Renin–Angiotensin–Aldosterone System Inhibitors and COVID-19 Infection or Hospitalization: A Cohort Study

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BACKGROUND

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) may increase the risk of coronavirus disease 2019 (COVID-19) infection or affect disease severity. Prior studies have not examined risks by medication dose.

METHODS

This retrospective cohort study included people aged ≥18 years enrolled in a US integrated healthcare system for at least 4 months as of 2/29/2020. Current ACEI and ARB use was identified from pharmacy data, and the estimated daily dose was calculated and standardized across medications. COVID-19 infections and hospitalizations were identified through 6/14/2020 from laboratory and hospitalization data. We used logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for race/ethnicity, obesity, and other covariates.

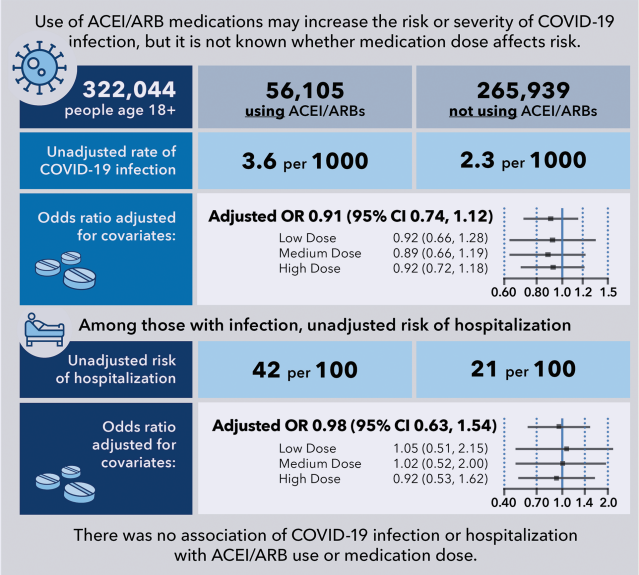
RESULTS

Among 322,044 individuals, 826 developed COVID-19 infection. Among people using ACEI/ARBs, 204/56,105 developed COVID-19 (3.6 per 1,000 individuals) compared with 622/265,939 without ACEI/ARB use (2.3 per 1,000), yielding an adjusted OR of 0.91 (95% CI 0.74–1.12). For use of <1 defined daily dose (DDD) vs. nonuse, the adjusted OR for infection was 0.92 (95% CI 0.66–1.28); for 1 to <2 DDDs, 0.89 (95% CI 0.66–1.19); and for ≥2 DDDs, 0.92 (95% CI 0.72–1.18). The OR was similar for ACEIs and ARBs and in subgroups by age and sex. 26% of people with COVID-19 infection were hospitalized; the adjusted OR for hospitalization in relation to ACEI/ARB use was 0.98 (95% CI 0.63–1.54), and there was no association with dose.

CONCLUSIONS

These findings support current recommendations that individuals on these medications continue their use.

GRAPHICAL ABSTRACT



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Use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), prescribed for nearly 25% of US adults,[1] may be a risk factor for coronavirus disease 2019 (COVID-19) because these drugs increase the expression of angiotensin-converting enzyme 2 (ACE2),[2] the receptor by which the SARS-CoV-2 coronavirus enters epithelial cells.[3] Concern about whether inhibitors of the renin–angiotensin–aldosterone system (RAAS) may increase

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susceptibility to COVID-19 has been so pronounced that professional societies issued advisories urging patients not to discontinue them and calling for more evidence.[4]

On the other hand, experimental evidence suggests that upregulation of ACE2 may protect against lung injury caused by severe coronavirus infection.[5] Among hospitalized patients with COVID-19 and hypertension, those on ACEI/ARBs had lower levels of high-sensitivity C-reactive protein and procalcitonin.[6] Most observational studies have focused on people hospitalized for COVID-19, examining whether ACEI/ARB use is associated with worse clinical outcomes.[6–9] While this sampling design addresses important questions, it selects for patients who are already infected and whose disease has become severe enough to require hospitalization, Such studies cannot shed light on the natural history of infection prior to hospitalization or whether the use of RAAS inhibitors may increase susceptibility to COVID-19. Three studies have examined the risk of infection in relation to RAAS use among people from well-characterized populations with information about prior medication exposures and health conditions.[10–12] These studies, set in Italy,[10] Spain,[11] and Denmark,[12] found no overall association between RAAS inhibitor use and COVID-19 infection. Testing patterns and case fatality rates may vary widely between countries.[13] No true population-based study has yet been conducted in the United States, which has a very different healthcare system and more racially diverse population than these European countries. While rigorous, these studies lacked information about smoking status, obesity, and race/ethnicity, which may be important confounders,[14–16] and their COVID-19 cases were disproportionately weighted toward hospitalized cases—lacking cases from the milder end of the spectrum. Finally, no study has yet examined the relationship between ACEI/ARB dose and risk of COVID-19 infection or severe disease.

