Association of renin–angiotensin–aldosterone system inhibition with Covid-19 hospitalization and all-cause mortality in the UK biobank

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Aims: With growing evidence on the protective effect of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in coronavirus disease 2019 (Covid-19), we aimed to thoroughly investigate the association between the use of major classes of antihypertensive medications and Covid-19 outcomes in comparison with the use of ACEIs and ARBs.

Methods: We conducted a population-based study in patients with pre-existing hypertension in the UK Biobank with data from the first 2 SARS-CoV-2 waves prior population-based vaccination. Multivariable logistic regression analysis was performed adjusting for a wide range of confounders.

Results: The use of either β-blockers (BBs), calcium-channel blockers (CCBs) or diuretics was associated with a higher risk of Covid-19 hospitalization compared to ACEI use (adjusted OR (95%CI): 1.66 [1.43–1.93]) and ARB use (1.53 [1.30–1.81]). The risk of 28-day mortality among Covid-19 patients was also increased among users of BBs, CCBs or diuretics when compared to ACEI users (1.74 [1.30–2.33]) but not when compared to ARB users (1.26 [0.93–1.71]). The association between BB, CCB or diuretic use (compared to ACEI use) and 28-day mortality among hospitalized Covid-19 patients narrowly missed statistical significance (1.47 [0.99–2.18]) but it was statistically significant when the analysis was restricted to patients hospitalized during the second SARS-CoV-2 wave (1.80 [1.15–2.83]).

Conclusion: Our results suggest protective effects of inhibition of the renin–angiotensin–aldosterone system on Covid-19 hospitalization and mortality, particularly with ACEI, among patients with pharmaceutically treated hypertension. If confirmed by randomized controlled trials, this finding could have high clinical relevance for treating hypertension during the SARS-CoV-2 pandemic.

KEYWORDS
angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, Covid-19, hospitalization, hypertension, mortality, SARS-CoV-2

The authors confirm that the PI for this paper is Dr Ben Schöttker and that they had direct access to data of the patients.

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1 | INTRODUCTION

There has been a debate over the role of renin-angiotensin-aldosterone system (RAAS) and RAAS inhibition in coronavirus disease 2019 (Covid-19). Angiotensin converting enzyme 2 (ACE2) is a transmembrane enzyme that functions as receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). After SARS-CoV-2 binds to ACE2 receptor, endocytosis of the viral complex results in ACE2 downregulation and accumulation of angiotensin II (AngII) with proinflammatory, vasoconstrictive and profibrotic effects. ACE2 is present in different organs including heart, kidney and lungs, the target organ for SARS-CoV-2. ACE2 also counteracts the activation of RAAS via degrading AngII to angiotensins 1–7 that exert their vasodilatory, anti-inflammatory and antiproliferative effects through mitochondrial assembly receptor.

The controversy about the use of ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in patients infected with SARS-CoV-2 started with findings that showed higher prevalence and mortality of patients with cardiovascular diseases such as hypertension among patients with Covid-19. Moreover, in an animal study, increased expression of ACE2 messenger RNA (mRNA) with the use of RAAS inhibitors was observed, suggesting higher susceptibility to SARS-CoV-2 among the users of these medications and hence it was hypothesized that their use might be related to Covid-19 severity and mortality. However, current findings do not support this association and evidence regarding beneficial effects of RAAS inhibition is growing, illustrating a potential protective effect of RAAS inhibitors in relation to severe clinical outcomes of Covid-19, particularly in patients with hypertension.

The favourable effect of RAAS inhibitors in Covid-19 needs investigation in a large cohort study considering the inadequate and conflicting evidence at hand. Therefore, we aimed to investigate the association of ACEIs and ARBs with adverse Covid-19 outcomes in comparison with other antihypertensive drugs in the large UK Biobank.

2 | METHODS

2.1 | Study population

The UK Biobank is a large population-based prospective cohort with about 500 000 participants living in the UK aged 40–69 years when recruited in 2006–2010. The collection of data involved a self-completed touch-screen questionnaire, a computer-assisted interview, physical and functional measures, and the collection of biological samples, as previously described in detail. The data are also linked to electronic health-related records, including death, cancer, hospital admissions and primary care records. The UK Biobank study has obtained ethical approval from regulatory authorities and all participants provided signed electronic informed consent.

The UK Biobank has released Covid-19 data for its participants starting from March 2020. The data comprises of diagnostic Covid-19 test data, primary care data provided directly by the system suppliers, hospital inpatient, critical care and death data that are being updated regularly. Currently, the primary care data are only available for England and study participants from Scotland and Wales needed to be excluded. A part of the primary care data are the prescription data of general practitioners (GPs). Participants from England with no recorded GP prescription data and those who died before March 2020 were further excluded from the analyses. Moreover, to account for the confounding by indication bias, only patients with pharmacologically treated hypertension were included. Finally, among 149 962 English study participants with recent use of antihypertensive medications, a total of 124 143 (82.8%) had diagnosed hypertension and could be included in the analyses.

