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Outcomes Associated with the Use of Renin-Angiotensin-Aldosterone System Blockade in Hospitalized Patients with SARS-CoV-2 Infection

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Abstract

Background Data regarding the benefits or harm associated with the continuation of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), especially the effect on inflammation, in patients who are hypertensive and hospitalized with coronavirus disease 2019 (COVID-19) in the United States are unclear.

Methods This is a single-center cohort study of patients sequentially hospitalized with COVID-19 at Stony Brook University Medical Center from March 7, 2020 to April 1, 2020, inclusive of these dates. Data collection included history of known comorbidities, medications, vital signs, and laboratory values (at admission and during the hospitalization). Outcomes include inflammatory burden (composite scores for multiple markers of inflammation), AKI, admission to the intensive care unit (ICU), need for invasive mechanical ventilation, and mortality.

Results Of the 300 patients in the study cohort, 80 patients (27%) had history of ACEI or ARB use before admission, with 61% (49/80) of these patients continuing the medications during hospitalization. Multivariable analysis revealed that the history of ACEI or ARB use before hospitalization was not associated with worse outcomes. In addition, the continuation of these agents during hospitalization was not associated with an increase in adverse outcomes and predicted fewer ICU admissions (odds ratio, 0.25; 95% CI, 0.08 to 0.81) with a decrease in the severity of inflammatory burden (peak C-reactive protein, 6.9±3.1 mg/dl, $P=0.03$; peak inflammation score, 2.3±1.1 unit reduction, $P=0.04$).

Conclusions Use of ACEI or ARBs before hospitalization was not associated with adverse outcomes in COVID-19, and the therapeutic benefits of continuing ACEI or ARB in patients hospitalized with COVID-19 was not offset by adverse outcomes.

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Introduction

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) originated in Wuhan, China, and has become a pandemic that spans multiple countries (1,2). Several recent studies have demonstrated that hypertension is highly prevalent among individuals with COVID-19, with an increased association in morbidity and mortality among patients hospitalized with COVID-19 (X. Zhao, B. Zhang, P. Li, C. Ma, J. Gu, P. Hou, Z. Guo, H. Wu, Y. Bai: Incidence, clinical characteristics and prognostic factor of patients with COVID-19: a systematic review and meta-analysis, 2020; doi:10.1101/2020.03.17.20037572). Two classes of medications widely used to treat hypertension are angiotensin-converting enzyme (ACE) inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) and they block the renin-angiotensin-aldosterone system (RAAS). Their use in patients with COVID-19 has been controversial, because SARS-CoV-2 uses ACE2 as a receptor for entry into the cell *via* its spike protein (3–6), leading to organ inflammation and injury (7). ACE2 mediates salutary effects by reducing inflammation and fibrosis through generation of angiotensin 1-9 and angiotensin 1-7, which counter the proinflammatory and profibrotic effects mediated by the classic angiotensin II (AngII) and its receptor angiotensin II type 1 receptor (AT1R) (7,8). It is postulated that, during normal homeostasis, AT1R is bound to ACE2 but when AngII levels are elevated, such as during lung infection with SARS-CoV-2, AngII binds to AT1R, and might lead to dissociation of ACE2, enabling viral entry and eventual cell injury (9). However, these ideas were based on cell culture and *in vivo* studies (9). Although there is concern that ACEIs or ARBs might upregulate the expression of ACE2 (10), leading to increased virulence, an alternate hypothesis exists in which these medications might mitigate viral entry by

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binding to AT1R, preventing displacement of ACE2, and hence reducing viral entry (9,11).

Individuals with preexisting cardiovascular disease are reported to have worse outcomes in the setting of COVID-19, especially those with hypertension and heart failure (12–15). This elevated morbidity and mortality in patients with COVID-19 raises the possibility that upregulation of ACE2 expression may lead to increased SARS-CoV-2 virulence (10). Several retrospective studies report that the use of ACEI/ARBs does not increase the incidence of COVID-19 or mortality and might also lower the levels of IL-6 production and peak viral load in patients (16–19), whereas a recent study from China demonstrated a potential reduction in mortality with the use of ACEI/ARBs in COVID-19 (20). However, it remains unclear whether continuation of these agents during hospitalization in patients who are acutely ill with COVID-19 is safe and/or efficacious in United States hospitals with differing demographics. Because ACEI/ARBs are generally cardioprotective (21), investigating the safety and therapeutic efficacy of these agents in patients hospitalized with COVID-19 is essential.