In a population-based setting with rich electronic health data, we evaluated the associations of ACEI and ARB use including medication dose with the risk of COVID-19 infection and, as a marker of severity, with hospitalization.

METHODS

We conducted a retrospective cohort study within Kaiser Permanente Washington (KPWA), an integrated healthcare system in Washington State. Members within the integrated group practice (IGP) receive all or nearly all care from KPWA. Because KPWA does not own or operate hospitals, when members need hospitalization they are cared for at contracted hospitals, which submit claims to KPWA for reimbursement. Because reimbursement depends on these records, data about these hospitalizations tend to be very accurate. The population eligible for these analyses was IGP members who were aged ≥18 years and enrolled in KPWA in February 2020 (the month before COVID-19 testing began at KPWA). To be included, members had to have at least 4 months of prior enrollment as of 2/29/2020 and additional enrollment beyond that date. The sample size was determined by the number of eligible people. Individuals were followed for study outcomes through 6/14/2020. Study procedures were approved by the Kaiser Permanente Washington Health Research Institute Institutional Review Board with a waiver of consent.

We used electronic pharmacy data to define exposure to RAAS inhibitors. Pharmacy data come from KPWA-owned pharmacies and in addition include medications dispensed at outside pharmacies (via claims data). Data were available in near-real-time, including dispensings up through the day prior to the data pull. Data include a member identification number, date of the fill, medication name and strength, number of pills dispensed, and estimated days' supply. "Current use" was defined as having a dispensed medication with a supply sufficient to last until 2/29/2020 or later, assuming 80% adherence. To estimate the daily dose, we multiplied the number of pills dispensed by pill strength and divided by the estimated days' supply for the dispensing. We then standardized these daily doses across medications by dividing by the World Health Organization's Defined Daily Dose for each medication (e.g., 10 mg of lisinopril).[17]

We defined COVID-19 infection as having a positive COVID-19 reverse-transcriptase polymerase chain reaction test or a hospitalization with a COVID-19 diagnosis code (patients admitted to contracted hospitals for severe illness would not necessarily have had prior COVID-19 testing at KPWA). In addition to laboratory test results from KPWA laboratories, we were able to access laboratory results from other healthcare systems that use the Epic medical record (available via CareEverywhere). Throughout the study period, KPWA followed Washington State testing guidelines regarding indications for testing. For much of this time, the guidelines recommended testing only individuals with severe illness and symptomatic patients with high-risk exposures or health conditions.[18] In some instances, a KPWA member had a hospitalization with a COVID-19 diagnosis but we could not identify a positive COVID test from a KPWA laboratory. To assess whether these apparent COVID-19 hospitalizations represented true cases, we reviewed medical records for 20 patients hospitalized with a COVID-19 diagnosis who did not have a positive COVID-19 polymerase chain reaction test within KPWA.

In defining our outcomes, we chose to include individuals hospitalized with a COVID-19 diagnosis but no positive laboratory test accessible to us as having both COVID-19 infection and hospitalization. Our rationale was that hospitalization for COVID-19 is a serious and important outcome and our priority was to avoid missing potential cases. This is especially important because limited testing in the United States in the early days of the pandemic resulted in many people not being tested until their symptoms became severe enough to warrant hospitalization.

We identified covariates from KPWA electronic health data. Demographic characteristics included age, sex, and self-reported race/ethnicity. We ascertained chronic medical conditions using diagnosis codes from inpatient and ambulatory visits; a condition was considered to be present if an individual had 1 or more codes for that condition in any setting in the prior 12 months. Use of other medications was determined from electronic pharmacy data. The KPWA EHR includes information about tobacco use (which patients are routinely asked about at clinic visits) and body

mass index, calculated from clinical measures of height and weight. Medications of interest included prednisone, insulin, and other classes of antihypertensive medications (calcium channel blockers, beta-blockers, thiazide diuretics, and loop diuretics.) See the Supplementary Material online for detailed variable specifications.

