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COVID-19 morbidity and mortality associated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers use among 14,129 patients with hypertension from a US integrated healthcare system

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ABSTRACT

Objective: Although recent evidence suggests no increased risk of severe COVID-19 outcomes associated with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) use, the relationship is less clear among patients with hypertension and diverse racial/ethnic groups. This study evaluates the risk of hospitalization and mortality among patients with hypertension and COVID-19 in a large US integrated healthcare system.

Methods: Patients with hypertension and COVID-19 (between March 1- September 1, 2020) on ACEIs or ARBs were compared with patients on other frequently used antihypertensive medications.

Results: Among 14,129 patients with hypertension and COVID-19 infection (mean age 60 years, 48% men, 58% Hispanic), 21% were admitted to the hospital within 30 days of COVID-19 infection. Of the hospitalized patients, 24% were admitted to intensive care units, 17% required mechanical ventilation, and 10% died within 30 days of COVID-19 infection. Exposure to ACEIs or ARBs prior to COVID-19 infection was not associated with an increased risk of hospitalization or all-cause mortality (rate ratios for ACEIs vs other antihypertensive medications = 0.98, 95% CI: 0.88, 1.08; ARBs vs others = 1.00, 95% CI: 0.90, 1.11) after applying inverse probability of treatment weights. These associations were consistent across racial/ethnic groups. Use of ACEIs or ARBs during hospitalization was associated with a lower risk of all-cause mortality (odds ratios for ACEIs or ARBs vs others = 0.50, 95% CI: 0.34, 0.72).

Conclusion: Our study findings support continuation of ACEI or ARB use for patients with hypertension during the COVID-19 pandemic and after COVID-19 infection.

1. Introduction

Early in the COVID-19 pandemic, there were concerns regarding increased risk of infection by SARS-CoV-2, the virus responsible for the COVID-19 pandemic, due to angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) use [1]. Current evidence suggests that ACEIs or ARBs are not associated with increased risk of infection or severity of COVID-19 [2]. However, the association between use of ACEIs or ARBs with severe COVID-19 outcomes such as hospitalization and death are less clear among patients with hypertension.

Many epidemiologic studies have investigated the use of ACEIs or ARBs in the general population with COVID-19 infection [3] rather than patients with hypertension. This approach may introduce collider bias since hypertension increases the likelihood of ACEI or ARB use and a test for COVID-19 [4]. Furthermore, the findings have not always been consistent in the different populations studied. One United States (US) study of 1735 patients who tested positive for COVID-19 early in the pandemic found that patients who took either ACEIs or ARBs were more likely to be admitted to the hospital compared to patients who did not take ACEIs or ARBs [5]. However, a recent meta-analysis of 25 studies conducted throughout the world showed that use of ACEIs or ARBs was

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Abbreviations

ACEI	angiotensin-converting enzyme inhibitor
ARB	angiotensin receptor blocker
AKI	acute kidney injury
BB	beta-blocker
BP	blood pressure
CAD	coronary artery disease
CCB	calcium channel blocker
CI	confidence interval
CKD	chronic kidney disease
COVID-19	coronavirus disease 2019
DNI	do not intubate
DNR	do not resuscitate
eGFR	estimated glomerular filtration rate
ICU	intensive care unit
IPTW	inverse probability treatment weighting
KPSC	Kaiser Permanente Southern California
OR	odds ratio
PS	propensity score
RR	rate ratio
RT-PCR	reverse transcription polymerase chain reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TD	thiazide diuretic

not associated with mortality in the general population, while use of ACEIs or ARBs was associated with decreased risk of mortality among patients with hypertension [6]. These studies varied by geographic location, demographics, cohort size, and definition of the reference group which makes it even more difficult to draw conclusions. Moreover, the associations between ACEIs or ARBs and severity of COVID-19 in various racial/ethnic groups in the US are largely unknown as many studies included relatively small homogenous populations.

The current study evaluated the risk of hospitalization and all-cause mortality among patients with hypertension and COVID-19 taking ACEIs or ARBs compared with other frequently used antihypertensive medications from a large and diverse racial/ethnic population in the US. This study also evaluated all-cause mortality associated with use of ACEIs or ARBs during hospitalization due to COVID-19.

2. Materials and methods

Anonymized data that support the findings of this study may be made available from the investigative team in the following conditions: 1) agreement to collaborate with the study team on all publications, 2) provision of external funding for administrative and investigator time necessary for this collaboration, 3) demonstration that the external investigative team is qualified and has documented evidence of training for human subjects protections, and 4) agreement to abide by the terms outlined in data use agreements between institutions.

