Renin–angiotensin system blockers and susceptibility to COVID-19: an international, open science, cohort analysis

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Summary

Background Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been postulated to affect susceptibility to COVID-19. Observational studies so far have lacked rigorous ascertainment adjustment and international generalisability. We aimed to determine whether use of ACEIs or ARBs is associated with an increased susceptibility to COVID-19 in patients with hypertension.

Methods In this international, open science, cohort analysis, we used electronic health records from Spain (Information Systems for Research in Primary Care [SIDIAP]) and the USA (Columbia University Irving Medical Center data warehouse [CUIMC] and Department of Veterans Affairs Observational Medical Outcomes Partnership [VA-OMOP]) to identify patients aged 18 years or older with at least one prescription for ACEIs and ARBs (target cohort) or calcium channel blockers (CCBs) and thiazide or thiazide-like diuretics (THZs; comparator cohort) between Nov 1, 2019, and Jan 31, 2020. Users were defined separately as receiving either monotherapy with these four drug classes, or monotherapy or combination therapy (combination use) with other antihypertensive medications. We assessed four outcomes: COVID-19 diagnosis; hospital admission with COVID-19; hospital admission with pneumonia; and hospital admission with pneumonia, acute respiratory distress syndrome, acute kidney injury, or sepsis. We built large-scale propensity score methods derived through a data-driven approach and negative control experiments across ten pairwise comparisons, with results meta-analysed to generate 1280 study effects. For each study effect, we did negative control outcome experiments using a possible 123 controls identified through a data-rich algorithm. This process used a set of predefined baseline patient characteristics to provide the most accurate prediction of treatment and balance among patient cohorts across characteristics. The study is registered with the EU Post-Authorisation Studies register, EUPAS35296.

Findings Among 1355 349 antihypertensive users (363 785 ACEI or ARB monotherapy users, 248 915 CCB or THZ monotherapy users, 711 799 ACEI or ARB combination users, and 473 076 CCB or THZ combination users) included in analyses, no association was observed between COVID-19 diagnosis and exposure to ACEI or ARB monotherapy versus CCB or THZ monotherapy (calibrated hazard ratio [HR] 0·98, 95% CI 0·84–1·14) or combination use exposure (1·01, 0·99–1·03). ACEIs alone similarly showed no relative risk difference when compared with CCB or THZ monotherapy (HR 0·91, 95% CI 0·68–1·21); with heterogeneity of >40% or combination use (0·95, 0·83–1·07). Directly comparing ACEIs with ARBs demonstrated a moderately lower risk with ACEIs, which was significant with combination use (HR 0·88, 95% CI 0·79–0·99) and non-significant for monotherapy (0·85, 0·69–1·05). We observed no significant difference between drug classes for risk of hospital admission with COVID-19, hospital admission with pneumonia, or hospital admission with pneumonia, acute respiratory distress syndrome, acute kidney injury, or sepsis across all comparisons.

Interpretation No clinically significant increased risk of COVID-19 diagnosis or hospital admission-related outcomes associated with ACEI or ARB use was observed, suggesting users should not discontinue or change their treatment to decrease their risk of COVID-19.

Funding Wellcome Trust, UK National Institute for Health Research, US National Institutes of Health, US Department of Veterans Affairs, Janssen Research & Development, IQVIA, South Korean Ministry of Health and Welfare Republic, Australian National Health and Medical Research Council, and European Health Data and Evidence Network.

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Research in context

Evidence before this study

We systematically searched PubMed, Embase, clinical trial registries, and preprint servers for research articles published from inception until March 27, 2020. No language restriction was applied. We found no investigations of the real-world safety of first-line antihypertensive medications involving COVID-19 diagnoses. Studies examining the association between renin-angiotensin system inhibitor use and COVID-19 susceptibility have since been published that report no COVID-19 risk or a lower risk associated with use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). However, these studies have small sample sizes, limited confounder adjustment, or methodological limitations such as immortal time bias and collider bias. We identified one small study directly comparing the effects of ACEI versus ARB use among symptomatic patients with COVID-19 that showed no difference in patient outcomes.

Added value of this study

This study comprehensively evaluates the safety of ACEIs and ARBs in COVID-19 by examining a large number of different comparisons using state-of-the-art methods to control for residual confounding and bias across a distributed network. Our study shows similar results across three databases from two countries. ACEI and ARB use does not confer increased risk of COVID-19 diagnosis; hospital admission with COVID-19; hospital admission with pneumonia; or hospital admission with pneumonia, acute respiratory distress syndrome, acute kidney injury, or sepsis compared with people taking calcium channel blockers and thiazide or thiazide-like diuretics.

Implications of all the available evidence

Use of ACEIs and ARBs does not affect COVID-19 susceptibility risk, and these results are in keeping with medicines regulatory and clinical society recommendations that patients should not alter their treatment with these medicines to reduce their COVID-19 risk.

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analytical code across all data sources in a consistent manner. The data sources included the Columbia University Irving Medical Center (New York, NY, USA) data warehouse (CUIMC), the Information Systems for Research in Primary Care (SIDIAP) database, and the US Department of Veterans Affairs OMOP (VA-OMOP) database. CUIMC EHRs contain data, including clinical diagnoses, prescriptions, laboratory tests, demographics, and COVID-19 tests and diagnosis, from approximately 6 million cumulative patients from the New York-Presbyterian Hospital and Columbia University Irving Medical Center in the USA. SIDIAP covers approximately 80% of the population of Catalonia (Spain), with approximately 6 million patients, and contains data collected since 2006 from general practice EHRs linked to hospital admissions, with information on diagnoses, prescriptions, laboratory tests, and lifestyle and sociodemographics, and the central database of RT-PCR COVID-19 tests. VA-OMOP covers approximately 12 million patients from 170 medical centres across the USA and includes administrative, clinical, laboratory, and pharmacy data repositories that are linked using unique patient identifiers.

All data partners received institution review board approval or waiver in accordance with their institutional governance guidelines. Use of SIDIAP was approved by the Clinical Research Ethics Committee of the Institut Universitari d’Investigació en Atenció Primària Jordi Gol (Barcelona, Spain; project code 20/070-PCV). Use of VA-OMOP was reviewed by the US Department of Veterans Affairs Central Institutional Review Board and was determined to meet the criteria for exemption under Exemption Category 4(3) and approved the request for Waiver of HIPAA Authorization. Use of CUIMC was approved by the Columbia University Institutional Review Board as an OHDSI network study (AAA07805).

Cohort eligibility, study period, and follow-up
Each cohort consisted of adults aged 18 years or older who received at least one outpatient prescription for an ACEI, ARB, calcium channel blocker (CCB), or thiazide or thiazide-like diuretic (THZ) between Nov 1, 2019, and Jan 31, 2020. The index date (ie, start of cohort follow-up) was set as the date of the last prescription in this time window (figure 1). We required patients to be observable in their data source for at least 180 days before the index date and have a diagnostic code for hypertension at any point before or including the index date. Cohort exit was the earliest of the occurrence of an outcome; the end of exposure, death, loss or deregistration from the database; or date of last data collection.

Exposures
The exposures of interest were four first-line antihypertensive drug classes: ACEIs, ARBs, CCBs, or THZs. Users were defined separately as receiving either...
(I) monotherapy or (2) monotherapy or combination therapy (combination use) with other antihypertensive medications. Our primary comparison examined outpatient exposure to RAS blockers (ACEI or ARBs) with exposure to CCBs or THZs (included as active comparators). Further investigation compared class exposure to ACEIs with exposure to ARBs separately, and individual classes to various active comparators, leading to ten different target–comparator pairings for monotherapy and combination use each, as listed in the appendix (pp 2–13). For patients on monotherapy, we required the absence of any other antihypertensive treatment between –180 days and 0 days before the index date. We defined continuous drug exposures from the start of follow-up by grouping sequential prescriptions that had at most a 30-day gap between prescriptions, and defined the end of exposure as the end of the last prescription’s drug supply in such a sequence.

Outcomes

We investigated four COVID-19-related outcomes: COVID-19 diagnosis; hospital admission with COVID-19; hospital admission with pneumonia; and hospital admission with pneumonia, acute respiratory distress syndrome, acute kidney injury, or sepsis. Positive COVID-19 PCR test results or SNOMED diagnostic codes defined COVID-19 status. COVID-19 antibody tests were not available when we did the study. The full details of the participant cohorts and outcome definitions used can be found in the protocol.

