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CLINICAL FOCUS: CURRENT ISSUES IN VENOUS THROMBOEMBOLISM
REVIEW

Prophylaxis and treatment of COVID-19 related venous thromboembolism

F.H.J. Kaptein, M.A.M. Stals, M.V. Huisman and F.A. Klok

Department of Medicine – Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands

ABSTRACT

COVID-19 pneumonia has been associated with high rates of thrombo-embolic complications, mostly venous thromboembolism (VTE), which is thought to be a combination of conventional VTE and in situ immunothrombosis in the pulmonary vascular tree. The incidence of thrombotic complications is dependent on setting (intensive care unit (ICU) versus general ward) and the threshold for performing diagnostic tests (screening versus diagnostic algorithms triggered by symptoms). Since these thrombotic complications are associated with in-hospital mortality, all current guidelines and consensus papers propose pharmacological thromboprophylaxis in all hospitalized patients with COVID-19. Several trials are ongoing to study the optimal intensity of anticoagulation for this purpose. As for the management of thrombotic complications, treatment regimens from non-COVID-19 guidelines can be adapted, with choice of anticoagulant drug class dependent on the situation. Parenteral anticoagulation is preferred for patients on ICUs or with impending clinical deterioration, while oral treatment can be started in stable patients. This review describes current knowledge on incidence and pathophysiology of COVID-19 associated VTE and provides an overview of guideline recommendations on thromboprophylaxis and treatment of established VTE in COVID-19 patients.

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Introduction

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a global pandemic by the World Health Organization (WHO) in March 2020. As of 26 November 2020, the WHO reports over 59 million confirmed cases of COVID-19 worldwide, and 1.4 million deaths [1].

Accumulating evidence reveals that coagulopathy is common in COVID-19 patients [2–4], and high incidences of thrombotic complications have been reported, which are foremost venous thromboembolism (VTE) occurring in patients admitted to Intensive Care Units (ICUs) [5–9]. In response to these critical findings, (inter)national guidelines have been rapidly released to address the diagnosis, prevention and treatment of VTE in COVID-19 patients, although high-quality evidence is still missing [10–16].

With better understanding of the characteristics of the SARS-CoV-2 virus and the pathophysiologic mechanism of the related coagulopathy, together with findings of autopsy studies in COVID-19 patients, it was recognized that the pulmonary vascular occlusions observed in COVID-19 patients consist of both in-situ immuno-thrombosis and 'classical' pulmonary thromboembolism [17–20]. As the research on COVID-19 is rapidly evolving, this review will address the current incidence, pathophysiology, guidelines on prophylaxis and suggested treatment of venous thromboembolism in COVID-19 patients.

Epidemiology

Since the start of the COVID-19 outbreak, numerous studies reported on the incidence or prevalence of VTE in hospitalized patients, with varying results ranging from 0% [21] to 85% [18]. This large variability is related to differences in patient case mix, hospital setting, study quality, and diagnostic protocols for VTE. In particular, studies in which VTE was diagnosed by screening reported the highest incidences, in contrast to those reporting incidences based on performing diagnostic tests in patients with VTE-specific symptoms only [22]. Comparing the results of all studies, irrespective of design, is therefore challenging and the validity of pooling this data is questionable. Even so, several meta-analyses have been published which provide more inside in the epidemiology of COVID-19 associated thrombotic complications. The meta-analysis with the largest number of included patients (66 studies, over 28 000 patients) reports an overall crude in-hospital VTE incidence of 14.1% (95% CI 11.6–16.9) [9]. Notably, this incidence could not be adjusted for the competing risk of mortality, nor was it indicated at which point in time during the course of disease the VTE diagnosis was confirmed. The largest variation in VTE rates was seen across different hospital settings (ICU vs. non-ICU hospitalized patients) and whether or not systematic screening with radiological imaging was performed. A prevalence of 40% deep-vein thrombosis (DVT) was found in patients screened with ultrasound, vs. 9.5% in those not screened. The difference in

CONTACT F.A. Klok f.a.klok@lumc.nl Department of Medicine - Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands

incidence of venous thrombotic complications between ICU and non-ICU patients was 23% vs. 7.9% respectively. The majority of the patients included in this meta-analysis used at least prophylactic anticoagulation, but as the thromboprophylaxis strategy was not consistently reported, the association between the use and dose of anticoagulation and incident VTE could not be assessed. Importantly, it was reported that thrombotic complications in COVID-19 are associated with mortality [23,24].

