ASSOCIATION OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS WITH THE RISK OF HOSPITALIZATION AND DEATH IN HYPTERTENSIVE PATIENTS WITH COVID-19

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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...
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,2,13 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. 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. 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 co-morbidities 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. A value >0.5 implies 2 drugs are in empirical equipoise, with a higher value indicating a lower likelihood of confounding by indication. Next, we evaluated whether our matching algorithm achieved a standardized difference of <10% between matched cohorts, suggestive of adequately matched groups. Third, we evaluated the success of our matching algorithm using negative control outcomes that are unlikely to be affected by the treatment assignment. 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 χ² 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. 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. 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 | 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                       | 406 (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       | 0.55                  |
| 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 (16.0%) | 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 | P Value |
|-----------------------------------|---------|-------------------------------|---------|
|                                   |         | ACE Inhibitor | ARB | Other | ACE Inhibitor vs Other | ARB vs Other | ACE Inhibitor vs ARB |
| 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 |
Table 1. Continued

| Variable                                      | Overall | Antihypertensive Drug Cohorts | P Value | 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 | 0.0003 |
| 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%) | 0.0020 | 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 |
risk, overall (HR in propensity-matched cohorts, ACE inhibitor, 0.98; 0.76–1.28; \( P=0.87 \); 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 | 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%) | 196 (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%) | 1430 (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)
| Variable                                             | Overall   | 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                |
| Variable                      | Overall | ACE Inhibitor | ARB       | Other       | ACE Inhibitor vs Other | ARB vs Other | ACE Inhibitor vs ARB |
|------------------------------|---------|---------------|-----------|-------------|------------------------|--------------|----------------------|
| Drug therapy                 |         |               |           |             |                        |              |                      |
| Antihypertensives            |         |               |           |             |                        |              |                      |
| **β-blockers**               | 4277    | 1112          | 1095      | 2070        | <0.0001                | <0.0001      | 0.17                 |
| **Nondihydropyridine**       | 3438    | 929           | 959       | 1550        | <0.0001                | 0.019        | 0.011                |
| Calcium channel blockers     | 2972    | 826           | 848       | 1298        | 0.0037                 | 0.62         | 0.031                |
| **Thiazide or thiazide-like**| 1650    | 512           | 702       | 436         | <0.0001                | <0.0001      | <0.0001              |
| **Loop diuretics**           | 2400    | 570           | 612       | 1218        | <0.0001                | <0.0001      | 0.010                |
| **Cenrally acting α-agonists**| 303     | 85            | 96        | 120         | 0.96                   | 0.14         | 0.19                 |
| **Potassium-sparing diuretics**| 112     | 21            | 22        | 69          | 0.00069                | 0.0028       | 0.85                 |
| **Mineralocorticoid**        | 435     | 93            | 135       | 207         | 0.00023                | 0.90         | 0.0012               |
| **Renin inhibitors**         | 0       | 0             | 0         | 0           | <0.0001                | <0.0001      | <0.0001              |
| **α-adrenergic blocking agents**| 247    | 70            | 76        | 101         | 0.97                   | 0.46         | 0.43                 |
| **Direct vasodilators**      | 515     | 110           | 159       | 246         | <0.0001                | 0.81         | 0.00044              |
| Place in therapy             |         |               |           |             |                        |              |                      |
| First-line                   | 6399    | 2361          | 2226      | 1812        | <0.0001                | <0.0001      | <0.0001              |
| Second-line                  | 5478    | 1405          | 1388      | 2685        | <0.0001                | <0.0001      | 0.052                |
| Number of antihypertensive classes |         |               |           |             |                        |              |                      |
| 1                            | 2322    | 442           | 312       | 1568        | <0.0001                | <0.0001      | <0.0001              |
| 2                            | 2625    | 850           | 692       | 1083        | 0.0047                 | 0.33         | 0.00048              |
| 3+                           | 2986    | 1069          | 1222      | 695         | <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    | 1528          | 1408      | 1836        | <0.0001                | <0.0001      | 0.32                 |
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...
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. 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. Of note, these receptors modulate the renin-angiotensin-aldosterone system, in the lung tissue. 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.

### 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 |
| | 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 |
| | 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 |
| 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 |
| | 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 |
| | 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 |

Pairwise comparisons from propensity score–matched cohorts. ACE indicates angiotensin-converting enzyme; and ARB, angiotensin receptor blocker.
of these mechanisms and endothelial damage.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{32,33}

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.