Statistical analysis

We undertook this study using all patients who met the eligibility criteria within each database. Therefore, we did not calculate the sample size a priori; instead, we provided a minimum detectable rate ratio (MDRR) for each target–comparator–outcome triplet across each data source. To adjust for potential measured confounding and to improve the balance between comparison cohorts, we built large-scale propensity score models for each comparison and data source using a consistent data-driven process through regularised regression. This process used a large set of predefined baseline patient characteristics (including age, sex, race [US data], and other demographics) and previous conditions, drug exposures, procedures, and health service use behaviours to provide the most accurate prediction of treatment and balance patient cohorts across many characteristics. For computational efficiency, we excluded all features that occurred in fewer than 0·1% of patients within the target and comparator cohorts before propensity score model fitting.

In separate analyses, we stratified patients into five propensity score quintiles or variable-ratio matched patients by propensity, and used Cox proportional hazards models to estimate hazard ratios (HRs) between alternative target and comparator treatments for the risk of each outcome in each data source. The regression conditioned on the propensity score strata or matching units, with treatment allocation as the sole explanatory variable. We aggregated HR estimates across data sources to produce meta-analytic estimates using a random-effects meta-analysis. We only included estimates that passed propensity score diagnostics in the main meta-analysis, with meta-analytic estimates based on all data sources provided as a sensitivity analysis. For both monotherapy and combination use of the ACEI, ARB, CCB, THZ, ACEI or ARB, and CCB or THZ class groups (ten pairwise comparisons) to study four outcomes in three data sources (plus one meta-analysis) using two propensity score–adjustment approaches, we generated 1280 study effects.

Residual study bias from unmeasured and systematic sources often remains in observational studies even after controlling for measured confounding through propensity score adjustment. For each study effect, we did negative control outcome experiments, for which the null hypothesis of no effect is believed to be true, using a possible 123 controls identified through a data-rich algorithm and validated in a previous antihypertensive comparative study. Using the empirical null distributions from these experiments, we calibrated each study effect HR estimate, its 95% CI, and the p value to reject the null hypothesis of no differential effect. We declared an HR as significantly different from no effect when its calibrated p value was less than 0·05 without correcting for multiple testing.

These study diagnostics were presented to clinicians and epidemiologists who were masked to the HRs generated by the models for evaluation to provide an unbiased assessment of their validity. The suite of diagnostics included the MDRR, the preference score (a transformation of the propensity score that adjusts for prevalence differences between populations) distributions to evaluate empirical equipoise and population generalisability, extensive patient characteristics to evaluate cohort balance before and after adjustment using the propensity score, negative control calibration plots to assess residual bias, and Kaplan-Meier plots to examine HR proportionality assumptions. We defined target and comparator cohorts to stand in empirical equipoise if the majority of patients in both carried preference scores between 0·3 and 0·7 and to achieve sufficient balance if all after-adjustment baseline characteristics returned an absolute standardised mean differences of less than 0·1. Heterogeneity following meta-analysis was defined by an \( \hat{I}^2 \) value of more than 40%.

We did this study using the open-source OHDSI CohortMethod R package with large-scale analytics made possible through the Cyclops R package. The prespecified ICARIUS protocol and start-to-finish open and executable source code are available online. To promote transparency and facilitate sharing and exploration of the complete result set, an interactive web application provides study diagnostics and results for all study effects.

The study is registered with the EU Post-Authorisation Studies register, EUPAS35296.
Role of the funding source
The funders of the study had no role in study design, study execution, data collection, data interpretation, writing of the report, or the decision to submit for publication, and all authors share responsibility for the decision to submit this work for publication. This was a federated data analysis, and no single author had access to all of the underlying data. TD-S, SF-B, and MA had access to the data in SIDIAP; TF and GH had access to the data in CUIMC; and SLD and KL had access to the data in VA-OMOP. DRM, MMC, SCY, GH, and MAS had full access to all aggregate results.

Results
Among 13,553,491 patients included in the analysis, 363,785 patients with hypertension who received ACEI or ARB monotherapy were compared with 248,915 patients who received CCB or THZ monotherapy, contributing 1,212,123 person-years and 81,261 person-years of follow-up, respectively. The overall incidence of COVID-19 diagnosis was 5·6 per 1000 person-years among patients who received ACEI or ARB monotherapy compared with 4·8 per 1000 person-years among those who received CCB or THZ monotherapy, although incidence rates varied by data source.

Corresponding patient cohort size and diagnosis incidence rates were 268,711 and 5·6 per 1000 person-years for ACEI (alone) monotherapy users and 92,485 and 5·1 per 1000 person-years for ARB (alone) monotherapy users. Cohorts for combination users (as monotherapy or combination therapy) were as large as 711,799 for ACEI or ARB users and 473,076 for CCB or THZ users.

The aggregated patient cohort size, follow-up duration, incidences of each COVID-19-related outcome, and MDRR for each drug comparison and database are shown in table 1. The appendix (pp 2–13) provides further cohort size and outcome event information for all ten pairwise cohort comparisons across all four outcomes.

Baseline characteristics of ACEI or ARB monotherapy users compared with CCB or THZ monotherapy users, before and after propensity score stratification, are shown in tables 2–4. There were baseline differences in sex, hyperlipidaemia, diabetes, renal impairment, heart failure, heart disease, atrial fibrillation, drugs for diabetes, lipid-modifying agents, antithrombotics, antacids, opioids, and race that varied by data source. Further information on the population characteristics for each cohort comparison and design evaluated for each data source are shown in the appendix (pp 14–162), one for each of the 60 comparisons across data sources. The number of baseline patient characteristics differed across comparison cohorts and data sources. The process generated more than 10,000 unique features in each data source; the number of characteristics present in at least 1% of patients in each comparison cohort ranged from 2,284 to 2,473 in SIDIAP, 2,657 to 3,366 in VA-OMOP, and 2,694 to 3,859 in CUIMC. After large-scale propensity score construction, followed by stratification or matching, standardised mean differences for all baseline characteristics were less than 0·1 in SIDIAP and VA-OMOP for each drug comparison, apart from the comparison between combination users of ARBs and CCBs or THZs in VA-OMOP. Standardised mean differences for all baseline characteristics before and after propensity score adjustment for ACEI or ARB monotherapy users

| Patients | Time, years | Events | MDRR |
|---|---|---|---|
| Target cohort | Comparator cohort | Target cohort | Comparator cohort | Target cohort | Comparator cohort |
| ACEIs or ARBs vs CCBs or THZs | | | | | |
| Monotherapy | | | | | |
| SIDIAP | 37,796 | 14,003 | 10,239 | 37,800 | 500 | 184 | 1·27 |
| VA-OMOP | 320,450 | 229,063 | 110,380 | 76,856 | 145 | 183 | 1·37 |
| CUIMC | 5539 | 5849 | 594 | 625 | 28 | 24 | 2·18 |
| Combination use | | | | | |
| SIDIAP | 45,239 | 19,007 | 12,654 | 5175 | 627 | 250 | 1·23 |
| VA-OMOP | 656,274 | 443,061 | 228,678 | 150,755 | 345 | 335 | 1·24 |
| CUIMC | 10,286 | 11,008 | 1128 | 1185 | 59 | 58 | 1·68 |
| ACEIs vs CCBs or THZs | | | | | |
| Monotherapy | | | | | |
| SIDIAP | 7653 | 14,003 | 1815 | 3780 | 95 | 184 | 1·43 |
| VA-OMOP | 82,872 | 229,063 | 28689 | 76,856 | 46 | 183 | 1·52 |
| CUIMC | 2860 | 5849 | 301 | 625 | 17 | 24 | 2·54 |
| Combination use | | | | | |
| SIDIAP | 9194 | 39,427 | 2457 | 10714 | 137 | 519 | 1·32 |
| VA-OMOP | 201,503 | 854,224 | 70,267 | 295,986 | 127 | 574 | 1·31 |
| CUIMC | 5669 | 14,271 | 629 | 1533 | 41 | 77 | 1·77 |
| ARBs vs CCBs or THZs | | | | | |
| Monotherapy | | | | | |
| SIDIAP | 30,787 | 14,003 | 8293 | 3780 | 398 | 184 | 1·28 |
| VA-OMOP | 235,348 | 229,063 | 28689 | 76,856 | 96 | 183 | 1·40 |
| CUIMC | 2576 | 5849 | 277 | 625 | 10 | 24 | 2·84 |
| Combination use | | | | | |
| SIDIAP | 44,239 | 23,923 | 9803 | 7941 | 485 | 399 | 1·21 |
| VA-OMOP | 457,557 | 639,500 | 158,721 | 221,239 | 218 | 494 | 1·24 |
| CUIMC | 5811 | 16,302 | 511 | 1754 | 18 | 83 | 1·94 |

