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ORIGINAL RESEARCH

Angiotensin-Converting Enzyme Inhibitors, Angiotensin II Receptor Blockers, and Outcomes in Patients Hospitalized for COVID-19

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BACKGROUND: Use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ACEi/ARB) is thought to affect COVID-19 through modulating levels of angiotensin-converting enzyme 2, the cell entry receptor for SARS-CoV2. We sought to assess the association between ACEi/ARB, biomarkers of inflammation, and outcomes in patients hospitalized for COVID-19.

METHODS AND RESULTS: We leveraged the ISIC (International Study of Inflammation in COVID-19), identified patients admitted for symptomatic COVID-19 between February 1, 2020 and June 1, 2021 for COVID-19, and examined the association between in-hospital ACEi/ARB use and all-cause death, need for ventilation, and need for dialysis. We estimated the causal effect of ACEi/ARB on the composite outcomes using marginal structural models accounting for serial blood pressure and serum creatinine measures. Of 2044 patients in ISIC, 1686 patients met inclusion criteria, of whom 398 (23.6%) patients who were previously on ACEi/ARB received at least 1 dose during their hospitalization for COVID-19. There were 215 deaths, 407 patients requiring mechanical ventilation, and 124 patients who required dialysis during their hospitalization. Prior ACEi/ARB use was associated with lower levels of soluble urokinase plasminogen activator receptor and C-reactive protein. In multivariable analysis, in-hospital ACEi/ARB use was associated with a lower risk of the composite outcome of in-hospital death, mechanical ventilation, or dialysis (adjusted hazard ratio 0.49, 95% CI [0.36–0.65]).

CONCLUSIONS: In patients hospitalized for COVID-19, ACEi/ARB use was associated with lower levels of inflammation and lower risk of in-hospital outcomes. Clinical trials will define the role of ACEi/ARB in the treatment of COVID-19.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT04818866.

Key Words: ACE inhibitors ■ angiotensin receptor blockers ■ COVID-19 ■ mortality ■ outcomes

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CLINICAL PERSPECTIVE

What Is New?

- Despite a larger burden of co-morbidities, patients hospitalized for COVID-19 on angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) have significantly better outcomes compared with those not on ACEi or ARB.
- This study used multiple approaches to evaluate the association between ACEi or ARB use and outcomes in patients hospitalized for COVID-19, including time-varying Cox modeling and marginal structural modeling accounting for important time-varying confounders such as daily mean arterial blood pressure and daily measures of serum creatinine.
- Use of ACEi or ARB were associated with significantly lower levels of inflammatory biomarkers after accounting for differences in clinical characteristics.

What Are the Clinical Implications?

- ACEi and ARB may have beneficial effects on outcomes of patients with COVID-19 and should not be discontinued unless clinically indicated.
- A plausible explanation for the observed benefit of ACEi and ARBs in COVID-19 is through the attenuation of inflammation that occurs via angiotensin II receptor blockade.
- Whether initiation of ACEi or ARB in patients with COVID-19 improves outcome merits study.

Nonstandard Abbreviations and Acronyms

ISIC	International Study of Inflammation in COVID-19
M²C²	Medicine COVID-19 Cohort
SuPAR	soluble urokinase plasminogen activator receptor

By June 2021, the COVID-19 global pandemic had resulted in more than 170 million confirmed cases of infection and more than 3.7 million deaths worldwide.[1] The SARS-CoV2—the pathogen behind this rampant disease[2]—has been shown to bear phylogenetic resemblance to the previous SARS-CoV coronavirus responsible for 2002 to 2004 SARS epidemic. Due to the homology between the SARS-CoV2 receptor binding domain with that of the previous strain,[3] it was postulated and then demonstrated that SARS-CoV2 uses the same receptor for entry into host cells, angiotensin-converting enzyme 2 (ACE2).[3–5]

The ACE2 receptor is a transmembrane carboxypeptidase that metabolizes the vasoconstrictive angiotensin II to the more vasodilatory angiotensin, providing a counterregulatory effect to the proinflammatory renin-angiotensin system cascade.[6–8] Activation of the renin-angiotensin system cascade has been implicated in modulation of immune cell function involving the cytokines tumor necrosis factor-α and interleukin-6, and activation of the proinflammatory transcription factor NF-kB in human monocytes.[9–12] ACE2 is found throughout the human body and is notably expressed by type I and type II pneumocytes.[13] Downregulation of ACE2 by SARS-CoV is thought to promote the development of acute respiratory distress syndrome.[4,14] ACE inhibitors (ACEi) and angiotensin receptor blockers (ARB), drug classes commonly used for the treatment of hypertension and heart failure, have been hypothesized to worsen lung injury in COVID-19 patients[4,15] through upregulation of ACE2 in various tissues.[16–18] However, recent studies have suggested that ACEi/ARB usage either before or during hospitalization was not associated with worse outcomes and may be beneficial in hospitalized patients with COVID-19.[19–31] Conclusions related to these observations are limited by the high risk of selection bias afforded by unaccounted confounders that would guide the use of ACEi/ARB such as severity of the disease, hemodynamic instability, and kidney function.

