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Epidemiology

Mortality from angiotensin-converting enzyme-inhibitors and angiotensin receptor blockers in people infected with COVID-19: a cohort study of 3.7 million people

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Background: Concerns have been raised that angiotensin-converting enzyme-inhibitors (ACE-I) and angiotensin receptor blockers (ARBs) might facilitate transmission of severe acute respiratory syndrome coronavirus 2 leading to more severe coronavirus disease (COVID-19) disease and an increased risk of mortality. We aimed to investigate the association between ACE-I/ARB treatment and risk of death amongst people with COVID-19 in the first 6 months of the pandemic.

Methods: We identified a cohort of adults diagnosed with either confirmed or probable COVID-19 (from 1 January to 21 June 2020) using computerized medical records from the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) primary care database. This comprised 465 general practices in England, United Kingdom with a nationally representative population of 3.7 million people. We constructed mixed-effects logistic regression models to quantify the association between ACE-I/ARBs and all-cause mortality among people with COVID-19, adjusted for sociodemographic factors, comorbidities, concurrent medication, smoking status, practice clustering, and household number.

Results: There were 9,586 COVID-19 cases in the sample and 1,463 (15.3%) died during the study period between 1 January 2020 and 21 June 2020. In adjusted analysis ACE-I and ARBs were not associated with all-cause mortality (adjusted odds ratio [OR] 1.02, 95% confidence interval [CI] 0.85–1.21 and OR 0.84, 95% CI 0.67–1.07, respectively).

Conclusion: Use of ACE-I/ARB, which are commonly used drugs, did not alter the odds of all-cause mortality amongst people diagnosed with COVID-19. Our findings should inform patient and prescriber decisions concerning continued use of these medications during the pandemic.

Key words: COVID-19, mortality, medication

Introduction

Coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to be a global health emergency. The virus has infected 244,509,671 and claimed the lives of 4.9 million people (as of 25 October 2021) worldwide. A key area of research has focussed on modifiable risk factors that could alter outcomes in COVID-19 disease. Several reports have highlighted the potential role of medications acting through the renin–angiotensin system (RAS) in modifying COVID-19 risk and outcomes.[1,2] SARS-CoV-2 binds to cells through angiotensin-converting enzyme 2 (ACE2) which is expressed by epithelial cells in the lung, kidney, heart, brain, and blood vessels. It is hypothesized that increased ACE2 activity in the lungs could encourage uncontrolled activation of the RAS.[3] While evidence in vivo in humans is limited, in mice models acute lung injury has been shown in response to SARS-CoV-1 spike protein.[4] It is therefore plausible that similar responses will be observed with SARS-CoV-2. Activation of ACE2 in the lungs might contribute to cytokine storm and the subsequent respiratory failure observed in many of those who have died from COVID-19.[5]

Our systematic review identified a number of routinely prescribed drugs that could alter ACE2 levels and activity.[6] The most frequently reported were angiotensin receptor blockers (ARBs) (n = 55) and ACE-I (n = 22). In 2019, over 65 million prescriptions were issued for these 2 classes of drugs in the United Kingdom to treat a variety of clinical conditions.[7–9] Given their widespread use and the plausible mechanistic link with COVID-19 mortality, clarity is needed about their safety.

Recent studies examining the link between ACI-I/ARB use and mortality amongst COVID-19 patients have shown conflicting results, with the majority of studies studying small

Key messages

- ACE-I/ARB had no association with all-cause mortality in patients with COVID-19.
- Our findings support continued adherence to these medications during the pandemic.
- We hope this provides reassurance to patients and healthcare practitioners.

numbers of patients in the hospital setting (predominantly based in China), often with incomplete prescribing data on ACE-I/ARB use before admission.[10] Studies conducted outside China include an observational study of 169 hospitals in Asia, Europe, and North America (n = 8,910), which showed no increased risk of hospital-specific mortality from ACE-I (2.1% vs. 6.1%; odds ratio [OR], 0.33; 95% confidence interval [CI], 0.20–0.54) or ARB (6.8% vs. 5.7%; OR, 1.23; 95% CI, 0.87–1.74) in COVID-19.[11] Community data were not captured, however, and this is where large numbers of COVID-19 deaths and widespread use of these drugs occur.

