Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Prevention of venous thromboembolism and haemostasis monitoring in patients with COVID-19: Updated proposals (April 2021)☆

From the French working group on perioperative haemostasis (GIHP) and the French study group on thrombosis and haemostasis (GFHT), in collaboration with the French Society of Anaesthesia and Intensive Care (SFAR)

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ABSTRACT

Background: COVID-19 is associated with a high risk of venous thromboembolism, particularly in critically ill patients. New knowledge has emerged since the initial GIHP/GFHT proposals were first published in April 2020. The objective of this work was to update these proposals to reflect recent knowledge.
Methods: A working group identified seven questions and conducted a comprehensive literature review. Proposals were made when consensus was reached within the working group and with other GIHP/GFHT members.
Results: We suggest standard-dose prophylactic anticoagulation for general inpatients and selected high-risk outpatients. For critically ill patients, we suggest the use of intermediate- or therapeutic-dose prophylactic anticoagulation depending on the D-dimer level and its dynamics. Seven to 10 days after hospital admission, we suggest switching to standard-dose prophylactic anticoagulation to reduce the bleeding risk for all patients until discharge. In patients with the highest thrombotic risk and treated

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with therapeutic-dose prophylactic anticoagulation, we suggest routine screening for thrombosis before de-escalation. We suggest adapting anticoagulation to body weight for each anticoagulation regimen. We suggest regular monitoring of hemostatic parameters, including D-dimer, in critically ill patients. We suggest monitoring intermediate- and therapeutic-dose prophylactic anticoagulation with anti-Xa activity.
Conclusion: The updated proposals follow a standardized approach to thromboprophylaxis, aimed at decreasing the incidence of symptomatic venous thromboembolism. We suggest a sequential strategy in critically ill patients to take the temporal relationship between the thrombotic and the bleeding risks into account.

1. Introduction

In April 2020, in response to the high thrombotic risk associated with COVID-19, the GIHP and GFHT published proposals for the prevention of venous thromboembolism (VTE) and haemostasis monitoring in patients with COVID-19 [1]. In February 2021, six authors from the proposals (CT, AM, AlG, AnG, SS, YG, PA) decided to update them. This update was justified by several points:

- The epidemiology of thrombotic complications has been described.
- Different anticoagulation regimens have been reported, and retrospective studies have suggested that higher-than-standard prophylactic anticoagulation may be beneficial.
- Initially underestimated, bleeding complications have emerged as a limitation of increased-dose anticoagulation and occur later than thrombotic events.
- The first results of large-scale randomised controlled studies on increased doses of anticoagulation have been published.
- Immunomodulatory therapies (corticosteroids, interleukin-6 receptor antagonists) are now widely used, but their effect on the thrombotic risk is unknown.
- Despite improved survival, thrombotic complications remain a concern [2].

2. Methodology

The workgroup defined seven questions and searched the literature for available evidence:

- Who should receive standard dose prophylactic anticoagulation?
- Should the dose of prophylactic anticoagulation be increased in critically ill patients?
- Who may benefit from therapeutic dose anticoagulation?
- Should anticoagulant dose be adjusted to body weight?
- What is the bleeding risk associated with COVID-19, and its temporal relationship with thrombotic risk?
- What is the minimal laboratory monitoring of haemostasis in hospitalised COVID-19 patients?
- How long is prophylactic anticoagulation warranted?

The workgroup performed five virtual meetings to review the advancement of the proposals. Tables and figure were sent to all members of the GIHP/GFHT by e-mail for further review. The full manuscript was sent on the 24th of April to all members of the GIHP/GFHT, and on the 28th of April to the GFHT for further review. Disagreements were solved posteriorly by consensus within the workgroup.

In these proposals (Fig. 1), we followed a standard approach of thromboprophylaxis, aiming to decrease the incidence of symptomatic VTE – pulmonary embolism and proximal deep vein thrombosis – to an acceptable rate without increasing too much the bleeding risk (for instance, less than 5% within 30 days for both types of events). Whether this approach is sufficient in the context of COVID-19-associated pathophysiology is unknown. These proposals are a synthesis of opinions based on a limited level of evidence and should not be considered as formal recommendations.

