.73 m^2, or a platelet count <25 000/μl. Three trials revealed improved outcomes with mostly therapeutic-dose LMWH: the large multiplatform trial showed reduced need for organ support and increased probability of survival to hospital discharge as part of the primary outcome; the HEP-COVID trial showed a reduction in the primary composite outcome of major thromboembolism and all-cause mortality; and the RAPID trial showed a reduction in the secondary outcome of mortality.[20–22] The multiplatform trial (ATTACC, ACTIV-4a, and REMAP-CAP) showed the greatest absolute treatment effect in the high Dd cohort (≥2 times the local laboratory upper limit of normal [ULN]),[20] while both HEP-COVID and RAPID selected patients with very high (>4 times ULN) or high (≥2 times ULN, irrespective of oxygen saturation) Dd levels.[21,22] HEP-COVID and RAPID also included requirements for supplemental oxygen or reduced oxygen saturation (≤93% on room air).[21,22] Moderately ill patients hospitalized for COVID-19 in non–critical care settings not requiring organ support and who have (1) low bleeding risk, and (2) elevated Dd levels (≥2 times ULN) or require supplemental oxygen or

have reduced oxygen saturation (≤93% on room air) are ideal candidates for therapeutic heparin anticoagulation as thromboprophylaxis. The most widely studied heparin anticoagulant in this setting is LMWH at weight-based therapeutic doses given subcutaneously.

4.2 | Special patient populations

4.2.1 | Pregnancy and post-partum patients

Statement 5

Thromboprophylaxis strategies in hospitalized pregnant and post-partum patients with COVID-19 have relied substantially on expert opinion given a preponderance of very limited data. While pregnancy confers a prothrombotic state due to many factors (e.g., increased factor VII, VIII, X, XII, fibrinogen; decreased protein S; altered fibrinolysis),[23] early observational studies, including those specifically of hospitalized patients, reported conflicting thrombosis rates associated with inconsistent or unclear thromboprophylaxis protocols.[24–27] A critical review of 35 professional society guidelines recommended a strategy of standard thromboprophylaxis, preferentially with LMWH, for all hospitalized ante-partum patients admitted primarily for COVID-19 pneumonia and without bleeding risk or anticipated delivery within 12 h; in cases of elevated bleeding risk (e.g., placenta previa), intravenous UFH could represent a safer alternative.[28] In light of a subsequent systematic review showing a nearly 3-fold increased rate of thromboembolic complications in pregnant patients with COVID-19 pneumonia compared to pregnant patients without COVID-19 during early waves of COVID-19 infection,[29] as well as randomized controlled trial data in non-pregnant populations,[20] experts affiliated with the Royal College of Obstetricians and Gynaecologists suggested a role for empiric treatment-dose UFH/LMWH on an individualized basis in moderately ill pregnant patients hospitalized due to COVID-19,[30] unless they were due to deliver. All ante-partum patients hospitalized for COVID-19 should receive standard-dose heparin thromboprophylaxis, preferably with LMWH. For moderately ill pregnant patients, empiric therapeutic-dose thromboprophylaxis, preferably with LMWH, should be considered on an individualized basis. For patients at high bleeding risk, intravenous weight-based UFH using a standardized nomogram should be considered. In cases of ongoing morbidity, or in patients up to 6 weeks post-partum, extended post-discharge prophylaxis may also be considered, especially in cases of high International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) score and/or elevated Dd, with low bleeding risk.[28,31]

4.3 | Pediatrics

4.3.1 | Statement 6

Observational studies indicate that much like the adult population, children <18 years of age hospitalized with COVID-19 are at increased risk of thromboembolic disease as well as a multisystem inflammatory syndrome phenotype, the pediatric multisystem inflammatory syndrome (PMIS).[32–34] A previous consensus-based clinical recommendation panel for anticoagulant thromboprophylaxis in children hospitalized for COVID-19 suggested the use of twice-daily subcutaneous LMWH thromboprophylaxis targeted to achieve a 4 h post-dose anti-Xa level of 0.2 to <0.5 U/ml (in the absence of contraindications) in combination with mechanical thromboprophylaxis using sequential compression stockings where feasible.[35] This recommendation included children with PMIS and markedly elevated Dd or those with added clinical risk factors for VTE.[35] For children who were clinically unstable or with severe renal impairment the same panel suggested the use of intravenous UFH given by continuous infusion.[35] More recently, the results of an open-label, multicenter phase 2 trial among 40 children <18 years of age hospitalized for primary COVID-19 with or without PMIS found twice-daily enoxaparin thromboprophylaxis (0.5 mg/kg/dose; max of 60 mg/dose) to be safe in achieving target anti-Xa levels without observed clinically relevant bleeding or related serious adverse events.[36] As such, twice daily weight-based LMWH at half the treatment dose should be considered for primary thromboprophylaxis in children hospitalized for COVID-19 with or without PMIS.

