Association of Renin–Angiotensin–Aldosterone System Blocker use with Covid-19 Hospitalization and All-cause Mortality in the UK Biobank

Fatemeh Safizadeh[1], Thi Ngoc Mai Nguyen[2], Hermann Brenner[2], and Ben Schöttker[2]

[1]Ludwig-Maximilians-Universität München
[2]Deutsches Krebsforschungszentrum

September 24, 2021

Abstract

Aim: The risk-benefit profile of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in coronavirus disease 2019 (Covid-19) is still a matter of debate. With growing evidence on the protective effect of this group of commonly used antihypertensives in 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. Multivariable logistic regression analysis was performed adjusting for a wide range of confounders. Results: The use of either beta-blockers (BBs), calcium-channel blockers (CCBs), or diuretics was associated with a higher risk of Covid-19 hospitalization compared to ACEI use (adjusted OR, 1.63; 95% CI, 1.40 to 1.90) and ARB use (adjusted OR, 1.50; 95% CI, 1.27 to 1.77). 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 (adjusted OR, 1.64; 95% CI, 1.23 to 2.19) but not when compared to ARB users (adjusted OR, 1.18; 95% CI, 0.87 to 1.59). However, no associations were observed when the same analysis was conducted among hospitalized Covid-19 patients only. Conclusion: Our results suggest protective effects of blocking of the renin-angiotensin-aldosterone system on Covid-19 hospitalization and mortality among patients with pharmaceutically treated hypertension, which should be addressed by randomized controlled trials. If confirmed, this finding could have high clinical relevance for treating hypertension during the SARS-CoV-2 pandemic.

Association of Renin–Angiotensin–Aldosterone System

Blocker use with Covid-19 hospitalization and all-cause mortality in the UK Biobank

Running head: RAAS blocker use and Covid-19 outcomes

Authors: Fatemeh Safizadeh PharmD[1, 2], Thi Ngoc Mai Nguyen MSc[1, 3], Hermann Brenner MD[1, 3], Ben Schöttker PhD [1, 3]

Affiliations:

1. Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Heidelberg, Germany
2. Institute for Medical Information Processing, Biometry and Epidemiology- IBE, LMU Munich, Munich, Germany
3. Network Aging Research, University of Heidelberg, Heidelberg, Germany

Corresponding author:

Dr. Ben Schöttker, Division of Clinical Epidemiology and Ageing Research, German Cancer Research Center, Im Neuenheimer Feld 581, D-69120 Heidelberg, Germany, Phone: +49 (0)6221 42 1355, email: b.schoettker@dkfz.de

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

Word count: 3712 Table count: 3 Figure count: 2

What is already known about this subject:

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

What this study adds:

This observational study suggests that blocking of the Renin–Angiotensin–Aldosterone System (RAAS) 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 ACEIs instead of other anti-hypertensive drugs were used.

Abstract

Aim: The risk-benefit profile of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in coronavirus disease 2019 (Covid-19) is still a matter of debate. With growing evidence on the protective effect of this group of commonly used antihypertensives in 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. Multivariable logistic regression analysis was performed adjusting for a wide range of confounders.

Results: The use of either beta-blockers (BBs), calcium-channel blockers (CCBs), or diuretics was associated with a higher risk of Covid-19 hospitalization compared to ACEI use (adjusted OR, 1.63; 95% CI, 1.40 to 1.90) and ARB use (adjusted OR, 1.50; 95% CI, 1.27 to 1.77). 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 (adjusted OR, 1.64; 95% CI, 1.23 to 2.19) but not when compared to ARB users (adjusted OR, 1.18; 95% CI, 0.87 to 1.59). However, no associations were observed when the same analysis was conducted among hospitalized Covid-19 patients only.

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

Introduction

There has been a debate over the role of renin-angiotensin-aldosterone system (RAAS) and RAAS blockers 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) [1]. After SARS-CoV-2 binds to ACE2 receptor, endocytosis of the viral complex results in ACE2 downregulation and accumulation of angiotensin II (AngII) with pro-inflammatory, vasoconstrictive, and pro-fibrotic 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 angiotensin (1-7) that exert their

vasodilatory, anti-inflammatory and antiproliferative effects through mitochondrial assembly (MAS) receptor [2-4].

