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Original Research

Inpatient Omission of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers Is Associated With Morbidity and Mortality in Coronavirus Disease 2019

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ABSTRACT

Purpose: Due to the affinity of severe acute respiratory syndrome coronavirus 2 for the human angiotensin-converting enzyme 2 (ACE2) receptor, use of ACE inhibitors and angiotensin receptor blockers (ARBs) has been a major concern for clinicians during the 2020 pandemic. Meta-analyses have affirmed that these agents do not worsen clinical outcomes in patients with severe acute respiratory syndrome coronavirus 2 infection. To date, only a limited number of studies have directly evaluated the safety of inpatient prescription of ACE inhibitors/ARBs during acute coronavirus disease 2019 (COVID-19) illness.

Methods: A retrospective cohort analysis was conducted to investigate the impact of inpatient provision of ACE inhibitors/ARBs on morbidity and mortality in patients admitted to the hospital with COVID-19. Relationships were explored by using linear and logistic regression.

Findings: A total of 612 adult patients met the inclusion criteria, of whom 151 (24.7%) patients were established on ACE inhibitors/ARBs. Despite correction for known confounders, discontinuation of ACE inhibitors/ARBs was highly predictive of worsened outcomes in COVID-19. The proportion of doses omitted in the hospital was significantly associated with increased mortality (OR, 9.59; 95% CI, 2.55–36.09; $P < 0.001$), maximum National Early Warning Score 2 (OR, 1.66; 95% CI, 1.27–2.17; $P < 0.001$), maximum oxygen requirements (OR, 3.00; 95% CI, 1.83–4.91; $P < 0.001$), and maximum C-reactive protein concentration (OR, 1.83; 95% CI, 1.06–3.17; $P = 0.030$).

Implications: Our data show a strong association between missed ACE inhibitor/ARB doses with increased morbidity and mortality. The available evidence supports continuation of currently accepted practice surrounding ACE inhibitor/ARB therapy in acute illness, which is to limit drug omission to established acute contraindications, to actively monitor such decisions, and to restart therapy as soon as it is safe to do so. (*Clin Ther*. 2021;43:e97–e110) © 2021 Elsevier HS Journals, Inc. (*Clin Ther.* 2021;43:e97–e110.) © 2021 Elsevier Inc.

Key words: Angiotensin-converting enzyme inhibitors, Angiotensin receptor blockers, COVID-19, Inpatient, SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.

INTRODUCTION

The number of confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in the United Kingdom since the start of the pandemic exceeds 2 million as of January 1, 2021.[1] Despite advances in both understanding and treatment,

Abbreviations: ACE, angiotensin converting enzyme; AKI, acute kidney injury; ARBs, angiotensin receptor blockers; CRP, C-reactive protein; CI, confidence interval; ICU, intensive care unit; L/min, litres per minute; mg/L, milligrams per litre; NEWS-2, national early warning score 2; OR, odds ratio.

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coronavirus disease 2019 (COVID-19) still has a high mortality compared with seasonal influenza.[2] Advances in our understanding of the management of COVID-19 are clearly necessary if we are to reduce the impact of the disease. SARS-CoV-2 and its association with preexisting comorbidities have been extensively described.[3] However, there remains a limited amount of evidence guiding clinicians on the safety of continuing, or discontinuing, patients' regular medications.

The safety of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in COVID-19 has been questioned. This concern emerged due to upregulation of the human ACE2 receptor associated with ACE inhibitor/ARB therapy and the emergence of evidence that this protein acts as a functional receptor for SARS-CoV-2.[4,5]

Since then, a rapidly evolving evidence base supporting the safety of long-term ACE inhibitor/ARB use in COVID-19 has been developed. Broadly, this evidence base suggests that antecedent ACE inhibitor/ARB therapy is not associated with worsened outcomes in COVID-19 and that their use might confer certain protective benefits.[6–14] The impact of ACE inhibitor/ARB provision during acute COVID-19 illness has been inadequately examined. To date, few studies have attempted to address this question. One retrospective cohort concluded that complete suspension of therapy in patients with hypertension and COVID-19 is associated with greater morbidity and mortality.[15] Whether these findings are generalizable to all patients receiving ACE inhibitors/ARBs, and whether sporadic omission of these agents might also affect prognosis, remains unclear. The purpose of the present study was to examine, in further detail, the effects of suspending ACE inhibitors/ARBs on outcomes in patients admitted to the hospital with COVID-19.