To better understand the link between ACEi/ARB use and outcomes in COVID-19, we leveraged the multicenter ISIC (International Study of Inflammation in COVID-19) and the M²C² (Michigan Medicine COVID-19 Cohort) to assess whether the use of ACEi/ARB is associated with improved outcomes while accounting for inflammation and daily measures of blood pressure and kidney function.

METHODS

The International Study of Inflammation in COVID-19

The ISIC is an ongoing multicenter observational study with the primary purpose of characterizing levels of various biomarkers of inflammation and their association with in-hospital outcomes of patients with COVID-19. Participating centers include University of Michigan in Ann Arbor, MI; Rush University in Chicago, IL; Copenhagen University of Hospital in Hvidovre, Denmark; Attikon University Hospital in Athens, Greece; the University of Thessaly in Greece; the University Hospital of Dusseldorf in Germany; and Charité University Medicine Berlin in Germany (Table S1). Inclusion criteria were (1) adult (≥18 years

old) patients hospitalized primarily for COVID-19, (2) a confirmed SARS-CoV-2 infection diagnosed through reverse transcriptase polymerase chain reaction test of nasopharyngeal or oropharyngeal samples, and (3) at least 1 blood sample collected during the hospitalization and stored for biomarker testing. Patients with a positive test for SARS-CoV-2 who were asymptomatic or not requiring supplemental oxygen and who were hospitalized for non-COVID-19 reasons were excluded. Manual chart review and data mining tools were used to gather details of the presentation, demographics, past medical history, home medications, clinical characteristics, laboratory studies, inpatient medical therapy, hospitalization course, and outcomes. All patients were followed until hospital discharge or death. Institutional review board approval and consent procedures were obtained separately at each site according to local institutional policies. Data from ISIC can be made available upon request through a collaborative process. Please contact penegonz@med.umich.edu for additional information.

The Michigan Medicine COVID-19 Cohort

The M^2C^2 is a prospective cohort study that systematically enrolled consecutive adults (≥18 years) with confirmed SARS-CoV-2 infection who were hospitalized specifically for COVID-19 at the University of Michigan from February 1, 2020 to June 1, 2021. In addition to the variables collected for ISIC, all blood pressure measurements and laboratory testing were extracted from the electronic medical records for the purpose of this analysis.

Study Design and Definitions

For the purpose of this study, we included patients hospitalized for COVID-19 (n=2044) during the period of February 1, 2020 to June 1, 2021, the date the database was locked for the purpose of this analysis. To limit the risk of selection bias, we excluded patients who were taking an ACEi/ARB before hospitalization but were discontinued during hospitalization (n=311), and those in whom an ACEi/ARB was initiated during hospitalization without a prior history of ACEi/ARB use (n=47) resulting in an analytic sample size of 1686 (Figure S1). Prior use of ACEi/ARB was determined through electronic medical record review of all active prescriptions and home medications noted in the chart. In-hospital use of ACEi/ARB was defined as the administration of at least 1 dose of any ACEi/ARB during the hospital course. For this analysis, ACEi/ARB users were defined as those who had an ACEi or ARB listed on their home medications and received a ACEi or ARB during hospitalization. By contrast, nonusers were defined as those who did not have either ACEi orARB listed among their home medications and did not receive either medication during their hospitalization. Biomarker levels measured within 48 hours of admission included suPAR (soluble urokinase plasminogen activator receptor), interleukin-6, C-reactive protein, D-dimer, ferritin, lactate dehydrogenase, and procalcitonin levels. The outcomes of interest were in-hospital death or discharge to hospice, the need for mechanical ventilation, and the need for dialysis or continuous renal replacement therapy.

Statistical Analysis

We first report clinical characteristics stratified by use of ACEi/ARB using categorical variables expressed as a number and percentage and continuous variables expressed as means (±SD) and medians (25th–75th interquartile range) for normally and nonnormally distributed data, respectively. We used chi-square or Fisher's exact tests to compare categorical variables and 2-sample *t* tests or Mann-Whitney *U* tests to compare normally distributed and nonnormally distributed continuous variables across groups, respectively.

ACEi/ARB and Biomarkers

We used linear regression to determine whether ACEi/ARB use was independently associated with biomarker levels, adjusting for age, sex, race, body mass index, a history of diabetes, hypertension, coronary artery disease, congestive heart failure, admission estimated glomerular filtration rate, and reported standardized estimates to allow for comparison of the strength of the association. Each biomarker was log transformed to base 2, interpreted as per 100% increase. Covariates were chosen a priori based on their known roles as risk factors for COVID-19 and indications for ACEi/ARB use.

ACEi/ARB and Outcomes

We represented the incidence of death, need for mechanical ventilation, and need for dialysis stratified by use of ACEi/ARB using bar graphs and examined the association between in-hospital ACEi/ARB use and the aforementioned outcomes using binary logistic regression. Variables in the main model were chosen a priori based on clinical relevance and included age, sex, race, body mass index, a history of diabetes, hypertension, coronary artery disease, congestive heart failure, admission estimated glomerular filtration rate, and institution of enrollment. In a separate model, we further adjusted for the mean arterial pressure on presentation.