4.4 | Chronic kidney disease and acute kidney injury

4.4.1 | Statement 7

Studies suggest that both the incidence and intensity of hypercoagulability presentations are higher in hospitalized COVID-19 patients with chronic kidney disease (CKD), which itself predisposes patients to cardiovascular complications.[37] Presentations range from arterial thrombosis and VTE (especially pulmonary embolism), renovascular thrombosis, disseminated intravascular coagulopathy, and end-organ failure.[37] The incidence of VTE may be as high as 36% in intensive care unit (ICU) patients.[38] In addition, the coagulopathy and overall mortality in COVID-19 patients with CKD may be worsened by their pre-existing cardiovascular co-morbidities and advanced age. Last, acute kidney injury (AKI) may be seen in as many as 19% and up to 63% of hospitalized COVID-19 patients and is associated with an over 3-fold increased risk of death, in addition to other adverse outcomes.[37,39] Although there is insufficient evidence to suggest specific anticoagulant strategies in COVID-19 patients with CKD or AKI, both observational studies and clinical trials support the use of standard prophylactic doses of LMWH (e.g., enoxaparin 40 mg subcutaneously daily) or UFH (5000 IU subcutaneously twice or thrice daily) down to a CrCl of 30 ml/min. In non–critically ill COVID-19 patients that meet criteria for therapeutic-dose heparin, therapeutic doses of LMWH (e.g., enoxaparin 1 mg/kg subcutaneously twice daily) may be the preferred agent down to a CrCl of 30 ml/min.[21,22] For CrCl of 15–29 ml/min, one should consider a renal dose adjustment of LMWH for both prophylaxis (e.g., enoxaparin 30 mg

subcutaneously daily) or treatment (e.g., enoxaparin 1 mg/kg subcutaneously every 24 h or 0.5 mg/kg subcutaneously twice daily). The preferred parenteral agent for patients with a CrCl < 15 ml/min should be UFH, which does not require renal adjustment for prophylactic doses (UFH 5000 IU subcutaneously twice daily) or for standard therapeutic dosing (80 IU/kg bolus intravenously followed by 18 IU/kg/hr infusion, monitored by heparin anti-Xa levels or by the activated partial thromboplastin time [APTT]).[39] In general, due to its high dependence on renal clearance, fondaparinux should be avoided in this population, especially in cases of fluctuating renal function or with a CrCl < 30 ml/min.

4.5 | Renal replacement therapy

4.5.1 | Statement 8

Critically ill patients hospitalized with COVID-19 pneumonia who develop AKI frequently require continuous renal replacement therapy (CRRT).[40] In these cases, not only does the hyperinflammatory state predispose patients to thrombosis, but it may also lead to thrombosis of the extracorporeal CRRT circuit.[41] Adding systemic UFH to regional citrate anticoagulation is associated with less frequent filter thrombosis without increased rates of bleeding and with similar rates of mortality compared to citrate alone.[42–45] If filter thrombosis occurs despite systemic UFH, an option is to consider an intravenous direct thrombin inhibitor such as argatroban monitored with a standardized APTT nomogram. Patients with COVID-19 pneumonia requiring CRRT have generally been excluded from trials of escalated-dose thromboprophylaxis, though in the INSPIRATION trial there was a non-significant increase in need for CRRT among patients receiving intermediate-dose enoxaparin.[46] Given the paucity and uncertainty of available evidence, standard-dose thromboprophylaxis should be used in this population (e.g., UFH 5000 IU subcutaneously twice daily or renal dose-adjusted LMWH given subcutaneously).

