Position paper

Venous thromboembolism in patients with COVID-19 (SARS-CoV-2 infection) – a position paper of the German Society of Angiology (DGA)

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Summary: As observed in other infections with a systemic inflammatory response, severe COVID-19 is associated with hypercoagulability and a prothrombotic state. Currently, there is growing evidence that pulmonary embolism and thrombosis contribute to adverse outcomes and increased mortality in critically ill patients with COVID-19. The optimal thromboprophylactic regimen for patients with COVID-19 is not known. Whereas pharmacologic thromboprophylaxis is generally recommended for all hospitalized COVID-19 patients, adequate dosing of anticoagulants remains a controversial issue. Therefore, we summarize current evidence from the available literature and, on behalf of the German Society of Angiology (DGA), we aim to provide advice to establish an improved and more uniform strategy for thromboprophylaxis in patients with COVID-19.

Keywords: Thromboembolism, deep vein thrombosis, pulmonary embolism, D-dimers, COVID-19

Introduction

Patients with COVID-19 (COrona VIrus Disease 2019 caused by the novel Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2)) mainly present with symptoms of upper and lower respiratory tract infection and with complications that are attributed to a cytokine burst and can result in systemic inflammatory response syndrome, acute respiratory distress syndrome (ARDS) and multiorgan failure (MOF). The Chinese Center for Disease Control and Prevention recently published a large case series of patients diagnosed with COVID-19. Among 72,314 cases, 81% were asymptomatic or had mild pneumonia; 14% had severe disease defined as dyspnea, tachypnea, hypoxia or more than 50% lung involvement on imaging and approximately 5% were critically ill and suffered from respiratory failure, septic shock, or multiorgan dysfunction or failure [1]. Among critically ill patients, the case fatality rate was 49%, whereas no deaths were reported among mild and moderate cases. As observed in other viral infections with a systemic inflammatory response, severe COVID-19 is associated with hypercoagulability and a prothrombotic state and can lead to sepsis-induced coagulopathy (SIC) and disseminated intravascular coagulation (DIC). Currently, there is growing evidence that pulmonary embolism (PE) and thrombosis contribute to adverse outcomes and increased mortality in critically ill patients with COVID-19.

Incidence of thromboembolism in COVID-19

Despite adequate thromboprophylaxis, the incidence of thromboembolic complications seems to be particularly high among intensive care unit (ICU) patients. Klok et al. analyzed the incidence of thromboembolism in a cohort

of 184 critically ill patients with COVID-19 admitted to the ICU of three Dutch hospitals [2]. All patients had received at least standard doses thromboprophylaxis. The cumulative incidence of both venous and arterial thrombotic complications was 49% (95% confidence interval (CI) 41–57%) [3]. Remarkably, more than 80% of thromboembolic episodes in ICU patients manifested as PE whereas deep vein thrombosis (DVT) of the upper or lower extremities and arterial thrombosis was less common [4]. Incidence rates of VTE in ICU patients with COVID-19 obviously are substantially higher than those observed in patients treated on ICU for other reasons. In the randomized controlled PROTECT study, that compared low-molecular-weight heparin (LMWH) with unfractionated heparin (UFH) for thromboprophylaxis in 3,764 ICU patients, VTE occurred in 5.1 and 5.8% of cases, respectively [4].

The high rate of thromboembolic events is in line with the results from other observational studies [5–10]. A single-center study from Italy – including 388 patients – reported an incidence of venous or arterial thromboembolism of 28% for ICU patients and 7% for patients on a general ward [5]. Middeldorp et al. investigated the incidence of objectively confirmed venous thromboembolism (VTE) in 198 hospitalized patients with COVID-19, among them 75 ICU patients [10]. The cumulative incidences of VTE at 7, 14 and 21 days were 16%, 33% and 42%, respectively. A French study group observed an incidence for PE of 21% among 107 consecutive COVID-19 patients admitted to the ICU due to pneumonia [6]. The frequency of PE was substantially higher in the COVID-19 cohort when compared to a cohort of 196 critically ill patients with a similar severity score treated in ICU during the same time interval in 2019 and to a cohort of 40 critically ill patients with influenza in ICU (PE-incidence 6.1% and 7.5%, respectively). Another French study group performed a systematic screening for DVT using complete compression ultrasonography (CCUS) in ICU patients with COVID-19 and found an overall rate of DVT of 69% [11]. The risk of asymptomatic DVT was higher in patients treated with prophylactic anticoagulation when compared to those receiving therapeutic doses (100% vs. 56%, respectively, $p = 0.03$) and was remarkably high among patients with therapeutic-dose anticoagulation. However, the interpretation of these findings is limited by the small number of patients ($n = 26$) included in this study.