We carried out descriptive analyses examining characteristics of the cohort stratified by exposure status (i.e., use of ACEI/ARBs). We used counts and proportions to describe categorical variables and means and SDs for continuous variables, and we calculated standardized mean differences[19,20] to examine covariate balance between groups. Next, within the entire cohort, we used logistic regression to estimate the odds of COVID-19 infection associated with RAAS inhibitor use with adjustment for age (<45, 45–64, and 65+ years), sex, race/ethnicity (categorized as non-Hispanic white, non-Hispanic Black, non-Hispanic Asian, non-Hispanic mixed or other race, or Hispanic), diabetes, hypertension, heart failure, prior myocardial infarction, asthma, chronic obstructive pulmonary disease, current tobacco use, renal disease, malignancy, Charlson comorbidity score[21] (categorized as 0, 1, and 2+), body mass index (categorized as underweight, <18.5 kg/m^2; normal weight, 18.5–24.9 kg/m^2; overweight, 25–29.9 kg/m^2; obese, 30–34.9 kg/m^2; and severely obese, ≥35 kg/m^2), and use of insulin, loop diuretics, and prednisone. Among those with COVID-19 infection, we used logistic regression to estimate the odds of hospitalization associated with RAAS inhibitor use with adjustment for a reduced set of covariates. To account for missing data on race/ethnicity (13%) and body mass index (27%), we used multiple imputation by chained equations[22] to generate 25 datasets with missing information imputed. Logistic regression models were estimated using these datasets and results were pooled following Rubin's rules.[23]

We conducted analyses examining the association between ACEI/ARB daily dose and risk of infection or hospitalization. The referent category was no use of ACEI/ARBs. The standardized daily dose was grouped as <1, 1 to <2, and ≥2 defined daily doses (DDDs) per day.

Secondary analyses for both infection and hospitalization risk evaluated associations for ACEI and ARB use separately and in subgroups by sex and age (<65 or ≥65 years). For the latter, we included interaction terms between each factor and RAAS inhibitor use in the models and tested significance with a Wald test of the interaction term. In sensitivity analyses, we examined other antihypertensive medications as "control exposures" to evaluate whether associations were specific to RAAS inhibitors. Because many chronic health conditions are indications for both COVID-19 testing and RAAS inhibitor use, we repeated our primary analyses of COVID-19 infection limited to individuals who underwent testing and separately, to those with an indication for RAAS inhibitors (hypertension, diabetes, heart failure, or prior myocardial infarction). For risk of infection, we conducted additional sensitivity analyses restricted to individuals taking at least 1 antihypertensive medication, adjusted for the number of medications.

Analyses were conducted using R version 3.5.3 (Vienna, Austria) including the mice package (version 3.8.0).

RESULTS

Figure 1 shows the selection of the study sample. There were 322,044 eligible individuals; their mean age was 51 years, 74% were non-Hispanic white and 46% were male. 56,105 (17%) were current users of ACEIs or ARBs. Lisinopril accounted for 96% of ACEI fills and losartan 97% of ARB fills. Individuals using ACEI/ARBs were older than nonusers, more likely to be obese, and more likely to have many chronic conditions, consistent with indications for RAAS inhibitor use (Table 1). Among ACEI/ARB users, 21% had a low daily dose (<1 DDD per day), 32% had a medium dose (1 to <2 DDD per day), and 47% a high dose (≥2 DDD per day).

Among 18,252 people tested for COVID-19 between 2/29/2020 and 6/14/2020, 796 (4.4%) tested positive. There were an additional 30 individuals hospitalized with a diagnosis of COVID-19 for whom we did not have access to a positive laboratory test result, yielding a total of 826 COVID-19 infections. For a sample of COVID-19 hospitalizations without a positive test at KPWA, we reviewed medical records and confirmed positive polymerase chain reaction results at outside institutions for 85% (17/20).

