Against Therapeutic Anticoagulation in Critically Ill COVID-19 Patients

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There were initially three clear lines of evidence in support of an association between thrombosis and coronavirus disease 2019 (COVID-19), as caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection. First, there was evidence of significant coagulation marker changes in some patients affected by COVID-19, primarily a moderate elevation in D-dimer, increase in fibrinogen levels, mildly prolonged prothrombin time, and some derangements in platelet counts.[1] Second, autopsy studies of patients that suffered fatal COVID-19 showed microthrombi in the lungs, thus demonstrating that the virus leads to a pulmonary coagulopathy, which may become systemic as the disease progresses.[2] Third, there were observational studies showing that there were higher rates of thrombotic complications in these patients, despite thromboprophylaxis.

Single-centered or single-country studies published early in the pandemic reported on the incidence of venous thromboembolism (VTE) in these patients, and as a result, many more studies were published, resulting in systematic reviews and meta-analyses that reported on summative rates of thrombosis. For example, a meta-analysis by Jiménez et al evaluated the totality of over 18,000 patients from among 48 studies, reporting an overall VTE incidence of 17% in hospitalized patients, despite thromboprophylaxis.[3] This is a higher rate than that observed pre-COVID times in hospitalized patients (1–3%). A sub-group analysis based on intensive care unit (ICU) coronavirus disease 2019 (COVID-19) patients alone showed that the thrombotic incidence is much higher in this setting (27.9%, 95% CI 22.1–34.1%), despite the use of thromboprophylaxis.[3] A different meta-analysis by Malas et al showed a VTE incidence of 31% (95% CI, 23–39%) in ICU patients compared with 5% (95% CI, 3–8%) in the non-ICU COVID-19 patient population. Nonetheless, both rates are higher than those observed in non-COVID hospitalized patients. Additionally, thrombosis in ICU COVID-19 patients was shown to increase the odds of mortality by as much as 74% (OR 1.74, 95% CI, 1.01–2.98).[4]

The risk of VTE in critically ill COVID-19 patients was found to range between 16 and 69% in several observational studies.[5–7] While anticoagulation, irrespective of dose used, showed benefit in mortality among ICU COVID-19 patients over no anticoagulation early in the pandemic, subsequent randomized trials have failed to show any benefit of both therapeutic and intermediate dose anticoagulation compared with that offered by prophylactic dose anticoagulation alone in critically-ill patients. Only one randomized controlled trial (RCT) showed a benefit of therapeutic anticoagulation in ICU COVID-19 patients, but it only comprised 20 patients who required mechanical ventilation.[8] These patients were randomized to either receive therapeutic enoxaparin or prophylactic anticoagulation. The therapeutic anticoagulation group had improved gas exchange as measured by arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2), had more ventilator-free days, and higher ratio of successful liberation from mechanical ventilation.

The INSPIRATION study[9] evaluated intermediate dose anticoagulation in a multicenter, open-label, RCT of 562 severely-ill COVID-19 patients admitted to the ICU, where low-molecular-weight heparin (LMWH) (enoxaparin 1 mg/kg daily or 0.6 mg/kg twice daily) was compared with standard prophylactic anticoagulation (enoxaparin 40 mg daily). At 30 days, there was no difference in primary outcome of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality. In another open-label RCT, Perepu et al[10] looked at intermediate dose anticoagulation compared with standard dose in 173 hospitalized patients (mostly ICU). There was no difference

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between intermediate and standard dose regarding all-cause mortality at 30 days.

The Multiplatform Randomized Clinical Trial group study, a collaboration between three publicly-funded trial platforms (ATTACC, ACTIV-4a, REMAP-CAP), evaluated therapeutic dose anticoagulation with heparin (unfractionated heparin [UFH] or LMWH) compared with thromboprophylaxis doses.[11] Therapeutic dose anticoagulation failed to show an increase in probability of survival and organ-free support days until the end of study (day 21). A signal for major bleeding was reported for the therapeutic dose anticoagulation group (3.8 vs. 2.3% in the usual care thromboprophylaxis group), whereas major thrombotic events were less frequent (6.4 vs. 10.4% in the usual care thromboprophylaxis group).

Additionally, in the HEP-COVID study,[12] 41,257 patients with COVID-19 and D-dimer levels more than four times the upper limit of normal or sepsis-induced coagulopathy score of 4 or greater were randomized to either standard prophylactic or intermediate dose LMWH or UFH versus therapeutic dose LMWH throughout hospitalization. As with other trials, the 72 patients in the ICU stratum did not have any benefit from therapeutic anticoagulation (risk ratio [RR], 0.89 [95% CI, 0.60–1.33]; $p = 0.56$) while there was a very large (but not statistically significant) increase in major bleeding (RR, 7.63 [95% CI, 0.43–136.69]; $p = 0.12$).

Based on the above data, there is a general consensus among society guidelines[13–18] about the use of only standard prophylactic dose of anticoagulation in critically ill patients admitted to the ICU with COVID-19 disease unless absolutely contraindicated due to high bleeding risk. LMWH is recommended over UFH because of less frequent patient interaction for dosing. It should also be noted that patients in the ICU with conditions warranting the use of therapeutic anticoagulation (e.g., atrial fibrillation or known VTE events) were excluded from these trials and should be treated with therapeutic anticoagulation as indicated.

In conclusion, while therapeutic LMWH is associated with improved outcomes in hospitalized COVID-19 patients who are not critically ill, particularly those with high D-dimer levels, a review of data suggests that patients who are critically ill and/or in the ICU do not benefit from therapeutic anticoagulation and in turn may have an increased risk of bleeding complications. Thus, in these patients, standard prophylactic dose of anticoagulation is recommended.

Conflict of Interest
None declared.

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