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Venous thromboembolism and antithrombotic therapy in COVID-19

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Summary

A distinctive feature of critically ill COVID-19 patients is higher susceptibility to venous thromboembolism (VTE) often presenting as isolated pulmonary embolism that may lead to sudden death. VTE episodes have been observed to occur despite standard prophylactic anticoagulation. It is therefore of crucial importance to choose the appropriate drug dose for therapeutic and prophylactic antithrombotic therapy in patients with COVID-19. The drugs of choice here are low molecular weight heparins (LMWHs). Several randomized clinical trials have compared the efficacy of prophylactic, intermediate and therapeutic dose LMWH in VTE prophylaxis in various clinical settings. The paper presents the most recent International Society on Thrombosis and Hemostasis *expert recommendations for anticoagulant prophylaxis in COVID-19. The recommendations were based on the outcome of recent clinical trials.*

Key words: venous thromboembolism (VTE), COVID-19, antithrombotic therapy, prophylactic anticoagulation, heparins, DOAC

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Introduction

From the very beginning of the COVID-19 pandemic, the disease caused by the coronavirus acute respiratory distress syndrome SARS-CoV-2, we were taken unawares not only by a dramatically severe and sometimes lethal course but also by clinical and laboratory manifestations rarely observed for other viral diseases.

Just after the outbreak of the epidemic, the Chinese clinicians observed (among others) a marked increase of D-dimer serum concentration in patients with COVID-19. Report analyses from ongoing trials indicated that exceptionally high D-dimer (DD) concentrations were mostly found in critically ill patients and those who died [1]. They were several fold higher (2.5–9 x) than the DD concentration observed in milder clinical course. At that time, hospitalization was to be considered for every patient with COVID-19 and markedly elevated DD concentration (a 3–4-fold increase), despite the absence of other severe symptoms [2].

In this initial period of the pandemic, reports from Europe [3, 4] and a number of communications from Poland signalled a significant frequency of VTE episodes in patients hospitalized for COVID-19, despite the use of standard prophylactic doses of low molecular weight heparins (LMWH). The threshold for clinical suspicion of VTE in all COVID-19 patients should therefore be very low and lead to prompt diagnostic testing. A sudden oxygen desaturation, sudden dyspnea,

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and/or a drop in blood pressure — on the other hand — should immediately raise the suspicion of pulmonary embolism.

Accurate estimation of the VTE frequency in COVID-19 is far from easy. The estimates vary significantly and depend on the period the studies were conducted (wave of the pandemic) and the analytical methods used (occurrence of symptomatic VTE vs. screening for VTE in patients hospitalized for COVID-19). In one of the latest meta-analyses the overall frequency of VTE in hospitalized patients is estimated at 14.7% (95% CI 12.1–17.6%), with significantly higher incidence of VTE episodes for critically ill patients hospitalized in intensive care units (23.2%; 95% CI 17.5–29.6%) vs. patients hospitalized in regular hospital wards (9.0%; 95% CI 6.9–11.4%) [5]. VTE episodes may also occur in COVID-19 patients after hospital discharge. This refers to about 1.55% of patients [6] and indicates the need for post-discharge venous thromboprophylaxis as well. It is worth emphasizing that the large differences in the frequency of arterial thromboembolism reported in various studies make it difficult to determine the actual impact of COVID-19 [5].

The pathogenesis of thromboembolism in the context of COVID-19 is poorly understood. However, the role of microcirculatory dysfunction is highlighted with particular stress on the combined effect of excessive inflammation and endothelial cell dysfunction, comonly known as immunothrombosis [7].

The dynamic situation and the rapidly growing body of evidence, make it crucial to choose appropriate prophylaxis and anticoagulant therapy as the essential concomitant treatment. Naturally, the drug of choice were heparins, either unfractionated (twice daily) or low molecular weight (LMWH). The latter were indicated for the convenience of use [8]. It was then said that — as long as there are no contraindications — pharmacological thromboprophylaxis should be initiated **for every patient hospitalized for COVID-19 (regardless of the reason for hospitalization and the patient's condition)** [6]. For obvious reasons, vitamin K antagonists should not be considered for antithrombotic prophylaxis during hospitalization. Likewise, direct oral anticoagulants (DOAC) are not recommended because of the possible interactions with the concurrently used antiviral drugs [9]. Naturally, the use of these drugs can be considered later, for post-discharge anticoagulation therapy.

