Journal of the American Heart Association

ORIGINAL RESEARCH

Association of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers With the Risk of Hospitalization and Death in Hypertensive Patients With COVID-19

Rohan Khera, MD, MS*; Callahan Clark, PharmD*; Yuan Lu, ScD; Yinglong Guo, MA, MS; Sheng Ren, PhD; Brandon Truax, MS; Erica S. Spatz, MD, MHS; Karthik Murugiah, MD; Zhenqiu Lin, PhD; Saad B. Omer, MBBS, MPH, PhD; Deneen Vojta, MD†; Harlan M. Krumholz, MD, SM†

BACKGROUND: Despite its clinical significance, the risk of severe infection requiring hospitalization among outpatients with severe acute respiratory syndrome coronavirus 2 infection who receive angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) remains uncertain.

METHODS AND RESULTS: In a propensity score–matched outpatient cohort (January–May 2020) of 2263 Medicare Advantage and commercially insured individuals with hypertension and a positive outpatient SARS-CoV-2, we determined the association of ACE inhibitors and ARBs with COVID-19 hospitalization. In a concurrent inpatient cohort of 7933 hospitalized with COVID-19, we tested their association with in-hospital mortality. The robustness of the observations was assessed in a contemporary cohort (May–August). In the outpatient study, neither ACE inhibitors (hazard ratio [HR], 0.77; 0.53–1.13, *P*=0.18) nor ARBs (HR, 0.88; 0.61–1.26, *P*=0.48) were associated with hospitalization risk. ACE inhibitors were associated with lower hospitalization risk in the older Medicare group (HR, 0.61; 0.41–0.93, *P*=0.02), but not the younger commercially insured group (HR, 2.14; 0.82–5.60, *P*=0.12; *P*-interaction 0.09). Neither ACE inhibitors nor ARBs were associated with lower hospitalization risk in either population in the validation cohort. In the primary inpatient study cohort, neither ACE inhibitors (HR, 0.97; 0.81–1.16; *P*=0.74) nor ARBs (HR, 1.15; 0.95–1.38, *P*=0.15) were associated with in-hospital mortality. These observations were consistent in the validation cohort.

CONCLUSIONS: ACE inhibitors and ARBs were not associated with COVID-19 hospitalization or mortality. Despite early evidence for a potential association between ACE inhibitors and severe COVID-19 prevention in older individuals, the inconsistency of this observation in recent data argues against a role for prophylaxis.

Key Words: angiotensin receptor blockers ■ angiotensin-converting enzyme inhibitors ■ COVID-19 ■ hypertension

Hypertension is a risk factor for severe infection with COVID-19.[1] During the early months of the spread of COVID-19, there was controversy regarding the use of 2 first-line antihypertensive agents—angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)—and whether their use

Correspondence to: Harlan M. Krumholz, MD, SM, 1 Church St, Suite 200, New Haven, CT 06510. E-mail: harlan.krumholz@yale.edu

*Dr Khera and Dr Clark contributed equally to this work as co-first authors.

†Dr Vojta and Dr Krumholz contributed equally to this work as co-senior authors.

Preprint posted on MedRxiv May 19, 2020. doi: https://doi.org/10.1101/2020.05.17.20104943.

Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.018086

For Sources of Funding and Disclosures, see page 19.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- In this national cohort study of Medicare Advantage and commercial insurance enrollees with hypertension and SARS-CoV-2 infection, the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, compared with the use of other antihypertensive agents, was not associated with an increased risk of hospitalization among outpatients and in-hospital mortality among inpatients.
- While early estimates in the pandemic found 40% lower risk of hospitalizations in an older Medicare population testing positive with SARS-CoV-2 as an outpatient, this effect could not be replicated in more recent data.

What Are the Clinical Implications?

- Our study findings do not support a change to the current use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers among patients with hypertension being managed in the outpatient setting and at risk of infection with SARS-CoV-2.
- Given the inconsistent association of angiotensin-converting enzyme inhibitors with lower risk of severe disease in older patients, our study does not support their use as prophylaxis against SARS-CoV-2.

exacerbated or mitigated the infection.[2–5] There have since been a series of studies that evaluated the association of these drugs with outcomes of patients hospitalized with COVID-19 and those studies did not find an increase in the risk of in-hospital mortality.[5–9] Other reports have also not found an association with the risk of infection with SARS-CoV-2.[7,10,11] In this present study, we describe the results of a national study that evaluated the association of ACE inhibitors and ARBs among patients with hypertension, using an active comparator design using high-quality national data, which were validated with updated data during the course of the pandemic.

The studies that have evaluated the association of ACE inhibitors and ARBs have been examined by systematic reviews that report vast variations in quality, with more than half not accounting for confounding through gaps in risk-adjustment, thus limiting their ability to make an inference on an association.[7,11] There are also frequent limitations in the design of studies because they lack an active comparator,[12,13] which is essential to account for the confounding effect of receiving a treatment of any kind on outcomes. Some of the studies evaluating the association of COVID-19 have also been limited by data sourced from a limited number of health facilities, from questionnaires rather than prescription data,[14] or drawn from the proportional use of these drugs among hospitalized individuals relative to the general population.[12] Specifically, most studies lack the ability to track a large number of individuals regardless of where they seek care,[10] which is particularly important in assessing hospitalization risk following SARS-CoV-2 infection. Furthermore, the studies, thus far, have also been single-time investigations, and have not assessed the consistency of the association as more data emerged. Of note, a recently published randomized trial did not find a deleterious effect of continuing ACE inhibitors/ARB during a COVID-19 hospitalization,[15] but included only 152 patients and does not provide information about risk of severe disease requiring hospitalization.

Our national study assessed the association of ACE inhibitors and ARBs with outcomes in individuals who had hypertension and who tested positive for SARS-CoV-2 in the outpatient setting. We specifically evaluated the association among those with hypertension who were receiving another antihypertensive agent, ensuring that we had an active comparator. Also, to provide information about the association in inpatients, we conducted a study of the association of ACE inhibitors and ARBs on mortality among individuals who had hypertension and who were hospitalized with COVID-19. We also validated the findings in a period following the initial evaluation.

METHODS

Data Sources

We used de-identified administrative claims for Medicare Advantage and commercially insured enrollees in a research database from a single large health insurance provider in the United States. The database contains medical (emergency, inpatient, and outpatient) and pharmacy claims for services submitted for third-party reimbursement, available as *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) and National Drug Codes claims, respectively.

We used 2 additional data sources. First, a limited outpatient data set included results for enrollees undergoing outpatient testing for SARS-CoV-2 at 49 hospital-based, freestanding outpatient, and third-party laboratories across the United States. Second, the inpatient COVID-19 data set included a daily updated record of COVID-19 inpatient admissions for all insurance enrollees with claims information, representing those admitted to a hospital with a primary or secondary diagnosis of COVID-19 (Table S1), along with

their current disposition (admitted, discharged, transferred, or died).

The data are proprietary and are not available for public use but can be made available to Editors and their approved auditors under a data use agreement to confirm the findings of the current study. The statistical code is available from the first and corresponding authors.

Primary Study Population

We constructed cohorts of enrollees for each of the 2 studies. First, for the outpatient study, we included individuals ≥18 years old with 6 or more months of enrollment in Medicare Advantage or commercial insurance from January through December 2019 and available claims data, a diagnosis of hypertension in claims and receiving 1 or more antihypertensive agents, and a positive test for SARS-CoV-2 in an outpatient setting between March 6, 2020 and May 3, 2020 (Figure S1). The Medicare Advantage and commercially insured individuals in the study represented all individuals with available claims in the UnitedHealth Group Clinical Discovery Database who satisfied the inclusion criteria.

Second, for the inpatient study, we identified an inpatient cohort of adults hospitalized with COVID-19. This included all patients (age ≥18 years) with at least 6 months of health insurance enrollment in 2019 with available claims data, a diagnosis of hypertension in 1 or more claims, who were receiving 1 or more antihypertensive agents, and were hospitalized with a primary or secondary diagnosis of COVID-19 between January 5, 2020 and May 10, 2020 (Figure S2).

For both studies, a diagnosis of hypertension was based on *ICD-10* codes (Table S1), and drug treatment for hypertension was defined by the receipt of 1 or more agents included in the 2017 American Heart Association hypertension guidelines.[16] These include first-line agents of ACE inhibitors, ARBs, thiazide and thiazide-like diuretics, and dihydropyridine and non-dihydropyridine calcium channel blockers, as well as second-line agents of β-adrenergic antagonists, α blockers, centrally acting α agonists, loop diuretics, potassium-sparing diuretics, mineralocorticoid receptor antagonists, and direct vasodilators (individual drugs listed in Table S2). Fixed-dose drug combinations were considered equivalent to taking the component drugs as individual drugs (Table S2). This information was defined by a pharmacy claim corresponding to a cumulative supply >30 days between July 1, 2019 and December 31, 2019.

Validation Study Population

We created 2 secondary outpatient and inpatient cohorts to assess the robustness of observations in a more contemporary population when lockdowns for COVID-19 were progressively relaxed nationally, and people potentially had different patterns of healthcare-seeking behavior compared with the early pandemic. These were defined in a manner identical to the primary cohorts but were drawn between May 4 and August 2, 2020.

Study Exposures

We identified 2 mutually exclusive exposure groups, including individuals receiving (1) ACE inhibitors, and (2) ARBs, with or without other agents. We used an active comparator for these analyses that included all remaining individuals with a diagnosis of hypertension who received 1 or more antihypertensive agents from drug classes other than ACE inhibitor or ARB. These agents include all first- and second-line antihypertensive agents based on the 2017 American Heart Association guidelines for hypertension.[16] In sensitivity analyses, we restricted the control group to individuals receiving at least 1 first-line antihypertensive agent.

Study Covariates

We combined information from inpatient and outpatient claims in 2019 to identify potential confounders of the association of the ACE inhibitors and ARB use and clinical outcomes. We included age, sex, race, conditions that would represent potential indications for selective use of ACE inhibitors or ARBs (diabetes mellitus, myocardial infarction, heart failure, and chronic kidney disease), and each of the additional comorbidities included in the Charlson Comorbidity Index (Table S1). Race was available only for Medicare Advantage enrollees. We included information on the total number of antihypertensive agents prescribed to enrollees by using pharmacy claims.

Study Outcomes

In the outpatient study, the primary outcome was inpatient hospitalization for COVID-19, defined as a hospitalization with a principal or secondary diagnosis of COVID-19 in a linked inpatient data set (Table S1). We assessed mortality during this inpatient hospitalization as a secondary outcome. In the inpatient study, the primary outcome was in-hospital mortality. In addition, we evaluated a secondary composite outcome of death or discharge to hospice and hospital length of stay.

Propensity Score Matching

In both outpatient and inpatient studies, we created propensity score–matched cohorts of individuals with hypertension, treated with ACE inhibitors, ARBs, or other antihypertensive medications. For example, we modeled the receipt of ACE inhibitor or another

antihypertensive (excluding ARB) to determine each person's likelihood of receiving these agents based on their measured clinical characteristics. We applied this strategy to different pairs of treatment comparisons (ACE inhibitor versus others, ARB versus others, and ACE inhibitor versus ARB). We pursued 100 iterations to find the lowest mean absolute standardized difference among matched variables. We matched our cohorts on age, sex, race, insurance type, conditions that may lead to selective use of ACE inhibitors and ARBs (ie, diabetes mellitus, myocardial infarction, heart failure, and chronic kidney disease), each of the comorbidities in the Charlson Comorbidity Index, and the number of antihypertensive agents present in claims. To account for regional clustering of care practices and response to the COVID-19 pandemic, we explicitly accounted for census region of laboratory testing site or inpatient facility in our models.

We evaluated the performance of propensity score matching using several strategies. First, we assessed the propensity score distributions in the unmatched and matched cohorts and calculated an equipoise metric to summarize the degree of overlap in characteristics of individuals receiving these drugs.[17,18] A value >0.5 implies 2 drugs are in empirical equipoise, with a higher value indicating a lower likelihood of confounding by indication.[18] Next, we evaluated whether our matching algorithm achieved a standardized difference of <10% between matched cohorts, suggestive of adequately matched groups.[17,19] Third, we evaluated the success of our matching algorithm using negative control outcomes that are unlikely to be affected by the treatment assignment.[17] These strategies were designed to evaluate the potential for residual confounding after creating propensity score–matched cohorts. Finally, we evaluated our observations for robustness by assessing treatment effects in 100 iterations of the propensity score matching–algorithm. Further details are included in Data S1.

Statistical Analysis

We describe differences between individuals treated with ACE inhibitors and ARBs compared with other antihypertensive agents, and between those treated with ACE inhibitors using χ^2 test for categorical variables and *t* test for continuous variables. Because the duration of follow-up was expected to vary across individuals in both outpatient and inpatient COVID-19 cohorts, we evaluated their effects in time-to-event analyses with Cox-Proportional Hazards models in both unadjusted and propensity score–matched cohorts. To reduce bias from residual differences in matched covariates in our evaluation of outcomes, we included the covariates included in our propensity score–matching algorithm as independent variables in these models.[20] We repeated these analyses without this additional covariate adjustment.

For the outpatient study, the index date was represented by the day of positive SARS-CoV-2 test as an outpatient, the period of the study was measured in days from the positive SARS-CoV-2 test, and the outcome of interest was hospitalization. For the outpatient analysis, we used Cox proportional hazards to assess pairwise hazards of hospitalization in propensity-matched groups of patients receiving ACE inhibitor, ARB, or controls.

For the inpatient study, the index date was represented by the first day of hospitalization with COVID-19, the period of the study was measured in days from admission, and the outcome of interest was death. Since hospitalization could end with either a person's death or being discharged alive, we created a cause-specific Cox proportional hazards model, which is a competing risk analysis.[21–23] In this model, patients still hospitalized at the end of the observation period were right censored. Among those who were no longer hospitalized, we assessed the hazards of the 2 competing outcomes: in-hospital death and alive-discharge, because these represent mutually exclusive events, wherein one precludes the other. Therefore, in the cause-specific Cox proportional hazards, the occurrence of death is treated as a right-censoring event for the outcome of being discharged alive, and an alive-discharge is treated as a right-censoring event for the death outcome. The design of our study focusing on comparative effectiveness favored the cause-specific hazard model as the appropriate analysis for competing-risk assessment.

Both outpatient analyses for hospitalization risk and inpatient analyses for mortality risk were right censored at the end of the observation period on May 10, 2020 for the primary analysis.

We evaluated quantitative and qualitative interactions between insurance type and treatment groups for the assessment of our outcomes. We also created propensity score–matched cohorts within each of the 2 insurance subgroups.

All analyses were repeated in the validation cohort, which included individuals who tested positive with SARS-CoV-2 or were hospitalized with COVID-19 between May and August 2020.

Analyses were performed using R 3.4.0 (CRAN) and Python 3.8.2. All hypothesis tests were 2-sided, with a level of significance set at 0.05, except for interaction tests where the level of significance was set at 0.10. Given the exploratory nature of study, statistical tests were not adjusted for multiple testing. The Yale Institutional Review Board and the UnitedHealth Group Office of Human Research Affairs exempted this study from other review, because all activities were limited to retrospective analysis of de-identified data

and accessed in accordance with Health Insurance Portability and Accountability Act regulations.

RESULTS

Characteristics of the Outpatient Cohort

Among 6885 individuals who tested positive for SARS-CoV-2 between January and May 2020 and had at least 6 months of enrollment in Medicare Advantage or commercial insurance, and in pharmacy benefits with their insurance, 2263 had a diagnosis of hypertension with the use of at least 1 antihypertensive drug (Figure S1). The primary outpatient study cohort included individuals from 44 states (Figure S3). A total of 1467 (64.8%) were Medicare Advantage enrollees and 796 (35.2%) of the cohort were commercially insured.

The characteristics of the 3 groups of patients receiving ACE inhibitors, ARBs, and other antihypertensive agents are compared in Table 1. Medicare Advantage and commercial insurance enrollees are compared in Table S3 and Figure S4. Medicare Advantage enrollees are older (median age 75 years; interquartile range [IQR], 70.0–82.0) (versus 46 years [IQR, 49.0–61.0] in commercially insured, $P<0.001$), with a higher prevalence of all comorbid conditions and median Charlson comorbidity score of 2 (IQR, 0–3), compared with 0 (IQR, 0–1) for the commercially insured ($P<0.001$) (Table S3). Hospitalization rates were also substantially higher in Medicare enrollees, compared with the commercially insured (14.5% versus 9.3%, $P<0.001$).

The characteristics of patients in the validation cohort were similar to the primary cohort (Table S4), though substantial geographic variation in case distribution occurred, with cases in the secondary study cohort shifting away from the Northeast (10.5% versus 37.4%) and into the South (66.9% versus 31.4%).

In the primary cohort, we matched 441 patients receiving ACE inhibitors to 441 patients receiving other antihypertensive agents (Figure S5), achieving <10% standardized differences for all covariates (Figure S6). Similarly, we matched 412 patients receiving ARB to 412 patients receiving other antihypertensive agents (Figure S5). The equipoise for comparisons of ACE inhibitors to other drugs, and for ACE inhibitors to ARB were >0.5 but were lower for the ARB comparisons. There were 1144 patients receiving ACE inhibitors and 995 patients who were receiving ARB and who were successfully matched to the same number of controls, respectively, in the secondary outpatient cohort.

Characteristics of the Inpatient Cohort

Among 12 566 patients who were hospitalized for COVID-19 with linked claims data, 7933 had had a diagnosis of hypertension and had an outpatient prescription for at least 1 antihypertensive drug (Figure S2). The primary inpatient cohort included patients from 47 states (Figure S3). Of the included patients, 92.0% were Medicare Advantage enrollees. The median age of hospitalized individuals was 77.0 years, and 54.6% were women; 29.9% of Medicare Advantage enrollees were Black. Groups are compared in Table 2. In the inpatient cohort, 1731 patients receiving ACE inhibitors and 1560 patients receiving ARBs were propensity score–matched to patients receiving other antihypertensive agents (Figure S7), with covariate standardized differences of <10% after matching (Figure S6). The equipoise for comparisons of ACE inhibitors to other drugs, and for ACE inhibitors to ARB were >0.5 but were lower for the ARB comparisons (Table 3). The inpatient validation cohort was similar to the primary cohort across all exposure groups (Table S5) except for geography (15.1% versus 42.0% in the Northeast; 61.9% versus 34.7% in the South).

Hospitalizations in the Outpatient Cohort

In the primary outpatient cohort, over a median 30 (IQR, 19–40) days from SARS-CoV-2 testing, individuals receiving ACE inhibitors were less frequently hospitalized than those receiving other antihypertensive agents (10.7% versus 14.4%, $P=0.03$). There was no significant association between ARB therapy and hospitalization rates (12.7% versus 14.4% in individuals receiving other antihypertensive agents, $P=0.36$). In propensity score–matched cohorts, use of neither ACE inhibitors nor ARB was significantly associated with risk of hospitalization (hazard ratio [HR], 0.77; 95% CI, 0.53–1.13, $P=0.18$ for ACE inhibitors, and 0.88; 0.61–1.26, $P=0.48$ for ARB, versus other antihypertensive agents) (Figure 1, Table 3, and Figure S8). There were no differences in falsification end points between propensity score–matched populations (Table S6).

There were differences between the association of ACE inhibitors and hospitalization risk across insurance groups ($P=0.09$ for interaction), with a lower risk of hospitalization in Medicare Advantage enrollees (HR, 0.61; 0.41–0.93, $P=0.02$) that was not observed in commercially insured individuals (HR, 2.14; 0.82–5.60, $P=0.12$) (Table 3).

In propensity score–matched analyses, ARB use was not significantly associated with lower hospitalization risk than in individuals receiving other antihypertensive agents (HR, 0.88; 0.61–1.26, $P=0.48$) (Figure 1). There were no significant differences in hospitalization rates between propensity score–matched cohorts of individuals receiving an ACE inhibitor, compared with ARB (HR, 0.91; 0.65–1.29, $P=0.60$). There were no significant interactions by insurance type and the association of ARB with outcomes ($P=0.55$ for interaction).

In the outpatient validation cohort, neither ACE inhibitor nor ARB was associated with hospitalization

Table 1. Characteristics of the Primary Outpatient Cohort

Variable	Overall	Antihypertensive Drug Cohorts					
		Cohort			*P* Value		
		ACE Inhibitor	ARB	Other	ACE Inhibitor vs Other	ARB vs Other	ACE Inhibitor vs ARB
Number of patients	2263 (100.0%)	722 (100.0%)	731 (100.0%)	810 (100.0%)	…	…	…
Age, median (IQR)	69.0 (59.0–78.0)	68.0 (57.0–76.0)	69.0 (59.0–76.0)	71.0 (60.2–80.0)	<0.0001	0.00012	0.086
Age range							
18–30 y	*	*	*	*	0.88	0.78	0.99
31– 40 y	63 (2.8%)	25 (3.5%)	14 (1.9%)	24 (3.0%)	0.68	0.25	0.096
41–50 y	171 (7.6%)	69 (9.6%)	56 (7.7%)	46 (5.7%)	0.0055	0.14	0.23
51–60 y	408 (18.0%)	138 (19.1%)	140 (19.2%)	130 (16.0%)	0.13	0.13	0.96
61–70 y	570 (25.2%)	189 (26.2%)	203 (27.8%)	178 (22.0%)	0.062	0.010	0.53
71–80 y	606 (26.8%)	185 (25.6%)	194 (26.5%)	227 (28.0%)	0.32	0.55	0.74
>80 y	435 (19.2%)	112 (15.5%)	121 (16.6%)	202 (24.9%)	<0.0001	<0.0001	0.64
Female sex	1189 (52.5%)	318 (44.0%)	392 (53.6%)	479 (59.1%)	<0.0001	0.033	0.00032
Medicare Advantage	1467 (64.8%)	434 (60.1%)	452 (61.8%)	581 (71.7%)	<0.0001	<0.0001	0.54
Location							
Urban	1059 (46.8%)	333 (46.1%)	336 (46.0%)	390 (48.1%)	0.46	0.42	0.99
Rural	434 (19.2%)	130 (18.0%)	142 (19.4%)	162 (20.0%)	0.35	0.83	0.53
Suburban	747 (33.0%)	244 (33.8%)	248 (33.9%)	255 (31.5%)	0.36	0.33	1.00
Unknown	23 (1.0%)	*	*	*	0.0043	0.62	0.040
Race[†]							
White	863 (38.1%)	270 (37.4%)	250 (34.2%)	343 (42.3%)	0.055	0.0012	0.22
Black	434 (19.2%)	113 (15.7%)	131 (17.9%)	190 (23.5%)	0.00017	0.0091	0.28
Hispanic	69 (3.0%)	21 (2.9%)	25 (3.4%)	23 (2.8%)	0.94	0.61	0.68
Asian	46 (2.0%)	15 (2.1%)	19 (2.6%)	12 (1.5%)	0.49	0.17	0.63
Native American	*	*	*	*	0.53	0.52	
Other	36 (1.6%)	*	*	*	0.63	0.041	0.19
Unknown	813 (35.9%)	293 (40.6%)	288 (39.4%)	232 (28.6%)	<0.0001	<0.0001	0.68
Geography							
Region of test site							
Northeast	847 (37.4%)	241 (33.4%)	242 (33.1%)	364 (44.9%)	<0.0001	<0.0001	0.96
South	711 (31.4%)	229 (31.7%)	275 (37.6%)	207 (25.6%)	0.0090	<0.0001	0.021
Midwest	175 (7.7%)	64 (8.9%)	53 (7.3%)	58 (7.2%)	0.26	0.98	0.30

(*Continued*)