Further data are required from large ethnically and geographically diverse cohorts. Moreover, as the pandemic progresses, a better understanding of the virus is emerging allowing for more detailed consideration of additional confounder and moderator variables. We therefore investigated the association between ACE-I/ARB and the risk of all-cause mortality amongst people with COVID-19 during the first 6 months of the pandemic.

Methods

Design and data source

We performed a cohort study using the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) database of primary care records.[12] This database includes rural and urban areas across England in the United Kingdom, and is one of the longest established primary care sentinel networks globally. It has supported Public Health England in national surveillance of communicable diseases in previous pandemics such as influenza and the current outbreak.[13] The main clinical coding systems that are used in the computerized medical records are Read 5 byte version 2 (Read V2), Clinical Terms Version 3 (CTV3), and their successor Systematised Nomenclature of Medicine Clinical Terms (SNOMED CT). They are used to code key clinical data on diagnoses, symptoms, examination findings, prescribed medications, investigations, laboratory tests, and results. Individual-level pseudonymized data are extracted from primary care records in patients who have not opted out through their GPs.

Study population

We included adults ≥18 years diagnosed with either confirmed or probable COVID-19 disease between 1 January and 21 June 2020. Confirmed cases were those with a positive RT-PCR assay for SARS-CoV-2 on nasal or pharyngeal swab (rapid antigen testing was not widely available during this period). Probable cases were diagnosed radiologically or clinically (based Public Health England's guidance early in the pandemic). Clinical symptoms included a new continuous cough, a loss/change in smell and/or taste, or a fever >37.8 degrees. Further information and our rationale for case definition, and detail on the RCGP RSC COVID-19 surveillance ontology has been reported in previous publications.[14,15]

Exposure: ACE-I/ARB use

We defined the exposure as 1 or more ACE-I or ARB prescriptions within 3 months from the 31 December 2019. Drug classes were examined separately. We included all ACE-I or ARBs listed in the most recent British National Formulary.

Outcome: all-cause mortality

The primary outcome was all-cause mortality during the follow-up period from 1 January 2020 until 21 June 2020 as recorded in the Oxford-RCGP RSC. The validity of the mortality outcome in the database has been described previously.[16]

Socioeconomic and household variables

We extracted data on age, sex, socioeconomic status, and ethnicity. For socioeconomic status we estimated practice-level deprivation using the English Index of Multiple Deprivation (IMD).[17] Values were categorized into quintiles of deprivation (IMD quintile 1 = most deprived; 5 = least deprived) with the 2 most deprived quintiles combined as recent work suggests that there is a low frequency of testing, leading to sparse data in the most deprived quintile.[17] Ethnicity was characterized using a combination of self-reported data recorded in the GP records on registration and information which infers ethnicity (such as language) using defined ontological approaches to maximize case identification.[18] Recent studies suggest that household size could be an important risk factor in acquiring COVID-19 so we included these variables as the most recently recorded prior to the index data (1 January 2020).[19] The UK registration-based system means that 1 individual is registered with a single GP practice giving a reliable denominator. The use of household number variables has been described in the database previously.[20] For urban–rural classification, we used the UK Office for National Statistics lookup tool at an individual-patient level basis and employed the Office for National Statistics Lower Super Output Area to estimate population density. Further detail can be found in a specific publication using this classification system.[21]

Clinical variables

Comorbidity variables included hypertension, coronary heart disease, type 1 diabetes, type 2 diabetes, chronic obstructive pulmonary disease (COPD), asthma, and chronic kidney disease (CKD stage 3–5); coded as any history before the 1 January 2020 index date. We included the last recorded body mass index (BMI) within 12 months of the index date. Records of prescriptions (within 6 months of the index date) for prednisolone and/or disease-modifying antirheumatic drugs were used as a surrogate for immunosuppression. Other drugs examined included antihypertensives, lipid- and

glucose-lowering medication, and inhalers (bronchodilaterors and steroids). The latest recording for smoking status was categorized as nonsmoker, active-smoker, or ex-smoker (within 12 months before the index date).