The controversy about the use of angiotensin-converting enzyme 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 [5]. 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 [6,7]. However, current findings do not support this association [8-12] and evidence regarding beneficial effects of RAAS blockers is growing, illustrating a potential protective effect of RAAS inhibitors in relation to Covid-19 through the ACE2/angiotensin 1-7/MAS axis and counteracting of the harmful effects of accumulated AngII [13,14].

The favorable 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 anti-hypertensive drugs in the large UK Biobank.

Methods

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 [15]. The data is 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 [16,17]. 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 (GP). 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 pharmaceutically 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.

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: 1) Covid-19 patients and 2) Hospitalized Covid-19 patients.

We used the Covid-19 data release from June 2, 2021, which included Covid-19 test data from March 16, 2020, onwards. However, we used only Covid-19 test data up to February 23, 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 March 23, 2021). In addition, we wanted to restrict the time of assessment of Covid-19 patients to have not too many study participants with SARS-CoV-2 vaccination in our study population. According to official statistics, on February 23, 2021, the prevalence of full SARS-CoV-2 vaccination in the UK was 1.2% [18].

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), beta-blocker (BB) (C07) and calcium-channel-blocker (CCB) (C08, C07FB, C09BB and C09DB). Recent use was defined as six months prior to Covid-19 test date for participants with Covid-19 positive test result and six months prior to onset of the SARS-CoV-2 pandemic in March 2020 for those with no Covid-19 infection.

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 assessment center for baseline examination and March 1, 2020 to the baseline age. The ethnic background was categorized as white, black, and other (all other ethnic groups combined) 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 [19]. The intensity of physical activity (low, moderate, high) was based on the international physical activity questionnaire (IPAQ). The grams 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/day or men with $<$ 40 g/day, and category II (moderate) including women with an alcohol consumption of 20-39.99 g/day or men with 40-59.99 g/day and category III (heavy) including women with an alcohol consumption of [?] 40 g/day or men with [?] 60 g/day.

Blood samples were donated and height, weight, systolic blood pressure (SBP) and diastolic blood pressure (DBP) measures were taken as part of the health assessments during the baseline examination in the recruiting centers. An Omron automated device (range returned: 0-255 mmHg) or a manual sphygmometer as an alternative were used for blood pressure measurements. High-density lipoprotein (HDL) cholesterol (mmol/L), low-density lipoprotein (LDL) cholesterol (mmol/L) and creatinine (µmol/L) were measured using enzyme immunoinhibition analysis, enzymatic protective selection analysis and enzymatic analysis on a Beckman Coulter AU5800, respectively. The estimated glomerular filtration rate (eGFR) was calculated based on the CKD-Epi equation [20] using serum creatinine and categorized to three levels: [?] 90 (mL/min/1.73m^2), [?] 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 March 16, 2020 (first recorded positive SARS-CoV-2 test in the UK Biobank study population). The comorbid conditions assessed were chronic obstructive pulmonary disease (COPD), 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 six months prior to March 2020. For the total number of drugs used by each participant, a shorter, three-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 co-morbidity, 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.

Statistical Analysis

Multivariable logistic regression models were fitted and odds ratios (OR) and corresponding 95% confidence intervals (CI) 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 two subpopulations of hypertensive patients: 1) Those who tested positive for SARS-CoV-2 and 2) those who were hospitalized due to Covid-19.

In a first round of analyses, ARB, CCB, BB and diuretics users were directly compared to ACEI users and in a second round of analyses the latter three 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 one 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 anti-hypertensives.

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 one 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, socio-economic deprivation, smoking status, physical activity, alcohol consumption, body mass index (BMI), SBP, DBP, HDL cholesterol, LDL cholesterol, 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.

All the 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. Analyses of the five imputed datasets were combined using the SAS procedure PROC MIANALYZE. Two-sided p values <0.05 were considered significant.

Results

Characteristics of the Study Population

A total of 124,143 patients with pharmaceutically treated hypertension were included in this analysis, among whom 4,592 (3.7%) patients had tested positive for Covid-19 and 1,015 (0.8%) got hospitalized due to Covid-19 between March 16, 2020, and February 23, 2021. The baseline characteristics of these three 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 deprivation, less education, higher prevalence of current smoking, abstinence from alcohol, and 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 three groups (approx. 26%).

