

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 complements the test type (antibody, PCR, etc.) as well as the result value (detected, not detected, not given/cancelled). Members with a qualified COVID-19 related hospital admission are included in the report when any diagnosis matches qualified ICD-10 codes as defined in **Table S1**. Suspected COVID-19 inpatient cases are manually reviewed daily by health plan clinical staff via clinical notes to determine an individual’s COVID-19 status. Each case is then manually flagged as either negative, confirmed, presumed positive, or needs clinical review. If a case is confirmed, it is not reviewed again. If a case is listed as negative or unknown, it is periodically reviewed for changes in the record. All others are reviewed and updated daily.

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

Estimation of Propensity Score Model

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

Matching Algorithm

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

Evaluation of the Propensity Score Matching

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

- (1) We assessed the propensity score distributions in the unmatched and matched cohorts and calculated an equipoise metric to summarize the degree of overlap in characteristics of patients receiving these drugs.^{17, 40} This represents the proportion of individuals in the unmatched groups that had a propensity score between 0.3 and 0.7, representing a state of equipoise between the two drugs. A value greater than 0.5 implies two drugs are in empirical equipoise, with a higher a value indicating a lower likelihood of confounding by indication.⁴⁰
- (2) We evaluated the standardized difference between matched covariates before and after propensity score matching. Specifically, we evaluated whether our matching algorithm achieved a standardized difference of <10% between matched cohort suggestive of adequately matched groups.^{17, 19}
- (3) We evaluated the success of our matching algorithm using negative control or falsification endpoints. We chose these negative controls from published data on hypertension drug evaluations using claims data. These endpoints were defined from the claim records for study participants between January 1, 2019 and December 31, 2019, and therefore, preceded the infection with SARS-CoV-2.¹⁷ The chosen falsification endpoints were based on the assertion that they are unlikely to be affected by the treatment assignment and a directional effect would represent covariate imbalance.

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

Table S1. ICD-10 codes.

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

Charlson Comorbidity Indices
Charlson Comorbidity Index

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

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

Metastatic Solid Tumor

C770, C771, C772, C773, C774, C775, C778, C779, C780, C781, C782, C783, C784, C785, C786, C787, C788, C789, C790, C791, C792, C793, C794, C795, C796, C797, C798, C799, C800, C801, C802, C809

Falsification Endpoints

Falsification Endpoints

Absent kidney

Anal and rectal polyp

Gastro-esophageal reflux disease

Herpes zoster without complications

Ingrown nail

Latent effects of motor vehicle accident

Nicotine dependence

Pain in wrist

Presbyopia

ICD-10 Codes

Q600, Q601, Q602, Z905

K600, K601

K210, K219

B029

L600

V877, V890, V892

F172%

M2553%

H524

Strain of rotator cuff capsule

S4342%

Wrist drop

M2133%

Table S2. Drug classes & generic names.

Antihypertensive Drugs

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

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

Additional drug classes of interest

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

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

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

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

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

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

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

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

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

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

Follow-up

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

* Race is unknown in all commercially insured enrollees.

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

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

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

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

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

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

Race is unknown in all commercially insured enrollees.

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

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

Falsification Endpoint	Overall		Medicare		Commercial		
	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)	
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	
ACE inhibitor vs Other	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	
ARB vs Other	Acid reflux	55 vs 70	0.75 (0.51–1.10); 0.15	43 vs 42	1.03 (0.65–1.63); 0.91	17 vs 23	0.70 (0.35–1.38); 0.30
	Anal and rectal polyps	*	NA	*	NA	*	NA
	Herpes zoster without complications	*	NA	*	NA	*	NA