PATIENTS AND METHODS

Study Design and Participants

A retrospective cohort analysis was performed including patients admitted to St. Helier Hospital in London, United Kingdom, with COVID-19 between January 1, 2020, and June 1, 2020. Infection in all cases was confirmed by detection of SARS-CoV-2 RNA obtained by oropharyngeal/nasal swab. Participants were included if they met the following criteria:

- Their admission was coded with COVID-19 as the primary or secondary reason for admission, or COVID-19 was documented as cause 1a or 1b on deceased patients' death certificates.
- Their admission had reached a primary end point (deceased or discharged) by July 23, 2020.
- The clinical coding of their admission was complete by July 23, 2020.

Diagnosis codes are ordered according to their clinical significance, in terms of related morbidity and implications for management, during each inpatient episode. Admissions for which the primary or secondary diagnosis was COVID-19 were selected to prevent morbidity associated with unrelated clinical sequelae in the context of mild cases of SARS-CoV-2 infection being reflected in analyses. Numerous SARS-CoV-2–positive patients were excluded for this reason and most likely represent mild cases, the implications of which are discussed in following sections.

All participants received a standardized COVID-19 treatment protocol alongside their regular medications, unless suspended for clinical reasons. Due to rapidly evolving guidelines, the protocol was modified during the period we studied. The temporal distribution of patients receiving ACE inhibitors/ARBs during the study period tracked with the sample size of the remainder of the cohort, and hence these changes are unlikely to have affected our results.

When assessing the effect of inpatient provision of ACE inhibitors/ARBs, patients were further excluded from analysis if they were palliated or died within 48 hours of admission. It was deemed unreasonable to assume that the effect of withholding these medications for 48 hours, or that discontinuation of these medications during palliative treatment, was sufficiently contributory to the outcome.

Data Collection

Participants' demographic characteristics, medical history, and admissions data were collated by our search engine for all inpatient admissions meeting the inclusion criteria. Laboratory values, clinical data, and details of ACE inhibitor/ARB prescription were extracted manually from hospital electronic records. ACE inhibitor/ARB prescriptions were identified from admissions documentation for their COVID-19–related admission. This information was cross-referenced with, where available, data regarding recent distribution of ACE inhibitors/ARBs from general practitioner records and with inpatient pharmacist

"medicine reconciliations" derived from individuals' NHS Summary Care Record.

DEFINITIONS

Outcome Measures

The primary study outcome was inpatient mortality. Secondary outcomes were intensive care unit (ICU) admission, length of stay, maximum oxygen requirement, maximum National Early Warning Score 2 (NEWS-2), maximum C-reactive protein (CRP) concentration, and maximum acute kidney injury (AKI) stage during admission. AKI was defined according to Kidney Disease: Improving Global Outcomes creatinine criteria for AKI.[16] The NEWS-2 score was calculated according to standards set by the Royal College of Physicians.[17]

Maximum Oxygen Requirement

The maximum oxygen requirement was defined as the highest flow rate of oxygen in liters per minute required by participants during admission for >2 sets of observations. A threshold of >2 sets of observations was selected to account for titration to saturations. Venturi devices were converted from percentages to approximate liters per minute as follows: 24% = 3 L/min, 28% = 5 L/min, 35% = 9 L/min, 40% = 11 L/min, and 60% = 13.5 L/min.[18] Patients requiring noninvasive or mechanical ventilation were assigned a maximal score of 15 L/min to allow for comparison with the remainder of the cohort.