Table 1. Continued

Variable	Overall	Antihypertensive Drug Cohorts					
		Cohort			*P* Value		
		ACE Inhibitor	ARB	Other	ACE Inhibitor vs Other	ARB vs Other	ACE Inhibitor vs ARB
West	202 (8.9%)	81 (11.2%)	64 (8.8%)	57 (7.0%)	0.0057	0.25	0.14
Unknown	328 (14.5%)	107 (14.8%)	97 (13.3%)	124 (15.3%)	0.85	0.29	0.44
State of test site							
New York	230 (10.2%)	54 (7.5%)	79 (10.8%)	97 (12.0%)	0.0042	0.52	0.035
New Jersey	303 (13.4%)	86 (11.9%)	93 (12.7%)	124 (15.3%)	0.064	0.17	0.70
Connecticut	136 (6.0%)	43 (6.0%)	36 (4.9%)	57 (7.0%)	0.45	0.10	0.45
Georgia	183 (8.1%)	58 (8.0%)	67 (9.2%)	58 (7.2%)	0.58	0.18	0.50
Florida	124 (5.5%)	38 (5.3%)	58 (7.9%)	28 (3.5%)	0.11	0.00021	0.052
Other	959 (42.4%)	336 (46.5%)	301 (41.2%)	322 (39.8%)	0.0086	0.61	0.045
Unknown	328 (14.5%)	107 (14.8%)	97 (13.3%)	124 (15.3%)	0.85	0.29	0.44
Comorbid conditions							
Diabetes mellitus without complications	911 (40.3%)	320 (44.3%)	321 (43.9%)	270 (33.3%)	<0.0001	<0.0001	0.92
Myocardial infarction	81 (3.6%)	16 (2.2%)	20 (2.7%)	45 (5.6%)	0.0013	0.0087	0.64
Chronic heart failure	326 (14.4%)	72 (10.0%)	99 (13.5%)	155 (19.1%)	<0.0001	0.0039	0.042
Chronic pulmonary disease	410 (18.1%)	100 (13.9%)	139 (19.0%)	171 (21.1%)	0.00026	0.34	0.0098
Peptic ulcer disease	19 (0.8%)	*	*	*	0.85	0.46	0.81
AIDS	22 (1.0%)	*	*	*	0.85	0.23	0.22
Rheumatologic disease	120 (5.3%)	28 (3.9%)	40 (5.5%)	52 (6.4%)	0.034	0.50	0.19
Diabetes mellitus, chronic complications	625 (27.6%)	225 (31.2%)	210 (28.7%)	190 (23.5%)	0.00087	0.022	0.34
Metastatic cancer	20 (0.9%)	*	*	*	0.41	0.40	0.77
Hemiplegia or paraplegia	92 (4.1%)	29 (4.0%)	15 (2.1%)	48 (5.9%)	0.11	0.00021	0.04
Liver disease, mild	106 (4.7%)	28 (3.9%)	34 (4.7%)	44 (5.4%)	0.19	0.56	0.55
Solid tumor without metastases	181 (8.0%)	41 (5.7%)	61 (8.3%)	79 (9.8%)	0.0041	0.38	0.059
Liver disease, moderate to severe	*	*	*	*	0.70	0.93	0.99
Dementia	250 (11.0%)	60 (8.3%)	43 (5.9%)	147 (18.1%)	<0.0001	<0.0001	0.089
Peripheral vascular disease	467 (20.6%)	122 (16.9%)	121 (16.6%)	224 (27.7%)	<0.0001	<0.0001	0.92
Renal failure, moderate to severe	359 (15.9%)	100 (13.9%)	93 (12.7%)	166 (20.5%)	0.00078	<0.0001	0.58
Cerebrovascular disease	289 (12.8%)	73 (10.1%)	83 (11.4%)	133 (16.4%)	0.00040	0.0053	0.50
Charlson Score, median (IQR)	2.0 (0.0–3.0)	1.0 (0.0–3.0)	1.0 (0.0–3.0)	2.0 (0.0–4.0)	<0.0001	0.00014	0.29

(*Continued*)

Table 1. Continued

Variable	Overall	Antihypertensive Drug Cohorts					
		Cohort			*P* Value		
		ACE Inhibitor	ARB	Other	ACE Inhibitor vs Other	ARB vs Other	ACE Inhibitor vs ARB
Drug therapy							
Antihypertensives							
β-blockers	911 (40.3%)	243 (33.7%)	265 (36.3%)	403 (49.8%)	<0.0001	<0.0001	0.33
Non-dihydropyridine calcium channel blockers	99 (4.4%)	19 (2.6%)	23 (3.1%)	57 (7.0%)	<0.0001	0.00089	0.67
Dihydropyridine calcium channel blockers	813 (35.9%)	215 (29.8%)	253 (34.6%)	345 (42.6%)	<0.0001	0.0016	0.056
Thiazide or thiazide-like diuretics	709 (31.3%)	236 (32.7%)	300 (41.0%)	173 (21.4%)	<0.0001	<0.0001	0.0012
Loop diuretics	328 (14.5%)	73 (10.1%)	84 (11.5%)	171 (21.1%)	<0.0001	<0.0001	0.45
Centrally acting α agonists	54 (2.4%)	*	*	*	0.0062	0.49	0.056
Potassium-sparing diuretics	56 (2.5%)	*	*	*	0.064	0.00046	0.40
Mineralocorticoid aldosterone antagonists	85 (3.8%)	15 (2.1%)	28 (3.8%)	42 (5.2%)	0.0021	0.25	0.069
Renin inhibitors	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			
α-adrenergic blocking agents	40 (1.8%)	*	*	*	0.18	0.91	0.22
Direct vasodilators	99 (4.4%)	27 (3.7%)	27 (3.7%)	45 (5.6%)	0.12	0.11	0.93
Place in therapy							
First-line	1964 (86.8%)	722 (100.0%)	731 (100.0%)	511 (63.1%)	<0.0001	<0.0001	
Second-line	1135 (50.2%)	290 (40.2%)	308 (42.1%)	537 (66.3%)	<0.0001	<0.0001	0.48
Number of antihypertensive classes							
1	822 (36.3%)	206 (28.5%)	148 (20.2%)	468 (57.8%)	<0.0001	<0.0001	0.00030
2	780 (34.5%)	271 (37.5%)	288 (39.4%)	221 (27.3%)	<0.0001	<0.0001	0.50
3+	661 (29.2%)	245 (33.9%)	295 (40.4%)	121 (14.9%)	<0.0001	<0.0001	0.013
Number, median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (2.0–3.0)	1.0 (1.0–2.0)	<0.0001	<0.0001	0.00019
Other drug therapies							
Statins	1210 (53.5%)	418 (57.9%)	401 (54.9%)	391 (48.3%)	0.00020	0.011	0.26
Other lipid-lowering agents	113 (5.0%)	37 (5.1%)	42 (5.7%)	34 (4.2%)	0.46	0.20	0.68
Oral anticoagulants	201 (8.9%)	48 (6.6%)	58 (7.9%)	95 (11.7%)	0.00089	0.016	0.40
Insulins	215 (9.5%)	77 (10.7%)	70 (9.6%)	68 (8.4%)	0.15	0.47	0.55
Oral antihyperglycemic agents	581 (25.7%)	234 (32.4%)	217 (29.7%)	130 (16.0%)	<0.0001	<0.0001	0.29

(*Continued*)

Table 1. Continued

Variable	Overall	Antihypertensive Drug Cohorts			*P* Value		
		Cohort					
		ACE Inhibitor	ARB	Other	ACE Inhibitor vs Other	ARB vs Other	ACE Inhibitor vs ARB
Follow-up							
Follow-up days, median (IQR)	30.0 (19.0–40.0)	30.0 (19.0–40.0)	31.0 (21.0–40.0)	29.0 (19.0–38.0)	0.35	0.011	0.13
Test to hospitalization, median (IQR)	4.0 (2.0–7.0)	4.0 (2.0–6.0)	4.0 (2.0–7.0)	5.0 (3.0–7.0)	0.40	0.51	0.83
Total hospitalized	287 (12.7%)	77 (10.7%)	93 (12.7%)	117 (14.4%)	0.032	0.36	0.25

The cohort includes individuals who had a positive test for SARS-CoV-2 in the outpatient setting. ACE indicates angiotensin-converting enzyme; ARB indicates angiotensin receptor blocker; and IQR, interquartile range.

*Cells with values <11 were suppressed in accordance with the Centers for Medicare and Medicare Services cell size suppression policy for values from 1 to 10.

†Race is unknown in all commercially insured enrollees.

risk, overall (HR in propensity-matched cohorts, ACE inhibitor, 0.98; 0.76–1.26; *P*=0.87, and ARB, 0.77; 0.59–1.02; *P*=0.07) or in the Medicare Advantage or commercially insured population (Figure 2, Table 4).

Among the individuals in the outpatient cohort who were hospitalized, there was no association with ACE inhibitor or ARB use with subsequent in-hospital mortality (Table S7).

Mortality in the Inpatient Cohort

Of the 7933 individuals hospitalized with COVID-19, 1128 (14.2%) died during hospitalization, 4722 (59.5%) were discharged alive, and 2083 (26.3%) were still hospitalized at the end of the observation period. A majority of deaths (90.1%) were among the Medicare Advantage population. The median length of stay (including individuals who died as well as those discharged alive) for COVID-19 hospitalizations was 6 (IQR, 3–11) days, which was similar across individuals who died (6 (IQR, 3–10) days) or were discharged alive (6 [IQR, 3–11] days) during the observation period.

Overall, the proportion of COVID-19 inpatients who died did not differ significantly in those on ACE inhibitor therapy before hospitalization compared with those on other antihypertensive agents (13.5% versus 13.9%, *P*=0.68). In the propensity matched–cohort of individuals receiving ACE inhibitors before hospitalization (Figures S6 and S7), in-hospital mortality was not significantly different from that of individuals on other antihypertensive drugs (HR, 0.97; 0.81–1.16, *P*=0.74; Figure 3, Table 3). Similarly, treatment with ARB did not have a significantly different risk of mortality compared with other antihypertensive agents (1.15; 0.95–1.38, *P*=0.15). There were no significant differences in mortality between individuals receiving ACE inhibitors and ARBs in the overall population, without a significant interaction between insurance group and treatment assignment and patient outcome (Figure 2, Table 3). These findings were consistent in our secondary outcome of in-hospital death or discharge to hospice (Table S8). There was also no association between treatment with ACE inhibitor or ARB on hospital length of stay (Table S9). There were no significant differences between our falsification outcomes in matched groups (Table S10). There were no significant differences in mortality across propensity-matched groups of hospitalized patients in the inpatient validation cohort (Figure 4, Table 4).

Sensitivity analyses that focused on individuals receiving at least 1 first-line antihypertensive agent in the control group, and that varied the covariate adjustment strategies, were consistent with the primary analysis (Tables S11 through S14).

Table 2. Characteristics of the Primary Inpatient Cohort

Variable	Overall	Cohort			*P* Value		
		ACE Inhibitor	ARB	Other	ACE Inhibitor vs Other	ARB vs Other	ACE Inhibitor vs ARB
Number of patients	7933	2361	2226	3346	<0.0001	<0.0001	<0.0001
Age, median (IQR)	77.0 (69.0–85.0)	76.0 (68.0–83.0)	76.0 (69.0–84.0)	78.0 (70.0–86.0)	<0.0001	<0.0001	0.12
Age range							
18–30 y	11 (0.1%)	*	*	*	0.39	0.93	0.79
31–40 y	30 (0.4%)	*	*	*	0.86	0.40	0.69
41–50 y	173 (2.2%)	60 (2.5%)	47 (2.1%)	66 (2.0%)	0.18	0.79	0.39
51–60 y	544 (6.9%)	172 (7.3%)	177 (8.0%)	195 (5.8%)	0.031	0.0022	0.43
61–70 y	1523 (19.2%)	499 (21.1%)	415 (18.6%)	609 (18.2%)	0.0064	0.70	0.038
71–80 y	2627 (33.1%)	822 (34.8%)	786 (35.3%)	1019 (30.5%)	0.00058	0.00017	0.75
>80 y	3025 (38.1%)	794 (33.6%)	792 (35.6%)	1439 (43.0%)	<0.0001	<0.0001	0.17
Female sex	4332 (54.6%)	1171 (49.6%)	1246 (56.0%)	1915 (57.2%)	<0.0001	0.37	<0.0001
Medicare Advantage	7296 (92.0%)	2152 (91.1%)	1991 (89.4%)	3153 (94.2%)	<0.0001	<0.0001	0.057
Location							
Urban	3574 (45.1%)	1047 (44.3%)	1048 (47.1%)	1479 (44.2%)	0.94	0.037	0.067
Rural	1623 (20.5%)	488 (20.7%)	463 (20.8%)	672 (20.1%)	0.61	0.54	0.94
Suburban	2714 (34.2%)	822 (34.8%)	708 (31.8%)	1184 (35.4%)	0.68	0.0062	0.033
Unknown	22 (0.3%)	*	*	*	0.37	0.88	0.48
Race†							
White	4486 (56.5%)	1352 (57.3%)	1117 (50.2%)	2017 (60.3%)	0.0024	<0.0001	<0.0001
Black	2181 (27.5%)	633 (26.8%)	636 (28.6%)	912 (27.3%)	0.73	0.30	0.19
Hispanic	209 (2.6%)	70 (3.0%)	67 (3.0%)	72 (2.2%)	0.063	0.054	1.00
Asian	137 (1.7%)	21 (0.9%)	73 (3.3%)	43 (1.3%)	0.20	<0.0001	<0.0001
Native American	*	*	*	*	0.012	0.31	0.33
Other	156 (2.0%)	38 (1.6%)	64 (2.9%)	54 (1.6%)	0.93	<0.001	0.0050
Unknown	756 (9.5%)	241 (10.2%)	267 (12.0%)	248 (7.4%)	0.00024	<0.0001	0.060
Geographic region							
Region of inpatient facility							
Northeast	3335 (42.0%)	950 (40.2%)	947 (42.5%)	1438 (43.0%)	0.041	0.77	0.12
South	2750 (34.7%)	807 (34.2%)	829 (37.2%)	1114 (33.3%)	0.50	0.0027	0.033
Midwest	1528 (19.3%)	482 (20.4%)	378 (17.0%)	668 (20.0%)	0.70	0.0058	0.0033
West	320 (4.0%)	122 (5.2%)	72 (3.2%)	126 (3.8%)	0.013	0.33	0.0015

(*Continued*)

Table 2. Continued

Variable	Overall	Cohort			*P* Value		
		ACE Inhibitor	ARB	Other	ACE Inhibitor vs Other	ARB vs Other	ACE Inhibitor vs ARB
State of inpatient facility							
New York	1226 (15.5%)	320 (13.6%)	386 (17.3%)	520 (15.5%)	0.040	0.081	0.00045
New Jersey	796 (10.0%)	212 (9.0%)	260 (11.7%)	324 (9.7%)	0.39	0.019	0.0031
Connecticut	779 (9.8%)	238 (10.1%)	206 (9.3%)	335 (10.0%)	0.97	0.37	0.37
Georgia	666 (8.4%)	188 (8.0%)	208 (9.3%)	270 (8.1%)	0.92	0.11	0.11
Florida	542 (6.8%)	141 (6.0%)	184 (8.3%)	217 (6.5%)	0.46	0.014	0.0030
Other	3924 (49.5%)	1262 (53.5%)	982 (44.1%)	1680 (50.2%)	0.017	<0.0001	<0.0001
Comorbid conditions							
Diabetes mellitus without complications	4022 (50.7%)	1339 (56.7%)	1237 (55.6%)	1446 (43.2%)	<0.0001	<0.0001	0.45
Myocardial infarction	425 (5.4%)	109 (4.6%)	123 (5.5%)	193 (5.8%)	0.064	0.75	0.18
Chronic heart failure	2469 (31.1%)	626 (26.5%)	656 (29.5%)	1187 (35.5%)	<0.0001	<0.0001	0.028
Chronic pulmonary disease	2266 (28.6%)	576 (24.4%)	588 (26.4%)	1102 (32.9%)	<0.0001	<0.0001	0.12
Peptic ulcer disease	133 (1.7%)	36 (1.5%)	39 (1.8%)	58 (1.7%)	0.61	0.96	0.62
AIDS	33 (0.4%)	*	*	*	0.60	0.50	0.21
Rheumatologic disease	435 (5.5%)	91 (3.9%)	146 (6.6%)	198 (5.9%)	0.00058	0.36	<0.0001
Diabetes mellitus, chronic complications	3081 (38.8%)	984 (41.7%)	963 (43.3%)	1134 (33.9%)	<0.0001	<0.0001	0.29
Metastatic cancer	146 (1.8%)	37 (1.6%)	36 (1.6%)	73 (2.2%)	0.12	0.16	0.99
Hemiplegia or paraplegia	596 (7.5%)	189 (8.0%)	110 (4.9%)	297 (8.9%)	0.27	<0.0001	<0.0001
Liver disease, mild	477 (6.0%)	120 (5.1%)	129 (5.8%)	228 (6.8%)	0.0084	0.14	0.32
Solid tumor without metastases	923 (11.6%)	265 (11.2%)	252 (11.3%)	406 (12.1%)	0.31	0.38	0.95
Liver disease, moderate to severe	66 (0.8%)	17 (0.7%)	12 (0.5%)	37 (1.1%)	0.18	0.038	0.56
Dementia	1645 (20.7%)	481 (20.4%)	344 (15.5%)	820 (24.5%)	0.00028	<0.0001	<0.0001
Peripheral vascular disease	2687 (33.9%)	755 (32.0%)	624 (28.0%)	1308 (39.1%)	<0.0001	<0.0001	0.0040
Renal failure, moderate to severe	2351 (29.6%)	592 (25.1%)	641 (28.8%)	1118 (33.4%)	<0.0001	<0.0001	0.0050
Cerebrovascular disease	1744 (22.0%)	507 (21.5%)	445 (20.0%)	792 (23.7%)	0.055	0.0014	0.23
Charlson Score, median (IQR)	3.0 (2.0–5.0)	3.0 (1.0–5.0)	3.0 (1.0–5.0)	3.0 (2.0–6.0)	<0.0001	<0.0001	0.77

(*Continued*)

Table 2. Continued

Variable	Overall	Cohort			*P* Value		
		ACE Inhibitor	ARB	Other	ACE Inhibitor vs Other	ARB vs Other	ACE Inhibitor vs ARB
Drug therapy							
Antihypertensives							
β-blockers	4277 (53.9%)	1112 (47.1%)	1095 (49.2%)	2070 (61.9%)	<0.0001	<0.0001	0.17
Nondihydropyridine calcium channel blockers	3438 (43.3%)	929 (39.3%)	959 (43.1%)	1550 (46.3%)	<0.0001	0.019	0.011
Dihydropyridine calcium channel blockers	2972 (37.5%)	826 (35.0%)	848 (38.1%)	1298 (38.8%)	0.0037	0.62	0.031
Thiazide or thiazide-like diuretics	1650 (20.8%)	512 (21.7%)	702 (31.5%)	436 (13.0%)	<0.0001	<0.0001	<0.0001
Loop diuretics	2400 (30.3%)	570 (24.1%)	612 (27.5%)	1218 (36.4%)	<0.0001	<0.0001	0.010
Centrally acting α agonists	303 (3.8%)	85 (3.6%)	98 (4.4%)	120 (3.6%)	0.96	0.14	0.19
Potassium-sparing diuretics	112 (1.4%)	21 (0.9%)	22 (1.0%)	69 (2.1%)	0.00069	0.0028	0.85
Mineralocorticoid aldosterone antagonists	435 (5.5%)	93 (3.9%)	135 (6.1%)	207 (6.2%)	0.00023	0.90	0.0012
Renin inhibitors	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	<0.0001	<0.0001	<0.0001
α-adrenergic blocking agents	247 (3.1%)	70 (3.0%)	76 (3.4%)	101 (3.0%)	0.97	0.46	0.43
Direct vasodilators	515 (6.5%)	110 (4.7%)	159 (7.1%)	246 (7.4%)	<0.0001	0.81	0.00044
Place in therapy							
First-line	6399 (80.7%)	2361 (100.0%)	2226 (100.0%)	1812 (54.2%)	<0.0001	<0.0001	<0.0001
Second-line	5478 (69.1%)	1405 (59.5%)	1388 (62.4%)	2685 (80.2%)	<0.0001	<0.0001	0.052
Number of antihypertensive classes							
1	2322 (29.3%)	442 (18.7%)	312 (14.0%)	1568 (46.9%)	<0.0001	<0.0001	<0.0001
2	2625 (33.1%)	850 (36.0%)	692 (31.1%)	1083 (32.4%)	0.0047	0.33	0.00048
3+	2986 (37.6%)	1069 (45.3%)	1222 (54.9%)	695 (20.8%)	<0.0001	<0.0001	<0.0001
Number, median (IQR)	2.0 (1.0–3.0)	2.0 (2.0–3.0)	3.0 (2.0–3.0)	2.0 (1.0–2.0)	<0.0001	<0.0001	<0.0001
Other drug therapies							
Statins	4772 (60.2%)	1528 (64.7%)	1408 (63.3%)	1836 (54.9%)	<0.0001	<0.0001	0.32

(*Continued*)

Table 2. Continued

Variable	Overall	Cohort			*P* Value		
		ACE Inhibitor	ARB	Other	ACE Inhibitor vs Other	ARB vs Other	ACE Inhibitor vs ARB
Other lipid-lowering agents	423 (5.3%)	119 (5.0%)	145 (6.5%)	159 (4.8%)	0.66	0.0055	0.038
Oral anticoagulants	1375 (17.3%)	384 (16.3%)	333 (15.0%)	658 (19.7%)	0.0012	<0.0001	0.24
Insulin	1373 (17.3%)	461 (19.5%)	421 (18.9%)	491 (14.7%)	<0.0001	<0.0001	0.62
Oral antihyperglycemic agents	2188 (27.6%)	820 (34.7%)	738 (33.2%)	630 (18.8%)	<0.0001	<0.0001	0.27
Follow-up							
Follow-up days, median (IQR)	6.0 (3.0–11.0)	6.0 (3.0–11.0)	6.0 (3.0–11.0)	7.0 (3.0–11.0)	0.80	0.96	0.78
Days to death, median (IQR)	6.0 (3.0–11.0)	7.0 (3.0–11.0)	7.0 (3.0–13.0)	5.0 (2.0–10.0)	0.0092	<0.0001	0.15
Total mortality	1130 (14.2%)	319 (13.5%)	345 (15.5%)	466 (13.9%)	0.70	0.088	0.048

The cohort includes individuals who were hospitalized with COVID-19. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; and IQR, interquartile range.
*Cells with values <11 were suppressed in accordance with the Centers for Medicare and Medicare Services cell size suppression policy for values from 1 to 10.
†Race is unknown in all commercially insured enrollees.

DISCUSSION

In this national study of ACE inhibitors and ARBs among patients with hypertension in the outpatient setting testing positive for SARS-CoV-2, we found that overall these drugs did not confer additional risk or benefit. While early data indicated that ACE inhibitors may be associated with a lower risk of hospitalization for COVID-19, more recent data did not demonstrate this association. Moreover, such an effect was not observed with ARBs. Among inpatients with COVID-19, we did not find a benefit or a harm of these medications. Collectively, the findings do not support a change to the current use of these medications or evaluating the use of ACE inhibitors to reduce the risk of severe SARS-CoV-2 infection.

Our study was restricted to individuals with hypertension who were receiving at least 1 antihypertensive agent, thereby limiting our assessment to individuals receiving treatment for the same chronic illness, and therefore, equally likely to seek care for healthcare needs for COVID-19. In all analyses, we explicitly compared individuals with equipoise for receiving either drug treatment. Moreover, we did not find any evidence of confounding by disease severity in choice of therapy in our assessment of falsification end points. Furthermore, our study included individuals from across the United States, thereby limiting the effect of hospital or regional care practices that may bias an evaluation of treatment effects.