In contrast to ICU patients, the occurrence of thromboembolic complications seems to be less likely in hospitalized patients treated on general wards. Two European studies reported thromboembolic incidence rates of 6.6–9.2% [5, 10]. In a recent prospective study from Spain 156 non-ICU patients with COVID-19 pneumonia and a D-dimer level > 1,000 µg/L were systematically screened for asymptomatic DVT [8]. CCUS of both legs, performed after a median hospitalization time of 9 days, revealed one proximal and 22 distal DVTs (14.7%, 95% CI 9.6–21.3). DVT patients had higher D-dimer levels than patients without DVT (4,527 µg/L vs. 2,050 µg/L; $p < 0.001$). The authors reported that a D-dimer cutoff value of 1,570 µg/L showed a sensitivity of 95.7%, specificity of 29.3%, positive predictive value of 19% and negative predictive value of 97.5% for the diagnosis of asymptomatic DVT.

VTE incidence in COVID-19 patients with only mild or moderate disease who are treated in an ambulatory setting has not been investigated yet.

Findings of autopsy studies

A German autopsy study performed at the Department of Legal Medicine of University Medical Center Hamburg-Eppendorf investigated the first 12 consecutive COVID-19-positive deaths occurring in Hamburg (Germany) [12]. Fresh thrombi in the lower extremity veins were detected in 58% of cases (7/12). Massive PE was the cause of death in 4 patients (33%) with thrombi obviously deriving from the deep veins of the lower extremities. In additional three patients DVT was found in the absence of PE. Another prospective autopsy study investigated 11 COVID-19 patients who had suffered from various stages of bilateral diffuse alveaolar damage [13]. VTE was not clinically suspected in any patient ante mortem. However, autopsy detected thrombosis in segmental and subsegmental pulmonary arteries in all patients and pulmonary infarction in 8 cases. These data suggest that classical VTE or primary pulmonary thrombosis may be an underlying etiology responsible for mortality in patients with severe COVID-19.

Haemostatic alterations

As a consequence of the systemic inflammatory response associated with COVID-19, abnormal coagulation parameters can occur. Increased levels of D-dimers, a prolongation of prothrombin time (PT) and activated partial thromboplastin time (aPTT) and thrombocytopenia seem to reflect disease severity and have been related to poor prognosis and higher mortality rates of COVID-19 patients [14–16]. Whether these haemostatic changes are specific of COVID-19 or are a consequence of a cytokine storm that precipitates the onset of systemic inflammatory response syndrome (SIRS), as observed in other viral disease, is still an issue of debate. Vascular inflammation seems to contribute to hypercoagulability and endothelial dysfunction in such patients. SARS-CoV-2 has been shown to enter human cells mainly by binding the angiotensin converting enzyme 2 (ACE-2), which is highly expressed in lung alveolar cells, the vascular endothelium and other cells [17, 18]. Only recently, a massive increase of von-Willebrand factor (VWF) and factor VIII activity has been observed in COVID-19 and attributed to endothelial damage [19]. Finally, haemostatic abnormalities can result in sepsis-induced coagulopathy and disseminated intravascular coagulation. In a Chinese retrospective study including 183 patients with COVID-19 pneumonia, 71% of non-survivors ulfilled the International Society of Thrombosis and Haemostasis (ISTH) criteria for overt DIC [16, 20].

Prognostic value of D-dimer testing

Elevated D-dimer levels is a common finding in patients with COVID-19. Analyzing data from 1,099 Chinese patients with laboratory-confirmed COVID-19, D-dimer levels exceeding 500 µg/L were detected in 46.4% [21]. The frequency of elevated D-dimers was 43% in non-severe disease and 60% in cases with severe COVID-19. Monitoring D-dimer has been proposed to be helpful for the early identification of severe cases. In a retrospective study from Wuhan, China, a D-dimer level > 1,000 µg/L at the time of admission to hospital was strongly associated with in-hospital death, even after multivariate adjustment (OR 18.4; 95% CI 2.6–129, p = 0.003) [22]. Older age and a higher SOFA (Sequential Organ Failure Assessment) score were identified as additional predictors of mortality.