Among individuals with RAAS inhibitor use, 204/56,105 developed COVID-19 infection (3.6 per 1,000 individuals) compared with 622/265,939 among nonusers (2.3 per 1,000). The unadjusted odds ratio (OR) for COVID-19 infection in

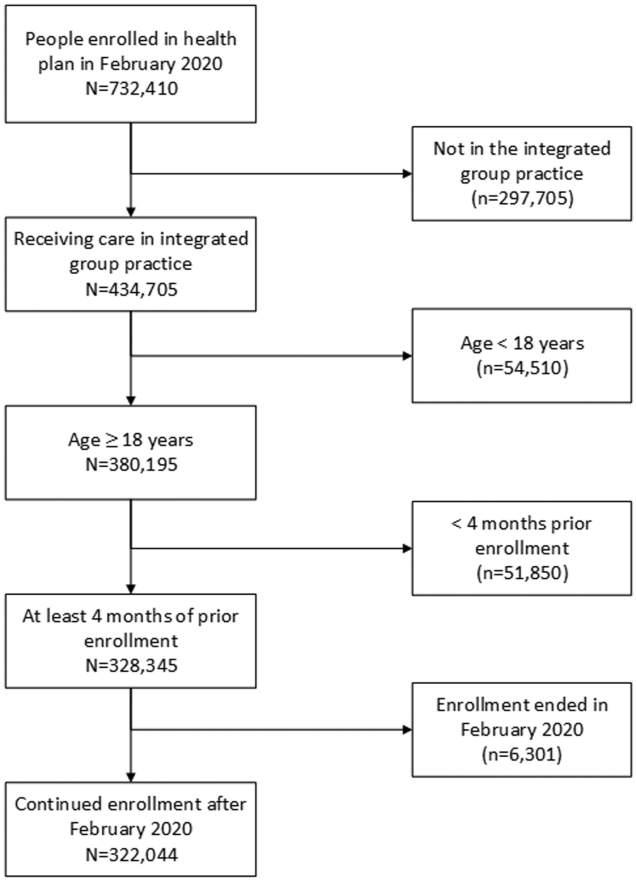

Figure 1. Selection of the study cohort.

Table 1. Characteristics of study population, by ACEI/ARB use

	ACEI/ARB users[a]	ACEI/ARB nonusers	
	N = 56,105	*N* = 265,939	Standardized mean difference
Age, mean (SD), years	66.0 (12.2)	47.9 (17.7)	1.190
Male, %	52.5	44.7	0.158
Race/ethnicity, %[b]			0.129
Non-Hispanic White	78.3	73.2	
Non-Hispanic Black	4.6	4.9	
Non-Hispanic Asian	9.4	11.3	
Non-Hispanic mixed race/other	3.3	4.2	
Hispanic	4.5	6.4	
Any ACEI/ARB indication, %	83.4	12.5	2.013
Diabetes	33.5	3.8	0.824
Hypertension	71.5	9.9	1.611
Heart failure	6.4	1.1	0.279
Prior myocardial infarction	7.0	1.1	0.302
Charlson comorbidity score, %			0.965
0	42.1	83.4	
1	21.6	9.3	
2+	36.3	7.4	
Asthma, %	8.2	5.2	0.119
COPD, %	6.0	1.9	0.210
Body mass index, %[b,c]			0.487
<18.5 kg/m^2	0.4	1.3	
18.5–24.9 kg/m^2	15.4	32.4	
25–29.9 kg/m^2	31.9	33.2	
30–34.9 kg/m^2	26.1	18.5	
≥35 kg/m^2	26.3	14.6	
Insulin use, %	11.4	1.1	0.434
Loop diuretic use, %	6.1	0.9	0.287
Prednisone use, %	6.3	3.5	0.131
Malignancy, %	5.9	2.6	0.167
Current smoker, %	6.9	5.7	0.049
Renal disease, %	12.2	2.3	0.391

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

[a]Current use was defined as having a dispensed medication with a supply sufficient to last until 2/29/2020 or later, assuming 80% adherence.

[b]Percent of nonmissing values. The number of people missing race/ethnicity was 2,629 (4.7%) among ACEI/ARB users and 38,946 (14.6%) among nonusers. BMI was missing for 3,548 ACEI/ARB users (6.3%) and 82,514 nonusers (31.0%).

