Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Renin–angiotensin–aldosterone system inhibitors and SARS-CoV-2 infection: an analysis from the veteran's affairs healthcare system

Alexander T Sandhu, MD, MS[a,1], Shun Kohsaka, MD[b], Shoutzu Lin, MS[c], Christopher Y Woo, MD, MS[d], Mary K. Goldstein, MD[c,e], and Paul A Heidenreich, MD, MS[a,c] *Stanford, CA; Tokyo, Japan; Palo Alto, CA*

Background Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are known to impact the functional receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The association between chronic therapy with these medications and infection risk remains unclear.

Objectives The objective was to determine the association between prior ACEI or ARB therapy and SARS-CoV-2 infection among patients with hypertension in the U.S. Veteran's Affairs health system.

Methods We compared the odds of SARS-CoV-2 infection among three groups: patients treated with ACEI, treated with ARB, or treated with alternate first-line anti-hypertensives without ACEI/ARB. We excluded patients with alternate indications for ACEI or ARB therapy. We performed an augmented inverse propensity weighted analysis with adjustment for demographics, region, comorbidities, vitals, and laboratory values.

Results Among 1,724,723 patients with treated hypertension, 659,180 were treated with ACEI, 310,651 with ARB, and 754,892 with neither. Before weighting, patients treated with ACEI or ARB were more likely to be diabetic and use more anti-hypertensives. There were 13,278 SARS-CoV-2 infections (0.8%) between February 12, 2020 and August 19, 2020. Patients treated with ACEI had lower odds of SARS-CoV-2 infection (odds ratio [OR] 0.93; 95% CI: 0.89-0.97) while those treated with ARB had similar odds (OR 1.02; 95% CI: 0.96-1.07) compared with patients treated with alternate first-line anti-hypertensives without ACEI/ARB. In falsification analyses, patients on ACEI did not have a difference in their odds of unrelated outcomes.

Conclusions Our results suggest the safety of continuing ACEI and ARB therapy. The association between ACEI therapy and lower odds of SARS-CoV-2 infection requires further investigation. (Am Heart J 2021;240:46–57.)

Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs), two of the most commonly prescribed chronic therapies for hypertension, have garnered widespread interest as they may impact the incidence or severity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1-4] Angiotensin-converting enzyme 2 receptor (ACE2) is the cellular receptor for the SARS-CoV-2 spike protein and is present in lungs.[1] Select animal models have shown ACEI and ARB therapy are associated with increased tissue ACE2 levels, although this has not been demonstrated in lung tissue or in humans.[5] However, this has sparked concerns that ACEI or ARB therapy may increase the risk of developing SARS-CoV-2 infection.[6,7]

To date, multiple observational studies have found mixed results regarding the association between chronic ACEI/ARB utilization and coronavirus disease 2019 (COVID-19) outcomes.[8-21] Early studies, including re-

From the [a]*Division of Cardiovascular Medicine, Department of Medicine, Stanford University, Stanford, CA,* [b]*Department of Cardiology, Keio University School of Medicine, Tokyo, Japan,* [c]*Medical Service, VA Palo Alto Health Care System, Palo Alto, CA,* [d]*Division of Cardiology, Kaiser Permanente, Santa Clara, CA,* [e]*Center for Health Policy and Primary Care and Outcomes Research, Department of Medicine, Stanford, CA*

[1] *Twitter: @ATSandhu*

Abbreviations: ACEI, Angiotensin-converting enzyme inhibitors; ARB, Angiotensin receptor blocker; Body mass index, BMI; CCB, calcium channel blocker; COVID-19, Coronavirus disease-2019; HF-Ref, heart failure with reduced ejection fraction; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VA, Veterans Affairs.

Submitted December 2, 2020; accepted June 7, 2021

Reprint requests: *Alexander T Sandhu, MD, MS, Stanford University, 870 Quarry Road Ext, Palo Alto, CA 94304*

E-mail address: ats114@stanford.edu.

0002-8703

https://doi.org/10.1016/j.ahj.2021.06.004

ports from Wuhan, China, demonstrated that hypertension was common among patients with SARS-CoV-2 infection and associated with worse outcomes,[4,22] leading to speculation that the increased risk may be related to ACEI or ARB treatment. Others have hypothesized that ACEI or ARB treatment may prevent the lung injury of SARS-CoV-2 given prior data that ACEI or ARB therapy may reduce lung injury with acute respiratory infection.[23,24] However, for most studies, the relatively modest sample sizes have yielded inadequate precision to detect small but potentially meaningful effects. Additionally, most studies included patients without hypertension or with alternate indications for ACEI/ARB therapy, which may introduce selection bias if the conditions treated by ACEI/ARB impact SARS-CoV-2 infection risk. Finally, studies that evaluated patients being tested or those infected – as opposed to a population-based cohort - may inaccurately estimate the effect on outcomes if ACEI/ARB therapy also impact the risk of contracting the disease or developing symptoms. Therefore, there remains limited population-based US data evaluating the association between ACEI/ARB therapy and SARS-CoV-2 infection.

With over 10% of the adult population over 40 taking ACEI therapy, understanding the impact on SARS-CoV-2 infection is critical.[25] We performed an observational cohort analysis among Veterans Affairs (VA) patients with a diagnosis of hypertension on at least one of the five most common anti-hypertensive therapy classes (ACEI, ARB, calcium channel blocker [CCB], thiazide diuretic, or beta-blocker). We compared the likelihood of being diagnosed with SARS-CoV-2 infection between patients with hypertension treated with ACEI, ARB, or neither therapy after excluding patients with alternate ACEI/ARB indications.

Methods

Data source

We used claims and electronic health records for all VA patients provided care in 2020. We extracted data from the VA National Corporate Data Warehouse including demographics, encounters, diagnoses, laboratory results, vital signs, and pharmacy dispensing records. Patients with positive tests for SARS-CoV-2 infection were identified using the COVID-19 Shared Data Resource.[26] This national dataset tracks veterans with positive SARS-CoV-2 lab tests either in VA facilities or outside the VA, including asymptomatic patients tested for surveillance or as a pre-procedure precaution. We included SARS-CoV-2 infections through August 19, 2020. The dataset also includes SARS-CoV-2-associated hospitalizations, defined as occurring within 15 days before or 60 days after a positive test.

Population

We included patients with an inpatient or outpatient diagnosis of hypertension in either the VA electronic health record or among non-VA fee basis claims in the year prior to February 12, 2020. The index date was set to February 12, 2020, since this was the day before symptom development for the first United States case of probable community transmission of SARS-CoV-2 infection.[27]

To be included, we required a medication fill for one of the five most common anti-hypertensives - ACEI, ARB, thiazide diuretics, CCBs, or beta-blockers - within the 6 months before February 12, 2020. The first-line drug requirement identified a more homogeneous population receiving standard treatment to improve the comparability of ACEI/ARB users and non-users. We excluded patients without therapy to reduce differences in hypertension severity or healthcare utilization.