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

Wrist drop

*

NA

*

NA

*

NA

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

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

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

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

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

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

ACE: angiotensin converting enzyme

ARB: Angiotensin II receptor blocker

CI: confidence interval

COVID-19: Coronavirus disease 2019

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

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

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

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

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

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

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

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

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

ACE: angiotensin converting enzyme

ARB: Angiotensin II receptor blocker

CI: Confidence interval

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

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

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

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

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

ACE: angiotensin converting enzyme

ARB: Angiotensin II receptor blocker

CI: Confidence interval

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

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

ACE: Angiotensin converting enzyme

ARB: Angiotensin II receptor blocker

CI: Confidence interval

COVID-19: Coronavirus disease 2019

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

Author (Year)	Country	Centers	Study Population	N	Outcomes	Cofounder Adjustment	Odds/Hazard Ratios (95% Confidence interval) or Observed %
de Abajo (2020) ¹²	Spain	Multicenter	All-comers	1,139	Hospitalization	(+)	<p>No association with COVID-19 hospitalization among any RAAS user, ACE inhibitor user, or ARB user.</p> <p>Hospitalization</p> <p>All RAAS: 0.94 (0.77–1.15)</p> <p>ACE: 0.80 (0.64–1.00)</p> <p>ARB: 1.10 (0.88–1.37)</p>
Reynolds (2020) ¹³	USA	Single center	All-comers; Hypertension	12,592; 1,002	SARS-CoV-2 infection; COVID-19 severity	(+)	<p>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.</p> <p>SARS-CoV-2 infection</p> <p>ACE/ARB: 0.5% (-2.6% to 3.6%)</p> <p>ACE: -2.5% (-6.7% to 1.6%)</p> <p>ARB: 2.2% (-1.9% to 6.3%)</p> <p>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.</p> <p>COVID-19 severity</p> <p>ACE/ARB: -0.1% (-3.7% to 3.5%)</p> <p>ACE: -1.9% (-6.6% to 2.8%)</p> <p>ARB: -1.4% (-6.1% to 3.3%)</p>

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

Morales (2020) ¹⁰	Spain & USA	Multicenter	Hypertension	612,700	COVID-19 diagnosis; COVID-19 Hospitalization; Hospitalization with pneumonia; Hospitalization with pneumonia, ARDS, AKI, or sepsis.	(+)	<p>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.</p> <p>COVID-19 diagnosis</p> <p>ACE/ARB as monotherapy: 0.98 (0.84 - 1.14); 0.76</p> <p>ACE/ARB with combination: 1.01 (0.90 - 1.15); 0.81</p> <p>ACE monotherapy: 0.91 (0.68 - 1.21); 0.51</p> <p>ARB monotherapy: 1.10 (0.89 - 1.35); 0.40</p> <p>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.</p>
Meng (2020) ³¹	China	Single center	Hypertension	42	COVID-19 severity	(-)	<p>A smaller proportion of those taking ACE/ARBs were categorized as having severe COVID-19 as compared to other antihypertensive drugs.</p> <p>COVID-19 severity</p> <p>ACE/ARB: 25.5% vs 48% of non-ACE/ARB group</p>
Son (2020) ⁴¹	South Korea	Multicenter	Hypertension	16,281	SARS-CoV-2 infection; COVID-19 severity	(+)	<p>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.</p> <p>SARS-CoV-2 infection</p> <p>RAAS: 1.161 (0.958–1.407); P > 0.05</p> <p>ICU admission</p> <p>RAAS 1.515 (0.402–5.701)</p> <p>Mortality</p> <p>RAAS: 1.363 (0.513–3.662)</p>
Xu (2020) ⁴²	China	Single center	Hypertension	101	Mortality; ICU admission; ventilation	(-)	<p>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.</p> <p>Mortality</p>

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

							<p>Hospital admission</p> <p>ACE/ARB: 0.39 (0.05-2.94); 0.365</p> <p>Oxygen use</p> <p>ACE/ARB: 0.51 (0.15-1.78); 0.292</p> <p>Non-invasive ventilation</p> <p>ACE/ARB: 0.58 (0.21-1.60); P= 0.296</p> <p>Mortality</p> <p>ACE/ARB: 0.56 (0.17-1.83); 0.341</p>
Yang (2020) ⁴⁶	China	Single center	All-comers; Hypertension	462	COVID-19 severity; Mortality	(-)	<p>No association between the use of ACE/ARB and critical COVID-19 illness or mortality was observed.</p> <p>COVID-19 severity</p> <p>ACE/ARB: 9.3% versus 22.9%; P=0.061</p> <p>Mortality</p> <p>AC/ARB: 4.7% versus 13.3%; P=0.216</p>
Gao (2020) ⁴⁷	China	Single center	All-comers; Hypertension	2877; 710	Mortality	(+)	<p>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.</p> <p>Mortality</p> <p>RAAS: 0.85 (0.28-2.58); 0.774</p>
Bravi (2020) ⁴⁸	Italy	Multicenter	All-comers; Hypertension	1,603 ; 543	COVID-19 severity; Mortality/ICU admission	(-) ; (+)	<p>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.</p> <p>COVID-19 mortality or ICU admission</p> <p>ACE/ARB: 54.2% vs 19.1%; P < 0.001</p> <p>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</p> <p>COVID-19 mortality or ICU admission</p>

							ACE/ARB: 0.87 (0.50–1.49); 0.6
Zhou (2020) ⁴⁹	China	Multicenter	All-comers; Hypertension	3,752	Mortality	(+)	<p>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.</p> <p>Mortality</p> <p>ACE/ARB: 0.39 (0.26–0.58); $P < 0.001$</p>
Li (2020) ⁵⁰	China	Single center	Hypertension	362	COVID-19 severity; Mortality	(-)	<p>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.</p> <p>COVID-19 severity</p> <p>ACE/ARB: (32.9% vs 30.7%; $P = .65$)</p> <p>Mortality</p> <p>ACE/ARB: (27.3% vs 33.0%; $P = .34$)</p>

Figure S1. Primary outpatient cohort selection flowsheet.