ACEIs—angiotensin-converting enzyme inhibitor. ARBs—angiotensin receptor blocker. CCBs—calcium channel blockers. CUIMC—Columbia University Irving Medical Center data warehouse. MDRR—minimum detectable risk ratio. SIDIAP—Information Systems for Research in Primary Care. THZs—thiazide or thiazide-like diuretic. VA-OMOP—US Department of Veterans Affairs Observational Medical Outcomes Partnership.
### Before stratification vs After stratification

| Age group, years | Target SIDIAP cohort (n=37796) | Comparator SIDIAP cohort (n=14003) | Standardised mean difference | Target SIDIAP cohort (n=37796) | Comparator SIDIAP cohort (n=14003) | Standardised mean difference |
|------------------|---------------------------------|-----------------------------------|-------------------------------|---------------------------------|-----------------------------------|-------------------------------|
| <25              | 0·1%                            | 0·1%                              | 0·00                          | 0·1%                            | 0·1%                              | –0·01                         |
| 25–29            | 0·2%                            | 0·2%                              | 0·00                          | 0·2%                            | 0·2%                              | –0·01                         |
| 30–34            | 0·6%                            | 0·6%                              | 0·01                          | 0·6%                            | 0·6%                              | 0·00                          |
| 35–39            | 1·6%                            | 1·0%                              | 0·04                          | 1·4%                            | 1·3%                              | 0·01                          |
| 40–44            | 3·8%                            | 2·3%                              | 0·08                          | 3·4%                            | 3·3%                              | 0·01                          |
| 45–49            | 7·0%                            | 5·0%                              | 0·08                          | 6·4%                            | 6·5%                              | 0·00                          |
| 50–54            | 10·4%                           | 7·9%                              | 0·09                          | 9·6%                            | 9·9%                              | –0·01                         |
| 55–59            | 12·5%                           | 10·2%                             | 0·07                          | 11·8%                           | 12·1%                             | –0·01                         |
| 60–64            | 13·7%                           | 12·5%                             | 0·03                          | 13·4%                           | 13·2%                             | –0·00                         |
| 65–69            | 13·4%                           | 13·4%                             | 0·00                          | 13·5%                           | 13·2%                             | 0·01                          |
| 70–74            | 12·9%                           | 14·6%                             | –0·05                         | 13·4%                           | 13·4%                             | 0·00                          |
| 75–79            | 9·8%                            | 12·7%                             | –0·09                         | 10·7%                           | 10·5%                             | 0·01                          |
| 80–84            | 6·8%                            | 9·0%                              | –0·08                         | 7·4%                            | 7·4%                              | 0·00                          |
| 85–89            | 4·7%                            | 6·5%                              | –0·08                         | 5·2%                            | 5·2%                              | 0·00                          |
| 90–94            | 2·1%                            | 2·9%                              | –0·06                         | 2·3%                            | 2·3%                              | 0·00                          |
| ≥95              | 0·5%                            | 0·8%                              | –0·04                         | 0·5%                            | 0·7%                              | –0·02                         |
| **Sex**          |                                 |                                   |                               |                                 |                                   |                               |
| Female           | 46·8%                           | 53·0%                             | –0·12                         | 48·9%                           | 47·8%                             | 0·02                          |
| Male             | 53·2%                           | 47·0%                             | –0·12                         | 51·1%                           | 52·2%                             | 0·02                          |
| **Medical history: general** |                          |                                   |                               |                                 |                                   |                               |
| Acute respiratory disease | 8·6% | 8·4% | 0·01 | 8·6% | 8·5% | 0·00 |
| Attention deficit hyperactivity disorder | 0·1% | 0·1% | 0   | 0·1% | 0·1% | 0   |
| Chronic liver disease | 1·5% | 1·7% | –0·02 | 1·6% | 1·7% | –0·01 |
| Chronic obstructive lung disease | 6·0% | 7·0% | –0·04 | 6·2% | 6·3% | 0   |
| Crohn’s disease | 0·2% | 0·2% | 0   | 0·2% | 0·2% | 0   |
| Dementia | 2·3% | 2·7% | –0·03 | 2·5% | 2·3% | 0   |
| Depressive disorder | 13·6% | 14·8% | –0·04 | 14·0% | 13·7% | 0   |
| Diabetes | 19·9% | 22·8% | –0·07 | 20·7% | 20·4% | 0   |
| Gastro-oesophageal reflux disease | 10·0% | 11·5% | –0·05 | 10·4% | 10·4% | 0   |
| Gastrointestinal haemorrhage | 0·7% | 0·8% | –0·01 | 0·7% | 0·7% | –0·01 |
| HIV infection | 0·5% | 0·4% | 0   | 0·5% | 0·4% | 0   |
| Hyperlipidaemia | 26·7% | 27·9% | –0·03 | 27·0% | 26·9% | 0   |
| Hypertensive disorder | 99·2% | 99·3% | –0·01 | 99·2% | 99·3% | 0   |
| Lesion of liver | 0·8% | 1·0% | –0·03 | 0·8% | 0·9% | –0·01 |
| Obesity | 34·6% | 37·5% | –0·06 | 35·5% | 35·6% | 0   |
| Osteoarthritis | 27·9% | 33·2% | –0·12 | 29·6% | 28·9% | 0   |
| Pneumonia | 0·7% | 0·6% | 0   | 0·7% | 0·6% | 0   |
| Psoriasis | 3·7% | 3·7% | 0   | 3·7% | 3·7% | 0   |
| Renal impairment | 8·1% | 13·8% | –0·18 | 9·4% | 10·0% | –0·02 |
| Rheumatoid arthritis | 0·4% | 0·5% | 0   | 0·5% | 0·4% | 0   |
| Schizophrenia | 0·5% | 0·5% | 0   | 0·5% | 0·5% | 0   |
| Ulcerative colitis | 0·4% | 0·5% | –0·01 | 0·4% | 0·4% | 0   |
| Urinary tract infectious disease | 4·9% | 5·3% | –0·02 | 5·1% | 4·9% | 0   |
| Viral hepatitis C | 1·2% | 1·2% | 0   | 1·2% | 1·2% | 0   |
| Visual system disorder | 36·5% | 42·0% | –0·11 | 38·1% | 37·5% | 0   |
| Atrial fibrillation | 3·8% | 4·6% | –0·04 | 4·3% | 3·9% | 0   |
| Cerebrovascular disease | 2·1% | 2·4% | –0·02 | 2·2% | 2·0% | 0   |
| Coronary arteriosclerosis | 0 | 0 | 0.01 | 0 | 0 | 0.01 |

(Table 2 continues next page)
We report the proportion of selected baseline characteristics and standardised mean difference among ACEI, ARB, CCB, and THZ users before and after propensity score stratification. Less extreme standard differences through stratification suggest improved balance between patient cohorts through propensity score adjustment. ACEI=angiotensin-converting enzyme inhibitor. ARB=angiotensin receptor blocker. CCB=calcium channel blocker. SIDIAP=Information Systems for Research in Primary Care. THZ=thiazide or thiazide-like diuretic.