COVID-19 is characterized by a severe immune response leading to a cytokine storm and acute respiratory distress syndrome (ARDS) in some individuals (22). Studies demonstrated the potential therapeutic effect of ACEI/ARBs in ARDS before the COVID-19 pandemic, albeit in observational retrospective studies (23). In addition to the AT1R blockade, the use of ARBs was also shown to protect against ARDS by upregulating anti-inflammatory pathways in an animal model of sepsis (24). However, the anti-inflammatory role of ACEI/ARBs in COVID-19 in patients who are acutely ill and hospitalized requires further investigation.

Suffolk County has been one of the hardest hit counties in New York State (NYS); it has the fifth most cases in NYS with 38,224 cases, and the sixth most deaths in NYS with 1754 deaths (25). To date, Suffolk County remains in the top ten counties for documented COVID-19 cases and deaths in the United States. The data on outcomes associated with the use of ACEI/ARBs in patients hospitalized with COVID-19, especially the effect of these medications on inflammatory markers, is limited in the United States. In this study, we compare the clinical characteristics, inflammatory burden, and clinical outcomes collectively in patients with COVID-19 on these agents before admission to hospital as well as in those who continued using them during hospitalization in the largest academic center in Suffolk County, New York.

Materials and Methods

Study Design and Participants

This is a single-center cohort study on patients sequentially hospitalized with COVID-19 at Stony Brook University Medical Center from March 7, 2020 to April 1, 2020, inclusive of these dates. Only patients hospitalized with COVID-19, confirmed by at least one positive result for SARS-CoV-2 on real-time PCR testing of nasopharyngeal samples, were included in this study. Patients <18 years of age, history of solid organ transplant, those on chronic immunosuppressive medications, and patients without a disposition (death or discharged alive) were excluded from the analysis. All patients included in the study cohort reached the final outcome in the study of either being discharged alive from the hospital or death. This study was approved by the Stony Brook University Institutional Review Board.

Data Collection and Definition of Variables

Demographic data were collected on patient's age, sex, body mass index, and comorbidities including hypertension, diabetes, coronary artery disease (CAD), vascular disease, heart failure, CKD, ESKD, chronic obstructive pulmonary disease (COPD), and other lung diseases. Data were collected from chart review in the patient's electronic health record (EHR) as determined by specific notation in the patient's records of these chronic illnesses, International Classification of Diseases, Ninth (ICD-9) or Tenth Revision (ICD-10) codes entered for each specific diagnosis, and documentation in the provider's note confirming the use of these medications before hospitalization. History of diabetes was determined by hemoglobin A1c >6.5% or if the patient was being treated with insulin formulations or oral hypoglycemics before hospitalization. History of CAD was determined by evidence of CAD on previous cardiac catheterization reports, regardless of the need for percutaneous coronary intervention. Vascular disease was defined as atherosclerotic vascular disease other than CAD, including history of cerebrovascular disease, carotid artery stenosis, or peripheral artery disease. History of heart failure was determined by presence of systolic or diastolic dysfunction, or both, on transthoracic echocardiogram. History of CKD was determined by documentation in the EHR and/or ICD-9/-10 codes. ESKD was defined as the chronic use of hemodialysis or peritoneal dialysis at home. History of COPD was defined using EHR documentation and ICD-9/-10 codes as well as obstructive defect present on prior pulmonary function tests. "Other lung diseases" included pulmonary diseases other than COPD, including asthma, obstructive sleep apnea, pulmonary hypertension, and presence of active lung malignancy defined using EHR documentation or ICD-9/-10 codes.

Data were collected on the use of ACEI or ARB before hospital presentation and whether that medication was continued or held on admission using the medication reconciliation records in the EHR. Patients were classified as having their ACEI or ARB held if the medication was held throughout the entire hospitalization. If they received any amount of ACEI or ARB during the hospitalization, they were classified as having these medications continued.

Systolic BP, diastolic BP, and mean arterial pressure were recorded on triage vitals on initial presentation to the emergency room. History of hypertension was determined by presence of antihypertensive medications on admission or sustained systolic BP >140 mm Hg and diastolic BP >90 mm Hg.

Admission laboratory data were defined as data collected in the first 48 hours of presentation and included serum creatinine (sCr) levels, potassium, eGFR, ferritin, lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), D-dimer, and C-reactive protein (CRP). eGFR was determined using the CKD-Epidemiology Collaboration equation (26). Two composite scores for inflammation were calculated, named "peak inflammation score" and "fold

change (FC) inflammation," based on the available laboratory data using methods based on previous reported studies (27). "Peak" laboratory values for sCr, ferritin, LDH, ESR, D-dimer, and CRP were also collected during the hospital course. FC was calculated for each of the inflammatory laboratory measures (ferritin, LDH, ESR, D-dimer, and CRP) by dividing the peak values by admission values to obtain an FC for each of these measurements. Quartiles were calculated for both peak values and FC values with respect to each inflammatory marker. Based on these quartile values, each patient was assigned a score ranging from zero to three based on the peak value and FC values (0, ≤first quartile; 1, first–second quartiles; 2, second–third quartiles; and 3, ≥third quartile). The sum of these values was calculated across the five inflammatory laboratory measures as a composite inflammatory score ranging from zero to 15 for both the peak inflammation score and FC inflammation score.