2.2 | Ascertainment of outcomes

Our primary outcome of interest was hospitalization due to Covid-19 and was identified from positive Covid-19 test results originated from a hospital setting. The secondary outcomes were 28-day all-cause mortality among: (i) Covid-19 patients and (ii) Hospitalized Covid-19 patients.

We used the Covid-19 data release from 2 June 2021, which included Covid-19 test data from 16 March 2020, onwards. However, we used only Covid-19 test data up to 23 February 2021, to have at least 28 days of mortality follow-up for all patients (the last date of death in the death data set available in June 2021 was 23 March 2021). In addition, we wanted to restrict the time of assessment of

What is already known about this subject

- There are inconclusive findings about potential beneficial effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in Covid-19.

What this study adds

- This observational study suggests that inhibition of the renin-angiotensin-aldosterone system might lead to lower Covid-19 hospitalization and mortality among patients with pharmaceutically treated hypertension.
- The best prognosis of Covid-19 patients with pharmaceutically treated hypertension was observed if angiotensin-converting enzyme inhibitors instead of other antihypertensive drugs were used.
Covid-19 patients to have not too many study participants with SARS-CoV-2 vaccination in our study population. According to official statistics, on 23 February 2021, the prevalence of full SARS-CoV-2 vaccination in the UK was 1.2%.17

2.3 | Exposures

Participants with recent use of antihypertensive medications as combination or monotherapy were identified from the GP data, using the ATC codes C02, C03, C07, C08 and C09. The antihypertensive treatment was then categorized to the following drug classes: ACEI (C09A and C09B), ARB (C09C and C09D), diuretic (C03, C02L, C07B, C07C, C07D, C08G, C09BA and C09DA), β-blocker (BB; C07) and calcium-channel blocker (CCB; C08, C07FB, C09BB and C09DB). Recent use was defined as 6 months prior to Covid-19 test date for participants with Covid-19 positive test result and 6 months prior to onset of the SARS-CoV-2 pandemic in March 2020 for those with no Covid-19 infection.

2.4 | Covariates

Sociodemographic, lifestyle and health-related data were taken from the touchscreen interview conducted at the baseline examination of the UK Biobank. Age at onset of the pandemic was calculated by adding the years passed between date of attending an assessment centre for baseline examination and 1 March 2020 to the baseline age. The ethnic background was categorized as white, black and other (all other ethnic groups combined), education according to years (≤9, 10–12, ≥13), and smoking status by never, former or current smoker. The Townsend deprivation index was calculated based on the participants living areas defined by the corresponding postal codes.20 The intensity of physical activity (low, moderate, high) was based on the International Physical Activity Questionnaire. The amount of ethanol consumed was estimated using the amount and type of beverages used and classified in to the WHO drinking categories as follows: abstainers, category I (mild) including women with an alcohol consumption of <20 g/d or men with <40 g/d, and category II (moderate) including women with an alcohol consumption of 20–39.99 g/d or men with 40–59.99 g/d and category III (heavy) including women with an alcohol consumption of ≥40 g/d or men with ≥60 g/d.

Blood samples were donated, and height, weight and systolic blood pressure (SBP) measures were taken as part of the health assessments during the baseline examination in the recruiting centres. An Omron automated device (range returned: 0–255 mmHg) or a manual sphygmomanometer were used for blood pressure measurements. Creatinine (μmol/L) was measured using enzymatic analysis on a Beckman Coulter AU5800. The estimated glomerular filtration rate (eGFR) was calculated based on the CKD-Epi Equation21 using serum creatinine and categorized to 3 levels: ≥90 (mL/min/1.73m²); ≥60–<90 (mL/min/1.73m²); and <60 (mL/min/1.73m²).

In addition to self-reported chronic diseases and major cardiovascular events in the touchscreen interview at baseline, GP diagnosis data were used to complete diagnoses as good as possible up to the baseline date for this analysis, which was 16 March 2020 (first recorded positive SARS-CoV-2 test in the UK Biobank study population). The comorbid conditions assessed were chronic obstructive pulmonary disease, diabetes mellitus, heart failure, coronary heart disease (CHD), history of myocardial infarction (MI) and history of stroke.

To specify the use of low-dose aspirin, lipid-lowering drugs and number of drugs concurrently used in participants only the GP data were used. The time window to find users of low-dose aspirin and lipid-lowering drugs was defined as 6 months prior to March 2020. For the total number of drugs used by each participant, a shorter, 3-month period prior to March 2020 was considered. Prescriptions with the same ATC code in this interval were only counted once.

In summary, age, all comorbidity and drug utilization information were up to date on the state of the onset of the SARS-CoV-2 pandemic (March 2020), while life-style-factors, physical health assessment measurements and biomarkers were on the state of the UK Biobank’s baseline examination from 2006–2010.

