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More on COVID-19 coagulopathy in Caucasian patients

We are grateful for the comments of Marrietta *et al.*[1] and welcome the opportunity to provide further details on the coagulopathy observed in our patients with coronavirus disease 2019 (COVID-19) infection.[2] The weight-adjusted low-molecular-weight heparin (LMWH) thromboprophylaxis used in the study is that routinely used for hospital in-patients in our institution, consistent with national recommendations.[3,4] With respect to the cohort of patients with COVID-19 enrolled in our study, it is important to highlight that 74% of patients received enoxaparin 40 mg (4000 iu) subcutaneously once daily. In 12% of patients, the dose of enoxaparin was reduced to 20 mg once daily due to a weight of < 50 kg (8%) or renal impairment (4%). In all, 11% of our cohort were already on extended-duration therapeutic anticoagulation at time of presentation with COVID-19 for a variety of reasons (including atrial fibrillation, mitral valve replacement, and cancer-associated venous thromboembolism) and consequently were maintained on the same during their admissions. Finally, 2% of patients did not receive thromboprophylaxis due to perceived increased bleeding risks. Of particular importance in respect to the point raised by Marrietta *et al.*[1], only one patient with COVID-19 actually received an enoxaparin dose of > 40 mg for thromboprophylaxis (due to increased body weight of > 100 kg). In summary therefore, the doses of LWMH used in our cohort are entirely consistent with best practice guidelines. In addition, none of our cohort developed any major bleeding or clinically relevant non-major bleeding complications.[5,6]

On the basis of the literature to date, it is clear that severe COVID-19 infection is associated with a predominantly prothrombotic disorder rather than bleeding phenotype. Consequently, like many others in the field, we have significant concerns that standard dose thromboprophylaxis may be not be adequate for some patients with severe COVID-19, and in particular those who require intensive care unit support. This hypothesis is supported by emerging data suggesting that the incidence of thrombotic complications in critically ill patients with COVID-19 may be >30%, even in patients receiving LMWH thromboprophylaxis.[7,8] To date, we have not increased our standard LMWH thromboprophylaxis treatment for patients with COVID-19, although that decision is under constant review. From the literature, it is clear that other centres have already elected to institute increased LMWH doses for selected patients with severe COVID-19 infection. Although the numbers of patients reported to date remains small, the use of higher-dose LMWH has not been associated with increased bleeding (reviewed in Connors and Levy[9]). Thankfully, international trials have been established to compare the pros and cons of therapeutic- *versus* prophylactic-dose LMWH in patients with COVID-19.

As ever, a *one-size-fits-all* approach to anticoagulant therapy will not be applicable for all patients with severe COVID-19 infection. To develop personalised treatment regimes, further insights into the pathophysiology underpinning COVID-19 coagulopathy and vasculopathy are essential. Whether clinical scores [Disseminated Intravascular Coagulation (DIC) and/or Sepsis-Induced Coagulopathy (SIC)] and/or coagulation biomarkers are useful in this setting remains to be defined. We agree entirely with Marrietta *et al.*[1] that the pulmonary intravascular coagulopathy (PIC) terminology advanced by Mc Gonagle *et al.*[10,11] is interesting and intuitively attractive. Additional studies will be necessary to dissect local thrombo-inflammatory responses induced by COVID-19 infection within the lungs. Nevertheless, with the tsunami of new COVID-19 data that continues to be published on a daily basis, it is already clear that the prothrombotic complications of severe COVID-19 are not confined to the microvasculature, or indeed to the lungs. Recent papers have described increased incidence of deep vein thrombosis, myocardial infarction and ischaemic stroke in patients with COVID-19.[7,8,12–16] Moreover, evidence of COVID-19 vasculopathy involving the microvasculature in other tissues has also been described.[17] Further clinical trials and multivariate analyses will be required to establish whether the risk of arterial thrombosis is increased in COVID-19 infection. Interestingly, however, some unusual clinical features have been described with respect to the clinical presentations associated with these complications. For example, ST-segment elevation on electrocardiogram has been reported in

patients with COVID-19 who had no evidence of coronary artery obstruction on angiography, suggesting that other mechanisms may be contributing to myocardial injury.[13–15] Similarly, case reports suggest that ischaemic strokes in COVID-19 may involve multi-territory infarcts and even occur in patients already on therapeutic anticoagulation.[16] Notwithstanding these emerging data, the immuno-coagulopathic changes in severe COVID-19 certainly appear to be unusual in nature. Furthermore, given the findings from autopsy studies,[18–20] it seems probable that disseminated microvascular coagulopathy within the lungs plays an important role in COVID-19 pathogenesis.

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