Statistical analysis

Baseline demographic and clinical characteristics were summarized and stratified as those on ACE-I, ARBs, or neither. We reported categorical data using counts and percentages, and for continuous data, we reported means with standard deviations. Univariable and multivariable logistic regression models were constructed with ACE-I and ARB examined separately in relation to all-cause mortality. The maximally adjusted model included variables for baseline sociodemographics (age, gender, ethnicity, IMD quintile), household size, BMI, and comorbidities (including hypertension). Mixed-effects models were performed to account for practice clustering (with random effect for practice). After conducting complete case analysis, we then used multiple imputation by chained equations to replace missing values for BMI, household size, IMD Quintile, and smoking status. Due to large amounts of missing ethnicity data (20%), multiple imputation could not be used for this variable and therefore missing data for ethnicity in the sensitivity analysis were assigned to the White ethnicity category. This was based on the assumption that the study population was comparable with the UK population, and >93% or more people without ethnicity recorded would be expected to be from a White ethnic group.[22] Statistical analyses were performed using R (Version 3.5.3). The level of significance was set at 5% and all statistical tests were 2 tailed. Model parameters were reported using ORs and 95% CIs. Our findings are reported in line with the STROBE and RECORD guidelines for observational studies using routinely collected health data.

Results

Baseline characteristics

The denominator population included 3,692,285 people registered with 465 GP practices within the RCGP RSC database. Within this sample, 9,586 people had COVID-19, 6,702 (69.9%) diagnosed via a positive test and 2,884 (30.1%) diagnosed clinically. The mean age of the total COVID-19 cohort was 60.5 years (SD 20.7); self-assigned ethnicity was predominantly White 6,156 (64.2%). Prescription of an ACE-I and ARB were recorded for 1,278 and 639 people, respectively. People prescribed these medications were more likely to be older, male and have multiple comorbidities, compared to those not prescribed these medications. Table 1 shows the baseline characteristics of patients with and without prescriptions of ACE-I and ARB. 1,463 (15.3%) died during follow-up. Mean follow-up to death, deregistration or the end of study was 162.9 days (SD 22.0). 1,463 (15.3%) died during follow-up. Those who died were more likely to be older males with comorbidities living in urban areas and from larger households. The sociodemographic and clinical characteristics amongst those who died are summarized in Table 2.

ACE-I/ARB use and odds of death

In unadjusted analysis, ACE-I and ARBs were associated with all-cause mortality in people with COVID-19. However, after adjusting for covariates, no association was present for either drug: ACE-I (OR 1.05, 95% CI 0.86–1.29) and ARB (OR 0.82, 95% CI 0.63–1.08). Similar results were observed in the imputed models: ACE-I (OR 1.02, 95% CI 0.85–1.21) and ARB (OR 0.84, 95% CI 0.67–1.07). These results are shown in Table 3 and the full output with covariates shown in Supplementary Material. Sensitivity analysis on complete cases and multiple imputed data support the findings in our primary analysis. We also restricted the model to include only confirmed COVID-19 cases (rather than probable cases) and similarly found no associations between our primary outcomes and ACE-I (OR 0.90, 95% CI 0.70–1.17) or ARB (OR 0.93, 95% CI 0.67–1.30) in adjusted models.

Discussion

Key findings

In this sample of 9,586 people with COVID-19 within a primary care setting, we found no evidence for an association between prior ACE-I or ARB use and all-cause mortality after adjusting for baseline demographics, comorbidities, household variables, and practice clustering.

Comparison with existing literature

Our findings are consistent with recent observational studies.[11,23–25] A recent study examined community deaths in a Danish sample of 4,480 people with COVID-19, and similarly reported no significant association with mortality (adjusted hazard ratio, 0.83).[25] However, this cohort included a predominantly White "native Danish" population limiting wider generalizability to ethnically diverse populations, who are more susceptible to mortality from COVID-19. Further studies have also been published but none report specifically on all-cause mortality in a UK population-based community sample.[26] Most examine mortality in the hospital setting which includes more severe COVID-19 disease, often with incomplete prescribing data on ACE-I/ARB use before admission.[11,23,24] One of the largest cohorts includes 169 hospitals in Asia, Europe, and North America with a sample of 8,910 people with COVID-19.[11] The authors report no increased risk of hospital-specific mortality from ACE-I (2.1% vs. 6.1%; OR, 0.33; 95% CI, 0.20–0.54) or ARB (6.8% vs. 5.7%; OR, 1.23; 95% CI, 0.87–1.74) in COVID-19. Earlier on in the pandemic, a few studies did report positive associations between ACE-I/ARB and mortality but these are likely to have been limited through confounding by age, sex, ethnicity, and comorbidities.[2,27] We observed similar significant associations in our unadjusted models, but none of these remained in our multivariable analysis.