The definition of AKI was based on Kidney Disease Improving Global Outcomes (KDIGO) for AKI (28). "AKI on admission" was defined as admission sCr ≥1.2 mg/dl except in those patients with preexisting CKD who had a documented baseline sCr within 3 months before admission, and where the change in sCr was <1.5 times than the sCr. "AKI during hospitalization" was defined as a rise in sCr of 0.3 mg/dl within any 48-hour time period during the hospitalization or ≥1.5 times increase from admission sCr based on KDIGO guidelines. Patients with ESKD receiving chronic dialysis treatments were excluded from this category.

Outcomes measured were AKI on admission, AKI during hospitalization, need for RRT (hemodialysis or continuous RRT), intensive care unit (ICU) admission, need for mechanical ventilation (MV), length of hospital stay, and final patient outcome of death versus discharge.

Statistical Analyses

Statistical analysis was conducted in SAS version 9.4 (SAS Institute, Cary, NC). Continuous variables were reported as mean (SD) or median (interquartile range) depending on normality. These variables were then compared by either an independent *t* test or ANOVA for parametric variables and Wilcoxon rank sum or Kruskal–Wallis test for nonparametric variables. Categoric variables were reported as counts (percentages) and compared by either a chi-squared test or Fisher exact test. The Fisher exact test was used when data were sparse and the sample size was limited. A generalized linear model was used for the multivariable analyses with a continuous outcome. A logistic regression was used for multivariable analyses with dichotomous outcomes. These models represented a combination of inferential and descriptive analyses. $P<0.05$ was considered statistically significant.

Results

Of the 317 patients hospitalized with real-time PCR–confirmed SARS-CoV-2 infection ≥18 years of age, 300 patients that met the inclusion criteria were included in the study (Figure 1). The mean age was 59.1±17.5 years with a significant proportion of patients with a history of hypertension (44%, 133/300), diabetes (25%, 74/300), and/or heart failure (15%, 44/300) (Supplemental Table 1). All patients had a disposition by the end of the study period, with 27% (81/300) requiring ICU admission and 87% (261/300) surviving their hospitalization. Nearly 27% of the

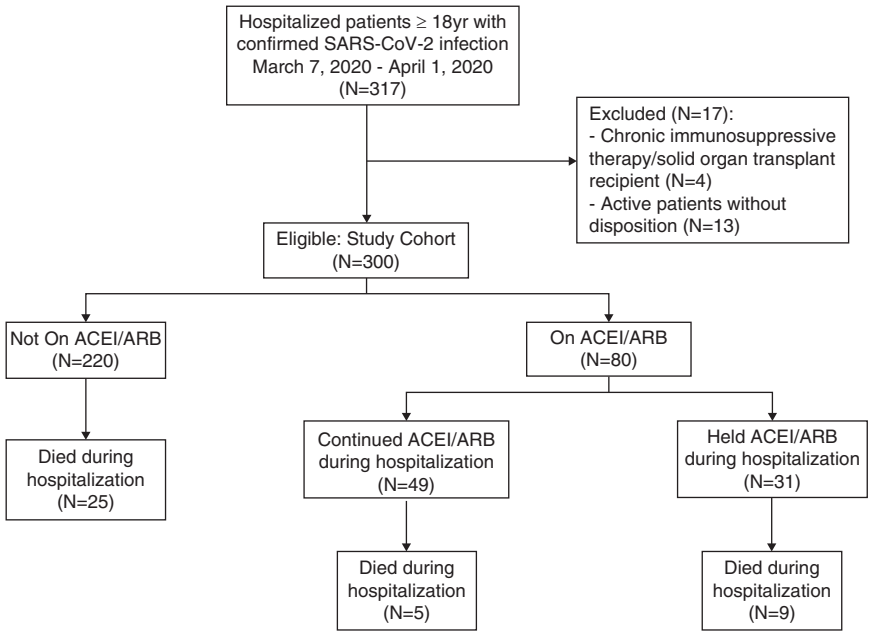

Figure 1. | Flowchart of the selection of the study cohort that had a history of ACEI/ARB use before hospitalization and the patients that were either continued or discontinued on these agents during hospitalization. Total number of individuals that died in each group is also provided. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 1. Clinical characteristics, laboratory values, and outcomes in the use of ACEI or ARB prior to hospitalization