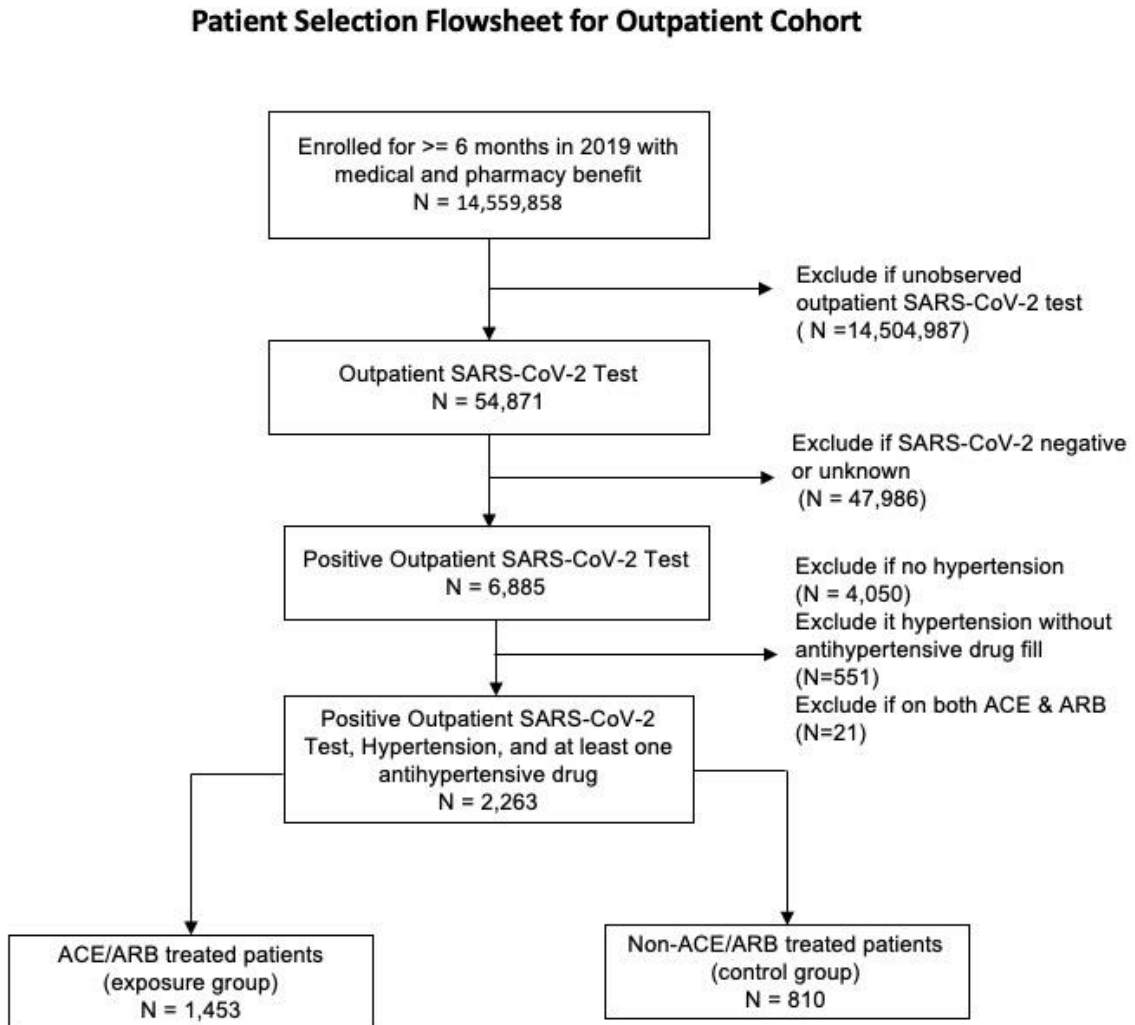


Figure S2. Primary inpatient cohort selection flowsheet.