| Medical history: neoplasms | Before stratification | After stratification |
|----------------------------|-----------------------|----------------------|
|                            | Target SIDIAP cohort  | Comparator SIDIAP cohort | Target SIDIAP cohort  | Comparator SIDIAP cohort |
|                            | (n=37 796)            | (n=14 003)           | (n=37 796)            | (n=14 003) |
| Heart disease              | 20·7%                 | 24·9%                | -0·10                 | 21·8%          | 21·8%                | 0·00 |
| Heart failure              | 1·7%                  | 2·1%                | -0·03                 | 1·8%           | 1·7%                | 0·00 |
| Ischaemic heart disease    | 3·9%                  | 4·7%                | -0·04                 | 4·1%           | 4·0%                | 0·01 |
| Peripheral vascular disease| 2·7%                  | 4·3%                | -0·08                 | 3·1%           | 3·2%                | -0·01 |
| Pulmonary embolism         | 0·5%                  | 0·6%                | -0·01                 | 0·6%           | 0·5%                | 0·01 |
| Venous thrombosis          | 1·0%                  | 1·1%                | -0·01                 | 1·1%           | 0·9%                | 0·01 |

| Medication use             | Before stratification | After stratification |
|----------------------------|-----------------------|----------------------|
|                            | Target SIDIAP cohort  | Comparator SIDIAP cohort | Target SIDIAP cohort  | Comparator SIDIAP cohort |
|                            | (n=37 796)            | (n=14 003)           | (n=37 796)            | (n=14 003) |
| Antibacterials for systemic use | 17·7%                 | 18·8%            | -0·03                | 18·0%           | 17·8%                | 0·00 |
| Antidepressants             | 16·9%                 | 18·1%            | -0·03                | 17·3%           | 17·0%                | 0·01 |
| Antiepileptics              | 7·0%                  | 8·0%              | -0·04                | 7·3%            | 7·2%                | 0·00 |
| Anti-inflammatory and antirheumatic products | 21·9%                 | 20·9%            | -0·03                | 21·7%           | 21·3%                | 0·01 |
| Antineoplastic agents       | 0·5%                  | 0·6%              | -0·01                | 0·6%            | 0·5%                | 0·01 |
| Antipsoretics               | 0·7%                  | 1·0%              | -0·04                | 0·7%            | 0·8%                | -0·01 |
| Antithrombotic agents       | 18·2%                 | 22·3%            | -0·10                | 19·4%           | 19·1%                | 0·01 |
| Drugs for acid-related disorders | 23·0%                 | 28·1%            | -0·12                | 24·5%           | 24·0%                | 0·01 |
| Drugs for obstructive airway diseases | 7·0%                  | 7·9%              | -0·03                | 7·3%            | 7·1%                | 0·00 |
| Drugs used in diabetes      | 15·3%                 | 18·2%            | -0·06                | 16·6%           | 16·2%                | 0·01 |
| Immunosuppressants          | 1·3%                  | 2·4%              | -0·08                | 1·5%            | 1·8%                | -0·02 |
| Lipid-modifying agents      | 29·8%                 | 32·9%            | -0·07                | 30·7%           | 30·7%                | 0·00 |
| Opioids                     | 9·2%                  | 11·4%             | -0·07                | 9·8%            | 9·8%                | 0·00 |
| Psychostimulants, agents used for attention deficit hyperactivity disorder, and nootropics | 1·2%                  | 1·4%              | -0·02                | 1·3%            | 1·2%                | 0·01 |

| Race                        | Before stratification | After stratification |
|----------------------------|-----------------------|----------------------|
|                            | Target SIDIAP cohort  | Comparator SIDIAP cohort | Target SIDIAP cohort  | Comparator SIDIAP cohort |
|                            | (n=37 796)            | (n=14 003)           | (n=37 796)            | (n=14 003) |
| American Indian or Alaska Native | …                      | …                    | …                      | …                      |
| Asian                       | …                      | …                    | …                      | …                      |
| Black or African American   | …                      | …                    | …                      | …                      |
| Native Hawaiian or other Pacific Islander | …                      | …                    | …                      | …                      |
| White                       | …                      | …                    | …                      | …                      |
| Other or unknown            | …                      | …                    | …                      | …                      |

| Ethnicity                   | Before stratification | After stratification |
|----------------------------|-----------------------|----------------------|
|                            | Target SIDIAP cohort  | Comparator SIDIAP cohort | Target SIDIAP cohort  | Comparator SIDIAP cohort |
|                            | (n=37 796)            | (n=14 003)           | (n=37 796)            | (n=14 003) |
| Hispanic or Latino         | …                      | …                    | …                      | …                      |
| Not Hispanic or Latino     | …                      | …                    | …                      | …                      |

Table 2: Baseline patient characteristics for prevalent use of ACEI or ARB (target) and CCB or THZ (comparator) monotherapy in the SIDIAP data source.
| Age group, years | Before stratification | After stratification |
|------------------|-----------------------|----------------------|
|                  | Target VA-OMOP cohort (n=320,450) | Comparator cohort (n=229,063) | Standardised mean difference |
|                  | Target VA-OMOP cohort (n=320,450) | Comparator cohort (n=229,063) | Standardised mean difference |
| <25              | 0.2%                  | 0.2%                  | 0.00 |
| 25-29            | 0.8%                  | 0.9%                  | -0.01 |
| 30-34            | 1.9%                  | 2.0%                  | -0.01 |
| 35-39            | 2.7%                  | 2.8%                  | -0.01 |
| 40-44            | 4.6%                  | 4.4%                  | 0.01 |
| 45-49            | 7.2%                  | 7.1%                  | 0.01 |
| 50-54            | 9.5%                  | 10.0%                 | -0.02 |
| 55-59            | 12.0%                 | 13.6%                 | -0.05 |
| 60-64            | 14.5%                 | 14.8%                 | -0.01 |
| 65-69            | 25.2%                 | 22.2%                 | 0.07 |
| 70-74            | 10.4%                 | 9.5%                  | 0.03 |
| 75-79            | 5.2%                  | 5.1%                  | 0.00 |
| 80-84            | 3.9%                  | 4.4%                  | -0.03 |
| 85-89            | 1.5%                  | 2.1%                  | -0.04 |
| ≥95              | 0.4%                  | 0.7%                  | -0.04 |
| **Sex**          |                       |                       |      |
| Female           | 5.2%                  | 9.0%                  | -0.15 |
| Male             | 94.8%                 | 91.0%                 | -0.15 |
| **Medical history: general** |                       |                       |      |
| Acute respiratory disease | 4.3%                  | 5.0%                  | -0.04 |
| Attention deficit hyperactivity disorder | 0.7%                  | 0.6%                  | 0.02 |
| Chronic liver disease | 1.6%                  | 2.5%                  | -0.06 |
| Chronic obstructive lung disease | 7.7%                  | 9.3%                  | -0.06 |
| Crohn's disease  | 0.2%                  | 0.2%                  | -0.01 |
| Dementia         | 2.0%                  | 2.4%                  | -0.03 |
| Depressive disorder | 16.7%                 | 17.7%                 | -0.03 |
| Diabetes         | 37.8%                 | 16.3%                 | 0.50 |
| Gastro-oesophageal reflux disease | 13.9%                 | 14.2%                 | -0.01 |
| Gastrointestinal haemorrhage | 0.6%                  | 0.8%                  | -0.02 |
| HIV infection    | 0.5%                  | 0.8%                  | -0.03 |
| Hyperlipidaemia  | 48.2%                 | 39.6%                 | 0.17 |
| Hypertensive disorder | 68.4%                 | 71.1%                 | -0.06 |
| Lesion of liver  | 1.2%                  | 1.6%                  | -0.03 |
| Obesity          | 12.7%                 | 10.6%                 | 0.06 |
| Osteoarthritis   | 14.5%                 | 15.8%                 | -0.04 |
| Pneumonia        | 0.7%                  | 0.9%                  | -0.03 |
| Psoriasis        | 1.2%                  | 1.0%                  | 0.02 |
| Renal impairment | 6.1%                  | 7.1%                  | -0.04 |
| Rheumatoid arthritis | 0.7%                  | 0.8%                  | 0.00 |
| Schizophrenia    | 0.8%                  | 1.2%                  | -0.03 |
| Ulcerative colitis | 0.3%                  | 0.3%                  | 0.00 |
| Urinary tract infectious disease | 1.3%                  | 1.5%                  | -0.02 |
| Viral hepatitis C | 1.0%                  | 2.0%                  | -0.08 |
| Visual system disorder | 28.5%                 | 27.7%                 | 0.02 |
| Atrial fibrillation | 2.8%                  | 2.3%                  | 0.04 |
| Cerebrovascular disease | 2.3%                  | 2.3%                  | 0.00 |
| Coronary arteriosclerosis | 6.4%                  | 4.4%                  | 0.09 |