Characteristics	History of ACEI and ARB Use		*P* Value
	Neither (*N*=220)	ACEI or ARB Use (*N*=80)	
Demographics			
Age	55.7±18.0	68.5±11.7	<0.001
Sex			
Male	118 (54%)	48 (60%)	0.33
Female	102 (46%)	32 (40%)	
BMI[a]	29.7±6.5	30.5±5.6	0.37
Comorbidities			
Hypertension	53 (24%)	80 (100%)	<0.001
Diabetes	37 (17%)	37 (46%)	<0.001
Coronary artery disease	27 (12%)	25 (31%)	<0.001
Vascular disease	14 (6%)	6 (8%)	0.73
Heart failure	21 (10%)	23 (29%)	<0.001
CKD	19 (9%)	15 (19%)	0.01
ESKD	2 (0.9%)	2 (3%)	0.29
Chronic obstructive pulmonary disease	10 (5%)	9 (11%)	0.04
Other lung disease	29 (13%)	6 (8%)	0.18
BP on admission, mm Hg			
SBP	126.4±20.4	128.7±24.1	0.41
DBP	74.4±11.2	70.7±11.9	0.01
MAP	91.9±13.1	89.6±13.8	0.20
Serum potassium on admission, mmol/L	4.1±0.5	4.2±0.6	0.15
Kidney function on admission			
AKI	24 (11%)	30 (38%)	<0.001
eGFR, ml/min per 1.73 m^2	92.0 (70.5–109)	58.0 (40.0–80.0)	<0.001
sCr, mg/dl	0.86 (0.70–1.1)	1.1 (0.87–1.6)	<0.001
Kidney function during hospitalization			
AKI	25 (11%)	22 (28%)	<0.001
RRT	3 (1%)	5 (6%)	0.03
HD	2 (0.9%)	5 (6%)	0.02
CRRT	2 (0.9%)	2 (3%)	0.30
Laboratory values (inflammation)			
Ferritin, ng/ml			
Admission[b]	607.0 (270.3–1243)	660.0 (335.5–1360)	0.47
Peak[c]	816 (351–1668)	912 (513–1839)	0.22
FC in level[b]	1.0 (1.0–1.6)	1.4 (1.0–2.4)	0.05
LDH, IU/L			
Admission[b]	317.5 (239–424)	303.5 (243–376)	0.34
Peak[c]	401.0 (296–550)	392 (322–570)	0.55
FC in level[b]	1.1 (1.0–1.4)	1.2 (1.0–1.8)	0.02
ESR, mm/h			
Admission[b]	40.0 (21–62)	44.0 (23–63)	0.61
Peak[c]	73.0 (44–95.5)	74.0 (47–100.5)	0.89
FC in level[b]	1.2 (1.0–2.1)	10 (1.0–2.1)	0.72
D-dimer, ng/ml			
Admission[b]	301 (198–503)	305 (173–486)	0.95
Peak[c]	680 (301–2582)	550 (322–2675)	0.84
FC in level[b]	1.2 (1.0–5.2)	1.1 (1.0–6.4)	0.93
CRP, mg/dl			
Admission[b]	6.2 (2.9–13.1)	7.7 (3.5–13.3)	0.32
Peak[c]	10.6 (5.0–22.4)	13.9 (7.9–27.8)	0.02
FC in level[b]	1.2 (1.0–2.4)	1.8 (1.0–3.1)	0.07
Inflammation scores (0–15)			
Peak inflammation score	6.0 (2.0–10.0)	7.0 (3.0–10.0)	0.09
FC inflammation score	3.0 (0–6.0)	4.0 (0–9.0)	0.10
Hospital outcomes			
ICU admission	59 (27%)	22 (28%)	0.91
Invasive mechanical ventilation	50 (23%)	19 (24%)	0.85
Patient outcome			
Discharged	195 (89%)	66 (83%)	0.16
Death	25 (11%)	14 (18%)	

Table 1. (Continued)

Characteristics	History of ACEI and ARB Use		*P* Value
	Neither (*N*=220)	ACEI or ARB Use (*N*=80)	
Length of stay, d	7.0 (11.0)	9.0 (10.5)	0.12

Data are presented as a number and percentage, median (25th–75th percentiles), or mean±SD. *P* value<0.05 considered statistically significant in analysis. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; SBP, systolic BP; DBP, diastolic BP; MAP, mean arterial pressure; sCr, serum creatinine; HD, hemodialysis; CRRT, continuous renal replacement therapy; FC, fold change; LDH, lactate dehydrogenase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ICU, intensive care unit.
[a]92% of patients had data available for BMI.
[b]51% of patients had data available for analysis for admission and FC values for ferritin, 86% was available for LDH, 46% was available for ESR, 59% was available for D-dimer, and 86% was available for CRP.
[c]79% of patients had data available for analysis for peak values for ferritin, 94% was available for LDH, 77% was available for ESR, 82% was available for D-dimer, and 94% was available for CRP.

patients hospitalized with COVID-19 had a history of ACEI or ARB use before admission, with no overlap in the use of these medications between the two groups. Whereas 18% (54/300) of patients presented with AKI on admission, 16% (47/300) developed *de novo* AKI during their hospitalization. Of the patients that presented with a history of ACEI/ARB use, 61% (49/80) had their medications continued.