3. Proposals

3.1. Who should receive standard dose prophylactic anticoagulation?

3.1.1. Outpatients

Data on the incidence of thrombotic complications in outpatients are limited. In non-hospitalised patients referred to computed tomography (CT) pulmonary angiography by an emergency department (n = 72), pulmonary embolism was identified in 18% CTs, and 38% of patients with pulmonary embolism had a moderate clinical type [3].

Along with the French Society of Vascular Medicine, we suggest standard dose prophylactic anticoagulation for selected high-risk outpatients with significant reduction of mobility associated with at least one risk factor among: BMI $>$ 30 kg/m^2, age $>$ 70 years, active cancer, personal history of venous thromboembolism (VTE), or major surgery within the last three months [4]. Patients who require home oxygen supplementation should be considered equivalent to hospitalised patients. For these patients, we suggest the use of standard-dose prophylactic anticoagulation.

3.1.2. Hospitalised patients

Among hospitalised ward patients, a meta-analysis reported a pooled incidence of deep vein thrombosis and pulmonary embolism (assessed by screening or clinical diagnosis) of 7.1% (95% CI, 4.8–9.8) [5]. This incidence is higher than in non-COVID viral pneumonia: Elgendy et al. reported an incidence of VTE of 1.0% among 455,629 hospitalised patients with a primary diagnosis of non-COVID-19 viral pneumonia [6]; Stals et al. reported a 30-day adjusted cumulative incidence for venous thrombotic complications of 3.6% (95% CI, 2.7–4.6) in influenza *versus* 23% (95% CI, 16–29) in COVID-19 hospitalised patients [7].

Reported rates of thrombotic complications vary considerably because of different screening strategies, different study designs (prospective *versus* retrospective), and different event inclusions (venous, arterial, or both).

The absence of prophylactic anticoagulation has been associated with an increase in the mortality of hospitalised COVID-19 patients [8]. In non-severe hospitalised patients, defined as an oxygen requirement equal to or less than 6 L/min, we suggest a standard-dose prophylactic anticoagulation. In individuals on long-term anticoagulation therapy, switching to parenteral anticoagulation may be considered to limit drug interactions and allow

