Should anticoagulants be used for venous thromboembolism (VTE) prophylaxis in COVID-19?

This clinical evidence summary outlines existing evidence on the use of anticoagulants for VTE prophylaxis in patients with COVID-19. The information may be revised as new evidence merges. The summary is not exhaustive of the subject matter and does not replace clinical judgement. The responsibility for making decisions appropriate to the circumstances of the individual patient remains at all times with the healthcare professional.

Background

Numerous reports have emerged regarding the hypercoagulable state and occurrence of VTE in COVID-19 patients. Early studies from China revealed derangements in inflammatory and coagulation markers, such as procalcitonin, C-reactive protein, fibrinogen, platelets, prothrombin time, activated partial thromboplastin time, and D-dimer.[1-3] Similar biochemical derangements have also been seen in subsequent reports from Italy,[4] France,[5] and UK.[6]

Differences in coagulation markers have been observed between those with severe and non-severe COVID-19.[1,2,4,7,8] D-dimer levels tend to be higher in severe COVID-19 infections,[1,2,4,7,8] but platelet count and clotting time (prothrombin time and activated partial thromboplastin time) are less consistent.[7] Non-survivors (case fatalities) tend to have prolonged clotting time, and higher D-dimer levels compared to survivors (2.12 mcg/ml vs 0.61 mcg/ml).[7] D-dimer greater than 1 mcg/ml has been found to be predictive of poor COVID-19 prognosis.[3]

While the true incidence of VTE in COVID-19 is unknown, it is currently estimated to be around 8% in all COVID-19 patients[1] and up to 69% in critically ill patients.[9-11] Differences in incidence have been observed between those with severe and non-severe COVID-19. In COVID-19 patients admitted to intensive care unit (ICU), VTE has ranged from 25% in China[2] to 69% in France,[9] and found to be markedly higher in non-survivors compared to survivors [based on the International Society on Thrombosis and Haemostasis (ISTH) criteria; 71.4% vs 0.6%].[10]

Several professional bodies around the world have published guidelines on anticoagulant thromboprophylaxis in COVID-19, although recommendations vary. This review examines available evidence regarding the prophylactic use of anticoagulants to reduce VTE in COVID-19.

Clinical evidence

Several studies have examined the prophylactic use of anticoagulants, mainly in the form of low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH), to reduce the risk of VTE in COVID-19 patients.[6,9-12] These are mostly observational studies in severe or critically ill COVID-19 patients, and they have not consistently shown a reduction in VTE with anticoagulant use. To shed more light on this, a phase 2 randomised open-label multicentre trial comparing tinzaparin or UFH to standard care is being conducted in France.[13]

No difference in overall mortality has been observed when thromboprophylaxis with either enoxaparin or UFH were given (29.7% in treatment group vs 30.3% in no-treatment group, p=0.91).[10] However, significant mortality reduction has been observed when treatment was given to patients with D-dimer more than six-fold of upper limit of normal (32.8% vs 52.4%, p=0.017) and patients with sepsis-induced coagulopathy (SIC) score of 4 or greater (40.0% vs 64.2%, p=0.029).[10] Significant reduction in in-hospital mortality has also been observed in mechanically ventilated patients given anticoagulants (29.1% vs 62.7%, p<0.001).[12]

ACE agency for care effectiveness
MINISTRY OF HEALTH SINGAPORE

The appropriate anticoagulation dose for COVID-19 patients is unclear. Llitjos *et al.* found VTE incidence to be higher when prophylactic doses of LMWH or UFH were given compared to therapeutic doses in 26 ICU patients at two French hospitals (100% vs 56%, p=0.03).[9] A phase 3 randomised open-label trial is in progress at a US hospital comparing the effectiveness of prophylactic versus higher-dose enoxaparin in hospitalised COVID-19 patients with a D-dimer of more than 0.5mcg/ml.[14]

Potential adverse effects of anticoagulants in COVID-19 patients need to be noted, particularly bleeding risks, as thrombocytopenia has been consistently observed in COVID-19 patients and found to be associated with disease severity and mortality.[15] Furthermore, case reports of bleeding have also emerged.[16,17] Besides bleeding risks, potential drug-drug interactions may exist between oral anticoagulants and investigational COVID-19 therapies, such as lopinavir/ritonavir, tocilizumab and azithromycin. Furthermore, renal adjustments are also required for some LMWH.