We excluded patients with alternate first-line indications for ACEI/ARB therapy: heart failure with reduced ejection fraction (HF-rEF), diabetic nephropathy, renal artery stenosis, or non-diabetic advanced chronic kidney disease (estimated glomerular filtration rate below 60 ml/min) (diagnosis codes listed in Supplement Table 2).[28,29] Patients with proteinuric chronic kidney disease have an indication for ACEI/ARB and those without proteinuria are less likely to be treated with ACEI/ARB.[30,31] Patients with these conditions who are not on ACEI/ARB therapy are more likely to have other unmeasured differences in patient characteristics, including milder disease severity, inaccurate diagnoses, greater frailty, or reluctance to take medications.[32,33] Excluding these patients was important because heart failure, diabetes, and chronic kidney disease have all been hypothesized as risk factors for SARS-CoV-2 infection.[34-36]

Given the challenges in accurately identifying patients with HF-rEF,[37] we used a combination of outpatient and inpatient systolic heart failure diagnostic codes (either two outpatient diagnoses or an inpatient primary diagnosis). Such patients are almost universally on ACEI/ARB; we would be unable to differentiate the impacts of HF-rEF and ACEI/ARB therapy. Patients with diabetes were identified using diagnoses, an elevated hemoglobin A1c, or insulin therapy. Coexisting nephropathy was identified by diagnoses of chronic kidney disease or proteinuria or an estimated glomerular filtration rate below 60 on their most recent laboratory results. We also excluded non-diabetic patients with an estimated glomerular filtration rate below 60. Renal artery stenosis was defined based on diagnostic codes alone. We excluded patients prescribed aliskiren given its potential effects on the renin-angiotensin system, and patients treated with both ACEI and ARB.

Defining exposures

We established two exposure cohorts: patients prescribed ACEI therapy and those prescribed ARB ther-

apy. These exposure cohorts were compared to patients without ACEI/ARB who were prescribed either thiazides, CCBs, or beta-blockers. Patients in both the exposure and control arm could receive thiazide, CCB, or beta-blocker therapy. To account for potential imbalance regarding hypertension severity, we adjusted for the total number of anti-hypertensive classes and systolic and diastolic blood pressure, as described below.

Covariate adjustment

We adjusted for additional patient characteristics which could potentially influence the likelihood of SARS-CoV-2 infection. Given the substantial geographic variation in risk, we adjusted for the VA's 19 geographically-based Veterans Integrated Service Networks and population density using census data.[38]

We captured patient demographics and socioeconomic status. Demographics included age, sex, and race/ethnicity. Race/ethnicity was stratified as Black, Hispanic, White, Asian, Native-American, Pacific Islander, Other, and missing. We included marital status and VA eligibility status. We evaluated community socioeconomic status using the Agency for Healthcare Research and Quality Socioeconomic Status index based on ZIP-code level data from the American Community Survey.[39,40]

We adjusted for medical comorbidities potentially associated with the risk of COVID-19 or likelihood of ACEI/ARB therapy using vital signs, diagnoses, medications, and lab values. Vital signs included most recent heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate, and oxygen saturation within 1 year before the index date. Body mass index (BMI) was calculated from height and weight. Non-physiologic vital signs were dropped (detailed in Supplement Table 1). We adjusted for comorbidities using diagnostic codes within the prior 2 years: chronic kidney disease, chronic obstructive pulmonary disease, diabetes, heart failure, ischemic heart disease, liver disease, other pulmonary disease, malignancy, and prior stroke (codes listed in Supplement Table 2). In addition, we used pharmacy records to measure insulin fills within 6 months before the index date. We included common laboratory tests previously found to be associated with disease morbidity across conditions including potentially COVID-19: estimated glomerular filtration rate based on the Modification of Diet in Renal Disease equation, hemoglobin, hemoglobin A1c, and sodium.[36,41,42] We used lab data within 1 year before the index date. Each lab value and vital sign was treated as a continuous variable. We identified frail patients based on the presence of at least 2 diagnoses previously used to evaluate frailty with claims data.[43] Finally, we adjusted for hospitalization within 1 year before the index date.

Statistical analysis

We performed descriptive analyses of the population stratified into three cohorts: ACEI therapy, ARB therapy or neither. Continuous variables are displayed as mean and standard deviation [SD] while categorical variables are listed as percentages. We compared differences across the cohorts using standardized mean differences with Cohen's *d*.

We assumed missing vital signs, labs, and BMI were missing at random and used multiple imputation using chained equations with linear regression to construct 40 imputed datasets.[44] We included all model variables in the imputation model. We added indicator variables for missing values given missingness may be informative.[45] We performed multiple sensitivity analyses around this approach. First, we dropped vitals, labs, and BMI from the analysis. Second, we performed a complete case analysis. Third, we repeated the multiple imputation but assumed missing variables were more extreme than predicted (1 standard deviation higher or lower risk than predicted). Finally, we used categorical values based on quintiles with missing indicators for lab, vitals, and BMI. For missing race/ethnicity, marital status, and VA eligibility, we included a missing category alone.

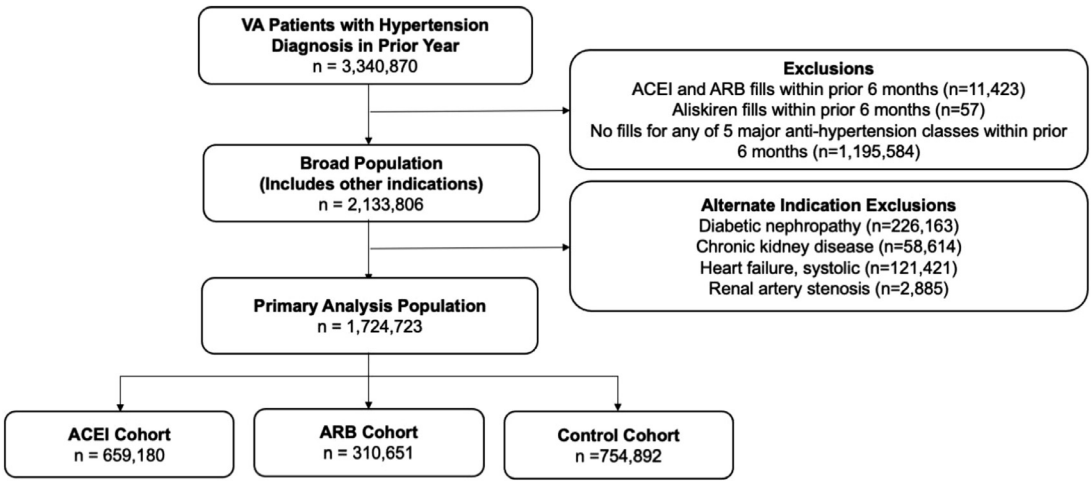
Primary analyses

The primary analysis was a comparison of the adjusted odds of SARS-CoV-2 infection between patients treated with ACEI, ARB, or neither. We used an augmented inverse-propensity weighted logistic regression model adjusted for patient demographics, geography, social risk, comorbidities, vital signs, and laboratory values.[46] We calculated stabilized propensity weights using a multinomial logistic regression that evaluated the propensity to be in each arm based on the same characteristics listed above.[47] We used robust standard errors. We then repeated the analysis for a second model that directly compared ACEI and ARB therapy.