2.5 | Statistical analysis

Multivariable logistic regression models were fitted and odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated for the risk of Covid-19 hospitalization and 28-day all-cause mortality associated with drug exposures of interest. Covid-19 hospitalization was addressed in the total population of patients with hypertension and 28-day all-cause mortality was evaluated in 2 sub-populations of hypertensive patients: (i) those who tested positive for SARS-CoV-2 and (ii) those who were hospitalized due to Covid-19.

In a first round of analyses, ARB, CCB, BB and diuretic users were directly compared to ACEI users and in a second round of analyses the latter 3 were directly compared to ARB users as the reference group. To increase the statistical power, in the third round of analyses, we combined users of either CCBs, BBs and diuretics as 1 exposure group and compared it first to ACEI users and second to ARB users. Moreover, unadjusted Kaplan–Meier curves were generated for the third round of analyses and log-rank tests were applied to test for different survival probabilities between the patients who received different classes of antihypertensives.

Patients receiving combinations of other antihypertensive drug classes and ACEIs or ARBs were only assigned to the ACEIs or ARBs users group, respectively. In sensitivity analysis, we removed patients that used drug combinations with ACEIs or ARBs from the respective analyses using 1 of these drug groups as the reference.

All models were first adjusted for age, sex and ethnic background only (simple model), and second for all potential confounders available in the UK Biobank (full model), which included age, sex, ethnic background, socioeconomic deprivation, smoking status, physical activity, alcohol consumption, body mass index (BMI), SBP, eGFR, chronic
obstructive pulmonary disease, diabetes mellitus, heart failure, CHD, history of MI, history of stroke, use of low-dose aspirin, use of lipid-lowering drugs and number of drugs concurrently used.

The linearity assumption of the continuous co-variables age, BMI, SBP, socioeconomic deprivation index and number of drugs was checked for the outcome “Covid-19 hospitalization in the total population” by modelling restricted cubic splines. Furthermore, we investigated potential interactions. The respective curves are shown in Figures S1–S5. As the linearity assumption was violated for all variables, these were modelled with the categories shown in Table 1. Finally, we investigated multicollinearity in the full model. After removal of diastolic blood pressure and high- and low-density lipoprotein cholesterol, values of multicollinearity metrics of all variables were in an acceptable range (condition index, 1.0–18.55, tolerance, 0.46–0.97; variance inflation, 1.03–2.16).

The main analyses were also conducted stratified by SARS-CoV-2 wave. We used 31 August 2020 as the cut-off date between the first wave (caused by original variant) and the second wave (caused by alpha variant) because the alpha variant became dominant in the UK in September 2020. Furthermore, we investigated potential interactions of ACEI and ARB use in the analysis with the highest statistical power to minimize the number of tests in this multiple testing situation. Thus, interaction terms of both ACEI and ARB use with all 20 covariates of the full model were tested with reference to a group of either CCB, BB or diuretics use for the outcome Covid-19 hospitalization. The P-value was adjusted for the 40 tests conducted according to the Bonferroni method and only interactions terms with P < 0.00125 were considered as statistically significant.

All analyses were conducted with SAS software, version 9.4. The MCMC algorithm of the SAS procedure PROC MI was utilized to impute missing covariate values. For the imputation model, only the variables of the full model (and no auxiliary variables) were used. The proportion of missing values was below 1% for all covariates except physical activity (22%) and the eGFR (7%; Table S1). Analyses of the 5 imputed datasets were combined using the SAS procedure PROC MIANALYZE. Two-sided P values <.05 were considered significant.

### 2.6 Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in [http://www.guidetopharmacology.org](http://www.guidetopharmacology.org), and are permanently archived in the Concise Guide to Pharmacology 2019/20.18,19

### 3 RESULTS

#### 3.1 Characteristics of the study population

A total of 124 143 patients with pharmaceutically treated hypertension were included in this analysis, among whom 4592 (3.7%) patients had tested positive for Covid-19 and 1015 (0.8%) got hospitalized due to Covid-19 between 16 March 2020 and 23 February 2021. The baseline characteristics of these 3 different populations are shown in Table 1. There are clear trends from the total population to all Covid-19 patients and to hospitalized Covid-19 patients with respect to a higher percentage of males, a higher BMI, higher prevalence of current smoking, abstinence from alcohol, low physical activity, higher prevalence of an eGFR <60 mL/min/1.73 m² and all other assessed comorbidities, and higher use of lipid-lowering drugs and drugs in general. Hospitalized Covid-19 patients were older, but all Covid-19 patients combined were on average younger than the total population. The use of ACEI was less frequent among all Covid-19 patients (41.1%) and hospitalized Covid-19 patients (38.1%) than among the total population (43.3%), but the prevalence of ARB use did not differ much between the 3 groups (approx. 26%).

