

Anticoagulant Therapy for Patients with Coronavirus Disease 2019: Urgent Need for Enhanced Awareness

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Abstract

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global pandemic. SARS-CoV-2 binds to the angiotensin-converting enzyme 2 receptor, which is abundantly expressed in vascular endothelial cells and damages these cells. Besides pneumonia-induced respiratory failure, thrombotic cardiovascular complications are increasingly emerging as a major COVID-19 symptom. Multiple retrospective studies have strongly suggested that anticoagulant therapy improves the prognosis of people with COVID-19. However, validation of the safety and effectiveness of anticoagulant therapy for COVID-19 and greater awareness of this clinical therapeutic option are urgently needed.

Keywords

COVID-19, SARS-CoV-2, thrombosis, anticoagulant

Disclosure: The authors have no conflicts of interest to declare.

Received: 25 May 2020 **Accepted:** 19 June 2020 **Citation:** *European Cardiology Review* 2020;15:e58. **DOI:** <https://doi.org/10.15420/ecr.2020.24>

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Coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has generated a pandemic that has heavily affected the global population, with more than 5.2 million infected and more than 337,000 deaths worldwide recorded between the end of 2019 and 24 May 2020.¹ In the absence of vaccines or specific targeted treatments, strategies to reduce the COVID-19 mortality rate have gained importance as a global need. However, the exact mechanisms underlying the disease progression of COVID-19 remain unknown. Worldwide, thrombotic findings, ranging from benign pedal skin lesions (known as COVID toe) to cerebral infarctions in asymptomatic to mildly ill young patients have been reported as manifestations of the disease. In addition to the pneumonia-induced respiratory failure, thrombotic cardiovascular complications are increasingly gaining importance as a major COVID-19 presentation.² This risk of thrombosis, if unaddressed, can cause severe damage even in patients with mild symptoms of pneumonia.

COVID-19 Hypercoagulability

Viral infections are associated with an increased risk of thrombosis. Coagulopathy was reported as a disease manifestation in the Spanish influenza pandemic of 1918, which killed about 50 million people worldwide. A case of SARS-related macrovascular complication of stroke was reported in Singapore during the SARS-CoV outbreak of 2004.³ Moreover, thrombosis is a common feature of viral infections, such as AIDS, dengue fever and Ebola virus disease. Among critically ill patients, the incidence of pulmonary thrombosis has been reported to be as high as 30% in COVID-19 patients, compared with 1.3% among non-COVID-19 patients.⁴ A study in the Netherlands of 184 critically ill

patients in intensive care (ICU) found that COVID-19-associated thrombotic complications occurred in 31% of their participants.⁵ An analysis of contrast-enhanced CT findings in a case series of ICU patients showed the presence of pulmonary artery thrombosis in 20.6% of 107 patients admitted to ICU with COVID-19, compared with 7.5% of 40 influenza patients admitted during the previous year.⁶ Anticoagulant therapy was administered in more than 90% of COVID-19 patients with thrombosis in this study and it appears that COVID-19 induces a greater hypercoagulability than other infections.

Pathogenesis of COVID-19-associated Thrombosis

The pathogenesis underlying the more hypercoagulable state in COVID-19 compared with other infections needs to be ascertained. SARS-CoV-2 infection induces the production of cytokines, such as interferons and interleukins, resulting in a systemic inflammatory reaction, which eventually causes the so-called cytokine storm.^{7,8} Higher cytokine concentrations can lead to systemic thrombus formation, with consequent pulmonary artery thrombosis, cerebral infarction, MI and lower limb arterial thrombosis. In addition to this typical inflammatory mechanism, direct injuries to the vascular endothelium by SARS-CoV-2 appear to be involved in COVID-19 thrombogenesis.⁹

Large amounts of angiotensin-converting enzyme 2 (ACE2), which mediates function of the ACE receptor as a SARS-CoV-2 receptor, are found in mucosal epithelial cells in the respiratory tract and in pulmonary alveolar tissue. Furthermore, ACE2 is expressed in other organs, such as the heart, kidneys and intestinal tract, as well as in high concentrations in vascular endothelial cells.¹⁰

In the initial stage of infection, SARS-CoV-2 uses ACE2 to enter vascular endothelial cells, thereby injuring the vascular endothelium, which has antithrombogenic properties. Then, platelet adhesion/aggregation and tissue factor release induce thrombus formation mainly in the microvasculature.^{9,11} Even in the absence of severe pneumonia or a cytokine storm, endovascular inflammation through the direct action of SARS-CoV-2 produces a hypercoagulable state, with consequent thrombosis at various sites.