History of ACEI/ARB Use before Hospitalization

Before hospitalization, patients on either ACEIs or ARBs were older (68.5±11.7 years) and had a higher prevalence of diabetes, CAD, heart failure, CKD, and COPD than those not on these medications (Table 1, Supplemental Table 2). Multivariable analysis shows that the use of either ACEIs or ARBs before hospitalization was not associated with AKI on admission or during hospitalization (Table 2). However, there was an association between prior use of ARB and lower eGFR on admission, suggesting the likely presence of CKD (Table 2). Prior use of either ACEIs or ARBs was not associated with worse outcomes (Tables 1 and 2, Supplemental Table 2).

Continuation of ACEIs/ARBs during Hospitalization

Analysis of the clinical characteristics, presenting laboratory values, and outcomes between the patients who held versus continued ACEIs/ARBs is shown (Table 3, Supplemental Tables 3 and 4). Continuation of ACEIs/ARBs was associated with a lower rate of AKI at admission with a trend toward a lower rate of AKI during hospitalization (Table 3). In addition, peak LDH, ESR, CRP levels, and peak inflammation scores were lower in those who continued their ACEIs/ARBs rather than those with the medications on hold (Table 3). Multivariable analysis affirmed the lower peak CRP (6.9±3.1 mg/dl; $P=0.03$) and inflammation score (2.3±1.1 unit reduction; $P=0.04$) with the continuation of ACEIs/ARBs during hospitalization after adjusting for potential confounders such as kidney dysfunction, hyperkalemia, and hypotension (Table 4). Similarly, the use of ARBs alone was associated with lower peak CRP (10.8±4.8 mg/dl;

Table 2. Multivariable analysis of predictors associated with key outcomes in the use of ACEI or ARB before hospitalization

Predictor	Probability of AKI on Admission(odds ratio; 95% CI)	Probability of AKI during Hospitalization(odds ratio; 95% CI)	eGFR on Admission		Length of Stay	
			Estimated Effect (SEM)	*P* Value	Estimated Effect (SEM)	*P* Value
Age, yr	1.02 (1.00 to 1.05)	1.01 (0.99 to 1.04)	−0.77 (0.07)	<0.001	−0.002 (0.03)	0.95
History of ARB use	2.23 (0.92 to 5.44)	1.34 (0.52 to 3.43)	−9.59 (3.64)	<0.01	3.13 (1.67)	0.06
History of ACEI use	1.01 (0.38 to 2.71)	0.81 (0.28 to 2.31)	−3.17 (3.86)	0.41	−1.86 (1.76)	0.29
Female sex	0.67 (0.34 to 1.32)	0.46 (0.22 to 0.95)[a]	−0.14 (2.08)	0.95	−1.56 (0.95)	0.10
Hypertension	3.41 (1.22 to 9.54)[a]	2.57 (0.92 to 7.17)	−4.57 (3.27)	0.16	0.60 (1.49)	0.69
Diabetes	1.43 (0.69 to 2.98)	1.40 (0.66 to 2.98)	−3.98 (2.58)	0.12	1.41 (1.18)	0.23
Coronary artery disease	1.55 (0.70 to 3.41)	0.92 (0.39 to 2.17)	−6.33 (3.12)	0.04	−0.59 (1.42)	0.68
Heart failure	1.52 (0.67 to 3.48)	2.22 (0.93 to 5.30)	−2.54 (3.32)	0.44	1.07 (1.51)	0.48
CKD	1.02 (0.41 to 2.50)	2.37 (0.97 to 5.75)	−35.28 (3.49)	<0.001	−0.61 (1.59)	0.70

Variables included in the multivariable analysis are based on select demographic and comorbidities significant from the exploratory analysis. For categoric values, odds ratios with 95% CIs are present. For continuous variables, estimated effects with SEMs are presented with associated *P* values. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
[a]$P<0.05$.