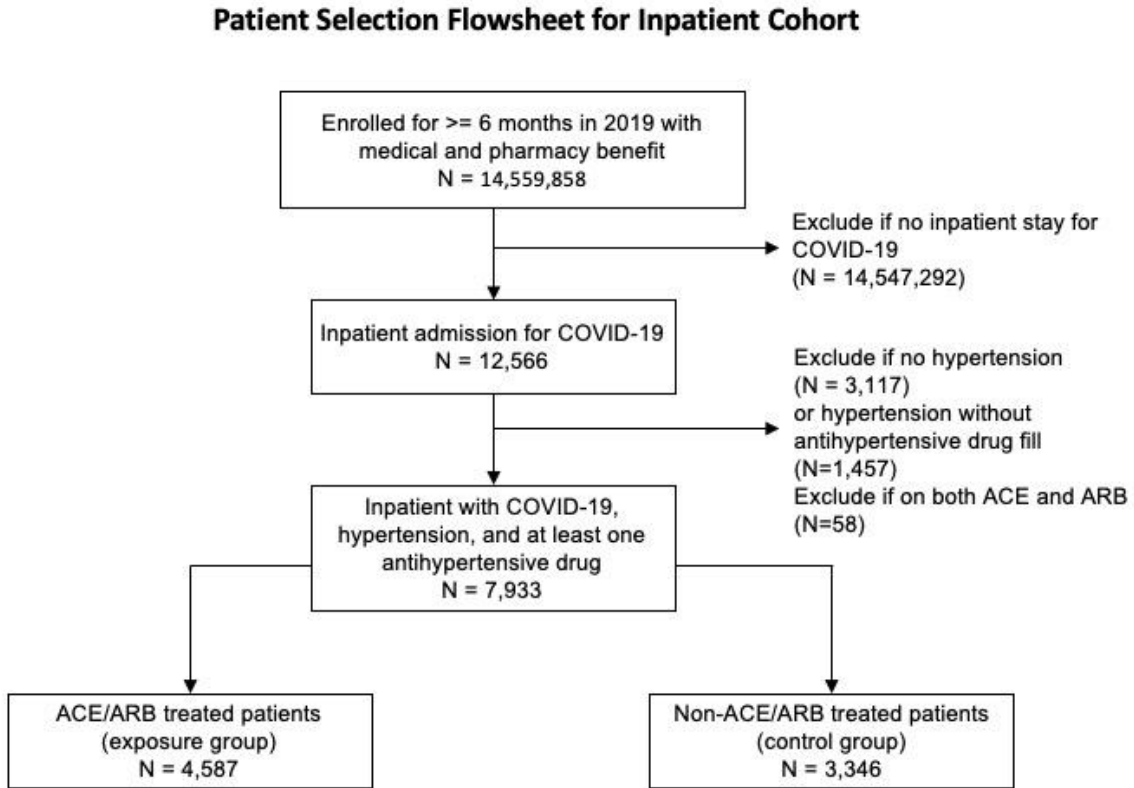
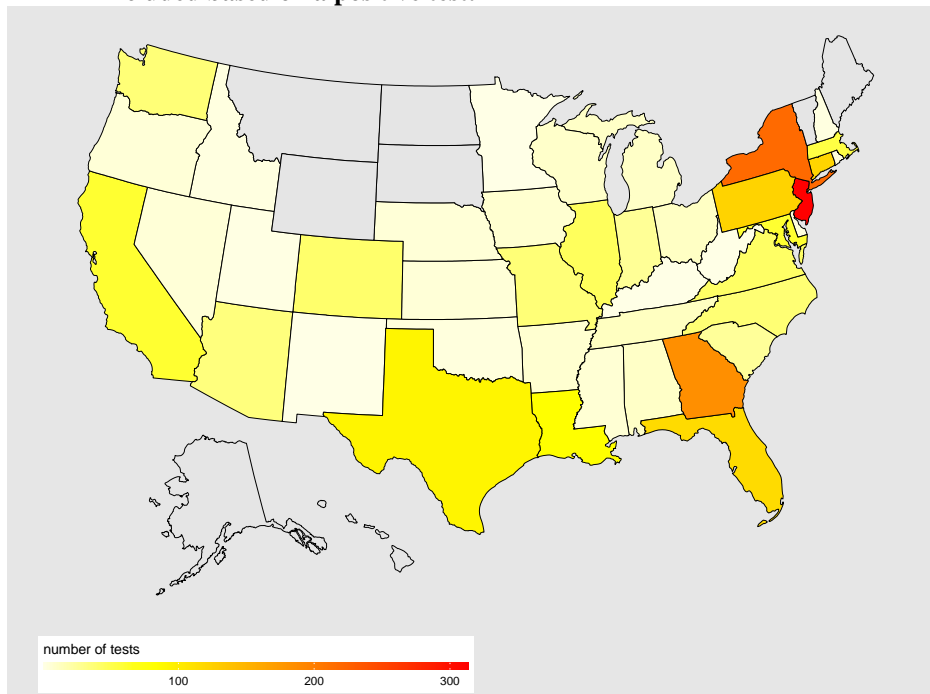


Figure S3. Distribution of individuals in the primary outpatient and inpatient cohorts.

