Anticoagulant management of COVID-19 patients with thrombotic complications

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BACKGROUND

SARS-CoV-2 (COVID-19), caused by the respiratory syndrome-coronavirus-2, has resulted in more than 674 million cases and caused more than 6.7 million deaths worldwide, with numbers still increasing every day. COVID-19 has been associated with thromboembolic disease, a common and potentially very serious manifestation. A few randomized and observational studies have investigated whether full-dose anticoagulation may improve outcomes compared with prophylactic dose heparin. Clinical, laboratory, and autopsy findings have found a close association between COVID-19 and thromboembolic disease.

METHODS

Effective strategies for treatment and prevention of the disease remain of paramount importance. We reviewed the recent literature for the use of anticoagulant therapies in COVID-19 patients and attempted to present AC Forum findings. A few details of the ongoing Anticoagulation trial, with 3,600 COVID-19 hospitalized patients not requiring ICU care and randomized to prophylactic-dose enoxaparin vs therapeutic-dose enoxaparin vs therapeutic dose apixaban, are also presented.

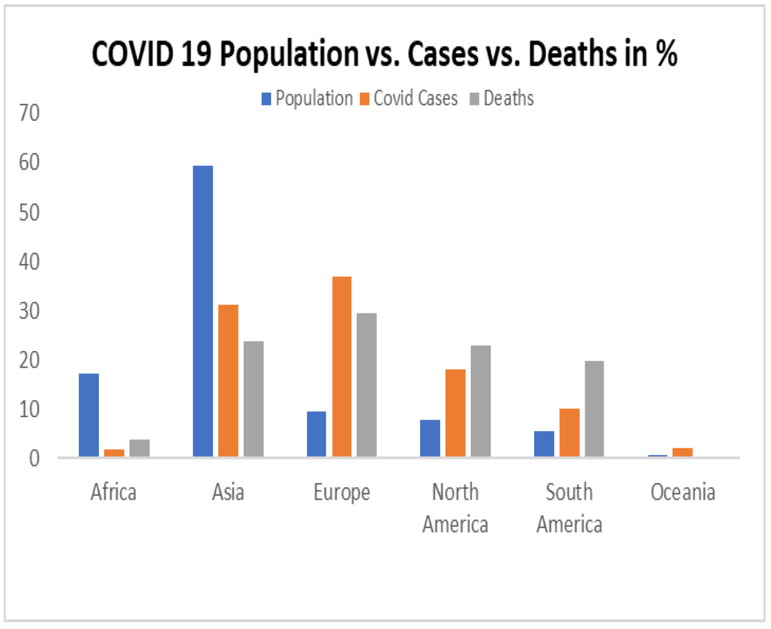

Figure 1: COVID-19 data from different continents

RESULTS

Acute COVID-19 infection is characterized by mononuclear cell reactivity and pan endothelialitis, contributing to a high incidence of thrombosis in large and small blood vessels, both arterial and venous. Therapeutic anticoagulation with LMWH or UFH is associated with improved outcomes in hospitalized patients with COVID-19 who are not critically ill or in the ICU setting. Patients who are critically ill in ICU do not benefit from therapeutic anticoagulation manifesting an increased risk for bleeding compared with patients receiving prophylactic dose. The beneficial effect of therapeutic anticoagulation is diminished, and the risk of hemorrhage is increased in patients with progressive severe disease. Clinical, laboratory, and autopsy findings support an association between coronavirus disease-2019 (COVID-19) and thromboembolic disease. These studies revealed that prophylactic-dose enoxaparin improves freedom from intubation and survival in hospitalized patients with COVID-19. The stages of therapeutic interventions are illustrated in Figure 2.

Mount Sinai Hospital Study Findings

- An observational study (N = 4,389): Link between in-hospital administration of anticoagulation and reduction in the risks of mortality
- More pronounced benefits with therapeutic as opposed to prophylactic dosing.
- Apixaban proved to be beneficial over LMWH.

ACForum findings/recommendations

- COVID-19 patients are at increased risk of VTE, and pharmacologic prophylaxis for hospitalized patients is recommended.
- Post-hospital pharmacologic prophylaxis be used selectively for patients at highest risk for VTE.
- Testing for anti-Xa assay considered over aPTT to monitor UFH dosing.
- A 3 month course of anticoagulation for patients with hospital associated VTE.

FREEDOM COVID ANTICOAGULATION TRIAL (Figure 3)

- Large-scale, prospective, open-label, randomized controlled comparative safety and effectiveness study enrolling patients in the United States, Central and South America, Europe and India.
- Enrol COVID-19 hospitalized patients not requiring ICU care that have been randomized to prophylactic-dose enoxaparin vs therapeutic-dose enoxaparin vs therapeutic dose apixaban.
- The primary objective is to determine whether therapeutic doses of enoxaparin or apixaban are superior to a prophylactic dose of enoxaparin in reducing the composite incidence of all-cause mortality, need for ICU level of care, systemic thromboembolism, or ischemic stroke at 30 days after randomization.