Table 3. Clinical Characteristics, laboratory values, and outcomes in the use of ACEI or ARB during hospitalization

Characteristic	Status of ACEI or ARB during Hospitalization		*P* Value
	Held (*N*=31)	Continued (*N*=49)	
Demographics			
Age	69.9±12.3	67.6±11.4	0.39
Sex			
Male	22 (71%)	26 (53%)	0.11
Female	9 (29%)	23 (47%)	
BMI[a]	30.4±6.1	30.5±5.4	0.92
Comorbidities			
Hypertension	31 (100%)	49 (100%)	N.A
Diabetes	15 (48%)	22 (45%)	0.76
Coronary artery disease	11 (36%)	14 (29%)	0.52
Vascular disease	4 (13%)	2 (4%)	0.20
Heart failure	8 (26%)	15 (31%)	0.64
CKD	7 (23%)	8 (16%)	0.49
ESKD	0 (0%)	2 (4%)	0.52
Chronic obstructive pulmonary disease	3 (10%)	6 (12%)	1.00
Other lung disease	1 (3%)	5 (10%)	0.40
BP on admission			
SBP, mm Hg	130.4±26.0	127.6±23.1	0.62
DBP, mm Hg	69.5±12.0	71.5±11.9	0.48
MAP, mm Hg	89.1±13.8	90.0±14.0	0.79
Serum potassium on admission, mmol/L	4.3±0.6	4.1±0.6	0.23
Kidney function on admission			
AKI	18 (58%)	12 (25%)	0.003
eGFR, ml/min per 1.73 m^2	43.0 (36.0–60.0)	71.0 (48.0–88.0)	0.004
sCr, mg/dl	1.4 (1.0–1.8)	1.0 (0.8–1.3)	<0.001
Kidney function during hospitalization			
AKI	12 (39%)	10 (20%)	0.07
RRT	2 (7%)	3 (6%)	1.00
HD	2 (7%)	3 (6%)	1.00
CRRT	1 (3%)	1 (2.0%)	1.00
Laboratory values (inflammation)			
Ferritin, ng/ml			
Admission[b]	596.9 (326–971.6)	826.0 (352–1490)	0.19
Peak[c]	829.3 (562–1839)	971.2 (434–1793)	1.00
FC in level[b]	1.4 (1.0–3.1)	1.3 (1.0–2.2)	0.34
LDH, IU/L			
Admission[b]	328.5 (247–438)	296.0 (243–358)	0.26
Peak[c]	465 (346–635)	372.0 (298–513)	0.04
FC in level[b]	1.2 (1.1–2.0)	1.2 (1.0–1.6)	0.38
ESR, mm/h			
Admission[b]	47.0 (33.5–74.5)	39.0 (19.0–53.0)	0.16
Peak[c]	81.5 (70.5–109.5)	55.0 (32.5–98.5)	0.02
FC in level[b]	1.8 (1.0–2.3)	1.1 (1.0–1.9)	0.26
D-dimer, ng/ml			
Admission[b]	291.0 (186–544)	322.0 (173–466)	0.66
Peak[c]	689.0 (392–2675)	512.0 (287–2377)	0.43
FC in level[b]	1.1 (1.0–14.3)	1.1 (1.0–4.0)	0.96
CRP, mg/dl			
Admission[b]	9.4 (3.6–15.3)	7.3 (3.3–11.4)	0.17
Peak[c]	19.9 (11.1–33.7)	12.2 (6.8–21.8)	0.03
FC in level[b]	2.0 (1.0–3.0)	1.6 (1.0–3.1)	0.64
Inflammation scores (0–15)			
Peak inflammation score	9.0 (7.0–12.0)	6.0 (3.0–10.0)	0.02
FC inflammation score	5.0 (1.0–11.0)	3.0 (0–9.0)	0.21
Hospital outcomes			
ICU admission	13 (42%)	9 (18%)	0.021
Invasive mechanical ventilation	10 (32%)	9 (18%)	0.15
Patient outcome			
Discharged	22 (71%)	44 (90%)	0.04
Death	9 (29%)	5 (10%)	

Table 3. (Continued)

Characteristic	Status of ACEI or ARB during Hospitalization		*P* Value
	Held (*N*=31)	Continued (*N*=49)	
Length of stay, d	9.0 (5.0–15.0)	7.0 (4.0–14.0)	0.50

Data are presented as a number and percentage, median (25th–75th percentiles), or mean±SD. *P* values <0.05 considered statistically significant in analysis. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; SBP, systolic BP; DBP, diastolic BP; MAP, mean arterial pressure; sCr, serum creatinine; HD, hemodialysis; CRRT, continuous RRT; FC, fold change; LDH, lactate dehydrogenase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ICU, intensive care unit.
[a]91% of patients had data available for BMI.
[b]51% of patients had data available for analysis for admission and FC values for ferritin, 86% was available for LDH, 46% was available for ESR, 59% was available for D-dimer, and 86% was available for CRP.
[c]79% of patients had data available for analysis for peak values for ferritin, 94% was available for LDH, 77% was available for ESR, 82% was available for D-dimer, and 94% was available for CRP.