(Table 3 continues on next page)
Table 3: Baseline patient characteristics for prevalent use of ACEI or ARB (target) and CCB or THZ (comparator) monotherapy in the VA-OMOP data source.
### Age group, years

| Age group, years | Before stratification | After stratification |
|------------------|-----------------------|----------------------|
|                  | Target CUIMC cohort (n=5539) | Comparator CUIMC cohort (n=5849) | Standardised mean difference | Target CUIMC cohort (n=5539) | Comparator CUIMC cohort (n=5849) | Standardised mean difference |
| <25              | 0.6%                  | 0.5%                 | 0.01                     | 0.7%                  | 0.4%                 | 0.04                     |
| 25–29            | 0.7%                  | 1.1%                 | -0.04                    | 0.8%                  | 0.8%                 | 0.00                     |
| 30–34            | 1.1%                  | 1.5%                 | -0.03                    | 1.3%                  | 1.2%                 | 0.01                     |
| 35–39            | 1.8%                  | 2.3%                 | -0.04                    | 2.0%                  | 1.9%                 | 0.01                     |
| 40–44            | 2.8%                  | 3.5%                 | -0.04                    | 2.8%                  | 3.1%                 | -0.02                    |
| 45–49            | 4.7%                  | 5.3%                 | -0.03                    | 5.1%                  | 4.9%                 | 0.01                     |
| 50–54            | 7.1%                  | 7.0%                 | 0.00                     | 7.3%                  | 6.6%                 | 0.03                     |
| 55–59            | 9.9%                  | 9.0%                 | 0.03                     | 9.7%                  | 9.2%                 | 0.02                     |
| 60–64            | 13.1%                 | 11.4%                | 0.05                     | 12.5%                 | 12.3%                | 0.01                     |
| 65–69            | 14.9%                 | 13.4%                | 0.04                     | 14.4%                 | 13.7%                | 0.02                     |
| 70–74            | 15.4%                 | 15.0%                | 0.01                     | 15.1%                 | 15.8%                | -0.02                    |
| 75–79            | 11.8%                 | 11.9%                | 0.00                     | 11.8%                 | 12.4%                | -0.02                    |
| 80–84            | 8.3%                  | 8.4%                 | 0.00                     | 8.1%                  | 8.6%                 | -0.02                    |
| 85–89            | 4.7%                  | 5.5%                 | -0.03                    | 5.0%                  | 5.3%                 | -0.01                    |
| 90–94            | 2.0%                  | 3.0%                 | -0.06                    | 2.3%                  | 2.7%                 | -0.03                    |
| ≥95              | 0.8%                  | 0.8%                 | 0.00                     | 1.0%                  | 0.8%                 | 0.02                     |

### Sex

|       | Before stratification | After stratification |
|-------|-----------------------|----------------------|
|       | Target CUIMC cohort (n=5539) | Comparator CUIMC cohort (n=5849) | Standardised mean difference | Target CUIMC cohort (n=5539) | Comparator CUIMC cohort (n=5849) | Standardised mean difference |
| Female| 50.1%                 | 58.7%                | -0.17                    | 55.2%                 | 53.9%                | 0.03                     |
| Male  | 49.9%                 | 41.3%                | -0.17                    | 44.8%                 | 46.1%                | 0.03                     |

### Medical history: general

**Acute respiratory disease**
- Target CUIMC cohort (n=5539): 3.6%
- Comparator CUIMC cohort (n=5849): 4.0%
- Standardised mean difference: -0.02

**Attention deficit hyperactivity disorder**
- Target CUIMC cohort (n=5539): 0.2%
- Comparator CUIMC cohort (n=5849): 0.2%
- Standardised mean difference: 0.00

**Chronic liver disease**
- Target CUIMC cohort (n=5539): 0.7%
- Comparator CUIMC cohort (n=5849): 1.2%
- Standardised mean difference: -0.05

**Chronic obstructive lung disease**
- Target CUIMC cohort (n=5539): 2.7%
- Comparator CUIMC cohort (n=5849): 3.1%
- Standardised mean difference: -0.02

**Crohn’s disease**
- Target CUIMC cohort (n=5539): 0.3%
- Comparator CUIMC cohort (n=5849): 0.2%
- Standardised mean difference: 0.01

**Dementia**
- Target CUIMC cohort (n=5539): 1.7%
- Comparator CUIMC cohort (n=5849): 2.3%
- Standardised mean difference: -0.04

**Depressive disorder**
- Target CUIMC cohort (n=5539): 4.9%
- Comparator CUIMC cohort (n=5849): 6.0%
- Standardised mean difference: -0.05

**Diabetes**
- Target CUIMC cohort (n=5539): 21.5%
- Comparator CUIMC cohort (n=5849): 13.2%
- Standardised mean difference: -0.22

**Gastro-oesophageal reflux disease**
- Target CUIMC cohort (n=5539): 7.1%
- Comparator CUIMC cohort (n=5849): 7.1%
- Standardised mean difference: 0.00

**Gastrointestinal haemorrhage**
- Target CUIMC cohort (n=5539): 0.8%
- Comparator CUIMC cohort (n=5849): 1.1%
- Standardised mean difference: -0.03

**HIV infection**
- Target CUIMC cohort (n=5539): 0.8%
- Comparator CUIMC cohort (n=5849): 1.7%
- Standardised mean difference: -0.02

**Hyperlipidaemia**
- Target CUIMC cohort (n=5539): 38.3%
- Comparator CUIMC cohort (n=5849): 33.1%
- Standardised mean difference: 0.11

**Hypertensive disorder**
- Target CUIMC cohort (n=5539): 61.1%
- Comparator CUIMC cohort (n=5849): 69.0%
- Standardised mean difference: -0.17

**Lesion of liver**
- Target CUIMC cohort (n=5539): 0.9%
- Comparator CUIMC cohort (n=5849): 1.5%
- Standardised mean difference: -0.06

**Obesity**
- Target CUIMC cohort (n=5539): 9.2%
- Comparator CUIMC cohort (n=5849): 9.8%
- Standardised mean difference: -0.02

**Osteoarthritis**
- Target CUIMC cohort (n=5539): 10.9%
- Comparator CUIMC cohort (n=5849): 12.2%
- Standardised mean difference: -0.04

**Pneumonia**
- Target CUIMC cohort (n=5539): 1.1%
- Comparator CUIMC cohort (n=5849): 1.9%
- Standardised mean difference: -0.06

**Psoriasis**
- Target CUIMC cohort (n=5539): 0.7%
- Comparator CUIMC cohort (n=5849): 0.5%
- Standardised mean difference: 0.03

**Renal impairment**
- Target CUIMC cohort (n=5539): 6.5%
- Comparator CUIMC cohort (n=5849): 9.7%
- Standardised mean difference: -0.12

**Rheumatoid arthritis**
- Target CUIMC cohort (n=5539): 0.8%
- Comparator CUIMC cohort (n=5849): 0.8%
- Standardised mean difference: 0.00

**Schizophrenia**
- Target CUIMC cohort (n=5539): 0.2%
- Comparator CUIMC cohort (n=5849): 0.3%
- Standardised mean difference: -0.02

**Ulcerative colitis**
- Target CUIMC cohort (n=5539): 0.2%
- Comparator CUIMC cohort (n=5849): 0.1%
- Standardised mean difference: 0.01

**Urinary tract infectious disease**
- Target CUIMC cohort (n=5539): 2.1%
- Comparator CUIMC cohort (n=5849): 2.8%
- Standardised mean difference: -0.05

**Viral hepatitis C**
- Target CUIMC cohort (n=5539): 0.4%
- Comparator CUIMC cohort (n=5849): 0.8%
- Standardised mean difference: -0.05

**Visual system disorder**
- Target CUIMC cohort (n=5539): 11.1%
- Comparator CUIMC cohort (n=5849): 10.2%
- Standardised mean difference: 0.03

**Atrial fibrillation**
- Target CUIMC cohort (n=5539): 5.3%
- Comparator CUIMC cohort (n=5849): 6.6%
- Standardised mean difference: -0.03

**Cerebrovascular disease**
- Target CUIMC cohort (n=5539): 5.3%
- Comparator CUIMC cohort (n=5849): 5.0%
- Standardised mean difference: 0.01

**Coronary arteriosclerosis**
- Target CUIMC cohort (n=5539): 22.0%
- Comparator CUIMC cohort (n=5849): 20.7%
- Standardised mean difference: 0.07

(Table 4 continues on next page)
Before stratification | After stratification
---|---
Target CUIMC cohort (n=5539) | Comparator CUIMC cohort (n=5849) | Standardised mean difference | Target CUIMC cohort (n=5539) | Comparator CUIMC cohort (n=5849) | Standardised mean difference