Inpatient Provision of ACE Inhibitors/ARBs

ACE inhibitor/ARB provision as an inpatient was expressed as the proportion of days that doses were received compared with the number of days that they were required. The number of days required was defined as the number of days as an inpatient, excluding days after palliation and excluding the first day of admission if they were admitted past 9:00 AM. Counts were adjusted to exclude the days after a palliative decision was made to prevent the discontinuation of ACE inhibitors/ARBs after palliation being reflected in further analyses. The first day was excluded if they were admitted after 9:00 AM as it was assumed that these patients would have taken their ACE inhibitors/ARBs at home before attendance.

Hypotension

To adjust for hypotension as a cause for withdrawal of ACE inhibitors/ARBs, and the morbidity associated with this action, the degree of hypotension during admission was estimated for patients taking regular ACE inhibitors/ARBs. Significant hypotension was defined as a systolic blood pressure <100 mm Hg based on clinical data showing an increased mortality below this level and consensus guidelines from the European Society of Intensive Care Medicine.[19–21] The total number of blood pressure recordings taken during admission, before palliation, and the number of readings with a systolic value <100 mm Hg were recorded. The proportion of hypotensive recordings compared with the total was calculated from this. The days before palliation were defined as the days up to and including the assumed date of palliation. The measure was adjusted for this parameter to reflect the degree of hypotension during the period in which the primary end point (death/discharge) was not yet assured.

Palliation

Patients were deemed to be palliated on the day that anticipatory medications were prescribed, which are received as standard care for dying patients at our center. The assumption was made that the decision to palliate was made on the same day.

STATISTICAL ANALYSIS

Categorical variables are expressed as count numbers and percentages. Continuous variables are expressed as means (SDs). Linear and logistic regressions were used to explore the relationships between the variables. Linear models were used where the dependent variable was continuous, whereas logistic models were used if the dependent was binary. Results are expressed as odds ratios (ORs) with their 95% CIs, and *P* values for each component of the regression.

In univariate analyses of mortality, mortality was considered the dependent variable, and ORs were calculated as the likelihood of mortality per unit increase in each parameter tested. When comparing patients taking regular ACE inhibitors/ARBs versus nonusers, ORs were calculated as the likelihood of a unit increase in each parameter associated with ACE inhibitor/ARB prescription, with ACE inhibitor/ARB prescription as the independent variable.

In multivariate analyses, the relationships between outcome measures and long-term ACE inhibitors/ARBs were adjusted for age, sex, and clinical indications for ACE inhibitor/ARB prescription. In multivariate analyses of inpatient ACE inhibitor/ARB provision, relevant confounding variables were selected based

on the premise that they might be associated with greater or lesser provision of ACE inhibitors/ARBs and might also influence morbidity or mortality. The "Enter" method was used, entering variables with a univariate logistic association with our primary outcome measure, mortality, with a P value of <0.2 into our models. Ethnicity was excluded in this manner. Having already adjusted for palliative omission of ACE inhibitors/ARBs, variables selected for adjustment were age, sex, comorbidities, ICU admission, maximum AKI stage, and hypotension.

No sample size calculation was performed because we were unable to find appropriate published data from which to calculate this factor when data collection was commenced. A two-sided α of <0.05 was considered statistically significant. All statistical analyses were performed by using SPSS version 27 (IBM SPSS Statistics, IBM Corporation, Armonk, New York).

RESULTS

Population Characteristics

A total of 612 adult inpatient admissions met the study inclusion criteria. The average age of the study cohort was 69.6 (17.8) years, of whom 354 (57.8%) were male. Eighty-six patients (14.1%) required admission to the ICU. A total of 281 patients died (45.9%), an elevated rate compared with our center's average inpatient mortality due to our inclusion criteria excluding mild or incidental cases. One hundred fifty-one (24.7%) patients in our cohort were taking ACE inhibitors/ARBs before admission, of whom 98 (16.0%) were prescribed ACE inhibitors, and 53 (8.7%) were prescribed ARBs (Table I). Data were complete for each participant.