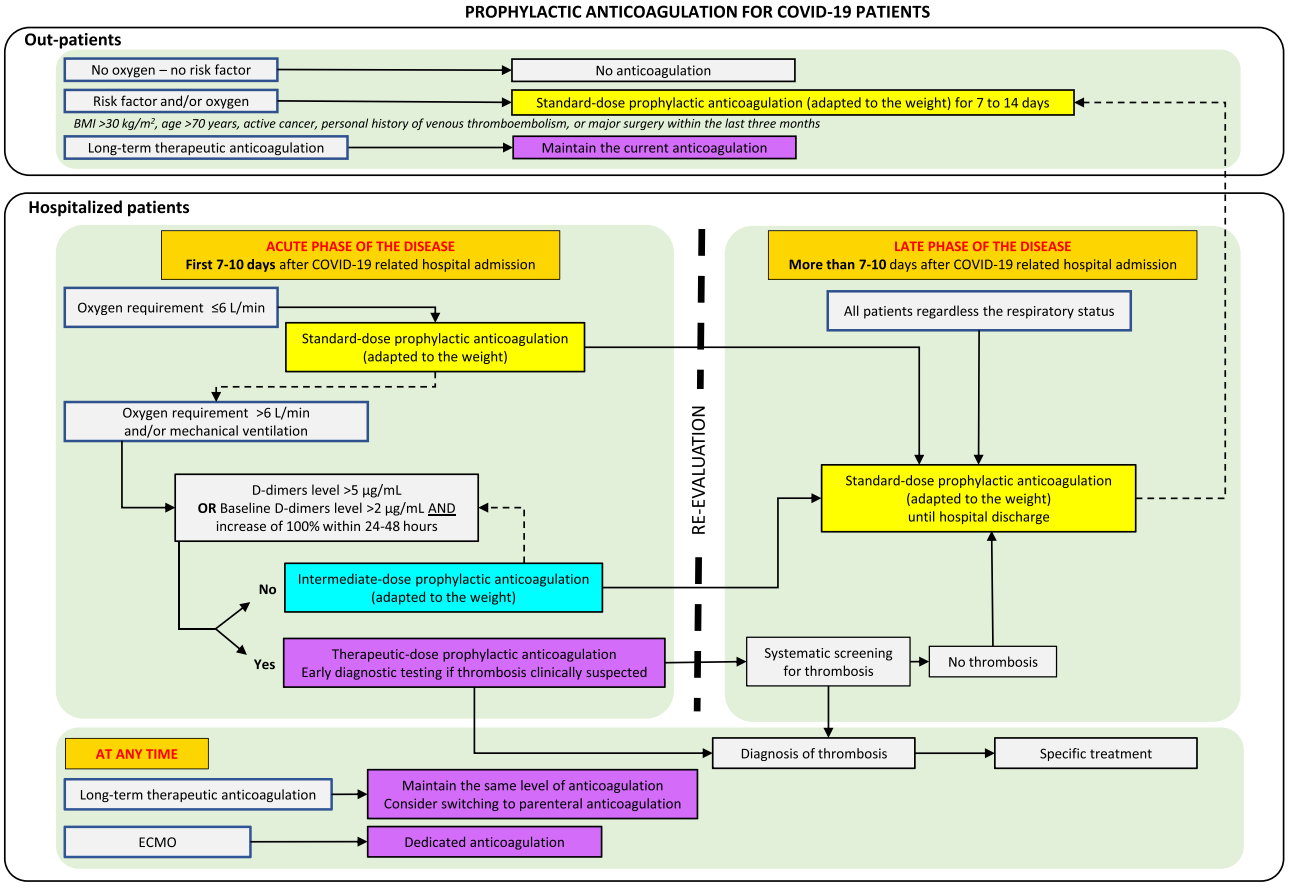

Fig. 1. Prophylactic anticoagulation for COVID-19 patients.

rapid dose adjustments if necessary. In patients in whom vitamin K antagonists are maintained, INR should be closely monitored.

3.2. Should the dose of prophylactic anticoagulation be increased in critically ill patients?

The incidence of venous thromboembolism is higher in critically ill patients compared to ward patients. Jimenez et al. reported an incidence of 27.9% (95% CI, 22.1–34.1) in critically ill patients [5]. Analysis from the first wave reported that COVID-19 ARDS patients developed more thrombotic complications compared to non-COVID-19 ARDS patients [9]. Intensive Care Unit (ICU) admission and the need for mechanical ventilation have been identified as independent risk factors for thrombosis in COVID-19 [10]. Thrombotic events are independently associated with mortality [11]. Based on this high thrombotic risk, many institutional and scientific society guidelines have proposed to increase the dose of prophylactic anticoagulation in critically ill patients [12,13].

Retrospective studies have suggested that increasing the dose of prophylactic anticoagulation from a standard dose to an intermediate or therapeutic dose in severe patients may be beneficial [14–16].

Several randomised controlled trials are still ongoing. One has been recently published, and another published preliminary results. In the INSPIRATION trial, intermediate-dose prophylactic anticoagulation did not significantly reduce the occurrence of the composite endpoint (30-day mortality, need for ECMO, thrombotic events) [17]. Although these results did not support the routine use of an increased dose of anticoagulation in severe COVID-19 patients, concerns about the applicability of these results have been raised [18]: despite a high mortality rate of 42%, the length of stay in the ICU was short *i.e.*, 6 days (median, IQR 2–11), and only 20% of patients underwent invasive mechanical ventilation, raising the question of the available ICU resources. Above all, the rate of thrombotic events in the standard-dose prophylactic anticoagulation group was very low, *i.e.*, 3.5%, suggesting that not all thrombotic events were diagnosed, resulting potentially in an underestimation of the benefit of intermediate-dose prophylactic anticoagulation.