Our observations extend the prior evidence of supporting safety of ACE inhibitor treatment in COVID-19.[8,13,24] Many studies thus far have had limitations with their data sources and study designs to adequately address the hypotheses focusing on the safety of ACE inhibitors and ARBs in COVID-19, and their potential efficacy in reducing the severity of the disease.[7,11] Our study adds to the literature by focusing on a large national population spanning the entire adult age range and including individuals across the United States, thereby overcoming the challenge of generalizability of studies that are based on single centers or hospitals in the same region. We show that these agents are not associated with harm in outpatient SARS-CoV-2-infected individuals and were able to track the same individuals across different outpatient and inpatient settings. We also use robust methods to account for confounding. This complements the studies of those who were hospitalized and focused on severity of disease and mortality in these patient groups.[13,25]

Our original study that focused on data from January through May had an intriguing finding. In the subgroup of individuals enrolled in Medicare Advantage, we found that ACE inhibitors were associated with a significantly lower risk of hospitalization following an infection with

Table 3. Hazard Ratio for Hospitalization Among Individuals Testing Positive for SARS-CoV-2 in the Outpatient Setting and for In-Hospital Death and Survival to Discharge Among Individuals Hospitalized for COVID-19 Between January and May, 2020

Comparison Group	Treatment	Control	Matched Treatment	Matched Control	Hazard Ratio (95% CI, *P* Value)	Equipoise Metric
Primary outpatient cohort—outcome: hospitalization						
Overall population						
ACE inhibitor vs other	722	810	441	441	0.77 (0.53, 1.13); *P*=0.18	0.68
ARB vs other	731	810	412	412	0.88 (0.61, 1.26); *P*=0.48	0.68
ACE inhibitor vs ARB	722	731	591	591	0.91 (0.65, 1.29); *P*=0.60	0.96
Medicare Advantage enrollees						
ACE vs other	581	434	296	296	0.61 (0.40, 0.93); *P*=0.02	0.67
ARB vs other	581	452	283	283	0.89 (0.59, 1.36); *P*=0.59	0.68
ACE vs ARB	452	434	352	352	0.88 (0.57, 1.36); *P*=0.56	0.96
Primary inpatient cohort—outcomes: in-hospital death/alive discharge						
Overall population						
ACE inhibitor vs other	2360	3338	1731	1731	In-hospital death: 0.97 (0.81, 1.16); *P*=0.74 Alive discharge: 1.03 (0.94, 1.12); *P*=0.57	0.56
ARB vs other	2224	3338	1560	1560	In-hospital death: 1.15 (0.95, 1.38); *P*=0.15 Alive discharge: 1.01 (0.93, 1.11); *P*=0.76	0.46
ACE inhibitor vs ARB	2360	2224	1882	1882	In-hospital death: 0.89 (0.75, 1.05); *P*=0.16 Alive discharge: 1.03 (0.95, 1.12); *P*=0.47	0.95
Medicare Advantage enrollees						
ACE vs other	2151	3145	1580	1580	In-hospital death: 0.89 (0.74, 1.07); *P*=0.20 Alive discharge: 1.03 (0.94, 1.13); *P*=0.48	0.56
ARB vs other	1989	3145	1425	1425	In-hospital death: 1.19 (0.99, 1.44); *P*=0.066 Alive discharge: 1.03 (0.93, 1.13); *P*=0.58	0.46
ACE vs ARB	2151	1989	1704	1704	In-hospital death: 0.88 (0.74, 1.04); *P*=0.14 Alive discharge: 1.01 (0.92, 1.10); *P*=0.89	0.95

Pairwise comparisons from propensity score–matched cohorts. ACE indicates angiotensin-converting enzyme; and ARB, angiotensin receptor blocker.

SARS-CoV-2 in the outpatient setting. Medicare is a federal health insurance program in the United States for adults aged 65 years and older, and certain younger individuals with disability and end-stage renal disease. Medicare Advantage is a subtype that includes coverage of inpatient, outpatient, and often prescriptions and is administered in conjunction with commercial insurance providers. Since Medicare predominantly includes individuals over 65 years of age, Medicare beneficiaries are older, more frequently have comorbidities, and are more vulnerable to severe COVID-19 disease.[13] These observations had prompted our team to plan a clinical trial for the prophylactic use of ACE inhibitors to prevent severe disease. However, our analyses in more contemporary data demonstrate that the original results do not represent a consistent association.

Our results inform the discussion of preclinical evidence that had suggested a possible protective role for ACE inhibitors in COVID-19. ACE inhibitors, but not ARBs, are associated with the upregulation of ACE-2 receptors.[3,4] Of note, these receptors modulate the renin-angiotensin-aldosterone system, in the lung tissue.[26] The presence of ACE-2 receptors is, therefore, suggested to exert a protective effect against the development of acute lung injury in infections with SARS coronaviruses, which lead to dysregulation

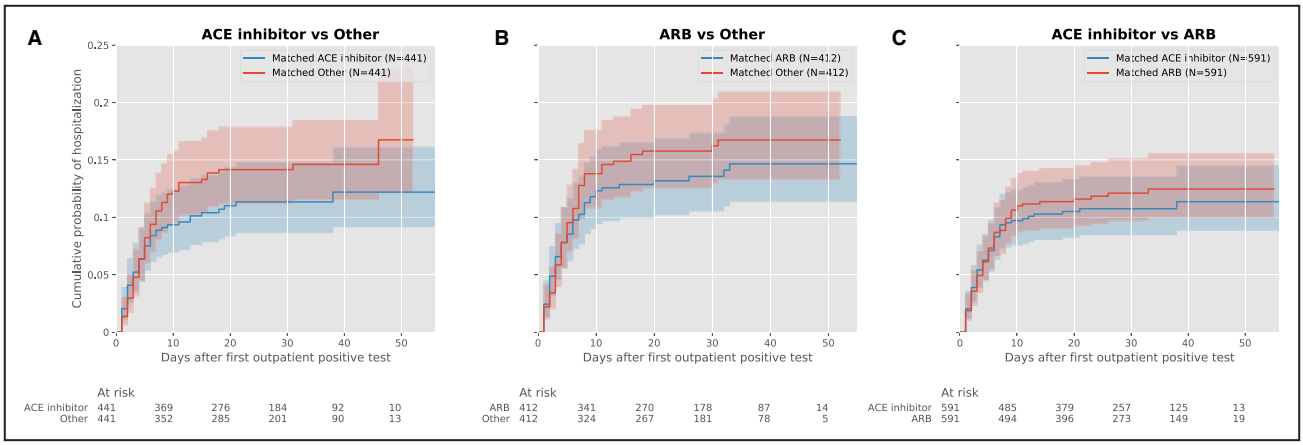


Figure 1. Cumulative event curves for hospitalization among hypertensive individuals with a positive SARS-CoV-2 test in the outpatient setting during January to May, 2020 (primary outpatient cohort) comparing (A) ACE inhibitor vs other; (B) ARB vs other; and (C) ACE inhibitor vs ARB.
Plots represent propensity score–matched groups. ACE indicates angiotensin-converting enzyme; and ARB, angiotensin receptor blocker.

of these mechanisms and endothelial damage.[27,28] Moreover, ACE-2 receptors are also present in the vascular endothelium, as well as in the renal tubular and intestinal epithelia, with uncertain role in the pathogenicity of SARS-CoV-2.[29,30] Our study did not, however, include an assessment of ACE-2 levels in study participants. Recent studies have also suggested a lower level of cytokines and peripheral blood T cells among patients with COVID-19 with hypertension who were receiving renin-angiotensin system inhibitors.[31] Prior evidence from randomized clinical trials and observational studies of identified a reduced risk of pneumonia with ACE inhibitors that is not observed with ARBs.[32,33]

Our observations do not support a clinical effect corresponding to either enhanced or decreased virulence of the virus with use of either ACE inhibitors or ARBs after accounting for confounding.

Our study of in-hospital outcomes adds to the literature on studies that have reached contrasting conclusions regarding the role of ACE inhibitor therapy and in-hospital mortality among hospitalized patients with COVID-19. We did not find a significant association with mortality, consistent with others who have not found such an association.[6,13,25,34,35] Our findings contrast with certain studies that have found lower mortality in hospitalized patients with COVID-19 treated with ACE inhibitors.[25,36] Notably, most studies that have

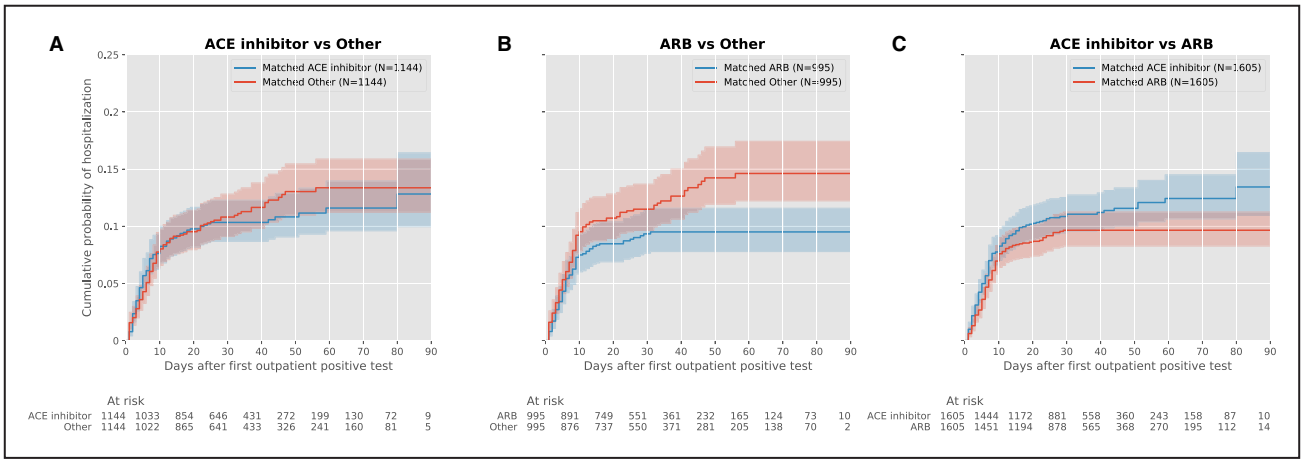


Figure 2. Cumulative event curves for hospitalization among hypertensive individuals with a positive SARS-CoV-2 test in the outpatient setting during May to August, 2020 (secondary outpatient cohort) comparing (A) ACE inhibitor vs other; (B) ARB vs other; (C) ACE inhibitor vs ARB.
Plots represent propensity score–matched groups. ACE indicates angiotensin-converting enzyme; and ARB, angiotensin receptor blocker.

Table 4. Hazard Ratio for Hospitalization Among Individuals Testing Positive for SARS-CoV-2 in the Outpatient Setting and for In-Hospital Death and Survival to Discharge Among Individuals Hospitalized for COVID-19 Between May and August, 2020

Comparison Group	Treatment	Control	Matched Treatment	Matched Control	Hazard Ratio (95% CI, *P* Value)	Equipoise Metric
Secondary outpatient cohort—outcome: hospitalization						
Overall population						
ACE inhibitor vs other	2152	1592	1144	1144	0.98 (0.76, 1.26); *P*=0.87	0.73
ARB vs other	1808	1592	995	995	0.77 (0.59, 1.02); *P*=0.067	0.69
ACE inhibitor vs ARB	2152	1808	1605	1605	1.26 (1.01, 1.57); *P*=0.040	0.97
Medicare Advantage enrollees						
ACE vs other	1181	972	673	673	0.91 (0.70, 1.19); *P*=0.51	0.73
ARB vs other	1077	972	569	569	0.77 (0.57, 1.04); *P*=0.084	0.64
ACE vs ARB	1181	1077	905	905	1.22 (0.94, 1.57); *P*=0.13	0.96
Secondary inpatient cohort—outcome: in-hospital death/alive discharge						
Overall population						
ACE inhibitor vs other	2660	3119	1819	1819	In-hospital death: 1.06 (0.85, 1.33); *P*=0.59 Alive discharge: 1.03 (0.96, 1.11); *P*=0.41	0.59
ARB vs other	2323	3119	1518	1518	In-hospital death: 1.04 (0.83, 1.31); *P*=0.72 Alive discharge: 0.97 (0.89, 1.06); *P*=0.52	0.44
ACE inhibitor vs ARB	2660	2323	1976	1976	In-hospital death: 1.01 (0.83, 1.24); *P*=0.89 Alive discharge: 1.02 (0.95, 1.1); *P*=0.59	0.93
Medicare Advantage enrollees						
ACE vs other	2352	2905	1659	1659	In-hospital death: 1.02 (0.82, 1.26); *P*=0.89 Alive discharge: 1.00 (0.92, 1.09); *P*=0.95	0.59
ARB vs other	2028	2905	1357	1357	In-hospital death: 1.03 (0.81, 1.31); *P*=0.78 Alive discharge: 1.03 (0.94, 1.13); *P*=0.53	0.44
ACE vs ARB	2352	2028	1721	1721	In-hospital death: 0.93 (0.75, 1.15); *P*=0.51 Alive discharge: 1.01 (0.93, 1.09); *P*=0.82	0.93

Pairwise comparisons from propensity score–matched cohorts. ACE indicates angiotensin-converting enzyme; and ARB, angiotensin receptor blocker.

evaluated mortality risk with COVID-19 before have not consistently been designed to detect potential causal association of drug therapy with outcomes, relied on case–control designs,[12,24] pursued potentially biased assessment by using comparators not receiving any therapy,[12,13] or are based on data from single health centers.[13,25] Among studies that are pending peer review, there is similarly no evidence of increased hospitalization or mortality risk (Table S15).[10,37]

Our study has important implications for 4 ongoing randomized trials because none of them align with the observations of our study.[7] Of the 4 trials, 3 are testing the use of ACE inhibitors or ARBs in the treatment of hospitalized patients with COVID-19, and 1 is using a 10-day course of ARBs after a positive SARS-CoV-2 test to prevent hospitalization.[7] However, our study suggests that ACE inhibitors are unlikely to play a role in reducing COVID-19-related hospitalizations or mortality.

The qualitative differences in the effect estimates observed in our primary and secondary analyses also highlight the challenges with observational studies designed to identify drugs that may have a role in the management of COVID-19, or for any other disease using real-world data, particularly during the rapidly evolving pandemic. While our primary analyses favored the role of ACE inhibitors in reducing hospitalization risk in SARS-CoV-2, this was not observed in larger more recent data. This emphasizes the need for independent validation of effectiveness findings in

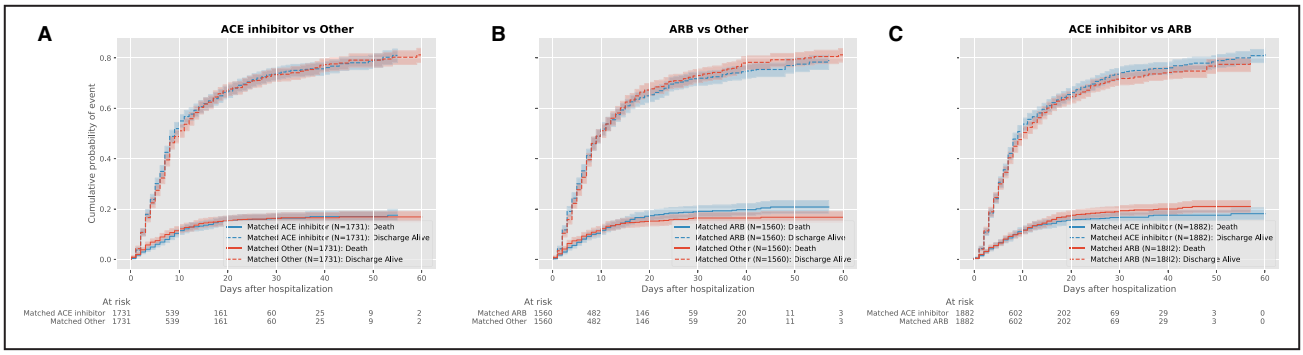


Figure 3. Cumulative event curves for in-hospital mortality among hypertensive individuals with hospitalization for COVID-19 during January to May, 2020 (primary inpatient cohort) comparing (A) ACE inhibitor vs other; (B) ARB vs other; and (C) ACE inhibitor vs ARB.

Plots represent propensity score–matched groups. ACE indicates angiotensin-converting enzyme; and ARB, angiotensin receptor blocker.

observational studies, which in spite of robust designs can lead to erroneous conclusions because of chance alone. The Observational Health Data Sciences and Informatics framework that iteratively tests each hypothesis in multiple discrete data sets to determine treatment effects is less prone to erroneous conclusions because of chance.[10,38]

The findings of our study should be interpreted in light of the following limitations. First, the study is observational, and despite robust methods, we cannot exclude the effects of residual confounding, which is a limitation for causal inference. Nevertheless, our assessment of the observations in 2 discrete data periods with potentially different care-seeking patterns allowed us to assess for consistency of effects over time. Second, we do not know the proportion of individuals who are receiving ACE inhibitors and ARBs and who continued to be treated with these drugs during the illness and the association of their continued use or cessation with patient outcomes. This is a limitation of most observational assessments.[39] Third, while the present study is one of the largest US studies on the association of ACE inhibitor and ARB use with both hospitalization and mortality risk with COVID-19, the number of individuals in the propensity-matched groups is smaller with a more limited number of events. Fourth, we focused on patients with hypertension receiving at least 1 antihypertensive agent to limit unmeasured confounding because these would represent individuals with comparable underlying health status. We also explicitly accounted for measured differences between groups through our propensity score matching. However, our focus may limit the generalizability of our comparisons to those not receiving any antihypertensive agents.

Fifth, all included data elements are contingent upon individuals seeking care for that ailment or filling a medication using their insurance provider and would not be captured if they chose to self-pay. Sixth, we cannot account for differences in timing of presentation relative to symptom onset. However, we limited the effect of differential presentation by individuals across

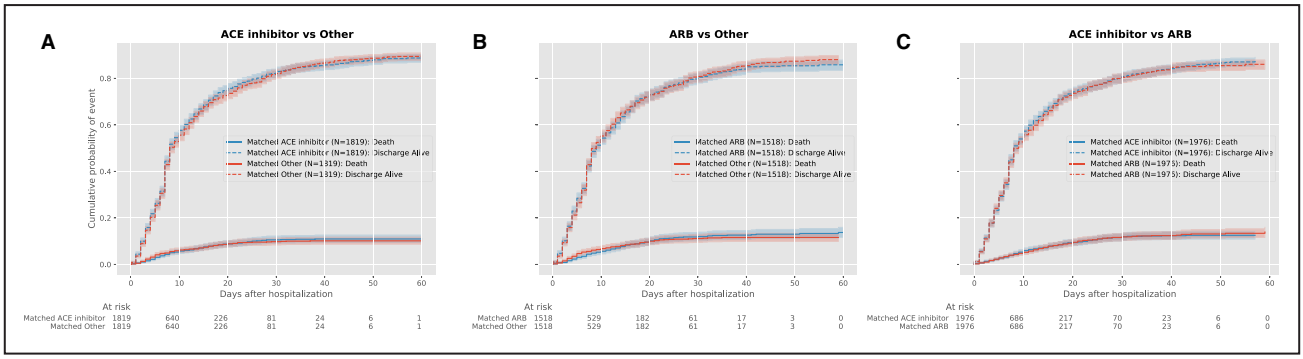


Figure 4. Cumulative event curves for in-hospital mortality among hypertensive individuals with hospitalization for COVID-19 during May to August, 2020 (secondary inpatient cohort) comparing (A) ACE inhibitor vs other; (B) ARB vs other; and (C) ACE inhibitor vs ARB.

Plots represent propensity score–matched groups. ACE indicates angiotensin-converting enzyme; and ARB, angiotensin receptor blocker.

exposure groups by focusing on those receiving treatment for the same medical comorbidity, ie, hypertension, and only varying the class of drugs. Moreover, we included individuals across the United States and accounted for clustering of cases, thereby limiting the effect of local practice patterns that may affect hospitalization thresholds. Therefore, it is unlikely that an individual's care-seeking behavior would be affected by knowledge of their underlying disease. Additionally, while our analyses of hospitalization used all available evidence for disease severity, we do not have granular details on real-time inpatient treatment of patients with COVID-19 and whether certain presentation or care characteristics are associated with in-hospital outcomes. Instead, our study evaluates the association of only prehospital factors with outcomes during hospitalization. Finally, we do not account for a possible dose–response relationship of ACE inhibitors or ARBs on SARS-CoV-2 hospitalization risk or COVID-19 mortality risk because we were unable to evaluate the effects of the drugs as a function of the total daily dose.

In conclusion, the use of ACE inhibitors and ARBs was not associated with the risk of hospitalization or mortality among those infected with SARS-CoV-2. Despite early evidence for a potential protective effect of ACE inhibitors in preventing severe disease in older individuals, the inconsistency of this observation in recent data argues against a role as prophylaxis against severe disease.

ARTICLE INFORMATION

Received July 24, 2020; accepted February 8, 2021.

Affiliations

Section of Cardiovascular Medicine (R.K., Y.L., E.S.S., K.M., Z.L., H.M.K.) and Section of Infectious Diseases (S.B.O.), Department of Internal Medicine, Yale School of Medicine, New Haven, CT; Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven, CT (R.K., Y.L., E.S.S., K.M., Z.L., H.M.K.); Research & Development at UnitedHealth Group, Minnetonka, MN, (C.C., Y.G., S.R., B.T., D.V.); Yale Institute for Global Health, New Haven, CT (S.B.O.); Department of Epidemiology of Microbial Diseases (S.B.O.) and Department of Health Policy and Management, Yale School of Public Health, New Haven, CT (H.M.K.).

Acknowledgments

Author contributions: Khera, Clark, Vojta, and Krumholz were responsible for the study concept and design. Guo, Ren, and Truax were responsible for the acquisition and analysis of data. All authors contributed to the interpretation of the data. Khera and Clark drafted the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version. Vojta and Krumholz are guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Sources of Funding

The study was funded by Research & Development (R&D) at UnitedHealth Group. The authors from UnitedHealth Group R&D participated in each aspect of the study, including its design and conduct, data management and analysis, interpretation of the results, as well as provided input on the manuscript for submission. Dr Khera reports support from the National Heart, Lung, and Blood Institute (K23HL153775-01A1) and the National Center for Advancing Translational Sciences (UL1TR001105) of the United States National Institutes of Health. Dr Lu is supported by the National Heart, Lung, and Blood Institute (K12HL138037) of the United States National Institutes of Health and the Yale Center for Implementation Science. The National Institutes of Health and the Yale Center for Implementation Science had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclosures

Dr Krumholz was a recipient of a research grant, through Yale, from Medtronic and the US Food and Drug Administration to develop methods for postmarket surveillance of medical devices; was a recipient of a research grant with Medtronic and is the recipient of a research grant from Johnson & Johnson, through Yale University, to support clinical trial data sharing; was a recipient of a research agreement, through Yale University, from the Shenzhen Center for Health Information for work to advance intelligent disease prevention and health promotion; collaborates with the National Center for Cardiovascular Diseases in Beijing; receives payment from the Arnold & Porter Law Firm for work related to the Sanofi clopidogrel litigation, from the Martin/Baughman Law Firm for work related to the Cook Celect IVC filter litigation, and from the Siegfried and Jensen Law Firm for work related to Vioxx litigation; chairs a Cardiac Scientific Advisory Board for UnitedHealth; was a participant/participant representative of the IBM Watson Health Life Sciences Board; is a member of the Advisory Board for Element Science, the Advisory Board for Facebook, and the Physician Advisory Board for Aetna; and is a co-founder of HugoHealth, a personal health information platform, and co-founder of Refactor Health, an enterprise healthcare artificial intelligence–augmented data management company. He is also an advisor to FPrime. Drs Lin, Spatz, and Murugiah work under contract with the Centers for Medicare & Medicaid Services to develop and maintain performance measures that are publicly reported. Dr Spatz receives support from the US Food and Drug Administration to support projects within the Yale-Mayo Clinic Center of Excellence in Regulatory Science and Innovation (CERSI); the National Institute on Minority Health and Health Disparities (U54MD010711-01) to study precision-based approaches to diagnosing and preventing hypertension; and the National Institute of Biomedical Imaging and Bioengineering (R01EB028106-01) to study a cuff-less blood pressure device. Drs Clark, Ren, Vojta, and Mr Guo and Mr Truax are full-time employees in Research & Development at UnitedHealth Group and own stock in the company. The remaining authors have no disclosures to report.

