Guidance for anticoagulation management in venous thromboembolism during the coronavirus disease 2019 pandemic in Poland

An expert opinion of the Section on Pulmonary Circulation of the Polish Cardiac Society

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ABSTRACT
The coronavirus disease 2019 (COVID-19) pandemic affects anticoagulation not only in those infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) but also in most patients who require daily anticoagulant therapy and are facing substantial limitations in medical care these days. Concomitant venous thromboembolism (VTE), a potential cause of unexplained deaths, has frequently been reported in patients with COVID-19, but its management is still challenging due to the complexity between antithrombotic therapy and hematological alterations. In the era of COVID-19 pandemic, it is highly recommended for patients who require chronic anticoagulation to continue therapy to prevent thromboembolic events. To avoid regular and frequent blood tests and unnecessary exposure to SARS-CoV-2 during contacts with medical personnel, direct oral anticoagulants should be strongly preferred whenever possible. Current evidence is insufficient to recommend routine pharmacological antithrombotic prophylaxis in all hospitalized patients with COVID-19. In patients with COVID-19 who are suspected of VTE or in whom the diagnosis is confirmed, parenteral therapy with low-molecular-weight heparin should be initiated in the absence of contraindications. If heparin-induced thrombocytopenia is suspected, nonheparin anticoagulants should be used such as bivalirudin or fondaparinux. In case of confirmed acute pulmonary embolism, treatment should be guided by risk stratification as defined in the current guidelines.

Introduction Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) has created an unprecedented challenge for healthcare systems and influenced management of patients with a broad spectrum of acute or chronic diseases. The COVID-19 pandemic has also affected anticoagulation not only in patients with already diagnosed SARS-CoV-2 infection but also in the majority of anticoagulated patients who are facing substantial limitations in everyday medical care. The current document provides practical guidance for anticoagulation management of both groups during the COVID-19 pandemic in Poland. We have analyzed available expert opinions from Europe

and United States regarding anticoagulation in the era of COVID-19 and we have considered Polish conditions.[1-3]

Patients without COVID-19 who require anticoagulation According to the currently available data, the majority of patients who receive oral anticoagulation in Poland are treated with direct oral anticoagulants (DOACs). However, approximately 40% of anticoagulated Polish patients still receive vitamin K antagonists (VKAs), that is, warfarin or acenocoumarol. Anticoagulation with VKAs requires close cooperation between the patient and the managing physician because regular control of international normalized ratio (INR) is vital for an effective and safe therapy and dose modification may be needed. The COVID-19 pandemic caused specific issues related to VKA therapy. Ambulatory INR measurements result in exposure to SARS-CoV-2 of both patients and medical personnel and increase the risk of infection. Moreover, regular INR measurements create significant workload for laboratories, which are currently dealing with limited resources. On the other hand, DOAC therapy requires less frequent blood testing to assess renal function, and the therapy can be predicted based on the initial renal function, age, and manufacturer recommendations. Based on the available data, the following guidance should be considered:

- When anticoagulation is initiated, DOACs should be preferred after excluding contraindications to avoid regular and frequent blood tests and unnecessary exposure to SARS-CoV-2 during contacts with medical personnel.
- Available data indicate that the anticoagulant therapy per se does not increase the risk of developing severe COVID-19 in patients infected with SARS-CoV-2.[1] All patients who require chronic anticoagulation should continue therapy to prevent life-threatening thromboembolic events.
- Switching from VKAs to DOACs should be considered whenever feasible. Such a change is especially indicated in patients on VKAs who have had labile INR in previous weeks or are not able to measure INR at home.
- When switching from VKAs to DOACs, it should be taken into account whether the new anticoagulant is available and affordable for the patient. Appropriate dosing regimens should be used and underdosing should be avoided. The choice of dabigatran, rivaroxaban, or apixaban should be left at the discretion of the treating physician.

However, some patients should not be treated with DOACs (TABLE 1).The European Heart Rhythm Association recommended that DOACs can be initiated immediately if the INR is 2 or less. If the INR is 2 to 2.5, DOACs can be started immediately or preferably on the next day.[4] For INR greater than 2.5, the actual INR value and the half-life of the VKA need to be taken into account to estimate the time when the INR value will likely drop to below this threshold value (half-life of acenocoumarol is 8–24 hours, while of warfarin, 36–48 hours). However, according to the summary of product characteristics, rivaroxaban can be started when INR is 3 or less (depending on the indication), and apixaban and dabigatran when INR is 2 or less.