[c]BMI categories were defined as follows: <18.5 kg/m^2, underweight; 18.5–24.9 kg/m^2, normal weight; 25–29.9 kg/m^2, overweight; 30–34.9 kg/m^2, obese; and ≥35 kg/m^2, severely obese.

relation to RAAS inhibitor use was 1.56 (95% confidence interval (CI) 1.33–1.82). After adjustment for covariates, the OR was 0.91 (95% CI 0.74–1.12). Risk of infection was strongly associated with race/ethnicity and obesity (Table 2). There was no association between the daily dose of ACEI/ARB and risk of infection (Figure 2); the adjusted OR for people taking a low dose (<1 DDD per day) compared with nonusers was 0.92 (95% CI 0.66–1.28), for a medium dose (1 to <2 DDD) it was 0.89 (95% CI 0.66–1.19), and for a high dose (≥2 DDD), 0.92 (95% CI 0.72–1.18).

Among individuals with COVID-19 infection, 217/826 (26.3%) were hospitalized, including 85/204 (41.7%) among RAAS inhibitor users and 132/622 (21.2%) among nonusers. The unadjusted OR for hospitalization comparing ACEI/

Table 2. Associations of ACEI/ARB use with risk of COVID-19 infection and hospitalization

	COVID-19 infection[a]	COVID-19 hospitalization[b]
	N = 322,044	*N* = 826[b]
	Adjusted OR (95% CI)	Adjusted OR (95% CI)
ACEI/ARB use	0.91 (0.74, 1.12)	0.98 (0.63, 1.54)
Male	0.92 (0.80, 1.06)	0.82 (0.57, 1.19)
Age in years		
18–44	Ref.[c]	Ref.[c]
45–64	1.29 (1.08, 1.53)	2.29 (1.31, 4.02)
65 and older	1.10 (0.88, 1.37)	7.04 (3.81, 13.03)
Race/ethnicity[d]		
Non-Hispanic White	Ref.[c]	Ref.[c]
Non-Hispanic Black	4.03 (3.19, 5.11)	1.20 (0.68, 2.12)
Non-Hispanic Asian	2.23 (1.71, 2.90)	0.94 (0.54, 1.63)
Non-Hispanic mixed race/other	0.90 (0.58, 1.40)	0.42 (0.11, 1.62)
Hispanic	2.67 (2.05, 3.47)	1.07 (0.49, 2.36)
ACEI/ARB indication		
Diabetes[e]	1.02 (0.77, 1.34)	1.52 (0.90, 2.58)
Hypertension	1.22 (1.00, 1.48)	1.27 (0.80, 2.00)
Heart failure[e]	1.56 (1.08, 2.26)	1.10 (0.53, 2.26)
Prior myocardial infarction[e]	0.94 (0.64, 1.38)	2.80 (1.15, 6.82)
Charlson comorbidity score		
0	Ref.[c]	Ref.[c]
1	1.54 (1.20, 1.97)	1.41 (0.79, 2.52)
2+	1.88 (1.37, 2.59)	1.79 (0.98, 3.26)
Asthma	0.71 (0.52, 0.96)	0.52 (0.25, 1.06)
COPD	1.10 (0.77, 1.58)	1.38 (0.63, 3.01)
Body mass index[d]		
<18.5 kg/m^2	1.07 (0.50, 2.30)	NA[f]
18.5–24.9 kg/m^2	Ref.[c]	NA[f]
25–29.9 kg/m^2	1.44 (1.16, 1.78)	NA[f]
30–34.9 kg/m^2	1.66 (1.31, 2.11)	NA[f]
≥35 kg/m^2	1.73 (1.32, 2.26)	NA[f]
Insulin use	1.21 (0.87, 1.69)	NA[f]
Loop diuretic use	1.30 (0.88, 1.92)	NA[f]
Prednisone use	1.61 (1.23, 2.10)	NA[f]
Malignancy[e]	0.79 (0.53, 1.17)	NA[f]
Current smoker	0.56 (0.39, 0.80)	NA[f]
Renal disease[e]	1.09 (0.80, 1.49)	NA[f]

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; NA, not applicable; OR, odds ratio; PCR, polymerase chain reaction.

[a]Defined as either a positive COVID-19 reverse-transcriptase PCR test or hospitalization with a COVID-19 diagnosis code.