(Continued from previous page)

| Heart disease | 27.7% | 25.0% | 0.06 | 26.4% | 26.2% | 0.00 |
| Heart failure | 4.2% | 2.4% | 0.10 | 3.5% | 2.8% | 0.04 |
| Ischaemic heart disease | 3.4% | 3.3% | 0.00 | 3.1% | 3.6% | -0.03 |
| Peripheral vascular disease | 3.9% | 3.2% | 0.04 | 3.4% | 3.3% | 0.00 |
| Pulmonary embolism | 0.3% | 0.5% | -0.02 | 0.4% | 0.4% | 0.00 |
| Venous thrombosis | 0.6% | 1.2% | -0.06 | 0.7% | 1.0% | -0.04 |

Medical history: neoplasms

| Haematological neoplasm | 1.8% | 1.8% | 0.00 | 1.8% | 1.5% | 0.03 |
| Malignant lymphoma | 1.0% | 1.3% | -0.03 | 1.0% | 1.2% | -0.02 |
| Malignant neoplasm of anorectum | 0.2% | 0.2% | 0.01 | 0.2% | 0.2% | 0.01 |
| Malignant neoplastic disease | 9.5% | 10.8% | -0.04 | 9.9% | 10.2% | -0.01 |
| Malignant tumour of breast | 1.7% | 1.7% | 0.00 | 1.9% | 1.5% | 0.03 |
| Malignant tumour of colon | 0.3% | 0.5% | -0.04 | 0.3% | 0.5% | -0.03 |
| Malignant tumour of lung | 0.5% | 0.6% | -0.02 | 0.6% | 0.6% | 0.00 |
| Malignant tumour of urinary bladder | 0.5% | 0.5% | 0.00 | 0.5% | 0.5% | 0.01 |
| Primary malignant neoplasm of prostate | 1.5% | 1.8% | -0.03 | 1.4% | 1.7% | -0.03 |

Medication use

| Antibacterials for systemic use | 25.7% | 27.1% | -0.03 | 26.1% | 25.7% | 0.01 |
| Antidepressants | 15.2% | 15.5% | -0.01 | 15.4% | 15.1% | 0.01 |
| Antiepileptics | 13.3% | 13.0% | 0.01 | 13.4% | 12.7% | 0.02 |
| Anti-inflammatory and antirheumatic products | 17.1% | 20.5% | -0.09 | 18.6% | 18.9% | -0.01 |
| Antineoplastic agents | 3.2% | 4.1% | -0.05 | 3.6% | 3.6% | 0.00 |
| Antipsoriatics | 0.6% | 1.3% | -0.08 | 0.7% | 1.1% | -0.04 |
| Antithrombotic agents | 21.9% | 22.5% | -0.02 | 21.7% | 22.0% | -0.01 |
| Drugs for acid-related disorders | 22.6% | 26.9% | -0.10 | 24.3% | 24.9% | -0.01 |
| Drugs for obstructive airway diseases | 14.0% | 15.1% | -0.03 | 14.5% | 14.3% | 0.00 |
| Drugs used in diabetes | 22.7% | 12.8% | 0.26 | 17.0% | 17.8% | -0.02 |
| Immunosuppressants | 5.4% | 7.7% | -0.09 | 6.6% | 6.3% | 0.01 |
| Lipid-modifying agents | 43.2% | 35.0% | 0.17 | 38.4% | 39.4% | -0.02 |
| Opioids | 10.3% | 14.4% | -0.12 | 11.6% | 12.6% | -0.03 |
| Psycholeptics | 14.3% | 15.9% | -0.05 | 15.1% | 15.1% | 0.00 |
| Psychostimulants, agents used for attention deficit hyperactivity disorder, and nootropics | 1.5% | 1.5% | 0.00 | 1.5% | 1.5% | 0.00 |

Race

| American Indian or Alaska Native | 0.2% | <0.1% | 0.04 | 0.2% | <0.1% | 0.04 |
| Asian | 2.3% | 2.1% | 0.02 | 2.3% | 2.2% | 0.02 |
| Black or African American | 5.9% | 10.8% | -0.18 | 8.3% | 8.3% | 0.00 |
| Native Hawaiian or other Pacific Islander | 0.8% | 0.6% | 0.02 | 0.9% | 0.5% | 0.04 |
| White | 36.4% | 31.0% | 0.11 | 33.3% | 33.9% | -0.01 |
| Other or unknown | 2.1% | 2.3% | -0.03 | 2.0% | 2.3% | -0.02 |

Ethnicity

| Hispanic or Latino | 11.5% | 13.9% | -0.07 | 12.6% | 13.1% | -0.01 |
| Not Hispanic or Latino | 35.3% | 34.4% | 0.02 | 34.3% | 35.2% | -0.02 |

We report the proportion of selected baseline characteristics and standardised mean difference among ACEI, ARB, CCB, and THZ users before and after propensity score stratification. Less extreme standard differences through stratification suggest improved balance between patient cohorts through propensity score adjustment.

ACEI=angiotensin-converting enzyme inhibitor. ARB=angiotensin receptor blocker. CCB=calcium channel blocker. CUIMC=Columbia University Irving Medical Center data warehouse. THZ=thiazide or thiazide-like diuretic.

Table 4: Baseline patient characteristics for prevalent use of ACEI or ARB (target) and CCB or THZ (comparator) monotherapy in the CUIMC data source
compared with CCB or THZ monotherapy users for all data sources are plotted in figure 2. In CUIMC, all but one drug comparison (ACEI vs ARB monotherapy) with propensity score stratification showed residual cohort imbalances, with a standardised mean difference of 0.1 or more, which involved baseline characteristics related to pregnancy, renal transplantation, and heart failure and use of sacubitril. However, these cohort comparisons all passed study diagnostics for the propensity score matching design. The appendix (pp 163–282) shows study diagnostics for all comparisons and includes negative control effect estimate distributions. The number of negative control outcomes analysed ranged from 33 to 80 in CUIMC, 49 to 65 in SIDIAP, and 99 to 105 in VA-OMOP (appendix pp 314–17).

Calibrated HRs for the relative risk of incident COVID-19 diagnosis are presented in table 3 and figure 3 for propensity score-stratified and propensity score-matched analyses. In SIDIAP, there were 37796 monotherapy and 45239 combination users of ACEIs or ARBs. Compared with use of CCBs, the risk of COVID-19 diagnosis with propensity score stratification was not significantly different (HR 1.02, 95% CI 0.86–1.21, with monotherapy and 1.06, 0.92–1.24, with combination use). In VA-OMOP, there were 320450 monotherapy and 656274 combination users of ACEIs or ARBs. Compared with CCB or THZ use in VA-OMOP, the risk of COVID-19 diagnosis was not significantly different (HR 0.91, 95% CI 0.71–1.71, with monotherapy and 0.98, 0.81–1.18, with combination use). Propensity score stratification in CUIMC with 5539 monotherapy users and 10286 combinations users of ACEI or ARB did not pass study diagnostics. The corresponding HRs for CUIMC using propensity score matching were 0.67 (95% CI 0.20–2.20) with monotherapy and 2.36 (0.98–5.68) with combination use. Meta-analytic HRs following propensity score stratification for ACEI or ARB use compared with CCB or THZ use were 0.91 (95% CI 0.89–1.07) with monotherapy and 0.98 (0.89–1.07) with combination use (table 5).

When comparing ACEI and ARB use separately to CCB or THZ use, we observed no significant difference with COVID-19 diagnosis for comparisons passing study diagnostics (table 3). For ACEI use, meta-analytic HRs following propensity score stratification were 0.91 (95% CI 0.68–1.21) for monotherapy (but with heterogeneity of more than 40%) and 0.95 (0.83–1.07) for combination use. For ARB use, meta-analytic HRs following propensity score stratification were 1.10 (95% CI 0.89–1.35) with monotherapy and 1.08 (0.89–1.31) with combination use. Propensity score matching, where comparisons from CUIMC passed all propensity score diagnostics, produced similar results (table 5).
Figure 3: Calibrated HRs for COVID-19-related outcomes for ACEI, ARB, CCB, and THZ prevalent use across data sources

Outcomes are COVID-19 diagnosis, hospital admission with COVID-19, hospital admission with pneumonia, and hospital admission with pneumonia, acute respiratory distress syndrome, acute kidney injury, or sepsis. We plot calibrated HRs and their 95% CIs (indicated by error bars) labelled by propensity score adjustment method. Greyed out data source entries do not pass study diagnostics and greyed out meta-analysis entries return a heterogeneity ($I^2$) value of more than 40%.