ACE inhibitors and Covid-19 Outcomes

In the total population, 1,015 (0.8%) got 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, 1.37; 95% CI, 1.17 to 1.60), BBs (adjusted OR, 1.53; 95% CI, 1.29 to 1.80) and diuretics (adjusted OR, 1.37; 95% CI, 1.16 to 1.63) 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, 0.94 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, 1.10 to 2.02), BBs (adjusted OR, 1.80; 95% CI, 1.33 to 2.46), diuretics (adjusted OR, 1.81; 95% CI, 1.32 to 2.46) and CCBs (adjusted OR, 1.35; 95% CI, 0.99 to 1.84) was associated with increased mortality and only the latter association scarcely missed statistical significance. 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 two outcomes. For this outcome, only the association of diuretic use compared to ACEI use was statistically significant (adjusted OR, 1.54; 95% CI, 1.01 to 2.34).

The use of CCBs, BBs and diuretics, combined as one group compared to the use of ACEIs, showed a significant association with hospitalization due to Covid-19 (odds ratio, 1.63; 95% CI, 1.40 to 1.90) and 28-day mortality among Covid-19 patients (odds ratio, 1.64; 95% CI, 1.23 to 2.19) whereas this association was not statistically significant in hospitalized patients with Covid-19 (odds ratio, 1.37; 95% CI, 0.93 to 2.01). The unadjusted Kaplan-Meier curves for the latter two 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=0.0002) but not among hospitalized Covid-19 patients (log-rank

p=0.15).

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, 1.26; 95% CI, 1.06 to 1.49 and adjusted OR, 1.28; 95% CI, 1.08 to 1.52), respectively. The use of CCBs was not significantly associated with this outcome in comparison with the use of ARBs (adjusted OR, 1.09; 95% CI, 0.93 to 1.29). However, combining CCB, BB and diuretic users into one group, the adjusted OR was statistically significant (1.50; 95% CI, 1.27 to 1.77). With respect to 28-day all-cause mortality in all Covid-19 patients and hospitalized Covid-19 patients, no associations were observed in the logistic regression model, and this was further confirmed by the Kaplan-Meier curves and log-rank tests (Figure 2, log rank p=0.36 for all Covid-19 patients and log rank p=0.46 for all Covid-19 inpatients).

Sensitivity Analysis

After removal of patients who used drug combinations with ACEIs or ARBs from the respective analyses using one of these drug groups as the reference, the results remained similar to the main analyses and showed unchanged conclusions in every case (please see Supplemental Tables S1 and S2). The only exception was that the non-significant association of the use of CCBs compared to ARBs with Covid-19 hospitalization in the total hypertensive population became statistically significant (adjusted OR, 1.23; 95% CI, 1.01 to 1.50).

Discussion

In this observational analysis in a large cohort of patients with hypertension, we observed increased risk of hospitalization due to Covid-19 among users of non-RAAS blocking anti-hypertensives compared to ACEIs and ARBs. Furthermore, the risk of 28-day all-cause mortality among hypertensive Covid-19 patients was increased if non-RAAS blocking anti-hypertensives were compared to ACEIs. No association was observed with 28-day all-cause mortality among hospitalized Covid-19 patients.

Our results are consistent with 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) [21]. A nation-wide 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 users [22]. These observations are verified by the first systematic reviews and meta-analyses specifically conducted for the hypertensive population [23]. 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) [24]. 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) [25]. Our findings are also in line with the French COVID cohort, a multicenter prospective cohort, which observed no significant association between the chronic use of RAAS blockers and mortality in hospitalized Covid-19 patients with hypertension [26].

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 one class of antihypertensives, RAAS agents, while comparing their association with Covid-19 outcomes to other antihypertensive medications. We found a different behavior 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 Sookoian, 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 [27].