- It is advised to reconsider indications for long-term anticoagulation. In patients with low risk of thromboembolic episode, anticoagulation should be stopped if, for example, a triggering factor was significant and transient, such as major surgery or trauma and the patient was successfully treated for more than the recommended 3 months.[5]
- It is recommended that patients who continue VKA anticoagulation avoid public transportation for blood sampling. The setup of outpatient clinics and patient flow should be modified in order to limit close personal contact.

TABLE 1. Contraindications for switching from warfarin to a direct oral anticoagulant

Switching from warfarin to a DOAC should not be considered in the following situations
• Prosthetic mechanical heart valve
• Moderate to severe mitral stenosis
• Patients requiring a higher INR than the standard INR range of 2–3
• Thrombotic APS, in particular manifesting with arterial thromboembolic, stroke, or myocardial infarction when APS test was positive 3 times
• Breastfeeding (in case of pregnancy, heparins are recommended)
• Severe renal impairment with CrCl <15 ml/min (for dabigatran <30 ml/min)
• Use of interacting drugs according to the summary of product characteristics for each DOAC, in particular ritonavir and lopinavir, or antiviral drugs which lead to increased anticoagulant effect of DOACs. Experts recommend not using rivaroxaban in patients with SARS-CoV-2 infection on these investigational COVID-19 medications[1a]

a No significant interactions have been reported with DOACs in subjects taking chloroquine or hydroxychloroquine.

Abbreviations: APS, antiphospholipid syndrome; COVID-19, coronavirus disease 2019; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; INR, international normalized ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

- In experienced compliant patients on stable anticoagulation with VKA, the frequency of INR monitoring may be decreased even to 10 to 14 weeks; however, such a strategy might be considered in rare cases only, including logistic problems with blood draw.
- In patients who have to continue VKA therapy, it is advised to control INR by self-testing or by a trained caregiver using, for example, a CoaguChek device (Roche). Dose adjustment, when needed, can be made by phone by the managing physician.
- Of note, if DOACs or VKAs cannot be used safely or are not available, low-molecular-weight heparins (LMWHs) can be considered as an alternative for patients who require long-term anticoagulation.[1] Self-injections by the patient or drug administration by a caregiver are advised.
- In patients without SARS-CoV-2 infection, the antiplatelet therapy regimen should follow the current guidelines.[6]

Patients with COVID-19 who require anticoagulation

Prothrombotic state in COVID-19

Coronavirus disease 2019 is associated with several hematological alterations.[7] Two typical hemostatic abnormalities observed in patients with COVID-19, that is, increased D-dimer levels and mild thrombocytopenia, were reported in over 40% of those with COVID-19 requiring hospitalization.[8] Other abnormalities frequently reported in COVID-19 included prolonged prothrombin time (PT) expressed also as INR, prolonged thrombin time, and shortened activated partial thromboplastin time (aPTT) typical of acute phase reaction.[9,10]

Prolongation of aPTT, PT, and thrombocytopenia are common particularly in those patients in whom clinical course is severe. It has been suggested that increased D-dimer concentrations and prolonged PT are associated with higher mortality in patients with COVID-19.[8] Disseminated intravascular coagulation is observed most often in severe cases of COVID-19 (about 2% of all hospitalized patients) and indicates poor prognosis, that is, 90% mortality.[11] The underlying condition contributing to disseminated intravascular coagulation in COVID-19 are bacterial superinfections, which should be treated aggressively. Regular laboratory monitoring of platelet count, PT, D-dimer concentrations, and fibrinogen levels in patients with COVID-19 is recommended to determine the severity of coagulopathy. Systemic inflammation, coagulation activation, and hypoxemia are potential predisposing factors for clot formation.