4.6 | Obesity and weight-adjusted thromboprophylaxis

4.6.1 | Statement 9

Obesity is a known risk factor for thrombosis, where a strong correlation exists between body mass index (BMI) and rates of VTE.[47] This thrombotic risk is noted particularly in COVID-19.[48] Reduced mobility and comorbid cardiovascular disease often seen in morbid obesity can increase rates of hospitalization and death in the setting of obesity and COVID-19.[49,50] Adipose tissue in an obese individual is metabolically active because adipocytes produce interleukin (IL)-6 and other cytokines predisposing to a prothrombotic state including increased activation of platelets and production of microparticles, in addition to producing plasminogen activator inhibitor-1.[51] In cases of COVID-19, obesity predisposes to further problems because adipose tissue, especially visceral fat, expresses the angiotensin converting enzyme 2 receptor and therefore it has been suggested that fat is a reservoir for the SARS-CoV-2 virus.[52,53]

Historically poor representation of obese patients in high-quality trials complicates VTE prophylaxis and treatment dosing guidance.[54] Before the COVID-19 pandemic, higher-than-standard-dose UFH and LMWH showed greater reductions in hospital-associated VTE without increases in bleeding among patients weighing >100 kg,[55] and observational studies[56] as well as a randomized controlled trial[57] showed that weight-based dosing of enoxaparin achieves target anti-Xa levels more often than fixed dosing. Yet, in the INSPIRATION trial, which evaluated intermediate-dose (0.5 mg/kg twice daily) enoxaparin thromboprophylaxis in critically ill COVID-19 patients, dosing was further increased (to 0.6 mg/kg twice daily) in patients with a BMI > 35 kg/m^2, without improved efficacy.[46] Trials of treatment-dose anticoagulants (including heparins and the DOAC rivaroxaban) in patients with either moderate or critical illness due to COVID-19 have not reported obesity subgroup data; however, in all primary studies the mean or median BMI was approximately 30 kg/m^2.[20–22,58] In hospitalized COVID-19 patients with Class I obesity (BMI 30–35 kg/m^2) thromboprophylaxis dosing may reasonably follow existing guidelines using low (prophylactic) dose LMWH (e.g., enoxaparin 40 mg subcutaneously daily) or UFH (e.g., 5000 IU subcutaneously twice or thrice daily).[59,60] Patients hospitalized for COVID-19 with Class II or greater obesity (BMI ≥35 kg/m^2) who do not meet criteria for therapeutic-dose heparin may be considered for escalated-dose heparins either using fixed intermediate dose LMWH (e.g., enoxaparin 40 mg subcutaneously twice daily) or a weight-based LMWH regimen (e.g., enoxaparin 0.5 mg/kg subcutaneous twice daily), which is typically ~50% higher than corresponding doses for non-obese patients.[59,61] Treatment of VTE associated with COVID-19 in obesity follows guidance for the non-COVID-19 population: weight-based dosing (e.g., enoxaparin 1 mg/kg twice daily) should be continued for the standard duration.[62] Moreover, there does not appear to be any firm basis for (1) dose-capping of heparins at extremes of weight, nor (2) deviating from standard, fixed dosing of DOACs.[54,63]

4.7 | Hospitalized patients with existing indications for antithrombotic therapy

4.7.1 | Statement 10

There is no firm basis to reduce pre-hospital anticoagulant dosing for hospitalized COVID-19 patients on therapeutic anticoagulation either for confirmed VTE or stroke prevention (as in atrial fibrillation or mechanical heart valve). For patients receiving a VKA such as warfarin, COVID-19 coagulopathy can manifest as INR prolongation, which is associated with Dd elevation and, accordingly, disease severity.[64] Patients prescribed VKA therapy who develop COVID-19 pneumonia exhibit a decreased time in therapeutic range

and increased variance of INR measurements.[13] Yet, observational studies have produced conflicting data on whether baseline use of oral anticoagulants including VKAs improves or worsens clinical outcomes among patients hospitalized with COVID-19 pneumonia.[65–67] Existing guidance does not compare oral anticoagulant therapies for COVID-19 inpatients and there is a lack of high-quality studies specifically on continuation of pre-hospital VKAs during admission.[59,68]

A major question in the anticoagulation of patients hospitalized for COVID-19 pneumonia is whether to continue DOACs in those patients with pre-existing indications. DOACs are substrates of P-glycoprotein (P-gp) and CYP3A4; drugs that interact strongly with these enzymes can alter DOAC levels.[11,12] This category includes many drugs used in the treatment of COVID-19 pneumonia, notably the antivirals ritonavir (a component of Paxlovid) and remdesivir, which can induce P-gp and inhibit CYP3A4.[69,70] Short-term dexamethasone treatment did not alter DOAC levels in a small study, although authors speculated longer exposure could lead to unfavorable clinical outcomes.[71] Lastly, SARS-CoV-2 itself directly alters IL-6 levels, which are known to affect CYP regulation.[72] Beyond drug–drug and disease–drug interactions, questions remain about the efficacy of DOACs in COVID-19 without an indication for oral anticoagulation as seen in one moderate-sized trial.[58] The ACTION trial showed that therapeutic dose of rivaroxaban 20 mg once daily for hospitalized COVID-19 patients who did not have an indication for OAC did not improve outcomes at 30 days and did increase bleeding compared to traditional prophylactic doses of heparin.[58]

