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Anticoagulant therapy in COVID-19 critically ill: Should we go for more?

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Kurzfassung: Antithrombotische Therapie sehr kranker COVID-19-Patienten. Kritisch kranke Patienten mit einer COVID-19-Infektion entwickeln häufig ein ausgeprägtes prothrombotisches Milieu, welches durch massiv erhöhte D-Dimer-Spiegel erkennbar ist, und durch klinischen Folgen, wie tiefe Venenthrombose, Lungenembolie oder Myokardinfarkt, den Krankheitsverlauf aggravieren kann. Aus diesem Grunde müssen Patienten, die im Rahmen einer COVID-19-Infektion entweder an einer Normalstation oder an einer Intensivstation hospitalisiert sind, ausreichend antikoaguliert werden. Dieses Manuskript fasst empfohlene antithrombotische Maßnahmen zusammen, die sich aus Expertenmeinung und Erfahrungswerten der ersten Wochen der COVID-19-Pandemie ergeben haben.

Schlüsselwörter: COVID-19-Infektion, prothrombotisches Milieu, tiefe Venenthrombose, Lungenembolie, Myokardinfarkt, antithrombotische Strategie

Abstract: Critically ill COVID-19 patients often develop a severe pro-thrombotic milieu, as reflected by the markedly increased d-dimer levels. Several cohort studies have reported high rates of thrombotic complications, including deep venous thrombosis (DVT) and pulmonary embolism (PE), myocardial infarction, stroke and microvascular thrombosis. Accordingly, COVID-19 patients who are hospitalized either at a normal, non-intensive care unit (ICU) or at the ICU need to receive appropriate dosages of anticoagulant therapy to prevent

or treat these thrombotic complications. This manuscript summarizes the institutional guidance for the antithrombotic prophylaxis and treatment of VTE as outlined by a multidisciplinary team of experts during the first weeks of the COVID-19 pandemic in Europe. Controlled studies are needed to verify the optimal anticoagulation for both prophylaxis and treatment. *J Kardiologie* 2020; 5 (27): 156–8.

Key words: COVID-19 infection, pro-thrombotic milieu, deep vein thrombosis, pulmonary embolism, myocardial infarction, antithrombotic strategy

Introduction

Since the first outbreak of Severe Acute Respiratory Syndrome (SARS) coronavirus-2 (SARS-CoV-2) induced pneumonia (Corona Virus Disease 19; COVID-19) in December 2019, the number of infections by this novel SARS-CoV-2 and subsequent need of hospitalization increased rapidly, first throughout China and later on towards Italy, subsequently Spain and the rest of Europe. SARS-CoV-2 virus, as other coronaviruses, causes a variety of symptoms ranging from mild rhinitis, fever, cough or diarrhea, to pneumonia and acute respiratory distress syndrome (ARDS) like critically illness with need of challenging ventilator support [1]. The number of hospitalizations, the need of intensive care and number of deaths is still rising worldwide. Currently, published mortality rates range between 2–4.3% (in few countries close to 10%), though true mortality is probably unknown in view of an underestimated denominator. Risk factors have not yet all been identified in large trials, but observational data and case series suggest arterial hypertension, diabetes mellitus and obesity as risk factors for severe disease. However, the underlying physiopathology of COVID-19 is still poorly understood.

Remarkably, patients with severe COVID-19 disease often present with high d-dimer levels [2, 3]. In a study of Tang et al., 71% of non-survivors and 0.6% of survivors met the criteria of disseminated intravascular coagulation during hospitaliza-

tion, suggesting coagulopathy being an important part of the severe disease spectrum [4]. These findings are further supported by a retrospective analysis of 449 COVID-19 patients by the same group, indicating a better prognosis in heparin treated patients, especially in the severely ill group (sequential organ failure assessment- [SOFA-] score ≥ 4) with highest d-dimer levels ($>$ six-fold upper limit of normal) [4–6]. Recent reports show higher incidence of pulmonary embolism and venous thromboembolism (VTE) [7] in COVID-19 patients when compared to non-COVID intensive care patients. Also, this underlying coagulopathy challenges extracorporeal membrane oxygenation (ECMO) or hemodialysis (HD) because of a higher incidence of filter clotting at the intensive care unit (ICU). Scarce histopathology reports in deceased COVID-19 patients describe clots in small vessels of all organs, not only the lungs but also the heart, liver and kidney [8–10].

Whether d-dimer levels are elevated due to coagulopathy, due to massive pro-inflammatory cytokine upregulation [11] or both is not entirely clear. Nevertheless, anticoagulation with (low molecular weight, LMW) heparin is part of best supportive care for COVID-19 patients due to its known antithrombotic, anti-inflammatory [12] and even hypothesized antiviral effects [13], in addition to its effect on reducing mortality and improving the PaO₂/FIO₂-ratio in severe ARDS [14]. An important question remains which dose of unfractionated or LMW heparin (LMWH) should be used in critically ill COVID-19 patients. Klok et al. showed a remarkably high incidence of venous and/or arterial thrombosis in critically ill COVID-19 patients (up to 31%) and strongly suggested to increase the prophylactic dose in those patients to high prophylactic doses, even in the absence of randomized data [15].

