Studying the coagulopathy of COVID-19

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Published **Online**
November 17, 2021
https://doi.org/10.1016/S0140-6736(21)01906-1

See **Online/Articles**
https://doi.org/10.1016/S0140-6736(21)01825-0

The coagulopathy caused by SARS-CoV-2 seen in patients hospitalised with COVID-19, especially those with severe or critical illness, is by now well established. Early reports in relatively small studies showing multifold elevated rates of both venous and arterial thromboembolism have given way to more sober estimates from much larger populational studies and systematic reviews or meta-analyses. Overall rates of venous thromboembolism, including in-situ pulmonary thrombosis, are approximately three-times higher than historical matched controls of hospitalised populations, whereas rates of arterial thromboembolism, including acute coronary syndromes and stroke, although still elevated, are lower than previously described.[1] Microvascular thrombotic mechanisms have been implicated in progression to acute respiratory distress syndrome and subsequent need for organ support, and autopsy studies have identified unsuspected pulmonary embolism or in-situ pulmonary arterial thrombosis in nearly 60% of patients, suggesting that thrombosis has an important role in mortality.[2,3] Proposed mechanisms for these microvessel thrombotic and intravascular coagulopathic mechanisms and classic macrovessel thromboembolism are complex and include patient-related risk factors seen in medical patients hospitalised with pneumonia and sepsis, as well as more SARS-CoV-2-dependent mechanisms, including endothelial dysfunction, hyperinflammation and cytokine storm, formation of neutrophil-extracellular traps, complement-system activation, hypofibrinolysis, and platelet-derived and coagulation-derived mechanisms of thrombin generation leading to thromboinflammation.[4]

Given this tendency for thrombotic complications with COVID-19, several multicentre randomised trials of antithrombotic therapies were launched globally as a logical next step to test whether the addition or escalated dosing of antithrombotic agents would provide further benefit to existing standards of care, and to understand the risk–benefit in terms of bleeding risk.[5] These trials have included anticoagulants with escalated or therapeutic doses being compared with standard prophylactic doses, anti-platelet agents, and fibrinolytic agents, as well as more novel approaches.[6] Trial designs have included adaptive, multiplatform, and Bayesian design frameworks, and the endpoints have included all-cause mortality, or composites including freedom from organ support or other surrogates of disease severity, and finally thrombosis.[5]

For the most part, randomised trials to date have not shown benefits of add-on or escalated antithrombotic therapy over usual standard of care. Published or preprint trials of escalated or treatment dose anticoagulants have not met their primary efficacy outcome in patients who are moderately or critically ill and hospitalised with COVID-19,[7–9] and the results of the large RECOVERY trial[10] published in *The Lancet* by the RECOVERY Collaborative Group showed no benefit of aspirin as an add-on therapy to reduce mortality in patients hospitalised with COVID-19.

How do we make sense of the overall negative results seen in antithrombotic trials in COVID-19 to date? The first answer is mechanistic, whereas other answers might pertain to the design of clinical trials themselves. Previous trials might have used suboptimal doses of anticoagulants in a highly thrombotic population,[9] or selected anticoagulants such as direct oral anticoagulants without potential for pleiotropic or anti-inflammatory properties presumed to exist with heparins in the setting of COVID-19-induced hyperinflammation.[2] Alternatively, as suggested by the authors in the RECOVERY trial,[10] previous trials might have selected an antithrombotic such as aspirin with a diminished role in intravascular coagulopathy and thrombosis, as non-platelet pathways might be more important determinants of adverse clinical outcomes.

