Thrombotic Events in COVID-19 Patients Not Requiring Hospitalization at the Time of Diagnosis

Background

COVID-19-associated coagulopathy (CAC) is an emerging phenomenon. The role of anticoagulation in treating CAC on the outpatient basis is currently being investigated in ACTIV-4B, a randomized clinical trial (RCT) funded by the National Institutes of Health (NIH). The primary endpoint is a composite of: deep venous thrombosis [DVT], pulmonary embolism [PE], arterial thromboembolism, myocardial infarction [MI], ischemic stroke [IS], hospitalization for other pulmonary events (i.e. hypoxemia, hypoxemic respiratory failure, ARDS), and all-cause mortality at 45 days among patients with both elevated hs-CRP/CRP and elevated d-dimer. Investigators assumed that the primary outcome would occur in 4-12% of the control group for the purposes of sample size calculation. However, there is uncertainty regarding whether this estimation reflects real-world occurrence.

Objective

To inform future sample size calculations pertaining to thrombosis in CAC, we describe occurrence of thrombotic events and death among patients aged 40-79 years not hospitalized at the time of COVID-19 identification.

Methods

We used electronic health record (EHR) data from 64 health care organizations (including inpatient and outpatient data), provided through the TriNetX Live™ platform in their USA network to identify COVID-19 cases in the outpatient setting from 2/20/2020 through 9/11/2020. The index date for each patient was the first date of positive COVID-19 antigen or PCR laboratory test or documented COVID-19 diagnosis (ICD-10 B97.29, U07.1, B34.2, B97.2, J12.81). To align with the RCT protocol, patients were excluded for: intracranial hemorrhage, ischemic stroke, bronchiectasis, or cancer in the 30 days prior; pregnancy in the 84 days prior; use of antithrombotic therapy from 183 to 2 days prior; and concurrent use of strong p-gp or CYP3A4 inhibitors or inducers. We assessed DVT, PE, MI, ischemic stroke or death in the inpatient and any care setting at 45 days post-index using ICD-10 codes from previous Sentinel analyses. Arterial thromboembolism (other than IS and MI) was not included because no known validated algorithms exist. Hospitalization for other pulmonary events were not included because the focus was on thrombotic events. We report occurrence of the primary outcome both overall and stratified by hs-CRP/ CRP (elevated defined as >10 mg/L) and d-dimer (elevated defined as >500 ng/mL for FEU or >250 ng/mL for DDU) levels up to one week post-index. To describe the real-world use of anticoagulation in outpatient-identified COVID-19, we also report the number of patients treated with anticoagulants on the same day or the day after index.

Results

89,640 non-hospitalized COVID-19 patients met the inclusion/exclusion criteria (mean age 55 years, 56% female). Overall, 0.6% and 1.0% of the sample experienced DVT, PE, MI, ischemic stroke or any-setting death in the inpatient and any care settings, respectively. A large majority of patients did not have hs-CRP/CRP or d-dimer data available (>95%), but we did identify 0.7% (n=590) of the sample with both elevated hs-CRP/CRP and elevated d-dimer. Among those, 3.4% and 6.8% developed DVT, PE, MI, ischemic stroke or died in the inpatient and any care setting, respectively. Approximately 3.7% of included patients (n=3,310) initiated treatment with any anticoagulant, antiplatelet, or thrombolytic on the same day or the day after index.

Limitations

Similar to all EHR data, we were unable to capture events occurring outside of the HCOs providing data, which may have resulted in underestimation of outcomes. However, because the TriNetX Live™ platform rounds all counts to the higher multiple of 10 to protect patient privacy, overestimation of the primary outcome is also possible. The unadjusted nature of this analysis means that confounding by indication may be present if patients at higher risk for CAC (especially those with elevated CRP and/or d-dimer) were anticoagulated shortly after index. Additionally, missing laboratory data was likely not at random. Finally, the sample was comprised of individuals who were relatively young and had a slightly higher proportion of females than males, which may limit comparisons to other studies.

Conclusions

Among adults aged 40-79 years with COVID-19 identified in the outpatient setting and both elevated d-dimer and hs-CRP/CRP, approximately 3.4% and 6.8% experienced DVT, PE, MI, ischemic stroke or death in the inpatient and any care setting, respectively. The proxy outcome in this study is similar to the outcome explored in the trial, with the exception that arterial thromboembolic events other than MI and stroke and specific pulmonary events were not included. These findings are comparable to the 4-12% estimation used to inform sample sizes in the RCT.