To address the risk of survivor bias attributed to the variability in timeline of in-hospital ACEi/ARB administration, we used Cox proportional hazards models to examine the association of in-hospital ACEi/ARB use as a time-dependent covariate with the composite

outcome of death, need for dialysis, and need for mechanical ventilation adjusting for the aforementioned covariates. Patients were censored at hospital discharge or June 1, 2021.

Estimating a Causal Effect for ACEi/ARB on Outcomes

We used marginal structural modeling to estimate the causal effect of ACEi/ARB on the composite outcome (death, mechanical ventilation, and dialysis) and to account for potential confounding by blood pressure and serum creatinine.[32] Serial measurements of blood pressure and serum creatinine during hospitalization measurements were available for M^2C^2. Thus, this analysis was restricted to patients at the University of Michigan (n=1357). Model parameters were estimated through inverse-probability-of-ACEi/ARB use weighting, allowing for appropriate adjustment for the time-varying confounders blood pressure and creatinine, which are risk factors for the outcome and are affected by previous ACEi/ARB use. In the first step, we calculated a stabilized weight for each subject at each hospital day. The numerator of the weight is informally the probability that the subject had observed treatment of ACEi/ARB conditional on baseline covariates (age, sex, race, body mass index, admission estimated glomerular filtration rate, and history of diabetes, coronary artery disease, hypertension, and congestive heart failure) and days in hospital. The denominator of the weight is the probability that the subject had their own observed treatment of ACEi/ARB, adjusting of blood pressure and creatinine measurements and days in hospital. In the second step, we fitted a time-dependent Cox model with baseline covariates (age, sex, race, body mass index, diabetes, hypertension, coronary artery disease, and congestive heart failure) and weighted each subject on each hospital day by the "stabilized" weight obtained from the first step. By weighting, we created, for a risk set on each hospital day, a pseudo-population in which blood pressure and creatinine are no longer confounders. Weighted Kaplan-Meier curves were plotted to visually compare survival free of the composite outcome by in-hospital ACEi/ARB use.

Sensitivity Analyses

To explore the possibility of effect modification attributed to differences in baseline characteristics among patients, we computed the time-dependent hazard ratios for the association between time to in-hospital ACEi/ARB use and the combined outcome of death, need for mechanical ventilation, or need for dialysis in relevant subgroups and performed tests of interaction. To assess whether our initial exclusion criteria affected the findings, we repeated the analysis in the overall cohort.

Data analysis was performed using R software, version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Overall, the cohort had a mean age of 58.9 years (range 19–102) and consisted of 57.1% men, and 19.5% Black individuals. A total of 398 (23.6%) patients who were on ACEi/ARB before hospitalization for COVID-19 received at least 1 dose during their hospitalization (Table 1). Patients on an ACEi/ARB were older (mean of 65 versus 57 years) and had significantly more comorbidities compared with the non-ACEi/ARB group including diabetes (54.8% versus 22.0%), coronary artery disease (24.4% versus 9.2%), and chronic kidney disease (17.8% versus 12.3%) (Table 1). Laboratory testing was overall similar between both groups, except for a lower estimated glomerular filtration rate in patients taking an ACEi/ARB.

ACEi/ARB and Inflammatory Biomarkers

In unadjusted analysis, we found no significant differences in admission levels of biomarkers of inflammation between patients on ACEi/ARB and those who were not (Table 1). However, after accounting for the differences in clinical characteristics, ACEi/ARB use was associated with lower levels of suPAR and C-reactive protein (Table 2).

Outcomes

Overall, there were a total of 215 (12.8%) deaths, 407 (24.1%) patients who required mechanical ventilation, and 124 (7.4%) patients who required dialysis during their hospitalization. Patients on an ACEi/ARB during hospitalization had overall lower in-hospital mortality (13.9% versus 9.9%, P=0.014) and incidence of requiring mechanical ventilation (25.4% versus 20.1%, P=0.037) compared with those who were not on an ACEi/ARB (Figure 1). Differences in the incidence of requiring dialysis between both groups were not statistically significant. In multivariable analysis using binary logistic regression, we found a significant decrease in the odds of in-hospital death, requiring mechanical ventilation, and dialysis in patients who received ACEi/ARB during their hospitalization (Figure 2). This association was more pronounced after adjusting for age,

Table 1. Clinical Characteristics and Laboratory Testing Stratified by In-Hospital ACEi/ARB Use