2.1. Study population

We identified adult patients with hypertension as of March 1, 2020 from the hypertension registry of Kaiser Permanente Southern California (KPSC), a large US integrated healthcare system. The hypertension registry consists of patients who were diagnosed with hypertension [7]. Patients with hypertension but not on antihypertensive medications were also included in the registry. The primary analysis was conducted among patients from the hypertension registry with COVID-19 infection between March 1 – September 1, 2020. COVID-19 infection was defined as a lab-confirmed, positive reverse transcription polymerase chain reaction (RT-PCR) test for COVID-19 or a diagnosis of COVID-19. The first date of a positive RT-PCR test result or a diagnosis of COVID-19 defined the index date. Patients were required to be continuously eligible as KPSC members for 12 months prior to the index date (baseline). A secondary analysis was conducted among patients who were hospitalized at a KPSC facility within 30 days after being tested or diagnosed with COVID-19 infection. To evaluate exposure to ACEIs or ARBs during hospitalization and associated mortality, we applied additional exclusion criteria that may have affected the inpatient ACEI or ARB use or mortality outcome. We excluded patients with a do-not-resuscitate or do-not-intubate (DNR/DNI) order, systolic blood pressure < 90 mm Hg at hospital admission, hyperkalemia ($K > 5.0$ mEq/L) at hospital admission, and acute kidney injury (AKI) within 3 days from hospital admission defined by an increase in serum creatinine by ≥ 0.3 mg/dL or ≥ 1.5 times the lowest serum creatinine value. We excluded patients who did not receive any antihypertension medication during hospitalization since these patients may not be stable enough to take any antihypertension medications. The study protocol was reviewed and approved by the KPSC institutional review board committee.

2.2. Antihypertensive medication exposure prior to COVID-19 infection

We used outpatient pharmacy records to define antihypertensive medication exposure prior to COVID-19 infection. KPSC is an integrated healthcare system where >95% of members have a pharmacy benefit and have an incentive to fill their medication within the system. The KPSC's pharmacy data system captures all dispensed prescriptions. Additionally, medications filled outside KPSC are captured through pharmacy claims. A fill of antihypertensive medication covering the index date defined medication exposure. We allowed a 20-day grace period prior to the index date to account for patients' medication-taking behavior. A gap of longer than 20 days from the index date was considered as having no antihypertensive medication. We classified antihypertensive medication groups as 1) any ACEIs, 2) any ARBs, 3) calcium channel blockers (CCB), beta-blockers (BB), or thiazide diuretics (TD) without the use of ACEIs or ARBs, 4) others (loop diuretics, potassium-sparing diuretics, centrally acting agents, alpha-blockers, and mineralocorticoid receptor antagonists) without the use of ACEIs or ARBs, and 5) no antihypertensive medication.

2.3. Antihypertensive medication exposure during hospitalization after COVID-19 infection

We evaluated the use of ACEIs or ARBs during hospitalization. Any receipt of ACEIs or ARBs were considered as medication exposure during hospitalization after COVID-19 infection. Patients who received CCBs, BBs, TDs, or other classes of medications without ACEIs or ARBs were categorized separately.

2.4. Outcomes

The primary outcomes of interest were hospitalization inside or outside KPSC or all-cause mortality, jointly and separately, within 30 days from COVID-19 infection. All-cause mortality within 30 days from COVID-19 infection was determined by hospital discharge records and membership files. Among hospitalized patients at a KPSC facility only, all-cause mortality within 30 days from COVID-19 infection was evaluated as a primary outcome. The secondary outcomes were admission to an intensive care unit (ICU), invasive ventilator use, cardiac injury defined by troponin I ≥ 0.04 ng/mL during hospitalization, and AKI defined by an increase in serum creatinine by ≥ 0.3 mg/dL within 2 days or ≥ 1.5 times the lowest serum creatinine value within the last 7 days during hospitalization [8].

2.5. Covariates

We evaluated age, sex, race/ethnicity, neighborhood income and education, insurance, body mass index categories (under/normal weight, overweight, obese, severely obese, morbidly obese), and smoking status at the index date. Outpatient blood pressure (BP) and laboratory measures closest and prior to the index date were defined as baseline values. The lowest BP measure was selected in the case of multiple BP measures in the same encounter. Comorbidities and outpatient medication use were evaluated during the 12-month baseline period. For hospitalized patients, we evaluated laboratory measures, oxygen saturation levels, temperature at the time of admission, timing of COVID-19 positivity or diagnosis, and medication use during hospitalization.