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



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

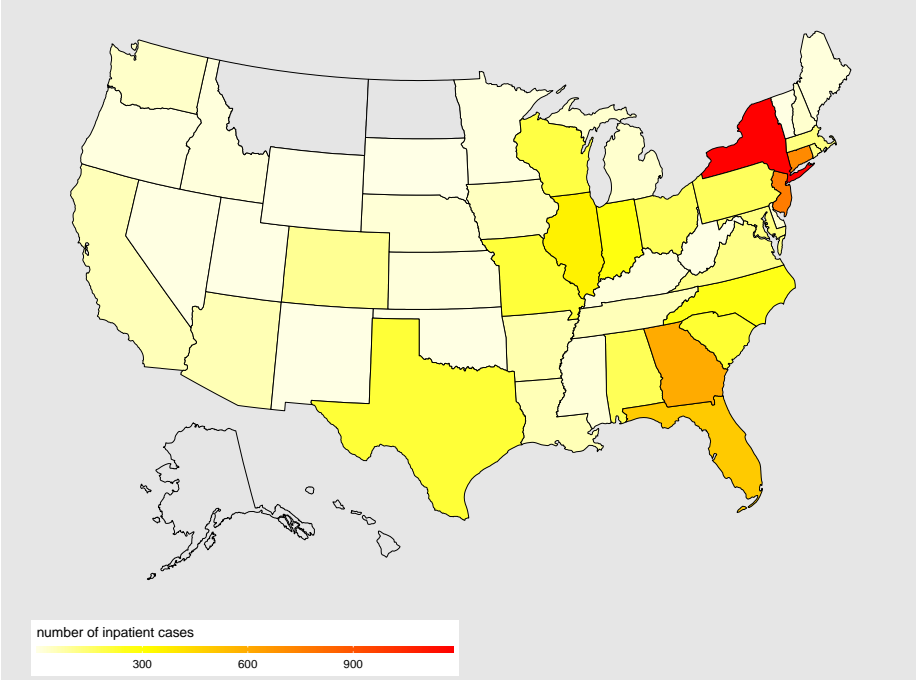
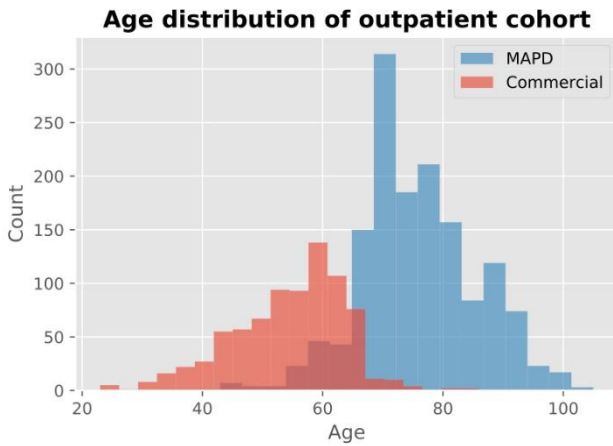
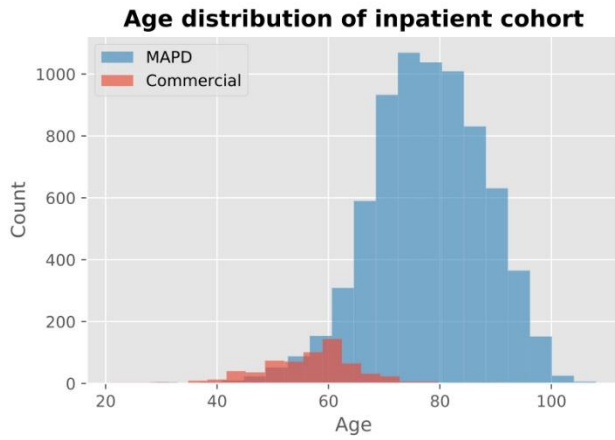


Figure S4. Histogram of age distributions of primary outpatient and inpatient cohorts, stratified by insurance type.

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



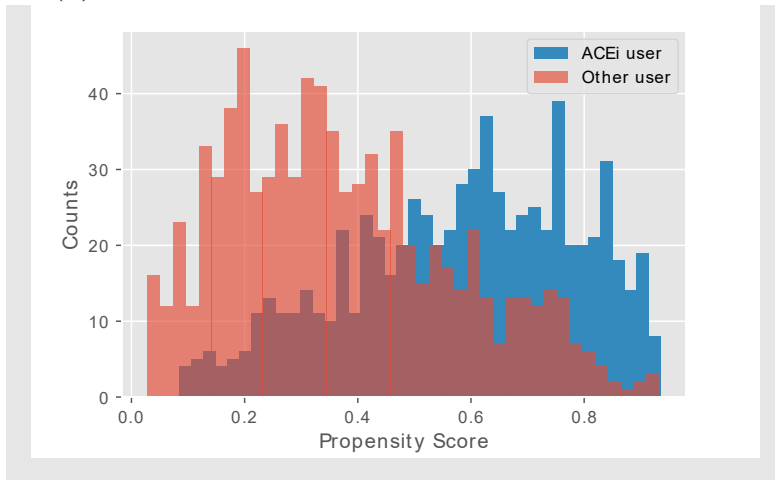
(B) Histogram of age distribution of the outpatient cohort, Medicare Advantage versus Commercial



