Letter to the Editor

Is prior antithrombotic use protective against COVID-19 infection? A cross-sectional study of the University of California Health patient population

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As COVID-19 infection rates rise worldwide and hospital capacities fall nationwide, increased attention is focused on determining who is most at risk for severe disease (1). While some patients are asymptomatic or have mild symptoms when diagnosed with a COVID-19 infection, those who are older, males, or have pre-existing comorbidities (obesity, cardiovascular disease, diabetes, or pulmonary disease) are at increased risk of severe COVID-19 and have higher mortality rates (2). This population overlaps significantly with patients who are taking antithrombotics; since they are typically older and have comorbidities (coronary artery disease, atrial fibrillation, venous thromboembolism, cerebral vascular attack, or peripheral artery disease) that further increase their risk of severe COVID-19. COVID-19 has been associated with a prothrombotic state, leading to increased risk of microvascular thrombosis, arterial, or venous thromboembolic disease. In critically ill patients, in addition to causing acute respiratory distress syndrome, COVID-19 results in a hypercoagulable state, with extensive thrombosis of the small vessels of the lungs, causing diffuse alveolar damage, and extrapulmonary organs (3,4). Coagulation factor X (FX) is a serine protease that is synthesized by the liver, with increased levels reported in patients with cardiopulmonary disease. Interestingly, these FX levels have resulted in an increased tendency to have higher infection rates, increased coagulation and inflammation activation, and fibrosis development (2). Over the past year, preliminary observations on anticoagulant therapy show an association with better outcomes in moderate and severe COVID-19 patients who require mechanical ventilation and have signs of coagulopathy. The use of various regimens of antithrombotics in disease management has been implemented; however, the benefit of prior use of antithrombotic medications has not been fully elucidated. We investigate whether patients with prior antithrombotic use for pre-existing conditions influences COVID-19 infection rates or disease mortality in a California-based population.

This cross-sectional study utilized the University of California COVID-19 Research Data Set (UC CORDS), a HIPAA-limited database of medical records for patients tested for COVID-19 across UC medical centers (5). Information regarding patient demographics, COVID-19 testing results, and mortality rates after COVID-19 testing

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Table 1 COVID-19 positive test rate and mortality rate of patients within the UC CORDS and those with antithrombotic use for at least 14 days prior to COVID-19 testing March 2020 to Oct 8, 2020

Antithrombotics	COVID-19 (+) test			COVID-19 (+) mortality^{+++}		
	Taking an antithrombotic, n (%)	Control^{+}, n	P value^{++}	Taking an antithrombotic, n (%)	Control^{+}, n	P value^{++}
Apixaban	196 (2.40%)	11,161 (3.75%)	<0.00001	31 (15.82%)	254 (2.28%)	<0.00001
Aspirin	1,288 (2.99%)	10,069 (3.83%)	<0.00001	107 (8.31%)	178 (1.77%)	<0.00001
Clopidogrel	250 (3.10%)	11,107 (3.73%)	0.0034	28 (11.20%)	257 (2.31%)	<0.00001
Enoxaparin	948 (3.75%)	10,409 (3.71%)	0.7073	85 (8.97%)	200 (1.92%)	<0.00001
Heparin	1433 (3.27%)	9,924 (3.79%)	<0.00001	147 (10.26%)	138 (1.39%)	<0.00001
Rivaroxaban	99 (2.38%)	11,258 (3.73%)	<0.00001	11 (11.11%)	274 (2.43%)	<0.00001
Warfarin	150 (2.88%)	11,207 (3.73%)	0.0014	19 (12.67%)	266 (2.37%)	<0.00001

$^{+}$, UC CORDS COVID-19 positive patients not taking an antithrombotic; $^{++}$, statistical analysis of those with antithrombotic use compared to those without antithrombotic use using Chi-squared tests; significant if P<0.05; $^{+++}$, death any time after COVID-19 positive test. UC CORDS, University of California COVID-19 Research Data Set.

were collected from March 8 to October 8, 2020. Data on patients taking common antithrombotic medications at least 14 days prior to COVID-19 testing (to ensure prior use) were collected, including: aspirin, clopidogrel, apixaban, heparin, enoxaparin, rivaroxaban and warfarin. Chi-squared tests were used for statistical analysis.