Univariate Analyses

Characteristics of Survivors Compared With Nonsurvivors

Advanced age and male sex were both significantly associated with an excess of mortality. All secondary outcomes were highly predictive of excess mortality in our cohort ($P < 0.001$) apart from length of stay ($P = 0.629$). A significant excess of mortality was also associated with long-term ACE inhibitor/ARB use in unadjusted studies. Accordingly, clinical indications for ACE inhibitor/ARB prescription, namely hypertension, heart failure, ischemic heart disease, and diabetes mellitus, displayed similar relationships (Table I).

Characteristics of ACE Inhibitor/ARB Users Compared With Nonusers

Comparison between users of ACE inhibitors/ARBs and nonusers found that users were significantly more likely to be elderly and to have a diagnosis of hypertension, heart failure, ischemic heart disease, or diabetes mellitus. ACE inhibitor/ARB use was similar for both sexes ($P = 0.488$). Outcomes in ACE inhibitor/ARB users were broadly poorer than in nonusers. Long-term ACE inhibitor/ARB use was significantly associated with increased mortality, ICU admission, and unit increases in NEWS-2 score, flow rate of oxygen required, and CRP concentration in unadjusted studies. Nonsignificant relationships were displayed between ACE inhibitor/ARB use and both AKI stage and length of stay (Table II).

Multivariate Analyses

Adjusted Effects of Long-Term ACE Inhibitor/ARB Use on Clinical Outcomes

In adjusted studies, prior ACE inhibitor/ARB use was associated with higher NEWS-2 score (OR of 1.16 [95% CI, 1.01–1.32] for a 5-point increase; $P = 0.030$), greater supplemental oxygen requirement (OR of 1.36 [95% CI, 1.06–1.74] for a 5 L/min increase; $P = 0.014$), and a greater rise in CRP (OR of 1.34 [95% CI, 1.04–1.73] for a 100 mg/L increase; $P = 0.024$). The adjusted relationships between prior ACE inhibitor/ARB use and both mortality (OR, 1.18; 95% CI, 0.77–1.82; $P = 0.447$) and AKI stage (OR, 0.97; 95% CI, 0.78–1.22; $P = 0.809$) were nonsignificant, however (Table III).

Adjusted Effects of Inpatient ACE Inhibitor/ARB Use on Clinical Outcomes

Before analysis, 21 of the 151 patients taking ACE inhibitors/ARBs were excluded because they were palliated or died within 48 hours of admission, the assumption being that provision or nonprovision of ACE inhibitors/ARBs in this period would not have been a major determinant of clinical outcomes. Fifteen (71.4%) of these patients were prescribed ACE inhibitors, and six (28.6%) were prescribed ARBs before admission.

Of the remaining 130 patients, the mean age was 73.7 (12.8) years, representing 77 (59.2%) male subjects and 53 (40.8%) female subjects. Twenty-nine (22.3%) patients were admitted to the ICU, and 63

Table I. Demographic and clinical characteristics of survivors compared with nonsurvivors. Columns 2 to 4 describe the population characteristics for: the entire cohort (column 2), survivors (column 3), and nonsurvivors (column 4). Column 5 describes the results of univariate logistic regressions comparing survivors with nonsurvivors. Odds ratios are expressed as the increase in mortality associated with a unit increase in each parameter tested. Column 6 presents the significance (α) of these associations.