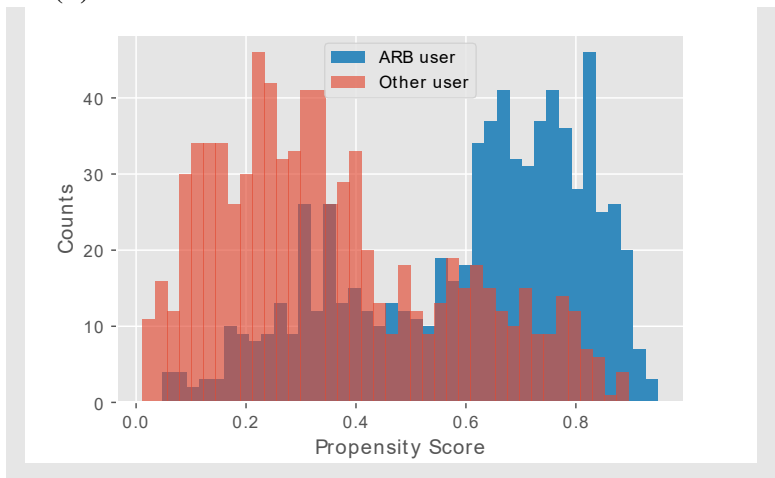
MAPD: Medicare Advantage with Part D coverage

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

(A) ACE inhibitor vs others



(B) ARB vs others



(C) ACE inhibitor vs ARB

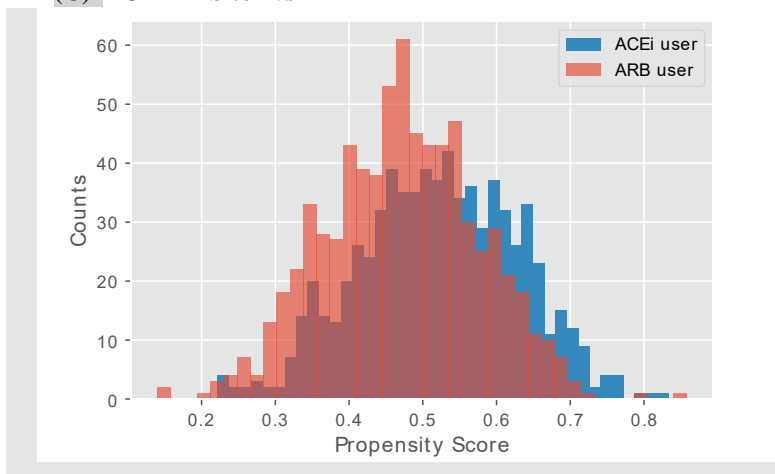
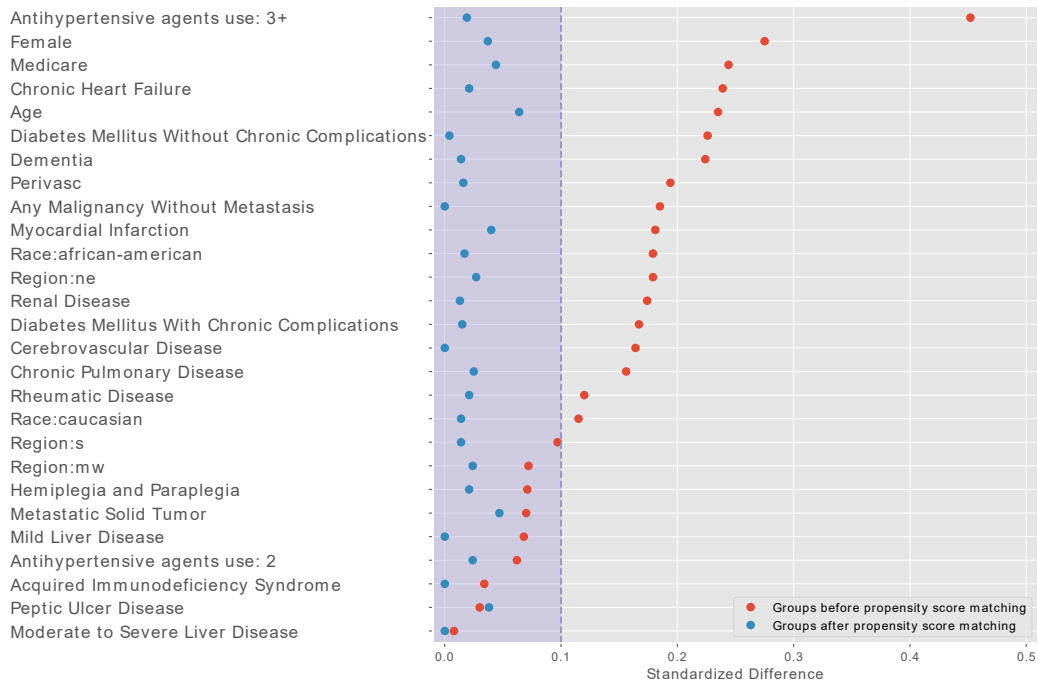


Figure S6. Standardized Differences Between Variables Before and After Propensity Matching.