Different results for ACEIs and ARBs in adverse Covid-19 outcomes can be explained by their different mode and mechanism of action in the RAAS [28]. It is noteworthy that ACEIs bind to ACE, an enzyme homologous to ACE2, yet with distinctly different binding sites. In other words, ACE2 activity is not directly affected by ACEIs, and they primarily exert their protective effect via decreasing Ang II levels by preventing the conversion of Ang I to Ang II, whereas ARBs block angiotensin II type 1 receptor (AT1 receptor), which results in an increase in Ang II levels, the substrate for ACE2 and activates the protective axis in RAAS. Furthermore, animal studies have shown increased expression of ACE2 mRNA and protein in various tissues more consistently with ARBs compared to ACEIs [29]. These differences might clarify the inconsistent results between ACEIs and ARBs to some extent.

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 one 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 life-style-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 co-morbidities 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. Another limitation is that drug utilization was based on prescribed medications and adherence

to the drug treatment could not be assessed.

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 wave 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 February 23, 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 [18]. Finally, our study population mainly consisted of the older (50% of the participants were between 66 and 76 years old (inter-quartile-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 blockers 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. A RCT with 659 hospitalized patients with mild to moderate Covid-19 and prior use of ACEIs or ARBs observed no effect of continuation versus discontinuation of these medications on the mean number of days alive and out of the hospital through 30 days [30], which is in agreement with our results because it seems that the potential protective effects are stronger in non-hospitalized than hospitalized Covid-19 patients. As soon as Covid-19 patients develop a severe course that requires inpatient care, the use of RAAS blockers may be too late and ineffective. A phase II RCT, which tested the efficacy of losartan on symptomatic outpatients with Covid-19 versus placebo showed no significant difference in hospitalization rate between the two arms [31]. However, the non-significant result should be interpreted with caution due to low event rate (losartan arm: 3 events versus 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 blockers 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.

Acknowledgements

This research has been conducted using the UK Biobank Resource under Application Number “62848”.

Conflict of Interests

The authors have no conflict of interest to disclose.

Sources of Funding

No funding was obtained or used for the presented research project. The UK Biobank was established by the Wellcome Trust medical charity, Medical Research Council, Department of Health, Scottish Government and the Northwest Regional Development Agency. It has also had funding from the Welsh Government, British Heart Foundation, Cancer Research UK and Diabetes UK. UK Biobank is supported by the National Health Service (NHS).

Ethics Approval

UK Biobank has approval from the North West Multi-center Research Ethics Committee (MREC), which covers the UK. It also sought the approval in England and Wales from the Patient Information Advisory Group (PIAG) for gaining access to information that would allow it to invite people to participate. PIAG

has since been replaced by the National Information Governance Board for Health & Social Care (NIGB). In Scotland, UK Biobank has approval from the Community Health Index Advisory Group (CHIAG).

Informed Consent

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

Author contributions

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.

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.

ORCID

Fatemeh Safizadeh - None

Thi Ngoc Mai Nguyen - None

Hermann Brenner - None

Ben Schottker - 0000-0002-1217-4521

References

1. Shang J, Ye G, Shi K, et al. Structural basis of receptor recognition by SARS-CoV-2. *Nature.* 2020;581(7807):221-224.

2. Kreutz R, Algharably EAE, Azizi M, et al. Hypertension, the renin-angiotensin system, and the risk of lower respiratory tract infections and lung injury: implications for COVID-19. *Cardiovasc Res.* 2020;116(10):1688-1699.

3. Del Turco S, Vianello A, Ragusa R, Caselli C, Basta G. COVID-19 and cardiovascular consequences: Is the endothelial dysfunction the hardest challenge? *Thromb Res.* 2020;196:143-151.

4. Mascolo A, Scavone C, Rafaniello C, et al. The Role of Renin-Angiotensin-Aldosterone System in the Heart and Lung: Focus on COVID-19. *Front Pharmacol.* 2021;12:667254.

5. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet.*2020;395(10223):497-506.

6. Diaz JH. Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19.*J Travel Med.* 2020;27(3).

7. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation.*2005;111(20):2605-2610.

8. Speth RC. Keep taking your ACE inhibitors and ARBs during the COVID 19 pandemic. *J Travel Med.* 2020;27(3).

9. Tomasoni D, Italia L, Adamo M, et al. COVID-19 and heart failure: from infection to inflammation and angiotensin II stimulation. Searching for evidence from a new disease. *Eur J Heart Fail.*2020;22(6):957-966.

10. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin-Angiotensin-Aldosterone System Inhibitors and Risk of Covid-19.*N Engl J Med.* 2020;382(25):2441-2448.

11. Ferrari F, Martins VM, Fuchs FD, Stein R. Renin-Angiotensin-Aldosterone System Inhibitors in COVID-19: A Review.*Clinics (Sao Paulo).* 2021;76:e2342.

12. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19.*N Engl J Med.* 2020;382(25):2431-2440.

13. Simko F, Hrenak J, Adamcova M, Paulis L. Renin-Angiotensin-Aldosterone System: Friend or Foe-The Matter of Balance. Insight on History, Therapeutic Implications and COVID-19 Interactions. *Int J Mol Sci.* 2021;22(6).

14. Alves M, Fernandes MA, Bahat G, et al. Protecting older patients with cardiovascular diseases from COVID-19 complications using current medications. *Eur Geriatr Med.* 2021.

15. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med.* 2015;12(3):e1001779.

16. UK Biobank. Facilitating COVID-19 research. https://www.ukbiobank.ac.uk/enable-your-research/about-our-data/covid-19-data. Published 2021. Updated 11/12/2020. Accessed 07/07/2021, 2021.

17. Khanji MY, Aung N, Chahal CAA, Petersen SE. COVID-19 and the UK Biobank-Opportunities and Challenges for Research and Collaboration With Other Large Population Studies. *Front Cardiovasc Med.* 2020;7:156.

18. Public Health England. Coronavirus (COVID-19) in the UK https://coronavirus.data.gov.uk/details/vaccinations. Published 2021. Updated 07/07/2021. Accessed 07/07/2021, 2021.

19. Townsend P. Deprivation. *Journal of Social Policy.*1987;16(2):125-146.

20. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604-612.

21. Hippisley-Cox J, Young D, Coupland C, et al. Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: cohort study including 8.3 million people. *Heart.*2020;106(19):1503-1511.

22. Savarese G, Benson L, Sundstrom J, Lund LH. Association between renin-angiotensin-aldosterone system inhibitor use and COVID-19 hospitalization and death: a 1.4 million patient nationwide registry analysis. *Eur J Heart Fail.* 2021;23(3):476-485.

23. Kaur U, Chakrabarti SS, Patel TK. Renin-angiotensin-aldosterone system blockers and region-specific variations in COVID-19 outcomes: findings from a systematic review and meta-analysis. *Ther Adv Drug Saf.* 2021;12:20420986211011345.

24. Ren L, Yu S, Xu W, Overton JL, Chiamvimonvat N, Thai PN. Lack of association of antihypertensive drugs with the risk and severity of COVID-19: A meta-analysis. *J Cardiol.* 2021;77(5):482-491.

25. Caldeira D, Alves M, Gouveia EMR, et al. Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers and the risk of COVID-19 infection or severe disease: Systematic review and meta-analysis. *Int J Cardiol Heart Vasc.* 2020;31:100627.

26. Gault N, Esposito-Farese M, Revest M, et al. Chronic use of renin-angiotensin-aldosterone system blockers and mortality in COVID-19: A multicenter prospective cohort and literature review. *Fundam Clin Pharmacol.* 2021.

27. Pirola CJ, Sookoian S. Estimation of Renin-Angiotensin-Aldosterone-System (RAAS)-Inhibitor effect on COVID-19 outcome: A Meta-analysis. *J Infect.* 2020;81(2):276-281.

28. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. *N Engl J Med.* 2020;382(17):1653-1659.

29. Danser AHJ, Epstein M, Batlle D. Renin-Angiotensin System Blockers and the COVID-19 Pandemic: At Present There Is No Evidence to Abandon Renin-Angiotensin System Blockers. *Hypertension.*2020;75(6):1382-1385.

30. Lopes RD, Macedo AVS, de Barros ESPGM, et al. Effect of Discontinuing vs Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on Days Alive and Out of the Hospital in Patients Admitted With COVID-19: A Randomized Clinical Trial.*JAMA.* 2021;325(3):254-264.

31. Puskarich MA, Cummins NW, Ingraham NE, et al. A multi-center phase II randomized clinical trial of losartan on symptomatic outpatients with COVID-19. *EClinicalMedicine.* 2021;37:100957.