As a secondary outcome, we evaluated the association between ACEI, ARB, or neither therapy and SARS-CoV-2-associated hospitalization. We used the hospitalization definition described above.

We performed stratified subgroup analyses based on age, race/ethnicity, AHRQ SES Index, diabetes, and ischemic heart disease. We divided continuous characteristics based on the median value. For race/ethnicity, we only included Black, Hispanic, and White given the small sample size and limited interpretability of the "Other" category. We re-estimated the propensity weights within each subgroup to reduce potential bias.[48] With two subgroups, we tested the heterogeneity of odds ratios by calculating log odds ratios and determining the Z statistic given we ran two independent models. For race/ethnicity, with three subgroups, we calculated Cochrane's Q statistic.[49]

Figure 1



Flow Diagram. Abbreviations: ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker. This figure displays the inclusion and exclusion of patients in the study.

Sensitivity analyses

First, we evaluated the association between ACEI/ARB therapy and falsification outcomes: influenza diagnosis, vertebral fracture or hip fracture/dislocation, and urinary tract infection (UTI). The diagnosis codes are listed in Supplement Table 2. We determined the frequency of each of these diagnoses in the inpatient or outpatient setting over the same period as our primary outcome.

Second, we performed a sensitivity analysis related to the control arm. A recent analysis found a large difference in COVID-19 hospitalization rates between patients treated with ACEI/ARB versus CCB.[50] This analysis raised the concern that risk may differ across the therapies in our control arm. To evaluate this, we performed an exploratory analysis with the following exposure arms: ACEI without ARB/CCB, ARB without ACEI/CCB, CCB without ACEI/ARB, and thiazide diuretic or beta-blocker without ACEI/ARB/CCB. We recalculated our propensity weights with four potential outcomes.

Third, we stratified our exposure into two groups: chronic versus only recent exposure. We defined chronic exposure as a medication fill both within 6 months before the index data and between 6-18 months while those with only recent exposure did not have a medication fill between 6-18 months. We excluded patients who switched exposures between the recent and prior exposure periods. We repeated our analysis in each subgroup.

Finally, we performed a quantitative bias analysis for the primary analysis. We calculated e-values for both the observed association and the confidence interval.[51] The e-value is the minimum strength of association of an unmeasured confounder with both therapy (ACEI or ARB) and outcome (SARS-CoV-2 infection) that would account for the observed association.

This study was approved by the Stanford Institutional Review Board. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Our study was funded by the AHA COVID-19 Rapid Response Award and the National Heart, Lung, and Blood Institute. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Results

We found 3,340,870 veterans with a hypertension diagnosis between February 12, 2019 and February 12, 2020. Figure 1 displays the study exclusions. We excluded 1,195,584 patients (35.8%) who were on neither ACEI, ARB, thiazide diuretic, CCB, or beta-blocker therapy, 11,480 patients (0.3%) with fills of both ACEI and ARB or aliskiren, and 409,083 patients (12.2%) due to alternate clinical indications besides hypertension for ACEI/ARB therapy. Following exclusions, we included 659,180 patients on ACEI, 310,651 on ARB, and 754,892 on neither.

The average patient age was 67.4 (SD 12.0 years) (Table I). The ACEI and ARB cohorts received more antihypertensive medication classes than the control cohort with neither. The largest source of imbalance between cohorts was diabetes status (Figure 2). Both ACEI and ARB cohorts had higher prevalence of diabetes and insulin utilization.

Across this population, we observed 13,278 SARS-CoV-2 infections (0.8%) between February 12, 2020 and Au-

Table I. Patient characteristics*

	Overall population 1,724,723	ACEI cohort 659,180	ARB cohort 310,651	Control Cohort 754,892	SMD, ACEI vs. Control	SMD, ARB vs. Control	SMD, ACEI vs. ARB
Sociodemographic Characteristics							
Age, years	67.4 (12.0)	67.4 (11.5)	68.2 (11.5)	67.1 (12.5)	0.02	0.09	-0.07
Female Sex, %	6.1	4.2	6.5	7.6	-0.14	-0.04	-0.10
Race/ethnicity, %							
Hispanic	5.6	6.3	5.9	4.8	0.07	0.05	0.02
Black	21.3	17.1	20.3	25.4	-0.20	-0.12	-0.08
White	65.6	69	65.5	62.7	0.13	0.06	0.07
Other	5.4	5.4	6.1	5.0	0.02	0.05	-0.03
Missing	2.2	2.2	2.2	2.1	0.01	0.01	0.00
Marital Status, %							
Married	56.1	55.7	61.8	54.2	0.03	0.16	-0.12
Divorced	24.3	24.9	21.5	24.9	0.00	-0.08	0.08
Never Married	10.1	10.1	8.1	11.0	-0.03	-0.10	0.07
Other	9.1	9	8.2	9.6	-0.02	-0.05	0.03
Missing	0.4	0.4	0.4	0.4	0.00	0.01	-0.01
AHRQ SES Index	50.2 (3.9)	50.2 (3.8)	50.4 (3.9)	50.2 (3.9)	-0.01	0.06	-0.07
Vitals, most recent prior to index date within last year							
Systolic blood pressure (mmHg)	134.9 (16.9)	134.7 (17.3)	136.6 (17.0)	134.5 (16.5)	0.01	0.12	-0.11
Diastolic blood pressure (mmHg)	77.7 (10.4)	77.3 (10.4)	77.7 (10.4)	78 (10.3)	-0.07	-0.03	-0.04
Heart rate (bpm)	74.1 (13.4)	74.3 (13.5)	73.7 (13.2)	74.1 (13.4)	0.01	-0.03	0.04
Respiratory Rate (rpm)	17.6 (1.8)	17.6 (1.8)	17.6 (1.8)	17.6 (1.8)	0.00	0.00	0.00
Oxygen saturation (%)	96.6 (2.2)	96.6 (2.1)	96.6 (2.2)	96.7 (2.2)	-0.03	-0.06	0.03
Comorbidities in last 2 years (%)							
Chronic obstructive pulmonary disease	20.2	18.8	21.2	20.9	-0.05	0.01	-0.06
Chronic kidney disease†	8.2	7.5	9.3	8.3	-0.03	0.03	-0.06
Diabetes	34.5	42.2	42.3	24.6	0.38	0.38	0.00
Heart failure	4.7	5.1	6.0	3.8	0.06	0.10	-0.04
Ischemic heart disease	22.0	23.4	24.5	19.7	0.09	0.12	-0.03
Ischemic stroke	3.7	4.1	3.6	3.4	0.03	0.01	0.02
Liver disease	7.3	7.2	6.9	7.7	-0.02	-0.03	0.01
Malignancy	10.5	10.0	10.3	10.9	-0.03	-0.02	-0.01
Other chronic lung disease	19.0	18.4	20.1	19.1	-0.02	0.03	-0.04
Other Medical Characteristics							
Admission, prior year, %	9.5	9.8	8.5	9.7	0.00	-0.04	0.05
BMI (kg/m^2)	30.9 (6.2)	30.9 (6.2)	31.8 (6.2)	30.4 (6.2)	0.08	0.22	-0.14
Frailty, %‡	4.8	4.7	4.5	5.0	-0.01	-0.02	0.01
Medications							
Anti-hypertensive medications, # of drug classes	1.9 (1.0)	2.1 (1.0)	2.3 (1.1)	1.6 (0.8)	0.61	0.84	-0.21
Hypertension Monotherapy, %	42.0	32.8	24.1	57.5	-0.51	-0.72	0.19
Insulin fills, %	10.3	13.6	13.7	6.0	0.26	0.26	0.00