Although D-dimer levels are commonly elevated in COVID-19 infection [25,26], patients who developed VTE have a markedly higher D-dimer level at baseline than those who did not develop VTE [9]. In addition to a clear association with thrombotic complications, higher D-dimer levels have also been implicated with poor outcome and mortality [2,27–31]. Hence, D-dimer levels have been widely used as prognostic marker in admitted COVID-19 patients. Although it has been suggested that (sudden) changes in D-dimer levels should trigger diagnostic tests for thrombotic events, or that D-dimer levels higher than a certain threshold indicate the need for higher intensity thromboprophylaxis, such practice has not been confirmed to improve outcomes nor recommended by guidelines [11,32–34].

The incidence of VTE in COVID-19 patients appears to be considerably higher compared to other critically ill [6,35] or ARDS patients [8], or in other respiratory virus infections known to lead to a procoagulant state [36,37]. Based on autopsy studies, in which all patients with COVID-19 showed various degrees of thrombosis in small and large pulmonary arteries, it was suggested that this was rather local thrombosis than from embolic origin [17,38]. On the other hand, studies where ultrasound screening of the legs on the ICU was performed showed DVT rates ranging from 69% to 85% [18,39], which supports the mechanism of 'classical' pulmonary thromboembolism (PE). These two pathophysiological mechanisms are not mutually exclusive, and both may contribute to the substantial burden of pulmonary artery occlusion and accompanying clinical phenotype observed in COVID-19 patients.

Pathophysiology

COVID-19 patients share similar risk factors for venous thromboembolism with the general population, including older age, immobility, obesity and a past history of VTE or cancer. For patients admitted to the ICU additional risk factors including sepsis, mechanical ventilation, and indwelling catheters have been described [40]. Although these VTE predictors are relatively common in admitted COVID-19 patients, as they are related to risk factors or treatment of a more severe disease course of COVID-19 [41], it was debated whether this could entirely explain the high incidence of venous thromboembolisms, and it raised the question whether there may be a (contributing) SARS-CoV-2 specific procoagulant mechanism.

Initial studies from China reported on SARS-CoV-2 related coagulopathy, mainly consisting of an increased D-dimer concentration and prolonged prothrombin time (PT), and to a lesser extent prolonged activated partial thromboplastin time (APTT) and increased fibrinogen degradation products (FDPs) [2,42]. This procoagulant state was shown to predict a bad prognosis in terms of survival [2,26,43]. Early descriptions of COVID-19 coagulopathy classified this disorder as a form of disseminated intravascular coagulation (DIC), although thrombocytopenia and consumption of coagulation factors seem to be rare [43,44].

The association between viral infection and thrombosis is not new, as there are many known crosslinks between immune pathways and coagulation pathways [45], but the extent of the COVID-19 pandemic has placed greater emphasis on this link [46]. The exact pathophysiology of COVID-19 related thrombosis has not yet been elucidated, but there are several, possibly synergistic mechanisms by which SARS-CoV-2 infection may result in macrovascular (via systemic pathways) and (local) microvascular thrombosis [47].

SARS-CoV-2 is a single-strand RNA coronavirus, which enters human cells primarily by binding to the angiotensin-converting enzyme 2 (ACE2) receptor. ACE2 is mainly expressed in airway epithelium (including alveolar epithelial type II cells), which is used by the virus to enter the host. ACE2 is, however, also widely expressed on vascular endothelial cells, which traverse multiple organs [48]. The virus-mediated engagement of ACE2 decreases its expression and activates the renin-angiotensin system (RAS), promoting platelet aggregation, and reducing the fibrinolytic activity [49]. Furthermore, the overproduction of early response proinflammatory cytokines (the so-called 'cytokine storm'), induced by the innate immunity activation, has been described to be responsible for the most severe manifestations of COVID-19. Among these cytokines, some have been demonstrated to induce vascular permeability and activate coagulation pathways [50]. Of these cytokines, IL-6 has been demonstrated to stimulate megakaryopoiesis and promote synthesis of coagulation factors [49].