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.\textsuperscript{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.\textsuperscript{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.
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

| 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.
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.\textsuperscript{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.\textsuperscript{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

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**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.

**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
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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-appointee 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 co-founder of HughHealth, 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 PPime. Drs Lin, Saha, 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
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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 fulfill 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 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.
| Inclusion Criteria | ICD-10 Codes |
|--------------------|--------------|
| Hypertension       | I10%, I11%, I12%, I13%, I15%, I16%, I67.4, N26.2 |
| COVID-19           | U071, U072, B9729 |

| Charlson Comorbidity Indices | 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, 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, K252, K259, K277, K269, K256, K268, 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, 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, G030, G031, G300, G308, G309, G311 |
| **Renal Disease** | I120, I131, N032, N033, N034, N035, N036, N037, N052, N051, N054, N055, N056, N057, N181, N182, N183, N184, N185, N186, N189, N250, Z940, 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, I458, 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, C052, C058, C059, C060, C061, C062, C068, C069, C080, C081, C083, C088, C089, C090, C091, C095, C098, C099,
C100, C101, C102, 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, C186, C187, C188, C189, C190, C195, C197, C199, C200, C202, C203, C207, C210, C211, C212, C218, C220, C221, C222, C223, C224, C227, 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, C342, C343, C345, C346, C347, C348, C349, C350, C351, C353, C354, C355, C356, C357, C358, C359, C360, C361, C362, C364, C365, C366, C368, C369, C370, C371, C372, C373, C374, C375, C376, C377, C378, C379, C380, C381, C382, C383, C384, C385, C386, C387, C388, C389, C390, C391, C392, C399, C400, C401, C402, C403, C404, C405, C406, C409, C410, C411, C412, C413, C414, C415, C417, C419, C430, C431, C432, C433, C434, C435, C436, C437, C438, C439, C440, C447, C450, C451, C452, C457, C460, C461, C462, C463, C464, C465, C466, 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, C515, C518, C519, C520, C521, C522, C524, C528, C530, C530, C531, C532, C533, C538, C539, C540, C541, C542, C543, C545, C548, C549, C550, C551, C556, C561, C562, C564, C568, C569, C570, C571, C572, C573, C574, C575, C576, C577, C578, C579, C580, C583, C585, C589, C600, C601, C602, C604, C605, C606, 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, C855, C858, C859, C860, C862, C883, C884, C888, C889, C900, C901, C902, C903, C904, C908, C909, C910, C911, C912, C913, C914, C915, C916, C919, C91a, C91z, C920, C920, C921, C922, C923, C924, C925, C926, C927, C929, C929, C932, C930, C931, C932, C933, C934, C938, C939, C939, C940, C942, C943, C944, C946, C948, C950, C952, C959, C960, C962, C964, C965, C966, C968, C969, C96a, C96z, C975

Metastatic Solid Tumor

Falsification Endpoints

ICD-10 Codes

| 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** | **Therapeutic Class** | **Generic Name** |
| **Use in Hypertension** | 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/amldipine bes, Perindopril erbumine, Quinapril/hydrochlorothiazide, Quinapril HCl, Ramipril, Trandolapril, Trandolapril/verapamil HCl |
| **First line** | Angiotensin II receptor antagonists | Azilsartan med/chlorthalidone, Azilsartan medoxomil, Candesartan/hydrochlorothiazide, Candesartan cilexetil, Eprosartan mesylate, Irbesartan, Irbesartan/hydrochlorothiazide, Losartan/hydrochlorothiazide, Losartan potassium, Olmesartan/amlodipin/hctz, Olmesartan, medoxomil, Sacubitril/valsartan, Telmisartan, Telmisartan/amlodipine, Telmisartan/hydrochlorothiazide, Valsartan, Valsartan/hydrochlorothiazide |
| Calcium-channel blocking agents, dihydropyridine | Calcium-channel blocking agents, non-dihydropyridine | Amlodipine benzoate, Amlodipine besylate, Amlodipine besylate/valsartan, Amlodipine/valsartan/hctz, Amlodipine es/olmesartan med, Amlodipine besylate/benazepril Felodipine, Isradipine, Nifedipine, Nisoldipine, olmesartan/amlodipin/hctz, telmisartan/amlodipine |
| Calcium-channel blocking agents, dihydropyridine | Diltiazem HCl, Verapamil HCl | Amiloride/hydrochlorothiazide, Amlodipine/valsartan/hctz, Azilsartan med/chlorthalidone, Benazepril/hydrochlorothiazide, Bisoprolol/hydrochlorothiazide, Bisoprolol fumarate/hct, 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 succinate, Metoprolol succinate/hctz, Nadolol, Nadolol/hydrochlorothiazide, Nebivolol HCl, Nebivolol HCl/hctz, Nebivolol/valsartan, Pindolol, Pranoprolol, Pranoprolol/hydrochlorothiazide, Propranolol/hydrochlorothiazide |
| Thiazide and thiazide-like diuretics | 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 succinate, Metoprolol tartrate, Nadolol, Nadolol/bendroflumethiazide, Nebivolol HCl, Nebivolol HCl/hctz, Nebivolol HCl/valsartan, Pindolol, Pranoprolol, Pranoprolol/hydrochlorothiazide, 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/hydrochlorothiazide