Based on these findings, various national guidelines were issued to adjust thromboprophylactic strategies, acknowledging there are no controlled studies to support their guidance [16,

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Table 1: Anticoagulation strategy for hospitalized COVID-19 patients at the University Hospitals Leuven.

Anticoagulation strategy in COVID-19 patients		
Patients characteristics	Anticoagulation regimen	Conditions
ICU admission	LMWH 50 IU/kg of anti-Xa, BID e.g. enoxaparin at least 4000 IE anti-Xa, BID	Platelets > 30.000/ μ l; No active bleed
ICU, CrCl < 30 ml/min	LMWH 50 IU/kg of anti-Xa, OD e.g. enoxaparin at least 4000 IE anti-Xa, OD	
CVWH, ECMO	UFH-infusion	
Non-ICU admission	LMWH 50 IU/kg of anti-Xa, OD e.g. enoxaparin at least 4000 IE anti-Xa, OD	
Non-ICU, CrCl < 30 ml/min	LMWH 50 IU/kg of anti-Xa, OD e.g. enoxaparin at least 4000 IE anti-Xa, OD	
Consider mechanical VTE-prophylaxis in case anticoagulant therapy is contra-indicated		
LMWH: low-molecular-weight heparin, ICU: intensive care unit, CrCl: Creatinine clearance, UFH: unfractionated heparin, CVWH: continuous veno-venous hemofiltration, ECMO: extracorporeal membrane oxygenation, OD: once daily, BID: twice daily		

Table 2: Follow-up strategy for hospitalized COVID-19 patients at the University Hospitals Leuven

Follow-up VTE-prophylaxis in COVID-19 patients	
Anti-Xa measurement	
ICU ward	Daily at morning bloods (8–10h after last LMWH-dose); aim anti-Xa levels of 0.15–0.40 IU/ml (prophylaxis) or 0.40–1.0 IU/ml therapeutic*
Non-ICU ward	1 or 2 times a week at morning bloods (8–10h after last LMWH-dose); aim anti-Xa levels of 0.15–0.40 IU/ml (prophylaxis) or 0.40–1.0 IU/ml therapeutic*
High vigilance for VTE-symptoms	
VTE: venous thromboembolism, ICU: intensive care unit, LMWH: low-molecular-weight heparin. *anti-Xa is not assessed at trough or at peak (but at morning bloods, 8–10 hours after LMWH-injection), explaining why recommended targets differ from guidance on peak- and trough levels.	

17]. Accordingly, the standard guidance for thrombo-prophylaxis at the COVID-19 ward and COVID-19 ICU was adjusted at University Hospitals Leuven and affiliated hospitals as well, as shown in table 1 and 2.

■ The COVID-19 non-ICU ward

At the non-ICU unit, every patient, independently of weight or kidney function, receives a prophylactic dose of at least 50 IU of anti-Xa LMWH per kg OD (e.g. in our institution enoxaparin 50 IU anti-Xa/kg OD). Prophylaxis is continued beyond the hospital setting for all patients with additional thromboembolic risk factors. There is a low threshold to routinely prescribe out of hospital thrombo-prophylaxis after discharge, e.g. for at least 10 days, and until complete recovery.

■ The COVID-19 ICU ward

Critically ill COVID-19 ICU-patients receive 50 IU of anti-Xa LMWH per kg BID (in our institution enoxaparin 50 IU anti-Xa/kg BID). Patients requiring therapeutic anticoagulation receive enoxaparin 100 IU of anti-Xa/kg LMWH BID.

At the ICU, the enoxaparin dose is monitored using serial anti-Xa measurements. We aim for anti-Xa levels of 0.15–0.40 IU/ml in prophylactic dose and > 0.4 IU/ml for patients receiving therapeutic anticoagulation, acknowledging that the anti-Xa measurement occurs approximately 8–10 hours after the evening enoxaparin injection (morning bloods at

ICU), hence does not represent peak nor trough measurement that are mostly used in guidelines to monitor or adjust dosing.

In patients supported by HD or ECMO, we advise continuous heparin infusion, aiming for anti-Xa 0.3–0.5 IU/ml (together with aPTT adjusted to 50–70s). Notably, anti-Xa and aPTT may differently reflect anticoagulant effect and coagulopathy, particularly in more severe ill patients, and hence offer the clinician complementary information [18].

For critically ill patients, we also recommend prolonged prophylactic anticoagulant therapy with heparin or LMWH, until full recovery or at least until mobilization. We discourage the use of oral anticoagulants because of uncertainties with respect to bioavailability in acutely ill COVID-19 patients [19]. We do not recommend routine screening for asymptomatic deep venous thrombosis, but perform a four-point compression ultrasound in addition to a planned echocardiography or other bedside echo investigations.

Although this regimen is based on scarce evidence and local consensus, the high burden of venous thromboembolism (VTE) as observed by many [20, 21] needs to be mitigated. We will document the rates of VTE and bleeding with this regimen and as part of the prospective follow-up, and as part of this management strategy will perform an ultrasound at day 14–21 or discharge. Hence, this effort joins many others to reduce the burden of VTE in COVID-19 patients.

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Conflict of Interest

Drs. Verhamme, Vanassche and Vandenbriele report grants and personal fees from Bayer Healthcare, Boehringer Ingelheim, Pfizer, BMS and Daiichi-Sankyo.

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