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



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

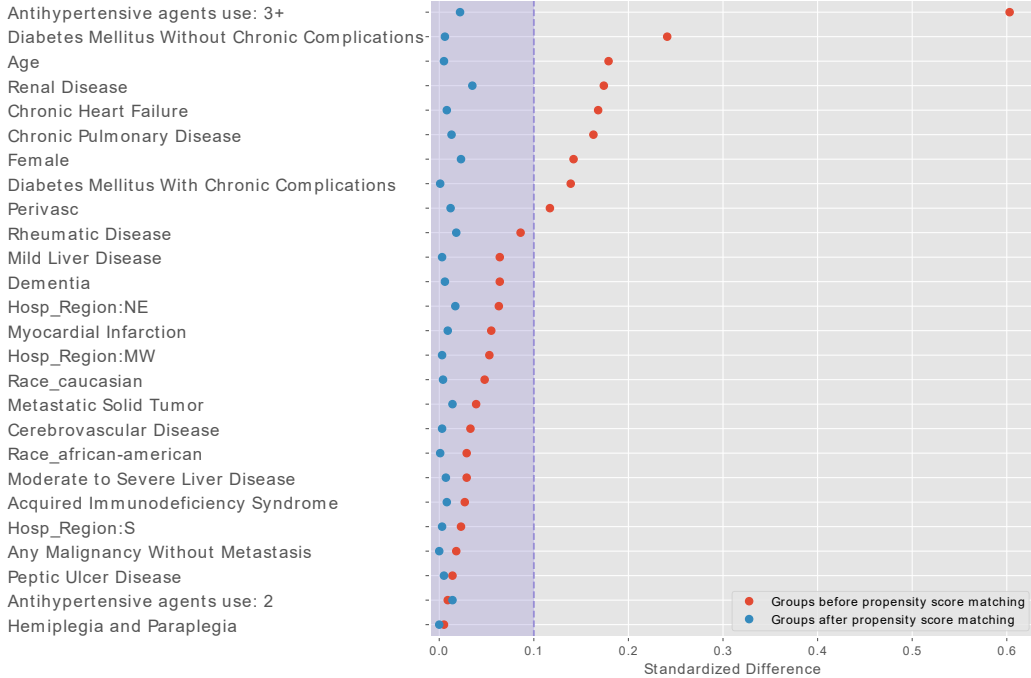
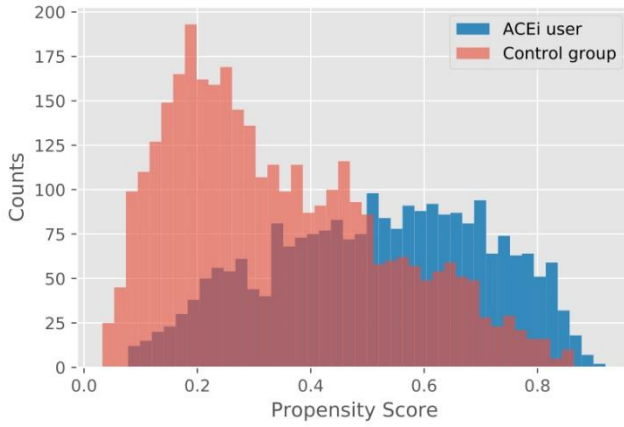
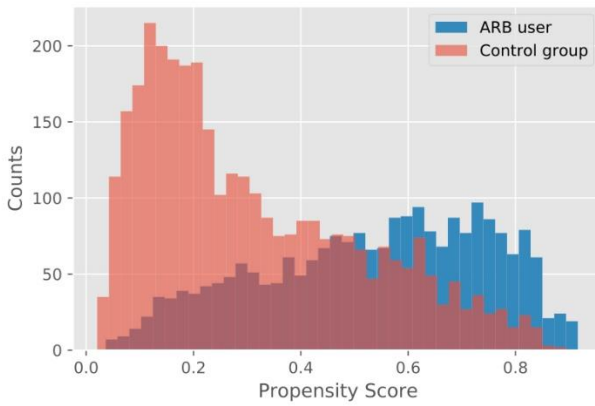


Figure S7. Propensity score distributions for treatment comparisons in the primary inpatient cohort.