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, Cholesteryamine/aspartame, Colesevelam HCl, Cholesteryamine (with sugar), Colestipol HCl, Niacin/simvastatin, Niacin/lovastatin, Niacin |
| Oral Glucose Lowering Agents       |                  | Acarbose, Migliitol, Metformin HCl, Sitagliptin phosphate, Linagliptin, Sitagliptin phos/metformin HCl, Saxagliptin HCl, Saxagliptin HCl/metformin HCl, Linagliptin/metformin HCl, Alogliptin benzoate, Alogliptin benzin/metformin HCl, Alogliptin benzn/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, Glimipiride, 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/eg 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/lisin 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.

| Variable                      | Outpatient | p-value Medicare vs Commercial | Inpatient | 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 |
| Condition                                                                 | Count 1 | Count 2 | Count 3 | p-value | Count 4 | Count 5 | Count 6 | p-value |
|--------------------------------------------------------------------------|---------|---------|---------|---------|---------|---------|---------|---------|
| 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 |
| Category                                    | 1st-line Use (%) | 2nd-line Use (%) | 3rd-line Use (%) | p-value   | 1st-line Use (%) | 2nd-line Use (%) | 3rd-line Use (%) |
|---------------------------------------------|------------------|------------------|------------------|-----------|------------------|------------------|------------------|
| **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%)        | 0.0016    | 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

| 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                |
| Category                  | Count | Percent | Count | Percent | Count | Percent | Count | Percent | p-Value | p-Value | p-Value |
|---------------------------|-------|---------|-------|---------|-------|---------|-------|---------|---------|---------|---------|
| 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%    | **    | 0%      | 15    | 0.8%    | **    | 0.0%    | 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  | <.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  |
| Condition                                      | 1989 | 1990 | 1991 | 1992 | p-value     |
|-----------------------------------------------|------|------|------|------|-------------|
| Chronic pulmonary disease                     | 845  | 270  | 299  | 276  | <.0001      |
| Peptic ulcer disease                          | 41   | 11   | 18   | 12   | 0.47        |
| AIDS                                          | 21   | 11   | **   | **   | 0.72        |
| Rheumatologic disease                         | 321  | 105  | 121  | 95   | 0.16        |
| Diabetes, chronic complications               | 1714 | 735  | 613  | 366  | <.0001      |
| Metastatic cancer                             | 31   | 13   | 7    | 11   | 0.90        |
| Hemiplegia or paraplegia                      | 155  | 61   | 36   | 58   | 0.19        |
| Liver disease, mild                           | 356  | 131  | 118  | 107  | 0.47        |
| Solid tumor without metastases                | 397  | 136  | 138  | 123  | 0.11        |
| Liver disease, moderate to severe             | **   | **   | 11   | 15   | 0.0028      |
| Dementia                                      | 353  | 113  | 62   | 178  | <.0001      |
| Peripheral vascular disease                   | 961  | 292  | 318  | 351  | <.0001      |
| Renal failure, moderate to severe             | 860  | 269  | 306  | 285  | <.0001      |
| Cerebrovascular disease                       | 551  | 171  | 183  | 197  | <.0001      |
| Charlson Score, median (IQR)                  | 1.0  | 1.0  | 2.0  | 1.0  | 0.0050      |

