ESC European Society of Cardiology
European Heart Journal - Cardiovascular Pharmacotherapy (2022) **8**, 336–337
https://doi.org/10.1093/ehjcvp/pvac009

Thromboprophylaxis for COVID-19-related coagulopathy: what next?

Patients hospitalized with coronavirus disease 2019 (COVID-19) are at high risk for micro- and macrovascular thromboembolic events due to thromboinflammation and the coagulopathy caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1,2] Because of its proven anticoagulation effect, coupled with possible antiviral and anti-inflammatory effects, heparin was the first candidate for prevention of adverse events in COVID-19 patients.[2] Yet, a recent meta-analysis of seven clinical trials using low-molecular-weight heparin (LMWH) or unfractionated heparin suggests no difference in all-cause death between the therapeutic-, i.e. escalated, and standard-dose anticoagulation in hospitalized COVID-19 patients without a formal indication for anticoagulation therapy.[3] The escalated dose significantly reduced the rates of pulmonary and other venous thromboembolism, but was associated with a higher bleeding risk.[3] The findings were consistent with regard to the disease severity (critically vs. non-critically ill COVID-19 patients).[3]

It is important to note that the aforementioned meta-analyis[3] did not include the most recent HEP-COVID trial,[4] the first randomized trial using a classic antithrombotic clinical trial design. This trial, similarly to another important report by the REMAP-CAP, ACTIV-4a, and ATTACC Investigators,[5] suggests that therapeutic-dose LMWH reduced the risk of thromboembolism and death in non-critically ill patients. These two well-designed studies strongly suggest the use of escalated anticoagulation in this group of hospitalized patients, particularly with elevated D-dimer levels.

In contrast, current data agree that escalation of heparin dose in critically ill COVID-19 patients requiring intensive care unit treatment provides no benefit,[3,4,6] so the anticoagulation strategy in such patients is uncertain. In addition to coagulopathy, hyperinflammation, and endothelial disruption, mechanisms responsible for the lack of a beneficial effect in critically ill patients may include lung-related mechanisms. First, therapeutic-dose anticoagulation may exacerbate alveolar haemorrhage in patients with severe pulmonary inflammation.[6] Second, the processes of intra-alveolar coagulation that through isolation of pulmonary pathogens may protect the host from disseminated infection and improve survival in COVID-19 are disturbed.[2] Third, heparin may also inhibit lung recovery and increase the risk of progressive lung injury by sequestering growth factors that contribute to lung repair.[7] Still, mechanisms of possible heparin-related interruption of lung-protective and reparative processes are to be further explored.

An important shortcoming of the antithrombotic trials in COVID-19 is that duration of therapy is not explicitly explored in terms of outcomes. Severely ill COVID-19 patients commonly have a more extended hospital stay and receive prolonged anticoagulation treatment. While a prothrombotic state may be expected at the beginning of the COVID-19 disease, in patients whose disease progresses to severe forms a disseminated intravascular coagulopathy (DIC)-like state may develop.[1,3] It has been estimated that the period of 10–12 days from symptom onset could be the point when a procoagulant state and the predominantly beneficial effect of the anticoagulation end and a DIC-like state begins to develop, thereby increasing the risk of bleeding,[3] especially with therapeutic-dose anticoagulation. Aligned with this is a finding of the HEP-COVID trial that the beneficial effect of therapeutic-dose LMWH was mainly observed within the first 14 days of hospitalization.[4] Accordingly, there is a possibility that a switch of the escalated anticoagulation to standard or intermediate dosing at this point could reduce the risk of bleeding, particularly among severely ill and other patients requiring prolonged anticoagulation. This regimen could be tested in future clinical trials in COVID-19 patients with elevated D-dimer levels and without a contraindication for such an approach.

The risk of heparin-associated bleeding is increased with advanced age, illness severity, longer hospital stay, cardiopulmonary resuscitation, and decreased white blood cell and platelet counts.[2] For this reason, such COVID-19 patients should be cautiously recruited in the therapeutic-dose arm, preferably as separate subgroups, and the duration of anticoagulation should be analysed. The presence of antiphospholipid antibodies should be investigated, whereas D-dimer levels, activated partial thromboplastin time, prothrombin time, and platelet count should be regularly monitored. Current evidence suggests that anticoagulants other than heparin or antiplatelet therapy do not provide a beneficial effect,[8,9] but combinations of anticoagulation regimens may be clinically tested. Finally, a better distinction between moderate and severe disease should be made, particularly with regard to lung injury and oxygen requirement. Taking all these factors into consideration in future trials could reveal COVID-19 patient subgroups who will clearly benefit from therapeutic-dose anticoagulation.