(*continued on next page*)

Table I. (*continued*)

Laboratory Values. most recent prior to index date within last year							
Estimated Glomerular Filtration Rate (mL/min/1.73m2)	77.8 (17.2)	78.4 (16.7)	77.0 (16.8)	77.7 (17.9)	0.04	-0.04	0.08
Hemoglobin (g/dl)	14.2 (1.6)	14.3 (1.5)	14.2 (1.5)	14.3 (1.6)	0.00	-0.05	0.05
Hemoglobin A1c (%)	6.4 (1.3)	6.6 (1.4)	6.6 (1.3)	6.2 (1.1)	0.33	0.31	0.03
Sodium (mEq/L)	139.1 (2.9)	138.9 (2.9)	139.1 (2.8)	139.2	-0.11	-0.02	-0.08

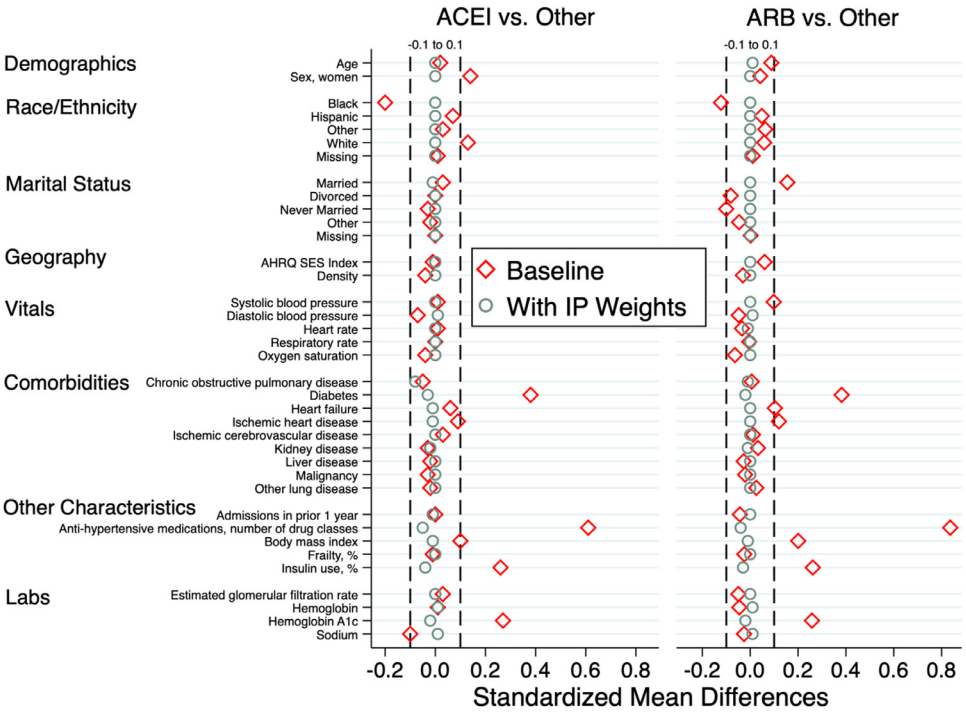
Abbreviations: ACEI: angiotensin-converting enzyme inhibitor; AHRQ SES: Agency for Healthcare Research and Quality Socioeconomic Status; ARB: angiotensin receptor blocker; BMI: body mass index; bpm: beats per minute; ICD: International Classification of Diseases; rpm: respirations per minute; SMD: Standardized mean differences.

* Categorical variables presented as percentages; continuous variables presented as mean (standard deviation). Proportion of missing variables for vital signs, BMI, and laboratory values detailed in Supplement Table 3.

† Defined based on ICD diagnosis codes as opposed to estimated glomerular filtration rate below.

‡ Defined as the presence of at least two ICD diagnosis codes indicating potential frailty.

Figure 2

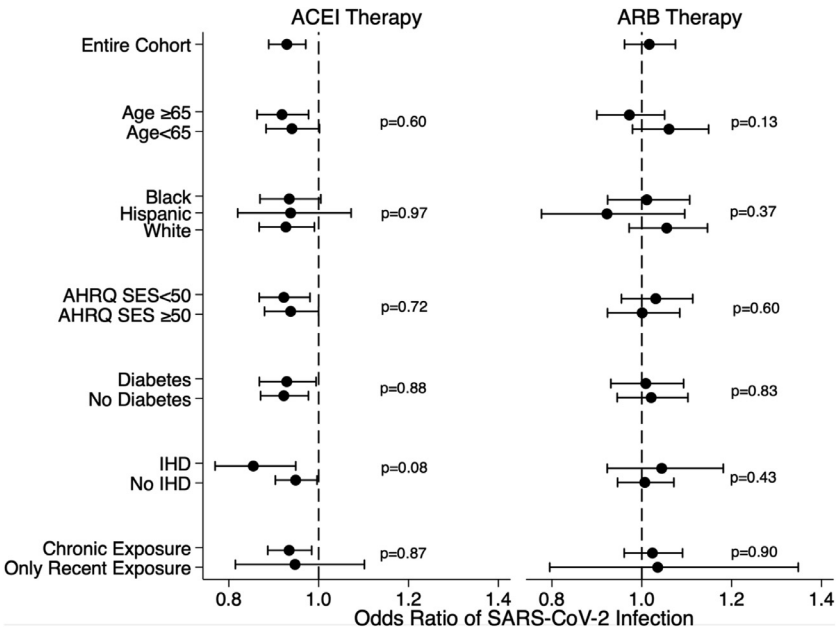


Standardized Mean Differences Before and After Adjustment.