Variables	Did not receive ACEi/ARB (n=1288)	ACEi/ARB (n=398)	*P* value
Age, y, n (%)			<0.001*
<45 y	300 (23.3)	32 (8.0)	
45–64 y	549 (42.6)	154 (38.7)	
65–79 y	313 (24.3)	157 (39.4)	
≥80 y	126 (9.8)	55 (13.8)	
Male sex, n (%)	558 (43.3)	165 (41.5)	0.55
Body mass index, kg/m^2, mean (SD)	31 (9)	33 (11)	0.001*
Black race, n (%)	248 (19.3)	80 (20.1)	0.76
History of tobacco use, n (%)	429 (33.3)	174 (43.7)	<0.001*
Hypertension, n (%)	488 (37.9)	371 (93.2)	<0.001*
Coronary artery disease, n (%)	119 (9.2)	97 (24.4)	<0.001*
Diabetes, n (%)	284 (22.0)	218 (54.8)	<0.001*
Congestive heart failure, n (%)	107 (8.3)	65 (16.3)	<0.001*
Chronic kidney disease, n (%)	158 (12.3)	71 (17.8)	0.006*
End-stage renal disease on dialysis, n (%)	43 (3.3)	7 (1.8)	0.15
Admission estimated glomerular filtration rate, mean (SD)	77 (32)	65 (28)	<0.001*
Presenting symptoms, n (%)			
Fever	831 (64.5)	229 (57.5)	0.014*
Shortness of breath	933 (72.4)	286 (71.9)	0.87
Diarrhea	356 (27.6)	108 (27.1)	0.90
Altered mental status	107 (8.3)	39 (9.8)	0.41
Hypoxia	525 (41.4)	147 (37.3)	0.16
Laboratory data, mean (SD)			
Hemoglobin, g/dL	12.9 (2.4)	12.8 (2.2)	0.49
White blood cell count, k/μL	7.4 (4.7)	7.0 (4.3)	0.19
Absolute neutrophil, count, k/μL	5.6 (3.6)	5.4 (2.8)	0.29
Absolute lymphocyte count, k/μL	1.2 (2.6)	1.1 (2.9)	0.70
Aspartate aminotransferase, IU/L	65.7 (221.4)	55.3 (71.1)	0.38
Alanine aminotransferase, IU/L	56.1 (304.6)	43.9 (56.5)	0.44
Total bilirubin, mg/dL	0.75 (1.3)	0.66 (0.4)	0.19
Inflammatory markers, median (interquartile range)			
Soluble urokinase plasminogen activator receptor, ng/mL	7.0 (5.0, 10.7)	7.7 (5.7, 10.3)	0.05
C-reactive protein, mg/dL	8.0 (4.1, 15.0)	7.3 (3.8, 13.9)	0.50
Lactate dehydrogenase, IU/L	1.4 (1.0, 1.9)	1.4 (1.1, 1.9)	0.25
Interleukin-6, pg/mL	18.4 (12.5, 94.0)	12.5 (12.5, 62.4)	0.75
Procalcitonin, ng/mL	0.40 (0.17, 1.43)	0.27 (0.12, 0.91)	0.06
Ferritin, ng/mL	659 (273, 1367)	636 (289, 1268)	0.49
D-dimer, FEU mg/L	0.92 (0.53, 1.91)	0.87 (0.53, 1.56)	0.31

ACEi/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; and IU, international units.
*Statistically significant *P* values at α=0.05.

sex, race, body mass index, and comorbidities. We similarly found ACEi/ARB use to be associated with lower odds of having prolonged hospitalization (>14 days), requiring admission to the intensive care unit, or experiencing acute respiratory distress syndrome (Table S2).

When examining the outcomes combined, in-hospital ACEi/ARB use was associated with lower odds (adjusted odds ratio [OR], 0.49; 95% CI, 0.36–0.66) of death, need for mechanical ventilation, or dialysis (Table 3). The effect size was similar when examining ACEi use (n=213, adjusted OR, 0.46; 95% CI, 0.31–0.67) and ARB use (n=185, adjusted OR, 0.53; 95% CI, 0.36–0.78) separately. The results were unchanged when using Cox proportional hazards modeling in-hospital ACEi/ARB as a time-dependent covariate (adjusted hazard ratio [HR], 0.48; 95% CI, 0.36–0.65) (Table 3). Further adjustment with inflammatory biomarkers in the models did not attenuate the association.

Finally, in estimating a causal effect of ACEi/ARB and accounting for serial blood pressure and creatinine measurements, we found ACEi/ARB use was associated with a lower risk of the composite outcome of death, need for mechanical ventilation or dialysis (HR, 0.35; 95% CI, 0.28– 0.82) (Figure 3).

Sensitivity Analyses

In sensitivity analyses, the inclusion of patients with prior ACEi/ARB use but discontinued ACEi ARB during hospitalization and those without prior ACEi/ARB use but initiated ACEi/ARB during hospitalization did not influence the results (Table S2). Additionally, we found the association between ACEi/ARB and lower odds of the combined outcome was stronger in patients with chronic kidney disease (*P* interaction=0.037) but did not differ according to age, sex, race, or other comorbidities (Figure 4). Associations between ACEi/ARB