The results support emerging data suggesting that ACE-I/ARB are not associated with worse prognosis or death in COVID-19.[28,29] However, our results also do not provide evidence of a protective association of these drugs in those infected with the virus, which some large observational studies have shown for hospital admission and ICU admission.[26] We did observe that ARBs had a lower odds of all-cause mortality compared to ACE-I in all our models, but none of these were statistically significant. The proposed mechanistic link between ACE-I/ARB and SARS-CoV-2 hypothesizes that ACE-I/ARB upregulates ACE2 receptors which are used by the virus to gain entry into the lungs.[30] ACE2 is upregulated by ACE-I and ARB thus potentially increases susceptibility to the virus. The subsequent dysregulation of ACE2 activity in the lungs

Table 1. Baseline characteristics of the COVID-19 cohort in the RCGP RSC database in the first 6 months of the pandemic presented by those on ACE-I, ARBs, or neither.

	Total (*N* = 9,586)	No ACE-I/ARB (*N* = 7,685)	ACE-I (*N* = 1,278)	ARB (*N* = 639)
Sociodemographic				
Age (years)[a]	60.5 (20.7)	57.9 (21.2)	70.0 (14.8)	72.1 (13.9)
Sex (male)	4,135 (43.1)	3,112 (40.5)	718 (56.2)	314 (49.1)
Ethnicity recorded	7,680 (80.1)	6,134 (79.8)	1,050 (82.2)	510 (79.8)
White	6,156 (64.2)	4,887 (63.6)	875 (68.5)	407 (63.7)
Asian	927 (9.7)	772 (10.0)	95 (7.4)	61 (9.5)
Black	412 (4.3)	327 (4.3)	60 (4.7)	25 (3.9)
Mixed and other	185 (1.9)	148 (1.9)	20 (1.6)	17 (2.7)
IMD quintile recorded	9,326 (97.3)	7,462 (97.1)	1,249 (97.7)	629 (98.4)
5 (least deprived)	1,992 (21.4)	1,606 (20.9)	233 (18.7)	157 (24.6)
4	1,879 (20.1)	1,512 (19.7)	243 (19.5)	125 (19.6)
3	1,851 (19.8)	1,469 (19.1)	256 (20.5)	129 (20.2)
1 and 2 (most deprived)	3,604 (38.6)	2,875 (37.4)	517 (41.3)	218 (34.1)
Household size recorded	9,439 (98.5)	7,562 (98.4)	1,261 (98.7)	630 (98.6)
1	2,405 (25.1)	1,808 (23.5)	396 (31.0)	206 (32.2)
2–4	4,785 (49.9)	3,827 (49.8)	648 (50.7)	319 (49.9)
5–8	1,038 (10.8)	907 (11.8)	86 (6.7)	45 (7.0)
≥9	1,211 (12.6)	1,020 (13.3)	131 (10.3)	60 (9.4)
Settlement or population density recorded	9,330 (97.3)	7,562 (98.4)	1,252 (98.0)	630 (98.6)
Rural	1,671 (17.4)	1,341 (17.4)	223 (17.4)	111 (17.4)
Urban	7,659 (79.9)	6,121 (79.6)	1,029 (80.5)	519 (81.2)
Clinical				
BMI recorded	8,923 (93.1)	7,059 (91.9)	1,253 (98.0)	627 (98.1)
BMI (kg/m^2)[a]	28.2 (6.7)	27.7 (6.6)	30.3 (6.7)	30.1 (6.5)
Smoking status recorded	9,362 (97.7)	7,474 (97.3)	1,265 (99.0)	639 (100.0)
Nonsmoker	3,353 (35.0)	2,887 (37.6)	295 (23.1)	172 (26.9)
Active-smoker	896 (9.3)	772 (10.0)	90 (7.0)	36 (5.6)
Ex-smoker	5,113 (53.3)	3,815 (49.6)	880 (68.9)	431 (67.4)
Hypertension	3,656 (38.1)	2,000 (26.0)	1,093 (85.5)	575 (90.0)
Coronary heart disease	868 (9.1)	461 (6.0)	289 (22.6)	123 (19.2)
Type 1 diabetes	59 (0.6)	41 (0.5)	12 (0.9)	6 (0.9)
Type 2 diabetes	1,845 (19.2)	1,044 (13.6)	549 (43.0)	260 (40.7)
CKD	1,364 (14.2)	863 (11.2)	310 (24.3)	196 (30.7)
Asthma	1,690 (17.6)	1,345 (17.5)	226 (17.7)	122 (19.1)
COPD	596 (6.2)	392 (5.1)	153 (12.0)	56 (8.8)
Medication				
Antihypertensive medication	3,332 (34.8)	1,431 (18.6)	1,278 (100.0)	639 (100.0)
Lipid-lowering medication	2,390 (24.9)	1,251 (16.3)	775 (60.6)	375 (58.7)
Hypoglycaemic medication	1,288 (13.4)	661 (8.6)	434 (34.0)	199 (31.1)
Inhalers	1,256 (13.1)	894 (11.6)	245 (19.2)	121 (18.9)
Immunosuppressants	634 (6.6)	427 (5.6)	142 (11.1)	69 (10.8)