After the initiation of the thrombotic process begins, a self-sustaining chain reaction ensues whereby a thrombus stimulates the formation of other thrombi, with a resultant rapid increase in systemic thrombosis and the severity of the patient's condition. A close correlation has been observed between blood levels of D-dimer, a fibrin degradation product, and COVID-19 disease severity.¹¹ D-dimer levels are markedly elevated in patients with severe COVID-19, despite no marked prolongation in prothrombin time or thrombocytopenia. These findings suggest that disseminated intravascular coagulation alone does not fully explain thrombosis in severe cases.¹¹

The risk of sudden death in patients with COVID-19 is linked to direct cardiac injury and myocarditis, with arrhythmic complications observed in 16.7% of 138 patients with COVID-19 seen in Wuhan, China, in January 2020.¹² Sudden death in COVID-19 patients may as well be attributable to MI or pulmonary infarction due to generalised thrombosis. Cerebral infarction in young patients without risk factors of arteriosclerosis are attributed to thrombosis due to SARS-CoV-2-induced endovascular injuries.^{13,14} Risk factors for higher severity of COVID-19 include advanced age, cardiovascular disease, hypertension, diabetes, smoking, chronic respiratory disease and malignant tumours.^{15,16} These factors are associated with endovascular dysfunction and increased coagulability and, therefore, the hypercoagulability may be a mechanism that contributes to the adverse outcomes of COVID-19.

Treatment of COVID-19-associated Hypercoagulability

Coagulative and fibrinolytic abnormalities are closely involved in the COVID-19 pathogenesis and have a big effect on prognosis. Therefore, the International Society on Thrombosis and Haemostasis (ISTH) issued an interim guidance recommending the measurement of D-dimer, fibrinogen, prothrombin time and platelet count in all COVID-19 patients.¹⁷ The onset of coagulopathy in COVID-19 patients is one of the most important signs of poor prognosis. As marked D-dimer elevation is a predictor of mortality, hospitalisation should be considered for patients with high D-dimer levels. For the treatment for COVID-19-associated hypercoagulability, the administration of anticoagulants has been reported to potentially improve prognosis according to findings from a retrospective study.¹⁸

A single-centre observational study including 2,773 COVID-19 patients at Mount Sinai Hospital in the US has reported that of 786 patients who received anticoagulation therapy, in-hospital mortality was 22.5%, with a median survival of 21 days, compared with 22.8% and 14 days median

survival in patients who did not.¹⁹ Among 395 critically ill patients managed with mechanical ventilation, the in-hospital mortality was 29.1% for those who did receive anticoagulation therapy and 62.7% for those who did not. No significant difference was observed in the incidence of haemorrhagic complications (3.0% and 1.9% in the groups with and without anticoagulation therapy, respectively).

In general, treatment with low-molecular-weight heparin is associated with a better prognosis in patients with a sepsis-induced coagulopathy score of ≥ 4 points.²⁰ However, the prothrombotic tendency in COVID-19 may be stronger than with other infections. The ISTH interim guidance proposes the use of anticoagulation therapy for a wide range of patients, recommending prophylactic administration of low-molecular-weight heparin for hospitalised COVID-19 patients with markedly elevated D-dimer levels or high fibrinogen levels.¹⁷ Most hospitalised patients will meet these criteria. However, the decision to hospitalise patients with COVID-19 cannot be based exclusively on the D-dimer level, considering that a multiparametric evaluation is necessary, especially in elderly patients.²¹

Antiplatelet agents are usually administered for patients with atherosclerotic cerebral infarction or MI, although anticoagulants may represent a mechanistically preferable choice over antiplatelet agents for COVID-19 patients. If the patient's general condition is favourable, then non-vitamin K antagonist oral anticoagulants (NOACs) may be an option. However, cautious use is advisable as blood levels may increase when NOAC is administered in combination with various antiviral agents. NOACs can present side-effects caused by the extensive interactions with the drugs currently in use for the therapy of patients with COVID-19, whereas low-molecular-weight heparins do not exhibit significant interactions; thus, the latter is currently the first choice drug to prevent thromboembolic phenomena in these patients.¹²

Investigating the anti-inflammatory role of low-molecular-weight heparin, as well as its supposed antiviral role, seems appropriate, considering that heparin sulphate may bind to SARS-CoV-2 spike protein to block viral attachment or entry.²² The risk of deep vein thrombosis in Chinese patients is generally one-quarter to one-third of that of white patients, whereas the risk in African-Americans is markedly higher than in white people.^{23,24} Therefore, ethnicity needs to be considered when determining anticoagulative strategies for COVID-19 patients. As pulmonary artery thrombosis is frequently observed even in patients undergoing anticoagulation therapy, anticoagulants need to be administered in sufficient amounts.

Awareness of the importance of anticoagulation therapy is currently low and anticoagulation therapy is not generally administered to COVID-19 patients due to fears of haemorrhage as a side-effect. Anticoagulation therapy may potentially result in a marked improvement of prognosis in COVID-19 patients. Therefore, efforts to rapidly increase awareness and fully establish the validity of the ISTH interim guidance are required. ■

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