Antiphospholipid antibodies

Antiphospholipid antibodies (APL) have been supposed to contribute to the increased risk of thromboembolic events in COVID-19. However, the prevalence of APL among COVID-19 patients with venous or arterial thrombosis seems to be only low (8–10%) [23–25]. It is important to note that not every positive APL test is clinically relevant. Low-titre APL are commonly present during infections, but the majority are transient and not associated with clinical consequences. Whereas antibodies against cardiolipin or beta-2-glycoprotein-I are detected with the use of solid-phase ELISA-based assays, clot-based assays are performed for the laboratory detection of lupus anticoagulants [26]. Thus, testing for lupus anticoagulants cannot be recommended in acutely ill patients who are likely to have coagulation disorders and are under anticoagulant therapy.

Thromboprophylaxis

Tang et al. performed a retrospective study at the Tongji hospital in Wuhan (China) and reported about 449 patients with severe COVID-19, of whom 99 patients (22%) received pharmacologic thromboprophylaxis for seven days or longer [27]. Ninety-four patients were treated with LMWH (enoxparin 4,000–6,000 IU once daily) and 5 patients received UFH (10,000–15,000 IU once daily). Compared to patients without thromboprophylaxis, prophylactic-dose heparin significantly reduced the 28-day mortality in patients with a sepsis-induced coagulopathy score $\geq$ 4 (40% vs. 64%, p = 0.029) or D-dimer levels > 3,000 µg/L (33% vs. 52%, p = 0.017). However, there was no survival benefit for patients treated with heparin (30.3% vs. 29.7%, p = 0.910).

It has been supposed that prophylactic doses of anticoagulants might not be sufficient to overcome hypercoagulability associated with severe COVID-19. Although it seems reasonable to use intermediate or therapeutic doses of anticoagulants in patients supposed to be at high risk for VTE, it is important to note that currently, there is not sufficient evidence to recommend higher doses than those commonly used for thromboprophylaxis in acutely ill medical patients.

A recent Belgian cross-sectional study reported 30 ICU patients with COVID-19 who received an intermediate LMWH dose regimen (i.e., enoxaparin 4,000 IU b.i.d. or 6,000 IU b.i.d. in cases with more than 100 kg) [28]. VTE occurred in 4 patients (13%), and the authors concluded that VTE prevalence was not higher than expected. However, study size was only small, and a control group was lacking. In the aforementioned study of Klok et al. 17 patients (9.2% of the study cohort) were on long-term therapeutic anticoagulation for various reasons [3]. In these 17 patients, 3 PEs were diagnosed (18%) despite continued anticoagulant therapy at ICU admission.

In a recent observational study from New York City (United States), data from 2,773 hospitalized COVID-19 patients were analyzed [29]. A total of 786 patients (28%) was treated with therapeutic-dose anticoagulation (median time from admission to initiation of therapy: 2 days (interquartile range (IQR) 0–5 days; median duration of anticoagulant therapy: 3 days (IQR 2–7 days)). In-hospital mortality of anticoagulated patients was 22.5% compared to 22.8% in patients who did not receive anticoagulant therapy. Anticoagulated patients were more likely to require invasive mechanical ventilation (29.8% vs 8.1%, p < 0.001). In mechanically ventilated patients (N = 395), in-hospital mortality was 29.1% for those receiving therapeutic-dose anticoagulation as compared to 62.7% in patients who did not receive anticoagulant therapy. In multivariate analysis, longer duration of anticoagulant therapy was associated with a reduced risk of mortality (hazard ratio (HR) 0.86 per day, 95% CI 0.82–0.89; p < 0.001). However, the indications for anticoagulant therapy were not reported and therefore, an indicational bias might limit the validity of data.

Randomised controlled trials investigating intensified prophylaxis protocols are *en route* (e.g., ClinicalTrials.Gov NCT04367831, NCT04373707, NCT04366960) and results – including the rates of major and clinically significant bleeding – have to be awaited.

Summary and recommendations

- The prevalence of thromboembolic events in all symptomatic COVID-19 patients is elevated and high in patients requiring intensive care. This is associated with adverse outcomes.
- Because of the high incidence of thromboembolic events, all patients hospitalized with moderate or severe COVID-19 should receive pharmacologic thromboprophylaxis unless there are strong contraindications (e.g., platelet count < 25/nL or active bleeding).
- The optimal thromboprophylactic regimen for patients with COVID-19 is not known.