Unless otherwise stated data are *n* (%). Sixteen people were treated with both an ACE-I and ARB.
[a]Data are mean (SD).

leads to neutrophil infiltration and uncontrolled activation of the RAS with lung injury and respiratory failure.[4,5] Our systematic review on this subject together with recent literature highlights that the action of ACE2 receptors, a key mediator of the effect of ACE-I/ARB on SARS-CoV-2, has been poorly studied in vivo within the lungs of humans, where it is likely to have the greatest effect in influencing COVID-19 outcomes.[6] Together with these previous findings, our work does not support the role of ACE-I/ARB in outcomes for COVID-19. Finally, we are not aware of any literature to-date examining the differences between COVID-19 variants and their interaction with RAS, or the effect of ACE-I/ARB on mortality from specific variants. We therefore suggest that future studies should consider exploring this area.

Table 2. Baseline characteristics of those who died in the COVID-19 RCGP RSC cohort within the first 6 months of the pandemic.

	Total (*N* = 9,586)	Nondecedent (*N* = 8,123)	Decedent (*N* = 1,463)
Sociodemographic			
Age (years)[a]	60.5 (20.7)	56.9 (19.9)	80.2 (11.7)
Sex (male)	4,135 (43.1)	3,336 (41.1)	799 (64.6)
Ethnicity recorded	7,680 (80.1)	6,534 (80.4)	1,146 (78.3)
White	6,156 (64.2)	5,143 (63.3)	1,013 (69.2)
Asian	927 (9.7)	860 (10.6)	67 (4.6)
Black	412 (4.3)	363 (4.5)	49 (3.3)
Mixed and other	185 (1.9)	168 (2.1)	17 (1.2)
IMD quintile recorded	9,326 (97.3)	7,889 (97.1)	1,445 (98.8)
5 (least deprived)	1,992 (21.4)	1,672 (20.6)	320 (21.9)
4	1,879 (20.1)	1,552 (19.1)	327 (22.4)
3	1,851 (19.8)	1,552 (19.1)	299 (20.4)
1 and 2 (most deprived)	3,604 (38.6)	3,113 (38.3)	499 (34.1)
Household size recorded	9,439 (98.5)	7,901 (97.3)	1,449 (99.0)
1	2,405 (25.1)	1,954 (24.1)	451 (30.8)
2–4	4,785 (49.9)	4,234 (52.1)	462 (31.6)
5–8	1,038 (10.8)	953 (11.7)	85 (5.8)
≥9	1,211 (12.6)	760 (9.4)	451 (30.8)
Settlement or population density recorded	9,330 (97.3)	7,891 (97.1)	1,439 (98.4)
Rural	1,671 (17.4)	1,405 (17.3)	266 (18.2)
Urban	7,659 (79.9)	6,486 (79.8)	1,173 (80.2)
Clinical			
BMI recorded	8,923 (93.1)	7,555 (93.0)	1,368 (93.5)
BMI (kg/m^2)[a]	28.2 (6.7)	28.5 (6.7)	26.9 (6.4)
Smoking status recorded	9,362 (97.7)	7,938 (97.7)	1,424 (97.3)
Nonsmoker	3,353 (35.0)	3,007 (37.0)	346 (23.7)
Active-smoker	896 (9.3)	803 (9.9)	93 (6.4)
Ex-smoker	5,113 (53.3)	4,128 (50.8)	985 (67.3)
Hypertension	3,656 (38.1)	2,726 (33.6)	930 (63.6)
Coronary heart disease	868 (9.1)	572 (7.0)	296 (20.2)
Type 1 diabetes	59 (0.6)	55 (0.7)	4 (0.3)
Type 2 diabetes	1,845 (19.2)	1,386 (17.1)	459 (31.4)
CKD	1,364 (14.2)	910 (11.2)	454 (31.0)
Asthma	1,690 (17.6)	1,498 (18.4)	192 (13.1)