2.6. Statistical analyses

Descriptive analysis was conducted to compare patient and clinical characteristics by antihypertensive medication exposure before COVID-19 infection or inpatient use among those hospitalized patients. The primary outcomes of hospitalization or all-cause mortality within 30 days of COVID-19 infection were compared across antihypertensive medication exposure groups among all patients with hypertension and COVID-19 infection using inverse probability treatment weighting (IPTW) with stabilized propensity scores (PS). PS representing the probability of receiving CCBs/BBs/TDs was estimated using logistic regression and accounted for patients' profile including age, sex, race/ethnicity, Elixhauser comorbidity index, body mass index, socioeconomic status, other comorbidities such as prior history of pneumonia, diabetes, heart failure, asthma, interstitial lung disease, and chronic obstructive pulmonary disease, and other medication use at baseline. Separate pseudo-populations using IPTW were established in comparison to patients on CCBs/BBs/TDs: 1) ACEIs, 2) ARBs, and 3) no antihypertensive medication. Other classes (loop diuretics, etc.) were not investigated due to a small sample size. To minimize potential bias from impact of extreme IPTWs, stabilized PS larger than 99th percentile or smaller than 1st percentile were trimmed [9]. The association between hospitalization or all-cause mortality and antihypertensive medication classes was assessed by Poisson regression with robust error variance and rate ratios (RRs) and 95% confidence intervals (CI) were reported in the pseudo-populations accounting for covariates with absolute standardized mean differences >0.1 to reduce residual imbalance. Logistic regression was performed in the same pseudo-populations for odds ratios (ORs) of all-cause mortality outcomes within 30 days of COVID-19 infection. To further investigate the association among different age, sex, and racial/ethnic subgroups, subgroup specific IPTW methods were applied [10].

The secondary analyses were conducted to determine the association between ACEIs or ARBs use during hospitalization after COVID-19 infection and the risk of all-cause mortality. PS representing the probability of receiving CCBs/BBs/TDs or other classes during hospitalization were estimated using logistic regression by using patient characteristics such as age, sex, race/ethnicity, pre-existing comorbidities and additional measures at hospital admission including the oxygen saturation levels, temperature, eGFR, troponin I, and B-type natriuretic peptide. ORs with 95% CIs for all-cause mortality associated with ACEI or ARB use during the hospital stay compared with CCB/BB/TD or other antihypertensive medication use were reported from logistic regression models after IPTWs. Associations with other common outcomes with >10% prevalence including admission to ICU, invasive ventilator use, AKI, and cardiac injury were assessed using Poisson regression with robust error variance after IPTW. In addition, we conducted sensitivity analyses for the subgroup of patients who were on ACEIs or ARBs prior to COVID-19 infection.

All statistical analyses were performed in SAS Enterprise Guide 7.1 (SAS Institute, Cary NC). A $p < 0.05$ is considered statistically significant with no multiplicity adjustment.

The study's sponsors had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

3. Results

We included 14,129 patients with hypertension and who tested positive for RT-PCR or had a diagnosis of COVID-19 (mean age 60 years, 48% men) (Supplemental Fig. S1). More than half of patients were Hispanic (58%) followed by non-Hispanic white (20%), non-Hispanic black (10%), and Asian/Pacific Islander (10%). Of the total, 33% were exposed to ACEIs, 18% to ARBs, 19% to CCBs/BBs/TDs, and 29% were not on antihypertensive medications at the time of COVID-19 infection (Table 1). Compared with patients on CCBs/BBs/TDs, a higher proportion of patients on ACEIs were male, Hispanic, and had diabetes. They also had a lower percentage of heart failure and arrythmia. Patients on ARBs were older, had a higher percentage of patients who were of Asian/Pacific Islander heritage and had diabetes compared with patients on CCBs/BBs/TDs. Patients not on antihypertensive medications were younger, had a higher percentage of patients who were Hispanic, had lower neighborhood income, higher BP, higher total cholesterol levels and had fewer comorbidities compared with patients on CCBs/BBs/TDs.

3.1. Outcomes associated with antihypertensive medication exposure prior to COVID-19 infection

Table 2 shows hospitalization, morbidity, and mortality outcomes by medication exposure prior to COVID-19 infection. Of the 14,129 patients with COVID-19 infection, 21% (N = 3010) were admitted to the hospital or died within 30 days from the infection. Over 97% were admitted to the hospital while 83 patients died without hospitalization. The percentages of hospitalization or all-cause mortality were similar across antihypertensive exposure groups of ACEIs, ARBs, and CCBs/BBs/TDs. After balancing patient characteristics using IPTW (Supplemental Figs. S2-S4), exposure to ACEIs or ARBs prior to COVID-19 infection was not associated with an increased risk of hospitalization or mortality (Fig. 1) (RR for ACEIs vs CCBs/BBs/TDs = 0.98, 95% CI: 0.88, 1.08; ARBs vs CCBs/BBs/TDs = 1.00, 95% CI: 0.90, 1.11). These findings were consistent across age, sex, and racial/ethnic subgroups. Exposure to ACEIs or ARBs prior to COVID-19 infection was not associated with all-cause mortality, but use of no antihypertensive medications prior to infection was associated with a higher risk of all-cause mortality compared with the CCB/BB/TD group (OR = 1.39, 95% CI: 1.10, 1.76) (Supplemental Fig. S5).