P=0.03) with a trend toward a lower peak inflammatory score (3.1±1.8 unit reduction; *P*=0.09) as compared with holding the ARB during hospitalization (Supplemental Table 5).

Holding ACEIs/ARBs during hospitalization was also associated with a higher rate of ICU admission (42%, 13/31) as compared with continuation of these medications (18%, 9/49) (*P*=0.02) (Table 3). Multivariable analysis confirmed that continuation of ACEIs/ARBs lowered the risk of ICU admission as compared with holding these agents (odds ratio [OR], 0.25; 95% CI, 0.08 to 0.81), after adjusting for similar confounders (Table 4). These findings were also confirmed with the use of ARB alone (OR, 0.06; 95% CI, 0.01 to 0.59) (Supplemental Table 5).

Although mortality was higher (29%, 9/31 versus 10%, 5/49; *P*=0.04) in the cohort in which ACEIs/ARBs were held during hospitalization (Table 3), in the multivariable analysis we only observed a trend toward lower mortality with the continuation of these agents (OR, 0.31; 95% CI, 0.08 to 1.23) (Table 4).

Discussion

To date, studies on the role of ACEIs/ARBs in COVID-19 have primarily focused on the effect of the use of these medications before hospitalization on overall outcomes (17–19). Unique to these previous studies, we report the following novel observations: (*1*) in addition to the lack of increase in adverse outcomes with the use of ACEIs/ARBs before hospitalization, there were no significant differences in the inflammatory burden or risk of AKI before or during hospitalization; and (*2*) the continuation of ACEIs/ARBs was associated with a lower adjusted risk of ICU admission and inflammatory burden as compared with holding these agents. Our findings reaffirmed the wisdom of real-time guidance issued by the American Society of Nephrology as well as jointly by the American Heart Association, American College of Cardiology, and Heart Failure Society of America during the peak of the pandemic in the United States.

Although our initial exploratory analysis demonstrated that prior use of ACEIs/ARBs was associated with AKI on admission and during hospitalization, this association was lost after adjusting for these comorbidities in the multivariable analysis. Only male sex and history of hypertension were associated with AKI during hospitalization and admission, respectively. Despite a higher burden of comorbid disease, these patients were not found to have a higher association with ICU admission, MV, length of hospital stay,

Table 4. Multivariable analysis of predictors associated with key outcomes in the use of ACEI or ARB during hospitalization

Predictors (*N*=80)	Probability of ICU Admission(odds ratio; 95% CI)	Probability of Death(odds ratio; 95% CI)	Peak CRP, mg/dl		Peak Inflammation Score	
			Estimated Effect (SEM)	*P* Value	Estimated Effect (SEM)	*P* Value
Age, yr	1.06 (1.00 to 1.12)	1.12 (1.03 to 1.21)[a]	0.21 (0.15)	0.16	0.00 (0.05)	0.96
Continuation of ACEI or ARB during hospitalization	0.25 (0.08 to 0.81)[b]	0.31 (0.08 to 1.26)	−6.85 (3.05)	0.03	−2.29 (1.08)	0.04
AKI on admission	2.12 (0.43 to 10.40)	1.69 (0.26 to 10.96)	2.82 (3.98)	0.48	0.59 (1.39)	0.67
sCr on admission	1.85 (0.93 to 3.65)	1.30 (0.52 to 3.25)	0.47 (1.89)	0.80	0.25 (0.67)	0.71
eGFR on admission	1.05 (1.00 to 1.09)[b]	1.02 (0.96 to 1.08)	0.08 (0.11)	0.44	0.02 (0.04)	0.54
Potassium on admission	1.33 (0.49 to 3.60)	1.23 (0.39 to 3.86)	−2.14 (2.52)	0.40	0.20 (0.89)	0.83
MAP on admission	1.04 (0.99 to 1.09)	1.04 (0.98 to 1.10)	0.13 (0.11)	0.25	0.02 (0.04)	0.62

Variables included in the multivariable analysis are based on select variables from the exploratory analysis.
For categoric values, odds ratios with 95% CIs are present. For continuous variables, estimated effects with SEMs are presented with associated *P* values. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICU, intensive care unit; CRP, C-reactive protein; sCr, serum creatinine; MAP, mean arterial pressure.
[a]*P*<0.05.
[b]*P*<0.01.

or death. Although these findings are suggestive of the salutary role of ACEIs/ARBs in lowering the burden of COVID-19 in patients with these comorbidities, this hypothesis will need to be further explored in prospective studies and larger cohorts with differing demographics.

