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## Type and dose of heparin in Covid-19: Reply

We thank the authors for their comments and feedback on the International Society on Thrombosis and Haemostasis interim guidance. Hypercoagulability is indeed a significant issue in Covid-19, and the hemostatic system is shifted markedly toward the procoagulant side in these patients. However, we cannot yet be certain that unfractionated heparin (UFH) is better than low molecular weight heparin (LMWH) in this scenario. Although UFH has been used for several years, it does have practical issues, mainly with respect to the need for frequent monitoring using activated partial thromboplastin time.<sup>1,2</sup> In addition, as the authors pointed out correctly, markedly increased acute phase reactants including fibrinogen could

contribute to heparin resistance making the use of UFH problematic (much more than LMWH).<sup>2</sup> Among the reasons for heparin resistance, antithrombin deficiency is not common in Covid-19 patients, at least in the published literature.<sup>3</sup> Despite these issues, UFH may still be preferred if there is marked renal impairment or need for reversibility for an urgent intervention.<sup>4</sup> One of the latter situations is if the patients progress despite anticoagulant therapy. The authors of the letter had recently published a case series on the use of tissue plasminogen activator in C-19 patients which is certainly a consideration in patients who progress despite anticoagulant therapy.<sup>5</sup>

At the time of writing the interim document, our aim was to highlight the urgent need to consider thromboprophylaxis in all patients who require hospital admission for Covid-19 to mitigate poor outcomes from the marked hypercoagulability. We do recognize


that, since then, it has frequently been suggested that higher doses of LMWH be given to Covid-19 patients to prevent venous thromboembolism. However, there is no demonstration that standard prophylactic doses are insufficient to prevent it. Pulmonary vessel occlusions that are observed in severe Covid-19 patients are caused by pulmonary thrombi, whose pathogenesis is unclear but likely to be associated with the severe pulmonary inflammation. Concerning the type of heparin, we cannot be certain that one type is better than the other; in other words, it is difficult to say UFH is better than LMWH. LMWH was chosen in the guidance because of the ease of use, no need for laboratory monitoring, and familiarity among the spectrum of doctors with varying experience. The question of whether *therapeutic* doses of either UFH or LMWH should be considered for all patients is currently unknown and the authors would currently reserve such a dose for those who have confirmed thrombosis including filter thrombosis. We are aware however that therapeutic dose is being administered in some centers where there is very high suspicion of pulmonary embolism and imaging is impractical. Although these approaches are reasonable, we stress that these approaches are undertaken in a trial setting.

#### CONFLICT OF INTEREST

Dr. Thachil has received honoraria from Bayer, BMS-Pfizer, Daichii-Sankyo, Boehringer, Mitsubishi, Novo Nordisk, Octapharma, Novartis, Amgen, Norgine, Alexion, Sobi, and CSL-Behring. All other authors declare no conflicts of interest.

#### AUTHOR CONTRIBUTIONS

Jecko Thachil and Marco Cattaneo wrote the response. Ning Tang, Satoshi Gando, Anna Falanga, Marcel Levi, Cary Clark, and Tsohiaki Iba gave comments. All authors approved the final submission.

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## Lupus anticoagulant is frequent in patients with Covid-19

Patients hospitalized for Covid-19 severe infection are more prone to excessive coagulation activation leading to thrombotic events.

Tang et al<sup>1</sup> discussed the importance of high D-dimer and fibrin degradation product level to determine the patient prognostic and the risk of thrombosis. However, they did not look at lupus anticoagulant (LAC). Zhang et al described three cases of thrombosis associated with antiphospholipid antibodies represented by