Strengths of FREEDOM Trial

- Adequately powered
- Significant representation from major continents
- No reliance on symptom event severity
- Find if apixaban is superior to enoxaparin

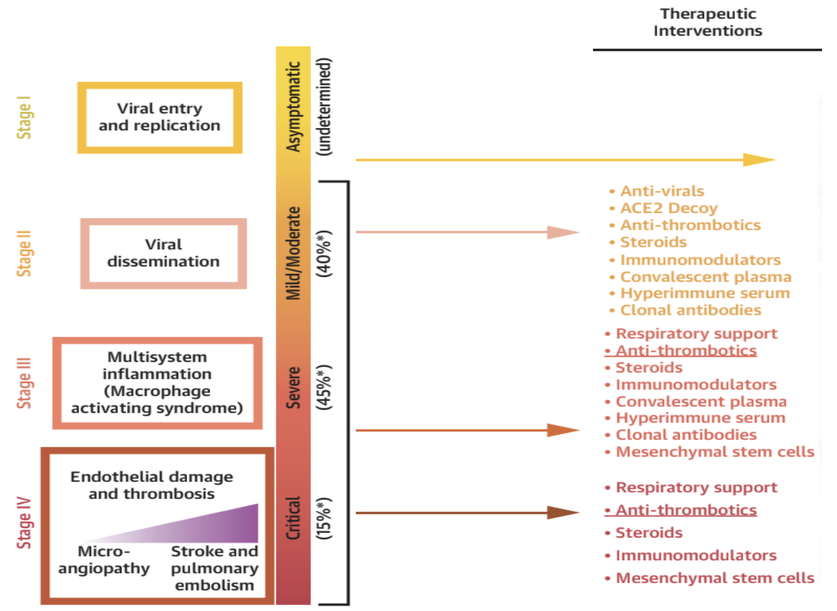

Figure 2: Stages of therapeutic interventions (From Farkouh, Fuster et al, 2022)

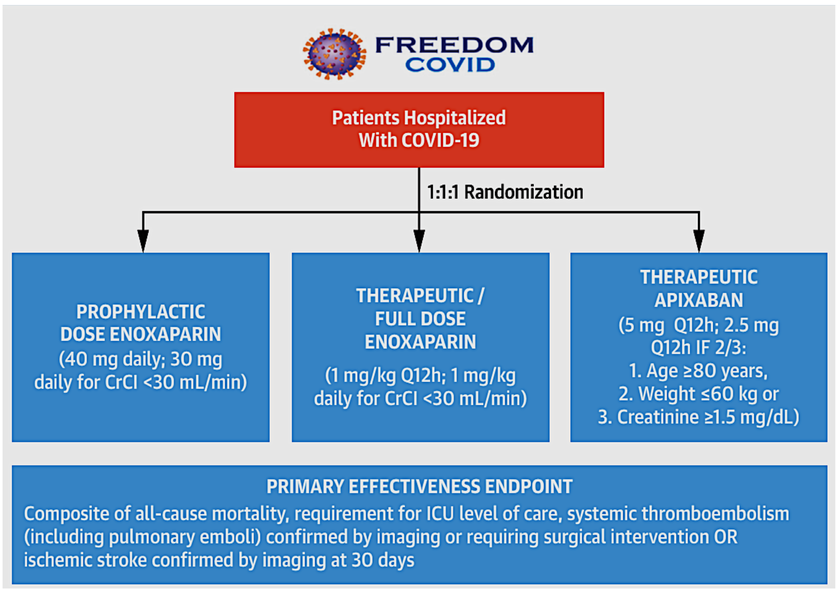

Figure 3: FREEDOM TRIAL (N=3600)

DISCUSSION / CONCLUSIONS

COVID-19 infection is characterized by mononuclear cell reactivity and pan endothelialitis contributing to a high incidence of thrombosis in large and small blood vessels and the outcomes following thrombotic complications could be improved by appropriate anticoagulation. The FREEDOM COVID-19 trial is expected to provide evidence if therapeutic doses of enoxaparin or apixaban are superior to a prophylactic dose of enoxaparin in reducing the composite incidence of all-cause mortality. Therapeutic anticoagulation with LMWH or UFH is associated with improved outcomes in hospitalized patients with COVID-19 who are not critically ill or in the ICU setting. Patients who are critically ill, do not benefit from therapeutic anticoagulation and manifest an increased risk for bleeding compared to patients on prophylaxis. The beneficial effect of therapeutic anticoagulation is diminished, and the risk of hemorrhage is increased.