Previous studies showed the increase in inflammatory markers in patients infected with SARS-CoV-2 (29) as well as higher levels of ferritin, LDH, D-dimer, and CRP in progressive COVID-19 (30–32), but the effect of ACEIs/ARBs on inflammation remains unclear. The need for ICU admission and subsequent invasive mechanical ventilatory support can occur in patients with severe illness due to the hyperinflammatory state in ARDS (33). In our study, holding ACEIs/ARBs was associated with higher ICU admissions and greater inflammatory burden as compared with the continuation of these agents during hospitalization. However, higher rates of AKI on admission were noted in patients that discontinued ACEIs/ARBs, suggesting a potential determining reason for holding these agents, albeit the association was lost in the multivariable analysis. Furthermore, the detrimental effects of discontinuing ACEIs/ARBs (higher ICU admissions and greater inflammatory burden) held true in the multivariable analysis after adjusting for factors that would have potentially contributed to the cessation of these agents in the hospitalized setting, such as hyperkalemia, hypotension, and AKI on admission. We observed similar trends with the continuation of ARBs alone. Unfortunately, due to the small sample size, we were unable to assess whether the continuation of ACEIs alone led to similar findings. Nonetheless, these data support previous studies on the use of ARBs for reducing the overall inflammatory burden by promoting the antifibrotic and anti-inflammatory effects of ACE2 effects in the lung (11,34).

Although we observed a trend toward lower mortality and fewer patients requiring MV with the continuation of ACEIs/ARBs as well as ARBs alone in the multivariable analysis, this did not reach statistical significance. Furthermore, our study cohort only included sequentially hospitalized patients with a disposition, but further studies would need to determine the effect of ACEIs/ARBs on patients with a prolonged hospital course beyond the study period. In addition, prospective studies comparing the *de novo* use of ACEIs/ARBs as compared with non-RAAS blockade will be required to determine the therapeutic benefits of these agents in patients hospitalized with COVID-19.

This study has some limitations. This was a single-center study with a relatively small cohort of 300 patients, but, in contrast to other studies, we have a 100% disposition in all our patients. In addition, missing laboratory values on inflammation in some patients may have skewed the data toward a more acutely ill cohort. Although we did not observe an increase in adverse outcomes with continuation of ACEIs/ARBs during hospitalization, the inherent nature of this cohort study prevents us from making conclusions about the therapeutic benefits of RAAS blockade in COVID-19 without supporting randomized controlled trials. As such, clinical trials involving the use of RAAS blockade in COVID-19 are currently underway (NCT04312009, NCT04366050).

In conclusion, the use of ACEIs/ARBs before hospitalization in patients infected with SARS-CoV-2 was not associated with progressive disease or mortality, and the continuation of these agents during hospitalization might reduce progression of disease by lowering the severity of inflammation and admission to the ICU.

Disclosures

All authors have nothing to disclose.

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Authors Contributions

S. Ahmad, M. Bloom, I. Chaudhri, F. Koraishy, S. Mallipattu, and H. Skopicki reviewed and edited the manuscript; S. Ahmad, M. Bloom, I. Chaudhri, F. Koraishy, L. Marcos, S. Mallipattu, and H. Skopicki conceptualized the study; S. Ahmad, F. Koraishy, S. Mallipattu, and H. Sahib were responsible for project administration; O. Bolotova, I. Chaudhri, L. Marcos, H. Sahib, and J. Yoo were responsible for data curation; I. Chaudhri, F. Koraishy, S. Mallipattu, L. Marcos, and H. Skopicki were responsible for investigation; I. Chaudhri, F. Koraishy, and H. Sahib were responsible for methodology; I. Chaudhri, F. Koraishy, and E. Taub were responsible for formal analysis; I. Chaudhri, F. Koraishy, S. Mallipattu, and H. Skopicki wrote the original draft; S. Mallipattu provided supervision; and all authors approved the final version of the manuscript.

Supplemental Material

This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0003792020/-/DCSupplemental.

Supplemental Table 1. Presenting clinical characteristics and laboratory values in the study patients.

Supplemental Table 2. Clinical characteristics, laboratory values, and outcomes in the use of ACEIs and ARBs prior to hospitalization.

Supplemental Table 3. Clinical characteristics, laboratory values, and outcomes in the use of ACEIs during hospitalization.

Supplemental Table 4. Clinical characteristics, laboratory values, and outcomes in the use of ARBs during hospitalization.

Supplemental Table 5. Multivariable analysis of predictors associated with key outcomes in the use of ARBs during hospitalization.

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