The still ongoing multiplatform randomised trial including the ATTAC, REMAP-CAP, and ACTIV-4 trials, has stopped enrolment of critically ill patients on the 19th of December 2020, due to a 99.8% probability of futility concerning therapeutic dose anticoagulation on their primary outcome (in-hospital mortality and 21-day organ support free days) [19]. The choice of this composite endpoint is questionable. In COVID-19 patients, organ failure is multifactorial. Concerning thromboprophylaxis, the primary endpoint in landmark studies was the incidence of venous thromboembolism [20–22]. Of note is the multiplatform trial found fewer thrombotic complications in the therapeutic dose group compared to the prophylactic dose group (5.7% *versus* 10.3%, respectively). Among the latter, 51% of patients received intermediate dose anticoagulation. Major bleeding complications were rare ($< 4\%$) and comparable between the two strategies.

Overall, these results do not rule out a potential benefit on thrombotic complications to increasing the anticoagulation in severe COVID-19 patients.

We suggest that patients with severe COVID-19, defined as an oxygen requirement greater than 6 L/min or a need for mechanical ventilation, receive at least intermediate dose prophylactic anticoagulation.

3.3. Who may benefit from therapeutic dose anticoagulation?

Apart from patients with a documented thrombosis, whether therapeutic dose anticoagulation could be beneficial as a thromboprophylaxis in subgroups of patients is still an open question. To stratify thrombotic risk among hospitalised patients, D-dimers have been extensively studied. Baseline D-dimers level above the upper limit of normal is associated with critical illness, thrombosis, acute kidney injury, and death [23]. In the CLOTVID cohort including non-ICU hospitalised patients, after adjustment of anticoagulant status and delay of follow-up, the combination of D-dimer level $\geq$ 2 μg/mL and neutrophils count $\geq$ 7.0 G/L on admission was associated with increased risk of ICU transfer or death [24]. The D-dimers level is related to thrombotic complications during COVID-19 but also the severity of the disease, especially the severity of lung injury.

There is no clear cut-off above which the diagnosis of thrombosis is certain, however several studies showed similar results. In the COVICLOT study [15], a D-dimers level > 5 μg/mL was associated with a positive predictive value of 50% for thrombotic complications (unpublished data). In hospitalised patients (ward and critically ill patients), diagnosis of venous thromboembolism during hospitalisation was independently associated with D-dimers level > 5611 ng/mL (OR 6.3, 95% CI 2.4–16.2) [25]. Among patients who underwent CT pulmonary angiography, the closest D-dimers levels to imaging request had a positive predictive value for pulmonary embolism of approximately 70% when values approached 5 μg/mL [26]. In non-mechanically ventilated patients, D-dimers levels > 5 μg/mL at admission was associated with venous thromboembolism in 46.7% of cases [27]. These data are from retrospective studies in which no systematic screening for thrombosis was applied, but all converge on a D-dimers threshold of 5 μg/mL.

The use of D-dimers for diagnosing thrombosis is noteworthy. Although a high level of D-dimers is specific for venous thromboembolism, the positive predictive value is low in many clinical settings where venous thromboembolism incidence is low [28]. However, in severe COVID-19 patients with a high burden of thrombotic complications, a D-dimers level > 5 μg/mL is associated with a remarkably high thrombotic risk, with a positive predictive value of at least 40–50%.

The main limitation with D-dimers is that D-Dimer testing demonstrates not strictly comparable results due to high variability within and among methods [29]. As a result, the optimal cut-off value could be adjusted based on assay methodology [30,31]. Furthermore, anticoagulant therapy lowers D-Dimers level [32].