Supplementary Material

Data S1
Tables S1–S15
Figures S1–S8
Reference 40

REFERENCES

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054–1062. DOI: 10.1016/S0140-6736(20)30566-3.
2. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med*. 2020;8:e21. DOI: 10.1016/S2213-2600(20)30116-8.
3. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. *JAMA Cardiol*. 2020;5:831–840. DOI: 10.1001/jamacardio.2020.1286.
4. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. *N Engl J Med*. 2020;382:1653–1659. DOI: 10.1056/NEJMsr2005760.
5. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol*. 2020;17:259–260. DOI: 10.1038/s41569-020-0360-5.
6. Li J, Wang X, Chen J, Zhang H, Deng A. Association of renin-angiotensin system inhibitors with severity or risk of death in patients with hypertension hospitalized for coronavirus disease 2019 (COVID-19) infection in Wuhan, China. *JAMA Cardiol*. 2020;5:825–830. DOI: 10.1001/jamacardio.2020.1624.
7. Mackey K, King VJ, Gurley S, Kiefer M, Liederbauer E, Vela K, Sonnen P, Kansagara D. 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.
8. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-angiotensin-aldosterone system blockers and the risk of Covid-19. *N Engl J Med*. 2020;382:2431–2440. DOI: 10.1056/NEJMoa2006923.
9. Palazzuoli A, Mancone M, De Ferrari GM, Forleo G, Secco GG, Ruocco GM, D'Ascenzo F, Monticone S, Paggi A, Vicenzi M, et al. Antecedent administration of angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists and survival after hospitalization for COVID-19 syndrome. *J Am Heart Assoc*. 2020;9:e017364. DOI: 10.1161/JAHA.120.017364.
10. Morales DR, Conover MM, You SC, Pratt N, Kostka K, Duarte-Salles T, Fernandez-Bertolin S, Aragon M, DuVall SL, Lynch K, et al. Renin-angiotensin system blockers and susceptibility to COVID-19: an international, open science, cohort analysis. *Lancet Digit Health*. 2021;3:e98–e114. DOI: 10.1016/S2589-7500(20)30289-2.
11. Volpe M, Battistoni A. Systematic review of the role of renin-angiotensin system inhibitors in late studies on Covid-19: a new challenge overcome? *Int J Cardiol*. 2020;321:150–154. DOI: 10.1016/j.ijcard.2020.07.041.
12. de Abajo FJ, Rodriguez-Martin S, Lerma V, Mejia-Abril G, Aguilar M, Garcia-Luque A, Laredo L, Laosa O, Centeno-Soto GA, Ángeles Gálvez M, et al. Use of renin-angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. *Lancet*. 2020;395:1705–1714. DOI: 10.1016/S0140-6736(20)31030-8.
13. Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Iturrate E, Johnson SB, Hausvater A, Newman JD, Berger JS, Bangalore S, et al. Renin-angiotensin-aldosterone system inhibitors and risk of Covid-19. *N Engl J Med*. 2020;382:2441–2448. DOI: 10.1056/NEJMoa2008975.
14. Iaccarino G, Grassi G, Borghi C, Ferri C, Salvetti M, Volpe M; Investigators S-R. Age and multimorbidity predict death among COVID-19 patients: results of the SARS-RAS study of the Italian Society of Hypertension. *Hypertension*. 2020;76:366–372. DOI: 10.1161/HYPERTENSIONAHA.120.15324.
15. Cohen JB, Hanff TC, William P, Sweitzer N, Rosado-Santander NR, Medina C, Rodriguez-Mori JE, Renna N, Chang TI, Corrales-Medina V, 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;9:275–284. DOI: 10.1016/S2213-2600(20)30558-0.
16. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 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. *Hypertension*. 2018;71:e13–e115. DOI: 10.1161/HYP.0000000000000065.
17. Suchard MA, Schuemie MJ, Krumholz HM, You SC, Chen R, Pratt N, Reich CG, Duke J, Madigan D, Hripcsak G, et al. Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis. *Lancet*. 2019;394:1816–1826. DOI: 10.1016/S0140-6736(19)32317-7.
18. Yoshida K, Solomon DH, Haneuse S, Kim SC, Patorno E, Tedeschi SK, Lyu H, Hernandez-Diaz S, Glynn RJ. A tool for empirical equipoise assessment in multigroup comparative effectiveness research. *Pharmacoepidemiol Drug Saf*. 2019;28:934–941. DOI: 10.1002/pds.4767.
19. Khera R, Cram P, Lu X, Vyas A, Gerke A, Rosenthal GE, Horwitz PA, Girotra S. Trends in the use of percutaneous ventricular assist devices: analysis of national inpatient sample data, 2007 through 2012. *JAMA Intern Med*. 2015;175:941–950. DOI: 10.1001/jamainternmed.2014.7856.
20. Nguyen TL, Collins GS, Spence J, Daures JP, Devereaux PJ, Landais P, Le Manach Y. Double-adjustment in propensity score matching analysis: choosing a threshold for considering residual imbalance. *BMC Med Res Methodol*. 2017;17:78. DOI: 10.1186/s12874-017-0338-0.
21. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation*. 2016;133:601–609. DOI: 10.1161/CIRCULATIONAHA.115.017719.
22. Dignam JJ, Zhang Q, Kocherginsky M. The use and interpretation of competing risks regression models. *Clin Cancer Res*. 2012;18:2301–2308. DOI: 10.1158/1078-0432.CCR-11-2097.
23. Taylor SL, Sen S, Greenhalgh DG, Lawless M, Curri T, Palmieri TL. A competing risk analysis for hospital length of stay in patients with burns. *JAMA Surg*. 2015;150:450–456. DOI: 10.1001/jamasurg.2014.3490.
24. Zhang P, Zhu L, Cai J, Lei F, Qin J-J, Xie J, Liu Y-M, Zhao Y-C, Huang X, Lin L, et al. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. *Circ Res*. 2020;126:1671–1681. DOI: 10.1161/CIRCRESAHA.120.317134.
25. Mehta N, Kalra A, Nowacki AS, Anjewierden S, Han Z, Bhat P, Carmona-Rubio AE, Jacob M, Procop GW, Harrington S, 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;5:1020–1026. DOI: 10.1001/jamacardio.2020.1855.
26. Rice GI, Thomas DA, Grant PJ, Turner AJ, Hooper NM. Evaluation of angiotensin-converting enzyme (ACE), its homologue ACE2 and neprilysin in angiotensin peptide metabolism. *Biochem J*. 2004;383:45–51. DOI: 10.1042/BJ20040634.
27. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan YI, Yang P, Zhang Y, Deng W, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med*. 2005;11:875–879. DOI: 10.1038/nm1267.
28. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell*. 2020;181:281–292.e6. DOI: 10.1016/j.cell.2020.02.058.
29. Hardenberg JB, Luft FC. Covid-19, ACE2 and the kidney. *Acta Physiol (Oxf)*. 2020;230:e13539. DOI: 10.1111/apha.13539.
30. Yang J, Petitjean SJL, Koehler M, Zhang Q, Dumitru AC, Chen W, Derclaye S, Vincent SP, Soumillion P, Alsteens D. Molecular interaction and inhibition of SARS-CoV-2 binding to the ACE2 receptor. *Nat Commun*. 2020;11:4541. DOI: 10.1038/s41467-020-18319-6.
31. Meng J, Xiao G, Zhang J, He X, Ou M, Bi J, Yang R, Di W, Wang Z, Li Z, et al. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. *Emerg Microbes Infect*. 2020;9:757–760. DOI: 10.1080/22221751.2020.1746200.
32. Caldeira D, Alarcao J, Vaz-Carneiro A, Costa J. Risk of pneumonia associated with use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers: systematic review and meta-analysis. *BMJ*. 2012;345:e4260. DOI: 10.1136/bmj.e4260.
33. Mortensen EM, Nakashima B, Cornell J, Copeland LA, Pugh MJ, Anzueto A, Good C, Restrepo MI, Downs JR, Frei CR, et al. Population-based study of statins, angiotensin II receptor blockers, and angiotensin-converting enzyme inhibitors on pneumonia-related outcomes. *Clin Infect Dis*. 2012;55:1466–1473. DOI: 10.1093/cid/cis733.
34. Jarcho JA, Ingelfinger JR, Hamel MB, D'Agostino RB Sr, Harrington DP. Inhibitors of the renin-angiotensin-aldosterone system and Covid-19. *N Engl J Med*. 2020;382:2462–2464. DOI: 10.1056/NEJMe2012924.
35. Usman MS, Siddiqi TJ, Khan MS, Ahmed A, Ali SS, Michos ED, Hall ME, Krasuski RA, Greene SJ, Butler J, et al. A meta-analysis of the relationship between renin-angiotensin-aldosterone system inhibitors and COVID-19. *Am J Cardiol*. 2020;130:159–161. DOI: 10.1016/j.amjcard.2020.05.038.
36. Fosbøl EL, Butt JH, Østergaard L, Andersson C, Selmer C, Kragholm K, Schou M, Phelps M, Gislason GH, Gerds TA, et al. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. *JAMA*. 2020;324:168–177. DOI: 10.1001/jama.2020.11301.
37. Bean DM, Kraljevic Z, Searle T, Bendayan R, Pickles A, Folarin A, Roguski L, Noor K, Shek A, O'Gallagher K, et al. ACE-inhibitors and angiotensin-2 receptor blockers are not associated with severe SARS-COVID19 infection in a multi-site UK acute Hospital Trust. *Eur J Heart Fail*. 2020;22:967–974. DOI: 10.1002/ejhf.1924.
38. Hripcsak G, Ryan PB, Duke JD, Shah NH, Park RW, Huser V, Suchard MA, Schuemie MJ, DeFalco FJ, Perotte A, et al. Characterizing treatment pathways at scale using the OHDSI network. *Proc Natl Acad Sci USA*. 2016;113:7329–7336. DOI: 10.1073/pnas.1510502113.
39. UnitedHealth Group. The PACE Study. Available at: https://www.unitedinresearch.com/studies/2. Accessed July 13, 2020.
40. Yoshida K, Solomon DH, Haneuse S, Kim SC, Patorno E, Tedeshi SK, Lyu H, Hernandez-Diaz S, Glynn RJ. Original article: a tool for empirical equipoise assessment in multi-group comparative effectiveness research. *Pharmacoepidemiol Drug Saf*. 2019;28:934–941. DOI: 10.1002/pds.4767.

SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Data Sources and Quality Control

Data entry: Medical and pharmacy claims data are captured, predominantly electronically, from sites of care seeking third-party reimbursement for both Medicare and commercial plans using the industry standard data collection forms HCFA/CMS-1500 for facility claims, UB04/CMS-1450 for professional services and outpatient claims, and NCPDP for pharmacy claims or their electronic equivalents. Structured data from these standardized forms are coded using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM), National Drug Codes (NDC), Current Procedural Terminology (CPT) codes, Logical Observation Identifiers Names and Codes (LOINC) codes, and Diagnosis Related Groups (DRG). This nomenclature ensures consistency of data collection across geographic regions, health systems, and payers throughout the United States.

Methods to Control for Errors in Sampling & Data Collection: Claims that do not adhere to the form or coding standards described above are rejected from reimbursement, minimizing the risk that inappropriately structured data are included in the database. Data specific to SARS-CoV-2 and COVID-19 has an additional Quality Control layer to control for errors in sampling and data collection; this is described below in the Quality Control section.

Data Relevance & Accuracy: Data are transferred into the UnitedHealth Group R&D Data Platform, where a dedicated team pursues data management to ensure accurate matching of source data to an individual. This protocol uses unique identifiers to match them to existing identifiers in the UHG R&D Data Platform to determine whether the individual already exists in the platform. A unique identification number is generated for each individual so that data from multiple sources can be linked back to that identification number. Individuals that fail to meet the matching criteria are excluded from the UHG R&D Data Platform to reduce the risk of erroneous linkage of records. Those whose claims do not fulfill basic standardized data structure requirements described previously are also excluded. During this, all member protected data are stored in a separate database that is only accessible by a designated engineering team. In addition to a persistent identifier being generated for each member, a de-identified primary key is also generated. The de-identified primary key is recycled every 6 months, at which time each member is assigned a new de-identified primary key. Data that are made available for research through the UHG Clinical Discovery Database use the de-identified primary key as the link across data tables. All protected information has been removed, ensuring any research performed is limited to retrospective analysis of de-identified data and accessed in accordance with Health Insurance Portability and Accountability Act regulations.

Sufficiency of basic data: As described above, individuals lacking enough data to be assigned a unique primary key are excluded from the UHG Clinical Discovery Database, as are members whose claims did not fulfil basic data structure requirements. In a given month in 2019, the UHG Clinical Discovery Database contained one or more claims from 5 million Medicare Advantage enrollees and 20 million commercially insured individuals. Further information on data sufficiency for the research performed in this manuscript can be found in the study selection flowsheets (Figure S1 and Figure S2).

Adequacy of possible derived data / Design of computer editing methods: To reduce the risk of introducing error to standardized, structured claims data, derivation of source data within the UHG Clinical Discovery Database is minimal. The Data Integration team loads, formats, and join the data to appropriate dimension tables. Dimension tables are combined with raw claims information to limit the number of times external tables need to be referenced. Researchers may request derived fields within data tables prepared specifically for a project. This process is managed by the Data Enrichment team, who creates data dictionaries to accompany derived fields. Tables containing derived data are stored separately from raw source data. Access to modify/edit source data is restricted to a subset of data specialists. Each step in the data flow has a restricted list of individuals able to perform any type of editing to the database, and access level varies by team (Data Integration, Data Enrichment). Researchers using the

UHG Clinical Discovery Database may not edit any source data or enrichment data. They are instead given access to "sandbox" locations where they may request editing access for the data tables used in their analyses.

Quality control: In addition to the quality control mechanisms described during the matching procedures to reject non-linkable or inappropriately structured data, a COVID-19 data source-specific layer of quality control is also present, given the rapidly evolving situation. SARS-CoV-2 lab tests included in the UHG Clinical Discovery Database exclude custom local codes or codes that are not present in the LOINC organization's guidance for mapping SARS-CoV-2 and COVID-19 related LOINC terms. Test information provided via the LOINC code compliments the test type (antibody, PCR, etc.) as well as the result value (detected, not detected, not given/cancelled). Members with a qualified COVID-19 related hospital admission are included in the report when any diagnosis matches qualified ICD-10 codes as defined in **Table S1**. Suspected COVID-19 inpatient cases are manually reviewed daily by health plan clinical staff via clinical notes to determine an individual's COVID-19 status. Each case is then manually flagged as either negative, confirmed, presumed positive, or needs clinical review. If a case is confirmed, it is not reviewed again. If a case is listed as negative or unknown, it is periodically reviewed for changes in the record. All others are reviewed and updated daily.

Differences across groups: While the data for Medicare Advantage and commercially insured enrollees is processed in a similar manner, these groups are substantially different. First, there are systematic differences in patient characteristics, most remarkably the older age and the higher prevalence of all comorbidities. These differences are tabulated in Table S3. Second, while Medicare includes all Medicare Advantage enrollees in the UHG Clinical Discovery Database, there are restrictions from individual employers on these use of data for research. Therefore, commercial insurance claims that are available for analyses are a subset of the overall commercially insured population.

Estimation of Propensity Score Model

In both outpatient and inpatient studies, we created propensity score-matched cohorts of patients with hypertension, treated with ACE inhibitors, ARBs or other antihypertensive medications. For this, we constructed a non-parsimonious multivariable logistic regression model with receipt of ACE inhibitors, ARB or other antihypertensive as the dependent variable. These analyses were conducted across pairs of comparisons. For example, we modeled the receipt ACE inhibitor or another other antihypertensive (excluding ARB) to determine each patient's probability of receiving these agents based on their measured clinical characteristics. For this, the receipt of ACE inhibitor or other agent (ACE = '1' and Other = '0') was used as a dependent variable in a logistic regression model and used a set of patient-level covariates as independent variables. These included patient age, sex, race, insurance type, conditions that may lead to selective use of ACE inhibitors and ARBs (i.e., diabetes, myocardial infarction, heart failure, and chronic kidney disease), each of the comorbidities in the Charlson Comorbidity Index (peripheral vascular disease, cerebrovascular disease, hemi- or paraplegia, dementia, chronic pulmonary disease, rheumatologic disease, diabetes with chronic complications, malignancy, metastatic solid tumor, mild liver disease, moderate-to-severe liver disease, acquired immunodeficiency syndrome or human immunodeficiency virus), and the number of antihypertensive agents used for the patient. To account for regional clustering of care practices and response to the COVID-19 pandemic, we explicitly accounted for census region of lab testing site or inpatient facility in our models. We applied this strategy to different pairs of treatment comparisons (ACE inhibitor vs others, ARB vs others, and ACE inhibitor vs ARB) to assess the propensity of being treated with either agent in pairwise comparisons.

Matching Algorithm

We used a dedicated algorithm that matched the "cases" to "controls" in one-to-one fashion for each of 3 comparisons - ACE inhibitor vs others, ARB vs others, and ACE inhibitor vs ARB. Such matched pairs were selected based on propensity scores with a caliper width of one-tenth of the standard deviation of the logit of the propensity score. The propensity score and matching algorithm were pursued over 100 iterations to find the lowest mean absolute standardized difference among matched variables.

Evaluation of the Propensity Score Matching

We evaluated the performance of propensity score matching using several strategies.

(1) We assessed the propensity score distributions in the unmatched and matched cohorts and calculated an equipoise metric to summarize the degree of overlap in characteristics of patients receiving these drugs.[17, 40] This represents the proportion of individuals in the unmatched groups that had a propensity score between 0.3 and 0.7, representing a state of equipoise between the two drugs. A value greater than 0.5 implies two drugs are in empirical equipoise, with a higher a value indicating a lower likelihood of confounding by indication.[40]
(2) We evaluated the standardized difference between matched covariates before and after propensity score matching. Specifically, we evaluated whether our matching algorithm achieved a standardized difference of <10% between matched cohort suggestive of adequately matched groups.[17, 19]
(3) We evaluated the success of our matching algorithm using negative control or falsification endpoints. We chose these negative controls from published data on hypertension drug evaluations using claims data. These endpoints were defined from the claim records for study participants between January 1, 2019 and December 31, 2019, and therefore, preceded the infection with SARS-CoV-2.[17] The chosen falsification endpoints were based on the assertion that they are unlikely to be affected by the treatment assignment and a directional effect would represent covariate imbalance.

These strategies were designed to evaluate the potential for residual confounding after creating propensity score matched cohorts. Finally, we evaluated our observations for robustness by assessing treatment effects in 100 iterations of the propensity score matching algorithm, evaluating whether our findings were consistent across these iterations that varied on the degree of matching of individual covariates.

Table S1. ICD-10 codes.

Inclusion Criteria

Inclusion Criteria	ICD-10 Codes
Hypertension	I10%, I11%, I12%, I13%, I15%, I16%, I67.4, N26.2
COVID-19	U071, U072, B9729

Charlson Comorbidity Indices

Charlson Comorbidity Index	ICD-10 Codes
Diabetes Mellitus Without Chronic Complications	E101, E106, E108, E109, E110, E111, E116, E118, E119, E130, E131, E136, E138, E139
Diabetes Mellitus With Chronic Conditions	E102, E103, E104, E105, E112, E113, E114, E115, E132, E133, E134, E135
Myocardial Infarction	I210, I211, I212, I213, I214, I219, I21a, I220, I221, I222, I228, I229, I251, I252, I253, I254, I255, I256, I257, I258, I259
Chronic Heart Failure	I099, I110, I130, I132, I255, I420, I425, I426, I427, I428, I429, I501, I502, I503, I504, I508, I509
Chronic Pulmonary Disease	J430, J431, J432, J438, J439, J440, J441, J449, J452, J453, J454, J455, J459, J470, J471, J479, J620, J628, J630, J631, J632, J633, J634, J635, J636, J660, J661, J662, J668, J670, J671, J672, J673, J674, J676, J677, J678, J679, J684, J701, J703
Peptic Ulcer Disease	K250, K282, K259, K277, K269, K256, K286, K272, K273, K285, K253, K270, K280, K275, K266, K281, K276, K274, K283, K287, K252, K251, K257, K260, K284, K289, K254, K263, K261, K267, K262, K264, K259, K271, K265, K255, K279
Acquired Immunodeficiency Syndrome	B200, B201, B202, B205, B209
Rheumatic Disease	M069, M315, M320, M321, M322, M323, M325, M328, M329, M330, M331, M332, M333, M334, M335, M336, M339, M340, M341, M342, M343, M344, M345, M346, M348, M349, M353, M360
Hemiplegia and Paraplegia	G114, G801, G802, G810, G811, G818, G819, G820, G821, G822, G825, G828, G829, G830, G831, G832
Mild Liver Disease	B187, B188, B189, K700, K701, K702, K703, K709, K713, K714, K715, K717, K730, K731, K732, K735, K736, K738, K739, K73q, K740, K741, K742, K743, K744, K745, K746, K760, K762, K763, K764, K768, K769, Z944
Moderate to Severe Liver Disease	C975, I850, I864, K704, K711, K721, K729, K765, K766, K767
Dementia	F015, F028, F039, G300, G301, G308, G309, G311
Renal Disease	I120, I131, N032, N033, N034, N035, N036, N037, N052, N053, N054, N055, N056, N057, N181, N182, N183, N184, N185, N186, N189, N250, Z490, Z940, Z992
Cerebrovascular Disease	G468, I690, G462, I606, G452, I682, I613, I634, I650, I668, I662, I670, G463, I679, I673, H340, I607, I669, G464, I692, I699, G454, I691, I620, I660, I658, I605, I635, I608, G461, I602, I616, G458, I676, I604, I699, I621, I600, I677, I672, G459, I609, I630
Any Malignancy Without Metastasis	C000, C001, C002, C003, C004, C005, C006, C008, C009, C010, C019, C020, C021, C022, C023, C024, C028, C029, C030, C031, C032, C034, C037, C038, C039, C040, C041, C044, C047, C048, C049, C050, C051, C051, C052, C058, C059, C060, C061, C062, C068, C069, C080, C081, C083, C088, C089, C090, C091, C095, C098, C099,

	C100, C101, C102, C103, C103, C104, C108, C109, C110, C111, C112, C113, C118, C119, C120, C122, C124, C127, C130, C131, C132, C134, C137, C138, C139, C140, C142, C148, C150, C151, C153, C154, C155, C158, C159, C160, C161, C162, C163, C164, C165, C166, C168, C169, C170, C171, C172, C173, C176, C177, C178, C179, C180, C181, C182, C183, C184, C185, C185, C186, C187, C188, C189, C190, C195, C197, C199, C200, C202, C203, C207, C210, C211, C212, C218, C220, C221, C222, C223, C224, C227, C228, C229, C237, C239, C240, C241, C244, C245, C248, C249, C250, C251, C252, C253, C254, C256, C257, C258, C259, C260, C261, C268, C269, C300, C301, C309, C310, C311, C312, C313, C314, C318, C319, C320, C321, C322, C323, C328, C329, C330, C333, C334, C340, C341, C341, C342, C343, C345, C346, C347, C348, C349, C374, C379, C380, C381, C382, C383, C384, C388, C390, C391, C392, C399, C400, C401, C402, C403, C404, C405, C408, C409, C410, C411, C412, C413, C414, C415, C417, C419, C430, C431, C432, C433, C434, C435, C436, C437, C437, C438, C439, C43, C450, C451, C452, C457, C458, C459, C460, C461, C462, C463, C464, C465, C467, C469, C470, C471, C472, C473, C474, C475, C476, C477, C478, C479, C480, C481, C482, C485, C488, C48a, C490, C491, C492, C493, C494, C495, C496, C498, C499, C49a, C500, C501, C502, C503, C504, C505, C506, C508, C509, C510, C511, C512, C513, C514, C518, C519, C520, C521, C522, C524, C528, C530, C530,C531, C538, C539, C540, C541, C542, C543, C548, C549, C550, C551, C560, C561, C562, C564, C568, C569, C570, C571, C572, C573, C574, C575, C576, C577, C578, C579, C580, C583, C585, C589, C600, C601, C602, C604, C605, C608, C609, C610, C614, C615, C616, C617, C618, C619, C61f, C620, C621, C628, C629, C630, C631, C632, C635, C637, C638, C639, C641, C642, C647, C649, C650, C651, C652, C658, C659, C661, C662, C669, C670, C671, C672, C673, C674, C675, C676, C677, C678, C679, C680, C681, C688, C689, C690, C691, C692, C693, C694, C695, C696, C698, C699, C700, C701, C709, C710, C711, C712, C713, C714, C715, C716, C717, C718, C719, C720, C721, C722, C723, C724, C725, C726, C729, C730, C731, C740, C741, C745, C748, C749, C750, C751, C752, C753, C754, C755, C758, C759, C760, C761, C762, C763, C764, C765, C768, C810, C811, C812, C813, C814, C817, C819, C820, C821, C822, C823, C824, C825, C826, C828, C829, C829, C830, C831, C833, C835, C837, C838, C839, C840, C841, C842, C844, C846, C847, C848, C849, C84a, C84z, C851, C852, C858, C859, C880, C882, C883, C884, C888, C889, C900, C901, C902, C903, C903, C908, C909, C910, C911, C912, C913, C914, C915, C916, C919, C91a, C91z, C920, C920, C921, C922, C923, C924, C925, C925, C926, C927, C929, C92a,C92z, C930, C931, C932, C933, C934, C938, C939, C93z, C940, C942, C943, C944, C946, C948, C950, C951, C952, C959, C960, C962, C964, C965, C966, C968, C969, C96a, C96z, C975
Metastatic Solid Tumor	C770, C771, C772, C773, C774, C775, C778, C779, C780, C781, C782, C783, C784, C785, C786, C787, C788, C789, C790, C791, C792, C793, C794, C795, C796, C797, C798, C799, C800, C801, C802, C809

Falsification Endpoints

Falsification Endpoints	ICD-10 Codes
Absent kidney	Q600, Q601, Q602, Z905
Anal and rectal polyp	K600, K601
Gastro-esophageal reflux disease	K210, K219
Herpes zoster without complications	B029
Ingrown nail	L600
Latent effects of motor vehicle accident	V877, V890, V892
Nicotine dependence	F172%
Pain in wrist	M2553%
Presbyopia	H524

Strain of rotator cuff capsule	S4342%
Wrist drop	M2133%

Table S2. Drug classes & generic names.