3.2. Outcomes associated with antihypertensive medication exposure during hospitalization after COVID-19 infection

Among 2921 patients who were hospitalized, we excluded 887 patients who were admitted to a facility outside of KPSC and 361 patients who did not receive any antihypertensive medications during hospitalization, leaving 1350 patients for secondary analysis. Details of excluded patients are shown in Supplemental Fig. S1. Of the 1350 hospitalized patients, about a half (51%) received ACEIs or ARBs after hospital admission, and the rest received CCBs/BBs/TDs or other classes of antihypertensive medications (Supplementary Table S1). Patient and clinical characteristics of hospitalized patients are shown in Supplementary Table S1. Patients who received ACEIs or ARBs during hospitalization were younger, had a higher percentage of Hispanic and a lower percentage of chronic kidney disease (CKD) and coronary artery disease (CAD) compared with patients who received other classes of antihypertensive medications during the hospitalization. Among patients who received ACEIs or ARBs prior to COVID-19 infection (N = 778), 67% continued ACEIs or ARBs after hospital admission while 33% received other classes of medications during the hospital stay

Table 1
Patient and clinical characteristics by antihypertensive drug exposure among patients with hypertension and COVID-19 (N = 14,129).

	ACEI	ARB	CCB or BB or TD	Other Antihypertensives*	No Antihypertensives
	(N = 4652)	(N = 2546)	(N = 2640)	(N = 150)	(N = 4141)
	Row Percent = 33%	18%	19%	1%	29%
Age in years	59.5 (12.6)	62.3 (12.4)	60.6 (14.3)	66.7 (14.7)	57.7 (16.0)
Men	2487 (53.5%)	1123 (44.1%)	1075 (40.7%)	100 (66.7%)	2007 (48.5%)
Race/ethnicity					
Asian/Pacific Islander	352 (7.6%)	420 (16.5%)	320 (12.1%)	14 (9.3%)	309 (7.5%)
Non-Hispanic Black	372 (8%)	241 (9.5%)	355 (13.4%)	11 (7.3%)	426 (10.3%)
Hispanic	2927 (62.9%)	1321 (51.9%)	1304 (49.4%)	79 (52.7%)	2520 (60.9%)
Non-Hispanic White	891 (19.2%)	502 (19.7%)	589 (22.3%)	44 (29.3%)	787 (19.0%)
Other/Unknown	110 (2.4%)	62 (2.4%)	72 (2.7%)	2 (1.3%)	99 (2.4%)
Neighborhood Income					
$0-49 k	1252 (26.9%)	608 (23.9%)	638 (24.2%)	34 (22.7%)	1178 (28.4%)
$50-79 k	2012 (43.3%)	1089 (42.8%)	1083 (41%)	70 (46.7%)	1749 (42.2%)
$80-99 k	781 (16.8%)	464 (18.2%)	517 (19.6%)	24 (16%)	689 (16.6%)
≥$100 k	603 (13%)	382 (15%)	401 (15.2%)	22 (14.7%)	516 (12.5%)
Missing	4 (0.1%)	3 (0.1%)	1 (0%)	–	9 (0.2%)
Neighborhood Education (% of ≥High School Graduate)					
0–75%	2307 (49.6%)	1122 (44.1%)	1098 (41.6%)	68 (45.3%)	1965 (47.5%)
76–100%	2343 (50.4%)	1421 (55.8%)	1541 (58.4%)	82 (54.7%)	2167 (52.3%)
Missing	2 (0%)	3 (0.1%)	1 (0%)	–	9 (0.2%)
Insurance Type					
Commercial	2911 (62.8%)	1431 (56.3%)	1588 (60.4%)	43 (28.7%)	2688 (65.1%)
Private pay	1221 (26.4%)	782 (30.8%)	671 (25.5%)	80 (53.3%)	912 (22.1%)
Medicare	296 (6.4%)	240 (9.4%)	266 (10.1%)	20 (13.3%)	273 (6.6%)
Medicaid	203 (4.4%)	87 (3.4%)	105 (4%)	7 (4.7%)	255 (6.2%)
Other/Missing	19 (0.4%)	6 (0.2%)	10 (0.4%)	–	13 (0.3%)
Body Mass Index (kg/m^2)	32.9 (7.2)	32.8 (7.0)	31.9 (7.0)	32.6 (7.8)	32.1 (7.7)
<25, Under/Normal Weight	380 (8.2%)	244 (9.6%)	331 (12.5%)	20 (13.3%)	577 (13.9%)
25–29.9, Overweight	1246 (26.8%)	692 (27.2%)	733 (27.8%)	44 (29.3%)	951 (23%)
