

## Criteria for choosing anticoagulant therapy in COVID 19 patients

Seyed Pouriya Hosseini Mehr<sup>1\*</sup>, Yuliia Dzekunova<sup>2</sup>, Valentyn Smorzhevskyi<sup>3</sup>

1 Dept of Cardiothoracic Surgery, Royal Papworth Hospital NHS Foundation Trust, Cambridge, United Kingdom

2 Dept of Plastic and Reconstructive Surgery, Shalimov National Institute of Surgery and Transplantology, Ukraine

3 Dept of Cardiac Surgery and Transplantation, Shalimov National Institute of Surgery and Transplantology, Ukraine

\* Corresponding Author: Seyed Pouriya Hosseini Mehr E-mail: [pouriyamehr@gmail.com](mailto:pouriyamehr@gmail.com)

### ABSTRACT

**Objective:** While COVID-19 continues to circulate around the world, there are still many uncertainties on how to treat patients infected with the potentially deadly virus and, more importantly, for how long!

COVID-19 causes many different symptoms, among which coagulopathy seems to play an essential role in the survival prognosis of patients. While WHO recommends thromboprophylaxis in all admitted covid patients, it is still not routinely used in many medical centers worldwide. It is also worth mentioning that there is no animosity on the anticoagulant agents' choice or the duration they should be prescribed. Recent data suggest that it is wise to prescribe a prophylactic dose of anticoagulant for a minimum of 3 months post-discharge to minimize the risk of thrombosis in COVID-19 patients.

**Keywords:** COVID-19, Thrombosis, Coronavirus, SARS-cov-2, coagulopathy, anticoagulants, DVT

### INTRODUCTION

While COVID-19 continues to circulate around the world, there are still many uncertainties on how to treat patients infected with the potentially deadly virus and, more importantly, for how long!

COVID-19 causes many different symptoms, among which coagulopathy seems to play an essential role in the survival prognosis of patients.

### MATERIALS and METHODS

A search was conducted through PubMed and Google Scholars using the keywords COVID-19, coagulopathy, thromboprophylaxis, thrombosis, and deep vein thrombosis.

While WHO recommends thromboprophylaxis in all admitted Covid patients (1), it is still not routinely used in many medical centers worldwide. It is also worth mentioning that there is no animosity on the anticoagulant agents' choice or the duration they should be prescribed. Recent data suggest that it is wise to prescribe a prophylactic dose of anticoagulant for a minimum of 3 months post-discharge to minimize the risk of thrombosis in COVID-19 patients (2, 3).

What is the Most suitable pharmacotherapy agent for COVID-19?

COVID-19 Hypercoagulable state has a specific inflammatory character which in some cases leads to thrombosis even in case of full-dose anticoagulant(4) therapy in hospitalized patients(4).

SO we need to define Criteria for an Ideal anticoagulant Agent for preventing COVID-19 induced Thrombosis.

### Review Article

Received 29-09-2022

Accepted 21-10-2022

Available Online: 22-10-2022

Published 30-10-2022

Distributed under  
Creative Commons CC-BY-NC 4.0

OPEN ACCESS



## Preventing Thromboembolic Events

Any agent used for thromboprophylaxis should effectively prevent clot formation and thrombosis. Low Molecular weight Heparins (LMWs) are currently the mainstay of preventing thromboembolic events in COVID-19 patients. In some cases, such as severe kidney dysfunction, as well as in the case of severely ill patients, Unfractionated heparin is used.

On the other hand, Direct Oral Anticoagulants such as Apixaban are getting more popular, especially for Post-hospital prevention of thromboembolic events.

However, emerging information suggests that hospitalized patients with SARS-COV-2 infection can still develop thromboembolic events despite the therapeutic dose of anticoagulant therapy with current agents (5).

## Wide therapeutic Window

Practically all currently used anticoagulant agents have relatively a narrow therapeutic window; this is especially of great concern in COVID-19 patients, who are more prone to bleeding due to the COVID-induced coagulopathy (6).

Well tolerable and appropriate for long-term use

Heparin is one of the oldest biological medicines and has an established place in preventing and treating venous thrombosis (7). Its long-term use may lead to severe side effects such as thrombocytopenia and Osteoporosis. LMWHs also may cause Osteoporosis, and as they are excreted through kidneys, LMWHs are contraindicated in patients with severe kidney dysfunction. Furthermore, both aforementioned classes need to be administered parentally, making them difficult to use for the post-discharge period. On the other hand, although the use of direct oral anticoagulants as a prophylactic measure seems to be a good choice in terms of compliance and ease of intake, it is associated with a relatively high risk of bleeding (8).

## Have an antidote in case reversal is needed

An ideal agent should have an effective antidote, as COVID-19 induced coagulopathy may need a reversal of anticoagulant agents. While protamine sulfate may completely reverse the heparin effect, its reversal impact on LMWHs is only partial at best. In terms of DOCS, there are currently two reversal agents available, Idarucizumab for the reversal of Dabigatran and Andexanet alfa for the reversal of Rivaroxaban and apixaban. So in severe cases, patients may require prothrombin complex concentrates (9).

## Anti-inflammatory effects

Cumulative evidence points to the inflammatory nature of the COVID-19 induced hypercoagulable state (10,11). Hence, it is essential that the pharmacotherapeutic agents used to prevent COVID-19 related thrombotic events have strong anti-inflammatory properties.