Antihypertensive Drugs Use in Hypertension	Therapeutic Class	Generic Name
First line	Angiotensin-converting enzyme inhibitors	Benazepril/hydrochlorothiazide, Benazepril HCl, Captopril, Captopril/hydrochlorothiazide, Enalapril/hydrochlorothiazide, Enalapril maleate, Fosinopril/hydrochlorothiazide, Fosinopril sodium, Lisinopril, Lisinopril/hydrochlorothiazide, moexipril/hydrochlorothiazide, Moexipril HCl, Perindopril arg/amlodipine bes, Perindopril erbumine, Quinapril/hydrochlorothiazide, Quinapril HCl, Ramipril, Trandolapril, Trandolapril/verapamil HCl
	Angiotensin II receptor antagonists	Azilsartan med/chlorthalidone, Azilsartan medoxomil, Candesartan/hydrochlorothiazid, Candesartan cilexetil, Eprosartan mesylate, Irbesartan, Irbesartan/hydrochlorothiazide, Losartan/hydrochlorothiazide, Losartan potassium, Olmesartan/amlodipin/hcthiazid, Olmesartan/hydrochlorothiazide, Olmesartan, medoxomil, Sacubitril/valsartan, Telmisartan, Telmisartan/amlodipine, Telmisartan/hydrochlorothiazid, Valsartan, Valsartan/hydrochlorothiazide
	Calcium-channel blocking agents, dihydropyridine	Amlodipine benzoate, Amlodipine besylate, Amlodipine besylate/valsartan, Amlodipine/valsartan/hcthiazid, Amlodipine es/olmesartan med, Amlodipine besylate/benazepril Felodipine, Isradipine, Nifedipine, Nisoldipine, olmesartan/amlodipin/hcthiazid, telmisartan/amlodipine
	Calcium-channel blocking agents, non-dihydropyridine	Diltiazem HCl, Verapamil HCl
	Thiazide and thiazide-like diuretics	Amiloride/hydrochlorothiazide , Amlodipine/valsartan/hcthiazid, Azilsartan med/chlorthalidone, Benazepril/hydrochlorothiazide, Bisoprolol/hydrochlorothiazide, Bisoprolol fumarate/hctz, Candesartan/hydrochlorothiazide, Captopril/hydrochlorothiazide, Clonidine HCl/chlorthalidone, Chlorothiazide, Hydrochlorothiazide, Chlorthalidone, Enalapril/hydrochlorothiazide, Fosinopril/hydrochlorothiazide, Indapamide, Irbesartan/hydrochlorothiazide, Lisinopril/hydrochlorothiazide, Losartan/hydrochlorothiazide, Methyldopa/hydrochlorothiazide, Metolazone, Metoprolol/hydrochlorothiazide, Metoprolol su/hydrochlorothiaz, Moexipril/hydrochlorothiazide, Nadolol/Bendroflumethiazide, Olmesartan/hydrochlorothiazide, Olmesartan/amlodipin/hcthiazid, Quinapril/hydrochlorothiazide, Trandolapril/verapamil HCl, triamterene/hydrochlorothiazide, Propranolol/hydrochlorothiazid
Second line	Alpha adrenergic antagonists	Doxazosin mesylate, Prazosin HCl, Terazosin HCl
	Beta-adrenergic blocking agents	Acebutolol HCl, Atenolol, Atenolol/chlorthalidone, Betaxolol HCl Bisoprolol/hydrochlorothiazide, Bisoprolol fumarate, Bisoprolol fumarate/hctz, Carvedilol, Carvedilol phosphate, Labetalol HCl, Metoprolol/hydrochlorothiazide, Metoprolol u/hydrochlorothiaz, Metoprolol succinate, Metoprolol tartrate, Nadolol, Nadolol/bendroflumethiazide, Nebivolol HCl, Nebivolol HCl/valsartan, Pindolol, Propranolol/hydrochlorothiazid, Propranolol HCl
	Central alpha-agonists	Clonidine, Clonidine HCl, Clonidine HCl/chlorthalidone, Guanfacine HCl, Methyldopa, Methyldopa/hydrochlorothiazide
	Direct vasodilators	Hydralazine HCl, isosorbide dinit/hydralazine, minoxidil

Loop diuretics	Bumetanide, Torsemide, Furosemide
Mineralocorticoid receptor antagonists	Epleronone, Spironolactone, Spironolactone micronized
Potassium-sparing diuretics	Amiloride HCl, Amiloride/hydrochlorothiazide, Triamterene, Triamterene/hydrochlorothiazid
Renin inhibitors	Aliskiren hemifumarate, Aliskiren/hydrochlorothiazide

Additional drug classes of interest

Therapeutic Class	Generic Name
Oral anticoagulants	Apixaban, Rivaroxaban, Betrixaban maleate, Edoxaban tosylate, Dabigatran etexilate mesylate, Warfarin sodium
Statins	Atorvastatin calcium, Simvastatin, Pitavastatin calcium, Pitavastatin magnesium, Amlodipine/atorvastatin, Lovastatin, Fluvastatin sodium, Niacin/lovastatin, Pravastatin sodium, Rosuvastatin calcium, Niacin/simvastatin
Other Lipid Lowering Agents	Fenofibrate, Fenofibrate micronized, Fenofibrate nanocrystallized, Ezetimibe, Ezetimibe/simvastatin, Cholestyramine/aspartame, Colesevelam HCl, Cholestyramine (with sugar), Colestipol HCl, Niacin/simvastatin, Niacin/lovastatin, Niacin
Oral Glucose Lowering Agents	Acarbose, Miglitol, Metformin HCl, Sitagliptin phosphate, Linagliptin, Sitagliptin phos/metformin HCl, Saxagliptin HCl, Saxagliptin HCl/metformin HCl, Linagliptin/metformin HCl, Alogliptin benzoate, Alogliptin benz/metformin HCl, Alogliptin benz/pioglitazone, Repaglinide, Nateglinide,Empagliflozin, Canagliflozin, Empagliflozin/metformin HCl, Canagliflozin/metformin HCl, Dapagliflozin propanediol, Empagliflozin/linagliptin, Dapagliflozin/metformin HCl, Ertugliflozin pidolate, Ertugliflozin/sitagliptin, Dapagliflozin/saxagliptin HCl, Ertugliflozin/metformin, Glipizide, Glimepiride, Glyburide, Glipizide/metformin HCl, Glyburide/metformin HCl, Glyburide,micronized, Glyburide micronized, Tolbutamide, Tolazamide, Pioglitazone HCl, Pioglitazone HCl/metformin HCl, Pioglitazone HCl/glimepiride, Rosiglitazone maleate
Insulins	Insulin nph hum/reg insulin hm, Insulin nph human isophane, Insulin glargine hum.rec.anlog, Insulin detemir, Insulin glargine,hum.rec.anlog, Insulin degludec, Insulin glargine/lixisenatide, Insulin degludec/liraglutide, Insulin lispro, Insulin lispro protamin/lispro, Insulin aspart, Insulin aspart prot/insuln asp, Insulin aspart (niacinamide), Insulin glulisine, Insulin regular, human,Insulin regular human, Insulin regular human, Insulin regular, human

Table S3. Characteristics of the primary Outpatient and Inpatient study cohorts, Medicare verses Commercial.

	Outpatient				Inpatient			
Variable	Overall	Medicare Advantage	Commercial	p-value Medicare vs Commercial	Overall	Medicare Advantage	Commercial	p-value Medicare vs Commercial
Number of Patients (% of population)	2263 (100%)	1467 (64.8%)	796 (35.2%	<0·0001	7933 (100%)	7296 (92.0%)	637 (8.0%)	<0.0001
Age, median (IQR)	69.0 (59.0–78.0)	75.0 (70.0–82.0)	56.0 (49.0–61.0)	<0.0001	77.0 (69.0–85.0)	78.0 (71.0–85.0)	57.0 (51.0–62.0)	<0.0001
Female	1189 (52.5%)	828 (56.4%)	361 (45.4%)	<0.0001	4332 (54.6%)	4075 (55.9%)	257 (40.3%)	<0.0001
Comorbid Conditions								
Diabetes without chronic complications	911 (40.3%)	669 (45.6%)	242 (30.4%)	<0.0001	4022 (50.7%)	3755 (51.5%)	267 (41.9%)	<0.0001
Myocardial infarction	81 (3.6%)	60 (4.1%)	21 (2.6%)	0.098	425 (5.4%)	402 (5.5%)	23 (3.6%)	0.051
Chronic heart failure	326 (14.4%)	295 (20.1%)	31 (3.9%)	<0.0001	2469 (31.1%)	2383 (32.7%)	86 (13.5%)	<0.0001
Chronic pulmonary disease	410 (18.1%)	310 (21.1%)	100 (12.6%)	<0.0001	2266 (28.6%)	2144 (29.4%)	122 (19.2%)	<0.0001
Peptic ulcer disease	19 (0.8%)	**	**	0.12	133 (1.7%)	122 (1.7%)	11 (1.7%)	0.95
Acquired immunodeficiency syndrome	22 (1.0%)	**	**	0.43	33 (0.4%)	**	**	<0.0001
Rheumatic disease	120 (5.3%)	82 (5.6%)	38 (4.8%)	0.47	435 (5.5%)	396 (5.4%)	39 (6.1%)	0.52
Diabetes with chronic complications	625 (27.6%)	481 (32.8%)	144 (18.1%)	<0.0001	3081 (38.8%)	2907 (39.8%)	174 (27.3%)	<0.0001
Metastatic solid tumor	20 (0.9%)	**	**	0.49	146 (1.8%)	131 (1.8%)	15 (2.4%)	0.39

Hemiplegia and paraplegia	92 (4.1%)	88 (6.0%)	4 (0.5%)	<0.0001	596 (7.5%)	**	**	<0.0001
Mild liver disease	106 (4.7%)	67 (4.6%)	39 (4.9%)	0.80	477 (6.0%)	420 (5.8%)	57 (8.9%)	0.0016
Any malignancy without metastasis	181 (8.0%)	139 (9.5%)	42 (5.3%)	0.00059	923 (11.6%)	870 (11.9%)	53 (8.3%)	0.0079
Moderate to severe liver disease	**	**	**	0.24	66 (0.8%)	**	**	0.59
Dementia	250 (11.0%)	249 (17.0%)	1 (0.1%)	<0.0001	1645 (20.7%)	**	**	<0.0001
Perivascular Disease	467 (20.6%)	428 (29.2%)	39 (4.9%)	<0.0001	2687 (33.9%)	2611 (35.8%)	76 (11.9%)	<0.0001
Renal disease	359 (15.9%)	318 (21.7%)	41 (5.2%)	<0.0001	2351 (29.6%)	2252 (30.9%)	99 (15.5%)	<0.0001
Cerebrovascular disease	289 (12.8%)	258 (17.6%)	31 (3.9%)	<0.0001	1744 (22.0%)	1694 (23.2%)	50 (7.8%)	<0.0001
Charlson score, median (IQR)	2.0 (0.0–3.0)	2.0 (1.0–4.0)	0.0 (0.0–1.0)	<0.0001	3.0 (2.0–5.0)	3.0 (2.0–5.0)	1.0 (0.0–3.0)	<0.0001
Drug Therapy								
Antihypertensives								
Angiotensin converting enzyme inhibitor	722 (31.9%)	434 (29.6%)	288 (36.2%)	0.0015	2361 (29.8%)	2152 (29.5%)	209 (32.8%)	0.087
Angiotensin II receptor blocker	731 (32.3%)	452 (30.8%)	279 (35.1%)	0.044	2226 (28.1%)	1991 (27.3%)	235 (36.9%)	<0.0001
Beta blocking agent	911 (40.3%)	682 (46.5%)	229 (28.8%)	<0.0001	4277 (53.9%)	4028 (55.2%)	249 (39.1%)	<0.0001
Calcium channel blockers, non-dihydropyridine	99 (4.4%)	73 (5.0%)	26 (3.3%)	0.073	3438 (43.3%)	3173 (43.5%)	265 (41.6%)	0.38
Calcium channel blockers, dihydropyridine	813 (35.9%)	549 (37.4%)	264 (33.2%)	0.049	2972 (37.5%)	2727 (37.4%)	245 (38.5%)	0.62
Thiazide or thiazide-like diuretic	709 (31.3%)	395 (26.9%)	314 (39.4%)	<0.0001	1650 (20.8%)	1425 (19.5%)	225 (35.3%)	<0.0001
Loop diuretic	328 (14.5%)	300 (20.4%)	28 (3.5%)	<0.0001	2400 (30.3%)	2323 (31.8%)	77 (12.1%)	<0.0001

Central alpha agent agonist	54 (2.4%)	43 (2.9%)	11 (1.4%)	0.031	303 (3.8%)	284 (3.9%)	19 (3.0%)	0.30
Potassium sparing diuretic	56 (2.5%)	35 (2.4%)	21 (2.6%)	0.82	112 (1.4%)	93 (1.3%)	19 (3.0%)	0.00087
Mineralocorticoid receptor antagonist	85 (3.8%)	67 (4.6%)	18 (2.3%)	0.0083	435 (5.5%)	398 (5.5%)	37 (5.8%)	0.78
Renin inhibitors	0 (0.0%)	0 (0.0%)	0 (0.0%)	<0·0001	0 (0.0%)	0 (0.0%)	0 (0.0%)	<0.0001
Alpha adrenergic blocking agents	40 (1.8%)	**	**	0.0042	247 (3.1%)	235 (3.2%)	12 (1.9%)	0.081
Direct vasodilators	99 (4.4%)	**	**	<0.0001	515 (6.5%)	493 (6.8%)	22 (3.5%)	0.0016
Place in therapy								
First-line drug user	1964 (86.8%)	1238 (84.4%)	726 (91.2%)	<0.0001	6399 (80.7%)	5822 (79.8%)	577 (90.6%)	<0.0001
Second-line drug user	1135 (50.2%)	864 (58.9%)	271 (34.0%)	<0.0001	5478 (69.1%)	5169 (70.8%)	309 (48.5%)	<0.0001
Number of antihypertensive classes								
1	822 (36.3%)	500 (34.1%)	322 (40.5%)	0.0031	2322 (29.3%)	2113 (29.0%)	209 (32.8%)	0.045
2	780 (34.5%)	473 (32.2%)	307 (38.6%)	0.0029	2625 (33.1%)	2400 (32.9%)	225 (35.3%)	0.23
3+	661 (29.2%)	494 (33.7%)	167 (21.0%)	<0.0001	2986 (37.6%)	2783 (38.1%)	203 (31.9%)	0.0020
Number of Anti-HTN agents used: median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–2.0)	<0.0001	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.0059
Other Drug Therapies								
Statins	1210 (53.5%)	892 (60.8%)	318 (39.9%)	<0.0001	4772 (60.2%)	4498 (61.7%)	274 (43.0%)	<0·0001
Other lipid-lowering agent	113 (5.0%)	82 (5.6%)	31 (3.9%)	0.096	423 (5.3%)	385 (5.3%)	38 (6.0%)	0.52
Oral anticoagulants	201 (8.9%)	179 (12.2%)	22 (2.8%)	<0.0001	1375 (17.3%)	1332 (18.3%)	43 (6.8%)	<0·0001
Insulin	215 (9.5%)	165 (11.2%)	50 (6.3%)	0.00016	1373 (17.3%)	1298 (17.8%)	75 (11.8%)	0.00015

Oral antihyperglycemic agents	581 (25.7%)	389 (26.5%)	192 (24.1%)	0.23	2188 (27.6%)	2000 (27.4%)	188 (29.5%)	0.27

** Cells with values < 11 were suppressed in accordance with the Centers for Medicare and Medicare Services cell size suppression policy for values from 1 to 10.

Table S4. Characteristics of the secondary outpatient cohort. The cohort includes individuals who had a positive test for SARS-CoV-2 in the outpatient setting between May and August, 2020.

Antihypertensive Drug Cohorts

		Cohort			p-value		
Variable	**Overall**	**ACE inhibitor**	**ARB**	**Other**	**ACE inhibitor vs Other**	**ARB vs Other**	**ACE inhibitor vs ARB**
Number of Patients	5552 (100%)	2152 (38.8%)	1808 (32.6%)	1592 (28.7%)	--	--	--
Age, median (IQR)	65.0 (54.0 - 74.0)	63.0 (54.0 - 73.0)	66.0 (55.0 - 74.0)	67.0 (54.0 - 77.0)	<.0001	0.15	0.00020
18 to 30 y	55 (1.0%)	19 (0.9%)	15 (0.8%)	21 (1.3%)	0.26	0.22	0.99
31 to 40 y	234 (4.2%)	97 (4.5%)	56 (3.1%)	81 (5.1%)	0.45	0.0043	0.027
41 to 50 y	715 (12.9%)	300 (13.9%)	201 (11.1%)	214 (13.4%)	0.70	0.044	0.0089
51 to 60 y	1210 (21.8%)	488 (22.7%)	412 (22.8%)	310 (19.5%)	0.020	0.021	0.96
61 to 70 y	1332 (24.0%)	560 (26.0%)	463 (25.6%)	309 (19.4%)	<.0001	<.0001	0.79
71 to 80 y	1307 (23.5%)	490 (22.8%)	459 (25.4%)	358 (22.5%)	0.87	0.053	0.059
> 80 y	699 (12.6%)	198 (9.2%)	202 (11.2%)	299 (18.8%)	<.0001	<.0001	0.046
Female sex	2974 (53.6%)	1020 (47.4%)	978 (54.1%)	976 (61.3%)	<.0001	<.0001	<.0001
Medicare Advantage	3230 (58.2%)	1181 (54.9%)	1077 (59.6%)	972 (61.1%)	0.00018	0.40	0.0033
Location							
Urban	2130 (38.4%)	800 (37.2%)	688 (38.1%)	642 (40.3%)	0.054	0.19	0.59
Rural	1326 (23.9%)	529 (24.6%)	431 (23.8%)	366 (23.0%)	0.28	0.59	0.61
Suburban	2056 (37.0%)	809 (37.6%)	672 (37.2%)	575 (36.1%)	0.37	0.55	0.81
Unknown	**	14 (0.7%)	17 (0.9%)	**	0.91	0.29	0.40
Race *							
Caucasian	1938 (34.9%)	730 (33.9%)	604 (33.4%)	604 (37.9%)	0.012	0.0065	0.76

African American	794 (14.3%)	253 (11.8%)	285 (15.8%)	256 (16.1%)	0.00016	0.84	0.00030
Hispanic	307 (5.5%)	124 (5.8%)	119 (6.6%)	64 (4.0%)	0.019	0.0013	0.32
Asian	30 (0.5%)	**	15 (0.8%)	**	0.56	0.34	0.056
Native American	**	0 (0.0%)	**	**	0.88	0.54	0.93
Other	45 (0.8%)	18 (0.8%)	18 (1.0%)	9 (0.6%)	0.44	0.22	0.72
Unknown	2436 (43.9%)	1020 (47.4%)	766 (42.4%)	650 (40.8%)	<.0001	0.38	0.0017
Geography							
Region of Test Site							
Northeast	585 (10.5%)	205 (9.5%)	134 (7.4%)	246 (15.5%)	<.0001	<.0001	0.021
South	3714 (66.9%)	1415 (65.8%)	1300 (71.9%)	999 (62.8%)	0.063	<.0001	<.0001
Midwest	423 (7.6%)	168 (7.8%)	117 (6.5%)	138 (8.7%)	0.37	0.018	0.12
West	609 (11.0%)	280 (13.0%)	187 (10.3%)	142 (8.9%)	0.00011	0.18	0.011
Unknown	221 (4.0%)	84 (3.9%)	70 (3.9%)	67 (4.2%)	0.70	0.68	0.98
State of Test Site							
Texas	1091 (19.7%)	481 (22.4%)	399 (22.1%)	211 (13.3%)	<.0001	<.0001	0.86
Florida	1047 (18.9%)	360 (16.7%)	375 (20.7%)	312 (19.6%)	0.027	0.43	0.0014
Arizona	412 (7.4%)	190 (8.8%)	120 (6.6%)	102 (6.4%)	0.0076	0.84	0.012
North Carolina	406 (7.3%)	151 (7.0%)	125 (6.9%)	130 (8.2%)	0.21	0.19	0.95
Georgia	335 (6.0%)	106 (4.9%)	110 (6.1%)	119 (7.5%)	0.0015	0.12	0.13
Other	2124 (38.3%)	819 (38.1%)	632 (35.0%)	673 (42.3%)	0.010	<.0001	0.047
Unknown	137 (2.5%)	45 (2.1%)	47 (2.6%)	45 (2.8%)	0.18	0.76	0.34
Comorbid Conditions							
Diabetes without complications	2310 (41.6%)	1004 (46.7%)	807 (44.6%)	499 (31.3%)	<.0001	<.0001	0.22
Myocardial infarction	165 (3.0%)	53 (2.5%)	46 (2.5%)	66 (4.1%)	0.0050	0.012	0.95
Chronic heart failure	675 (12.2%)	199 (9.2%)	220 (12.2%)	256 (16.1%)	<.0001	0.0012	0.0034

Chronic pulmonary disease	845 (15.2%)	270 (12.5%)	299 (16.5%)	276 (17.3%)	<.0001	0.57	0.00043
Peptic ulcer disease	41 (0.7%)	11 (0.5%)	18 (1.0%)	12 (0.8%)	0.47	0.57	0.11
AIDS	21 (0.4%)	11 (0.5%)	**	**	0.72	0.60	0.22
Rheumatologic disease	321 (5.8%)	105 (4.9%)	121 (6.7%)	95 (6.0%)	0.16	0.43	0.017
Diabetes, chronic complications	1714 (30.9%)	735 (34.2%)	613 (33.9%)	366 (23.0%)	<.0001	<.0001	0.90
Metastatic cancer	31 (0.6%)	13 (0.6%)	7 (0.4%)	11 (0.7%)	0.90	0.33	0.46
Hemiplegia or paraplegia	155 (2.8%)	61 (2.8%)	36 (2.0%)	58 (3.6%)	0.19	0.0047	0.11
Liver disease, mild	356 (6.4%)	131 (6.1%)	118 (6.5%)	107 (6.7%)	0.47	0.87	0.62
Solid tumor without metastases	397 (7.2%)	136 (6.3%)	138 (7.6%)	123 (7.7%)	0.11	0.97	0.12
Liver disease, moderate to severe	**	**	11 (0.6%)	15 (0.9%)	0.0028	0.36	0.058
Dementia	353 (6.4%)	113 (5.3%)	62 (3.4%)	178 (11.2%)	<.0001	<.0001	0.0069
Peripheral vascular disease	961 (17.3%)	292 (13.6%)	318 (17.6%)	351 (22.0%)	<.0001	0.0013	0.00057
Renal failure, moderate to severe	860 (15.5%)	269 (12.5%)	306 (16.9%)	285 (17.9%)	<.0001	0.48	<.0001
Cerebrovascular disease	551 (9.9%)	171 (7.9%)	183 (10.1%)	197 (12.4%)	<.0001	0.043	0.020
Charlson Score, median (IQR)	1.0 (0.0 - 3.0)	1.0 (0.0 - 3.0)	2.0 (0.0 - 3.0)	1.0 (0.0 - 3.0)	0.0050	0.91	0.0017
Drug Therapy							
Antihypertensives							
Beta blockers	2043 (36.8%)	598 (27.8%)	611 (33.8%)	834 (52.4%)	<.0001	<.0001	<.0001
Non-dihydropyridine calcium channel blockers	195 (3.5%)	53 (2.5%)	54 (3.0%)	88 (5.5%)	<.0001	0.00031	0.36
Dihydropyridine calcium channel blockers	1656 (29.8%)	502 (23.3%)	538 (29.8%)	616 (38.7%)	<.0001	<.0001	<.0001
Thiazide or thiazide-like diuretics	1857 (33.4%)	674 (31.3%)	786 (43.5%)	397 (24.9%)	<.0001	<.0001	<.0001
Loop diuretics	663 (11.9%)	193 (9.0%)	190 (10.5%)	280 (17.6%)	<.0001	<.0001	0.11