30–34.9, Obese	1240 (26.7%)	699 (27.5%)	708 (26.8%)	37 (24.7%)	960 (23.2%)
35–39.9, Severely Obese	766 (16.5%)	457 (17.9%)	389 (14.7%)	12 (8%)	575 (13.9%)
≥40, Morbidly Obese	606 (13%)	317 (12.5%)	292 (11.1%)	31 (20.7%)	474 (11.4%)
Missing	250 (5%)	121 (4%)	156 (4%)	8 (2%)	395 (10%)
Smoking					
Current	126 (2.7%)	52 (2%)	76 (2.9%)	5 (3.3%)	136 (3.3%)
Former	1273 (27.4%)	727 (28.6%)	689 (26.1%)	65 (43.3%)	971 (23.4%)
Never	2880 (61.9%)	1627 (63.9%)	1686 (63.9%)	71 (47.3%)	2419 (58.4%)
Missing	373 (8%)	140 (5.5%)	189 (7.2%)	9 (6%)	615 (14.9%)
Blood Pressure (BP) (mmHg)					
Systolic BP (SBP)	129.1 (14.2)	131.5 (14.7)	129.8 (14.0)	128.3 (16.5)	131.1 (14.5)
Diastolic BP (DBP)	73.2 (11.6)	72.9 (12.3)	74.0 (12.1)	72.3 (12.4)	76.4 (12.7)
SBP/DBP <140/90	3529 (75.9%)	1878 (73.8%)	2001 (75.8%)	116 (77.3%)	2519 (60.8%)
SBP/DBP <130/80	1726 (37.1%)	838 (32.9%)	903 (34.2%)	60 (40.0%)	1079 (26.1%)
Labs					
HbA1c (%)	7.1 (1.8)	7.0 (1.6)	6.5 (1.4)	6.6 (1.6)	7.0 (2.1)
Total Cholesterol (mg/dL)	167.0 (45.6)	163.0 (42.8)	172.9 (43.3)	156.5 (44.5)	176.5 (45.5)
HDL-C (mg/dL)	45.8 (12.7)	46.6 (12.9)	48.6 (14.3)	46.6 (16.4)	46.8 (13.0)
LDL-C (mg/dL)	93.0 (36.1)	88.9 (34.5)	97.5 (35.9)	88.4 (39.7)	103.2 (37.9)
Triglycerides (mg/dL)	175.4 (205.1)	169.3 (136.6)	156.8 (94.3)	134.4 (76.1)	166.2 (117.9)
Pre-existing conditions					
Elixhauser comorbidity score					
0	219 (4.7%)	78 (3.1%)	147 (5.6%)	4 (2.7%)	598 (14.4%)
1–3	2997 (64.4%)	1426 (56%)	1566 (59.3%)	64 (42.7%)	2282 (55.1%)
4+	1436 (30.9%)	1042 (40.9%)	927 (35.1%)	82 (54.7%)	1261 (30.5%)
Diabetes	1987 (42.7%)	1185 (46.5%)	682 (25.8%)	57 (38%)	1119 (27%)
Heart failure	90 (1.9%)	85 (3.3%)	112 (4.2%)	15 (10%)	70 (1.7%)
CAD	281 (6%)	224 (8.8%)	207 (7.8%)	19 (12.7%)	216 (5.2%)
CKD	268 (5.8%)	241 (9.5%)	215 (8.1%)	21 (14%)	174 (4.2%)
Asthma	310 (6.7%)	306 (12%)	276 (10.5%)	20 (13.3%)	265 (6.4%)
COPD	120 (2.6%)	104 (4.1%)	128 (4.8%)	9 (6%)	120 (2.9%)
Arrhythmia	473 (10.2%)	341 (13.4%)	459 (17.4%)	27 (18%)	476 (11.5%)
Valvular Disease	112 (2.4%)	83 (3.3%)	132 (5%)	14 (9.3%)	106 (2.6%)
Pulmonary Circulation Disease	75 (1.6%)	53 (2.1%)	81 (3.1%)	11 (7.3%)	72 (1.7%)
PVD	725 (15.6%)	579 (22.7%)	571 (21.6%)	57 (38%)	717 (17.3%)
Cancer	127 (2.7%)	74 (2.9%)	82 (3.1%)	0 (0%)	79 (1.9%)
Outpatient Medications Prior to the Index Date					
Lipid lowering	3036 (65.3%)	1791 (70.3%)	1346 (51%)	91 (60.7%)	1340 (32.4%)
Antiplatelets	384 (8.3%)	292 (11.5%)	199 (7.5%)	14 (9.3%)	179 (4.3%)
Insulin	798 (17.2%)	473 (18.6%)	207 (7.8%)	21 (14%)	383 (9.2%)
Oral hypoglycemics	1928 (41.4%)	1062 (41.7%)	540 (20.5%)	37 (24.7%)	878 (21.2%)

Mean (SD) or N (%) are reported. Abbreviations: ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BP = blood pressure; CCB = calcium channel blockers; BB = beta-blockers; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DBP = diastolic blood pressure; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PVD = peripheral vascular disease; SBP = systolic blood pressure; TD = thiazide diuretics. *Other antihypertensive medications include loop diuretics, potassium-sparing diuretics, centrally acting agents, alpha-blockers, and mineralocorticoid receptor antagonists, without the use of ACEIs or ARBs.