Variable	Entire Population (N = 612)	Survivors (n = 331)	Non-Survivors (n = 281)	Odds Ratio (95% CI)	*P*
Demographic characteristics					
Age, mean (SD), years*	69.6 (17.8)	63.1 (18.5)	77.2 (13.3)	1.71 (1.53–1.92)	<0.001
Male sex	354 (57.8%)	175 (52.9%)	179 (63.7%)	1.56 (1.13–2.17)	0.007
Outcomes					
Intensive care admission	86 (14.1%)	28 (8.5%)	58 (20.6%)	2.81 (1.74–4.56)	<0.001
Length of stay, days	12.1 (13.7)	12.4 (14.3)	11.8 (12.9)	1.00 (0.99–1.01)	0.629
Maximum NEWS-2	8.2 (3.4)	6.3 (2.8)	10.4 (2.6)	1.81 (1.64–1.99)	<0.001
Maximum oxygen, L/min	7.8 (6.2)	4.4 (5.2)	11.9 (4.7)	1.27 (1.22–1.31)	<0.001
Maximum AKI stage	0.89 (1.14)	0.60 (1.01)	1.24 (1.19)	1.67 (1.44–1.94)	<0.001
Maximum CRP, mg/L†	196 (128)	152 (109)	248 (128)	1.95 (1.67–2.27)	<0.001
Comorbidities					
Hypertension	299 (48.9%)	136 (41.1%)	163 (58.0%)	1.98 (1.43–2.73)	<0.001
Heart failure	57 (9.3%)	20 (6.0%)	37 (13.2%)	2.36 (1.33–4.17)	0.003
Ischemic heart disease	97 (15.8%)	31 (9.4%)	66 (23.5%)	2.97 (1.87–4.71)	<0.001
Diabetes mellitus	166 (27.1%)	79 (23.9%)	87 (31.0%)	1.43 (1.00–2.05)	0.050
ACE inhibitors/ARBs	151 (24.7%)	67 (20.2%)	84 (29.9%)	1.68 (1.16–2.43)	0.006

ACE = angiotensin-converting enzyme; AKI = acute kidney injury; ARB = angiotensin receptor blockers; CRP = C-reactive protein; NEWS-2 = National Early Warning Score 2.

* OR for 10 years' increase.

† OR for 100 mg/L increase.

Table II. Demographic and clinical characteristics of angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) users compared with nonusers. Columns 2 to 4 describe the population characteristics for: the entire cohort (column 2), ACE inhibitor/ARB users (column 3), and nonusers (column 4). Column 5 describes the results of univariate logistic regressions comparing users of ACE inhibitors/ARBs versus nonusers. Odds ratios are expressed as the likelihood of a unit increase in each parameter associated with ACE inhibitor/ARB use. Column 6 presents the significance (α) of these associations. Values are given as mean (SD) unless otherwise indicated.

Variable	Entire Population (N = 612)	ACE Inhibitor/ARB Users (n = 151)	ACE Inhibitor/ARB Non-Users (n = 461)	Odds Ratio (95% CI)	*P*
Demographic characteristics					
Age, years*	69.6 (17.8)	74.5 (13.0)	68.0 (18.4)	1.92 (1.39–2.65)	<0.001
Male sex	354 (57.8%)	91 (60.3%)	263 (57.0%)	1.14 (0.79–1.66)	0.488
Outcomes					
Mortality	281 (45.9%)	84 (55.6%)	197 (42.7%)	1.68 (1.16–2.43)	0.006
Intensive care admission	86 (14.1%)	32 (21.2%)	54 (11.7%)	2.03 (1.25–3.28)	0.004
Length of stay, days	12.1 (13.7)	13.1 (12.3)	11.8 (14.1)	3.44 (0.28–42.75)	0.336
Maximum NEWS-2	8.2 (3.4)	9.0 (3.0)	7.9 (3.5)	2.84 (1.52–5.29)	0.001
Maximum oxygen, L/min	7.8 (6.2)	9.4 (6.0)	7.3 (6.2)	8.43 (2.72–26.18)	<0.001
Maximum AKI stage	0.89 (1.14)	1.03 (1.15)	0.85 (1.13)	1.20 (0.98–1.48)	0.083
Maximum CRP, mg/L†	196 (128)	225 (140)	187 (122)	1.46 (1.16–1.85)	0.001
Comorbidities					
Hypertension	299 (48.9%)	125 (82.8%)	174 (37.7%)	7.93 (4.99–12.59)	<0.001
Heart failure	57 (9.3%)	21 (13.9%)	36 (7.8%)	1.91 (1.08–3.38)	0.027
Ischemic heart disease	97 (15.8%)	33 (21.9%)	64 (13.9%)	1.73 (1.09–2.77)	0.021
Diabetes mellitus	166 (27.1%)	62 (41.1%)	104 (22.6%)	2.39 (1.62–3.54)	<0.001

AKI = acute kidney injury; CRP = C-reactive protein; NEWS-2 = National Early Warning Score 2.
* OR for 10 years' increase.
† OR for 100 mg/L increase.