DOACs also lack anti-inflammatory and other immune-modulating pleiotropic effects of heparins observed *in vitro*.[73] In terms of antiplatelet agents, both a large multiplatform trial as well as other trials have highlighted that coupled with therapeutic-dose anticoagulation for thromboprophylaxis, the use of antiplatelet therapy poses a significant increased risk of bleeding.[74,75]

Based on these observations, patients prescribed pre-hospital VKAs should continue these drugs in-hospital at the prescribed target INR range (usually 2.0 to 3.0 or 2.5 to 3.5) and the INR should be frequently monitored. If there is INR instability, consideration should be made to switch to therapeutic-dose heparins (preferably LMWH) during hospitalization. For patients prescribed pre-hospital therapeutic-dose DOACs, consideration should be made to switch to parenteral therapeutic-dose heparin in-hospital, either LMWH with renal dose adjustment if the CrCl is 15–29 ml/min or dose-adjusted intravenous UFH if CrCl < 15 ml/min (refer to Statement 7). This is due to potential for multiple interactions of DOACs with SARS-CoV-2 itself or anti-viral or immunosuppressant therapy, or potential loss of efficacy due to lack of immunomodulatory effects, or other factors compared with heparins.[59,68] Patients who are on antiplatelet agents on admission should continue these drugs with continued assessment of the risk–benefit of their antiplatelet treatment in light of the use of anticoagulation for thromboprophylaxis. Consideration with antiplatelet therapy needs to be given to those requiring therapeutic anticoagulation for thromboprophylaxis, as this group is at high risk of bleeding. For patients who were previously receiving 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; for example, it would be reasonable to continue antiplatelet therapy in patients with a recent acute coronary syndrome or in those with a coronary stent.

5 | HOSPITALIZED CRITICAL CARE COVID-19 POPULATIONS

Critical illness due to COVID-19 signifies a life-threatening condition requiring immediate organ support, such as invasive or non-invasive positive pressure ventilation, high-flow supplemental oxygen therapy, vasopressor or inotrope support, extracorporeal membrane oxygenation, or CRRT, irrespective of patient location within a hospital (as high COVID-19 admission volumes may necessitate makeshift/temporary critical care areas, in addition to named critical care units).[20–22,46,58,59,68]

5.1 | Heparin thromboprophylaxis versus no thromboprophylaxis in critical settings

5.1.1 | Statement 11

Three observational studies compared the use of heparin thromboprophylaxis versus no heparin thromboprophylaxis in patients hospitalized for COVID-19 in which a small percentage (<10%) contained patients in critical care settings.[16,76,77] Two of those studies showed a decrease in mortality with low (prophylactic) dose LMWH/UFH versus no heparin thromboprophylaxis, with an absolute risk reduction in death of 4.4% in one study.[16] In another study the mortality benefit was only evident among those with a very high Dd level (>10 μg/ml).[76] There was no significant increase in bleeding events and/or transfusion requirement as reported in two studies.[16,77] No data were reported on the incidence of VTE, although routine low-dose heparin thromboprophylaxis in non–COVID-19 ICU patients has been recommended in previous antithrombotic guidelines as low dose heparin has been shown to reduce VTE.[78] The use of low (prophylactic) dose LMWH or UFH should be strongly considered over no heparin thromboprophylaxis in hospitalized, critically ill COVID-19 patients to reduce the risk of VTE or death.

5.2 | Heparin dose when ward patients on therapeutic dose LMWH become critically ill

5.2.1 | Statement 12

In trials of hospitalized non–critically ill COVID-19 patients comparing therapeutic heparin to standard-of-care anticoagulation, approximately 5%–10% of patients developed severe illness requiring mechanical intubation and ICU level of care.[20–22] In ICU settings of the same trials, therapeutic UFH/LMWH was associated with a

multifold increase in major bleeding, including critical site bleeding.[21,79] Both the National Institutes of Health and National Institute for Health and Care Excellence guidelines on the topic suggest dose reduction of heparin if a hospitalized COVID-19 patient on a medical ward on therapeutic anticoagulation develops critical illness.[68,80] As such, given the increased bleeding risk in critically ill patients on therapeutic heparin, for those hospitalized COVID-19 patients on therapeutic dose heparin in a ward setting who develop severe illness and require transfer to the ICU, it would be prudent to switch from therapeutic dose UFH/LMWH to a *prophylactic dose* of heparin, unless the patient has confirmed thrombosis, atrial fibrillation, or another indication for therapeutic anticoagulation.