Table 2
Hospitalization, morbidity and mortality outcomes by antihypertensive drug exposure prior to COVID-19 infection.

	ACEI	ARB	CCB or BB or TD	Other Antihypertensives*	No Antihypertensive Medications
Patients with COVID-19 (N = 14,129)	4652	2546	2640	150	4141
Hospitalization or all-cause mortality within 30 days from COVID-19 infection	891 (19.2%)	617 (24.2%)	578 (21.9%)	58 (38.7%)	866 (20.9%)
All-cause mortality within 30 days from COVID-19 infection	176 (3.8%)	113 (4.4%)	122 (4.6%)	18 (12.0%)	220 (5.3%)
Hospitalized** Patients with COVID-19 (N = 1350)	453	325	255	21	296
Hospital length of stay, days (median, IQR)	7 (5, 12)	7 (5, 13)	8 (5, 15)	7 (4, 12)	7 (5, 12)
Admission to Intensive Care Unit	117 (25.8%)	75 (23.1%)	60 (23.5%)	8 (38.1%)	60 (20.3%)
Invasive Ventilator Use	90 (19.9%)	58 (17.8%)	41 (16.1%)	2 (9.5%)	44 (14.9%)
Acute Kidney Injury[a]	100 (22.1%)	65 (20.0%)	48 (18.8%)	2 (9.5%)	49 (16.6%)
Cardiac Injury[b]	107 (23.6%)	68 (20.9%)	69 (27.1%)	10 (47.6%)	78 (26.4%)
All-cause mortality	42 (9.3%)	29 (8.9%)	23 (9.0%)	3 (14.3%)	37 (12.5%)

Abbreviations: ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BB = beta-blockers; CCB = calcium channel blockers; CI = confidence interval; TD = thiazide diuretics. *Other antihypertensive medications include loop diuretics, potassium-sparing diuretics, centrally acting agents, alpha-blockers, and mineralocorticoid receptor antagonists, without the use of ACEIs or ARBs. **at KPSC facility. Patients with DNR/DNI, SBP <90 mm Hg at admission, hyperkalemia at admission, AKI within 3 days of admission, no hypertension medication during hospitalization were excluded.

[a] increase in serum creatinine by ≥ 0.3 mg/dL within 2 days or to ≥1.5 times the lowest serum creatinine value within the last 7 days.

[b] troponin I during hospitalization ≥0.04 ng/mL.

(discontinued ACEIs or ARBs) (Table 3).

Of the hospitalized patients, 24% were admitted to the ICU, 17% required mechanical ventilation, 20% had AKI, 25% had cardiac injury, and 10% died. These percentages were similar across antihypertensive exposure groups prior to hospital admission (Table 2), however, these percentages were lower for those who used ACEIs or ARBs compared with other classes of medications during the hospital stay (Table 3). The OR for all-cause mortality was 0.50 (95% CI 0.34, 0.72) for ACEI or ARB use during hospitalization vs CCB/BB/TD/other medications after applying IPTW, and these findings were consistent with those who were previously exposed to ACEIs or ARBs prior to hospital admission (OR = 0.38; 95% CI 0.23, 0.61).

4. Discussion

Our study evaluated morbidity and mortality of COVID-19 among patients with hypertension and COVID-19 infection in a large US integrated healthcare system. Our previous study reported no association between ACEI or ARB use and COVID-19 infection among 824,650 patients with hypertension [11]. The current analysis further evaluated morbidity and mortality among those infected with COVID-19 and hospitalized within 30 days of infection. In this racially and ethnically