It remains unclear whether SARS-CoV-2 can induce antiphospholipid antibodies. Three cases of thrombosis associated with antiphospholipid antibodies, namely anticardiolipin and anti-β2-glycoprotein I, have been reported.[12] An increased rate of positive lupus anticoagulant has been observed in patients with COVID-19.[13] It might be suggested that all patients with COVID-19 in whom antiphospholipid antibodies have been detected should be closely monitored and receive thromboprophylaxis even without history of any thromboembolism. Of note, there is evidence that hydroxychloroquine, used in some patients with COVID-19 and often with antiphospholipid syndrome (APS), displayed some antithrombotic properties, documented especially in subjects with elevated titers of antiphospholipid antibodies.[14] APS diagnostic workup should be repeated after discharge and also after 3 months since the first measurement.

Risk of venous thromboembolism and thromboprophylaxis

The incidence of venous thromboembolism (VTE) in patients with COVID-19 may be up to 30% of infected patients managed in intensive care units.[8] The rate of VTE reported in general wards ranges from 5% to 10% of patients with COVID-19.[15] The most common manifestation of VTE in patients with COVID-19 is isolated pulmonary embolism (PE).[15-17] Most of patients with COVID-19 diagnosed with VTE have no history of previous VTE episodes.[15] Of note, VTE in about 30% of patients with COVID-19 in the scenario of viral infection can be asymptomatic, which increases the risk of death.[18,19] The diagnosis of VTE in COVID-19 increases mortality 2.5-fold.[19] D-dimer levels should be monitored and a sudden rise of this marker after an initial decrease in blood with concomitant respiratory failure might suggest VTE.

Lack of validated criteria for the assessment of clinical probability of VTE in patients with COVID-19 and significant epidemiologic limitations related to transportation and imaging make the VTE diagnosis challenging. Generally, COVID-19 is considered a risk factor for thromboembolic complications but does not seem to be associated with increased bleeding risk.

In all patients with COVID-19, VTE risk should be assessed using a risk assessment model validated for acutely ill medical patients, preferably used in a given institution. The VTE risk stratification should be repeated along with bleeding risk assessment during the course of COVID-19. Some experts recommend the Padua or IMPROVE risk assessment models in patients with mild COVID-19, while the Caprini scoring system is recommended for surgical or trauma patients suspected of or diagnosed with COVID-19.[20] Outpatients with mild COVID-19 should not receive pharmacological thromboprophylaxis, but increased mobility and appropriate hydration, in particular in the presence of fever or vomiting, should be encouraged. The current OVID trial will assess whether a prophylactic dose of enoxaparin reduces early

mortality and hospitalizations in symptomatic outpatients with COVID-19 compared with placebo. It has been shown using the Padua model that 40% of hospitalized patients with COVID-19 are at high risk of VTE.[21] Pharmacological thromboprophylaxis should be used based on the current prevention guidelines. Low-molecular-weight heparins given subcutaneously once or twice daily should be considered in hospitalized patients with COVID-19 at elevated risk of VTE (intermediate dose at very high VTE risk) unless there are absolute contraindications and bleeding risk is low-to-moderate. All severe and critically ill patients with COVID-19 have a strong indication for VTE prophylaxis in the absence of contraindications.[20] Current evidence is insufficient to recommend routine pharmacological thromboprophylaxis in all hospitalized patients with COVID-19.[1] Current real-life studies showed the use of thromboprophylaxis in all patients with COVID-19 in the intensive care units, which, however, is associated with the rate of VTE approximately 27%, including half of all the cases were diagnosed within 24 hours of hospital admission.[15] The failure rate of LMWH prophylaxis in patients with severe COVID-19 is estimated at about 20%, which is a much higher rate as compared with 1% in most LMWH trials in acutely ill medical patients (and similar to the values reported in sepsis), leading to a suggestion that higher doses of LMWH should be used.[6,19] Even a therapeutic dose of LMWH can fail to prevent VTE in the intensive care setting.[18] An alternative is unfractionated heparin given twice daily and this anticoagulant is preferred in patients with chronic kidney disease stage 4 or 5 unless anti-Xa measurement is available. In pregnant women with COVID-19, the assessment of VTE risk should be performed and pharmacological thromboprophylaxis should be considered in those who are hospitalized, especially if other VTE risk factors are present, for example, age above 35 years, obesity, thrombophilia, history of VTE.[20] The use of extended thromboprophylaxis in patients with COVID-19 after hospital discharge should be considered if the VTE risk stratification indicates persistently elevated VTE risk due to, for example, comorbidities such as active cancer, prolonged immobilization, as well as D-dimer concentrations higher than twice the upper reference range.[1] However, there are no specific data available on the efficacy and safety of such a strategy. If heparin-induced thrombocytopenia is suspected, nonheparin anticoagulants—such as bivalirudin over fondaparinux—should be used. If bivalirudin is unavailable, fondaparinux might be considered.[20] Therefore, it is recommended that heparin, particularly LMWH, for the primary prophylaxis of VTE should be considered in all hospitalized patients with SARS-CoV-2 infection.