5.3 | Critically ill patient selection for add-on antiplatelet therapy

5.3.1 | Statement 13

Despite many *in vitro* studies showing that platelets are activated in hospitalized patients with COVID-19 pneumonia,[81] multiple trials in moderate COVID-19 patients showed no benefit of add-on antiplatelet therapy to anticoagulants in improving clinical outcomes and conversely increased bleeding risk.[74,75] The REMAP-CAP trial in critically ill COVID-19 patients compared the use of add-on therapy with either low-dose aspirin or clopidogrel or other $P2Y_{12}$ inhibitors and found no benefit in improving the primary outcome of survival and freedom from organ support at 21 days with the different classes of antiplatelet agents.[82] However, there was a significant improvement in the secondary outcome of all-cause mortality until discharge.[82] Patients in this trial were at low risk of bleeding, did not receive therapeutic-dose anticoagulation, and received gastric acid suppression. Although routine use of add-on antiplatelet therapy in critically ill COVID-19 patients should not be used as per the ISTH COVID-19 Antithrombotic Guidelines, select critically ill patients at low bleeding risk, not on therapeutic anticoagulation, and receiving gastric acid suppression may be considered for add-on antiplatelet therapy with low-dose aspirin or a $P2Y_{12}$ inhibitor in addition to standard low-dose heparin thromboprophylaxis, provided that the patient does not have an indication for therapeutic anticoagulation.

5.4 | Management of acute thrombosis in COVID-19 in-patients

5.4.1 | Statement 14

The principles of management of in-hospital acute thrombotic episodes in those with COVID-19 pneumonia should be the same as the management of thrombosis in other hospitalized patients; that is, the use of parenteral anticoagulation and consideration of a temporary inferior vena cava filter in case of an absolute contraindication for anticoagulation. As previously discussed, DOACs are not ideal agents due to multiple potential drug–drug and disease–drug interactions and potential for reduced efficacy in this setting.[72] A feature of COVID-19 pneumonia is an acute inflammatory state and thus greatly increased levels of fibrinogen and factor VIII that may, in addition to high levels of factor VIII, affect APTT level interpretation through a pseudoheparin resistance effect.[83] For patients hospitalized for COVID-19 with an acute thrombotic event, the use of LMWH or UFH should be considered over a DOAC, with weight-based therapeutic-dose LMWH at twice daily dosing as the preferred agent. For patients with a high BMI, the use of weight-adjusted LMWH and the use of anti-Xa trough and peak levels to assess adequate anticoagulation on one occasion after 48 h can be considered. For patients on intravenous UFH, weight-adjusted and nomogram-based monitoring with anti-Xa levels should be preferred over APTT monitoring.

5.5 | Management of heparin-induced thrombocytopenia with/without thrombosis in COVID-19 in-patients

5.5.1 | Statement 15

For hospitalized COVID-19 patients either suspected of heparin-induced thrombocytopenia with/without thrombosis (HIT/HITT) or having confirmed HIT/HITT, treatment principles should follow those of non-COVID-19 hospitalized populations, namely initial treatment with a non-heparin based parenteral agent (e.g., an intravenous direct thrombin inhibitor such as argatroban using a standardized APTT nomogram or the pentasaccharide fondaparinux, given at treatment doses of 5–10 mg subcutaneously daily adjusted by weight), followed by dose-adjusted warfarin once the diagnosis is confirmed and platelet counts have stabilized.[84] Although DOACs have been used to treat HIT/HITT in non–COVID-19 hospitalized populations, they should be avoided as initial therapy in hospitalized COVID-19 patients due to the previously described potential for drug–disease and important drug–drug interactions with anti-viral medications as well as potential lack of DOACs' efficacy compared to parenteral agents in hospitalized COVID-19 patients as shown in the ACTION study.[58]