#### 3.2 ACEIs and Covid-19 outcomes

In the total population, 1015 (0.8%) were hospitalized due to Covid-19. Of all Covid-19 patients, 346 (7.5%) and among Covid-19 inpatients, 225 (22.2%) died within 28 days after Covid-19 diagnosis. Table 2 shows the associations of ARB, CCB, BB and diuretic use with these severe courses of SARS-CoV-2 infection in comparison with ACEI use. Although there were some differences in the results of the simple and full model, no pattern of always stronger or weaker results was observed and the results of the fully adjusted model are considered to be the main results and are being referenced in the following text.

As summarized in Table 2, higher risk of Covid-19 hospitalization was associated with the use of CCBs (adjusted OR, 1.39; 95% CI, 1.19 to 1.63), BBs (adjusted OR, 1.54; 95% CI, 1.30 to 1.81) and diuretics (adjusted OR, 1.40; 95% CI, 1.18 to 1.66) compared to the use of ACEIs in the total population with hypertension, whereas ARB use was not significantly associated with this outcome in comparison to ACEIs (adjusted OR, 1.10; 95% CI, 0.93 to 1.29).

For the outcome 28-day mortality in all Covid-19 patients and again in comparison with ACEI use, the use of ARBs (adjusted OR, 1.49; 95% CI, 1.09 to 2.02), CCBs (adjusted OR, 1.38; 95% CI, 1.01 to 1.89), BBs (adjusted OR, 1.88; 95% CI, 1.37 to 2.57) and diuretics (adjusted OR, 1.90; 95% CI, 1.38 to 2.60) was associated with increased mortality. No statistically significant association was observed for ARB, CCB and BB use for the outcome 28-day mortality in hospitalized Covid-19 patients in comparison with the use of ACEIs but OR point estimates were similar to those observed for the other 2 outcomes. For this outcome, only the association of diuretic use compared to ACEI use was statistically significant (adjusted OR, 1.56; 95% CI, 1.01 to 2.40).

The use of CCBs, BBs and diuretics, combined as 1 group compared to the use of ACEIs, showed a significant association with hospitalization due to Covid-19 (OR, 1.66; 95% CI, 1.43 to 1.93) and 28-day mortality among Covid-19 patients (OR, 1.74; 95% CI, 1.30 to 2.33) whereas this association narrowly missed statistically significant
| Characteristics | Total population | Covid-19 patients | Hospitalized Covid-19 patients |
|-----------------|------------------|-------------------|-------------------------------|
|                 | \(n_{\text{total}}\) | \(n(\%)^a\) | \(n_{\text{total}}\) | \(n(\%)^a\) | \(n_{\text{total}}\) | \(n(\%)^a\) |
| Age (y)         | 124 143          | 4592              | 1015                          |
| \(\leq 70\)    | 48 291 (38.9)    | 2359 (51.4)       | 298 (29.4)                    |
| \(>70\)–\(75\) | 35 866 (28.9)    | 1002 (21.8)       | 262 (25.8)                    |
| \(>75\)–\(80\) | 34 413 (27.7)    | 1057 (23.0)       | 379 (37.3)                    |
| \(>80\)        | 5573 (4.5)       | 174 (3.8)         | 76 (7.5)                      |
| Sex             | 124 143          | 4592              | 1015                          |
| Male            | 62 633 (50.5)    | 2465 (53.7)       | 601 (59.2)                    |
| Female          | 61 510 (49.6)    | 2127 (46.3)       | 414 (40.8)                    |
| Ethnicity       | 123 402          | 4554              | 1006                          |
| White           | 114 920 (93.1)   | 3982 (87.4)       | 886 (88.1)                    |
| Black           | 3016 (2.4)       | 198 (4.4)         | 52 (5.2)                      |
| Other           | 5466 (4.4)       | 374 (8.2)         | 68 (6.8)                      |
| BMI (kg/m\(^2\))| 123 302          | 4541              | 997                           |
| \(<22\)         | 4901 (4.0)       | 114 (2.5)         | 31 (3.1)                      |
| 22–\(<25\)     | 19 044 (15.5)    | 549 (12.1)        | 101 (10.1)                    |
| 25–\(<30\)     | 53 475 (43.4)    | 1776 (39.1)       | 340 (34.1)                    |
| 30–\(<35\)     | 30 929 (25.1)    | 1331 (29.3)       | 313 (31.4)                    |
| 35–\(<40\)     | 10 479 (8.5)     | 525 (11.6)        | 141 (14.1)                    |
| \(\geq 40\)    | 4474 (3.6)       | 246 (5.4)         | 71 (7.1)                      |
| Deprivation index | 124 000         | 4587              | 1015                          |
| \(<-3.9\)      | 24 163 (19.5)    | 647 (14.1)        | 116 (11.4)                    |
| -3.9–\(<-2.7\) | 25 471 (20.5)    | 795 (17.3)        | 163 (16.1)                    |
| -2.7–\(<-1.2\) | 24 557 (19.8)    | 828 (18.1)        | 180 (17.7)                    |
| -1.2–\(<1.6\)  | 25 158 (20.3)    | 997 (21.7)        | 235 (23.2)                    |
| \(\geq 1.6\)   | 24 651 (19.9)    | 1320 (28.8)       | 321 (31.6)                    |
| Education (y)   | 120 963          | 4413              | 971                           |
| \(<9\)          | 33 919 (28.0)    | 1422 (32.2)       | 400 (41.2)                    |
| 10–12           | 44 834 (37.1)    | 1733 (39.3)       | 327 (33.7)                    |
| \(\geq 13\)    | 42 210 (34.9)    | 1258 (28.5)       | 244 (25.1)                    |
| Smoking         | 123 816          | 4568              | 1010                          |
| Never           | 64 204 (51.9)    | 2267 (49.6)       | 423 (41.9)                    |
| Former          | 48 322 (39.0)    | 1817 (39.8)       | 471 (46.6)                    |
| Current         | 11 290 (9.1)     | 484 (10.6)        | 116 (11.5)                    |
| Alcohol consumption | 123 678       | 4564              | 1007                          |
| Abstainer       | 41 154 (33.3)    | 1768 (38.7)       | 443 (44.0)                    |
| WHO category I  | 46 836 (37.9)    | 1622 (35.5)       | 349 (34.7)                    |
| WHO category I  | 19 397 (15.7)    | 615 (13.5)        | 117 (11.6)                    |
| WHO category III| 16 291 (13.2)    | 559 (12.3)        | 98 (9.7)                      |
| Physical activity | 96 663           | 3447              | 752                           |
| Low             | 19 992 (20.7)    | 817 (23.7)        | 187 (24.9)                    |
| Moderate        | 40 126 (41.5)    | 1342 (38.9)       | 282 (37.5)                    |
| High            | 36 545 (37.8)    | 1288 (37.4)       | 283 (37.6)                    |
| SBP (mmHg)      | 123 777          | 4571              | 1010                          |
| \(<130\)        | 15 344 (12.4)    | 690 (15.1)        | 151 (15.0)                    |