Table 2. ACEi/ARB Use and Biomarkers of Thrombo-Inflammation

	Biomarker, standardized β, *P* value						
	SuPAR	C-reactive protein	Lactate dehydrogenase	Interleukin-6	Procalcitonin	Ferritin	D-dimer
ACEi/ARB use	−0.080, *P*=0.001*	−0.055, *P*=0.038*	−0.008, *P*=0.76	−0.032, *P*=0.45	0.003, *P*=0.93	−0.001, *P*=0.96	−0.044, *P*=0.11
Age	−0.063, *P*=0.030	−0.030, *P*=0.34	−0.098, *P*=0.003	−0.074, *P*=0.15	0.010, *P*=0.76	−0.032, *P*=0.32	−0.015, *P*=0.64
Male sex	0.001, *P*=0.95	−0.030, *P*=0.23	−0.084, *P*=0.001	−0.056, *P*=0.17	−0.007, *P*=0.78	−0.116, *P*<0.001	−0.027, *P*=0.31
Body-mass index	0.078, *P*=0.002	0.065, *P*=0.015	0.081, *P*=0.004	−0.004, *P*=0.94	−0.025, *P*=0.37	0.015, *P*=0.57	−0.022, *P*=0.43
Black race	−0.021, *P*=0.38	0.049, *P*=0.05	0.099, *P*<0.001	−0.026, *P*=0.52	0.012, *P*=0.66	0.077, *P*=0.003	−0.034, *P*=0.20
Diabetes	0.046, *P*=0.07	0.033, *P*=0.23	−0.037, *P*=0.20	0.044, *P*=0.33	−0.015, *P*=0.60	0.006, *P*=0.83	0.035, *P*=0.22
Hypertension	0.014, *P*=0.61	−0.009, *P*=0.76	−0.051, *P*=0.11	0.044, *P*=0.37	−0.046, *P*=0.15	−0.026, *P*=0.40	0.039, *P*=0.22
Coronary artery disease	0.023, *P*=0.36	0.001, *P*=0.98	−0.028, *P*=0.32	−0.032, *P*=0.47	−0.008, *P*=0.79	−0.042, *P*=0.13	−0.025, *P*=0.37
Heart failure	0.049, *P*=0.049	−0.026, *P*=0.32	0.009, *P*=0.75	0.003, *P*=0.94	−0.011, *P*=0.70	−0.045, *P*=0.10	−0.01, *P*=0.71
Admission estimated glomerular filtration rate	−0.325, *P*<0.001	−0.080, *P*=0.010	−0.117, *P*<0.001	−0.048, *P*=0.33	−0.054, *P*=0.10	−0.135, *P*<0.001	−0.039, *P*=0.22

ACEi/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; and SuPAR, soluble urokinase plasminogen activator receptor.
*Statistically significant *P* values at α=0.05 for associations between ACEi/ARB and biomarkers.

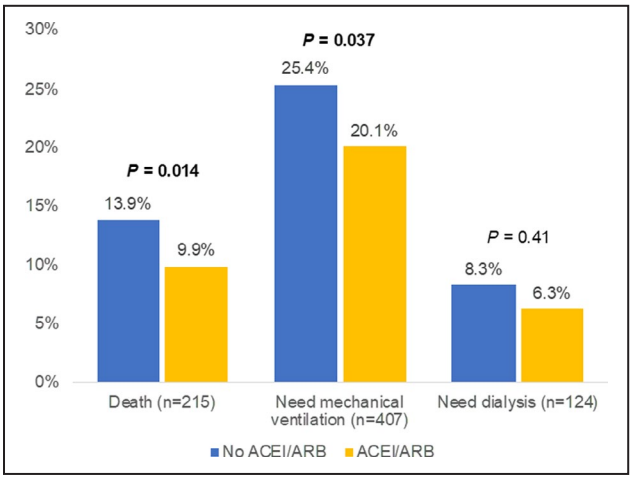

Figure 1. Cumulative incidence of outcomes by in-hospital use of ACEi/ARB.
Bar graphs showing the cumulative incidence of death, need for mechanical ventilation, and need for renal replacement therapy by in-hospital use of ACEi/ARB. ACEi/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

use and outcomes in the overall cohort (n=2044) were consistent with the analysis in our defined subpopulation (Table S2).

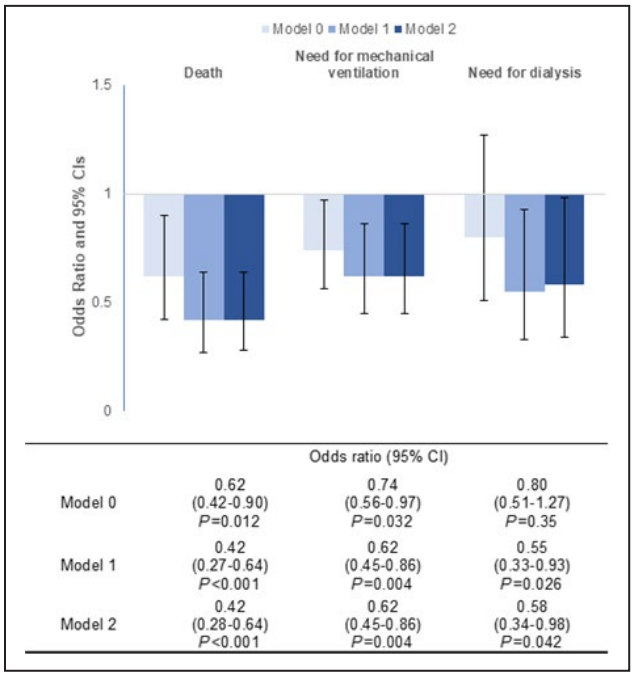

Figure 2. In-hospital ACEi/ARB use and risk of death, need for mechanical ventilation, and need for renal replacement therapy.
Bar graph depicting the odds ratio (OR) and 95% CI for the 3 different outcomes using 3 different models to calculate odds ratios. Model 0 was unadjusted. Model 1 was adjusted for age, sex, race, BMI, diabetes, hypertension, coronary artery disease, congestive heart failure, admission GFR, and institution. Model 2 incorporated the aforementioned variables in addition to mean arterial pressure on presentation. ACEi/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; and GFR, glomerular filtration rate.

