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Thromboprophylaxis in patients with COVID-19

Małgorzata Dybowska[1], Dariusz Dybowski[2], Monika Szturmowicz[1], Katarzyna Lewandowska[1], Małgorzata Sobiecka[1], Dorota Wyrostkiewicz[1], Witold Tomkowski[1]

[1]National Tuberculosis and Lung Diseases Research Institute Warsaw, Poland
[2]Masovian Cancer Hospital, Wieliszew, Poland

Abstract

For two years, the entire world has been grappling with the new challenge that is the COVID-19 pandemic. In December 2019 in China's largest province, Wuhan, Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), was detected in a patient with severe respiratory failure. Shortly after, infections were detected in all regions of the world.

So far, 265 million infections have been confirmed around the world, and 5.2 million of those infected have died due to COVID-19.

Infection with SARS-CoV-2 is associated with an increased risk of cardiovascular complications, especially thromboembolic complications.

Low-molecular-weight-heparin presents a basic form of prophylaxis against thromboembolic complications in individuals who are ill with COVID-19.

Controversy still exists regarding the optimal dose of LMWH depending on disease severity, this problem requires further randomized trials.

Key words: thromboprophylaxis, COVID-19 thrombosis

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Introduction

For two years, the entire world has been grappling with the new challenge that is the COVID-19 pandemic. In December 2019 in China's largest province, Wuhan, Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), was detected in a patient with severe respiratory failure [1]. Shortly after, infections were detected in all regions of the world [2]. In March 2020, the World Health Organization announced the Coronavirus Disease-19, COVID-19, pandemic, caused by SARS-CoV-2 [2]. So far, 265 million infections have been confirmed around the world, and 5.2 million of those infected have died due to COVID-19 [3].

During infection with SARS-CoV-2, patients develop interstitial lung inflammation, which predominantly has symptoms of fever, dry cough, and progressive dyspnea [4].

The course of infection is variable: from asymptomatic, to mild or moderate infective symptoms, to a severe and critical course of infection accompanied with dyspnea and the development of acute respiratory distress syndrome (ARDS) [4].

Most patients hospitalized due to COVID-19, present with increased body temperature and dry cough. After a few days (typically 5–7), dyspnea appears, which becomes more severe in the following days, or even hours, and may be the reason for urgent intubation mechanical ventilation [4].

According to WHO data, the mortality of COVID-19 occurs mostly in the elderly patients and in those with comorbidities such as chronic obstructive pulmonary

Address for correspondence: Małgorzata Dybowska, National Tuberculosis and Lung Diseases, Research Institute, Plocka 26, 01–138 Warsaw, Poland, e-mail: dybowska@mp.pl

disease, diabetes, hypertension, coronary artery disease, type B hepatitis, neoplastic diseases, chronic kidney diseases, and interstitial lung diseases [4–6].

Incidence of thromboembolic disease in patients with COVID-19

On the basis of numerous observations, it is known that infections with SARS CoV-2 are associated with a greater risk of cardiovascular complications, especially arterial and venous thrombosis [7].

Thromboembolic complications are particularly common among hospitalized patients with moderate or severe SARS-CoV-2 infections.-

Mechanisms of thrombotic complications in COVID-19 patients

Hyperactivity of the clotting system is a common symptom of severe COVID-19 [8, 9].

Invasion of the SARS-CoV-2 virus into endothelial cells leads to their damage and initiation of a local inflammatory reaction which promotes greater vessel permeability. Further damage of the endothelial cells, decreases the production of nitric oxide and prostacyclin I, weakening their anticoagulative properties. Moreover, an activation of neutrophils, and the formation of neutrophil extracellular traps (NETs), promotes thrombosis [10]. It has been demonstrated that NETs play a significant role in the pathogenesis of thrombosis through the activation of blood platelets, adhesion of neutrophils to the endothelial wall, and the activation of the intrinsic and extrinsic coagulation cascade [11].