Displays the standardized mean differences between treatment arms at baseline and after inverse propensity weighting. One imputed dataset was randomly selected among the 40 datasets to calculate standardized mean differences after imputation and inverse propensity weighting. Multiple datasets were compared with minimal difference in the standardized mean differences. Characteristics across each cohort after inverse propensity weighting are detailed in Supplement Table 4. Standardized mean differences between ACEI and ARB cohorts before and after IP weighting are listed in Supplement Table 5.

Abbreviations: ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; AHRQ SES: Agency for Healthcare Research and Quality Socioeconomic Status; IP: inverse propensity.

Figure 3



Forest Plot of Sub-group Analyses.

This figure displays odds ratios for each subgroup. Chronic exposure refers to patients with ACEI or ARB prescription fills both within the prior 6 months before index date and between 6 and 18 months. Only recent exposure includes only patients with a medication fill within the prior 6 months without earlier medication fills. Propensity weights were recalculated within each subgroup. We list the *P*-values for significant differences in the odds ratios across subgroups. For characteristics with two subgroups, the statistical significance of differences in odds ratios between the two groups were tested by calculating z-statistics for the difference in log(odds ratios). The odds ratios for race – which we divided into three subgroups – was compared using Cochrane's Q statistic.

Abbreviations: ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; AHRQ SES: Agency for Healthcare Research and Quality Socioeconomic Status; IHD: ischemic heart disease.

gust 19, 2020. There were 4,734 infections (0.7%) in the ACEI cohort, 2,542 in the ARB cohort (0.8%), and 6,002 (0.8%) in the control cohort. Among these 13,278 infections, there were 3,330 hospitalizations (25.1%).

Adjusted analyses

We calculated propensity weights as the inverse probability of each patient being in their respective cohort. The propensity weight balance is displayed in Supplement Figure 1. Following inverse propensity weighting, baseline characteristics were well-balanced across the cohorts (Figure 2).

Using inverse propensity weights and adjustment for baseline characteristics, we evaluated the association between ACEI or ARB therapy with SARS-CoV-2 infection. Treatment with ACEI was associated with lower odds of SARS-CoV-2 infection (OR 0.93; 95% CI: 0.89-0.97). Treatment with an ARB was not associated with a difference in the odds of SARS-CoV-2 infection (OR 1.02; 95% CI: 0.96-1.07). The e-values for ACEI therapy, compared with the control arm, were 1.36 and 1.21 for the point estimate and the confidence interval, respectively. In the model directly comparing ACEI and ARB therapy, we found ACEI therapy was associated with lower odds of SARS-CoV-2 infection (OR 0.92; 95% CI: 0.87-0.96). The e-values for ACEI therapy, compared with ARB, were 1.42 and 1.27 for the point estimate and the confidence interval, respectively.

Treatment with an ACEI was also associated with lower odds of hospitalization (OR 0.90; 95% CI: 0.82-0.98). ARB treatment was not significantly associated with the odds of hospitalization (OR 0.91; 95% CI: 0.81-1.02)

We conducted subgroup analyses across patient characteristics (Figure 3). While the point estimates differed, we did not find evidence of statistically significant heterogeneity. Stratifying patients based on a marker of chronic exposure (medication fill between 6-18 months before the index date) led to 1,353,770 patients with chronic exposure and 282,964 with only recent exposure. There was not significant heterogeneity between these groups.

Sensitivity analyses

We evaluated the association between ACEI and ARB therapy with alternate outcomes (Supplement Figure 2). We find no significant association between ACEI therapy and diagnoses of influenza, fractures, or UTIs. However, we did find a significant association between ARBs and lower odds of both UTI (OR 0.84; 95% CI: 0.77-0.92) and vertebral/hip fracture (OR 0.81; 95% CI: 0.73-0.90).

We performed an exploratory analysis, which included 1,403,750 patients, in which we separated CCB therapy from our other control treatments. Compared with a control group on thiazide or beta-blockers but not CCB, neither ACEI nor ARB were significantly associated with the odds of SARS-CoV-2 infection (OR 0.97; 95% CI: 0.92-1.03 for ACEI and OR 1.04; 95% CI: 0.96-1.12 for ARB). However, CCB therapy was associated with higher odds of SARS-CoV-2 infection (OR 1.08 95% CI: 1.02-1.15) compared with thiazide or beta-blocker therapy.

Finally, we repeated our primary analysis with multiple sensitivity analyses around our approach to missing data. We found no substantial difference in our results across these analyses (results listed in Supplement Table 6).

Discussion

Among VA patients with medically treated hypertension, neither ACEI nor ARB therapy were associated with higher odds of SARS-CoV-2 infection. ACEI therapy was associated with lower odds of SARS-CoV-2 infection compared with alternate anti-hypertensives. In an exploratory analysis in which we separated our control population into those on CCB versus other anti-hypertensives, CCBs were associated with higher odds of SARS-CoV-2 infection compared with patients on ACEI/ARB/other anti-hypertensives. Overall, our results support existing evidence and society guidelines that neither ACEI nor ARB therapy should be discontinued due to concerns of SARS-CoV-2 infection.[52,53]

Multiple studies have evaluated the association between ACEI/ARB therapy and COVID-19 diagnosis. Most studies have found no significant association between either therapy and COVID-19 diagnoses. However, there are important differences both across existing studies and with ours with regards to the study design and results. Several studies evaluated test positivity among a population being tested or evaluated severe adverse outcomes among those hospitalized for SARS-CoV-2. These designs introduce potential collider bias if the exposure – ACEI or ARB – influence the likelihood of having symptomatic infection leading to testing or hospitalization. Therefore, we evaluated a broader population. However, our approach may also introduce collider bias if the likelihood of being tested is associated with anti-hypertensive therapy independent of symptoms (e.g., patients on ACEI being more likely to be tested given the initial concerns about ACEIs). Second, including patients with non-hypertension indications for ACEI or ARB (e.g., HF-rEF) could impact the findings because conditions like heart failure and chronic kidney disease are associated with more severe COVID-19 outcomes.[35,36,54] We excluded patients with strong non-hypertension indications for ACEI/ARB given concern that differences in condition severity between arms would introduce bias. Finally, many studies have limited sample sizes with relatively imprecise estimates of association. Our study included a large cohort on ACEI/ARB, adjusted for detailed patient characteristics in addition to administrative data, and excluded patients with alternate therapy indications.

