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Increased Mortality in Antecedent Combined Renin–Angiotensin System Inhibitors and Antiplatelets Compared With Antiplatelets Alone in Hospitalized Patients With COVID-19

To the Editor:

Novel coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) has resulted in a high-mortality pandemic. Angiotensin-converting enzyme 2 (ACE2) promotes systemic vasodilation and has anti-inflammatory effects.[1] ACE2 also serves as a receptor for SARS-CoV2 viral entry into the host cells.[2] Some studies suggest that inhibitors of the renin–angiotensin system (RAS) including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers increase ACE2 expression in the lung, heart, and kidney tissues[3,4]; however, another study suggests the opposite.[5] With initial speculation that RAS inhibitors may worsen clinical outcomes in patients with COVID-19, a study from Italy showed that patients taking prehospital RAS inhibitors had a reduced risk of inpatient death.[6]

SARS-CoV-2 infection is associated with platelet hyperreactivity that is independent of ACE2 receptors because these receptors are not detected on platelets.[7] Platelet activation likely contributes to the thromboinflammation in COVID-19, and the inhibition of pathways related to their activation can possibly improve the outcomes during COVID-19 infection.[8] However, the benefit of prehospitalization usage of low-dose aspirin remained uncertain.[9–11] The outcomes of combined RAS inhibitors and antiplatelets are not well studied, and to the best of our knowledge, there is no study on the outcomes of hospitalized patients with COVID-19 who were taking both RAS inhibitors and antiplatelets compared with antiplatelets alone. Therefore, in this study, we aimed to assess the outcomes of patients taking both RAS inhibitors and antiplatelets before hospitalization.

This is a retrospective, multi-institutional (8 trinity health system hospitals) cohort study of patients older than 18 years admitted to Saint Joseph Mercy Health System hospitals between March 10, 2020, and May 3, 2020, with polymerase chain reaction proven SARS-CoV-2 infection. The study protocol was approved by the Saint Joseph Mercy Oakland Institutional Review Board; individual patient consent was waived. A broad spectrum of variables was collected, including baseline demographic characteristics (age, sex, race, and social history), comorbid conditions (coronary artery disease, heart failure, atrial fibrillation [AFib], hypertension, diabetes mellitus [DM], pulmonary disease, chronic kidney disease [CKD], autoimmune disease, and cancer), and maximum oxygen requirement. Group 1 was defined as prehospital antiplatelet usage alone, and group 2 was defined as prehospital RAS inhibitors and antiplatelet usage. The primary outcome was mortality within 90 days. The secondary outcomes were readmission rate, intensive care unit (ICU) admission rate, and intubation rate. Categorical

variables were reported as frequencies, and continuous variables as mean ±SD or median. For comparisons of continuous variables, the Student *t*-test was used; for categorical variables, the χ^2 test was used. Multivariable logistic regression was performed to identify independent predictors of 90-day mortality. Survival curves were generated using the Kaplan–Meier method and compared by using the log-rank statistic. All analyses were performed using R version 1.2.1335. All tests were two-sided with $P < 0.05$ indicating statistical significance.

A total of 144 patients were included in the analysis, 53.8% were male. 66.1% were African American, 26.6% White, and 6.9% other ethnicities. The mean body

Table 1. Baseline characteristics of patients admitted with COVID-19, stratified into 2 groups: those using antiplatelets and those using antiplatelets with ACEI.