The entry of the virus in endothelial cells may lead to direct endothelial injury (characterized by elevated levels of von Willebrand factor (vWF)) and 'endothelialitis' (marked by the presence of activated neutrophils and macrophages). This can trigger excessive thrombin production, inhibit fibrinolysis and activate complement pathways, initiating thrombo-inflammation [17,51]. Furthermore, platelet-neutrophil cross-communication can result in various proinflammatory effects [47,52]. Activated neutrophils may form neutrophil extracellular traps (NETs), a web-like structure consisting of DNA and proteins, to trap and kill microbes. However, dysregulated NETosis can lead to thrombosis: NETs activate platelets and include fibrin, resulting in the formation of an immunothrombus [53]. Platelets detect foreign pathogens through pattern recognition receptors and can activate neutrophils through chemokine and coagulation factor signaling. A positive-feedback loop may be formed, which initiates and sustains the immuno-thrombosis cascade [52].

As previously mentioned, thrombocytopenia is not common in COVID-19 patients [44]. However, this finding has been correlated with increased risk of disease severity and mortality [54]. On the other hand, thrombocytosis has also been reported in moderately severe cases [55]. Proposed mechanisms are stimulation of thrombopoiesis by proinflammatory cytokines, and by interaction between vWF and megakaryocytes due to endothelial injury. It is possible that thrombocytopenia is on the more severe end of the same spectrum, where the cytokine storm

eventually leads to inhibition of hematopoiesis, an autoimmune response against platelets is triggered, and/or continuous consumptive coagulopathy resulting from sustained inflammation is present [44,56].

Varying presence of antiphospholipid antibodies in patients with COVID-19 have been described [57–61], noting that these antibodies can arise transiently in patients with critical illness and various infections with no direct association with thrombotic episodes [62]. The most consistent finding is a high prevalence of lupus anticoagulant [8,63,64], but with contrasting results whether this correlates with thrombotic events [65,66]. As functional assays of lupus anticoagulant may be influenced by concomitant anticoagulation and/or high levels of C reactive protein, these results are difficult to interpret [67,68].

Altogether, a complex interaction between SARS-CoV-2, immune and inflammatory mechanisms and coagulation pathways exists, both on local and systemic level. The extent of micro- and macrovascular thrombosis has been related to disease severity, but it could be debated whether thrombotic complications are the cause or consequence of clinical deterioration. Regardless, adequate preventive and treatment strategies for thrombotic complications are of utmost importance in severely affected COVID-19 patients.

Diagnosis

Patients with COVID-19 infection often present with respiratory symptoms and have been described to report chest pain and hemoptysis [25]. These symptoms largely overlap with the notorious nonspecific presentation of acute PE [69]. Considering the high incidence of thrombotic complications in COVID-19 patients, physicians must have a low threshold for considering the presence of VTE. Unexpected respiratory worsening, unexplained tachycardia, hypotension, PE-specific ECG changes, and symptoms indicative of deep vein thrombosis of the extremities should trigger targeted diagnostic testing. It is recommended however, to only order diagnostic tests for PE when it is clinically suspected, and not apply screening strategies [10,12,16]. The specificity of D-dimer tests may be lower in patients with COVID-19 compared to other clinical settings. Even so, to rationalize the deployment of resources and personnel for transporting a patient to the radiology department with all the associated isolation precautions, it is still advised to follow diagnostic algorithms starting with pretest probability assessment and D-dimer testing, especially when pretest probability-dependent D-dimer thresholds are being used [70–72]. In case of signs of DVT, a compression ultrasonography of the affected extremity is the test of choice.