Table 3. Multivariable Analysis of the Association Between In-Hospital ACEi/ARB Use and Outcomes

Variables	Death, mechanical ventilation, or dialysis (n=480)			
	Odds ratio* (95% CI)	*P* value	Hazard ratio† (95% CI)	*P* value
In-hospital ACEi/ARB use	0.49 (0.36–0.66)	<0.001‡	0.48 (0.36–0.65)	<0.001‡
Age, per 10 y	1.00 (0.91–1.08)	0.90	0.94 (0.88–1.00)	0.06
Male sex	1.43 (1.14–1.80)	0.002‡	1.21 (1.00–1.46)	0.046‡
Black race	1.29 (0.98–1.71)	0.07	1.27 (1.02–1.59)	0.030‡
Body mass index, per 5 kg/m^2	1.13 (1.06–1.21)	<0.001‡	1.07 (1.03–1.11)	<0.001‡
Diabetes	1.12 (0.86–1.46)	0.41	1.08 (0.88–1.33)	0.46
Hypertension	1.22 (0.93–1.61)	0.15	1.24 (1.00–1.55)	0.05
Coronary artery disease	0.99 (0.69–1.41)	0.93	1.12 (0.84–1.48)	0.45
Congestive heart failure	0.96 (0.66–1.39)	0.82	0.83 (0.62–1.11)	0.21
Admission eGFR, per 5 mL/min higher	0.95 (0.93–0.98)	<0.001‡	0.95 (0.94–0.97)	<0.001‡

ACEi/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; and eGFR, estimated glomerular filtration rate.

*Based on binary logistic regression model adjusted for age, sex, race, body mass index, diabetes, hypertension, coronary artery disease, congestive heart failure, and admission eGFR.

†Based on time-dependent Cox proportional hazards model adjusted for age, sex, race, body mass index, diabetes, hypertension, coronary artery disease, congestive heart failure, and admission eGFR.

‡ Based on time-dependent Cox proportional hazards model adjusted for age, sex, race, body mass index, diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, and admission eGFR.

DISCUSSION

In this multicenter observational study of patients hospitalized for COVID-19, patients previously on ACEi/ARB who were treated with ACEi/ARB during their hospitalization had better in-hospital outcomes compared with those not on ACEi/ARB despite having a significantly higher burden of comorbidities. Prior use of ACEi/ARB was associated with overall lower levels of inflammatory biomarkers on admission when accounting for comorbidities, suggesting an attenuated inflammatory response to SARS-CoV-2 in recipients of ACEi/ARB as a potential mechanism for the benefits observed in these patients. These findings support guidelines issued by various medical societies recommending the continued use of these medications as indicated.[33,34] Through marginal structural modeling estimating causal effects, we highlight the potential causal link between the use of ACEi/ARB and better COVID-19 related outcomes, which is currently undergoing study in a randomized clinical trial setting.[26]

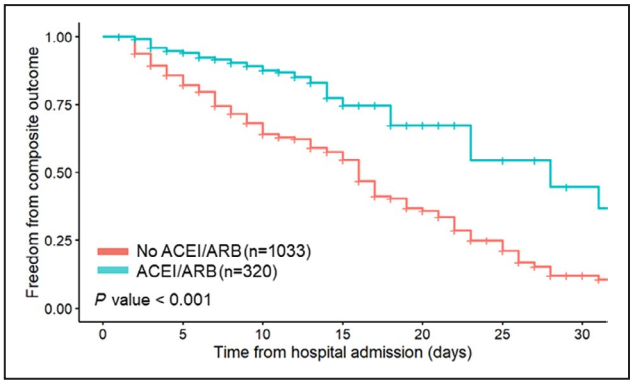

Figure 3. Weighted Kaplan-Meier curve comparing survival by in-hospital ACEi/ARB use.
Weighted Kaplan-Meier curve depicting survival probabilities of combined outcome of death, need for mechanical ventilation, or dialysis by in-hospital ACEi/ARB over 30 days of hospitalization. Based on marginal structural model with weights accounting for age, sex, race, BMI, diabetes, hypertension, coronary artery disease, congestive heart failure, and serial measurements of blood pressure and serum creatinine. ACEi/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; and BMI, body mass index.

We address limitations of prior observational studies examining the association between ACEi/ARB and outcomes in several ways. First, we do not limit our analysis to patients with hypertension as was done in most other studies, as there are other indications for the use of ACEi/ARB including diabetes, chronic kidney disease, and congestive heart failure. In sensitivity analysis we found improved outcomes across these relevant patient subgroups. Although other cohorts included all patients with a positive SARS-CoV-2 test, we included only patients presenting with and hospitalized primarily for symptomatic COVID-19—a population that would be the target of a therapeutic trial. We have excluded patients who had ACEi/ARB completely discontinued during their hospitalization and those who were newly started on ACEi/ARB to minimize selection bias, as the former represents a higher risk patient group and the latter a lower risk patient group, which would both skew findings toward the benefits of ACEi/ARB. Additionally, our study is the first that incorporates granular and longitudinal data with daily in-hospital creatinine and blood pressure values. Lastly, we examined the association between ACEi/ARB and outcomes using several approaches,