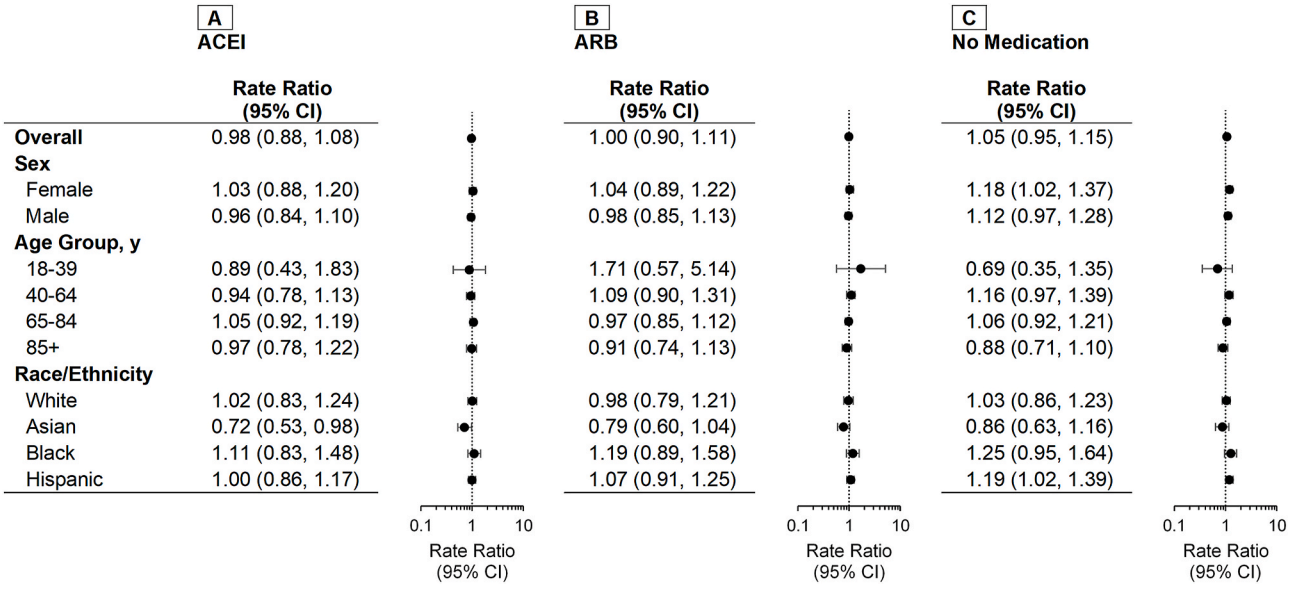

Fig. 1. Rate Ratios of Hospitalization or Mortality Outcomes Associated with Antihypertensive Drug Exposure Prior to COVID-19 for Patients with Hypertension and COVID-19 Stratified by Age, Sex, and Race/ethnicity. Outcome = Hospitalization or death within 30 days of COVID-19 Infection. Inverse probability of treatment weights was used for covariate adjustment.

Table 3
Morbidity and Mortality Outcomes by ACEI or ARB use vs Other Class of Antihypertensive Medications During Hospitalization.

	ACEI or ARB use during Hospitalization	CCB/BB/TD/other class use during hospitalization	Odds ratios or Rate Ratio* (95% CI)
			ACEI or ARB (vs CCB/BB/TD/other Classes)
Hospitalized** Patients with COVID-19 (N = 1350)	690	660	
Admission to Intensive Care Unit	138 (20.0%)	182 (27.6%)	0.71 (0.56–0.90)
Invasive Ventilator Use	106 (15.4%)	129 (19.5%)	0.76 (0.57–1.01)
Acute Kidney Injury[a]	118 (17.1%)	146 (22.1%)	0.82 (0.62–1.09)
Cardiac Injury[b]	131 (19.0%)	201 (30.5%)	0.87 (0.69–1.10)
All-cause mortality	44 (6.4%)	90 (13.6%)	0.50 (0.34-0.72)
Hospitalized and Exposed to ACEI/ARB prior to COVID-19 (N = 778)	523	255	
All-cause mortality	32 (6.1%)	39 (15.3%)	0.38 (0.23-0.61)

*Adjusted using inverse probability of treatment weights based on age, sex, race/ethnicity, body mass index, neighborhood income and education, blood pressure <140/90 mm Hg, Elixhauser comorbidity score, baseline comorbidities, outpatient medication use, troponin I, B-type natriuretic peptide at hospital admission, estimated glomerular filtration rate at hospitalization or 1-year before hospitalization in case of no inpatient measurements. Odds ratios were reported for outcomes ≤10% whereas rate ratios were reported for outcomes >10%. **at KPSC facility. Patients with DNR/DNI, SBP <90 mm Hg at admission, hyperkalemia at admission, AKI within 3 days of admission, no hypertension medication during hospitalization were excluded.

[a] increase in serum creatinine by ≥ 0.3 mg/dL within 2 days or to ≥1.5 times the lowest serum creatinine value within the last 7 days.

[b] troponin I during hospitalization ≥0.04 ng/mL.

diverse population of patients with hypertension, we found that exposure to ACEIs or ARBs prior to COVID-19 infection was not associated with hospitalization or mortality outcomes. However, among hospitalized patients, ACEI or ARB use during hospitalization was associated with a lower risk of mortality compared with use of other classes of antihypertensive medications.