The changes in D-dimers levels over time can also help identify patients likely to develop thrombosis, as a D-dimers increment of 1.5-fold was strongly associated with the diagnosis of thrombosis in COVID-19 patients [33]. Progression curves of D-dimers also showed a rapid increase before the diagnosis of thrombotic events [14,34].

In selected patients with a very high thrombotic risk defined by a D-dimers level > 5 μg/mL or a rapid increase of D-dimers level (for instance, at least twice from a baseline value > 2 μg/mL within 24–48 h), we suggest initiating therapeutic dose prophylactic anticoagulation and screening for thrombosis.

Patients requiring extracorporeal membrane oxygenation (ECMO) represent a subgroup of the most severe patients, where a very high incidence of thrombotic complications has been reported, including pump and oxygenator clotting. However, data on anticoagulation in this setting are still limited. In patients on ECMO, we suggest using a dedicated anticoagulation protocol, targeting a therapeutic level of anticoagulation.

3.4. Should anticoagulant dose be adjusted to body weight?

As a high prevalence of obesity is observed, particularly in severe COVID-19 patients [35], anticoagulant regimens should take into account patients' body weight or body mass index. Weight-adjusted dose thromboprophylaxis could reduce venous thromboembolism in obese non-COVID-19 hospitalised patients [36]. For therapeutic dosing, guidelines suggest dose selection according to actual body weight, but capped dose are often used in clinical practice [37,38].

We suggest that anticoagulation be adapted to the weight or body mass index. Anticoagulant drug and dose for prophylaxis according to body mass index and creatinine clearance are shown in Table 1.

3.5. What is the bleeding risk associated with COVID-19, and its temporal relationship with thrombotic risk?

First underreported, pooled incidence of bleeding was found to be 7.8% (95% CI, 2.6–15.3) for all type of bleeding and 3.9% (95% CI,

Table 1
Anticoagulant drug and dose for prophylaxis according to body mass index and creatinine clearance.

Creatinine clearance	BMI	Standard dose prophylaxis	Intermediate dose prophylaxis	Therapeutic dose prophylaxis
> 30 mL/min	< 30	LMWH *e.g.*, enoxaparin 4000 IU/24 h[a]	LMWH *e.g.* enoxaparin 4000 IU/12 h	LMWH *e.g.* enoxaparin 100 IU/kg/12 h, without exceeding 10,000 IU/12 h
	> 30	LMWH *e.g.*, enoxaparin 4000 IU/12 h	LMWH *e.g.* enoxaparin 6000 IU/12 h	
15–30 mL/min	< 30	LMWH *e.g.*, enoxaparin 2000 IU/24 h	UFH bolus then 200 IU/kg/24 h continuous infusion to titrate to anti-Xa target	UFH bolus then 500 IU/kg/24 h continuous infusion to titrate to anti-Xa target
	> 30	LMWH *e.g.*, enoxaparin 2000 IU/12 h		
< 15 mL/min	< 30	UFH 5000 IU/12 h subcutaneous or continuous infusion		
	> 30	UFH 5000 IU/8 h subcutaneous or continuous infusion		
Target anti-Xa activity		None	LMWH: avoid overdose (< 1.5 IU/mL for enoxaparin and tinzaparin)	LMWH: avoid overdose (< 1.5 IU/mL for enoxaparin and tinzaparin)
			UFH: detectable activity and < 0.5 IU/mL	UFH: 0.5–0.7 IU/mL

BMI: body mass index (kg/m^2); LMWH: Low-molecular-weight heparin; UFH: unfractionated heparin.
[a] Other options include tinzaparin 3500 IU/24 h; dalteparin 5000 IU/24 h; fondaparinux 2.5 mg/24h if creatinine clearance > 50 mL/min.

1.2–7.9) for major bleeding, without clear difference between critically ill and ward patients [5]. In a retrospective cohort of ICU patients, Halaby and al. reported an incidence of major bleeding of 14.8%, although the bleeding risk did not differ from other severe viral infections (HR 1.26; 95% CI 0.86–1.86) [39].