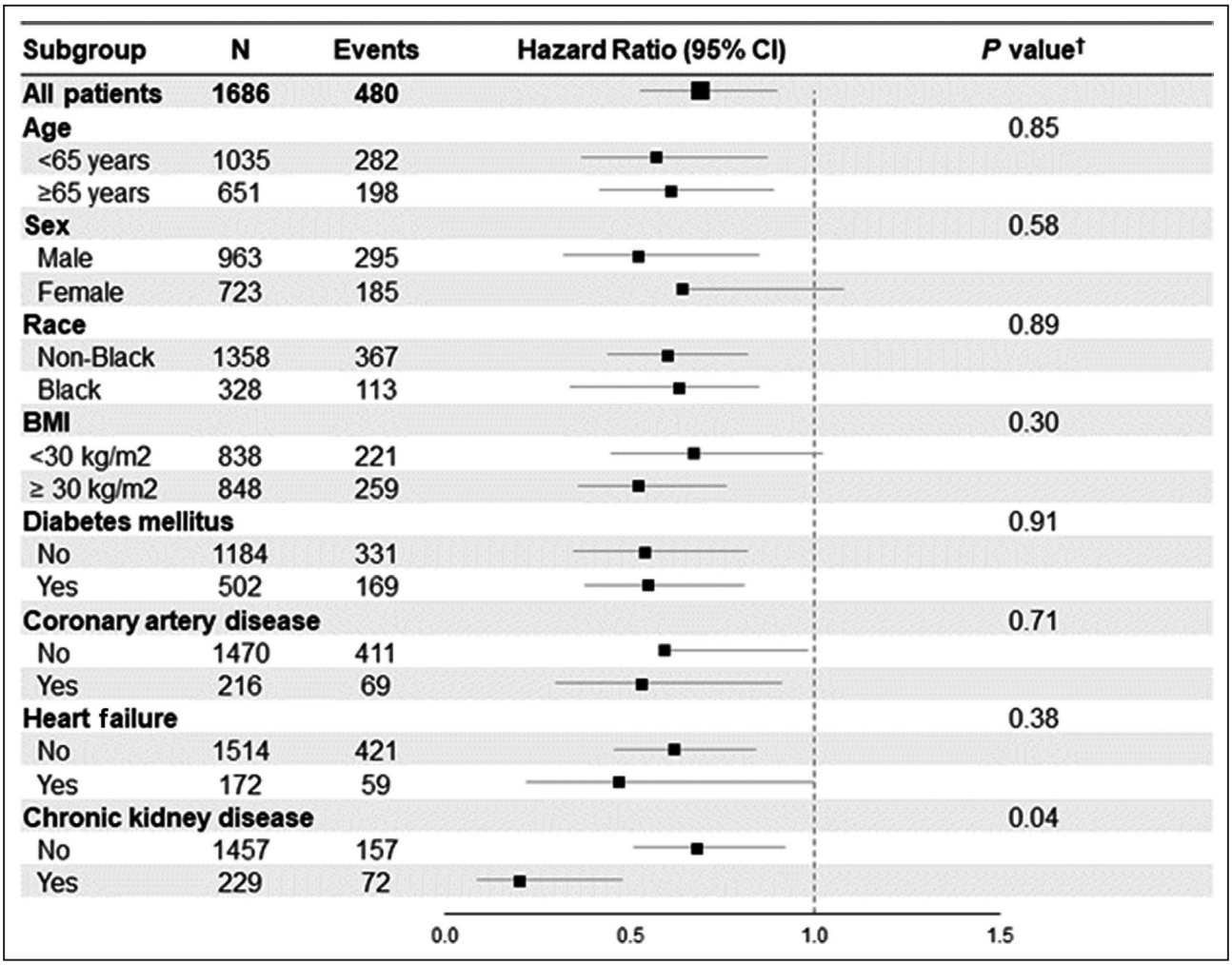

Figure 4. Hazard ratio of the combined outcome of death, need for mechanical ventilation or dialysis for in-hospital ACEi/ARB use stratified by subgroups.

Forest plot showing the hazard ratios for the combined outcome of death, need for mechanical ventilation, or dialysis for in-hospital ACEi/ARB use stratified by subgroups using a time-dependent Cox proportional hazards model. †*P* value for test of interaction. ACEi/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; and BMI, body mass index.

including marginal structural modeling which allows us to estimate causal inferences while accounting for the most important confounders (serial blood pressure measurements and creatinine levels) and the risk of survivor bias.

The mechanisms by which ACEi/ARB could improve COVID-19 related outcomes are unclear. Initial fears regarding the risks of ACEi/ARB in COVID-19 have largely been based on murine and human studies that have shown increased ACE2 expression in various tissues after ACEi/ARB administration[16–18] and the discovery that ACE2 serves as the SARS-CoV-2 host receptor.[5,35] Conversely, studies have demonstrated that ACE2 has a lung protective effect in patients with acute respiratory distress syndrome, further complicating the overall theoretical role that ACEi/ARB may have in patients with COVID-19.[15] Our study provides supportive evidence for a beneficial impact of ACEi/ARB in patients with COVID-19, which may be becauseof its purported lung protective mechanisms. In sensitivity analyses we found the association to be stronger in patients with chronic kidney disease, consistent with its known renoprotective effects in this patient subgroup.