ACEI=angiotensin-converting enzyme inhibitor. ARB=angiotensin receptor blocker. CCB=calcium channel blocker. CUIMC=Columbia University Irving Medical Center data warehouse. HR=hazard ratio. SIDIAP=Information Systems for Research in Primary Care. THZ=thiazide or thiazide-like diuretic. VA-OMOP=US Department of Veterans Affairs Observational Medical Outcomes Partnership.
| Propensity score stratified | Propensity score matched |
|-----------------------------|---------------------------|
| **ACEIs or ARBs vs CCBs or THZs** | **ACEIs or ARBs vs CCBs or THZs** |
| **Monotherapy** | **Combination use** |
| SIDIAP | 1.02 (0.86–1.21) | 1.16 (0.93–1.44) | 0.24 |
| VA-OMOP | 0.91 (0.71–1.17) | 1.06 (0.76–1.46) | 0.74 |
| CUIMC | 1.46 (0.83–2.62)* | 0.66 (0.20–2.00) | 0.53 |
| Meta-analysis | 0.98 (0.84–1.14) | 1.10 (0.92–1.32) | 0.31 |
| **Combination use** | | | |
| SIDIAP | 1.06 (0.92–1.24) | 1.02 (0.85–1.23) | 0.76 |
| VA-OMOP | 0.98 (0.81–1.18) | 1.03 (0.83–1.29) | 0.77 |
| CUIMC | 1.28 (0.86–1.90)* | 2.36 (0.98–5.68) | 0.06 |
| Meta-analysis | 1.01 (0.90–1.15) | 1.09 (0.84–1.41)† | 0.54† |
| **ACEIs vs CCBs or THZs** | **ACEIs vs CCBs or THZs** |
| **Monotherapy** | **Combination use** |
| SIDIAP | 1.05 (0.88–1.25) | 0.68 | 1.14 (0.90–1.43) | 0.34 |
| VA-OMOP | 0.77 (0.57–1.03) | 0.07 | 1.00 (0.70–1.44) | 0.96 |
| CUIMC | 0.90 (0.40–2.00)* | 0.79* | 0.92 (0.43–1.80) | 0.86 |
| Meta-analysis | 0.91 (0.68–1.21)* | 0.53† | 1.08 (0.89–1.31) | 0.45 |
| **Combination use** | | | |
| SIDIAP | 0.98 (0.86–1.12) | 0.75 | 0.95 (0.79–1.15) | 0.66 |
| VA-OMOP | 0.91 (0.75–1.10) | 0.33 | 0.87 (0.70–1.08) | 0.21 |
| CUIMC | 0.65 (0.38–1.22)* | 0.14* | 0.45 (0.17–1.18) | 0.11 |
| Meta-analysis | 0.95 (0.83–1.07) | 0.38 | 0.88 (0.75–1.04) | 0.14 |
| **ARBs vs CCBs or THZs** | **ARBs vs CCBs or THZs** |
| **Monotherapy** | **Combination use** |
| SIDIAP | 1.01 (0.79–1.30) | 0.76 | 0.98 (0.69–1.39) | 0.81 |
| VA-OMOP | 1.11 (0.78–1.58) | 0.57 | 1.18 (0.80–1.76) | 0.41 |
| CUIMC | 1.72 (0.87–3.40)* | 0.13* | 2.25 (0.43–11.66) | 0.34 |
| Meta-analysis | 1.10 (0.89–1.35) | 0.40 | 1.16 (0.89–1.50) | 0.28 |
| **Combination use** | | | |
| SIDIAP | 1.08 (0.89–1.31) | 0.47 | 1.06 (0.84–1.33) | 0.65 |
| VA-OMOP | 1.21 (0.99–1.49)* | 0.07* | 1.17 (0.93–1.47) | 0.19 |
| CUIMC | 1.69 (1.22–2.55)* | 0.02* | 1.31 (0.61–2.51) | 0.51 |
| Meta-analysis | 1.08 (0.89–1.31) | 0.49 | 1.16 (0.99–1.36) | 0.08 |
| **ACEIs vs ARBs** | **ACEIs vs ARBs** |
| **Monotherapy** | **Combination use** |
| SIDIAP | 1.05 (0.83–1.33) | 0.70 | 1.01 (0.77–1.32) | 0.79 |
| VA-OMOP | 0.73 (0.51–1.04) | 0.09 | 0.75 (0.52–1.10) | 0.15 |
| CUIMC | 0.61 (0.27–1.38) | 0.25 | 0.22 (0.02–6.30)* | 0.24* |
| Meta-analysis | 0.85 (0.69–1.05) | 0.14 | 0.86 (0.69–1.07) | 0.18 |
| **Combination use** | | | |
| SIDIAP | 0.93 (0.79–1.10) | 0.46 | 0.95 (0.74–1.22) | 0.67 |
| VA-OMOP | 0.84 (0.71–1.09) | 0.04 | 0.85 (0.71–1.02) | 0.08 |
| CUIMC | 0.58 (0.38–0.87)* | 0.01* | 0.54 (0.21–1.26) | 0.20 |
| Meta-analysis | 0.83 (0.79–0.99) | 0.03 | 0.87 (0.77–0.99) | 0.04 |

ACEI=angiotensin-converting enzyme inhibitor. ARB=angiotensin receptor blocker. CCB=calcium channel blocker. CUIMC=Columbia University Irving Medical Center data warehouse. HR=hazard ratio. SIDIAP=Information Systems for Research in Primary Care. THZ=thiazide or thiazide-like diuretic. VA-OMOP=US Department of Veterans Affairs Observational Medical Outcomes Partnership. *Data source entries do not pass study diagnostics and not included in the meta-analytic estimate. †Entries return heterogeneity (I²) values of more than 40%.

Table 5: Risk of COVID-19 diagnosis among users of ACEIs, ARBs, CCBs, and THZs

Calibrated HRs for the risk of hospital admission with COVID-19 are presented in figure 3. We observed no significant association between incident hospital admission with COVID-19 for the comparison with ACEI or ARB use, evaluated either together or separately, compared with CCB or THZ use. For ACEI use compared with ARB use, using propensity score stratification, meta-analytic HRs were 0.88 (95% CI 0.66–1.17) for monotherapy and 0.93 (0.82–1.07) with combination use.

No significant associations with the risk of pneumonia were observed with any drug comparison that satisfied study diagnostics. No significant associations with the risk of hospital admission with pneumonia, acute respiratory distress syndrome, acute kidney injury, or sepsis were observed with any drug comparison that satisfied study diagnostics in SIDIAP and CUIMC. In VA-OMOP, no significant difference was observed in comparisons between ARB versus CCB or THZ use (HR 1.09, 95% CI 0.90–1.29) or ACEI versus ARB use (1.02, 0.85–1.21) and the risk of hospital admission with pneumonia, acute respiratory distress syndrome, acute kidney injury, or sepsis, although small significant associations were observed with ACEI versus CCB or THZ (1.17, 1.01–1.36; appendix p 290).

Discussion

In this multicentre cohort study following more than 1.3 million patients with hypertension from the USA and Spain, we observed no clear association of increased risk of COVID-19 diagnosis, hospital admission, or subsequent complications associated with the outpatient prevalent ACEI or ARB use. Our findings support recent regulatory and clinical society recommendations that patients should not halt their ACEI or ARB therapy despite previously posited mechanisms of increased COVID-19 risk.43–46 Indeed, de Abajo and colleagues clearly demonstrate that with similar indicated treatments is crucial for reducing the risk of bias resulting from confounding by indication (eg, hypertension), in which the absence of treatment indicates either too mild a disease to warrant pharmacological treatment (eg, mild hypertension under control with lifestyle and diet changes), the presence of contraindications, or extreme frailty precluding the use of preventive medicines (eg, at the end of life).43–46
of being admitted to hospital with COVID-19, with an estimated odds ratio of 0·48 (95% CI 0·34–0·69) for severe cases and 0·57 (0·43–0·75) for less severe cases.\(^4\)