The use of therapeutic dose anticoagulation might increase the rate of bleeding [5,39], although the global bleeding risk remains low in prospective studies [17,19]. This could limit the benefit of therapeutic dose prophylactic anticoagulation in unselected patients.

There is a temporal relationship between COVID-19 disease progression and associated thrombotic and haemorrhagic risks. Based on the analysis of 22 studies (13 of which included critically ill patients) and using a quantile estimation method, thrombotic events occurred 7.0 (5.9–8.2) days after admission, whereas haemorrhagic events occurred 11.4 (8.6–14.1) days after admission [18]. These results are consistent with published data where an increase in thrombin generation associated with a decrease in global fibrinolytic capacity is observed during the first week of ICU hospitalisation followed by a gradual return to normal, along with a decrease in the COVID-19-related inflammatory syndrome [40]. The thrombotic risk seems to be predominant within 7–10 days after hospital admission, then the bleeding risk increases after this period. We suggest a sequential strategy in critically ill patients, where prophylactic anticoagulation is increased for 7–10 days, then decreased to standard dose thromboprophylaxis.

3.6. What is the minimal laboratory monitoring of haemostasis in hospitalised COVID-19 patients?

To assess the thrombotic risk of hospitalised patients, D-dimers can help identify patients with severe disease, and thus patients at high thrombotic risk. In critically ill patients, we suggest monitoring D-dimers level every 24−48 h during the first 7–10 days, when most thrombotic events occur.

Initially proposed as a marker of thrombotic risk in COVID-19 patients, fibrinogen levels have not been associated with thrombotic risk in most studies and therefore cannot be used to identify patients at risk for thrombosis [27,41].

Platelet count, prothrombin time, and fibrinogen level can help diagnose heparin-induced thrombocytopaenia and disseminated intravascular coagulation (DIC), although these conditions are infrequent in COVID-19 patients [42]. DIC is associated with an increased risk of bleeding and therefore should prompt physicians to reduce the dose of anticoagulation. Fibrinogen, as an acute phase reactant, can decrease the efficacy of heparin infusion and lead to increased dose requirements. The decrease in fibrinogen levels can lead to unfractionated heparin overdose and bleeding complications [43]. In critically ill patients, we suggest monitoring those parameters [platelet count, prothrombin time, fibrinogen] frequently in the acute phase of the disease, for instance every 24−72 h. In ward patients, the platelet count should be monitored once or twice a week to detect heparin-induced thrombocytopaenia if standard dose unfractionated heparin is used [44].

Concerning unfractionated heparin (UFH) monitoring, the use of activated partial thromboplastin time (aPTT) may be inappropriate due to the hyper inflammatory status of the disease. Anti-Xa activity, although not fully standardised [45], may be more suitable to monitor UFH, since it is less dependent on pre-analytical conditions and less vulnerable to laboratory interference [40]. Heparin resistance is frequently observed in critically ill COVID-19 patients [46] and is likely due to high factor VIII and fibrinogen levels [47]. In this condition, the aPTT is less prolonged or normalises whereas the activity of heparin is unaffected, as assessed by anti-Xa assay. Thus, adjusting the heparin dose based on aPTT could result in heparin overdose and bleeding complications. In critically ill patients with a hyper inflammatory state, we strongly suggest that intermediate and therapeutic dose UFH should be monitored with an anti-Xa assay.

If UFH is used, we suggest a target anti-Xa level of 0.5−0.7 IU/mL for the therapeutic dose. Despite lack of evidence, we suggest that heparin infusion is adapted to a detectable anti-Xa level without exceeding 0.5 IU/mL for the intermediate dose.

UFH binds non-specifically to plasma proteins, leading to a variable anticoagulant effect over time, especially if a hyper inflammatory state is present [48]. Low-molecular-weight heparins present a more predictable dose-response than UFH and are preferred in most cases. Still, pharmacokinetic properties of low-molecular-weight heparins compounds are not superimposable, especially regarding their elimination by the kidney. Low-molecular-weight heparins with less dependent renal elimination such as tinzaparin or dalteparin may be considered in patients with renal impairment.