NETs initiate the coagulation process in pulmonary capillaries as well as in veins and arteries, which may lead to damage of multiple organs such as lungs, heart, kidneys, and others [12].

The activation of the endothelium due to SARS-CoV-2 infection may lead to an increased expression of plasminogen activation inhibitor-1 (PAI-1), tissue factor (TF), and release of von Willebrand Factor (vWF). During the course of infection, however, there is a decrease in the activity of thrombomodulin and tissue plasminogen activator (t-PA), while serine proteases are released from neutrophils, such as neutrophilic elastase, promote prothrombotic actions through the proteolysis of fibrinolysis inhibitors [13–17].

It is most likely that, through their synergistic actions, all mentioned mechanisms lead to the development of COVID-19 dependent thrombophilia resulting in coagulation process in vessels of both small and large diameter.

Laboratory findings in patients with COVID-19

Increased prothrombotic activity in many COVID-19 patients may be indicated by high levels of fibrin degradation products (D-dimers), increased concentration of fibrinogen, and/or low concentrations of anti-thrombin [14].

Furthermore, laboratory research confirms a prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT) as well as increased concentrations of factor VIII [14].

Among routine tests, the best marker for determining the risk of thrombotic complications in COVID-19 patients is the determination of D-dimers level [14]. In addition, high concentrations of D-dimers are one of the indicators of poor prognosis in COVID-19 [17, 18].

In a prospective observational study on the population of Polish patients treated in the intensive care unit (ICU), significantly higher levels of D-dimers were detected in patients who developed severe respiratory distress syndrome [19].

Based on autopsy reports, the presence of micro-thrombosis of the pulmonary vessels is correlated with the profound respiratory insufficiency in COVID-19 [20]. The other cause of acute respiratory failure is the increased permeability of the pulmonary capillaries, with hyaline membrane formation in pulmonary alveoli and the development of diffuse alveolar damage (DAD) [20].

Dynamic decrease of the oxygen saturation of hemoglobin and increase in D-dimers are often indicators of small pulmonary vessels thrombosis. These changes may be not visualized in computed tomography angiography (angio-CT) or classical angiography of the pulmonary arteries.

In addition to in situ thrombotic changes in pulmonary vessels, venous thromboembolic diseases are often diagnosed in patients infected with SARS-CoV-2.

Thromboprophylaxis

In the available literature, there are discrepancies regarding the use of thromboprophylaxis in COVID-19 patients. There is no agreement concerning the type of drugs used as well as their doses.

Many scientific societies, including the European Society of Cardiology (ESC), the International Society of Thrombosis and Hemostasis (ISTH), the American Heart Association (AHA), the American College of Cardiology (ACC), have published recommendations regarding the thromboprophylaxis and treatment of thromboembolic consequences in COVID-19 patients [21–26].

Table 1. Padua prediction score

Active cancer (metastases and/or chemoradiotherapy in the previous 6 months)	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Bedrest for ≥ 3 days	3
Thrombophilia	3
Recent (≤ 1 month) trauma and/or surgery	2
Elderly age (≥ 70 years)	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (BMI ≥ 30 kg/m^2)	1
Ongoing hormonal treatment	1
High risk of VTE: ≥ 4 points	

Table 2. IMPROVE-DD score for VTE

Variable	Score
Prior episode of VTE	3
Thrombophilia	2
Paralysis of the lower extremity during the hospitalization	2
Current malignancy	2
D-dimer ≥ 2 x Upper Limit of Normal (UNL)	2
Immobilization at least 7 days	1
Intensive Care Unit or Critical Care Unit admission	1
Age more than 60 years	1
score 0–1 (low risk), score 2–3 (moderate risk), score ≥ 4 (high risk)	

Analyses of these documents show that so far, there is no single, universally accepted, and recommended algorithm of thromboprophylaxis in COVD-19 patients.