(A) ACE inhibitor vs others



(B) ARB vs others



(C) ACE inhibitor vs ARB

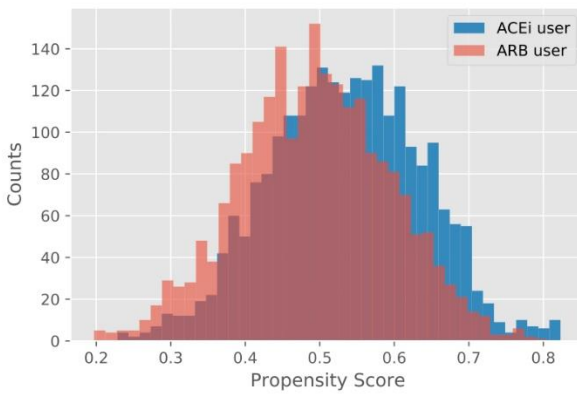
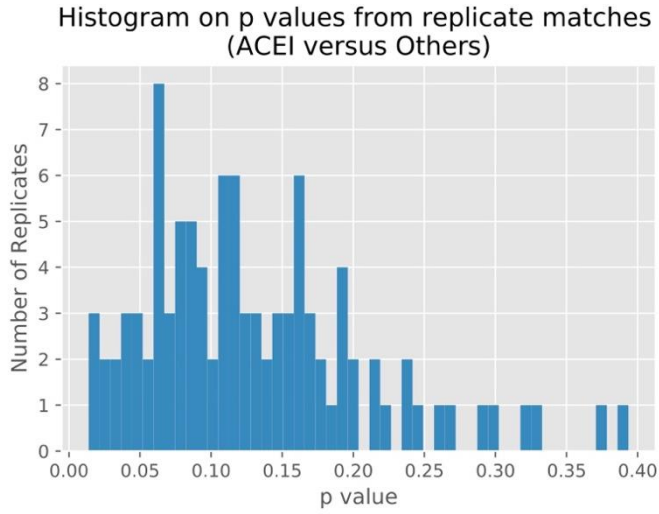
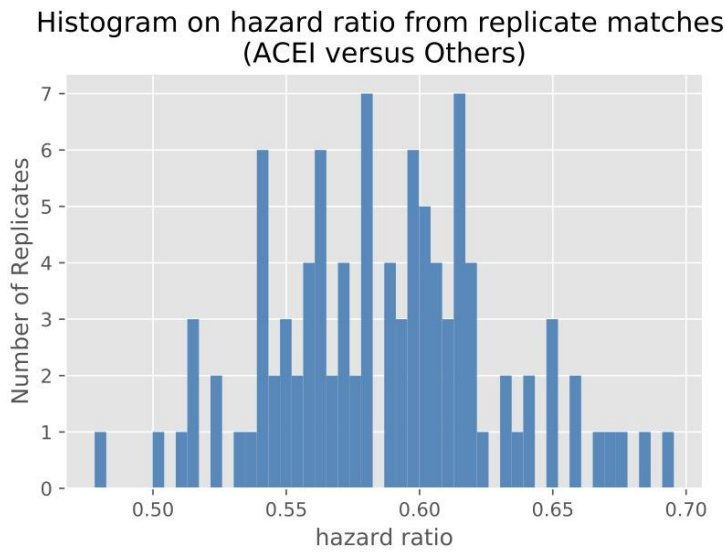


Figure S8. Histogram on p-values and adjusted hazard ratios from 100 matches, primary outpatient cohort.

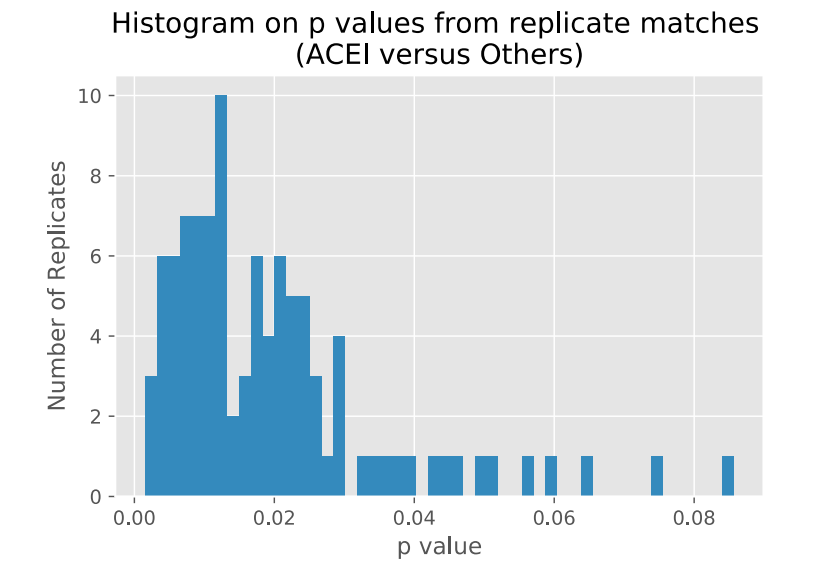
(A) ACE inhibitor versus others in full population, histogram of p-values



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



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



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