	Antiplatelets only (N = 103)	Antiplatelets + home ACEI (N = 41)	*P*	Effect size (CI)
Age				
Mean (SD)	75 (13)	74 (14)	0.81	0.078 (−0.29 to 0.44)
BMI				
Mean (SD)	27 (9)	29 (6.8)	0.054	−0.19 (−0.56 to 0.18)
Race				
Not Hispanic	91% (94)	93% (38)	0.9	0.039 (0 to 0.2)
Hispanic	1.9% (2)	2.4% (1)		
Unknown	6.8% (7)	4.9% (2)		
Sex				
Male	44% (45)	59% (24)	0.15	0.55 (0.25 to 1.2)
ICU admission	14% (14)	17% (7)	0.79	1.3 (0.41 to 3.8)
Intubation	13% (13)	7.3% (3)	0.54	0.55 (0.095 to 2.2)
Oxygen support	74% (76)	73% (30)	1	0.97 (0.4 to 2.4)
Mortality in 3 mo	25% (26)	44% (18)	**0.046**	2.3 (1 to 5.3)
Hypertension	84% (87)	93% (38)	0.3	2.3 (0.61 to 13)
Diabetes mellitus	35% (36)	59% (24)	**0.016**	2.6 (1.2 to 5.9)
Cerebrovascular accidents	25% (26)	27% (11)	1	1.1 (0.43 to 2.6)
COPD	23% (24)	12% (5)	0.2	0.46 (0.13 to 1.4)
Asthma	3.9% (4)	4.9% (2)	1	1.3 (0.11 to 9.3)
Obstructive sleep apnea	12% (12)	17% (7)	0.55	1.6 (0.48 to 4.7)
Smoking				
Never	30% (31)	37% (15)		
Former	35% (36)	29% (12)	0.84	0.076 (0 to 0.24)
Current	15% (15)	12% (5)		
Unknown	20% (21)	22% (9)		
Chronic kidney disease	39% (40)	27% (11)	0.24	0.58 (0.23 to 1.4)
Coronary artery disease	41% (42)	49% (20)	0.49	1.4 (0.62 to 3)
Deep vein thrombosis	7.8% (8)	4.9% (2)	0.8	0.61 (0.061 to 3.3)
Pulmonary embolism	2.9% (3)	0% (0)	0.65	0 (0 to 6.1)
History of AFib	16% (16)	20% (8)	0.74	1.3 (0.44 to 3.6)
Malignancy	15% (15)	17% (7)	0.9	1.2 (0.38 to 3.5)
New PE	3.9% (4)	4.9% (2)	1	1.3 (0.11 to 9.3)
New stroke	2.9% (3)	7.3% (3)	0.46	2.6 (0.34 to 20)
MI during hospitalization	1.9% (2)	2.4% (1)	1	1.3 (0.021 to 25)
New-onset AFib	5.8% (6)	4.9% (2)	1	0.83 (0.079 to 4.9)

P values in bold statistically significant (<0.05).
MI, myocardial infarction.

mass index (BMI) was 33.2 ± 8.8 kg/m^2, and 54.0% of patients were nonsmokers (Table 1). One hundred three patients had prehospital antiplatelet usage (group 1) only, whereas 41 patients had combined antiplatelet and RAS inhibitor usage (group 2). The mean age for group 1 was 75 + 13 years and 74 + 14 years in group 2. The mean BMI for 2 groups were 27 + 9 and 29 + 6.8, respectively, (P = 0.25, odds ratio [OR]: −0.19, 95% confidence interval [CI] [0.56–0.18]). Thirty-five percent of patients in group 1 and 59% in group 2 were diabetic (P = 0.016, OR: 2.6, 95% CI [1.2–5.9]. The multivariable logistic regression model showed that age, hospital length of stay, intubation status, oxygen requirement, history of AFib, and myocardial infarction during hospitalization were independently associated with higher mortality (see **Supplementary Table 1**, **Supplemental Digital Content 1**, http://links.lww.com/AJT/A100). The 90-day mortality rate of group 1 and group 2 was 25% (n = 26) versus 44% (n = 18) (P = 0.046, OR: 2.3, 95% CI [1–5.3]). The ICU admission rate was 14% versus 17% (P = 0.79, OR: 1.3, 95% CI [0.41–3.8]), and the rate of intubation was 13% versus 7.3% (P = 0.54, OR: 0.55, 95% CI [0.095–2.2]). The Kaplan–Meier plots demonstrated that the risk of mortality was different between 2 groups (P < 0.05, OR: 2.303, 95% CI [1.003–5.286]) (Figure 1).