If low-molecular-weight heparin is used, we suggest monitoring the peak anti-Xa level (4 h after the third injection) for intermediate and therapeutic dose to avoid overdose. The anti-Xa level defining an overdose is different for each molecule, for instance 1.5 IU/mL for enoxaparin or tinzaparin.

Summarised biological monitoring is presented in Table 2.

3.7. How long is prophylactic anticoagulation warranted?

Among outpatients, the French Society of Vascular Medicine suggests a standard dose thromboprophylaxis (with low-molecu-

Table 2
Laboratory monitoring of haemostasis.

	Thrombotic risk assessment	HIT, DIC and bleeding risk assessment	Heparin monitoring
Oxygen requirement $\leq$ 6 L/min	D-dimers At admission, and each time clinical status deteriorates	Platelet count, PT, Fibrinogen Platelet count once or twice weekly if UFH is used (risk of HIT)	anti-Xa activity LMWH Standard dose: none
Oxygen requirement $>$ 6 L/min and/or mechanical ventilation	Every 24−48 h until day 7–10	Every 24–72 h	Intermediate and therapeutic dose: at least one peak anti-Xa activity (4 h after $\geq$ 3 injections) to avoid overdose. Limit is different among molecules, *e.g.*, $<$ 1.5 IU/mL for enoxaparin and tinzaparin UFH Standard dose: none Intermediate dose: daily measurement, target a detectable activity and $<$ 0.5 IU/mL Therapeutic dose: daily measurement, target 0.5–0.7 UI/mL

HIT: heparin-induced thrombocytopaenia. DIC: disseminated intravascular coagulation. PT: prothrombin time. LMWH: low molecular weight heparin. UFH: unfractionated heparin.

lar-weight heparin or fondaparinux) if risk factors are present, during 7–14 days [4]. Risk factors include, in addition to a significant reduction in mobility: BMI $>$ 30 kg/m^2, age $>$70 years, active cancer, personal history of VTE, and major surgery within the last three months.

Among severe patients, we suggest a total duration of increased-dose prophylactic anticoagulation (either intermediate or therapeutic) of 7–10 days, according to the described course of the disease.

In patients with a very high thrombotic risk, on therapeutic dose prophylactic anticoagulation, we suggest systematic screening for thrombosis before de-escalation at days 7–10. These patients are suspected of having thrombosis until proven otherwise. Systematic screening may include CT pulmonary angiography, compression ultrasonography, or other diagnostic imaging available. In the absence of diagnosed thrombosis, a standard-dose, weight-adapted thromboprophylaxis would limit thrombotic complications until discharge. If a thrombotic complication is diagnosed, appropriate antithrombotic treatment can be initiated according to its localisation and severity. In this subgroup of patients, appropriate diagnostic testing could occur before day 7 if clinical suspicion of thrombosis is present.

In all other cases of hospitalised patients, standard dose thromboprophylaxis is indicated until discharge.

After hospital discharge, a prolonged thromboprophylaxis should be decided on a case-by-case basis. The risk of post-discharge venous thromboembolism appears to be similar to other acute medical illnesses [49]. Age over 75 and prior history of venous thromboembolism are strongly associated with post-discharge thrombotic complications [50].

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Conflicts of interest

JHL: participation on a Data Safety Monitoring Board or Advisory Board for Instrumentation Labs, Merck, Octapharma.

YG: honoraria and travel fees from Aguettant, Bayer-Healthcare, Bristol-Myers-Squibb/Pfizer, CSL Behring, Octapharma, Roche, Sanofi, and Sobi.

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The other authors have no competing interest to declare.

Author contributions

AlG, CT, AM: Conceptualization, Writing - Original Draft, Writing - Review & Editing, Validation. **JHL**: Writing - Review & Editing, Validation. **PA, YG, AnG**: Writing - Review & Editing, Supervision, Validation. **PN**: Supervision, Validation. **DG, DL, ST**: Validation.

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