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# Hypercoagulable state in COVID-19 with diabetes mellitus and obesity: Is therapeutic-dose or higher-dose anticoagulant thromboprophylaxis necessary?

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*To the Editor,*

Diabetes mellitus (DM) and obesity are independent risk factors associated with severity of Coronavirus disease 2019 (COVID-19) [1–4]. Hypercoagulable state along with impaired immune response and heightened inflammatory response are hypothesized as the underlying mechanism of the unfavorable outcomes in patients with these comorbidities [5–7]. COVID-19 patients with DM are more likely to develop hypercoagulable state as reflected by elevated D-dimer and fibrinogen, and the association is affected by blood glucose control [8,9]. Furthermore, obesity is long known as an established risk factor for thrombosis due to hyperactivity of coagulation factors, hypo-functioning of fibrinolysis, chronic inflammatory state, increased oxidative stress, and endothelial dysfunction [10]. Despite the promising results in reducing mortality among hospitalized patients with severe COVID-19 using standard-dose anticoagulation thromboprophylaxis [11], the incidence of venous thromboembolism (VTE) remains high [12]. This ignites the interest in therapeutic-dose or higher-dose anticoagulant thromboprophylaxis for severe COVID-19 patients with these specific comorbidities.

The optimal dose for anticoagulant thromboprophylaxis in the severe and critically-ill COVID-19 patients remains uncertain with the current available guidelines recommend different approaches [13–15]. The American College of Chest Physicians is suggesting the standard-dose anticoagulant thromboprophylaxis (e.g., enoxaparin 40–60 mg daily SC) in all critically ill COVID-19 patients due to insufficient evidence to justify the higher intensity of thromboprophylaxis [13], while two other guidelines recommend risk stratification in considering higher-dose anticoagulant thromboprophylaxis [14,15]. This is particularly in obese patients (BMI $\geq$ 30 kg/m2) where the intermediate dose of thromboprophylaxis (e.g., enoxaparin 0.5 mg/kg twice-daily SC) is suggested. A more aggressive strategy with therapeutic doses of anticoagulant (e.g., enoxaparin 1 mg/kg twice-daily SC) is proposed by the French guideline in the settings of a marked inflammatory syndrome and/or hypercoagulability (e.g., fibrinogen >800 mg/dl and/or D-dimers concentration to >3 μg/ml) and/or very high-risk features of thrombosis (BMI > 30 kg/m$^2$ with added risk factors for thromboembolism in addition to high-flow nasal oxygen therapy or mechanical ventilation, the use of extracorporeal membrane oxygenation (ECMO), unexplained catheter thrombosis, and dialysis filter thrombosis) [14]. The evidence to support the recommendations on these guidelines is scarce and based mainly on retrospective cohort studies. For instance, there is only one study that assessed the benefit of therapeutic-dose anticoagulation and reported similar in-hospital mortality rates in those patients treated with therapeutic-dose anticoagulation as compared to those who did not receive therapeutic-dose anticoagulation [16]. However, they found a reduced in-hospital mortality rate among mechanically ventilated patients (29.1% vs 62.7%) with comparable bleeding events (3% vs 1.9%).

It is undeniably intriguing to use specific drugs or approaches based on the small evidence especially during this pandemic where physicians are trying to use the best treatment available that they think may save their patients. Although some drugs are seemingly effective [17,18], we should tread carefully. There are several drugs that were initially viewed as promising [19], but turn out to be inefficacious with a higher risk of adverse events. Therefore, until further results of ongoing randomized controlled trials (RCT) emerge, we recommend using standard-dose anticoagulation for routine thromboprophylaxis strategy in all hospitalized COVID-19 patients, while intermediate-dose anticoagulation thromboprophylaxis may be considered in specific circumstances (e.g obese patients) after cautious assessment of bleeding risk.

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## Declaration of competing interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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