Previous studies have consistently shown no difference in the odds of COVID-19 related outcomes with ACEI or ARB therapy. There are, however, important differences across studies. Hippisley-Cox and colleagues found a significant association with lower risk of COVID-19 diagnosis for both ACEI (HR 0.71; 95% CI: 0.67-0.94) and ARB therapy (HR 0.63; 95% CI 0.59-0.67) in a general practice database in England.[9] Their primary analysis included the general population with and without hypertension and hypertensive therapy. Adjusting for the number of hypertension drugs attenuated the association for both drugs (ACEI HR: 0.87 [95% CI 0.72-1.05] and ARB HR: 0.82 [95% CI: 0.68 to 0.99]). Comparing ACEI/ARB therapy to non-users will lead to an imbalance in hypertension severity, which is important given the potential relationship between hypertension and COVID-19 related outcomes. This imbalance is also present in our study, which is why we adjusted for the number of anti-hypertensives and prior blood pressure.

Two large studies found non-significant associations between ACEI/ARB therapy and COVID-19 related outcomes but had substantially different point estimates across ACEIs and ARBs, potentially suggestive of heterogeneity across these therapies. De Abajo and colleagues compared hospitalized COVID-19 patients with hypertension with matched controls without COVID-19 in Madrid, Spain.[11] Compared with alternate anti-hypertensives, the adjusted odds ratio for COVID-19 hospitalization was 0.80 (95% CI: 0.64-1.00) for ACEIs compared with 1.10 (95% CI: 0.88-1.37) for ARBs. Fosbøl and colleagues evaluated severe COVID-19 outcomes among hypertension patients without heart failure or chronic kidney disease.[8] They found a hazard ratio of 0.85 (95% CI: 0.70-1.01) for ACEI therapy compared with 1.15 (95% CI: 0.96-1.37) for ARBs. We found a significant association between ACEI therapy and lower odds of SARS-CoV-2 infection but not for ARB therapy. Interpreting our ARB results are challenging. While the falsification endpoints were consistently negative for ACEI, we also found lower odds of vertebral/hip fracture and UTI with ARB therapy. This is suggestive of residual confounding and potential downward bias in our ARB estimates.

While most raised concerns that ACEI/ARB therapy may increase COVID-19 risk due to upregulated ACE2

levels, there is also a biologic mechanism by which these therapies may reduce risk.[55] Angiotensin II drives lung injury and inflammation. ACEIs decrease production of Angiotensin II and ARBs blocks its effect. ACEIs and ARBs may have different effects on SARS-CoV-2 given they act via different mechanisms and have differential effects on ACE2 levels. In animal models, losartan led to greater increases in ACE2 levels compared with lisinopril, although this is not consistently observed with renal ACE2 levels.[5] There is limited data regarding the impact on pulmonary ACE2 levels, the impact in human tissue, or how changes in ACE2 levels impact SARS-CoV-2 infection and severity.[55] Overall, the difference in our results between ACEI and ARB should be interpreted with caution. However, this remains an important question worth further evaluation given ACEI and ARB therapy are often clinically interchangeable.

Semenzato and colleagues compared ACEI and ARB therapy with CCB therapy among 1.8 million individuals with hypertension in France.[50] They found ACEI and ARB therapy were associated with significantly lower rates of COVID-19 hospitalization (ACEI HR: 0.74 [95% CI, 0.65–0.83] and ARB HR: 0.84 [0.76–0.93]). In this context, we performed an exploratory analysis in which we separated patients on CCBs from each arm. Compared to the beta-blocker/thiazide control group, ACEI and ARB had similar odds of SARS-CoV-2 infection but CCB users had higher adjusted odds. These findings are exploratory and there is potential confounding related to anti-hypertensive selection. For example, CCBs do not require lab monitoring and may be preferable for patients with difficulty getting blood draws. However, these results suggest the importance of further evaluation of CCBs with SARS-CoV-2 infection.

In addition to observational studies, there are now two randomized clinical trials that have evaluated the safety of continued ACEI/ARB therapy among hospitalized patients with COVID-19.[56,57] In both trials, continuation of ACEI/ARB therapy was not associated with adverse outcomes. Although this does not directly address the initial risk of infection, this is consistent with the lack of evidence regarding increased risk of SARS-CoV-2 infection among patients on chronic therapy.

There are multiple important strengths of our analysis. First, this national US study includes a racially gi population, which is a potential contributor to differences in outcomes, including those related to comorbidities and socioeconomic characteristics. Second, we adjust important characteristics that are often absent in administrative data: laboratory values and vital signs. We also adjusted for social risk, an important factor in this pandemic. Third, our large sample allowed us to restrict our analysis to a population with hypertension without other indications for ACEI/ARB therapy while still providing precise estimates.

Limitations

There are important limitations to our analysis. First, our quantitative bias analysis suggested modest unmeasured confounding could account for our findings. While we used a large set of covariates based on our current understanding of risk factors for SARS-CoV-2 infection and anti-hypertensive selection, there is still potential confounding. Our ARB falsification analysis findings accentuate this concern. We selected these falsification endpoints given an expectation that ACEI/ARB therapy would not affect outcomes. An alternate explanation would be an improper selection of a priori falsification endpoints given limited studies suggesting lower risk of fracture with ARB than ACEI therapy.[58] However, this has not been seen with UTIs.

The second limitation is potential exposure measurement error given we classified exposure based on medication fills within 6 months. This potentially classified patients as ACEI or ARB users despite being non-adherent or having stopped therapy. However, most ACEI/ARB treatment is chronic as seen in our analysis. Additionally, such bias would generally attenuate finding towards the null. We also have potential measurement error in identifying infections given not all patients were tested for SARS-CoV-2 and the VA dataset may miss some infections outside of the VA.

Third, there is potential time-related bias because our study does not account for patients with less time at risk for developing infection due to death without SARS-Cov2 infection. Finally, the risk of infection has marked spatiotemporal variation. Small differences in regional utilization of ACEI/ARB may have important effects. We controlled for patient region and geographic characteristics, but additional analyses with more granular geographic data will be important.

Conclusions

We found ACEI therapy was associated with lower odds of SARS-CoV-2 infection in a VA population with medically-treated hypertension. Given the current evidence and the clinical benefits of ACEI/ARB therapy for multiple conditions, neither ongoing ACEI nor ARB therapy should be stopped due to risks of developing COVID-19 infection. In an exploratory analysis, we found the odds of SARS-CoV-2 infection were similar between ACEI, ARB, and beta-blocker/thiazide users but were higher among CCB users. Further analyses to evaluate potential protective effects of ACEI therapy or an increase in risk with CCB therapy will be important.