**Drug Therapy**

**Antihypertensives**

| Category                                      | 1989 | 1990 | 1991 | 1992 | p-value     |
|-----------------------------------------------|------|------|------|------|-------------|
| Beta blockers                                 | 2043 | 598  | 611  | 834  | <.0001      |
| Non-dihydropyridine calcium channel blockers | 195  | 53   | 54   | 88   | <.0001      |
| Dihydropyridine calcium channel blockers     | 1656 | 502  | 538  | 616  | <.0001      |
| Thiazide or thiazide-like diuretics           | 1857 | 674  | 786  | 397  | <.0001      |
| Loop diuretics                                | 663  | 193  | 190  | 280  | <.0001      |
| Drug Class                          | Count (Percentage) | Count (Percentage) | Count (Percentage) | Count (Percentage) | p-Value | p-Value | p-Value |
|------------------------------------|--------------------|--------------------|--------------------|--------------------|---------|---------|---------|
| 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  | <.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                          | 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 | <.001 | 0.044 |
|-----------------------------------|--------------------|--------------------|--------------------|--------------------|--------|-------|-------|
| Follow-up days, median (IQR)      |                    |                    |                    |                    |        |       |       |
| 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.

| Variable              | Cohort                  | p-value |
|-----------------------|-------------------------|---------|
|                       | 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\%) | <.0001 | <.0001 | 0.70 |
| 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 |
| Race          | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) |
|--------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| 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 | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) |
|-------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| 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      |           |           |

| State of Inpatient Facility | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) |
|-----------------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| 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         | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) | Count (%) |
|-----------------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| 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   |           |           |
| Condition                                      | N       | %     | N       | %     | N       | %     | N       | %     | P-value  |
|-----------------------------------------------|---------|-------|---------|-------|---------|-------|---------|-------|----------|
| Peptic ulcer disease                          | 120     | 1.5%  | 36      | 1.4%  | 29      | 1.2%  | 55      | 1.8%  | 0.26     |
| AIDS                                          | 45      | 0.6%  | 11      | 0.4%  | 14      | 0.6%  | 20      | 0.6%  | 0.32     |
| Rheumatologic disease                         | 504     | 6.2%  | 134     | 5.0%  | 162     | 7.0%  | 208     | 6.7%  | 0.011    |
| Diabetes, chronic complications               | 3493    | 43.0% | 1232    | 46.3% | 1076    | 46.3% | 1185    | 37.9% | <.0001   |
| Metastatic cancer                             | 112     | 1.4%  | 33      | 1.2%  | 33      | 1.4%  | 46      | 1.5%  | 0.52     |
| Hemiplegia or paraplegia                      | 637     | 7.9%  | 201     | 7.5%  | 130     | 5.6%  | 306     | 9.8%  | 0.0031   |
| Liver disease, mild                           | 529     | 6.5%  | 163     | 6.1%  | 162     | 7.0%  | 204     | 6.5%  | 0.56     |
| Solid tumor without metastases                | 827     | 10.2% | 259     | 9.7%  | 250     | 10.8% | 318     | 10.2% | 0.60     |
| Liver disease, moderate to severe             | 68      | 0.8%  | 17      | 0.6%  | 15      | 0.6%  | 36      | 1.2%  | 0.057    |
| Dementia                                      | 1882    | 23.2% | 602     | 22.6% | 375     | 16.1% | 905     | 29.0% | <.0001   |
| Peripheral vascular disease                   | 2698    | 33.3% | 813     | 30.5% | 704     | 30.3% | 1181    | 37.8% | <.0001   |
| Renal failure, moderate to severe             | 2540    | 31.3% | 709     | 26.6% | 699     | 30.1% | 1132    | 36.2% | <.0001   |
| Cerebrovascular disease                       | 1748    | 21.5% | 524     | 19.7% | 461     | 19.8% | 763     | 24.4% | <.0001   |
| 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   |

**Drug Therapy**

**Antihypertensives**

| Category                                      | N       | %     | N       | %     | N       | %     | N       | %     | P-value  |
|-----------------------------------------------|---------|-------|---------|-------|---------|-------|---------|-------|----------|
| Beta blockers                                 | 4202    | 51.8% | 1186    | 44.5% | 1143    | 49.2% | 1873    | 59.9% | <.0001   |
| Non-dihydropyridine calcium channel blockers  | 3452    | 42.5% | 1004    | 37.7% | 1005    | 43.2% | 1443    | 46.2% | <.0001   |
| Dihydropyridine calcium channel blockers      | 3015    | 37.2% | 889     | 33.4% | 900     | 38.7% | 1226    | 39.2% | <.0001   |
| Thiazide or thiazide-like diuretics            | 1951    | 24.0% | 618     | 23.2% | 840     | 36.1% | 493     | 15.8% | <.0001   |
| Loop diuretics                                | 2381    | 29.3% | 639     | 24.0% | 628     | 27.0% | 1114    | 35.6% | <.0001   |
| Centrally acting alpha agonists                | 287     | 3.5%  | 76      | 2.9%  | 97      | 4.2%  | 114     | 3.6%  | 0.11     |
| Potassium sparing diuretics                    | 139     | 1.7%  | 39      | 1.5%  | 29      | 1.2%  | 71      | 2.3%  | 0.032    |
| Drug Class                      | First-line Count | First-line Median (IQR) | Second-line Count | Second-line Median (IQR) | p-value 1 | p-value 2 | p-value 3 |
|---------------------------------|------------------|-------------------------|-------------------|--------------------------|-----------|-----------|-----------|
| 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%) | ** | ** | 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) |
| 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          |
| 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 |
| Condition                                           | 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 |
| 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 |