6 | POST-HOSPITAL DISCHARGE PERIOD

Although early retrospective reports suggested a low risk of post-hospital discharge adverse events and mortality for up to 45 days in patients hospitalized for COVID-19, a large prospective registry revealed a 90-day rate of arterial and venous thromboembolic events of ~3.2% and an all-cause mortality rate of 4.8%.[85–88] Studies suggest that patients with classic cardiovascular risk factors or renal comorbidities, ICU stay, or an IMPROVE VTE risk score of 4 or more or a score of 2 or 3 plus an elevated Dd (>2X ULN), are associated with an increased risk of thrombotic events and mortality

in the post-discharge period.[88,89] The IMPROVE VTE risk model with or without elevated Dd and the IMPROVE-DD VTE risk model that incorporates elevated Dd (>2X ULN) have both been externally validated in multiple studies of hospitalized COVID-19 populations to identify a high-risk hospitalized COVID-19 population for thrombosis and death that would likely benefit from extended thromboprophylaxis.[90–92]

6.1 | Patient selection for extended post-hospital discharge thromboprophylaxis

6.1.1 | Statement 16

The MICHELLE randomized trial was able to identify a high-risk hospitalized COVID population using an IMPROVE VTE score of 4 or more or a score of 2–3 and elevated Dd (>2X ULN).[93] The trial selected patients at low risk of bleeding. The results showed benefit from a 35-day course of rivaroxaban 10 mg daily versus no anticoagulation at hospital discharge in reducing the primary outcome of major thromboembolism and cardiovascular death (9% versus 3%, relative risk 0.33, 95% confidence interval [CI] 0.12–0.90, $p = 0.029$).[93] There was no major bleeding in either group. An individualized approach should be used to identify high-risk hospitalized COVID-19 patients for extended thromboprophylaxis with a DOAC (rivaroxaban 10 mg daily) for approximately 35 days. Evidence suggests these patients can be identified using an IMPROVE VTE score of 4 or more or a score of 2–3 with elevated Dd (>2X ULN) at any time during their hospitalization but ideally closer to hospital discharge, provided that they are at low bleeding risk. For pregnant patients hospitalized for COVID-19, consideration should be given for heparin thromboprophylaxis (preferably LMWH) for 10 to 42 days post-discharge, depending on the severity of the presentation.[28]

6.2 | Transition from hospital-based parenteral anticoagulation to the post-discharge outpatient setting

6.2.1 | Statement 17

Parenteral heparins (including LMWH and UFH in patients with renal insufficiency) are preferred to oral anticoagulants in hospitalized COVID-19 patients due to potential for INR instability with warfarin[13] and drug–drug and disease–drug interactions, as well potential loss of efficacy with DOACs.[58,69,70] However, oral anticoagulation in favor of DOACs is preferred for at least 3 to 6 months in patients with confirmed VTE, with the possibility to extend treatment if the recurrence risk for VTE is elevated.[94] As such COVID-19 inpatients can be switched from parenteral heparins (either subcutaneous LMWH or intravenous UFH) to oral anticoagulant therapy with a DOAC or warfarin upon hospital discharge according to the usual local practice.

AUTHOR CONTRIBUTIONS

ACS, JMC, JDD, MK, BJH, TRK, RDL, and SS all contributed to data collection, data synthesis and interpretation, and the writing of this manuscript.

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CONFLICTS OF INTEREST

A. C. Spyropoulos—no relevant conflicts for present work. Consultant and advisory board from Janssen, Bayer, Boehringer-Ingelheim, Sanofi, ATLAS Group. Research support from Janssen, Boehringer-Ingelheim. J. M. Connors—no relevant conflicts for present work. Consulting fees or honoraria from Abbott, Alnylam, Bristol-Meyers Squibb, Pfizer, Roche, Sanofi, Werfen. Research funding to the institution from CSL Behring. B. J. Hunt—no relevant conflicts for the present work. Takes no personal monies from pharmaceutical companies. J. D. Douketis—no relevant conflicts for present work. Consulting fees or honoraria from Janssen, Pfizer, Leo Pharma, Servier Canada, and Sanofi. M. Goldin—research grant support and speaking honoraria from Janssen Scientific Affairs, LLC (not related to current manuscript). T. R. Kotila—no conflicts of interest to report. R. D. Lopes—grants from Bristol-Myers Squibb, GlaxoSmithKline plc., Medtronic, Pfizer, Bayer, Sanofi; consulting fees from Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Novo Nordisk, GlaxoSmithKline plc., Medtronic, Merck, Pfizer, Portola, Sanofi; and honoraria for lectures from Bristol-Myers Squibb, Pfizer, Daiichi Sankyo, Novo Nordisk, and Bayer. S. Schulman—honoraria from Daiichi-Sankyo, Boehringer-Ingelheim, Bayer, Sanofi, Servier, Bristol-Myers Squibb, and research grant from Octapharma.

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