COPD	596 (6.2)	418 (5.1)	178 (12.2)
Medication			
Antihypertensive medication	3,332 (34.8)	2,533 (31.2)	799 (54.6)
Lipid-lowering medication	2,390 (24.9)	1,810 (22.3)	580 (39.6)
Hypoglycaemic medication	1,288 (13.4)	986 (12.1)	302 (20.6)
Inhalers	1,256 (13.1)	1,008 (12.4)	248 (17.0)
Immunosuppressants	634 (6.6)	484 (6.0)	150 (10.3)

Strengths and limitations

We report one of the largest observational studies specifically examining ACE-I/ARB and all-cause mortality using primary care data from 465 GP practices representing 3.7 million people across England, United Kingdom. A key strength is the size and quality of the database used. The RCGP RSC database has wide coverage, is representative of the population and hence the results are likely to be generalizable. It is updated twice weekly with comprehensive and validated variables that have high levels of completeness allowing real-time and accurate assessment during the pandemic.[12] We additionally used standardized coding required for National Health Service payment and administrative purposes, and data are therefore more likely to be of high quality. We also controlled for important potential confounders (including hypertension) as part of adjusted regression models.

However, the case definition of COVID-19 has been changing throughout the pandemic as understanding improves and as testing becomes more widely available. We included

Table 3. Association between ACE-I/ARB, and the risk of death in the RCGP RSC COVID-19 cohort (n = 9,586).

		OR	95% CI		P
Unadjusted model		1			
	ACE-I	1.80	1.55	2.10	<0.001
	ARBs	1.54	1.25	1.90	<0.001
Adjusted model[a]		1			
	ACE-I	1.05	0.86	1.29	0.64
	ARBs	0.82	0.63	1.08	0.15
Adjusted imputed model[b]		1			
	ACE-I	1.02	0.85	1.21	0.87
	ARBs	0.84	0.67	1.07	0.16

The initial unadjusted and adjusted models were conducted as a complete case analysis. Full table of outputs can be found in Supplement Material.
[a]The model was adjusted for age, sex, IMD quintile, ethnicity, household variables, comorbidities (including hypertension), medication use, smoking status, and practice clustering.
[b]Imputed for BMI, household size, IMD quintile, and smoking status. Missing ethnicity data were assigned to the White category as described in the text. We then ran the same model as shown above.

laboratory confirmed cases alongside probable cases based on clinical presentation because of inconsistency with national testing programmes, and also as testing may not have been available to some individuals (such as those in care homes or nursing homes), potentially leading to under-ascertainment. Furthermore, rapid antigen testing was not widely available during the first wave of the pandemic.