TABLE 1 Characteristics of the study population of patients with hypertension, overall Covid-19 and hospitalized Covid-19 patient subpopulations

\(^a\) n\(\pm\) represents the number of patients with the characteristic among the total population.
in hospitalized patients with Covid-19 (OR, 1.47; 95% CI, 0.99 to 2.18). The unadjusted Kaplan–Meier curves for the latter 2 survival analyses are shown in Figure 1 and log-rank tests came the same conclusion as the logistic regression model: A significant association with 28-day mortality among all Covid-19 patients (log-rank $P = .0002$) but not among hospitalized Covid-19 patients (log-rank $P = .15$).

Stratified by SARS-CoV2 wave, associations were weaker for the first wave (Table S2) and stronger for the second wave (Table S3). The results for the first wave need to be interpreted with caution due to low case numbers, which were not sufficient to analyse mortality endpoints in Covid-19 patients. The results for the second wave were comparable to those reported for first and second waves combined. However, some not significant findings for the outcome 28-day mortality in hospitalized Covid-19 patients were statistically significant (e.g., comparison of the use of CCBs, BBs and diuretics combined as 1 group with the use of ACEIs: OR, 1.80; 95% CI, 1.15 to 2.83).

**Table 1** (Continued)

| Characteristics            | Total population | Covid-19 patients | Hospitalized Covid-19 patients |
|----------------------------|------------------|-------------------|-------------------------------|
|                            | $n_{\text{total}}$ | $n$ (%)           | $n_{\text{total}}$ | $n$ (%)           | $n_{\text{total}}$ | $n$ (%)           |
| Age: 130–150               | 115 497          | 45 594 (36.8)     | 4237            | 2383 (56.2)      | 934               | 434 (46.5)       |
| Age: 150–170               |                  | 42 692 (34.5)     | 1451 (31.7)     | 319 (31.6)       |                  | 171 (16.9)       |
| Age: $\geq$170             |                  | 20 147 (16.3)     | 618 (13.5)      |                 | 171 (16.9)       |                 |

| eGFR (mL/min/1.73 m$^2$)   |                  |                   |                  |                  |                  |                  |
| $\geq$90                  |                  | 60 713 (52.6)     | 2383 (56.2)      | 434 (46.5)       |                  |                  |
| $\geq$60–$<90$            |                  | 50 349 (43.6)     | 1670 (39.4)      | 426 (45.6)       |                  |                  |
| $<60$                     |                  | 4435 (3.8)        | 184 (4.3)        | 74 (7.9)         |                  |                  |

| Comorbidities              |                  |                   |                  |                  |                  |                  |
| Diabetes mellitus          | 124 140          | 26 902 (21.7)     | 4591            | 1375 (30.0)      | 1014             | 394 (38.9)       |
| COPD                       | 124 136          | 7169 (5.8)        | 4591            | 369 (8.0)        | 1014             | 145 (14.3)       |
| CHD                        | 124 138          | 14 364 (11.6)     | 4592            | 647 (14.1)       | 1015             | 225 (22.2)       |
| Heart failure              | 124 136          | 4166 (3.4)        | 4591            | 268 (5.8)        | 1014             | 124 (12.2)       |
| History of stroke          | 124 137          | 6410 (5.2)        | 4592            | 380 (8.3)        | 1015             | 152 (15.0)       |
| History of MI              | 124 136          | 7749 (6.2)        | 4591            | 380 (8.3)        | 1014             | 131 (12.9)       |