- High-risk prophylactic-dose LMWH (e.g., enoxaparin 4.000 IU once daily) is the recommended therapy of choice for primary thromboprophylaxis in hospitalized patients with COVID-19. Fondaparinux is an alternative option (2.5 mg once daily), especially in patients with a history of heparin-induced thrombocytopenia. If fondaparinux is used, the dose has to be reduced to 1.5 mg once daily in patients with an estimated glomerular filtration rate (eGFR) in the range of 20–50 mL/min.
- In cases with severe renal impairment or acute renal failure (eGFR < 30 mL/min), anti-factor-Xa monitoring (target anti-Xa activity 0.1–0.3 U/mL) is advised to avoid overdosing of LMWH due to cumulation. Alternatively, prophylactic-dose unfractionated heparin (UFH) is recommended.
- Mechanical thromboprophylaxis with graduated compression stockings (GCS) or intermittent pneumatic compression (IPC) may be additionally considered, and is an option if pharmacologic thromboprophylaxis is contraindicated (e.g., because of acute bleeding or a high risk for major bleeding).
- Coagulation abnormalities are a prognostic indicator of poor outcomes and increased mortality. D-dimer levels, PT, aPTT and platelet count should be measured in all patients admitted to hospital, and may be helpful to identify patients at risk of adverse outcomes.
- Because the risk of thromboembolic complications increases with the level of D-dimers, some experts advised an intensified thromboprophylaxis for patients with severe COVID-19 and D-dimers exceeding 1,500–3,000 µg/L. In the absence of conclusive data from ongoing clinical trials, we advise against the routine use of intensified anticoagulant therapy on the basis of elevated D-Dimer levels alone. However, an intermediate-dose regimen (i.e., double-prophylactic or 50–75% of full-therapeutic dose) may be considered on an individual basis in patients at high-risk for thrombotic complications (e.g., previous VTE, active cancer, high-risk thrombophilia, severe obesity with BMI > 35 kg/m^2 or multiple risk factors).
- Elevated D-dimer levels is a common finding in patients with COVID-19 and does not warrant routine investigation for acute VTE in the absence of clinical symptoms. However, if typical symptoms of VTE occur, thromboembolic disease should be considered and diagnostic imaging (e.g., CCUS, CT pulmonary angiography) performed immediately to confirm or exclude VTE. PE should be considered particularly in cases with acute onset or deterioration of dyspnea (especially if not corresponding to known respiratory pathologies), haemodynamic instability or very high D-dimer levels (> 5,000 µg/L).
- An individual risk assessment should be repeated at hospital discharge weighing the risks of thromboembolic and bleeding complications. Patients at high risk for VTE should receive post-discharge thromboprophylaxis for at least 1–2 weeks. Of note, there is currently no evidence that this effectively lowers the risk of VTE.
- The optimal strategy to prevent VTE in COVID-19 patients with mild or moderate disease and treated in an ambulatory setting is not known. We therefore refer to the current German guideline recommendations of thromboprophylaxis in medically ill patients [30]. We recommend an individual risk assessment for all COVID-19 patients, and in the presence of severe or multiple VTE risk factors (e.g., age > 70 years, malignant disease, heart failure, BMI > 35 kg/m^2, prolonged immobilisation $\geq$ 3 days, high risk of dehydration) pharmacologic thromboprophylaxis should be considered.
- All outpatients with COVID-19 should be encouraged to remain active with regular mobilization and ankle pump movements, to avoid dehydration and to drink an appropriate volume of fluid during quarantine at home.
- If VTE is confirmed by objective imaging, therapeutic-dose anticoagulant therapy should be initiated with an anticoagulant approved for this indication. In the same manner as VTE related to other transient risk factors, anticoagulant therapy for COVID-19-related VTE should be continued for at least 3 months.

Conclusions

Because there is a lack of adequate study data, management strategies for the prevention of VTE in patients with COVID-19 have to be deduced from observational studies and extrapolated from recommendations for medically ill patients. Currently, there is consensus that all hospitalized patients with COVID-19 should receive pharmacologic thromboprophylaxis [31–34], although the optimal dosing regimen remains unclear. In outpatients, the decision for or against thromboprophylaxis must be made on an individual basis weighing the risk of VTE against the risk of adverse side effects such as severe bleeding complications. We are aware that some issues currently remain controversial. Therefore, it can be expected that some recommendations might need an update according to the results of ongoing clinical studies.

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History
Published online: 05.06.2020

Conflicts of interests
No conflicts of interest exist.

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