Centrally acting alpha agonists	124 (2.2%)	35 (1.6%)	42 (2.3%)	47 (3.0%)	0.0086	0.30	0.14
Potassium sparing diuretics	121 (2.2%)	26 (1.2%)	22 (1.2%)	73 (4.6%)	<.0001	<.0001	0.90
Mineralocorticoid aldosterone antagonists	196 (3.5%)	43 (2.0%)	72 (4.0%)	81 (5.1%)	<.0001	0.14	0.00031
Renin inhibitors	**	0 (0.0%)	0 (0.0%)	**	0.88	0.95	--
Alpha adrenergic blocking agents	111 (2.0%)	37 (1.7%)	29 (1.6%)	45 (2.8%)	0.030	0.020	0.87
Direct vasodilators	167 (3.0%)	35 (1.6%)	71 (3.9%)	61 (3.8%)	<.0001	0.96	<.0001
Place in Therapy							
First Line Drug User	4941 (89.0%)	2152	1808	981 (61.6%)	<.0001	<.0001	
Second Line Drug User	2560 (46.1%)	735 (34.2%)	743 (41.1%)	1082 (68.0%)	<.0001	<.0001	<.0001
Number of Antihypertensive Classes							
1	2118 (38.1%)	757 (35.2%)	431 (23.8%)	930 (58.4%)	<.0001	<.0001	<.0001
2	1948 (35.1%)	823 (38.2%)	670 (37.1%)	455 (28.6%)	<.0001	<.0001	0.46
3+	1486 (26.8%)	572 (26.6%)	707 (39.1%)	207 (13.0%)	<.0001	<.0001	<.0001
Number, median (IQR)	2.0 (1.0 - 3.0)	2.0 (1.0 - 3.0)	2.0 (2.0 - 3.0)	1.0 (1.0 - 2.0)	<.0001	<.0001	<.0001
Other Drug Therapies							
Statins	2848 (51.3%)	1182 (54.9%)	978 (54.1%)	688 (43.2%)	<.0001	<.0001	0.62
Other lipid lowering agents	267 (4.8%)	108 (5.0%)	94 (5.2%)	65 (4.1%)	0.20	0.15	0.85
Oral anticoagulants	394 (7.1%)	114 (5.3%)	129 (7.1%)	151 (9.5%)	<.0001	0.015	0.020
Insulins	512 (9.2%)	201 (9.3%)	197 (10.9%)	114 (7.2%)	0.021	0.00021	0.12
Oral antihyperglycemic agents	1629 (29.3%)	769 (35.7%)	602 (33.3%)	258 (16.2%)	<.0001	<.0001	0.12

Follow-up							
Follow-up days, median (IQR)	35.0 (24.0 - 54.0)	35.0 (23.8 - 52.2)	33.0 (23.0 - 50.0)	37.0 (24.0 - 65.0)	<.0001	<.0001	0.044
Test to hospitalization, median (IQR)	6.0 (3.0 - 10.0)	6.0 (3.0 - 11.0)	6.0 (3.0 - 9.0)	7.0 (3.0 - 13.0)	0.18	0.014	0.24
Total hospitalized	624 (11.2%)	233 (10.8%)	182 (10.1%)	209 (13.1%)	0.035	0.0062	0.47

* Race is unknown in all commercially insured enrollees.

** Cells with values < 11 were suppressed in accordance with the Centers for Medicare and Medicare Services cell size suppression policy for values from 1 to 10.

Table S5. Characteristics of the secondary inpatient cohort. The cohort includes individuals who were hospitalized with COVID-19 between May and August, 2020.

	Cohort				p-value		
Variable	**Overall**	**ACE inhibitor**	**ARB**	**Other**	**ACE inhibitor vs Other**	**ARB vs Other**	**ACE inhibitor vs ARB**
Number of Patients	8114 (100%)	2663 (32.8%)	2325 (28.7%)	3126 (38.5%)			
Age, median (IQR)	76.0 (68.0 - 84.0)	75.0 (67.0 - 83.0)	74.0 (67.0 - 82.0)	77.5 (69.0 - 86.0)	<.0001	<.0001	0.70
Age Range							
18 to 30 y	11 (0.1%)	**	**	**	0.58	0.82	0.56
31 to 40 y	45 (0.6%)	17 (0.6%)	11 (0.5%)	17 (0.5%)	0.77	0.87	0.56
41 to 50 y	237 (2.9%)	88 (3.3%)	64 (2.8%)	85 (2.7%)	0.22	0.99	0.29
51 to 60 y	715 (8.8%)	260 (9.8%)	222 (9.5%)	233 (7.5%)	0.0020	0.0066	0.83
61 to 70 y	1686 (20.8%)	584 (21.9%)	536 (23.1%)	566 (18.1%)	0.00032	<.0001	0.36
71 to 80 y	2652 (32.7%)	894 (33.6%)	802 (34.5%)	956 (30.6%)	0.016	0.0025	0.51
> 80 y	2768 (34.1%)	818 (30.7%)	686 (29.5%)	1264 (40.4%)	<.0001	<.0001	0.37
Female sex	4783 (58.9%)	1432 (53.8%)	1412 (60.7%)	1939 (62.0%)	<.0001	0.34	<.0001
Medicare Advantage	7291 (89.9%)	2353 (88.4%)	2026 (87.1%)	2912 (93.2%)	<.0001	<.0001	0.20
Location							
Urban	2817 (34.7%)	892 (33.5%)	834 (35.9%)	1091 (34.9%)	0.27	0.48	0.084
Rural	2362 (29.1%)	820 (30.8%)	692 (29.8%)	850 (27.2%)	0.0028	0.040	0.45
Suburban	2915 (35.9%)	942 (35.4%)	793 (34.1%)	1180 (37.7%)	0.066	0.0062	0.36
Unknown	20 (0.2%)	**	**	**	0.27	0.62	0.80
Race *							
Caucasian	4304 (53.0%)	1435 (53.9%)	1062 (45.7%)	1807 (57.8%)	0.0030	<.0001	<.0001
African American	2305 (28.4%)	679 (25.5%)	737 (31.7%)	889 (28.4%)	0.013	0.010	<.0001

Hispanic	321 (4.0%)	116 (4.4%)	115 (4.9%)	90 (2.9%)	0.0032	<.0001	0.36
Asian	53 (0.7%)	19 (0.7%)	13 (0.6%)	21 (0.7%)	0.97	0.73	0.61
Native American	13 (0.2%)	**	**	**	0.38	0.96	0.26
Other	90 (1.1%)	31 (1.2%)	32 (1.4%)	27 (0.9%)	0.31	0.094	0.59
Unknown	1028 (12.7%)	376 (14.1%)	364 (15.7%)	288 (9.2%)	<.0001	<.0001	0.14
Geographic Region							
Region of Inpatient Facility							
Northeast	1228 (15.1%)	387 (14.5%)	239 (10.3%)	602 (19.3%)	<.0001	<.0001	<.0001
South	5022 (61.9%)	1630 (61.2%)	1607 (69.1%)	1785 (57.1%)	0.0017	<.0001	<.0001
Midwest	1413 (17.4%)	480 (18.0%)	354 (15.2%)	579 (18.5%)	0.65	0.0016	0.0092
West	450 (5.5%)	165 (6.2%)	125 (5.4%)	160 (5.1%)	0.086	0.72	0.24
Unknown	**	**	0 (0.0%)	0 (0.0%)	0.94	<.0001	0.95
State of Inpatient Facility							
Florida	1208 (14.9%)	368 (13.8%)	440 (18.9%)	400 (12.8%)	0.27	<.0001	<.0001
Georgia	894 (11.0%)	263 (9.9%)	274 (11.8%)	357 (11.4%)	0.064	0.71	0.034
New York	354 (4.4%)	95 (3.6%)	70 (3.0%)	189 (6.0%)	<.0001	<.0001	0.31
Texas	834 (10.3%)	318 (11.9%)	264 (11.4%)	252 (8.1%)	<.0001	<.0001	0.55
Connecticut	339 (4.2%)	109 (4.1%)	70 (3.0%)	160 (5.1%)	0.074	0.00017	0.048
Other	4485 (55.3%)	1510 (56.7%)	1207 (51.9%)	1768 (56.6%)	0.93	0.00073	0.00078
Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	<.0001	<.0001	<.0001
Comorbid Conditions							
Diabetes without complications	4394 (54.2%)	1575 (59.1%)	1340 (57.6%)	1479 (47.3%)	<.0001	<.0001	0.29
Myocardial infarction	390 (4.8%)	100 (3.8%)	123 (5.3%)	167 (5.3%)	0.0050	0.98	0.011
Chronic heart failure	2378 (29.3%)	642 (24.1%)	653 (28.1%)	1083 (34.6%)	<.0001	<.0001	0.0016
Chronic pulmonary disease	2249 (27.7%)	633 (23.8%)	650 (28.0%)	966 (30.9%)	<.0001	0.020	0.00083

Peptic ulcer disease	120 (1.5%)	36 (1.4%)	29 (1.2%)	55 (1.8%)	0.26	0.16	0.84
AIDS	45 (0.6%)	11 (0.4%)	14 (0.6%)	20 (0.6%)	0.32	1.00	0.46
Rheumatologic disease	504 (6.2%)	134 (5.0%)	162 (7.0%)	208 (6.7%)	0.011	0.69	0.0047
Diabetes, chronic complications	3493 (43.0%)	1232 (46.3%)	1076 (46.3%)	1185 (37.9%)	<.0001	<.0001	0.99
Metastatic cancer	112 (1.4%)	33 (1.2%)	33 (1.4%)	46 (1.5%)	0.52	0.96	0.67
Hemiplegia or paraplegia	637 (7.9%)	201 (7.5%)	130 (5.6%)	306 (9.8%)	0.0031	<.0001	0.0067
Liver disease, mild	529 (6.5%)	163 (6.1%)	162 (7.0%)	204 (6.5%)	0.56	0.56	0.25
Solid tumor without metastases	827 (10.2%)	259 (9.7%)	250 (10.8%)	318 (10.2%)	0.60	0.52	0.25
Liver disease, moderate to severe	68 (0.8%)	17 (0.6%)	15 (0.6%)	36 (1.2%)	0.057	0.075	0.88
Dementia	1882 (23.2%)	602 (22.6%)	375 (16.1%)	905 (29.0%)	<.0001	<.0001	<.0001
Peripheral vascular disease	2698 (33.3%)	813 (30.5%)	704 (30.3%)	1181 (37.8%)	<.0001	<.0001	0.87
Renal failure, moderate to severe	2540 (31.3%)	709 (26.6%)	699 (30.1%)	1132 (36.2%)	<.0001	<.0001	0.0078
Cerebrovascular disease	1748 (21.5%)	524 (19.7%)	461 (19.8%)	763 (24.4%)	<.0001	<.0001	0.92
Charlson Score, median (IQR)	3.0 (2.0 - 4.0)	3.0 (2.0 - 4.0)	3.0 (1.0 - 4.0)	3.0 (2.0 - 5.0)	<.0001	<.0001	0.18
Drug Therapy							
Antihypertensives							
Beta blockers	4202 (51.8%)	1186 (44.5%)	1143 (49.2%)	1873 (59.9%)	<.0001	<.0001	0.0012
Non-dihydropyridine calcium channel blockers	3452 (42.5%)	1004 (37.7%)	1005 (43.2%)	1443 (46.2%)	<.0001	0.033	<.0001
Dihydropyridine calcium channel blockers	3015 (37.2%)	889 (33.4%)	900 (38.7%)	1226 (39.2%)	<.0001	0.72	0.00010
Thiazide or thiazide-like diuretics	1951 (24.0%)	618 (23.2%)	840 (36.1%)	493 (15.8%)	<.0001	<.0001	<.0001
Loop diuretics	2381 (29.3%)	639 (24.0%)	628 (27.0%)	1114 (35.6%)	<.0001	<.0001	0.016
Centrally acting alpha agonists	287 (3.5%)	76 (2.9%)	97 (4.2%)	114 (3.6%)	0.11	0.36	0.014
Potassium sparing diuretics	139 (1.7%)	39 (1.5%)	29 (1.2%)	71 (2.3%)	0.032	0.0073	0.59

Mineralocorticoid aldosterone antagonists	460 (5.7%)	122 (4.6%)	133 (5.7%)	205 (6.6%)	0.0014	0.23	0.079
Renin inhibitors	**	0 (0.0%)	**v	**	0.55	0.80	0.95
Alpha adrenergic blocking agents	255 (3.1%)	73 (2.7%)	72 (3.1%)	110 (3.5%)	0.11	0.43	0.51
Direct vasodilators	564 (7.0%)	128 (4.8%)	181 (7.8%)	255 (8.2%)	<.0001	0.65	<.0001
Place in Therapy							
First-line	6722 (82.8%)	2663	2325	1734 (55.5%)	<.0001	<.0001	<.0001
Second-line	5490 (67.7%)	1524 (57.2%)	1470 (63.2%)	2496 (79.8%)	<.0001	<.0001	<.0001
Number of Antihypertensive Classes							
1	2317 (28.6%)	556 (20.9%)	321 (13.8%)	1440 (46.1%)	<.0001	<.0001	<.0001
2	2676 (33.0%)	939 (35.3%)	693 (29.8%)	1044 (33.4%)	0.14	0.0054	<.0001
3+	3121 (38.5%)	1168 (43.9%)	1311 (56.4%)	642 (20.5%)	<.0001	<.0001	<.0001
Number, median (IQR)	2.0 (1.0 - 3.0)	2.0 (2.0 - 3.0)	3.0 (2.0 - 4.0)	2.0 (1.0 - 2.0)	<.0001	<.0001	<.0001
Other Drug Therapies							
Statins	4876 (60.1%)	1710 (64.2%)	1487 (64.0%)	1679 (53.7%)	<.0001	<.0001	0.87
Other lipid lowering agents	480 (5.9%)	149 (5.6%)	167 (7.2%)	164 (5.2%)	0.60	0.0037	0.025
Oral anticoagulants	1277 (15.7%)	348 (13.1%)	317 (13.6%)	612 (19.6%)	<.0001	<.0001	0.59
Insulin	1566 (19.3%)	550 (20.7%)	497 (21.4%)	519 (16.6%)	<.0001	<.0001	0.55
Oral antihyperglycemic agents	2521 (31.1%)	1021 (38.3%)	845 (36.3%)	655 (21.0%)	<.0001	<.0001	0.15
Follow-up							
Follow-up days, median (IQR)	7.0 (4.0 - 13.0)	7.0 (4.0 - 12.0)	7.0 (4.0 - 12.0)	7.0 (4.0 - 13.0)	0.22	0.0078	0.15
Days to death, median (IQR)	8.0 (4.0 - 15.0)	8.0 (4.5 - 16.0)	10.0 (5.0 - 17.0)	6.0 (4.0 - 14.0)	0.0052	<.0001	0.18
Total mortality	765 (9.4%)	247 (9.3%)	222 (9.5%)	296 (9.5%)	0.84	0.96	0.78

Race is unknown in all commercially insured enrollees.

** Cells with values < 11 were suppressed in accordance with the Centers for Medicare and Medicare Services cell size suppression policy for values from 1 to 10.

Table S6. Odds ratios for falsification endpoints by exposure and insurance type in primary outpatient cohort.

	Falsification Endpoint	Overall		Medicare		Commercial	
		N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)
ACE inhibitor vs Other	Absent kidney	*	NA	*	NA	*	NA
	Acid reflux	59 vs 80	0.70 (0.48–1.00); 0.053	46 vs 42	1.11 (0.71–1.75); 0.64	11 vs 23	0.43 (0.20–0.92); 0.030
	Anal and rectal polyps	*	NA	*	NA	*	NA
	Herpes zoster without complications	*	NA	*	NA	*	NA
	Ingrowing nail	10 vs 12	0.83 (0.35–1.94); 0.67	7 vs 12	0.57 (0.22–1.48); 0.25	*	NA
	Late effects of motor vehicle accident	*	NA	*	NA	*	NA
	Nicotine dependence	7 vs 9	0.77 (0.29–2.10); 0.61	7 vs 6	1.17 (0.39–3.53); 0.78	3 vs 7	0.41 (0.10–1.64); 0.21
	Pain in wrist	11 vs 7	1.59 (0.61–4.13); 0.34	8 vs 6	1.34 (0.46–3.92); 0.59	*	NA
	Presbyopia	22 vs 22	1.00 (0.55–1.83); 1.00	18 vs 19	0.94 (0.49–1.84); 0.87	5 vs 1	5.16 (0.59–44.81); 0.14
	Strain of rotator cuff capsule	*	NA	*	NA	*	NA
	Wrist drop	*	NA	*	NA	*	NA
ARB vs Other	Absent kidney	*	NA	*	NA	*	NA
	Acid reflux	55 vs 70	0.75 (0.51–1.10); 0.15	43 vs 42	1.03 (0.65–1.63); 0.91	17 vs 23	0.70 (0.35–1.38); 0.30
	Anal and rectal polyps	*	NA	*	NA	*	NA
	Herpes zoster without complications	*	NA	*	NA	*	NA

	Ingrowing nail	7 vs 12	0.58 (0.22–1.48); 0.25	10 vs 8	1.26 (0.49–3.24); 0.63	*	NA
	Late effects of motor vehicle accident	*	NA	*	NA	*	NA
	Nicotine dependence	7 vs 14	0.49 (0.20–1.23); 0.13	5 vs 7	0.71 (0.22–2.26); 0.56	3 vs 7	0.41 (0.10–1.64); 0.21
	Pain in wrist	7 vs 9	0.77 (0.29–2.10); 0.61	5 vs 4	1.25 (0.33–4.72); 0.74	*	NA
	Presbyopia	15 vs 22	0.67 (0.34–1.31); 0.24	14 vs 16	0.87 (0.42–1.81); 0.71	*	NA
	Strain of rotator cuff capsule	*	NA	*	NA	*	NA
	Wrist drop	*	NA	*	NA	*	NA
	Absent kidney	*	NA	*	NA	*	NA
	Acid reflux	70 vs 86	0.79 (0.56–1.11); 0.17	54 vs 58	0.92 (0.61–1.38); 0.68	15 vs 28	0.50 (0.26–0.97); 0.040
	Anal and rectal polyps	*	NA	*	NA	*	NA
	Herpes zoster without complications	*	0.50 (0.09–2.73); 0.42	*	NA	*	NA
	Ingrowing nail	11 vs 9	1.23 (0.50–2.98); 0.65	10 vs 11	0.91 (0.38–2.16); 0.82	*	NA
ACE inhibitor vs ARB	Late effects of motor vehicle accident	*	NA	*	NA	*	NA
	Nicotine dependence	13 vs 7	1.88 (0.74–4.74); 0.18	8 vs 5	1.61 (0.52–4.98); 0.41	5 vs 2	2.54 (0.49–13.21); 0.27
	Pain in wrist	11 vs 11	1.00 (0.43–2.32); 1.00	6 vs 8	0.75 (0.26–2.17); 0.59	*	NA
	Presbyopia	32 vs 21	1.55 (0.89–2.73); 0.12	22 vs 21	1.05 (0.57–1.95); 0.87	7 vs 1	7.20 (0.88–59.01); 0.066
	Strain of rotator cuff capsule	*	NA	*	NA	*	NA

Wrist drop	*	NA	*	NA	*	NA

NA = Not Applicable. Odds Ratios were not calculated when ≤5 patients in each group had a claim relating to the falsification endpoint.

Table S7. Secondary outcome of in-hospital mortality in the primary outpatient cohort of SARS-CoV-2 positive patients.

	Number of patients in matched groups		In-hospital death events in matched groups		In-hospital mortality
Comparison Group	**Treatment Group**	**Control Group**	**Treatment Group**	**Control Group**	**Adjusted Hazard Ratio (95% CI; P-value)**
Overall population					
ACE inhibitor vs Other	441	441	7	9	0.71 (0.25, 2.03); 0.52
ARB vs Other	412	412	4	8	0.48 (0.14, 1.66); 0.24
ACE inhibitor vs ARB	591	591	7	7	1.12 (0.36, 3.47); 0.84
Medicare Advantage					
ACE inhibitor vs Other	296	296	6	8	0.68 (0.23, 2.03); 0.49
ARB vs Other	283	283	6	7	0.78 (0.25, 2.41); 0.67
ACE inhibitor vs ARB	352	352	4	7	0.50 (0.13, 1.87); 0.30

ACE: angiotensin converting enzyme
ARB: Angiotensin II receptor blocker
CI: confidence interval

Table S8. Association of ACE inhibitor and ARB therapy on in-hospital mortality or discharge to hospice care in the primary COVID-19 inpatient cohort.

	In-hospital Mortality	Survival to Discharge
Comparison Group	**Hazard Ratio (95% CI, P-value)**	**Hazard Ratio (95% CI, P-value)**
Overall population		
ACE inhibitor vs Other	0.90 (0.76, 1.07); 0.23	1.03 (0.95, 1.13); 0.48
ARB vs Other	1.08 (0.91, 1.28); 0.41	1.04 (0.96, 1.14); 0.40
ACE inhibitor vs ARB	0.85 (0.73, 1.00); 0.043	1.04 (0.96, 1.13); 0.32
Medicare Advantage		
ACE vs Other	0.90 (0.76, 1.07); 0.22	1.08 (0.99, 1.19); 0.083
ARB vs Other	1.09 (0.92, 1.30); 0.31	1.03 (0.93, 1.13); 0.60
ACE vs ARB	0.86 (0.73, 1.01); 0.073	1.05 (0.96, 1.15); 0.25

ACE: angiotensin converting enzyme
ARB: Angiotensin II receptor blocker
CI: confidence interval
COVID-19: Coronavirus disease 2019

Table S9. Length of stay (median days, IQR) for primary COVID-19 inpatient cohort after propensity score matching.

	Died or Survived			Died			Survived		
Comparison Group	**Both**	**Treatment**	**Control**	**Both**	**Treatment**	**Control**	**Both**	**Treatment**	**Control**
Overall Population									
ACE vs Other	6.0 (3.0–11.0)	6.0 (3.0–10.0)	7.0 (3.0–11.0)	6.0 (3.0–10.0)	7.0 (3.0–10.0)	5.0 (2.0–9.0)	6.0 (3.0–9.0)	6.0 (3.0–9.0)	6.0 (3.0–10.0)
ARB vs Other	6.0 (3.0–11.0)	6.0 (3.0–11.0)	6.0 (3.0–11.0)	6.0 (3.0–11.0)	7.0 (3.0–12.0)	4.0 (2.0–9.0)	6.0 (3.0–10.0)	6.0 (3.0–10.0)	6.0 (3.0–10.0)
ACE vs ARB	6.0 (3.0–11.0)	6.0 (3.0–11.0)	6.0 (3.0–11.0)	6.0 (3.0–11.0)	6.0 (3.0–10.8)	7.0 (3.0–12.0)	6.0 (3.0–10.0)	6.0 (3.0–9.0)	6.0 (3.0–10.0)
Medicare Advantage									
ACE vs Other	7.0 (3.0–11.0)	7.0 (3.0–11.0)	6.5 (3.0–11.0)	6.0 (3.0–10.0)	7.0 (3.0–10.0)	5.0 (3.0–10.0)	6.0 (3.0–10.0)	6.0 (3.0–9.0)	6.0 (3.0–10.0)
ARB vs Other	7.0 (3.0–12.0)	6.0 (3.0–12.0)	7.0 (3.0–12.0)	6.0 (3.0–11.0)	7.0 (3.0–13.0)	5.0 (3.0–11.0)	6.0 (3.0–10.0)	6.0 (3.0–10.0)	6.0 (3.0–10.0)
ACE vs ARB	6.0 (3.0–11.0)	6.0 (3.0–11.0)	6.0 (3.0–11.0)	7.0 (3.0–12.0)	6.0 (3.0–11.0)	7.0 (3.0–12.0)	6.0 (3.0–10.0)	6.0 (3.0–10.0)	6.0 (3.0–10.0)

ACE: angiotensin converting enzyme
ARB: Angiotensin II receptor blocker
COVID-19: Coronavirus disease 2019
IQR: Interquartile range

Table S10. Odds ratios for falsification endpoints by exposure and insurance type, primary inpatient cohort.