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

	Total Population	Total Population	Total Population	Covid-19 patients	Covid-19 patients	Covid-19 patients	Hospitalized Covid-19 patients	Hospitalized Covid-19 patients	Ho Co 19 pa
Characteristics	**N $_{total}$**	**N (%)***	**Mean (SD)**	**N $_{total}$**	**N (%)***	**Mean (SD)**	**N $_{total}$**	**N (%)***	**M (S**
Age (years)	124,143		70.6 (7.1)	4592		68.3 (8.2)	1015		72. (7.
Sex Male	124,143	62,633 (50.5)		4592	2465 (53.7)	2451 (53.9)	1015	601 (59.2)	
Female		61,510 (49.6)			2127 (46.3)			414 (40.8)	
Ethnicity	123,402	114,920 (93.1)		4554	3982 (87.4)		1006	886 (88.1)	
White		3016 (2.4)			198 (4.4)			52 (5.2)	
Black		5466 (4.4)			374 (8.2)			68 (6.8)	
Other									
BMI (kg/m2)	123,302		29.2 (5.1)	4541		30.3 (5.4)	997		30. (5.
Deprivation index	124,000		-1.2 (3.1)	4587		-0.4 (3.4)	1015		-0. (3.
Education (years)	121,066		12.2 (3.4)	4420		11.6 (3.3)	974		11. (3.
Smoking	123,816	64,204 (51.9)		4568	2267 (49.6)		1010	423 (41.9)	
Never		48,322 (39.0)			1817 (39.8)			471 (46.6)	
Former		11,290 (9.1)			484 (10.6)			116 (11.5)	
Current									

	Total Population	Total Population	Total Population	Covid-19 patients	Covid-19 patients	Covid-19 patients	Hospitalized Covid-19 patients	Hospitalized Covid-19 patients	Ho Co 19 pa
Alcohol consumption	123,678	41,154 (33.3)		4564	1768 (38.7)		1007	443 (44.0)	
Abstainer		46,836 (37.9)			1622 (35.5)	615		349 (34.7)	
WHO Category I		19,397 (15.7)			559 (12.3)			117 (11.6)	
WHO Category II		16,291 (13.2)						98 (9.7)	
WHO Category III									
Physical activity	96,663	19,992 (20.7)		3447	817 (23.7)		752	187 (24.9)	
Low		40,126 (41.5)			1342 (38.9)			282 (37.5)	
Moderate		36,545 (37.8)			1288 (37.4)			283 (37.6)	
High									
SBP (mmHg)	123,777		151.0 (19.2)	4571		148.9 (19.2)	1010		150 (20
DBP (mmHg)	123,781		87.0 (10.8)	4571		87.1 (11.1)	1010		85. (11
HDL cholesterol (mmol/L)	106,065		1.4 (0.4)	3895		1.3 (0.4)	849		1.3 (0.
LDL cholesterol (mmol/L)	115,349		3.4 (0.9)	4231		3.4 (0.9)	932		3.2 (0.
eGFR (mL/min/1.73 m^2)	115,497	60,713 (52.6)		4237	2383 (56.2)		934	434 (46.5)	
[?] 90		50,349 (43.6)			1670 (39.4)	184		426 (45.6)	
[?] 60 - <90		4435 (3.8)			(4.3)			74 (7.9)	
< 60									
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)	

	Total Population	Total Population	Total Population	Covid-19 patients	Covid-19 patients	Covid-19 patients	Hospitalized Covid-19 patients	Hospitalized Covid-19 patients	Ho Co 19 pa
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		4.9 (3.0)	4592		5.6 (3.7)	1015		7.1 (4.
Antihypertensive drugs+	124,143	53,796 (43.3)		4592	1888 (41.1)		1015	387 (38.1)	
ACEI		31,917 (25.7)			1217 (26.5)			264 (26.0)	
ARB		32,668 (26.3)			1324 (28.8)			402 (39.6)	
Diuretic		55,288 (44.5)			2119 (46.2)			456 (44.9)	
CCB		32,504 (26.2)			1286 (28.0)			407 (40.1)	
BB		661 (0.5)			23 (0.5)			6 (0.6)	
Other									

* The percentages might not add up to100 due to rounding.