In the initial phase of the pandemic, there was no sufficient evidence to clearly define the optimal prophylactic dose of LMWH recommended in different clinical situations of patients hospitalized for COVID-19. Despite standard antithrombotic therapy, VTE episodes were still reported so it was suggested to increase the prophylactic LMWH dose, e.g. enoxaparin 2 × 40 mg, initiation of intermediate doses — e.g. 1 mg (100 IU)/kg bw once daily, or therapeutic LMWH dose for patients hospitalized in the ICU [10].

Uncertainty led to initiation of randomized clinical trials (RCTs), the results of which were published mostly in 2021 [11–17]. RCTs were also focused on antiplatelet drugs [18–21] as well as on rivaroxaban (DOAC) in the post-discharge thromboprophylaxis following hospitalization for COVID-19 [22]. All the above, supplemented with results of cohort studies (non cited) inspired the currently published recommendations of the *International Society on Thrombosis and Haemostasis* regarding anticoagulation in patients with COVID-19 [23].

Twelve (12) such recommendations were presented, categorized by: class of recommendation (COR) = class (strength) of recommendation, level of evidence (LOE) = level (quality) of evidence. Simplified description of those categories in given in Table 1.

The above ISTH expert-group recommendations were based on the literature data available until March 2022. The publication of new guidelines and recommendations addressing unresolved problems and doubts was announced to appear

Table 1. Simplified description of classification of recommendation and level of evidence used by ISTH experts [23]

Class (strength) of recommendation	Level (quality) of evidence
Class 1 — strong (significant benefit)	**Level A** — high-quality evidence; strong methodology
Class 2a — moderate (moderate benefit)	**Level B–R** — moderate-quality evidence from RCTs
Class 2b — weak (likely benefit) moderate quality	**Level B–NR** — moderate-quality evidence from nonrandomized studies
Class 3 — no benefit (benefit = risk) or harm (risk > benefit)	**Level C–LD** — limited data; observational studies, registers
	Level C–EO — expert opinion

with the emergence of new reliable outcome of clinical trials.

Recommendations for antithrombotic therapy for non-hospitalized patients (outpatients)

1. In non-hospitalized patients with symptomatic COVID-19, initiation of antiplatelet therapy is **not effective** to reduce risk of hospitalization, arterial or venous thrombosis, or mortality (Class 3 — no benefits; B–R).
2. In non-hospitalized patients with symptomatic COVID-19, initiation of direct oral anticoagulant (DOAC) therapy is **not effective** to reduce risk of hospitalization, arterial or venous thrombosis, or mortality (Class 3 — no benefits; B–R)*.
3. In non-hospitalized patients with COVID-19 at higher risk of disease progression, initiation of **sulodexide** therapy within 3 days of symptom onset **may be considered** to reduce risk of hospitalization (2–b; B–R) [17]

***Note:** usually there is no rationale for patients on home-therapy for chronic cardiovascular diseases to discontinue DOAC [24]. The initiation of direct-acting antivirals for outpatients does however require a change of approach. The same issue of *Journal of Thrombosis and Haemostasis* that presents these recommendations presents an article with several good practice statements for antithrombotic therapy in the management of COVID-19. These however are not based on randomized clinical trials with participation of COVID-19 patients [25]. The first expert opinion presented in this article refers to possible interferences between antiviral drugs prescribed for outpatients (e.g. Paxlovid) and direct factor Xa inhibitors. Their concomitant use may cause drug-drug interactions after DOAC exposure and increase in DOAC bioavailability [inhibition of cytochrome P450 (CYP) 3A4]. It is therefore recommended to discontinue factor Xa inhibitors for the time of Paxlovid intake and elimination (7–8 days in all). An example here are press reports from several months back when Joe Biden, President of the United States, then suffering from COVID-19, had to temporarily discontinue his "blood thinning" medication. It is mandatory to closely follow *Summary of Product Characteristics* of direct antiviral drugs used in the management of COVID-19.