Heparin, LMWHs, and DOACS all have shown noticeable but not sufficient anti-inflammatory properties to tackle the viral-related thrombo-inflammation (12–14).

## DISCUSSION

While the current treatment protocols fail to fully prevent thrombosis in COVID-19 hospitalized patients, changing the administration route could help potentiate the anticoagulatory effect of the medications while reducing the possible complications. A good example is the case of nebulized heparin, where the medications are delivered directly into the lung and can prevent and even resolve the microthrombotic events in the lungs (15,16).

Another interesting agent that has been used off-label among other indications for treating reperfusion injury and diabetic microvascular complications is Sulodexide (17), which has, among other properties, Anticoagulant, antiaggregant and anti-inflammatory properties (18). It can be injected or taken by mouth as heparin sulfate, a member of the short heparin family, can readily pass through the enterocytes and get into circulation.

## CONCLUSION

To conclude, while there has been good progress in identifying and treating the thromboembolic complications of COVID-19, there is currently no clear pharmacologic agent that could completely address the hypercoagulable state induced by SARS-COV2 infection. Hence more research is required in order to identify and address the mechanisms through which the thrombo-inflammation could be adequately managed. Furthermore, guidelines need to include a post-discharge thromboprophylactic regimen to prevent late-onset thrombosis.

**Acknowledgments:** None

**Conflict of interest:** The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Author Contributions:** HMSP, DY, SV: Study design, Literature review, Data collection and processing, HSMP: Writing, Revisions

**Ethical approval:** All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

## REFERENCES

1. WHO recommends follow-up care, low-dose anticoagulants for COVID-19 patients [Internet]. [cited 2021 Apr 9]. Available from: <https://www.who.int/news-room/feature-stories/detail/who-recommends-follow-up-care-low-dose-anticoagulants-for-covid-19-patients>
2. Barnes GD, Burnett A, Allen A, Blumenstein M, Clark NP, Cuker A, et al. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. *J Thromb Thrombolysis*. 2020 May 21;1–10.
3. Kaptein FHJ, Stals MAM, Huisman MV, Klok FA. Prophylaxis and treatment of COVID-19 related venous thromboembolism. *Postgrad Med*. :1–9.

4. Garcia-Olivé I, Sintés H, Radua J, Abad Capa J, Rosell A. D-dimer in patients infected with COVID-19 and suspected pulmonary embolism. *Respir Med*. 2020 Aug;169:106023.
5. Ataallah B, Sharma A, Tamanna S, Ng J, Haggerty G. Major Thrombotic Event Despite Anticoagulation in a Patient With COVID-19. *Cureus* [Internet]. 12(6). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7389143/>
6. COVID-19 and Coagulopathy - Hematology.org [Internet]. [cited 2021 Apr 9]. Available from: <https://www.hematology.org:443/covid-19/covid-19-and-coagulopathy>
7. Heparin and low-molecular-weight heparin - PubMed [Internet]. [cited 2021 Jan 24]. Available from: <https://pubmed.ncbi.nlm.nih.gov/18449410/>
8. A L, Da G, Gh L, M C. Direct oral anticoagulant (DOAC) versus low-molecular-weight heparin (LMWH) for treatment of cancer associated thrombosis (CAT): A systematic review and meta-analysis [Internet]. *Thrombosis research*. 2019 [cited 2021 Apr 9]. Available from: <https://pubmed.ncbi.nlm.nih.gov/29506866/>
9. Kustos SA, Fasinu PS. Direct-Acting Oral Anticoagulants and Their Reversal Agents—An Update. *Medicines* [Internet]. 2019 Oct 15;6(4). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6963825/>
10. Abou-Ismaïl MY, Diamond A, Kapoor S, Arafah Y, Nayak L. The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. *Thromb Res*. 2020 Oct;194:101–15.
11. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study [Internet]. [cited 2020 Oct 15]. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7326446/>
12. E Y. The anti-inflammatory effects of heparin and related compounds [Internet]. *Thrombosis research*. 2008 [cited 2021 Jan 24]. Available from: <https://pubmed.ncbi.nlm.nih.gov/17727922/>
13. H K, T N, I M. Anti-inflammatory effect of factor-Xa inhibitors in Japanese patients with atrial fibrillation [Internet]. *Heart and vessels*. 2017 [cited 2021 Jan 25]. Available from: <https://pubmed.ncbi.nlm.nih.gov/28283738/?dopt=Abstract>
14. Nakase T, Moroi J, Ishikawa T. Anti-inflammatory and antiplatelet effects of non-vitamin K antagonist oral anticoagulants in acute phase of ischemic stroke patients. *Clin Transl Med* [Internet]. 2018 Jan 12;7. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5768575/>
15. Nebulized Heparin for the Treatment of COVID-19 Induced Lung Injury - Full Text View - ClinicalTrials.gov [Internet]. [cited 2021 Jan 24]. Available from: <https://clinicaltrials.gov/ct2/show/NCT04397510>
16. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. 2020 May 4;1–10.
17. Coccheri S, Mannello F. Development and use of sulodexide in vascular diseases: implications for treatment. *Drug Des Devel Ther*. 2013 Dec 24;8:49–65.
18. Szolnok G. Sulodexide may be a real alternative to low molecular weight heparins in the prevention of COVID-19 induced vascular complications. *Dermatol Ther*. n/a(n/a):e14437.