Another potential mechanism for the benefits of ACEi/ARB is through the attenuation of the inflammatory response. ACEi/ARB have previously been shown to attenuate vascular microinflammation in hypertensive patients via angiotensin II receptor blockade and are associated with reduced levels of inflammatory cytokines such as C-reactive protein, a mechanism that could theoretically counter the inflammatory state of COVID-19.[12,36,37] We found use of ACEi/ARB was indeed associated with lower levels of suPAR and C-reactive protein measured on admission, consistent with the prior observations of an anti-inflammatory effect for ACEi/ARB. Serial biomarker measurements

could shed further light on whether in-hospital ACEi/ARB use affects the course of the inflammatory response. Lastly, the early diversion of the survival curves in our study suggests that the benefits of ACEi/ARB are likely derived from prior use rather than acute use of ACEi/ARB. Clinical trial evidence for the effectiveness of ACEi/ARB in improving COVID-19-related outcomes will spur experimental research to further delineate underlying mechanisms and perhaps identify new indications for the use of ACEi/ARB in the context of the COVID-19 pandemic.

Limitations

The major limitation of the study is its observational nature. Although we have carefully characterized and adjusted for known confounders in this multipronged analysis, no amount of adjustment can fully account for all potential confounders, and ultimately a randomized study is needed to confirm the benefit of ACEi/ARB in COVID-19. The University of Michigan M^2C^2 was unfortunately the only ISIC site with serial blood pressure and creatinine measurements available; however, it is the largest contributing site (n=1357) in which findings were consistent with the overall cohort.

CONCLUSIONS

Among patients hospitalized for symptomatic COVID-19, use of ACEi/ARB was associated with lower levels of inflammatory markers and lower risk of in-hospital outcomes after accounting for numerous confounders including serial blood pressure, creatinine measures, and survivor bias. In the absence of acute contraindications to ACEi/ARB such as hypotension or hemodynamic instability, ACEi/ARB should be continued or resumed. Whether patients hospitalized for COVID-19 without an indication for ACEi/ARB would benefit from treatment warrants evaluation in a clinical trial setting.

ARTICLE INFORMATION

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Disclosures

Eugen-Olsen is a cofounder, shareholder, and chief scientific officer of Virogates. Reiser is cofounder of Trisaq, a biotechnology company developing drugs targeting suPAR. Hayek and Reiser are members of the scientific advisory board of Walden Biosciences. Giamarellos-Bourboulis has received honoraria from Abbott CH, Angelini Italy, InflaRx GmbH, MSD Greece, XBiotech Inc., and B·R·A·H·M·S GmbH (Thermo Fisher Scientific); independent educational grants from AbbVie Inc, Abbott CH, Astellas Pharma Europe, AxisShield, bioMérieux Inc, Novartis, InflaRx GmbH, and XBiotech Inc; and funding from the FrameWork 7 program HemoSpec (granted to the National and Kapodistrian University of Athens), the Horizon2020 Marie-Curie Project European Sepsis Academy (granted to the National and Kapodistrian University of Athens), and the Horizon 2020 European Grant ImmunoSep (granted to the Hellenic Institute for the Study of Sepsis). The remaining authors have no disclosures to report.

Supplemental Material

Appendix S1. ISIC Investigators
Tables S1–S2
Figure S1

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Supplemental Material

Appendix S1. ISIC Investigators

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Table S1. Participating centers and number of patients included in the substudy.

Institution	Number of patients included
University of Michigan in Ann Arbor, MI USA	1608
Rush University, Chicago, IL USA	105
University of Copenhagen at Hvidovre, Denmark	89
Attikon University Hospital in Athens, Greece	90
University Hospital of Dusseldorf, Germany	27
University of Thessaly, Greece	29
Charite de Berlin, Germany	78
University Hospital of Cologne, Germany	18
Total	**2044**

Table S2. In-hospital ACEi/ARB use and risk of death, need for mechanical ventilation, and need for renal replacement therapy in overall cohort (N=2,044).

	Death		Need for Mechanical Ventilation		Need for Renal Replacement Therapy	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Model 0	0.57 (0.41, 0.81)	0.002	0.75 (0.59, 0.96)	0.024	0.63 (0.42, 0.96)	0.03
Model 1	0.44 (0.30, 0.63)	<0.001	0.66 (0.50, 0.87)	0.003	0.64 (0.48, 0.87)	0.004
Model 2	0.45 (0.31, 0.66)	<0.001	0.67 (0.51, 0.88)	0.005	0.54 (0.34, 0.87)	0.012

Model 0: Unadjusted

Model 1: age, sex, race, BMI, diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, admission GFR, and institution

Model 2: Model 1 + baseline mean arterial pressure

Overall cohort including patients taking an ACEi/ARB prior to hospitalization but were discontinued during hospitalization and those in whom an ACEi/ARB was initiated during hospitalization.

Figure S1. Study sample flow chart.