[b]Analyses of risk of COVID-19 hospitalization were limited to the population with COVID-19 infection.

[c]Used as reference group in the logistic regression model.

[d]Multiple imputation was used to impute missing BMI and race/ethnicity; see Methods for details.

[e]Coefficients for diabetes, heart failure, prior myocardial infarction, malignancy, and renal disease should be interpreted with caution as these variables are also included in the Charlson comorbidity score.

[f]Due to the limited sample size of individuals who tested positive for COVID-19, we could not adjust for as many covariates in the analysis of COVID-19 hospitalization and *a priori* selected these covariates not to include in the model.

ARB use to nonuse was 2.65 (95% CI 1.89–3.72), and the fully adjusted OR was 0.98 (95% CI 0.63–1.54). No association was seen between ACEI/ARB dose and hospitalization (Figure 3); for people taking a high daily dose, the adjusted OR for hospitalization was 0.92 (95% CI 0.53–1.62) compared with nonuse.

In sensitivity analyses, the adjusted OR for COVID-19 infection was similar for ACEI and ARB users and in subgroups by age and sex (Figure 2). Risk estimates for ACEIs and ARBs were slightly higher than for thiazides, beta-blockers, or calcium channel blockers (Figure 2). Findings changed little after restricting to individuals with an indication for RAAS inhibitor therapy, those tested for COVID-19, or those treated with antihypertensive medications. In sensitivity analyses examining COVID-19 hospitalization (Figure 3), the adjusted OR for ACEIs was 0.81 (95% CI 0.50–1.31) and for ARBs, 1.29 (0.75–2.24). ACEI/ARB use was not associated with risk of COVID hospitalization for people under age 65 or age 65+. Results appeared modestly different by sex, with an adjusted OR for ACEI/ARB use that was lower in women than in men, but this difference was not statistically significant ($P = 0.16$).

DISCUSSION

In this population-based cohort study set within a US healthcare system, there was no significant association between use of RAAS inhibitors and the risk of COVID-19 infection or hospitalization, including no association of these outcomes with ACEI/ARB daily dose. This is the first study to our knowledge that has examined the association of medication dose with COVID-19 outcomes.

Most published studies have focused on the risk of complications among hospitalized patients.[6–9] Our finding for infection risk is consistent with several other population-based studies,[10–12] including a case–control study from Italy where the adjusted OR for infection in relation to ACEI/ARB use was 0.95 (95% CI 0.86–1.05)[10] and a study from Denmark where the adjusted OR was 1.05 (95% CI 0.80–1.36).[12] Examining this question in the United States is important because of differences in the clinical context, COVID-19 testing practices and case fatality rates,[13] and the distribution of race/ethnicity in the population.

A recent systematic review assessed the association between RAAS inhibitor use and COVID-19 infection and outcomes[24]; they concluded that there is "moderate-certainty evidence" from 3 studies that ACEI/ARB use does not increase infection risk and stronger evidence that ACEI/ARB use does not increase the risk of severe outcomes. They noted limitations of prior studies including that many were small or did not adjust for important confounders, and that for some of the smaller studies, it was unclear how prior RAAS inhibitor use was ascertained. The 3 large population-based studies[10–12] of this question (one of which was included in the systematic review[10]) were all set in Europe. They have many strengths and offer important evidence, but gaps still remain. When identifying COVID-19 infections, one study focused solely on hospitalized cases[11] and a second ascertained only patients diagnosed in hospitals or hospital-based clinics.[12] The cases identified thus represent more severe cases on the disease spectrum, and there remains a need for studies including cases with milder disease diagnosed in