	Falsification Endpoint	Overall Population		Medicare	
		N	OR (95% CI)	N	OR (95% CI)
ACE inhibitor vs Other	Absent kidney	4 vs 4	0.33 (0.078, 1.10); P=0.076	*	NA
	Acid reflux	340 vs 387	0.97 (0.81, 1.18); P=0.82	338 vs 357	1.08 (0.89, 1.32); P=0.44
	Anal/rectal polyps	*	NA	*	NA
	Herpes zoster without complications	27 vs 27	0.78 (0.32, 1.87); P=0.69	28 vs 28	0.71 (0.28, 1.73); P=0.54
	Ingrowing nail	95 vs 102	1.12 (0.81, 1.56); P=0.52	98 vs 106	1.12 (0.79, 1.58); P=0.56
	Late effects of motor vehicle accident	7 vs 9	0.75 (0.11, 4.44); P=1.00	7 vs 8	2.00 (0.28, 22.16); P=0.69
	Nicotine dependence	65 vs 71	1.45 (1.01, 2.07); P=0.040	61 vs 65	1.59 (1.08, 2.35); P=0.016
	Pain in wrist	49 vs 53	0.62 (0.38, 1.02); P=0.061	48 vs 51	0.64 (0.38, 1.09); P=0.11
	Presbyopia	124 vs 122	0.94 (0.67, 1.30); P=0.75	121 vs 121	0.84 (0.60, 1.17); P=0.33
	Strain of rotator cuff capsule	*	NA	*	NA
	Wrist drop	*	NA	*	NA
ARB vs Other	Absent kidney	5 vs 6	1.18 (0.49, 2.93); P=0.84	3 vs 5	1.00 (0.39, 2.55); P=1.00
	Acid reflux	342 vs 335	1.13 (0.93, 1.37); P=0.21	311 vs 292	1.12 (0.92, 1.37); P=0.28
	Anal/rectal polyps	*	NA	*	NA
	Herpes zoster without complications	17 vs 15	0.66 (0.29, 1.46); P=0.36	19 vs 16	0.91 (0.34, 2.36); P=1.00
	Ingrowing nail	74 vs 90	1.2 (0.83, 1.70); P=0.39	69 vs 81	1.21 (0.85, 1.73); P=0.30
	Late effects of motor vehicle accident	9 vs 8	0.83 (0.20, 3.28); P=1.00	1 vs 4	1.00 (0.19, 5.38); P=1.00
	Nicotine dependence	43 vs 43	1.03 (0.71, 1.52); P=0.93	39 vs 35	1.12 (0.75, 1.71); P=0.62
	Pain in wrist	47 vs 52	0.89 (0.54, 1.46); P=0.72	45 vs 43	0.76 (0.46, 1.24); P=0.29
	Presbyopia	115 vs 111	0.77 (0.54, 1.10); P=0.16	109 vs 111	0.89 (0.62, 1.29); P=0.59
	Strain of rotator cuff capsule	5 vs 3	NA	*	NA

	Wrist drop	*	NA	*	NA
	Absent kidney	6 vs 6	0.37 (0.12, 1.01); P=0.052	3 vs 7	0.36 (0.10, 1.00); P=0.062
	Acid reflux	352 vs 403	0.87 (0.731, 1.05); P=0.15	334 vs 370	0.90 (0.75, 1.10); P=0.31
	Anal/rectal polyps	*	NA	*	NA
	Herpes zoster without complications	20 vs 20	0.94 (0.46, 1.95); P=1	15 vs 15	1.00 (0.43, 2.30); P=1.00
	Ingrowing nail	89 vs 77	0.91 (0.66, 1.25); P=0.58	91 vs 79	0.84 (0.61, 1.16); P=0.30
ACE inhibitor vs ARB	Late effects of motor vehicle accident	10 vs 8	0.71 (0.18, 2.62); P=0.77	9 vs 7	1.25 (0.27, 6.31); P=1.00
	Nicotine dependence	53 vs 53	1.3 (0.91, 1.75); P=0.17	43 vs 46	1.33 (0.93, 1.90); P=0.12
	Pain in wrist	47 vs 51	0.75 (0.46, 1.20); P=0.25	48 vs 52	0.70 (0.41, 1.16); P=0.18
	Presbyopia	144 vs 138	0.87 (0.62, 1.22); P=0.45	133 vs 126	0.89 (0.63, 1.26); P=0.56
	Strain of rotator cuff capsule	*	0.80 (0.16, 3.72); P=1.00	*	NA
	Wrist drop	*	NA	*	NA

NA = Not Applicable; Odds Ratios not calculated when ≤5 patients in each group had a claim relating to the falsification endpoint.

Table S11. Hazard ratio for hospitalization among individuals testing positive for SARS-CoV-2 in the primary outpatient cohort, where control arm uses first-line antihypertensive drugs only.

Comparison Group	Treatment	Control	Matched	Hospitalization Hazard Ratio (95% CI, P-value)	Equipoise Metric
Overall population					
ACE inhibitor vs Other	722	511	364	0.75 (0.48, 1.17); 0.20	0.66
ARB vs Other	731	511	366	0.80 (0.54, 1.17); 0.25	0.60
ACE inhibitor vs ARB	722	731	589	0.88 (0.63, 1.23); 0.46	0.94
Medicare Advantage					
ACE vs Other	434	352	249	0.56 (0.35, 0.90); 0.016	0.66
ARB vs Other	452	352	245	0.81 (0.53, 1.24); 0.34	0.62
ACE vs ARB	434	452	350	0.91 (0.60, 1.39); 0.67	0.92

ACE: angiotensin converting enzyme
ARB: Angiotensin II receptor blocker
CI: Confidence interval

Table S12. Hazard ratio for mortality in primary cohort of hospitalized COVID-19 patients, where control arm uses first-line antihypertensive drugs only.

Comparison Group	Treatment	Control	Matched	Mortality Hazard Ratio (95% CI, P-value)	Survival Hazard Ratio (95% CI, P-value)	Equipoise Metric
Overall population						
ACE inhibitor vs Other	2360	1807	1465	0.96 (0.79, 1.17); 0.70	1.00 (0.91, 1.10); 0.95	0.76
ARB vs Other	2224	1807	1360	1.01 (0.83, 1.23); 0.91	0.98 (0.89, 1.08); 0.66	0.67
ACE inhibitor vs ARB	2360	2224	1878	0.89 (0.75, 1.05); 0.16	1.03 (0.95, 1.12); 0.52	0.95
Medicare Advantage						
ACE vs Other	2151	1674	1352	0.86 (0.70, 1.05); 0.13	1.02 (0.92, 1.12); 0.75	0.77
ARB vs Other	1989	1674	1248	1.08 (0.89, 1.31); 0.44	0.95 (0.86, 1.06); 0.40	0.68
ACE vs ARB	2151	1989	1707	0.83 (0.70, 0.99); 0.036	1.03 (0.94, 1.12); 0.55	0.95

ACE: angiotensin converting enzyme
ARB: Angiotensin II receptor blocker
CI: Confidence interval
COVID-19: Coronavirus disease 2019

Table S13. Unadjusted hazard ratio for hospitalization in primary cohort of outpatient SARS-CoV-2 positive patients.

Comparison Group	Matched Size	Hospitalization Hazard Ratio (95% CI, P-value)	Equipoise Metric
Overall population			
ACE inhibitor vs other	441	0.78 (0.54, 1.14); 0.20	0.54
ARB vs other	412	0.86 (0.60, 1.22); 0.39	0.46
ACE inhibitor vs ARB	591	0.90 (0.64, 1.27); 0.55	0.94
Medicare Advantage			
ACE inhibitor vs other	296	0.64 (0.42, 0.97); 0.037	0.55
ARB vs other	283	0.88 (0.58, 1.33); 0.54	0.49
ACE inhibitor vs ARB	352	0.86 (0.56, 1.33); 0.50	0.92

ACE: angiotensin converting enzyme
ARB: Angiotensin II receptor blocker
CI: Confidence interval

Table S14. Unadjusted hazard ratio for mortality in primary cohort of hospitalized COVID-19 patients.

Comparison Group	Treatment	Control	Matched	Mortality Hazard Ratio (95% CI, P-value)	Survival to Discharge Hazard Ratio (95% CI, P-value)	Equipoise Metric
Overall population						
ACE inhibitor vs Other	2360	3338	1731	0.98 (0.82, 1.18); 0.85	1.02 (0.94, 1.11); 0.62	0.56
ARB vs Other	2224	3338	1560	1.13 (0.94, 1.36); 0.20	1 (0.91, 1.09); 0.98	0.46
ACE inhibitor vs ARB	2360	2224	1882	0.90 (0.76, 1.07); 0.23	1.04 (0.95, 1.13); 0.39	0.95
Medicare Advantage						
ACE vs Other	2151	3145	1580	0.91 (0.75, 1.09); 0.29	1.03 (0.94, 1.13); 0.49	0.56
ARB vs Other	1989	3145	1425	1.20 (0.99, 1.45); 0.060	1.00 (0.91, 1.10); 0.97	0.46
ACE vs ARB	2151	1989	1704	0.89 (0.75, 1.06); 0.19	1.01 (0.93, 1.11); 0.77	0.95

ACE: Angiotensin converting enzyme
ARB: Angiotensin II receptor blocker
CI: Confidence interval
COVID-19: Coronavirus disease 2019

Table S15. Studies evaluating the association of the use of ACE inhibitor and ARBs with COVID-19 severity and mortality.

Author (Year)	Country	Centers	Study Population	N	Outcomes	Cofounder Adjustment	Odds/Hazard Ratios (95% Confidence interval) or Observed %
de Abajo (2020) [12]	Spain	Multicenter	All-comers	1,139	Hospitalization	(+)	No association with COVID-19 hospitalization among any RAAS user, ACE inhibitor user, or ARB user. **Hospitalization** All RAAS: 0.94 (0.77–1.15) ACE: 0.80 (0.64–1.00) ARB: 1.10 (0.88–1.37)
Reynolds (2020) [13]	USA	Single center	All-comers; Hypertension	12,592; 1,002	SARS-CoV-2 infection; COVID-19 severity	(+)	No association with likelihood of positive PCR test in the ACE/ARB, ACE inhibitor, or ARB groups among all matched patients (+/- Hypertension). Similar findings for the Hypertension cohort. **SARS-CoV-2 infection** ACE/ARB: 0.5% (−2.6% to 3.6%) ACE: −2.5% (−6.7% to 1.6%) ARB: 2.2% (−1.9% to 6.3%) No association with ACE/ARB, ACE or ARB use and percentage of people with severe COVID-19 illness (ICU, ventilation, death) among All-comers (+/- Hypertension). Similar findings for the Hypertension cohort. **COVID-19 severity** ACE/ARB: −0.1% (−3.7% to 3.5%) ACE: −1.9% (−6.6% to 2.8%) ARB: −1.4% (−6.1% to 3.3%)

Zhang (2020) [24]	China	Multicenter	Hypertension	1,128	Mortality	(+)	Lower risk of all-cause mortality was associated with in-hospital ACE/ARB use in hospitalized COVID-19 patients with Hypertension compared to those not receiving in-hospital ACE inhibitor or ARB. **mortality** ACE/ARB: 0.37 [95% CI, 0.15–0.89]; *P*=0.03)
Mehta (2020) [25]	USA	Multicenter	All-comers	18,472	SARS-CoV-2 infection	(+)	No association was found with ACE/ARB use and the likelihood of a positive SARS-CoV-2 test. **SARS-CoV-2 infection** ACE/ARB: 0.97 (0.81-1.15)
Fosbøl (2020) [36]	Denmark	Multicenter	All-comers; Hypertension	4,480 **;** 571	Mortality; COVID-19 diagnosis	(+)	No association was observed with prior ACE/ARB use and COVID-19 mortality among All-comers (+/- Hypertension) compared to non-users. **Mortality** ACE/ARB: 0.83 (0.67-1.03); 0.09 No association was observed with ACE/ARB use and COVID-19 diagnosis compared with users of other antihypertensives. **COVID-19 diagnosis** ACE/ARB: 1.05 (0.80-1.36); 0.67 ACE: 0.85 (0.70-1.01); 0.08 ARB: 1.15 (0.96-1.37); P=0.11
Bean (2020) [37]	United Kingdom	Multicenter	All-comers	1,200	Mortality/ICU admission	(+)	Prior ACE/ARB was associated with reduced mortality or ICU admission compared to non-users. **Mortality/ICU** ACE/ARB: 0.63 (0.47 – 0.84); P < 0.01 0.63 (95% con□dence interval 0.47–0.84, P < 0.01

Morales (2020) [10]	Spain & USA	Multicenter	Hypertension	612,700	COVID-19 diagnosis; COVID-19 Hospitalization; Hospitalization with pneumonia; Hospitalization with pneumonia, ARDS, AKI, or sepsis.	(+)	No significant difference in COVID-19 diagnosis was associated with meta-analytic HRs after propensity scoring stratification or matching for any set of mono- and combination therapy drug comparisons to other first-line antihypertensive drugs. **COVID-19 diagnosis** ACE/ARB as monotherapy: 0.98 (0.84 - 1.14); 0.76 ACE/ARB with combination: 1.01 (0.90 - 1.15); 0.81 ACE monotherapy: 0.91 (0.68 - 1.21); 0.51 ARB monotherapy: 1.10 (0.89 - 1.35); 0.40 No associations between COVID-19 hospitalization, pneumonia hospitalization, or pneumonia/ARDS/AKI/sepsis were observed for any of the meta-analytic HRs in the drug comparisons.
Meng (2020) [31]	China	Single center	Hypertension	42	COVID-19 severity	(-)	A smaller proportion of those taking ACE/ARBs were categorized as having severe COVID-19 as compared to other antihypertensive drugs. **COVID-19 severity** ACE/ARB: 25.5% vs 48% of non-ACE/ARB group
Son (2020) [41]	South Korea	Multicenter	Hypertension	16,281	SARS-CoV-2 infection; COVID-19 severity	(+)	No association between risk of SARS-CoV-2 infection or COVID-19 severity (ICU admission or mortality) and RAAS inhibitor use was observed compared to non-users. **SARS-CoV-2 infection** RAAS: 1.161 (0.958–1.407); P > 0.05 **ICU admission** RAAS 1.515 (0.402–5.701) **Mortality** RAAS: 1.363 (0.513–3.662)
Xu (2020) [42]	China	Single center	Hypertension	101	Mortality; ICU admission; ventilation	(-)	No association of prior or in-hospital ACE/ARB use observed with death, ICU admission, or mechanical ventilation when compared to those using other antihypertensives. **Mortality**

							ACE/ARB: 0.73 (0.29–1.82); P= 0.4994 **ICU Admission** ACE/ARB: 0.65 (0.25–1.70); 0.3798 **Mechanical ventilation** ACE/ARB: 0.87 (0.31–2.43); P= 0.79
López-Otero (2020) [43]	Spain	Single center	All-comers	965	Mortality; heart failure; Hospitalization; ICU admission; MACE	(+)	No association between prior use of ACE/ARB was found with mortality, heart failure, hospitalization, ICU admission, or MACE when compared to non-users. **Mortality** ACE/ARB: 0.62 (0.17-2.26); .486) **Heart failure** ACE/ARB: 1.37 (0.39-4.77); .622 **Hospitalization** ACE/ARB: 0.85 (0.45-1.64); .638 **ICU admission** ACE/ARB: 0.87 (0.30-2.50); .798 **Major adverse cardiovascular events (MACE)** AE/ARB: 1.06 (0.39-2.83); .915
Amat-Santos (2020) [44]	Spain	Multicenter	post-TAVR	102	COVID-19 diagnosis	RCT	No association between use of the ACE inhibitor ramipril and COVID-19 diagnosis (1.150 [0.351 - 3.768]; NR) compared to non-RAAS users.
Felice (2020) [45]	Italy	Single center	Hypertension	133	COVID-19 Hospitalization; oxygen; non-invasive ventilation; ICU admission; Mortality;	(+)	ACE/ARB use was associated with a ***reduced rate of admission to intensive care*** compared to non-users. (0.25 [0.09-0.66]; P= 0.006) No association observed between ACE/ARB use or hospital admission, oxygen, non-invasive ventilation, or mortality.

							Hospital admission ACE/ARB: 0.39 (0.05-2.94); 0.365 **Oxygen use** ACE/ARB: 0.51 (0.15-1.78); 0.292 **Non-invasive ventilation** ACE/ARB: 0.58 (0.21-1.60); P= 0.296 **Mortality** ACE/ARB: 0.56 (0.17-1.83); 0.341
Yang (2020) [46]	China	Single center	All-comers; Hypertension	462	COVID-19 severity; Mortality	(-)	No association between the use of ACE/ARB and critical COVID-19 illness or mortality was observed. **COVID-19 severity** ACE/ARB: 9.3% versus 22.9%; *P*=0.061 **Mortality** AC/ARB: 4.7% versus 13.3%; *P*=0.216
Gao (2020) [47]	China	Single center	All-comers; Hypertension	2877; 710	Mortality	(+)	No difference in mortality was observed between RAAS users and non-users. A comparison of All-comers found that those with hypertension had an increased relative risk of mortality compared to those without. **Mortality** RAAS: 0.85 (0.28-2.58); 0.774
Bravi (2020) [48]	Italy	Multicenter	All-comers; Hypertension	1,603 ; 543	COVID-19 severity; Mortality/ICU admission	(-) ; (+)	In unadjusted analysis, All-comers with very severe or fatal COVID-19 were more likely to be treated with ACE/ARBs than those with mild disease. **COVID-19 mortality or ICU admission** ACE/ARB: 54.2% vs 19.1%; P < 0.001 Among those with Hypertension and adjusting for comorbidities, no association was observed between ACE/ARB use and likelihood of developing very severe/lethal COVID-19 compared to non-users **COVID-19 mortality or ICU admission**

							ACE/ARB: 0.87 (0.50–1.49); 0.6
Zhou (2020) [49]	China	Multicenter	All-comers; Hypertension	3,752	Mortality	(+)	Among All-comers, in-hospital use of ACE/ARB was associated with lower 28-day COVID-19 morality risk compared to non-users, with similar findings for a Hypertension cohort. **Mortality** ACE/ARB: 0.39 (0.26–0.58); *P*<0.001
Li (2020) [50]	China	Single center	Hypertension	362	COVID-19 severity; Mortality	(-)	Among those with hypertension hospitalized for COVID-19, there was no difference observed between rates of ACE/ARB use in those with severe vs non-severe disease, nor was there a difference in ACE/ARB use for COVID-19 survivors vs non-survivors. **COVID-19 severity** ACE/ARB: (32.9% vs 30.7%; *P* = .65) **Mortality** ACE/ARB: (27.3% vs 33.0%; *P* = .34)

Figure S1. Primary outpatient cohort selection flowsheet.

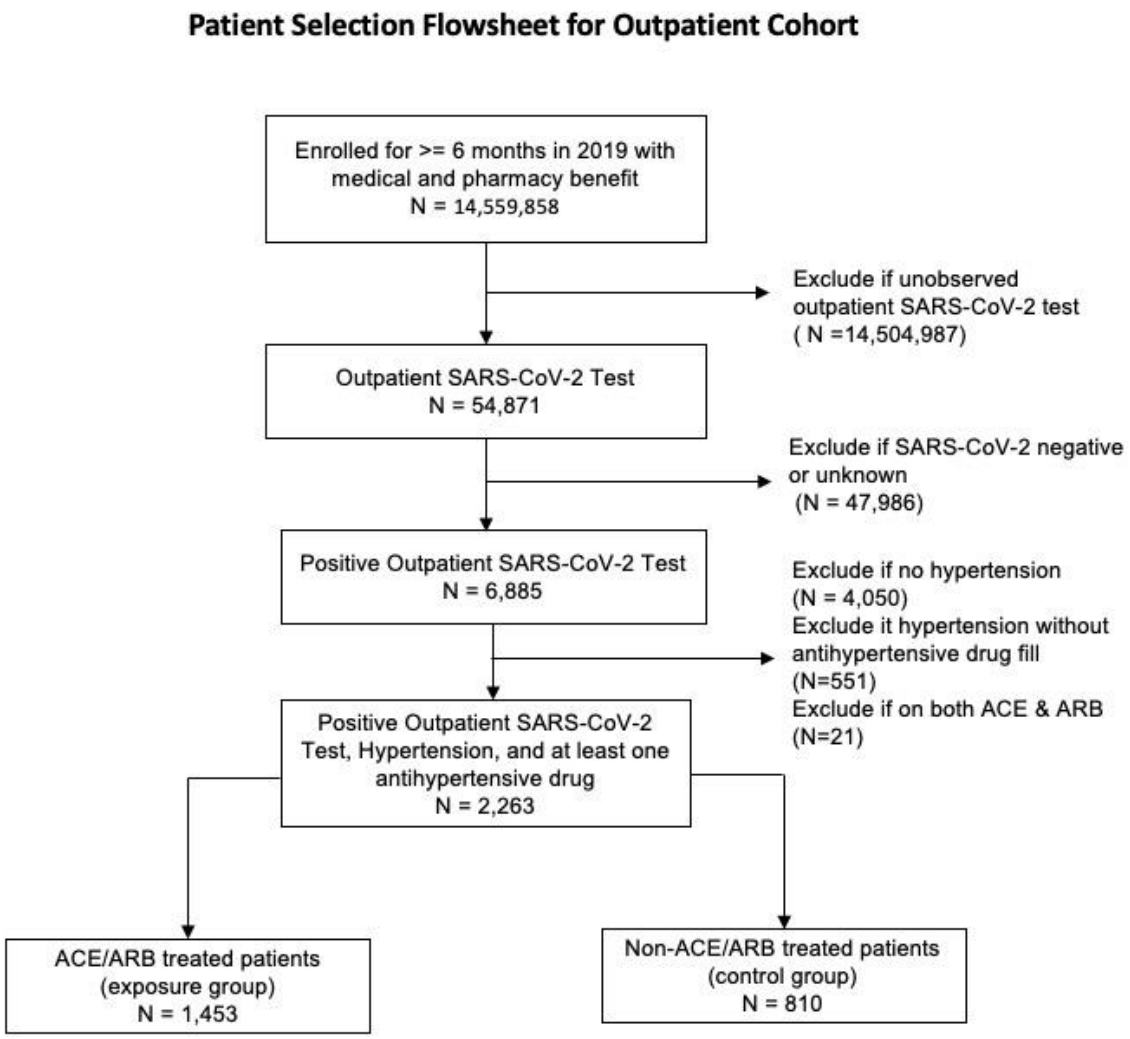


Figure S2. Primary inpatient cohort selection flowsheet.