Data on the severity of COVID-19 illness, as well as data on the method of temperature measurement, were also not available. It is possible that not all those with probable COVID-19 actually had the virus. However, in our previous study of mortality in people with known COVID-19 status, those diagnosed clinically had a very similar odds of mortality as those diagnosed following laboratory tests.[31] Furthermore, clinical symptoms may not have been consistently recorded and given that COVID-19 codes were relatively new to practices, and uptake may not have been universal. However, additional sensitivity analyses restricting our model to include only confirmed COVID-19 cases produced similar results. Finally, the first wave of the pandemic also occurred prior to the routine introduction of COVID-19 vaccines, and we were therefore unable to examine this as a potential modulator of COVID-19 severity.

Data on our main outcome (all-cause mortality) were also not externally validated through linkage with ONS or HES data which may result in misclassification of the outcome although we expect this to be small in magnitude since the fact of death is well recorded in primary care electronic systems. We were also unable to separate out causes of mortality to distinguish those that occurred as a direct result of COVID-19. There were significant changes in the classification of COVID-19 mortality as Government guidance changed, and there was significant uncertainty about accuracy of electronic coding and certification of death nationally with regard to COVID-19-specific mortality in the first few months of the pandemic. Furthermore, whilst COVID-19-specific mortality was available as a variable, however it may not have been widely used in primary care records, and the exacts dates were not considered sufficiently robust. All-cause mortality is likely to be a more reliable measure especially in the early part of the pandemic in which our study is set.

We also acknowledge that our sample will over-represent people in the population who presented with more severe symptoms (thus making our results susceptible to collider bias), because early in the pandemic COVID-19 testing was restricted to those admitted to hospital. People with milder symptoms or who are less likely to present to health care services such as young men, people from low socioeconomic groups or those from ethnic minority groups are likely to be under-represented in our sample. To improve inclusion of those with mild symptoms or those who were asymptomatic, serology results from screening programmes could be helpful in future cohorts. In terms of ACE-I and ARB prescriptions, we defined the exposure as 1 or more prescriptions within 3 months, and our study assumes that people prescribed these medications were taking them, but we did not include any measures of adherence or examine the number of prescriptions issued. Finally, our study is also limited by potential residual/unmeasured confounding and risk of misclassification, as an inherent limitation of the retrospective cohort design.

Conclusions

We found no significant associations between use of ACE-I or ARB, and all-cause mortality in COVID-19. Our findings are consistent with calls from professional organizations including the British and Irish Hypertension Society, European Hypertension Society, and Renal Association encouraging continued adherence to these medications during the pandemic.

Supplementary material

Supplementary material is available at *Family Practice* online.

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Authors' contributions

HD-M contributed to the inception of the study, developed the study design, and wrote the first draft, edited, and contributed to subsequent versions of the manuscript. WH led the data analysis and revised the manuscript. MJ and BS provided advice on statistical methods and revised the paper. CRW and MF revised the paper. SJG and JH-C contributed to the study

design and revised the paper. SL and AL provided expertise on the RCGP database and revised the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Ethical approval

This study received approval from the RCGP RSC study approval committee (RSC_0920) and the University of Southampton Research Ethics committee (56309).

Conflict of interest

The authors declare that no support from any organization and no financial relationships have influenced the submitted work. SL has held grants from Eli Lilly Company, GlaxoSmithKline, Takeda, AstraZeneca, and Novo Nordisk Limited for investigator-led research. JH-C reports that the CTSU receives research grants from the pharmaceutical industry that are governed by University of Oxford contracts that protects its independence, and has a staff policy of not taking personal payments from industry. From 01.02.2019, JH-C is Professor of Clinical Epidemiology and General Practice at the University of Oxford. She is founder and director of QResearch database which is not-for-profit organization with EMIS (leading commercial supplier of IT for 55% of general practices in the United Kingdom). JH-C is co-owner of ClinRisk Ltd and was a paid director until June 2019. ClinRisk Ltd develops open and closed source software to ensure the reliable and updatable implementation of clinical risk equations within clinical computer systems to help improve patient care outside the submitted work. No other authors have any competing interests to declare.

Patient involvement

Patients and members of the public contributed to the setting the research question, the outcome measures, the design and have been invited to support the dissemination.

Data availability

Data are available with an application to the RCGP: https://www.rcgp.org.uk/clinical-and-research/our-programmes/research-and-surveillance-centre/supporting-research-teams.

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