Prognosis

Several studies have suggested a higher risk of mortality in COVID-19 patients with thrombotic complications [7,23,24,73]. This association was confirmed in a recent meta-analysis (pooling data from 42 studies that had enrolled a total of 8271 patients): the occurrence of thrombotic complications in acutely ill and critically ill patients with COVID-19 was associated with a 74% increased odds of overall mortality compared to COVID-19 patients without thrombotic complications (13% vs 23%) [74]. In addition to short-term morbidity and mortality, thrombotic complications may also aggravate chronic complications of COVID-19 and slow physical recovery. In general, the post-thrombotic syndrome and the post-pulmonary embolism syndrome have been reported to occur in 50% of VTE survivors [75]. These long-term complications have a major impact on quality of life and are associated with a considerable symptom burden, higher risks of depression, unemployment, social isolation as well as excess health-care costs [75–85]. It may be hypothesized that the prevalence of the post-thrombotic syndrome and the post-pulmonary embolism will be even higher in COVID-19 patients than in the general population, as thrombus resolution is hampered by inflammation, one of the hallmarks of COVID-19. Although this has not been studied yet in COVID-19, considering the high incidence of COVID-19 associated PE, health-care providers should be aware of chronic thromboembolic pulmonary hypertension (CTEPH) [69,86,87]. The usual incidence of CTEPH after acute PE is 2–3% [88]. Because of low awareness among physicians and suboptimal health-care utilization, the diagnostic delay of CTEPH often exceeds 1 year, which is associated with worse prognosis [89,90]. Current guidelines provide recommendations for optimal follow-up of patients with PE, including strategies for early CTEPH detection [91,92]. These recommendations are also applicable to patients with COVID-19 associated PE. One of the key steps in these algorithms is the routine assessment of persistent symptoms using validated, preferably patient-reported, outcome measures [92–94]. One other important strategy to early diagnose CTEPH is the dedicated assessment of radiological signs of chronic blood clots or preexisting right ventricular overload, because it has been shown that such radiological features are strong predictors of future CTEPH [95,96]. The diagnosis of CTEPH should always be confirmed with invasive measurement of the pulmonary artery pressure via right heart catheterization. Patients with suspected or confirmed CTEPH should be referred to expert centers where the optimal treatment can be determined.

Prophylaxis

From initial reports there is some evidence that patients who used long-term anticoagulation at hospital admission were at lower risk for developing thromboembolic complications [22,24]. However, no effect on ICU admission [97] or association with mortality was found [24,97–100]. Thromboprophylaxis versus no prophylaxis in critically ill COVID-19 patients was suggested to reduce mortality when the Sepsis-Induced Coagulopathy (SIC) score was ≥4, but not in patients with a score <4. The prophylactic effect on thrombotic complications was not reported [33].

International guidelines have been developed rapidly, mainly based on expert consensus as high-quality evidence is lacking. All large international scientific organizations recommend anticoagulant thromboprophylaxis in all hospitalized COVID-19 patients, in the absence of contraindications (Table 1) [10–13,101,102]. However, it is emphasized that the optimal thromboprophylaxis strategy in COVID-19 patients is still uncertain. The use of validated standardized VTE risk assessment scores as the Padua score is usually not advised,

Table 1. Overview of guidelines on prophylaxis and treatment of VTE in COVID-19.

	Prophylaxis in acutely ill patients (non-ICU)	Prophylaxis in critically ill patients (ICU)	Post-discharge thromboprophylaxis	Treatment of VTE
ISTH	Routine thromboprophylaxis with standard-dose LMWH (or UFH) in all patients. Intermediate dose LMWH may be considered. Modification based on extremes in body weight, severe thrombocytopenia or deteriorating renal function.	Routine thromboprophylaxis with standard-dose UFH or LMWH in all patients. Intermediate dose LMWH can be considered. Patients with obesity should be considered for a 50% increase in dose.	Extended post-discharge thromboprophylaxis should be considered in patients that meet high VTE risk criteria. Duration: at least 14 days, up to 30 days.	Established guidelines should be used, with advantages of LMWH in the inpatient setting and DOACs in the post-hospital discharge setting. Minimum duration of 3 months.
CHEST	Anticoagulant thromboprophylaxis in all patients. Preferred agent LMWH or fondaparinux, followed by UFH, followed by DOAC. Standard prophylactic dose is advised.	Anticoagulant thromboprophylaxis in all patients. Preferred agent LMWH, followed by UFH, followed by fondaparinux or DOAC. Standard prophylactic dose is advised. If anticoagulation is contraindicated, mechanical prophylaxis is advised.	No extended thromboprophylaxis advised.	In shock, systemically administered thrombolysis is suggested. In ICU patients parenteral anticoagulation, LMWH preferred over UFH. In patients without any drug-interactions on general wards a DOAC can be considered. For outpatient management DOACs are recommended. Minimum duration of 3 months.
ESC	Standard dose prophylaxis in all patients.	Standard dose prophylaxis in all patients	Not mentioned.	Following current ESC PE guidelines: UFH, LMWH or DOAC, depending on the possibility of oral treatment, renal function etc. Caution of interaction with DOACs (should be particularly avoided in lopinavir/ritonavir use). Duration not mentioned.
ASH	All patients should receive pharmacologic thromboprophylaxis with LMWH over UFH. Dose adjustment for obesity may be used per institutional guidance. When anticoagulants are contraindicated, use mechanical prophylaxis. Standard prophylaxis dose is advised. Participation in clinical trials on intensified doses is recommended.	See non-ICU patients.	Can be considered based on the individual patients' VTE risk factors at time of discharge.	LMWH and UFH preferred in critically ill. DOACs should be used with caution (drug-drug interaction). Duration not mentioned.
ERS/ATS	Not mentioned	Not mentioned	No suggestion for or against extended thromboprophylaxis.	Duration of 3 months. No recommendations on type or dose of anticoagulation.
NIH	Hospitalized adults should receive standard prophylaxis conform non-COVID-19 patients.	See non-ICU patients.	Extended VTE prophylaxis can be considered in patients who are at low risk for bleeding and high risk for VTE as per protocols for patients without COVID-19.	Management with therapeutic doses of anticoagulant therapy as per standard of care for patients without COVID-19.
NICE	Pharmacological VTE prophylaxis with standard prophylactic dose of LMWH in all patients (second choice: UFH or fondaparinux). Consider adjusting the dose for extremes of body weight or impaired renal function.	In patients with advanced respiratory support, consider intermediate dose prophylaxis.	Can be considered if the risk of VTE outweighs the risk of bleeding (conform non-COVID-19 protocols).	Not mentioned.