| Medications                |                  |                   |                  |                  |                  |                  |
| Lipid lowering drugs       | 124 143          | 78 262 (63.0)     | 4592            | 2925 (63.7)      | 1015             | 718 (70.7)       |
| Low-dose aspirin           | 124 143          | 19 651 (15.8)     | 4592            | 720 (15.7)       | 1015             | 205 (20.2)       |
| No. of drugs               | 124 143          | 112              | 4592            | 1015             |                  |                  |
| $\leq$2                   | 27 994 (22.6)    | 926 (20.2)        | 113 (11.1)      |                  |                  |                  |
| 3                         | 18 963 (15.3)    | 558 (12.2)        | 81 (8.0)        |                  |                  |                  |
| 4                         | 18 112 (14.6)    | 521 (11.4)        | 83 (8.2)        |                  |                  |                  |
| 5                         | 15 601 (12.6)    | 548 (11.9)        | 123 (12.1)      |                  |                  |                  |
| 6                         | 12 363 (10.0)    | 441 (9.6)         | 104 (10.3)      |                  |                  |                  |
| 7                         | 9 448 (7.6)      | 394 (8.6)         | 93 (9.2)        |                  |                  |                  |
| $\geq$8                   | 21 662 (17.5)    | 1204 (26.2)       | 418 (41.2)      |                  |                  |                  |

| Antihypertensive drugs†   | 124 143          | 4592              | 1015            |                  |                  |                  |
| ACEI                      | 53 796 (43.3)    | 1888 (41.1)       | 387 (38.1)      |                  |                  |                  |
| ARB                       | 31 917 (25.7)    | 1217 (26.5)       | 264 (26.0)      |                  |                  |                  |
| Diuretic                  | 32 668 (26.3)    | 1324 (28.8)       | 402 (39.6)      |                  |                  |                  |
| CCB                       | 55 288 (44.5)    | 2119 (46.2)       | 456 (44.9)      |                  |                  |                  |
| BB                        | 32 504 (26.2)    | 1286 (28.0)       | 407 (40.1)      |                  |                  |                  |
| Other                     | 661 (0.5)        | 23 (0.5)          | 6 (0.6)         |                  |                  |                  |

†The percentages do not add up to 100 due to combination therapies with different classes of antihypertensives.

Covid-19, coronavirus disease 2019; SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; MI, myocardial infarction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker; BB, β-blocker.

aThe percentages might not add up to 100 due to rounding.
TABLE 2  Associations of ARB, CCB, BB and diuretic use in comparison with ACEI use with: (i) Covid-19 hospitalization in the total population with hypertension; (ii) 28-day all-cause mortality in all Covid-19 infected patients; and (iii) 28-day all-cause mortality in hospitalized Covid-19 infected patients

| Antihypertensive medication | Covid-19 hospitalization in the total population | 28-day mortality in Covid-19 patients | 28-day mortality in hospitalized Covid-19 patients |
|----------------------------|-----------------------------------------------|-----------------------------------|-----------------------------------------------|
|                            | n<sub>total</sub> | n<sub>case</sub> | OR (95%CI) | n<sub>total</sub> | n<sub>case</sub> | OR (95%CI) | n<sub>total</sub> | n<sub>case</sub> | OR (95%CI) |
| ACEI                       | 53 796          | 387        | Ref.       | 1888          | 111        | Ref.       | 387          | 77          | Ref.       |
| ARB                        | 30 995          | 256        | 1.12 (0.96–1.32) | 1196          | 97        | 1.48 (1.11–1.99) | 256          | 57          | 1.26 (0.84–1.89) |
| ACEI                       | 53 796          | 387        | Ref.       | 1888          | 111        | Ref.       | 387          | 77          | Ref.       |
| CCB                        | 36 616          | 305        | 1.13 (0.97–1.32) | 1396          | 97        | 1.26 (0.94–1.70) | 305          | 66          | 1.19 (0.81–1.74) |
| ACEI                       | 53 796          | 387        | Ref.       | 1888          | 111        | Ref.       | 387          | 77          | Ref.       |
| BB                         | 18 878          | 258        | 1.83 (1.56–2.15) | 789           | 104       | 2.02 (1.51–2.71) | 258          | 68          | 1.42 (0.97–2.08) |
| ACEI                       | 53 796          | 387        | Ref.       | 1888          | 111        | Ref.       | 387          | 77          | Ref.       |
| Diuretic                   | 19 433          | 242        | 1.72 (1.45–2.03) | 814           | 110       | 2.15 (1.60–2.88) | 242          | 69          | 1.60 (1.08–2.36) |
| ACEI                       | 53 796          | 387        | Ref.       | 1888          | 111        | Ref.       | 387          | 77          | Ref.       |
| CCB/BB/diuretic            | 38 691          | 366        | 1.33 (1.15–1.54) | 1485          | 137       | 1.62 (1.24–2.14) | 366          | 90          | 1.34 (0.94–1.92) |