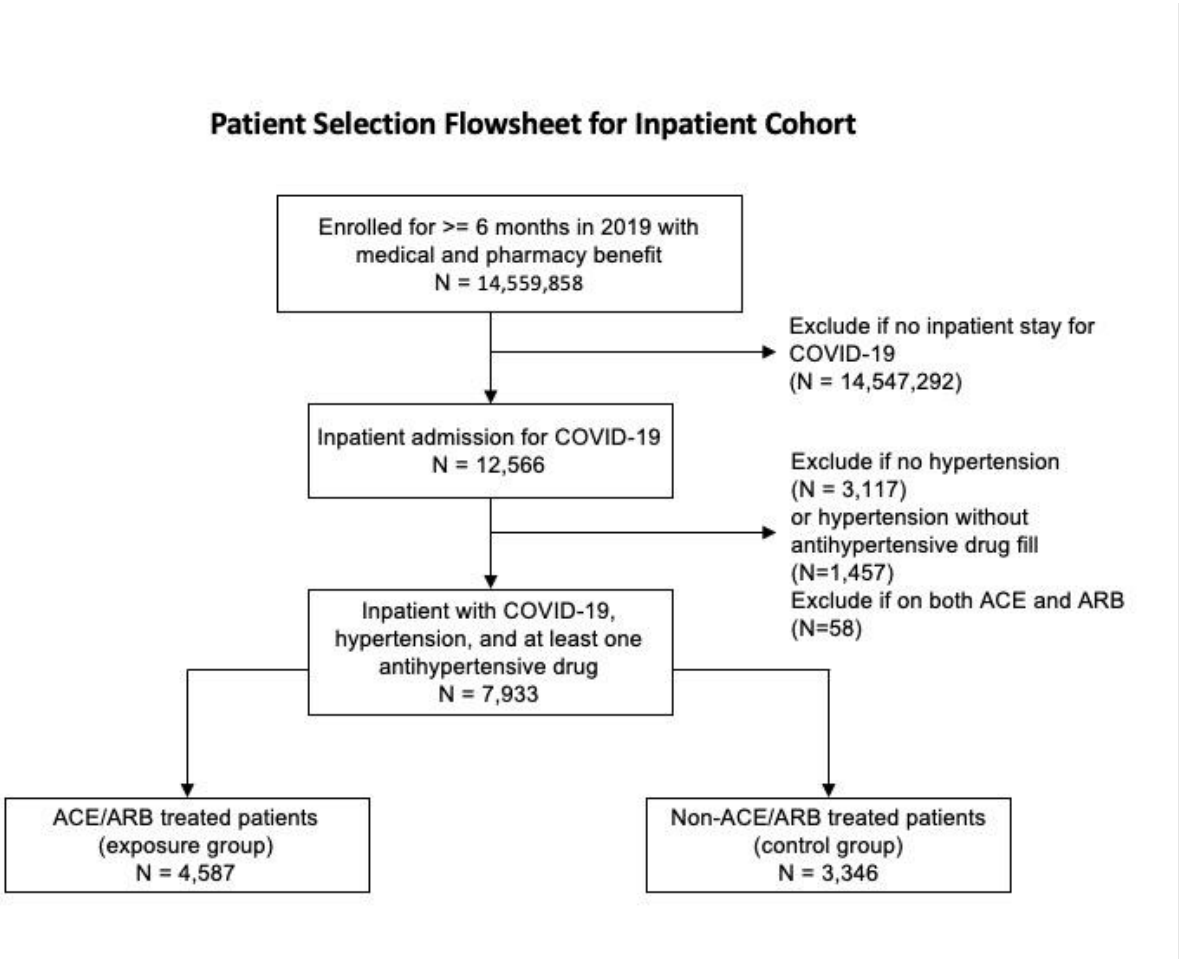
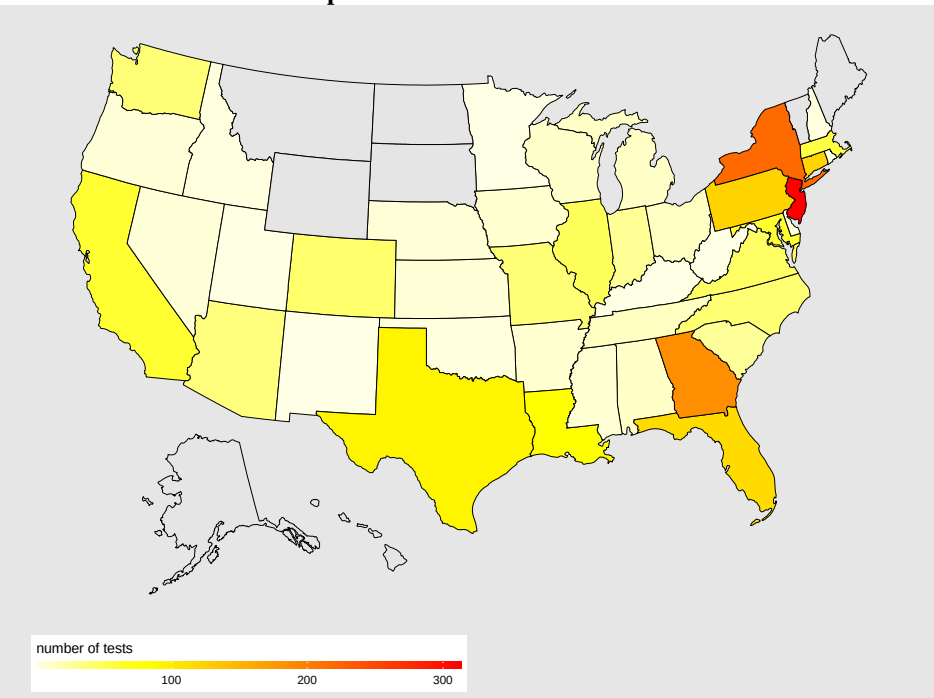


Figure S3. Distribution of individuals in the primary outpatient and inpatient cohorts.

(A) SARS-CoV-2 test geographic distribution: number of tests by state. Patients in 44 states were included based on a positive test.



(B) COVID-19 inpatient case distribution: number of inpatient cases by state. COVID-19 hospitalizations included in the study are represented in 47 states.

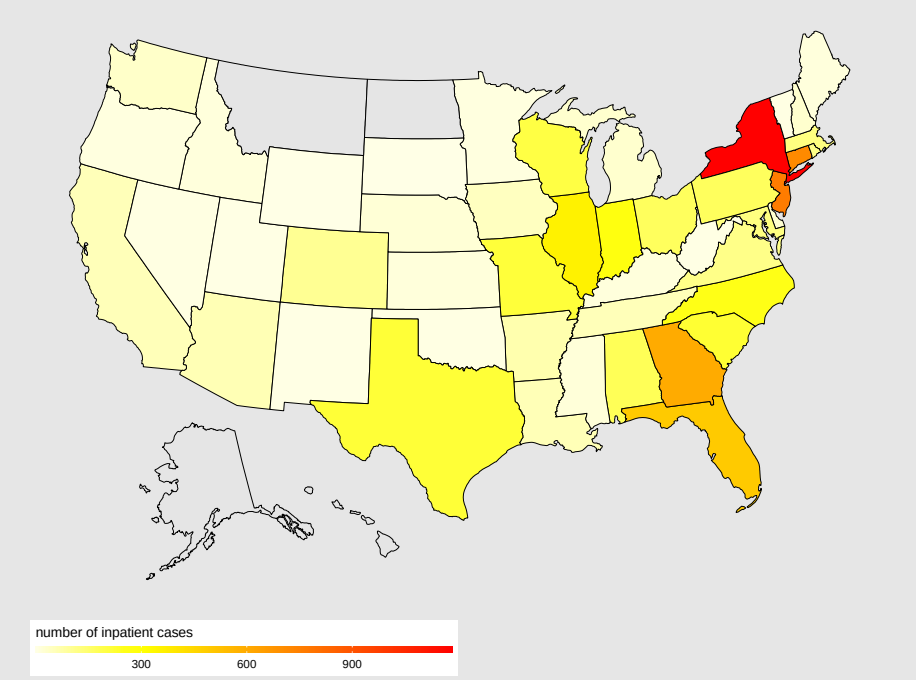
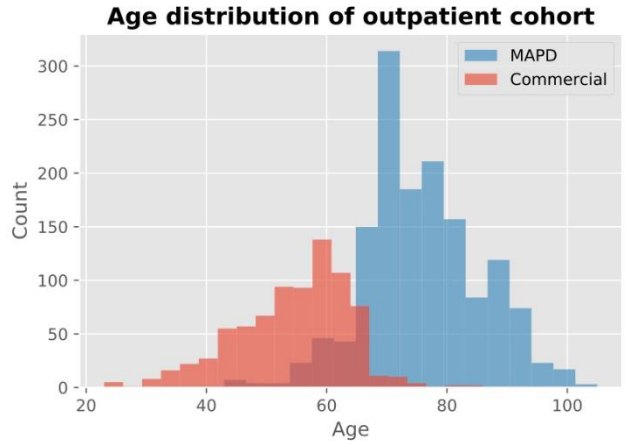
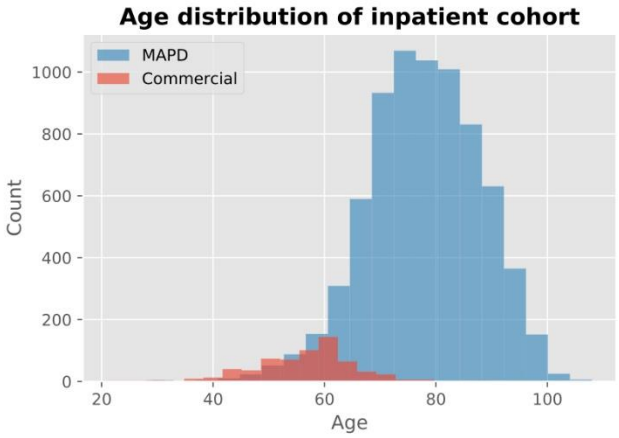

number of inpatient cases
300
600
900

Figure S4. Histogram of age distributions of primary outpatient and inpatient cohorts, stratified by insurance type.

(A) Histogram of age distribution of the outpatient cohort, Medicare Advantage verses Commercial



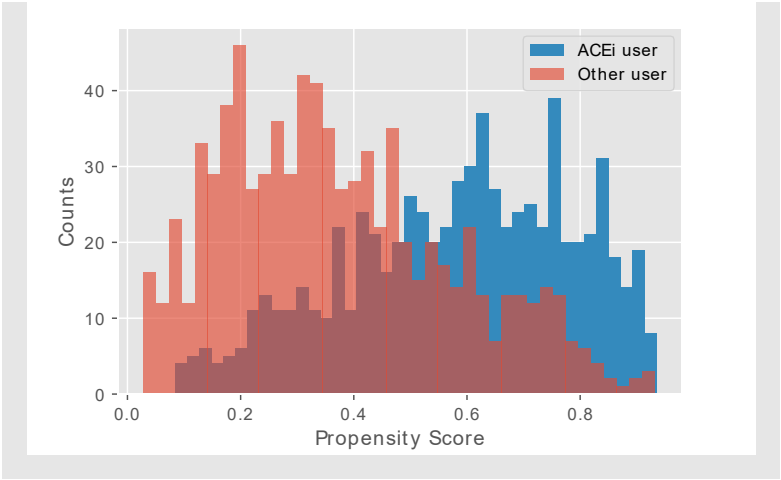
(B) Histogram of age distribution of the outpatient cohort, Medicare Advantage verses Commercial



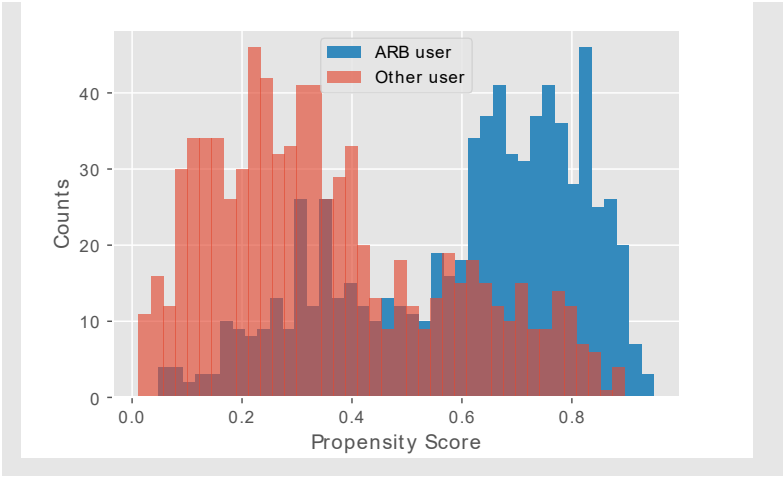
MAPD: Medicare Advantage with Part D coverage

Figure S5. Propensity score distributions for treatment comparisons in the primary outpatient cohort.

(A) ACE inhibitor vs others



(B) ARB vs others



(C) ACE inhibitor vs ARB

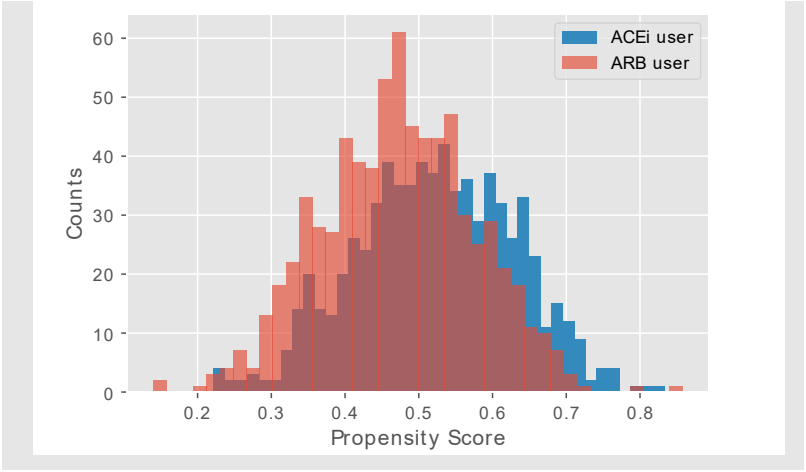
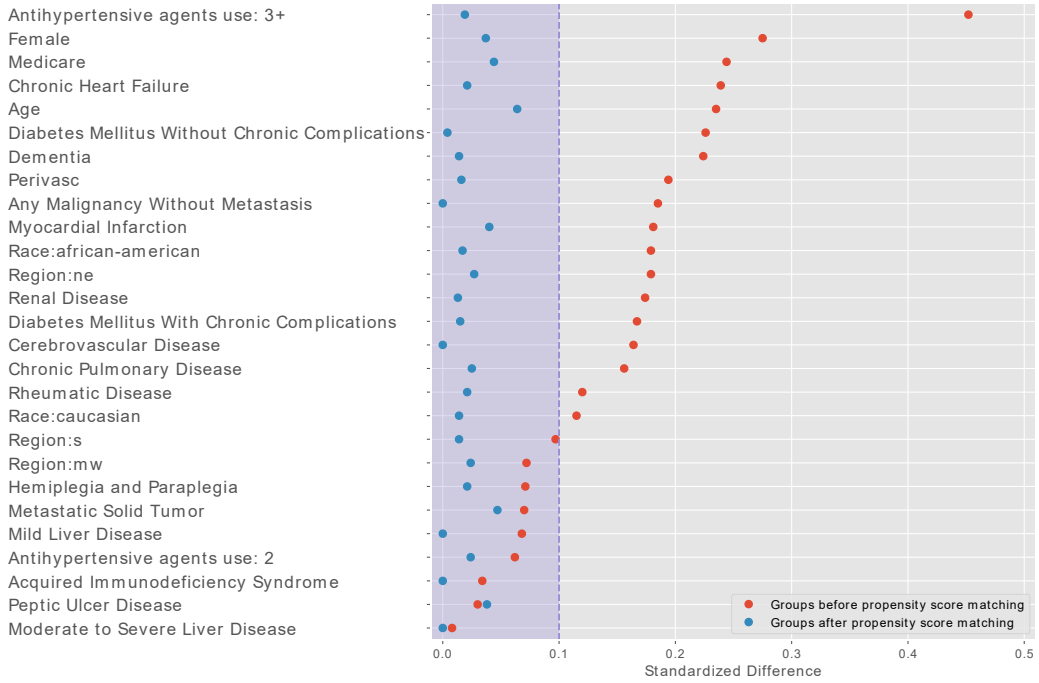


Figure S6. Standardized Differences Between Variables Before and After Propensity Matching.

(A) ACE Inhibitor vs Other Anti-hypertensive Agent: *Outpatient Cohort*



(B) ACE Inhibitor vs Other Anti-hypertensive Agent: *Inpatient Cohort*

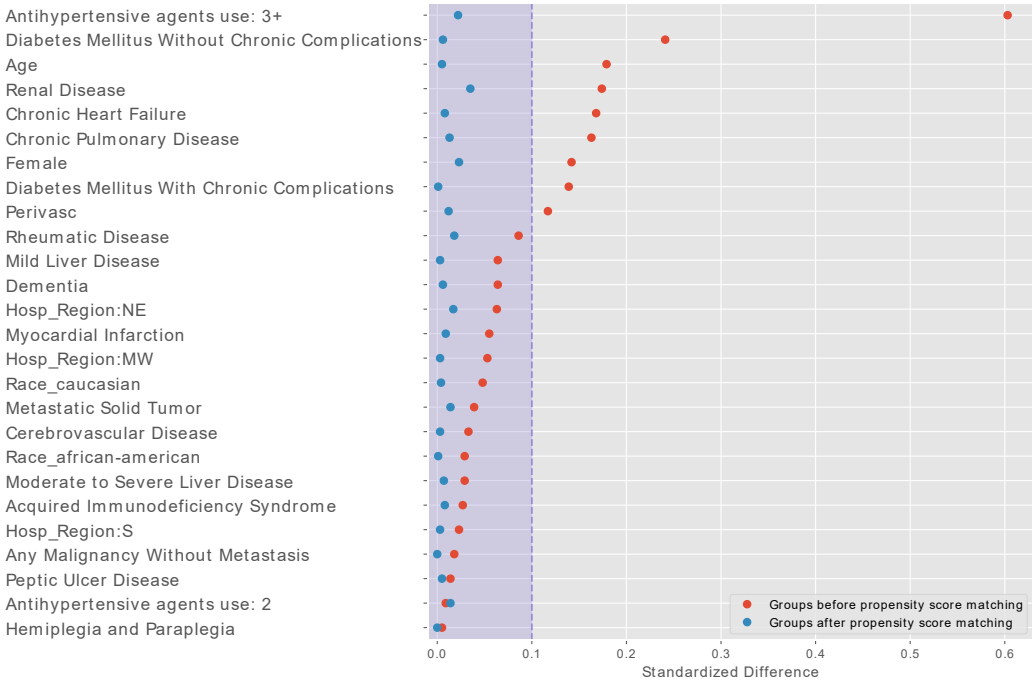
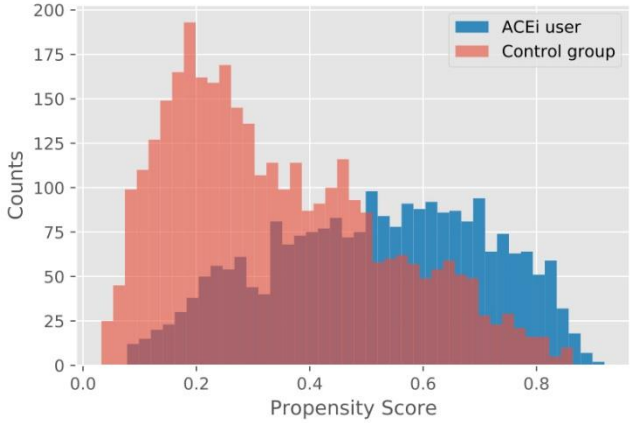
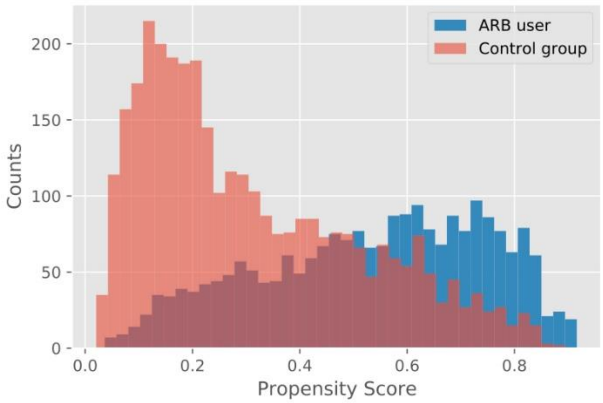


Figure S7. Propensity score distributions for treatment comparisons in the primary inpatient cohort.

(A) ACE inhibitor vs others



(B) ARB vs others



(C) ACE inhibitor vs ARB

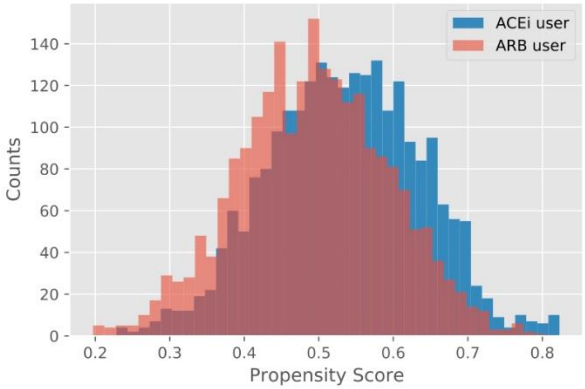
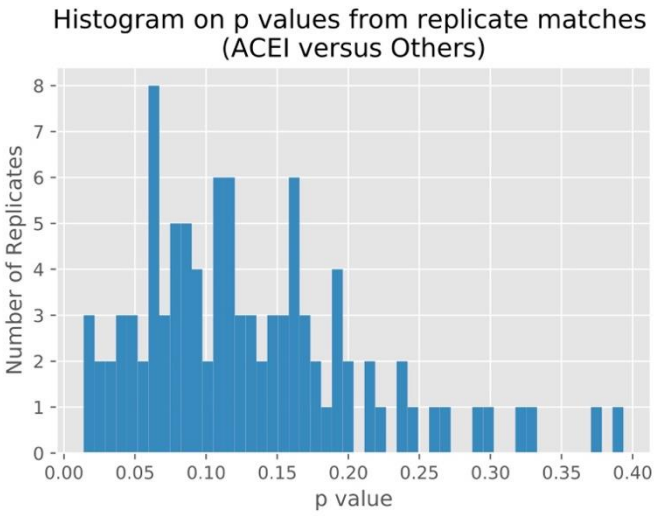
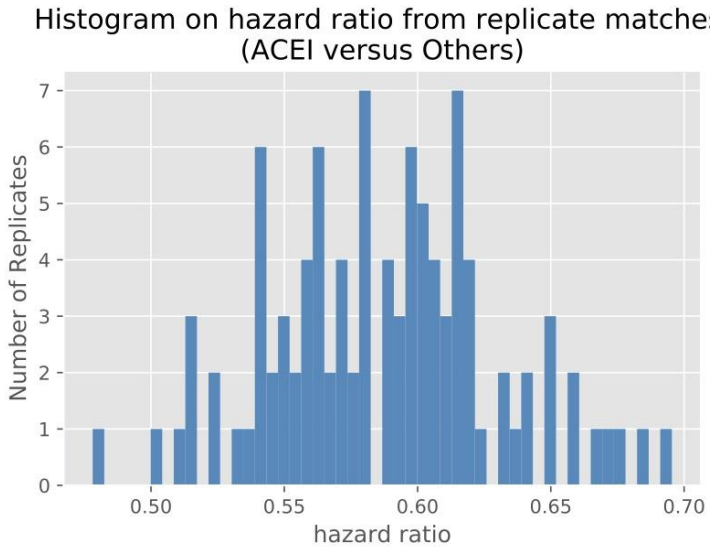


Figure S8. Histogram on p-values and adjusted hazard ratios from 100 matches, primary outpatient cohort.

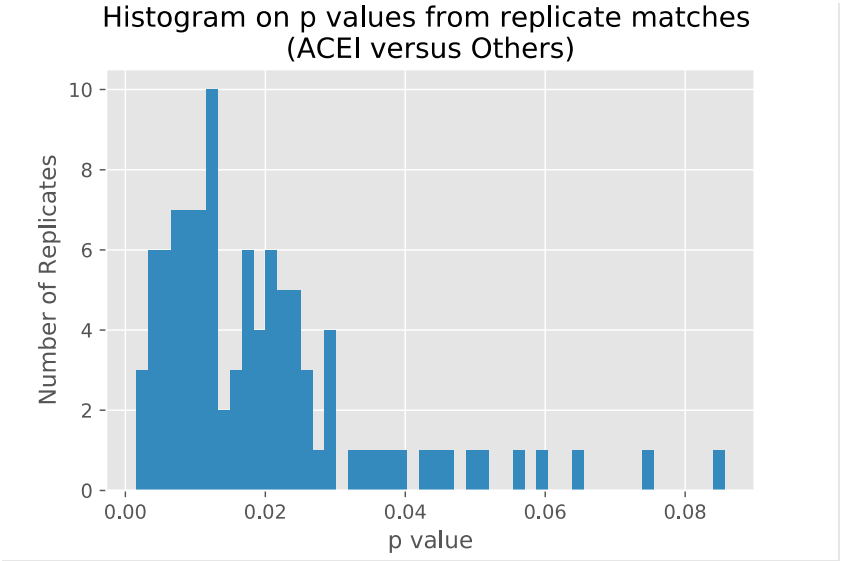
(A) ACE inhibitor versus others in full population, histogram of p-values



(B) ACE inhibitor versus others in the full population, histogram of hazard ratios



(C) ACE inhibitor versus others in Medicare Advantage population, histogram of p-values



(D) ACE inhibitor versus others in Medicare Advantage population, histogram of hazard ratios