The authors reply:

We appreciate the comments from Piagnerelli et al (1) on the optimal thromboprophylactic dose of heparins in coronavirus disease 2019 (COVID-19), recent article (2) published in *Critical Care Medicine*. The standard prophylactic dose of low-molecular-weight heparin (LMWH) for thromboembolism prevention was recommended in most of the initially published guidelines, including our International Society on Thrombosis and Haemostasis (ISTH) interim guidance (3). The standard dose was recommended because there had not been sufficient evidence at that time, and the understanding of pathogenesis had not been properly understood. That situation has not changed and the recent American College of Cardiology guidance recommends enoxaparin 40 mg daily or a similar LMWH regimen (e.g., dalteparin 5,000 U daily) for hospitalized patients with COVID-19 eligible for anticoagulation (4). Indeed, the optimal dose setting is difficult because the pathogenesis of thrombus formation is complex and multifactorial. Different from the ordinal thromboembolism caused by deep vein thrombosis, many additional factors are involved in the development of pulmonary emboli in COVID-19. As noted in our review, the derangement of vascular endothelial cells, platelet activation, and profound inflammation are involved. As a result, the frequency of thrombosis in COVID-19 remains high despite anticoagulation with heparins, and thromboembolism risk differs depending multiple patient factors, and therefore, it can be a reasonable approach to increase the dose for high-risk patients. The recent guidance released from ISTH recommended a routine thromboprophylaxis with standard-dose unfractionated heparin (UFH) or LMWH with LMWH as the preferred agent for all admitted patients, and in such condition, 30% of experts considered the use of intermediate-dose LMWH (5). This guidance also suggested dose modification based on extremes of body weight or deteriorating renal function. For the ICU patients, guidance recommends routine thromboprophylaxis with prophylactic-dose UFH or LMWH, and 50% of experts supported the intermediate-dose of LMWH in high-risk patients. While the guidance did not recommend the treatment-dose heparin for primary prevention, 60% of the experts responded considered multimodal thromboprophylaxis to include mechanical methods. As a result, the dose should be determined based on the risk-benefit balance. Several clinical trials comparing different doses of heparins are planned or initiated (https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=low-molecular-weight-heparin&cntry=&state=&city=&dist=). Until we achieve definitive results, we agree with the many societies that state that the standard prophylaxis dose should be used. In addition to ISTH, World Health Organization, National Institute of Health, all recommend standard prophylactic dose heparin. Recently, Klok et al (6) reported the crude cumulative frequency of the thrombosis was 57% (95% CI, 47–67%), even though the patients received pharmacological thromboprophylaxis. Although it is understandable to think that a higher dose of anticoagulation is necessary, the use of higher doses of anticoagulation does not appear to decrease all-cause mortality (hazard ratio, 0.79, 95% CI, 0.35–1.8).

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