Funding

This work was funded by an American Heart Association COVID-19 and Its Cardiovascular Impact Rapid Response Grant (Award # 813396). AS receives research

support from the National Heart, Lung, and Blood Institute (1K23HL151672-01).

Disclosures

AS consults for Acumen, LLC. SK reports receiving unrestricted grants from Daiichi Sankyo and Bayer and lecture fees from Bayer and Bristol-Myers Squibb outside the submitted work. Views expressed are those of the authors and not necessarily those of the Department of Veterans Affairs or other affiliated institutions. The remaining authors (SL, CW, MG, PH) have no disclosures.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2021.06.004.

References

1. Sommerstein R, Gräni C. Rapid response: RE: Preventing a covid-19 pandemic: ACE inhibitors as a potential risk factor for fatal Covid-19. BMJ 2020;368:m8102. doi:10.1161/CIRCULATIONAHA.104.510461.
2. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation 2005;111:2605–10. doi:10.1161/CIRCULATIONAHA.104.510461.
3. Furuhashi M, Moniwa N, Mita T, et al. Urinary angiotensin-converting enzyme 2 in hypertensive patients may be increased by olmesartan, an angiotensin II receptor blocker. Am J Hypertens 2015;28:15–21. doi:10.1093/ajh/hpu086.
4. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020;180:934–43. doi:10.1001/jamainternmed.2020.0994.
5. South AM, Diz DI, Chappell MC. COVID-19, ACE2, and the cardiovascular consequences. Am J Physiol Heart Circ Physiol 2020;318 H1084-H1090. doi:10.1152/ajpheart.00217.2020.
6. Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? J Hypertens 2020;38:781–2. doi:10.1097/HJH.0000000000002450.
7. Vaduganathan M, Vardeny O, Michel T, et al. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med 2020;382:1653–9. doi:10.1056/NEJMsr2005760.
8. Fosbøl EL, Butt JH, Østergaard L, et al. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. JAMA 2020;324:168–77. doi:10.1001/jama.2020.11301.
9. Hippisley-Cox J, Tan PS, Coupland C. Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: cohort study including 8.3 million people. Heart 2020 heartjnl-2020-318312. doi:10.1136/heartjnl-2020-318312.
10. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin-angiotensin-aldosterone system inhibitors and risk of covid-19. N Engl J Med 2020;382:2441–8. doi:10.1056/NEJMoa2008975.
11. de Abajo FJ, Rodríguez-Martín S, Lerma V, et alMED-ACE2-COVID19 study group. Use of renin-angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. Lancet. 2020;395:1705–14. doi:10.1016/S0140-6736(20)31030-8.
12. Mancia G, Rea F, Ludergnani M, et al. Renin-Angiotensin-aldosterone system blockers and the risk of Covid-19. N Engl J Med 2020;382:2431–40. doi:10.1056/NEJMoa2006923.
13. Mehta N, Kalra A, Nowacki AS, et al. Association of use of angiotensin-converting enzyme inhibitors and angiotensin ii receptor blockers with testing positive for coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5:1020–6. doi:10.1001/jamacardio.2020.1855.
14. Jung SY, Choi JC, You SH, Kim WY. Association of Renin-angiotensin-aldosterone system inhibitors with coronavirus disease 2019 (COVID-19)- related outcomes in korea: a nationwide population-based cohort study. Clin Infect Dis 2020;71:2121–8. doi:10.1093/cid/ciaa624.
15. Chodick G, Nutman A, Yiekutiel N, Shalev V. Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers are not associated with increased risk of SARS-CoV-2 infection. J Travel Med 2020;27:taaa069. doi:10.1093/jtm/taaa069.
16. Dublin S, Walker R, Floyd JS, et al. Renin-angiotensin-aldosterone system inhibitors and COVID-19 infection or hospitalization: a cohort study. Am J Hypertens 2020:hpaa168. doi:10.1093/ajh/hpaa168.
17. Trifirò G, Massari M, Da Cas R, et al. ITA-COVID-19: RAAS inhibitor group. renin-angiotensin-aldosterone system inhibitors and risk of death in patients hospitalised with covid-19: a retrospective Italian cohort study of 43,000 patients. Drug Saf. 2020;43:1297–308. doi:10.1007/s40264-020-00994-5.
18. Khera R, Clark C, Lu Y, et al. Association of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers with the risk of hospitalization and death in hypertensive patients with coronavirus disease-19. J Am Heart Assoc 2021. doi:10.1161/JAHA.120.018086.
19. An J, Wei R, Zhou H, et al. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers use and covid-19 infection among 824 650 patients with hypertension from a us integrated healthcare system. J Am Heart Assoc 2021;10. doi:10.1161/JAHA.120.019669.
20. Rentsch CT, Kidwai-Khan F, Tate JP, et al. Covid-19 testing, hospital admission, and intensive care among 2,026,227 United States Veterans Aged 54-75 Years. medRxiv [Preprint] 2020 2020.04.09.20059964. doi:10.1101/2020.04.09.20059964.
21. Derington CG, Cohen JB, Mohanty AF, et al. Angiotensin II receptor blocker or angiotensin-converting enzyme inhibitor use and COVID-19-related outcomes among US Veterans. PLoS One 2021;16.
22. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–62. doi:10.1016/S0140-6736(20)30566-3.
23. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the

