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. Similar biochemical derangements have also been seen in subsequent reports from Italy, France, and UK.

Differences in coagulation markers have been observed between those with severe and non-severe COVID-19. D-dimer levels tend to be higher in severe COVID-19 infections, but platelet count and clotting time (prothrombin time and activated partial thromboplastin time) are less consistent. 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). D-dimer greater than 1 mcg/ml has been found to be predictive of poor COVID-19 prognosis.

While the true incidence of VTE in COVID-19 is unknown, it is currently estimated to be around 8% in all COVID-19 patients and up to 69% in critically ill patients. 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 to 69% in France, 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%].

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. 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.

No significant 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). 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). Significant reduction in hospital mortality has also been observed in mechanically ventilated patients given anticoagulants (29.1% vs 62.7%, p<0.001).
The appropriate anticoagulation dose for COVID-19 patients is unclear. Littjos 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). 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.

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. Furthermore, case reports of bleeding have also emerged. 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):

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| **WHO – Clinical management of COVID-19 (27 May 2020)**<sup>18</sup> | - 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)**<sup>19</sup> | - 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)**<sup>20</sup> | - 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 |
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