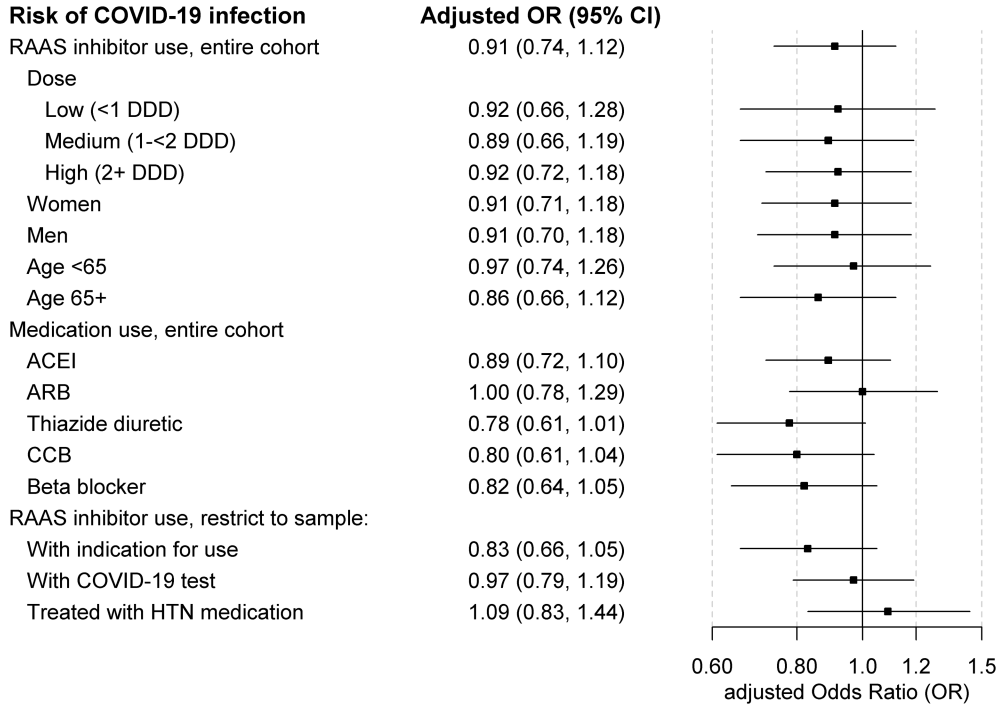

Figure 2. Odds of COVID-19 infection in relation to use of RAAS inhibitors. Estimates are adjusted for age, sex, race/ethnicity, diabetes, hypertension, HF, prior MI, asthma, COPD, current tobacco use, renal disease, malignancy, Charlson comorbidity score, BMI, and use of insulin, loop diuretics, and prednisone. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DDD, defined daily dose; HF, heart failure; HTN, hypertension; MI, myocardial infarction; OR, adjusted odds ratio; RAAS, renin–angiotensin–aldosterone system.

