

Hypercoagulability and thrombosis in COVID-19: a modifiable cause for mortality?

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This editorial refers to ‘Pulmonary embolism in patients with COVID-19: incidence, risk factors, clinical characteristics, and outcome’, by O. Miró et al. doi:10.1093/eurheartj/ehab314.

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected >180 million people globally, and the count is still rising.¹ Although most people have mild disease and recover within a few weeks, COVID-19 has disrupted healthcare systems around the world,² caused at least 3.9 million deaths,¹ and is associated with long-term health effects,^{3–6} some of which are yet to be fully characterized.

The hallmarks of COVID-19 are viraemia, inflammation, hypercoagulability, and organ dysfunction.⁷ The most common clinical manifestations of hypercoagulability are venous thrombo-embolism (VTE) followed by stroke, myocardial infarction, and acute peripheral artery occlusion.³ However, autopsy studies demonstrate small vessel platelet–fibrin thrombi (microvascular thrombosis) in ~80% of cases,⁸ implicating thrombosis as a major cause of organ dysfunction and death. Mechanisms of hypercoagulability remain incompletely understood, but there is increasing evidence that a dysregulated immune response plays a central role. In the early stages of infection, SARS-CoV-2 is localized to the respiratory tract where it enters epithelial and endothelial cells via the angiotensin-converting enzyme 2 (ACE2) receptor and causes local injury. In more advanced stages, disseminated and unchecked viral replication induces widespread endothelialopathy that is accompanied by a florid maladaptive inflammatory response, increasing hypercoagulability and multiorgan dysfunction.

Case series have reported VTE in 4.8–46% of hospitalized patients with COVID-19,³ with the highest rates in critically ill patients admitted to the intensive care unit, often despite prophylactic anticoagulation.⁹ Furthermore, meta-analysis data suggest that COVID-19 patients with VTE have a 2.1-fold higher risk of mortality than those without VTE,¹⁰ prompting calls for routine use of intensified thromboprophylaxis to improve outcomes. However, it is unclear from the published data to what extent hospitalization and the use of thromboprophylaxis contributed to the observed risk of VTE, and whether

preventing VTE in patients with COVID-19 improves outcomes remains unresolved.

Miró and colleagues took a different approach to many of the earlier studies by focusing their study of VTE in COVID-19 on outpatients. Their study, published in this issue of the *European Heart Journal*, included patients presenting between 1 March and 30 April 2020 to one of 62 emergency rooms that provide care to about one-third of the Spanish population.¹¹ Their study has at least three important findings. First, among the 74 814 outpatients with COVID-19, a total of 368 were diagnosed with pulmonary embolism (PE), which is ~9-fold higher than the rate of PE in those without COVID-19 presenting during the same period (i.e. between 1 March and 30 April) in either 2019 or 2020 (standardized incidence: 310.1 vs. 34.7 per 100 000 person-years). Although the overall incidence of PE was low (~0.5%), their data highlight the importance of COVID-19 as a risk factor for PE. Second, compared with non-COVID-19 patients with PE, patients with COVID-19 and PE were less likely to have a history of VTE or to be receiving chronic oestrogen therapy, more likely to present with fever, diarrhoea or pulmonary infiltrates, and less likely to have accompanying leg pain or swelling, or a D-dimer >1000 ng/mL; and their thrombosis was less likely to involve the main pulmonary arteries, although there was no difference between groups in the proportion of patients with right ventricular dysfunction. These findings provide valuable insights into the manifestations of PE in patients with COVID-19, but it is unclear if this information will help to refine the approach to diagnosis because there was substantial overlap in the clinical presentation of COVID-19 patients with or without PE. Third, although patients diagnosed with PE in the context of COVID-19 had higher in-hospital mortality than those who were diagnosed with PE who did not have COVID-19 (16.0% vs. 6.5%), mortality in COVID-19 patients was similar irrespective of the diagnosis of PE (16.0% vs. 16.6%).

Table 1 Completed trials of intensified anticoagulant therapy vs. standard dose thromboprophylaxis in hospitalized patients with COVID-19

Trial	COVID-19 population	Experimental treatment ^a	Major thrombosis	Major bleeding	Mortality
NIH multiplatform trial ^{12,13} ATTACC/	Non-critically ill (n = 2219)	Therapeutic LMWH/UFH	1.4% vs. 2.7% ^b	1.9% vs. 0.9% ^b	7.3% vs. 8.2% ^c
ACTIV-4a/REMAP-CAP	Critically ill in ICU (n = 1074)	Therapeutic LMWH/UFH	5.7% vs. 10.3% ^b	3.1% vs. 2.4% ^c	35.7% vs. 34.7% ^c
INSPIRATION ¹⁴	Critically ill in ICU (n = 562)	Intermediate dose enoxaparin (1 mg/kg daily)	3.3% vs. 3.5% ^c (VTE)	2.5% vs. 1.4% ^c	43.1% vs. 40.9% ^c
ACTION (NCT04394377) ¹⁵	Elevated D-dimer (n = 615)	Rivaroxaban 20 mg daily (stable patients) or enoxaparin 1 mg/kg twice daily (unstable patients)	4.0% vs. 6.0% ^c (VTE)	3.0% vs. 1.0% ^c	11% vs. 8% ^c

ICU, intensive care unit; LMWH, low molecular weight heparin; NIH, National Institutes of Health; UFH, unfractionated heparin; VTE, venous thrombo-embolism.

^aControl treatment was an approved prophylactic dose of UFH or LMWH.

^bP-value or confidence interval not reported.

^cNot significant.

Strengths of this study include focus on non-hospitalized patients, large sample size, consistency of the findings using multiple control groups, and focus on PE which is the most serious manifestation of VTE. Limitations include the potential for underestimating PE incidence because not all patients with symptoms present to emergency rooms, and not all patients who had symptoms compatible with the diagnosis were investigated for PE. It is also possible that COVID-19 patients were more likely than those without COVID-19 to undergo investigation for PE, potentially leading to higher estimates of PE rates.

Perhaps the most important insight provided by Miró and colleagues is that although the diagnosis of PE in patients with COVID-19 was associated with higher intensive care unit admission rates, it was not associated with an increased risk of death. It remains possible that the study was underpowered to detect differences in survival, but the results would be consistent with the conclusion that PE is not a modifiable risk factor for death in patients with COVID-19.

What are the implications of these findings for clinical practice? The data provided by Miró and colleagues lend further support to the importance of COVID-19 as a risk factor for VTE. At the same time, in the absence of high-quality evidence demonstrating a benefit of therapies that prevent thrombo-embolism, their finding of a lack of association between PE and death in patients with COVID-19 should prompt further caution in the routine adoption of intensified anticoagulant strategies that can increase bleeding. By reducing blood flow to the lungs, large vessel thrombo-embolism has the potential to worsen respiratory function in patients with COVID-19. However microvascular complications may be the most important thrombo-embolic complications in these patients, and it is unclear if these can be prevented with therapeutic anticoagulation. Consistent with this conclusion, randomized trials of intensified thromboprophylaxis using intermediate or therapeutic doses of anticoagulation have so far failed to demonstrate mortality benefits in a combined total of 4470 hospitalized patients with COVID-19, despite apparently reducing

major thrombosis including VTE in some trials (Table 1).^{12–15} More than 70 randomized trials of antithrombotic therapy are currently ongoing in patients with COVID-19, and their successful completion should help to clarify this issue.¹⁶

Conflict of interest: none declared.

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