**ACE inhibitor vs ARB**
|                  | Odds Ratios |
|-----------------|-------------|
| Wrist drop      | *           |

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.

| Comparison Group | Number of patients in matched groups | In-hospital death events in matched groups | In-hospital mortality |
|------------------|-------------------------------------|------------------------------------------|----------------------|
|                  | 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.

| Comparison Group          | In-hospital Mortality | Survival to Discharge |
|---------------------------|-----------------------|-----------------------|
|                           | 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.

| Comparison Group | Died or Survived | Died | Survived |
|------------------|------------------|------|----------|
|                  | Both             | Treatment | Control | Both | Treatment | Control | Both | Treatment | Control |
| Overall Population | 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) |
| ACE 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) |
| 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) | 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) |
| 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 (3.0–11.0) | 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 | 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) |
| ACE 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) |
| ARB vs Other     | 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 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)    |
| 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              |
| 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              |
| Condition                                      | Comparison 1 | Comparison 2 | Odds Ratio (95% CI) | P-value |
|-----------------------------------------------|--------------|--------------|---------------------|---------|
| Wrist drop                                    | *            | NA           | *                   | NA      |
| Absent kidney                                 | 6 vs 6       | 3 vs 7       | 0.37 (0.12, 1.01); P=0.052 |         |
| Acid reflux                                   | 352 vs 403   | 334 vs 370   | 0.87 (0.731, 1.05); P=0.15 |         |
| Anal/rectal polyps                            | *            | NA           | *                   | NA      |
| Herpes zoster without complications           | 20 vs 20     | 15 vs 15     | 0.94 (0.46, 1.95); P=1 |         |
| Ingrowing nail                                | 89 vs 77     | 91 vs 79     | 0.91 (0.66, 1.25); P=0.58 |         |
| ACE inhibitor vs ARB                          | 10 vs 8      | 9 vs 7       | 0.71 (0.18, 2.62); P=0.77 |         |
| Nicotine dependence                          | 53 vs 53     | 43 vs 46     | 1.3 (0.91, 1.75); P=0.17 |         |
| Pain in wrist                                 | 47 vs 51     | 48 vs 52     | 0.75 (0.46, 1.20); P=0.25 |         |
| Presbyopia                                    | 144 vs 138   | 133 vs 126   | 0.87 (0.62, 1.22); P=0.45 |         |
| 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      | 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      | 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%) |
| Last Name | Country | Study Design | Population | Outcomes | Findings |
|-----------|---------|--------------|------------|----------|----------|
| Zhang (2020) | 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.  
ACE/ARB: 0.37 [95% CI, 0.15–0.89]; P=0.03 |
| Mehta (2020) | 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) | 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) | 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% confidence interval 0.47–0.84, P < 0.01 |
| Authors  | Country | Center Type | Diagnosis | Event Count | Event Description | HR (95% CI) | p-Value | Findings |
|---------|---------|-------------|------------|-------------|------------------|-------------|---------|----------|
| Morales (2020) | 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**<br>ACE/ARB as monotherapy: 0.98 (0.84 - 1.14); 0.76<br>ACE/ARB with combination: 1.01 (0.90 - 1.15); 0.81<br>ACE monotherapy: 0.91 (0.68 - 1.21); 0.51<br>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) | 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**<br>ACE/ARB: 25.5% vs 48% of non-ACE/ARB group | |
| Son (2020) | 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**<br>RAAS: 1.161 (0.958–1.407); P > 0.05<br>**ICU admission**<br>RAAS 1.515 (0.402–5.701)<br>**Mortality**<br>RAAS: 1.363 (0.513–3.662) | |
| Xu (2020) | 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** | |
| Study                      | Country | Study Design | Setting | Sample Size | Event | Results                                                                                                                                 |
|---------------------------|---------|--------------|---------|-------------|-------|------------------------------------------------------------------------------------------------------------------------------------------|
| 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. |
| Amat-Santos (2020) 44      | Spain   | Multicenter  | post-TAVR | 102         | COVID-19 diagnosis                        | 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. |
| Study | Country | Center Type | Study Population | Sample Size | Outcomes | Effect Size | p-Value | Summary |
|-------|---------|-------------|------------------|-------------|----------|-------------|--------|---------|
| Yang (2020) | China | Single center | All-comers; Hypertension | 462 | COVID-19 severity; Mortality | (-) | 0.365 | No association between the use of ACE/ARB and critical COVID-19 illness or mortality was observed. |
| Gao (2020) | China | Single center | All-comers; Hypertension | 2877; 710 | Mortality | (+) | 0.061 | 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. |
| Bravi (2020) | Italy | Multicenter | All-comers; Hypertension | 1,603; 543 | COVID-19 severity; Mortality/ICU admission | (-) ; (+) | 0.774 | 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. |

