More on: ‘COVID-19 coagulopathy in Caucasian patients’

We read with interest the report from Fogarty et al.1 about coronavirus disease 2019 (COVID-19) coagulopathy in Caucasian patients. However, we think that some aspects of this report may deserve further attention. The major concern regards the doses of low-molecular-weight heparin (LMWH) used for thromboprophylaxis in this study. Indeed, the authors report on a weight-adjusted dose of enoxaparin higher than that registered in Europe for the prophylaxis of venous thromboembolism (VTE) in hospitalised acutely ill medical patients. We are aware that a pro-thrombotic derangement of the haemostatic system has been found in most severe forms of COVID-19 infections,2 and that this finding negatively affects the prognosis in patients with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pneumonia.3 In these patients, LMWH at doses registered for prevention of VTE, i.e. enoxaparin 4000 iu subcutaneously daily, has been shown to be associated with a reduced risk of death4 and is currently recommended by the World Health Organization, as well as by scientific societies.5–7 LMWH has also been shown to protect glycocalyx from shedding, displaying anti-inflammatory and immunomodulatory properties.8 Of note, in vitro and in vivo experimental studies have shown that human coronaviruses utilise heparin sulphate proteoglycans for attachment to target cells,9 suggesting a role for heparin in the therapeutic armamentarium against COVID-19. It is therefore conceivable that higher doses of LMWH than those used for VTE prevention in acutely ill medical patients, might improve anti-inflammatory activity, mitigate cytokines storm and improve the disease prognosis.

However, evidence is not yet available as to whether higher doses of heparin can improve the prognosis of patients with more severe COVID-19 without affecting the safety related to bleeding.

Relevant to this, it would have been advisable that the authors reported the rate of major bleeding and kidney impairment requiring LMWH dose adjustment in their study population. Pending further evidence, we suggest more caution in suggesting the use LMWH doses higher than those used for VTE prophylaxis, outside of either an established diagnosis of VTE or of a clinical trial.

Moreover, we observe that the coagulopathy was assessed by the International Society for Thrombosis and Hemostasis (ISTH) Scientific and Standardization Committee (SSC) overt Disseminated Intravascular Coagulation (DIC) score. In our opinion, a proper and possibly, more tailored approach would have been to use the more focussed Sepsis Induced Coagulopathy score,10 which has already been adopted in the specific setting of patients with COVID-19.3

This approach would have been advisable in order to strengthen the message conveyed by the authors that the coagulopathy observed in patients with COVID-19 is a quite different pathophysiological entity compared with the classical picture of DIC. Relevant to this, the expression ‘pulmonary intravascular coagulopathy (PIC)’ proposed by the authors fits well with the peculiar clinical and pathological pictures of coagulopathy and severe acute respiratory distress syndrome often observed in SARS-CoV-2 pneumonia.

Future trials will hopefully address the compelling clinical issues related to efficacy and safety of either a more intense anti-coagulation with LMWH or the use of unfractionated heparin in patients with severe COVID-19.

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First published online 22 May 2020
doi: 10.1111/bjh.16772

References
1. Fogarty H, Townsend L, Cheallaigh CN, Bergin C, Martin-Loeches I, Browne P, et al. Coagulopathy in Caucasian patients. Br J Haematol. 2020 [Epub ahead of print]. https://doi.org/10.1111/bjh.16749.
2. Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangkul V, et al. Hypercoagulability of COVID-19 patients in Intensive Care Unit. A report of thromboelastography findings and other parameters of hemostasis. J Thromb Haemost. 2020 [Epub ahead of print]. https://doi.org/10.1111/jth.14850.
3. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18:844–7.
4. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020 [Epub ahead of print]. https://doi.org/10.1111/jth.14817.
5. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected. Interim guidance 28 January 2020. Available at: https://www.who.int/docs/defaultsource/coronaviruse/clinical-management-of-novel-cov.pdf. Accessed April 2020
6. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020;18:1023–6.
7. Marietta M, Ageno W, Antoni A, De Candia E, Gresele P, Marcucci R, et al. COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SIES). Blood Transfus. 2020 [Epub ahead of print]. https://doi.org/10.2450/2020.0083-20.
8. Li X, Ma X. The role of heparin in sepsis: much more than just an anticoagulant. Br J Haematol. 2017;179:389–98.

9. Milewska A, Zarębski M, Nowak P, Stozek K, Potempa J, Pyrc K. Human coronavirus NL63 utilizes heparan sulfate proteoglycans for attachment to target cells. J Virol. 2014;88:13221–30.
10. Iba T, Levy JH, Warkentin TE, Thachil J, van der Poll T, Levi M, et al. Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. J Thromb Haemost. 2019;17:1989–94.

More on COVID-19 coagulopathy in Caucasian patients

We are grateful for the comments of Marrietta et al. and welcome the opportunity to provide further details on the coagulopathy observed in our patients with coronavirus disease 2019 (COVID-19) infection. 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. 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-dose LMWH treatment 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., 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.

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 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. 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). 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. that the pulmonary intravascular coagulopathy (PIC) terminology advanced by Mc Gonagle et al. 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. Moreover, evidence of COVID-19 vasculopathy involving the microvasculature in other tissues has also been described. 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...