The common practice in patients hospitalized due to COVID-19 is the administration of prophylactic doses of low-molecular-weight-heparin (LMWH). General contraindications to this type of therapy are severe thrombocytopenia (< 25 G L-1), active bleeding, or high risk of hemorrhagic complications with erythrocyte counts of < 50 G L-1 [26–28].

In efforts to optimize the dose of heparin in thromboprophylaxis, it is important to consider kidney function, body weight, erythrocyte count, the concentration of fibrinogen, and APTT and anti-Xa results [29].

In Poland, the document in force containing complex diagnostic-therapeutic protocols regarding therapy of those sick with COVID-19, which was created on behalf of the Ministry of Health, are the guidelines from the Agency for Health Technology Assessment and Tariff System (AHTAT) established on 25.04.2020, last updated on 14.10.2021 [30].

In the light of these guidelines, it is also recommended to administer prophylactic doses of LMWH in hospitalized COVID-19 patients as well as in outpatients showing risk factors of VTE. The proposed doses used in those with preserved kidney function and appropriate body weight are: 40 mg of enoxaparin, 0.4 ml of nadroparin, or 5000 IU — once daily) [30].

The use of the Padua scale is suggested for assessing the risk of VTE in infected patients undergoing home isolation (Table 1). [30]. In contrast, ASH recommendations suggest the use of the IMPROVE-DD scale in this regard [25, 31] (Table 2).

Increasing the dose of LMWH in thromboprophylaxis may be considered in individual cases, in patients witha high risk of thrombotic complications, however, most scientific societies do not recommend routine administration of therapeutic doses of LMWH in patients infected with SARS-CoV-2.

This issue, therefore, remains open to discussion.

A recently published meta-analysis of 7 studies summarizing the effectiveness and safety of standard versus intermediate doses of LMWH used in thromboprophylaxis concluded that the intermediate dose of LMWH appears to be safe and that it is associated with additional benefits in terms of survival, though most data was sourced from retrospective analyses [32].

In randomized clinical trials carried out amongst hospitalized patients (REMAP-CAP, ATTACC, and ACTIV-4A) comparing the effectiveness and safety of prophylactic doses of LMWH versus therapeutic doses in patients with severe or moderate courses of COVID-19, there have been no determined benefits of higher doses of antithrombotic drugs in the following aspects: mortality, the prevalence of episodes of acute thromboembolic disease, the prevalence of arterial thromboses, necessity to use ECMO, duration of mechanical ventilation, presentation of thromboembolic complications, the prevalence of hemorrhagic complications in patients requiring treatment in the ICU [33].

However, these studies showed that in patients who were not critically ill, which was defined as no need of organ support, the final probability of the superiority of therapeutic-dose anticoagulation over usual-care thromboprophylaxis was 97.3% in the high D-dimer cohort, 92.9% in the low D-dimer cohort, and 97.3% in the unknown D-dimer cohort [34]. Severe hemorrhage was documented in 1.9% of patients receiving

a therapeutic dose, and in 0.9% of patients receiving standard thromboprophylaxis [34]. On the basis of this data, it can be estimated that for every 1000 hospitalized patients with moderate severity of COVID-19, therapeutic doses of LMWH in comparison to standard thromboprophylaxis diminished the need for organ support in an additional 40 patients, at the cost of 7 additional severe hemorrhages [34]. The benefits from this type of strategy were more visible in patients with a high level of D-dimers than in the group with low levels [34]. Patients with high levels of D-dimers were generally older and most often had comorbid diseases [34].

As stated, these benefits were not confirmed in critically ill patients. It is most likely that therapeutic doses of heparin cannot influence the inflammatory cascade, thrombosis, and organ damage in patients with end-stage of COVID-19 disease, however, these actions may require consideration in the initial infection stage and/or in patients with moderate courses of disease [35–37].