cardiovascular system. Nat Rev Cardiol 2020;17:259–60. doi:10.1038/s41569-020-0360-5.
24. Karram T, Abbasi A, Keidar S, et al. Effects of spironolactone and eprosartan on cardiac remodeling and angiotensin-converting enzyme isoforms in rats with experimental heart failure. Am J Physiol Heart Circ Physiol 2005;289:H1351–8. doi:10.1152/ajpheart.01186.2004.
25. Hales CM, Servais J, Martin CB, Kohen D. Prescription drug use among adults aged 40-79 in the United States and Canada. NCHS Data Brief 2019:1–8.
26. Department of Veterans Affairs, Office of Research and Development. COVID-19 Shared Data Resource. Available at: https://vhacdwdwhweb100.vha.med.va.gov/phenotype/index.php/COVID-19:Shared_Data_Resource. Accessed. Accessed November 3, 2020.
27. Jorden MA, Rudman SL, Villarino E, et alCDC COVID-19 Response Team. Bemis K, Simmons CR, Jespersen M, Iberg Johnson J, Mytty E, Arends KD, Henderson JJ, Mathes RW, Weng CX, Duchin J, Lenahan J, Close N, Bedford T, Boeckh M, Chu HY, Englund JA, Famulare M, Nickerson DA, Rieder MJ, Shendure J, Starita LM. Evidence for Limited Early Spread of COVID-19 Within the United States, January-February 2020. MMWR Morb Mortal Wkly Rep 2020;69:680–4. doi:10.15585/mmwr.mm6922e1.
28. Yancy CW, Jessup M, Bozkurt B, Butler J. Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147–239. doi:10.1016/j.jacc.2013.05.019.
29. Whelton PK, Carey RM, Aronow WS. Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2018;138 e426-e483. doi:10.1161/CIR.0000000000000597.
30. Zhou M, Daubresse M, Stafford RS, Alexander GC. National trends in the ambulatory treatment of hypertension in the United States, 1997-2012. PLoS One 2015;10. doi:10.1371/journal.pone.0119292.
31. Ku E, McCulloch CE, Vittinghoff E, et al. Use of antihypertensive agents and association with risk of adverse outcomes in chronic kidney disease: focus on angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. J Am Heart Assoc 2018;7. doi:10.1161/JAHA.118.009992.
32. Greene SJ, Butler J, Albert NM, et al. Medical therapy for heart failure with reduced ejection fraction: The CHAMP-HF Registry. J Am Coll Cardiol 2018;72:351–66. doi:10.1016/j.jacc.2018.04.070.
33. Murphy DP, Drawz PE, Foley RN. Trends in angiotensin-converting enzyme inhibitor and angiotensin ii receptor blocker use among those with impaired kidney function in the United States. J Am Soc Nephrol 2019;30:1314–21. doi:10.1681/ASN.2018100971.
34. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13. doi:10.1016/S0140-6736(20)30211-7.
35. Garg S, Kim L, Whitaker M, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 - COVID-NET, 14 States, March 1-30, 2020. MMWR Morb Mortal Wkly Rep 2020;69:458–64. doi:10.15585/mmwr.mm6915e3.
36. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584:430–6. doi:10.1038/s41586-020-2521-4.
37. Heidenreich PA, Natarajan S, Bahrami H. Accuracy of administrative coding to identify reduced and preserved left ventricular ejection fraction. J Card Fail 2019;25:486–9. doi:10.1016/j.cardfail.2019.01.019.
38. US Census Bureau. American Community Survey. 2018; https://www.census.gov/programs-surveys/acs/about.html. Accessed February 9, 2019.
39. Bonito AJ, Bann C, Eicheldinger C, Carpenter L. Creation of New Race-Ethnicity Codes and Socioeconomic Status (SES) Indicators for Medicare Beneficiaries: Final Report; 2008 https://archive.ahrq.gov/research/findings/final-reports/medicareindicators/medicareindicators1.html Accessed May 1, 2020.
40. Figueroa JF, Joynt Maddox KE, Beaulieu N, et al. Concentration of potentially preventable spending among high-cost medicare subpopulations: an observational study. Ann Intern Med 2017;167:706–13. doi:10.7326/M17-0767.
41. Merzon E, Green I, Shpigelman M, et al. Haemoglobin A1c is a predictor of COVID-19 severity in patients with diabetes. Diabetes Metab Res Rev 2020:e3398. doi:10.1002/dmrr.3398.
42. Tao Z, Xu J, Chen W, et al. Anemia is associated with severe illness in COVID-19: A retrospective cohort study. J Med Virol 2021;93:1478–88. doi:10.1002/jmv.26444.
43. Kohsaka S, Sandhu AT, Parizo JT, et al. Association of diagnostic coding-based frailty and outcomes in patients with heart failure: a report from the veterans affairs health system. J Am Heart Assoc 2020;9. doi:10.1161/JAHA.120.016502.
44. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med 2011;30:377–99. doi:10.1002/sim.4067.
45. Sperrin M, Martin GP. Multiple imputation with missing indicators as proxies for unmeasured variables: simulation study. BMC Med Res Methodol 2020;20:185. doi:10.1186/s12874-020-01068-x.
46. Hirano K, Imbens GW. Estimation of causal effects using propensity score weighting: an application to data on right heart catheterization. Health Serv Outcomes Res Methodol 2001;2:259–78. doi:10.1023/A:1020371312283.
47. Xu S, Ross C, Raebel MA, et al. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. Value Health 2010;13:273–7. doi:10.1111/j.1524-4733.2009.00671.x.
48. Izem R, Liao J, Hu M, et al. Comparison of propensity score methods for pre-specified subgroup analysis with survival data. J Biopharm Stat 2020;30:734–51. doi:10.1080/10543406.2020.1730868.
49. West SL, Gartlehner G, Mansfield AJ, et al. Comparative

Effectiveness Review Methods: Clinical Heterogeneity [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2010 Table 7, Summary of common statistical approaches to test for heterogeneity. Available from: https://www.ncbi.nlm.nih.gov/books/NBK53317/table/ch3.t2/.

50. Semenzato L, Botton J, Drouin J, et al. Antihypertensive Drugs and COVID-19 Risk: A cohort study of 2 million hypertensive patients. hypertension. 2021;77:833-842. doi:10.1161/HYPERTENSIONAHA.120.16314.
51. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the e-value. Ann Intern Med 2017;167:268–74. doi:10.7326/M16-2607.
52. American College of Cardiology. HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19; March 17, 2020 https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19 Accessed May 1, 2020.
53. Mackey K, King VJ, Gurley S, et al. Risks and impact of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers on SARS-CoV-2 infection in adults: a living systematic review. Ann Intern Med 2020;173:195–203. doi:10.7326/M20-1515.
54. Chen R, Liang W, Jiang M, et al. Medical treatment expert group for covid-19. risk factors of fatal outcome in hospitalized subjects with coronavirus disease 2019 from a nationwide analysis in China. Chest 2020;158:97–105. doi:10.1016/j.chest.2020.04.010.
55. South AM, Tomlinson L, Edmonston D, et al. Controversies of renin-angiotensin system inhibition during the COVID-19 pandemic. Nat Rev Nephrol 2020;16:305–7. doi:10.1038/s41581-020-0279-4.
56. Lopes RD, Macedo AVS, de Barros E Silva PGM, et al. Effect of discontinuing vs continuing angiotensin-converting enzyme inhibitors and angiotensin ii receptor blockers on days alive and out of the hospital in patients admitted with covid-19: a randomized clinical trial. JAMA 2021;325:254–64. doi:10.1001/jama.2020.25864.
57. Cohen JB, Hanff TC, William P, et al. Continuation versus discontinuation of renin-angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial. Lancet Respir Med 2021;9:275–84. doi:10.1016/S2213-2600(20)30558-0.
58. Kwok T, Leung J, Barrett-Connor E. Osteoporotic Fractures in Men (MrOS) Research Group. ARB users exhibit a lower fracture incidence than ACE inhibitor users among older hypertensive men. Age Ageing 2017;46:57–64. doi:10.1093/ageing/afw150.