**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

**COVID-19 severity**

ACE/ARB: 9.3% versus 22.9%; P=0.061

**Mortality**

ACE/ARB: 4.7% versus 13.3%; P=0.216

**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
| Study | Country | Setting | Condition | Sample Size | Outcome | Rate (ACE/ARB) | Rate (Non-ACE/ARB) | p-value |
|-------|---------|---------|-----------|-------------|---------|---------------|-------------------|---------|
| Zhou (2020) | China | Multicenter | All-comers; Hypertension | 3,752 | Mortality (+) | ACE/ARB: 0.87 (0.50–1.49); 0.6 | Among All-comers, in-hospital use of ACE/ARB was associated with lower 28-day COVID-19 mortality risk compared to non-users, with similar findings for a Hypertension cohort. |
| Li (2020) | China | Single center | Hypertension | 362 | COVID-19 severity; Mortality (-) | ACE/ARB: 0.39 (0.26–0.58); P<0.001 | 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. |

**ACE/ARB**: Angiotensin Converting Enzyme Inhibitors/Angiotensin Receptor Blockers

**COVID-19**: Coronavirus Disease 2019

**Mortality**: Outcome of interest

**P-value**: Statistical significance of the results.
Figure S1. Primary outpatient cohort selection flowsheet.

**Patient Selection Flowsheet for Outpatient Cohort**

1. Enrolled for \( \geq 6 \) months in 2019 with medical and pharmacy benefit
   \( N = 14,559,858 \)
   - Exclude if unobserved outpatient SARS-CoV-2 test \( (N = 14,504,987) \)

2. Outpatient SARS-CoV-2 Test
   \( N = 54,671 \)
   - Exclude if SARS-CoV-2 negative or unknown \( (N = 47,986) \)

3. Positive Outpatient SARS-CoV-2 Test
   \( N = 6,885 \)
   - Exclude if no hypertension \( (N = 4,050) \)
   - Exclude if hypertension without antihypertensive drug fill \( (N = 551) \)
   - Exclude if on both ACE & ARB \( (N = 21) \)

4. Positive Outpatient SARS-CoV-2 Test, Hypertension, and at least one antihypertensive drug
   \( N = 2,283 \)

5. ACE/ARB treated patients (exposure group)
   \( N = 1,453 \)

6. Non-ACE/ARB treated patients (control group)
   \( N = 810 \)
Figure S2. Primary inpatient cohort selection flowsheet.

Patient Selection Flowsheet for Inpatient Cohort

Enrolled for >= 6 months in 2019 with medical and pharmacy benefit
N = 14,559,858

Exclude if no inpatient stay for COVID-19
(N = 14,547,292)

Inpatient admission for COVID-19
N = 12,566

Exclude if no hypertension (N = 3,117)
or hypertension without antihypertensive drug fill (N=1,457)
Exclude if on both ACE and ARB (N=58)

Inpatient with COVID-19, hypertension, and at least one antihypertensive drug
N = 7,933

ACE/ARB treated patients (exposure group)
N = 4,587

Non-ACE/ARB treated patients (control group)
N = 3,346
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.
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 inpatient 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

Histogram on p values from replicate matches (ACEI versus Others)

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

Histogram on hazard ratio from replicate matches (ACEI versus Others)