Early in the pandemic, there were concerns regarding the use of ACEIs or ARBs, widely used antihypertensive medications, due to their potential increased susceptibility and/or severity of COVID-19 based on a hypothesis generated by animal models [1]. The subsequent epidemiologic studies consistently found no associations between previous exposure of ACEIs or ARBs and COVID-19 infection and its severity. However, many studies included only a single center, relatively small populations, homogenous racial/ethnic groups, or a general population of patients with and without hypertension. Therefore, it was still unclear whether these findings were consistent across racially/ethnically diverse groups of patients with hypertension who tested positive for COVID-19. The consistent findings of no association between ACEI or ARB use and hospitalization or mortality in age, sex, and racial/ethnic subgroups from our study reassures that ACEIs or ARBs should be continued for all patients with hypertension.

Although quite a number of cohort studies from different countries have examined the associations between inpatient exposure of ACEIs or ARBs and severe outcomes of COVID-19, the study findings have not been consistent [2]. Studies conducted early in the pandemic in the US reported higher hospitalization or ICU admission rates among ACEI or ARB users [5], while studies conducted in China found a lower risk of hospitalization or mortality associated with ACEIs or ARBs [12,13]. Recent cohort studies suggest that the lower risk of severe outcomes associated with ACEI or ARB use was potentially due to healthy user bias [14,15], and this has not been addressed clearly in many studies. To avoid these biases, we investigated ACEI or ARB exposure before and after COVID-19 infection separately, excluded patients who did not receive any antihypertensive medications during hospitalization post COVID-19 infection, and excluded patients who potentially were unable to continue receiving ACEIs or ARBs after hospital admission due to AKI, hyperkalemia, hypotension, and DNR/DNI status. Around 30% of the hospitalized patients met these criteria and were excluded from the analysis.

Our study findings suggest that inpatient use of ACEIs or ARBs after COVID-19 infection would provide further benefits in reducing mortality. These findings are confirmation of no harm from continuation of ACEIs or ARBs for patients with hypertension even after COVID-19 infection, but still hypothesis-generating in terms of preventing severe outcomes of COVID-19 due to the retrospective nature of the study. Two recently conducted randomized controlled trials reported neither harms nor benefits with continuation of ACEIs or ARBs compared with discontinuation of these agents after hospitalization due to COVID-19. However, the first trial to report, BRACE CORONA [16], included a relatively young population (mean age 55 years) with a low mortality rate (3%), which may be different from the real-world population. The population of the second trial, REPLACE COVID [17], may be more comparable to the population in clinical practice although the sample size was relatively small (N = 152) and 23% discontinued ACEIs or ARBs in the continuation arm. However, both studies evaluated patients who had been on ACEIs or ARBs prior to admission and compared continuation versus changing to a different hypertension medication. Our study evaluated all hypertensive patients hospitalized for COVID-19 and compared those who continued or initiated ACEs or ARBs with patients who were on other antihypertensive medication classes. Currently ongoing randomized controlled trials such as RASCOVID-19 may provide us with more definite answers.

Our study findings showed an increased risk of all-cause mortality for those without antihypertensive medication exposure prior to COVID-19 infection compared to those with CCB/BB/TD use. Unmeasured confounding such as nonadherent behaviors, essential worker occupations, and socioenvironmental conditions such as crowded housing and reliance on public transportation [18] may have contributed to these findings. However, this may also suggest proper antihypertensive treatment could provide additional benefits of preventing worse COVID-19 outcomes in patients with hypertension. Previous studies hypothesize underlying atherosclerosis as a potential contributor to worse COVID-19 outcomes [19,20], which warrants further investigation.

This study has several strengths and limitations. Our study is one of the largest cohort studies investigating patients with hypertension and COVID-19 infection in the US. Our study shows no harms associated with ACEI or ARB exposure before and after COVID-19 infection across different race/ethnic groups. However, this study did not fully capture death outside of the hospital since the state death records were not included for the analysis. Also, we evaluated hospital outcomes only among patients who were stable enough to continue antihypertensive medications and thus we may not have accounted for patients who were initially admitted with severe illness. Moreover, we evaluated all-cause hospitalization and it is possible that patients may have been hospitalized due to other reasons after COVID-19 infection. We were not able to evaluate 887 patients admitted outside of KPSC facilities due to data limitations such as inpatient medication use, ICU admissions, or

ventilator use. Although we captured most of the outpatient medication use, <5% patients with hypertension may have received their medications outside KPSC, which may not be captured correctly. Lastly, we cannot confirm medication adherence. Patients who refilled medications may not take medications as directed.

5. Conclusions

The current study showed that exposure to ACEIs or ARBs prior to COVID-19 infection was not associated with an increased risk of hospitalization or all-cause mortality. The study results reinforce that patients with hypertension should continue their ACEIs or ARBs as recommended by scientific communities during the COVID-19 pandemic. Currently ongoing randomized controlled trials may confirm our findings of a lower risk of all-cause mortality associated with ACEIs or ARBs during hospitalization.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijchy.2021.100088.

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Credit author statement

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