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

Abbreviations: *Covid-19* coronavirus disease 2019 *SD*standard deviation *BMI* Body Mass Index *SBP* systolic blood pressure *DBP* diastolic blood pressure *HDL* high density lipoprotein *LDL* low density lipoprotein *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* beta-blocker

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 the all Covid-19 infected patients, and iii) 28-day all-cause mortality in the hospitalized Covid-19 infected patients

Antihypertensive medication	Covid-19 hospitalization in total population	Covid-19 hospitalization in total population
	$\mathbf{n_{total}}$	$\mathbf{n_{case}}$
ACEI	53796	387
ARB	30995	256
ACEI	53796	387
CCB	36616	305
ACEI	53796	387

Antihypertensive medication	Covid-19 hospitalization in total population	Covid-19 hospitalization in total population
BB	18878	258
ACEI	53796	387
Diuretic	19433	242
ACEI	53796	387
CCB/BB/Diuretic	38691	366

*Adjusted for age, sex, and ethnic background

+Adjusted for age, sex, ethnic background, socio-economic deprivation, smoking, physical activity, alcohol consumption, BMI, SBP, DBP, HDL cholesterol, LDL cholesterol, 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.

Abbreviations: *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* beta-blocker *Ref.* Reference

Table 3. Associations of CCB, BB and diuretic use in comparison with ARB use with i) Covid-19 hospitalization in the total population with hypertension, ii) 28-day all-cause mortality in the all Covid-19 infected patients, and iii) 28-day all-cause mortality in the hospitalized Covid-19 infected patients

Antihypertensive medication				Covid-19 hospitalization in total population	Covid-19
	$\mathbf{n_{total}}$	$\mathbf{n_{case}}$	**OR (95%CI) * Simple model***	**OR (95%CI) * Simple model***	**OR (95% Full mod**
ARB	31917	264	Ref.	Ref.	Ref.
CCB	44816	345	0.91 (0.78-1.07)	0.91 (0.78-1.07)	1.09 (0.93
ARB	31917	264	Ref.	Ref.	Ref.
BB	24550	305	1.45 (1.23-1.72)	1.45 (1.23-1.72)	1.26 (1.06
ARB	31917	264	Ref.	Ref.	Ref.
Diuretic	23286	297	1.54 (1.31-1.83)	1.54 (1.31-1.83)	1.28 (1.08
ARB	31917	264	Ref.	Ref.	Ref.
CCB/BB/Diuretic	38691	366	1.15 (0.98-1.35)	1.15 (0.98-1.35)	1.50 (1.27

*Adjusted for age, sex, and ethnic background

+Adjusted for age, sex, ethnic background, socio-economic deprivation, smoking, physical activity, alcohol consumption, BMI, SBP, DBP, HDL cholesterol, LDL cholesterol, 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.

Abbreviations: *Covid-19* coronavirus disease 2019 *OR* odds ratio *CI* confidence interval *ARB* angiotensin receptor blocker *CCB* calcium-channel blocker *BB* beta-blocker*Ref.* Reference

Figure Legends

Figure 1. Kaplan Meier curves of 28-day survival among all hypertensive Covid-19 patients (A) and those hospitalized for Covid-19 (B) for comparison of users of either CCB, BB or diuretics (solid line) and ACEI (dash line).

Abbreviations: ACEI indicates angiotensin-converting enzyme inhibitor, CCB calcium-channel blocker, BB beta-blocker

Figure 2. Kaplan Meier curves of 28-day survival among all hypertensive Covid-19 patients (A) and those hospitalized for Covid-19 (B) for comparison of users of either CCB, BB or diuretics (solid line) and ARB (dash line).

Abbreviations: ARB indicates angiotensin receptor blocker, CCB calcium-channel blocker, BB beta-blocker

Hosted file

`Figure1.docx` available at https://authorea.com/users/435850/articles/538592-association-of-renin-angiotensin-aldosterone-system-blocker-use-with-covid-19-hospitalization-and-all-cause-mortality-in-the-uk-biobank

Hosted file

`Figure 2.docx` available at https://authorea.com/users/435850/articles/538592-association-of-renin-angiotensin-aldosterone-system-blocker-use-with-covid-19-hospitalization-and-all-cause-mortality-in-the-uk-biobank