Recommendations from professional bodies

Notwithstanding the clinical evidence outlined above, a number of professional bodies, including the World Health Organization (WHO), support the prophylactic use of anticoagulants (LMWH or UFH) in COVID-19 patients. Several professional bodies recommend routine prophylaxis in all hospitalised patients, whereas the Australian guidelines recommend use in moderate COVID-19 cases. The US National Institutes of Health (NIH) disagree with the routine prophylactic use of anticoagulants and recommend standard care as per other hospitalised patients.

Key recommendations from the individual professional bodies are as follows (please refer to the source publications for full details):

WHO – Clinical management of COVID-19 (27 May 2020)[18]	• Use pharmacological prophylaxis (such as LMWH), according to local and international standards, in adults and adolescents hospitalised with COVID-19 when not contraindicated • For those with contraindications, use mechanical prophylaxis, such as intermittent pneumatic compression devices
ISTH – Clinical guidance on the diagnosis, prevention and treatment of venous thromboembolism in hospitalized patients with COVID-19 (27 May 2020)[19]	• Thromboprophylaxis with standard-dose LMWH (preferred) or UFH should be used in hospitalised patients after careful assessment of bleeding risk • Intermediate-dose LMWH may also be considered (more so in ICU or high-risk patients) • Treatment-dose heparin should not be considered for primary prevention until trial results are available • Extended post-discharge thromboprophylaxis should be considered for high-VTE-risk patients, with post-discharge duration of at least 14 days, and up to 30 days
Journal of the American College of Cardiology (JACC) – COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up (16 June 2020)[20]	• For outpatients with mild COVID-19, encourage increased mobility, and consider pharmacologic prophylaxis after risk assessment on an individual case basis • Hospitalised patients with moderate or severe COVID-19 should undergo risk stratification for VTE prophylaxis, and prophylactic doses of anticoagulation should be administered (if not contraindicated) • There are insufficient data to consider routine therapeutic or intermediate-dose UFH or LMWH

European Society of Cardiology – Guidance for the diagnosis and management of CV disease during the COVID-19 pandemic (10 June 2020)[21]	• Consider anticoagulation at standard prophylactic doses in all patients admitted with COVID-19
Australian guideline for the clinical care of people with COVID-19 (11 June 2020)[22]	• Use prophylactic doses of anticoagulants, preferably LMWH, in adults with moderate COVID-19 unless contraindicated • Consider using increased prophylactic dosing in adults with severe or critical COVID-19 unless contraindicated
NIH – Antithrombotic therapy in patients with COVID-19 (12 May 2020)[23]	• Anticoagulants and antiplatelets should not be initiated in non-hospitalised patients • Hospitalised patients should receive VTE prophylaxis or treatment as per the standard of care for other hospitalised patients • Hospitalised patients should not be routinely discharged on VTE prophylaxis
CHEST – Prevention, diagnosis and treatment of venous thromboembolism in patients with COVID-19 (26 May 2020)[24]	• Anticoagulant thromboprophylaxis (LMWH most favoured) in absence of contraindications in both acutely ill hospitalised and critically ill patients • Current standard prophylactic dosing recommended over intermediate or full treatment dosing

Conclusion

Currently, there is insufficient evidence to recommend for or against the use of anticoagulants for VTE prophylaxis in COVID-19 patients.

- Studies suggest hypercoagulability and increased VTE in severe or critically ill COVID-19 patients. However, such evidence may be limited by small sample sizes and the likelihood of bias and confounding.
- The role of thromboprophylaxis with anticoagulants in reducing mortality in severe or critically ill COVID-19 patients requires further evaluation.
- Clinical benefits and risks should be weighed if prophylactic anticoagulants are used, particularly bleeding risks. Potential drug-drug interactions and renal dosing adjustments should also be considered.
- Choice of anticoagulant is usually LMWH or UFH.