Treatment of patients with venous thromboembolism In patients with COVID-19 suspected of VTE or in whom the diagnosis is confirmed, parenteral therapy with LMWH should be initiated in the absence of contraindications.[1,20] Unfractionated heparin should be reserved for patients with strong indications to its use because treatment with unfractionated heparin requires time to achieve therapeutic aPTT and is associated with additional nurse exposure for frequent blood draws.[1] At discharge, DOACs or LMWHs at recommended dosing regimens should be preferred to limit contact of patients with healthcare workers.[1] It should be mentioned that some clinicians use an intermediate or therapeutic dose of LMWH in patients with COVID-19, based on the assumption that such strategy not only has a higher preventive value, but it may treat VTE, as demonstrated in a small study from China in which D-dimer levels higher than 1500 ng/ml have a sensitivity of 85% and specificity of 88.5% for detecting VTE events in patients with COVID-19.[6,7] A decision to use such a strategy should be taken on the individual case-by-case basis.

Following recommendations regarding anticoagulation should be considered in patients with COVID-19:

- When acute pulmonary embolism is confirmed, treatment should be guided by risk stratification as defined in the current European Society of Cardiology guidelines.[8] Patients with hemodynamic instability should receive immediate reperfusion therapy preferably with thrombolytics. Hemodynamically stable patients may be treated with LMWH or a DOAC.
- Of note, DOACs may have significant interactions with drugs used for COVID-19, especially with lopinavir/ritonavir via the inhibition of cytochrome P450 3A4 (CYP3A4) and/or P-glycoprotein (P-gp). In such cases, the bleeding risk may be elevated and when lopinavir/ritonavir is administered DOACs should be avoided.
- Importantly, no major interactions have been reported between drugs for COVID-19 and heparin. Pharmacotherapy selection should include in the decision-making process a possibility of rapid cardiorespiratory decompensation caused by SARS-CoV-2 infection.

Experts recommend e-consultations in hospitals using pulmonary embolism response teams. Experts advocate that catheter-directed therapies of acute PE or insertion of inferior vena cava filters should be avoided and reserved only for the most critical situations.[1] In the case of hemodynamic instability in high-risk PE, according to the classification by the European Society of Cardiology, systemic fibrinolysis is indicated in patients with COVID-19.[1,5,20]

This statement will be modified along with the development of knowledge and therapeutic measures in the management of COVID-19.

SUPPLEMENTARY MATERIAL

The Polish version of the paper is available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

CONFLICT OF INTEREST DK received lecture honoraria and congress travel grants from Bayer, Boehringer Ingelheim, and Pfizer. AU received lecture honoraria from Bayer, Boehringer Ingelheim, and Pfizer. GK received lecture honoraria from Bayer, Boehringer Ingelheim, and Bristol-Myers Squibb. TH declares no conflict of interest. AT received honoraria for lectures and consultations from Bayer and Pfizer and congress travel grants from Pfizer. TM-K received honoraria for lectures from Bayer, Boehringer Ingelheim and Pfizer and congress travel grants from Bayer and Boehringer Ingelheim. JW received lecture honoraria or grant support from Alexion, Alnylam Pharmaceuticals, Baxalta, CSL Behring, Ferring Pharmaceuticals, Novo Nordisk, Octapharma, Rigel Pharmaceuticals, Roche, Sanofi / Genzyme, Shire/Takeda, Siemens, Sobi, Werfen. PP received lecture honoraria and congress travel grants from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb and Pfizer.

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