We observed one nominally significant meta-analysis difference: users of ACEI combination therapy had a lower risk of COVID-19 diagnosis when compared with users of ARB combination therapy. There was, however, no corresponding difference detected in hospital admission or complications. Therefore, the observed association might be due to chance or residual bias. Even if true, there is only a 12% difference, and therefore favouring ACEIs over ARBs for mitigating COVID-19 is not strongly supported by our result. There is limited evidence directly comparing the risk of COVID-19 between ACEI and ARB use. Several studies have reported main effect odds ratios lower than 1 with ACEIs compared with ARBs, ranging from 0·61 (95% CI 0·41–0·93) to 0·92 (0·64–1·32) for ACEIs and 0·88 (0·61–1·26) to 1·10 (0·88–1·37) for ARBs.\(^38,40–43\)

Notably, one study comparing 124 ACEI users admitted to hospital with COVID-19 matched to 248 ARB users found no difference in the risk of 28-day all-cause mortality.\(^47\)

Animal models suggest that although ACEIs increase ACE2 gene expression, they do not alter ACE2 activity, unlike ARBs, providing a potential mechanism for why differential effects might occur.\(^46\) However, recent studies in humans have identified no difference in ACE2 levels following exposure to ACEI or ARB use.\(^48–51\)

Therefore, our findings could also be explained by residual confounding, as suggested by recent comparisons of the incidence of Staphylococcus aureus infection and other outcomes between ACEI and ARB use, which suggest that ARB use is not a perfect comparator for ACEI use, although no large-scale propensity score adjustment was used.\(^32\)

Furthermore, one study has reported an increased risk of hospital admission with COVID-19 and intensive care unit admission associated with use of ACEIs and ARBs.\(^41\)

Although we did not observe a consistent increased risk of hospital admission with COVID-19, we did observe an increased risk of hospital admission with pneumonia, acute respiratory distress syndrome, acute kidney injury, or sepsis largely driven by ACEI use compared with CCB or THZ use. This finding might be related to the higher incidence of acute kidney injury associated with ACEI use because no increased risk was observed for pneumonia, and acute kidney injury would be considerably more frequent than acute respiratory distress syndrome or sepsis.

We used an open science approach to apply analyses across a network of observational databases so results can be directly compared and interpreted in aggregate. For these analyses, we used active comparators to reduce confounding by indication and, for the first time in such a study, applied large-scale propensity adjustment with full diagnostics and did a large set of negative control experiments. We published the study protocol ahead of time and kept results blinded when assessing propensity score diagnostics, helping to address concerns about reproducibility, robustness, and transparency that have emerged.\(^23\) Our study has also been recognised by the European Medicines Agency ENCePP Guide on Methodological Standards in Pharmacoepidemiology for COVID-19 studies.\(^24\)

We examined outpatient prevalent use of antihypertensive therapy because a new-user design in the context of COVID-19, which has widely affected the provision of routine care, is infeasible. Therefore, mediators on the causal pathway between exposure and outcome might be included in the adjustment. However, this might not necessarily result in bias, as COVID-19 is a new illness and will not have affected the decision to initiate one drug over another. Similarly, biological mechanisms relating to ACE2 expression might require chronic exposure, hindering a new-user design. Previous treatment remains highly correlated with many baseline features that our large-scale propensity model considers when balancing patients and can provide some protection against this potential bias.

Furthermore, we defined COVID-19 diagnosis through the presence of diagnostic codes or positive test results that will underestimate the number of true COVID-19 cases, the extent of which will vary by site due to differences in testing strategies. To address this potential limitation, we included a hospital admission-based COVID-19 outcome and observed similar results. Differences in the incidence of outcomes were noted between data sources, with VA-OMOP having much lower incidence than SIDIAP and CUIMC. This finding might relate to differences in the capture of COVID-19 diagnosis and hospital admission within each database, and differences in baseline community incidence. For example, the population in CUIMC are from New York City, which was the epicentre for US cases during the conduct of the study. Finally, although exposure is based on prescription information, we cannot determine whether the patient ingested their medication. Nevertheless, these data are representative of how patients use such medications in the real world. Although we have used a rigorous approach to observational research,\(^32\) residual confounding is still possible.

Our findings stand in agreement with regulatory and clinical society advice that ACEI and ARB therapy should not warrant class switching to reduce COVID-19 susceptibility.

**Contributors**

DRM, MMC, SCY, and MAS conceived the study. DRM, MMC, SCY, NP, KoB, CS, MEM, CGI, FN, TMA, RWP, DP-A, PRR, GH, and MAS developed the study protocol. MMC, SCY, JW, AGS, MJS, PRR, RDW, and MAS developed analysis tools. KK, TD-S, SF-B, MA, SLD, KL, TF, and GH executed the study in their data sources. TD-S, SF-B, and MA had access to the data in SIDIAP; TF and GH had access to the data in CUIMC; and SLD and KL had access to the data in VA-OMOP. DRM,
MMC, SCY, GH, and MAS had full access to all aggregate results. All authors contributed to the analysis of results and writing of the manuscript.

Declaration of interests
MAS reports grants from the US National Institutes of Health and IQVIA, and personal fees from Janssen Research & Development and Private Health Management, during the conduct of the study. DRM is supported by a Wellcome Trust Clinical Research Development Fellowship (grant 214588/Z/18/Z) and reports grants from the Scottish Chief Scientist Office, Health Data Research UK, the UK National Institute for Health Research, and Tenovus, outside the submitted work. KvB is partly funded by the European Health Data and Evidence Network project, which has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement number 806968; the Joint Undertaking receives support from the EU’s Horizon 2020 programme. SLD reports grants from Anolix, Anellas Pharma, AstraZeneca Pharmaceuticals, Boehringer Ingelheim International, Celgene, Eli Lilly and Company, Genentech, Genomic Health, Gilead Sciences, GlaxoSmithKline, Innocin Pharmaceuticals, Janssen Pharmaceuticals, Kanter Health, Myriad Genetic Laboratories, Novartis International, and Parcsel International, through the University of Utah (Salt Lake City, UT, USA) and the Western Institute for Biomedical Research (Salt Lake City, UT, USA), outside the submitted work. GH reports grants from the US NIH National Library of Medicine, during the conduct of the study, and grants from Janssen Research, outside the submitted work. KK is an employee of IQVIA. HMK reports personal fees from UnitedHealth, IBM Watson Health, Element Science, Aetna, Facebook, Siegfried & Jensen Law Firm, Arnold & Porter Law Firm, Ben C Martin Law Firm, and the National Center for Cardiovascular Diseases (Beijing, China); ownership of Hugo Health and Refactor Health; contracts from the US Centers for Medicare & Medicaid Services; and grants from Medtronic, US Food and Drug Administration, Johnson and Johnson, and Shenzhen Center for Health Information, outside the submitted work. JCEL reports grants from the UK Medical Research Council and Versus Arthritis (UK), outside the submitted work. FN was an employee at AstraZeneca until September, 2019, outside the submitted work. AP-U reports grants from Fundacion Alfonso Martin Escudero and the UK Medical Research Council, outside the submitted work. DP-A reports grants from Aegon, UCB Biopharma, and Les Laboratoires Servier: personal fees (paid to his department) from Aegon and UCB Biopharma; and support for training programmes organised by his department from Innovative Medicines Initiative-funded European Health Data and Evidence Network and European Medical Information Framework consortia, and Synapse Management Partners. PRR reports grants from the Innovative Medicines Initiative and Janssen Research & Development, during the conduct of the study. MMC is an employee of Janssen Research & Development, during the conduct of the study. PBR, JW, and MJ is employees of Janssen Research & Development and shareholders in Johnson & Johnson, during the conduct of the study. AGS reports personal fees from Janssen Research & Development, outside the submitted work. CA, MA, TMA, CS, TD-S, TF, SF-B, CGL, KL, MEM, RW, NP, AEW, RDW, SCY, and LZ declare no competing interests.

Data sharing
As this is a distributed data analysis, individual patient-level data from each database cannot be shared due to database governance restrictions. The supplement is available online. The prespecified ICARIUS protocol and start-to-finish open and executable source code are available online. To promote transparency and facilitate sharing and exploration of the complete result set, an interactive web application provides study diagnostics and results for all study effects.

Acknowledgments
This study was funded by the Wellcome Trust, the UK National Institute for Health Research, the US National Institutes of Health, the US Department of Veterans Affairs, Janssen Research & Development, IQVIA, the South Korean Ministry of Health and Welfare Republic, the Australian National Health and Medical Research Council, and European Health Data and Evidence Network. We acknowledge the tremendous work and dedication of the 350 participants from 30 nations in the March, 2020, OHDSI COVID-19 Virtual Study-a-thon, without whom this study could not have been realised.

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