Note: Bold print indicates statistically significant effect estimates (P < .05).
†Adjusted for age, sex, ethnic background, socioeconomic deprivation, smoking, physical activity, alcohol consumption, BMI, SBP, eGFR, COPD, diabetes mellitus, heart failure, CHD, history of MI, history of stroke, use of low-dose aspirin, use of lipid-lowering drugs and number of drugs concurrently used.
Covid-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker; BB, β-blocker; Ref., reference.

aAdjusted for age, sex and ethnic background.
3.3 ARBs and Covid-19 outcomes

Table 3 shows the same analyses as Table 2 except that we used ARBs as the reference group. Again, no pattern of always stronger or weaker results was observed and the results of the fully adjusted model are considered to be the main results and are being referenced in the following text. Hypertensive patients who had been taking BBs and diuretics had higher risk of Covid-19 hospitalization (adjusted OR, 1.27; 95% CI, 1.07 to 1.51 and adjusted OR, 1.29; 95% CI, 1.09 to 1.54), respectively. The use of CCBs was not significantly associated with this outcome in comparison with the use of ARBs (adjusted OR, 1.10; 95% CI, 0.93 to 1.30). However, combining CCB, BB and
The only interaction detected with statistical significance after correction for multiple testing was between ARB use (with reference to ACEIs) and CHD with respect to the outcome Covid-19 hospitalization risk (Table S8).

After removal of patients with a diagnosis of CHD and SHI from the respective analyses using 1 of these drug groups as reference, the results remained similar to the main analyses and showed unchanged conclusions in every case (Tables S6 and S7). The association between CCB, BB or diuretics use and Covid-19 hospitalization risk was not observed for ACEI use and ACEI use was associated with increased all-cause mortality among patients with CHD. Furthermore, the risk of 28-day mortality among patients with CHD showed unchanged conclusions in every case (Tables S5) in analyses with ARBs as the reference. The results for second wave were comparable to those reported for first and second wave combined, and the same associations were statistically significant (Table S5).

Note: Bold print indicates statistically significant effect estimates (P < .05).

*Adjusted for age, sex, ethnic background, socioeconomic deprivation, smoking, physical activity, alcohol consumption, BMI, SBP, eGFR, COPD, diabetes mellitus, heart failure, CHD, history of MI, history of stroke, use of low-dose aspirin, use of lipid-lowering drugs and number of drugs concurrently used.

Covid-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker; BB, β-blocker; Ref., reference.

†Adjusted for age, sex and ethnic background.

Table S8. Covid-19 hospitalization risk (Table S8).
Covid-19 patients narrowly missed statistical significance but it was statistically significant when the analysis was restricted to patients hospitalized during the second SARS-CoV-2 wave.

Our results are consistent with previous studies suggesting a better prognosis for Covid-19 patients using RAAS inhibitors. A large cohort of 8.3 million people in the UK showed reduced risk of Covid-19 RT-PCR positive disease in patients taking ACEIs (OR, 0.72; 95% CI, 0.68–0.76) and ARBs (OR, 0.63; 95% CI, 0.59–0.67). A nationwide registry analysis of 1.4 million patients in Sweden also found a decreased risk of hospitalization/mortality due to Covid-19 (OR, 0.86; 95% CI, 0.81–0.91) and lower all-cause mortality in outpatients with Covid-19 (hazard ratio, 0.89; 95% CI, 0.82–0.96) among ACEI/ARB.
These observations are verified by systematic reviews and meta-analyses. Ren et al. reported a lower disease severity and mortality of Covid-19 in hypertensive patients with prior usage of ACEIs/ARBs (pooled risk ratio 0.81, 95% CI 0.66–0.99, and pooled risk ratio 0.77, 95% CI 0.66–0.91, respectively). Caldeira et al. observed a reduced mortality among patients with Covid-19 and hypertension treated with ACEIs/ARBs (pooled risk ratio 0.76, 95%CI 0.59–0.98). Our findings are also in line with the French COVID cohort, a multicentre prospective cohort, which observed no significant association between the chronic use of RAAS inhibitors and mortality in hospitalized Covid-19 patients with hypertension.

Unlike previous studies, we compared the association of ACEIs and ARBs with Covid-19 outcomes directly to other major antihypertensive drug classes separately and all together, whereas most other studies have only done the latter. Moreover, most of the previous studies have considered ACEIs and ARBs as 1 class of antihypertensives, RAAS agents, while comparing their association with Covid-19 outcomes to other antihypertensive medications. We found a different behaviour between ACEIs and ARBs with ACEI use being associated with lower risks of Covid-19 hospitalization and 28-day all-cause mortality. This is in line with a meta-analysis conducted by Pirola and Soo koian, which observed a reduced risk of death and critical disease among hypertensive patients with Covid-19 only for ACEIs and not for ARBs or a combined group of ACEIs/ARBs.