Note: ISTH: International Society on Thrombosis and Haemostasis, CHEST: American College of Chest Physicians, ESC: European Society of Cardiology, ASH: American Society of Hematology, ERS: European Respiratory Society, ATS: American Thoracic Society, NIH: National Institute of Health, NICE: National Institute of Health and Care Excellence.

as the optimal risk stratification in COVID-19 requires further study [10]. The same applies for bleeding risk assessment [12]. Low-molecular weight heparin (LMWH) is the preferred anticoagulant agent, as it is parenteral and usually administered once daily (in contrast to unfractionated heparin (UFH). The use of direct oral anticoagulation (DOAC) agents as prophylaxis can be considered, but with caution as the risk of rapid deterioration in hospitalized COVID-19 patients is substantial, and several antiviral and investigational treatments for COVID-19 may potentiate or interfere with DOACs [10,12]. For instance, concurrent use of lopinavir/ritonavir and DOACs has to be avoided, to avoid increased plasma levels of DOACs [103]. Interaction with remdesivir has not been studied, but is unlikely based on metabolism and clearance [104]. Dexamethasone could theoretically decrease plasma concentrations of DOACs (via inducing CYP3A4 and P-gp), although the magnitude of this interaction is likely limited [104]. Therefore, coadministration of DOACs during remdesivir and dexamethasone treatment is considered safe. Mechanical thromboprophylaxis can be applied when anticoagulants are contraindicated, especially in the critically ill [12,14].

Based on the emerging evidence suggesting increased thrombogenicity with COVID-19 and the high incidence of VTE despite standard thromboprophylaxis, a double or intermediate dose of LMWH was suggested to be the standard of care, or even a therapeutic dose of anticoagulation, especially for critically ill patients on the ICU. Many institutions adopted such intensified thromboprophylactic strategies, supported by a few retrospective cohort studies [105–107]. However, others have shown conflicting results [108,109]. Increased doses of anticoagulation are usually associated with increased bleeding risk [110]. Notably, several studies on intermediate-dose thromboprophylaxis did not show more major bleeding events compared to standard prophylactic doses [106,111], in contrast to those studies in which intermediate and therapeutic doses were pooled [112,113]. As these studies were all observational, with low sample sizes, firm conclusions cannot be drawn. Most guidelines state that there is insufficient evidence to justify increased intensity anticoagulant thromboprophylaxis. Standard dose thromboprophylaxis is recommended in general ward patients, possibly adjusted for extreme body weight, renal function or thrombocytopenia according to product monographs [10,14,102]. Although it was shown that the risk of VTE is particularly high in COVID-19 patients admitted to the ICU, standard thromboprophylaxis is generally recommended in these patients as well [12,14,101]. Nevertheless, some guidelines, especially guidelines based on expert opinion, suggest that an increased or intermediate dose in ICU patients may be considered [10,102]. There are currently several randomized trials ongoing that aim to assess the efficacy and safety of intensified thromboprophylaxis regimens. These trials will provide the evidence needed to allow for strong guideline recommendations.