The conclusion regarding the lack of effectiveness in LMWH in critically ill COVID -19 patients requires careful consideration due to the fact that patients who are in a critical state are often in shock and require pressor amines, which greatly limit the availability of subcutaneously administered drugs, including LMWH [38].

Orally administered antithrombotic drugs which are not vitamin K antagonists (NOACs) in the prophylaxis of thromboembolic complications as well as in the treatment of patients infected with SARS-CoV-2 are not recommended due to the possibility of NOAC interactions, especially with antiviral drugs used in COVID-19 therapy. In addition, as shown in the ACTION study which compared the administration of 20 mg rivaroxaban in patients hospitalized due to COVID-19 with an increased level of D-dimers, and then continuing the drug for the next 30 days following hospital discharge, versus the use of a prophylactic dose of enoxaparin during patient hospitalization, no improvement was seen, but the increase of the prevalence of hemorrhagic complications in the group treated with rivaroxaban in comparison with a prophylactic dose of LMWH [39].

It is worth noting that the beneficial influence of heparin during SARS-CoV-2 infection surpasses its antithrombotic actions [40–42]. Heparin shows anti-inflammatory properties due to the neutralization of chemokines and cytokines, inhibits leukocyte migration, neutralizes NETs, and inhibits the activity of heparinase which is responsible for vessel permeability. In addition, it presents antiviral activity due to its action on viral spike protein binding on the ACE2 receptor, which is used by the virus to enter host cells [40–42]. For these reasons, LMWH appears to be a drug of choice during active infection and in events when there is a maintained chronic inflammatory state [40–42].

Antiplatelet therapy may have a beneficial influence in severely ill patients through several mechanisms including inhibition of platelet aggregation, reduction of platelet-derived inflammation, and blocking thrombogenic NETs [43]. However, in observational studies carried out to date, and in a large, randomized study (RECOVERY) which involved over 14,000 patients, aspirin administered at a dose of 150 mg/day was not associated with decreased mortality among patients who did not require treatment with mechanical ventilation [44]. In the group of those treated with aspirin, fewer thromboembolic complications were observed, however, the prevalence of severe hemorrhage was also larger [44]. In addition, the use of aspirin was associated with faster discharge from the hospital [44].

Treatment of VTE patients

In case of the development of acute pulmonary embolism and/or deep vein thrombosis, it is necessary to follow the current guidelines, in which the preferred drug is low-molecular-weight-heparin administered in therapeutic doses (in patients with preserved kidney function): 1 mg/kg b.w. enoxaparin, 0.01 ml/kg b.w. nadroparin, or 100 IU/kg b.w. dalteparin — each administered 2 x day). Administration of unfractionated heparin should be rather limited to due epidemiological reasons in the context of the necessity to monitor anticoagulation and risk of infection of personnel due to more prevalent contact with infected patients [30].

In the case of patients infected with COVID-19 with a preference for LMWH, it should be noted that there are no significant interactions with drugs used in experimental therapies.

It is recommended to be cautious when administering new oral antithrombotic drugs (NOAC). There may be interactions with several specific antiviral drugs (for example, lopinavir and ritonavir), which increase the risk of hemorrhage [45]. For this reason, most guidelines do not recommend the use of NOACs in hospitalized patients, instead, heparin therapy is recommended. In accordance with ISTH guidelines, treatment with NOAC should be considered after discharge from the ICU [27].

So far, there is a lack of specific data regarding the adaptation of thromboprophylaxis and treatment in patients with acute kidney failure which requires long-term renal replacement therapy, with thrombocytopenia, or in individuals with low body mass.

Conclusions

Infection with SARS-CoV-2 is associated with an increased risk of cardiovascular complications, especially thromboembolic complications [7].

Low-molecular-weight-heparin presents a basic form of prophylaxis against thromboembolic complications in individuals who are ill with COVID-19.

Controversy still exists regarding the optimal dose of LMWH depending on disease severity, this problem requires further randomized trials.

Conflict of interest

None.

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