Different results for ACEIs and ARBs in adverse Covid-19 outcomes might be related to their different mode and mechanism of action in the RAAS. However, currently it is only possible to speculate about the mechanisms and further studies on the molecular pathways involved are needed.

One strength of this study is that we used data from the UK Biobank with extensive data collected on lifestyle and sociodemographic characteristics of the participants and linked electronic health records. On the 1 hand, this enabled us to adjust for many important confounders not usually available in other studies using claims data. On the other hand, a limitation is that lifestyle-factors, physical health assessment measurements and biomarkers were assessed 10–14 years prior to the Covid-19 pandemic and could have changed in that time. However, the most important co-morbidity information could be updated until the date of the onset of the pandemic by linked primary care records. However, we cannot exclude that the combination of self-reported disease from the cohort’s baseline and the primary care records to identify comorbidities has led to some misclassification and underreporting of diagnoses in. In addition, despite extensive covariate adjustments, there may be additional unmeasured confounders that could have affected our results (e.g., prescriptions of corticosteroids and heparin during hospitalization). Another limitation is that drug utilization was based on prescribed medications and adherence to the drug treatment could not be assessed. Last but not least, a further limitation is the rather low statistical power for the outcome 28-day mortality of hospitalized Covid-19 patients, which can lead to the absence of statistically significant findings but should not be interpreted as evidence for no associations, because these may be detected by future, larger studies.

Another strength of this study is that we included Covid-19 data in a large time window, so that we covered the entire first and second SARS-CoV-2 waves in UK, while most studies were limited to a shorter period (usually the first wave of the pandemic in the respective country). During the early stages of the pandemic, only symptomatic patients were tested due to the limited testing capacity, which resulted in patient populations with overrepresentation of severe Covid-19 disease cases.

By setting the cut-off date for extracting Covid-19 infection data to 23 February 2021, we think that vaccination against Covid-19 did not substantially influence our results because the vaccination campaign in the UK started slowly in December 2020 and by the time of our cut-off date, only 1.2% of the English population were fully vaccinated. As most of the Covid-19 cases in our analyses origin from the second SARS-CoV-2 wave in the UK (caused by the alpha variant) and the results from the second wave only were comparable to those from first and second waves combined, our results can be generalized to a clinical situation, in which some effective drugs against Covid-19 are being known and used off-label (corticosteroids and heparin), whereas SARS-CoV-2 vaccinations and antiviral treatments (e.g. Paxlovid and Molnupiravir) were not yet available. Studies from more recent SARS-CoV-2 waves may get different results due to a different clinical situation and are therefore needed. Finally, our study population mainly consisted of the older (50% of the participants were between 66 and 76 years old [interquartile range]), Caucasian, hypertensive population and hence the results might not apply in other populations.

In summary, our findings suggest a better prognosis of Covid-19 patients in pharmaceutically treated hypertension if RAAS inhibitors are being used and the potential protective effects were stronger for ACEIs than ARBs. However, results from randomized controlled trials (RCTs) are needed to confirm this finding from an observational study because residual confounding cannot be excluded. An RCT with 659 hospitalized patients with mild to moderate Covid-19 and prior use of ACEIs or ARBs observed no effect of continuation vs. discontinuation of these medications on the mean number of days alive and out of the hospital up to 30 days, which is in agreement with our results because it seems that the potential protective effects are stronger in nonhospitalized than hospitalized Covid-19 patients. A phase II RCT, which tested the efficacy of losartan on symptomatic outpatients with Covid-19 vs. placebo, also showed no significant difference in hospitalization rate between the 2 arms. However, the nonsignificant result should be interpreted with caution due to low event rate (losartan arm: 3 events vs. placebo arm: 1 event and short duration of follow-up of this phase II trial. The results of more RCTs should help to elucidate the causality of the observed protective associations of RAAS inhibitors on adverse Covid-19 outcomes. If our results would be confirmed in RCTs, this could have high clinical relevance for treating hypertension during the SARS-CoV-2 pandemic.

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COMPETING INTERESTS

The authors have no conflict of interest to disclose.

CONTRIBUTORS

F.S. and B.S. designed the research; F.S. analysed the data and B.S. checked the analysis code; F.S. drafted the manuscript and B.S. revised it; T.N.M.N. and H.B. contributed important intellectual content to the discussion. All authors were involved in the interpretation and discussion of results.

INFORMED CONSENT

Written informed consent was obtained from all individual participants included in the study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the UK Biobank. Restrictions apply to the availability of these data, which were used under license for this study. Data and analysis code (SAS) are available [https://www.ukbiobank.ac.uk/] with the permission of UK Biobank after approval of a research proposal and payment of a fee.

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