References

1. Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020. doi: 10.1111/jth.14768.
2. Cui S, Chen S, Li X, et al. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost. 2020. doi: 10.1111/jth.14830.
3. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020. doi: 10.1016/S0140-6786(20)30566-3.
4. Spieza L, Boscolo A, Poletto F, et al. COVID-19-related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. Thromb Haemost. 2020. doi: 10.1055/s-0040-1710018.
5. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020. doi: 10/1007/200134-020-06062-x.
6. Fogarty H, Townsend L, Cheallaigh CN, et al. COVID-19 coagulopathy in Caucasian patients. Br J Haematol 2020. doi:10.1111/bjh.16749.
7. Violi F, Pastori D, Cangemi R, et al. Hypercoagulation and antithrombotic treatment in coronavirus 2019: a new challenge. Thromb Haemost 2020. doi: 10.1055/2-0040-1710317.
8. Feng Y, Ling Y, Bai T, et al. COVID-19 with different severity: a multi-center study of clinical features. Am J Respi Crit Care Med 2020. doi: 10.1164/rccm.202002-0445OC.
9. Llitjos J, Chochois C, Monsallier J, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost. 2020. doi: 10.1111/jth.14869.
10. Tang N, Bai H, Chen X et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J THromb Haemostat 2020. doi: 10.1111/jth.14817.
11. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020. doi: 10.1016/j.thromres.2020.04.013.
12. Paranjpe I, Fuster V, Lala A, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J Am Coll Cardiol 2020. doi: 10.1016/j/jack.2020.05.001.
13. ClinicalTrials.gov [Internet]. Identifier NCT04344756. Trial evaluating efficacy and safety of anticoagulation in patients with COVID-19 infection, nested in the Corimmuno-19 cohort (CORIMMUNO-COAG). Estimated study completion date 30 September 2020; 2020 [cited 2020 June 16]. Available from: https://clinicaltrials.gov/ct2/show/NCT04344756
14. ClinicalTrials.gov [Internet]. Identifier NCT04359277. A randomized trial of anticoagulation strategies in COVID-19. Estimated study completion date 16 April 2021; 2020 [cited 2020 June 16]. Available from: https://clinicaltrials.gov/ct2/show/NCT04359277
15. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. Clinica Chimica Acta. 2020. doi: 10.1016/j.cca.2020.03.022.
16. Conti CB, Henchi S, Coppeta GP, et al. Bleeding in COVID-19 severe pneumonia: the other side of abnormal coagulation pattern?. Eur J Intern Med. 2020. doi:10.1016/j.ejim.2020.05.002.
17. Lucatelli P, De Rubeis G, Citone M, et al. Heparin-related major bleeding in COVID-19-positive patient: perspective from the outbreak. Cardiovasc Intervent Radiol. 2020. doi:10.1007/200270-020-02532-3.
18. World Health Organization [Internet]. Clinical management of COVID-19 interim guidance 27 May 2020; 2020 [cited 2020 June 16]. Available from: https://who.int/publications/i/item/clinical-management-of-covid-19
19. Spyropoulos AC, Levy JH, Ageno W, et al. Scientific and standardization committee communication: clinical guidance on the diagnosis, prevention and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemostat. 2020. doi: 10.1111/jth.14929.
20. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. J Am Coll Cardiol. 2020. doi: 10.1016/j.jacc.2020.04.031.
21. European Society of Cardiology [Internet]. ESC Guidance for the diagnosis and management of CV disease during the COVID-19 pandemic; 2020 [cited 2020 June 16]. Available from: http://escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance
22. Australian National COVID-19 Clinical Evidence Taskforce [Internet]. Australian guidelines for the clinical care of people with COVID-19; 2020 [cited 2020 June 16]. Available from: http://app.magicapp.org/#/guideline/L4Q5An/section/L0Or0j
23. National Institutes of Health [Internet]. Antithrombotic therapy in patients with COVID-19; 2020 [cited 2020 June 16]. Available from: https://covid19treatmentguidelines.nih.gov/antithrombotic-therapy
24. Moores LK, Tritschler T, Brosnahan S, et al. Prevention, diagnosis and treatment of venous thromboembolism in patients with COVID-19: CHEST guidelines and expert panel report. CHEST. 2020. doi: 10.1016/j.chest.2020.05.559.