Angiotensin-converting enzyme 2 (ACE2) serves as a receptor for both SARS-CoV-1 and SARS-CoV-2. Researchers have raised the concerns that the use of Renin-angiotensin-aldosterone-system inhibitors could be associated with a higher risk of infection. In addition, COVID-19 infection is well-known to increase predisposition to hypercoagulability, resulting in thromboinflammation in patients. Some studies suggest that patients with COVID-19 taking antiplatelets had less severe infection, whereas others showed no beneficial effect of antiplatelets. We compared patients taking only antiplatelets (group 1) with those taking both RAS inhibitors and antiplatelets (group 2). Group 2 had a significantly higher mortality in 90 days. It could be possibly explained by the increased expression or activation of some receptors on platelets worsening the thromboinflammation systemically. However, patients who were on RAS inhibitors may have more comorbidities such as CKDs, hypertension, and DM with complications such as proteinuria. The logistic regression model indicated that only age, hospital length of stay, mechanical ventilation, oxygen requirement, hypertension, history of AFib, and acute myocardial infarction during hospitalization were independent predictors for 90-day mortality in all groups after adjusting for hypertension, diabetes, CKD, and DM. The model however showed that neither the use of antiplatelets nor combination of antiplatelets and RAS inhibitors was the independent predictor of mortality.

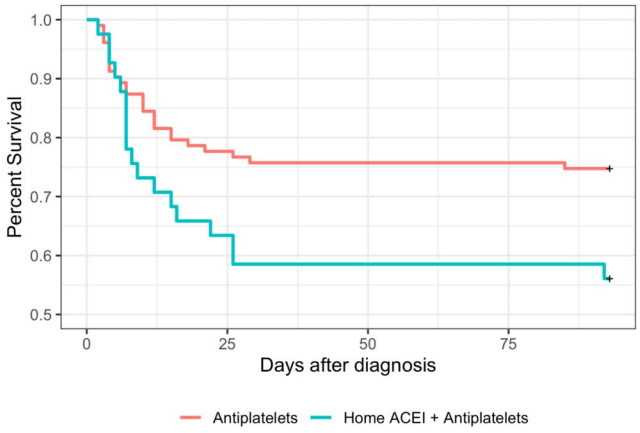

FIGURE 1. Kaplan–Meier curve for 90-day mortality. Group 1 (red) was defined as prehospital antiplatelet usage only, and group 2 (green) was defined as prehospital RAS inhibitor and antiplatelet usage. The odds ratio for 90-day mortality was 2.303126, 95% CI [1.0037–5.2860], P value = 0.04395 comparing group 1 with group 2.

Consistent with international society recommendations and clinical trials, we suggest continuing renin–angiotensin system inhibitor therapy in patients admitted to hospital with COVID-19[12,13] because several cardiac-related comorbidities including hypertension and acute myocardial are independent factors for higher mortality themselves. Further clinical trials and, more importantly, translational research is needed to investigate the causal inference on antecedent usage of antiplatelets and/or RAS inhibitors in patients with COVID-19.

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Cisatracurium-Associated Malignant Hyperthermia During Severe Sars-CoV-2 Infection

To the Editor:

Malignant hyperthermia (MH) is an uncommon but potentially life-threatening pharmacogenetic disorder that affects skeletal muscles. It is seen in response to volatile anesthetic agents and depolarizing neuromuscular blocker (NM blocker), succinylcholine. MH occurrence with a nondepolarizing NM blocker is a very rare phenomenon. Here, we report a case of cisatracurium-induced MH in an intensive care setting.

A 60-year-old gentleman with a medical history significant for dyslipidemia and solitary kidney was hospitalized because of worsening shortness of breath. He tested positive for SARS-CoV-2 6 days before presentation. His vitals on presentation: oxygen saturation of 92% on heated high flow nasal cannula with FiO2 60%, blood pressure 130/80 mm Hg, heart rate 95/min, and respiratory rate 48/min. Physical examination was unremarkable except for coarse breath sounds. Computed tomography angiogram of the chest was negative for pulmonary embolism; however, it showed extensive bilateral ground-glass airspace opacities. He was started on dexamethasone, remdesivir, and broad-spectrum antibiotics. His respiratory distress worsened,