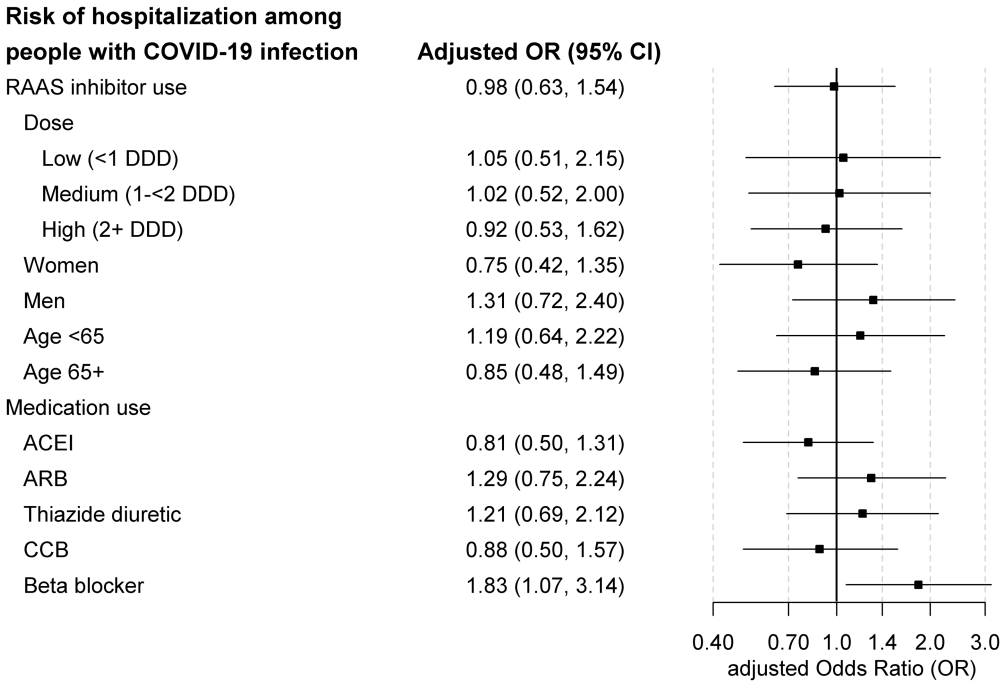

Figure 3. Odds of COVID-19 hospitalization in relation to use of RAAS inhibitors, among individuals with COVID-19 infection. Estimates are adjusted for age, sex, race/ethnicity, diabetes, hypertension, HF, prior MI, asthma or COPD, and Charlson comorbidity score. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DDD, defined daily dose; HF, heart failure; MI, myocardial infarction; OR, adjusted odds ratio; RAAS, renin–angiotensin–aldosterone system.

the ambulatory setting. The definition of exposure varied across studies, with potential for misclassification, and none of these studies included information about ACEI or ARB daily dose.

We also observed a 4-fold higher risk of infection among Black people and a 2.7-fold risk of infection for Hispanics compared with non-Hispanic whites. These findings are consistent with prior studies that reported higher risk of hospitalization due to COVID-19 among Black[14] or Hispanic[14,16] people. In addition, we observed a significantly lower risk of infection among current smokers (OR 0.56, 95% CI 0.39–0.80). This finding is consistent with a number of prior studies including a meta-analysis of 17 studies that reported a combined relative risk of 0.74, with 95% credible interval of 0.58–0.93, for the association between current smoking and COVID-19 infection.[25] The potential biologic mechanism for an association between smoking and lower risk of COVID-19 infection is unclear. One study reported that nicotine downregulates expression of the ACE2 receptor, by which SARS-CoV-2 enters epithelial cells.[26] The reported association could also be due to bias, including bias due to selective testing for COVID-19. Respiratory symptoms (more common in current smokers) are a common indication for testing, and smokers are more likely to have chronic conditions such as chronic lung disease which early in the pandemic were often a prerequisite for testing. At the same time, smokers are at higher risk for many viral and bacterial respiratory infections, which could make them more likely than nonsmokers to have an illness other than COVID-19 as the cause of their symptoms. These factors could contribute to an apparent "protective effect" of smoking in the absence of a causal association.

This study provides additional evidence that RAAS inhibitors do not increase the risk of SARS-CoV-2 infection. Strengths include the ability to examine the risk of COVID-19 infection including both outpatient and hospitalized cases arising in a well-defined population with extensive electronic health data and complete capture of clinical events. We were able to estimate people's daily dose of ACEI/ARBs and to adjust for characteristics typically missing from large healthcare databases such as smoking, body mass index, and race/ethnicity, characteristics which seem to have strong associations with risk of COVID-19 infection or more severe disease.[14–16] Longitudinal data available for patients for years prior to the start of follow-up improve the accuracy of ascertaining chronic illnesses and prior medication use.

Limitations of observational studies such as this one include measurement error, selection bias, and residual confounding. Because KPWA testing practices followed state guidelines, we lack information about milder cases or those in low-risk populations, for whom COVID-19 testing was not considered to be indicated throughout most of the study period. We could be missing hospitalizations for people who tested positive during follow-up and were hospitalized after the end of our follow-up period. In defining our outcomes, we included as having COVID-19 infection some individuals hospitalized with a diagnosis of COVID-19 for whom we could not identify a positive laboratory test result. This could have led to bias because these individuals would not have been identified as infected had they not

experienced a hospitalization. At the same time, if we had defined them as not experiencing COVID-19 infection, this choice could have led to misclassification of outcome status. There is no clear right answer in this situation. We believe that our approach is unlikely to have caused substantial bias, for several reasons. First, the number of individuals involved (30) is small compared with the total number with COVID-19 infection or hospitalization in our study. Second, we do not expect an association between ACEI/ARB use and this method of case ascertainment. Third, our results changed little in sensitivity analyses that could have shed light on any resulting bias, including analyses limited to people with a COVID-19 test and those with a chronic illness that is both an indication for ACEI/ARB use and a risk factor for COVID-19 testing and/or hospitalization.

In conclusion, these findings do not support an adverse effect of RAAS inhibitors on the risk of COVID-19 infection or hospitalization, including among individuals taking the highest doses of these medications. Our results provide additional support for clinical guidelines recommending that patients currently taking these medications need not stop them.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *American Journal of Hypertension* online.

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