Have we set too high a bar in the design of antithrombotic clinical trials in COVID-19? With time, we have reduced the mortality of severe COVID-19 with improvements in critical care and by using various combinations of generalised and selected anti-inflammatory and immunomodulatory agents. In the pre-COVID-19 era, the reason we gave antithrombotics in patients with pneumonia and sepsis was not to change the course of disease, but rather to reduce macrovessel thromboembolism, and if we were lucky, to reduce mortality presumably from thromboembolic mechanisms. Traditional anti-thrombotic clinical trial designs in patients who are hospitalised used a composite of thromboembolic

disease and mortality as primary endpoints in enriched populations, and it was the rare trial that gave us reductions in mortality alone if thrombotic causes were the dominant driver.[11] Whether antithrombotics reduce thrombotic microangiopathy is still a matter of debate. And yet, the entire premise of many COVID-19 antithrombotic clinical trial designs, which are based on primary endpoints of mortality or disease severity, is that they would have potential to reduce thrombotic microangiopathy and ameliorate the course of disease on the basis of thromboinflammatory mechanisms. It can indeed be a slippery slope to base an entire clinical trial design on an unproven hypothesis.

We should step back and reflect on primary principles in studying thrombotic mechanisms of COVID-19. The reason why the HEP-COVID trial[12] yielded a clear result despite its modest size in answering the trial hypothesis was that it used a traditional antithrombotic clinical trial design.[12] HEP-COVID used an agent with established efficacy in thromboembolic disease at an optimal dose (therapeutic low molecular weight heparin), selected a highly enriched population using a validated strategy (elevated D dimers), and used an endpoint that was specific to the mechanism of intervention (a composite of major thromboembolism and mortality). Although it can be argued that the urgency of the pandemic required broader outcomes to speed up discovery, perhaps the time has come for us to rethink how we study the coagulopathy of COVID-19, returning to principles that led to traditional antithrombotic clinical trial designs.

ACS declares research grants and consulting fees from Janssen Research & Development LLC, Bayer, Portola, Boehringer Ingelheim, Bristol-Meyers Squibb, and the ATLAS group, unrelated to the area of work commented on here. MPB declares grants from Janssen to CPC Clinical Research and grants to CPC Clinical Research from Amgen, AstraZeneca, Bayer, Janssen, Merck, Novo Nordisk, and Pfizer, outside the area of work commented on here.

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1 Spyropoulos AC, Weitz JI. Hospitalized COVID-19 patients and venous thromboembolism: a perfect storm. *Circulation* 2020; **142:** 129–32.
2 Berger JS, Connors JM. Anticoagulation in COVID-19: reaction to the ACTION trial. *Lancet* 2021; **397:** 2226–28.
3 Wichmann D, Sperhake JP, Lütgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. *Ann Intern Med* 2020; **173:** 268–77.
4 Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. *J Am Coll Cardiol* 2020; **75:** 2950–73.
5 Tritschler T, Mathieu ME, Skeith L, et al. Anticoagulant interventions in hospitalized patients with COVID-19: a scoping review of randomized controlled trials and call for international collaboration. *J Thromb Haemost* 2020; **18:** 2958–67.
6 Bikdeli B, Madhavan MV, Gupta A, et al. Pharmacological agents targeting thromboinflammation in COVID-19: review and implications for future research. *Thromb Haemost* 2020; **120:** 1004–24.
7 Zarychanski R. Therapeutic anticoagulation in critically ill patients with COVID-19: preliminary report. *medRxiv* 2021; published online March 12. DOI: https://doi.org/10.1101/2021.03.10.21252749.
8 Lopes RD, de Barros e Silva PGM, Furtado RHM, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. *Lancet* 2021; **397:** 2253–63.
9 Sadeghipour P, Talasaz AH, Rashidi F, et al. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinic. *JAMA* 2021; **325:** 1620–30.
10 Landray MJ, Horby PW, Pessoa-Amorim G, et al. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021; published online Nov 17. https://doi.org/10.1016/S0140-6736(21)01825-0.
11 Rodgers A, MacMahon S, Collins R, Prentice C. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet* 2000; **355:** 1295–302.
12 Spyropoulos AC, Goldin M, Giannis D, et al. Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high risk hospitalized patients with COVID-19: the HEP-COVID randomized clinical trial. *JAMA Intern Med* 2021; published online Oct 7. https://doi.org/10.1001/jamainternmed.2021.6203.