Recommendations for antithrombotic therapy for non-critically ill patients hospitalized for COVID-19

1. In non-critically ill patients hospitalized for COVID-19, low (prophylactic) dose low molecular weight heparins (LMWH) or unfractionated heparin (UFH) **is recommended** in preference to no LMWH or UFH to reduce the risk of thromboembolism and possibly death. Such approach is preferable to abstaining from prophylactic administration of heparin (Class 1; B–NR).
2. 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 the risk of thromboembolism and end organ failure (1; A).

***Note** — this refers to patients qualified/enrolled for three randomized clinical trials, who were at high risk of disease progression and at low risk of bleeding [12]).

3. 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 the risk of thromboembolism and other adverse outcomes (3 — no benefits; B–R).
4. In non-critically ill patients hospitalized for COVID-19, **add-on-treatment with an antiplatelet agent** is potentially harmful and **should not be used** (3 — harm; A).
5. In non-critically ill patients hospitalized for COVID-19, therapeutic dose DOAC **is not effective** to reduce the risk of thromboembolism and other adverse outcomes (3 — no benefit; B–R).

Recommendations for antithrombotic therapy for critically ill patients* hospitalized for COVID-19

1. In critically ill patients hospitalized for COVID-19, **intermediate dose LMWH/UFH is not recommended** over prophylactic dose LMWH/UFH to reduce the risk of adverse events, including mortality and thromboembolism (3 — no benefit; B–R).
2. In critically ill patients hospitalized for COVID-19, therapeutic dose **LMWH/UFH is not recommended** over usual-care or prophylactic dose LMWH/UFH (3 — no benefit; B–R).

3. In select critically ill patients hospitalized for COVID-19, **add-on-treatment with an antiplatelet agent to prophylactic dose LMWH/UFH is not well established**, but might be considered to reduce **mortality** (2b; B–R).

***Note:** experts define **critically ill patients** with COVID 19 as persons hospitalized in a life-threatening condition requiring immediate organ support such as invasive or non-invasive ventilation, high-flow supplemental oxygen therapy, vasopressor or inotrope support, extracorporeal membrane oxygenation (ECMO), or continuous renal replacement therapy.

Recommendations for antithrombotic therapy for patients discharged from hospital

1. In select patients who have been hospitalized for COVID-19, post-discharge treatment with prophylactic dose **rivaroxaban** for approximately 30 days **may be considered** to reduce the risk of VTE (2b; B–R).

In the clinical trials that supported this recommendation, rivaroxaban 10 mg vs. placebo was administered to patients at higher risk of VTE (demonstrated by a total modified IMPROVE (*International Medical Prevention Registry on Venous Thromboembolism*) VTE risk score of ≥ 4 or 2–3 points with higher D-dimer concentration > 2× the upper limit [26].

Independent of the presented recommendations, there are ongoing meta-analyses of the currently available clinical trials on various aspects of anticoagulant treatment in COVID-19. One of them focused on the effectivity of therapeutic vs intermediate (prophylactic) dose heparin on mortality and thrombotic events in all patients who participated in randomized clinical trials [27]. The pooled analysis demonstrated no advantage of therapeutic dose over intermediate (prophylactic) dose heparin as regards mortality or reduction of the frequency of arterial thromboembolism. The therapeutic dose did however reduce the frequency of venous thromboembolism (2.7% vs. 5.9%, RR = 0.47, 95% CI 0.35–0.63). The reduction of VTE episodes was at the expense of somewhat higher frequency of major bleeds (2.5% vs. 1.4%). As expected, the rate of major bleeding was higher in patients on therapeutic dose. Even if the full anticoagulation did not reduce the risk of death, the positive impact on VTE is of clinical relevance for the management and the potentially harmful long term effects of VTE; in accordance with this, for VTE and major bleeding the NTT (number needed to treat) and NNH (number needed to harm) were 31 and 90 respectively.

The outcome of ongoing clinical trials will most likely result in the publication of new recommendations, as well as in the elaboration or modification of those already available. The ultimate aim is to develop an optimal antithrombotic therapy for various clinical conditions associated with COVID-19 in patients who are at higher risk of venous thromboembolism.

Conflict of interest: none declared

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