A total of 305,981 patients were tested within UC CORDS, with a 3.71% COVID-19 positive test rate (n=11,357, 48% men, average age 42). Significantly lower COVID-19 infection rates were noted among patients on antithrombotic medications, in comparison to those not taking antithrombotics, except enoxaparin (*Table 1*). The lowest COVID-19 infection rate was noted with rivaroxaban at 2.38% (n=99, 62% men, average age 62, P<0.00001) (Figure S1). Patients on enoxaparin had a 3.75% positive test rate (n=948, 53% men, average age 56), which was not significantly different from those not taking enoxaparin (P=0.7073).

The overall UC CORDS mortality rate of COVID-19 positive patients was 2.51% (n=285, 61% men, average age 70) (*Table 1*). COVID-19 positive patients on any antithrombotic had significantly higher mortality rates compared to those not taking antithrombotics; with patients on apixaban having the highest mortality rate at 15.82% (n=31, 58% men, average age 77, P<0.00001) and those on aspirin having the lowest mortality rate at 8.31% (n=107, 67% men, average age 74, P<0.00001).

In this UC CORDS dataset, prior antithrombotic use was not associated with improved mortality rates after COVID-19 infection. However, COVID-19 infection rates were lower, suggesting a potential protective effect. COVID-19 is associated with a progressive inflammatory cytokine storm and coagulation dysfunction. Anticoagulants, such as heparin, enoxaparin, and apixaban, have associated anti-inflammatory effects and known ability to block viral action through inhibiting host cell proteases (6). In particular, heparin has been shown to have significant binding affinity to the spike protein (S-protein) of SARS-CoV-2 *in-vitro*, suggesting viral infection inhibition (7). Furthermore, numerous studies have shown that systemic anticoagulation with therapeutic heparin can reduce mortality in mechanically ventilated patients (6). While infection rates are reduced, the increased mortality rate is likely related to the overall older patient population. Similarly, underlying comorbidities play a role; however, these were not accounted for in the study due to the comprehensive de-identified database. Limitations include a small sample size on antithrombotics, generalizability of results due to patients solely within a California-based population, use of deidentified, tertiary center data which lacked clinical details including confounding variables (medication dose and frequency, exact cause of death, age, BMI, patient comorbidities, and use of dual anticoagulant and anti-platelet therapy) and ability to determine statistical significance between average ages of each group, or longitudinal follow-up. Future studies with identifiable

data may better elucidate the connection between antithrombotics and COVID-19.

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Footnote

Provenance and Peer Review: This article was a standard submission to the journal. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://aob.amegroups.com/article/view/10.21037/aob-21-75/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

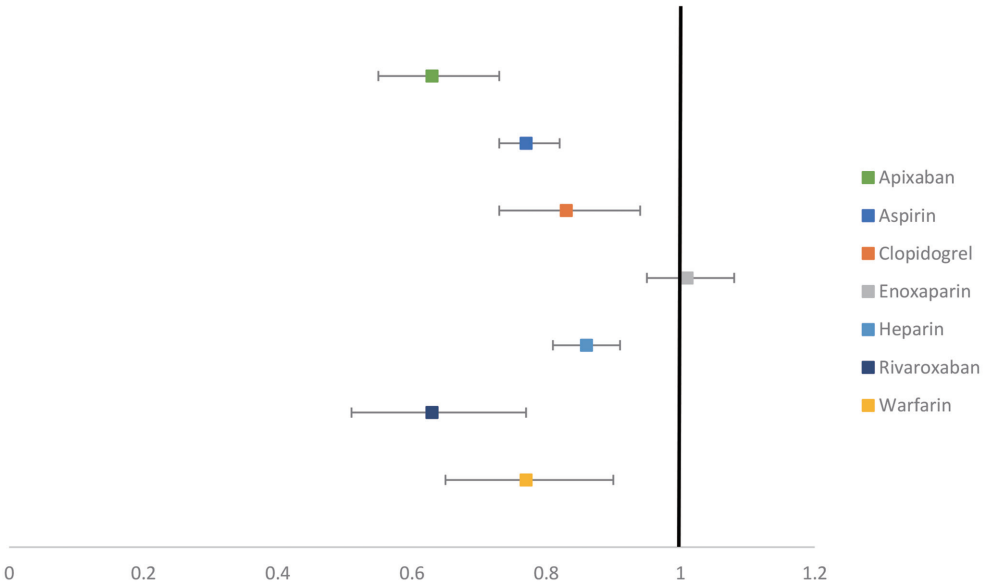

Figure S1 Forest plot of odds ratios (OR), lower confidence intervals, and upper confidence intervals of COVID-19 infection rates for UC CORDS patients on antithrombotics.

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