Conflict of interest: none declared.

References

1. Thachil J, Cushman M, Srivastava A. A proposal for staging COVID-19 coagulopathy. *Res Pract Thromb Haemost* 2020;**4**:731–736.
2. Hippensteel JA, LaRiviere WB, Colbert JF, Langouët-Astrié CJ, Schmidt EP. Heparin as a therapy for COVID-19: current evidence and future possibilities. *Am J Physiol Lung Cell Mol Physiol* 2020;**319**:L211–L217.
3. Ortega-Paz L, Galli M, Capodanno D, Franchi F, Rollini F, Bikdeli B, Mehran R, Montalescot G, Gibson CM, Lopes RD, Andreotti F, Angiolillo DJ. Safety and efficacy of different prophylactic anticoagulation dosing regimens in critically and non-critically ill patients with COVID-19: a systematic review and meta-analysis of randomized controlled trials. *Eur Heart J Cardiovasc Pharmacother*; doi.org/10.1093/ehjcvp/pvab070. Published online ahead of print 14 September 2021.
4. Spyropoulos AC, Goldin M, Giannis D, Diab W, Wang J, Khanijo S, Mignatti A, Gianos E, Cohen M, Sharifova G, Lund JM, Tafur A, Lewis PA, Cohoon KP, Rahman H, Sison CP, Lesser ML, Ochani K, Agrawal N, Hsia J, Anderson VE, Bonaca M, Halperin JL, Weitz JI, HEP-COVID Investigators. 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;**181**:1612–1620.
5. The ATTACC, ACTIV-4a, and REMAP-CAP Investigators. Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. *N Engl J Med* 2021;**385**:790–802.
6. The REMAP-CAP, ACTIV-4a, and ATTACC Investigators. Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. *N Engl J Med* 2021;**385**:777–789.
7. LaRivière WB, Liao S, McMurtry SA, Oshima K, Han X, Zhang F, Yan S, Haeger SM, Ransom M, Bastarache JA, Linhardt RJ, Schmidt EP, Yang Y. Alveolar heparan sulfate shedding impedes recovery from bleomycin-induced lung injury. *Am J Physiol Lung Cell Mol Physiol* 2020;**318**:L1198–L1210.
8. Connors JM, Brooks MM, Sciurba FC, Krishnan JA, Bledsoe JR, Kindzelski A, Baucom AL, Kirwan BA, Eng H, Martin D, Zaharris E, Everett B, Castro L, Shapiro NL, Lin JY, Hou PC, Pepine CJ, Handberg E, Haight DO, Wilson JW, Majercik S, Fu Z, Zhong Y, Venugopal V, Beach S, Wisniewski S, Ridker PM; ACTIV-4B Investigators. Effect of antithrombotic therapy on clinical outcomes in outpatients with clinically stable symptomatic COVID-19: the ACTIV-4B randomized clinical trial. *JAMA* 2021;**326**:1703–1712.

9. Lopes RD, de Barros E Silva PGM, Furtado RHM, Macedo AVS, Bronhara B, Damiani LP, Barbosa LM, de Aveiro Morata J, Ramacciotti E, de Aquino Martins P, de Oliveira AL, Nunes VS, Ritt LEF, Rocha AT, Tramujas L, Santos SV, Diaz DRA, Viana LS, Melro LMG, de Alcântara Chaud MS, Figueiredo EL, Neuenschwander FC, Dracoulakis MDA, Lima RGSD, de Souza Dantas VC, Fernandes ACS, Gebara OCE, Hernandes ME, Queiroz DAR, Veiga VC, Canesin MF, de Faria LM, Feitosa-Filho GS, Gazzana MB, Liporace IL, de Oliveira Twardowsky A, Maia LN, Machado FR, de Matos Soeiro A, Conceição-Souza GE, Armaganijan L, Guimarães PO, Rosa RG, Azevedo LCP, Alexander JH, Avezum A, Cavalcanti AB, Berwanger O; ACTION Coalition COVID-19 Brazil IV Investigators. 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 Lancet North Am Ed* 2021;**397**:2253–2263.

Viktor Čulić [1,2,*], Riccardo Vio[3] and Riccardo Proietti[4]

[1]Department of Cardiology and Angiology, University Hospital Centre Split, Šoltanska 1, 21000 Split, Croatia; [2]Department of Clinical Propedeutics, University of Split School of Medicine, Split, Croatia; [3]Cardiology Unit, Department of Cardiothoracic and Vascular Medicine, Ospedale dell'Angelo, Venice, Italy; and [4]Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool, UK

* Corresponding author. Tel: +385 21 55 7289, Fax: +385 21 55 7385, Email: viktor.culic@st.t-com.hr