Patients who already use long-term anticoagulation at presentation should continue their therapeutic dose unless contraindicated by a change in clinical circumstances. Switching oral anticoagulation to LMWH should be considered upon hospital admission, especially with impending clinical deterioration [102]. For patients with extracorporeal circuits as extracorporeal membrane oxygenation or continuous renal replacement therapy, standard institutional protocols should be applied [14].

It is known that the risk of hospital-associated VTE extends for up to 6 weeks post-discharge in medically ill patients with a high VTE risk, as those with pneumonia, sepsis and post-ICU admission [114], but the efficacy and safety of extended thromboprophylaxis in COVID-19 patients is still unclear [115,116]. Extended prophylaxis with LMWH or DOAC may be considered in patients with a high VTE and a low bleeding risk [10,102,117].

Treatment

The optimal treatment of VTE in hospitalized COVID-19 patients has not been studied yet. Currently, standard management conform non-COVID guidelines is generally advised (Table 1). In patients with confirmed PE and hypotension or signs of obstructive shock direct reperfusion therapy, usually with systemic thrombolytics, is indicated [12,101]. It was proposed to lower the threshold for thrombolytics because of the combined hypoxemic effects of impaired arterial perfusion and infectious lung inflammation, possibly exacerbating the clinical course of COVID-19 pneumonia [118,119]. However, this strategy is not supported by evidence nor recommended by current guidelines. In critically ill patients, parenteral anticoagulation is advised over oral anticoagulation, with a preference for UFH in patients with a high bleeding risk or in anticipation of invasive procedures [12]. In acutely ill patients on general wards, initial LMWH treatment may have advantages (in terms of drug–drug interactions and risk of rapid clinical deterioration) over oral treatment, although oral anticoagulation is suitable for clinically stable patients without contraindications. DOACs provide advantages over vitamin K antagonists (VKAs), especially in the post-hospital setting, as they are safer, and do not involve the need for routine monitoring [10,12,101,120]. VTE in COVID-19 patients is considered to be provoked by a reversible risk factor, so generally, a treatment duration of 3 months is advised conform non-COVID guidelines.

Abovementioned strategies are mainly aimed at macrovascular thrombosis. Concerning the virus-induced coagulopathy and microvascular thrombosis, the cornerstone should be treatment of the underlying infection [121]. No specific antiviral therapy for SARS-CoV-2 is available, but remdesivir was shown to shorten time to recovery in hospitalized COVID-19 patients [122], and dexamethasone led to decreased mortality in patients requiring supplemental oxygen [123]. It is, however, unknown if this more advanced anti-COVID-19 therapy reduces thrombotic complications as well.

Other therapies to impair the interaction between proinflammatory and procoagulant mechanisms have been proposed, as targeting cytokines (mainly IL-6), impairing NETosis [124,125] or complement inhibition [126]. Several clinical studies on tocilizumab (anti-IL-6 receptor antagonist) in COVID-19 have been published, but thrombotic complications are not always addressed [127] and if so, conflicting results are found

[128–131]. Of the other novel therapeutic targets for COVID-19 associated thrombosis, clinical results are lacking.

Conclusion

The clinical course of hospitalized patients with COVID-19 pneumonia is often complicated by venous and arterial thrombotic events. This high risk of thrombosis is fueled by a complex interaction between SARS-CoV-2, immune and inflammatory mechanisms and coagulation pathways, although the exact underlying pathomechanism has not yet been elucidated. Because of this, all hospitalized patients with COVID-19 require strict thromboprophylaxis unless contraindicated. The optimal thromboprophylactic strategy, i.e. the intensity of anticoagulation, is still subject of debate, and randomized trials are ongoing. Treatment of COVID-19 related VTE is mostly in line with regular non-COVID-19 guidelines. The choice of the anticoagulant agent is dependent on the clinical circumstances, with a preference for parenteral treatment in critically ill patients and those with impending respiratory insufficiency. Furthermore, enhanced anti-COVID-19 therapy to attenuate the interplay between inflammation and coagulation may be beneficial for the prevention and treatment of thrombotic complications, but this requires further studies.

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ORCID

F.H.J. Kaptein http://orcid.org/0000-0003-2274-4820

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