(48.4%) died. The average proportion of pre-palliative doses of ACE inhibitors/ARBs received as an inpatient was 36.5%. Twenty (15.4%) patients received ACE inhibitors/ARBs on every day of admission, whereas 55 (42.3%) received no doses as an inpatient. For patients who received ACE inhibitors/ARBs, the average proportion of doses received was 63.3%. It is worth noting that 20 (69.0%) of 29 patients admitted to the ICU received no doses of ACE inhibitors/ARBs during admission, and of those who did, none received ACE inhibitors/ARBs in the ICU. It is common practice at our center to discontinue regular antihypertensive medications in patients admitted to the ICU. Hence, all multivariate analyses adjusted for ICU admission to avoid conflating the mortality associated with critical illness requiring ICU admission with the effect of ACE inhibitor/ARB provision. The mortality rate of patients admitted to the ICU who received at least 1 dose of their ACE inhibitors/ARBs was comparable to those who received no doses (22.2% and 33.3%, respectively) in this small subgroup.

Lower inpatient provision of ACE inhibitors/ARBs when adjusted for factors that might prompt discontinuation of these medications was highly predictive

Table III. Adjusted effects of long-term angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) use on clinical outcomes. Column 2 displays the results of univariate linear and logistic regressions describing the unadjusted associations between each parameter and each outcome variable. Column 3 presents the adjusted relationships between these variables when entered into multivariate linear and logistic regressions with all parameters listed. Column 4 presents the significance (α) of the adjusted associations.

Outcome Variable	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	*P* for Adjusted Relationship
Mortality			
Regular ACE inhibitors/ARBs	1.68 (1.16–2.43)	1.18 (0.77–1.82)	0.447
Age, years*	1.71 (1.53–1.92)	1.67 (1.48–1.90)	<0.001
Male sex	1.56 (1.13–2.17)	1.68 (1.16–2.42)	0.006
Hypertension	1.98 (1.43–2.73)	1.08 (0.73–1.60)	0.685
Heart failure	2.36 (1.33–4.17)	1.23 (0.67–2.26)	0.509
Ischemic heart disease	2.97 (1.87–4.71)	1.58 (0.95–2.60)	0.075
Diabetes mellitus	1.43 (1.00–2.05)	1.24 (0.83–1.85)	0.300
Maximum NEWS-2†			
Regular ACE inhibitors/ARBs	1.23 (1.09–1.40)	1.16 (1.01–1.32)	0.030
Age, years*	1.10 (1.07–1.14)	1.10 (1.07–1.14)	<0.001
Male sex	1.07 (0.96–1.20)	1.06 (0.96–1.19)	0.250
Hypertension	1.14 (1.02–1.27)	0.95 (0.85–1.08)	0.445
Heart failure	1.13 (0.94–1.37)	0.99 (0.82–1.19)	0.902
Ischemic heart disease	1.18 (1.02–1.37)	1.01 (0.87–1.18)	0.848
Diabetes mellitus	1.15 (1.01–1.29)	1.10 (0.97–1.24)	0.130
Maximum oxygen (L/min)‡			
Regular ACE inhibitors/ARBs	1.53 (1.22–1.92)	1.36 (1.06–1.74)	0.014
Age, years*	1.10 (1.04–1.16)	1.07 (1.01–1.14)	0.023
Male sex	1.43 (1.18–1.75)	1.40 (1.15–1.71)	0.001
Hypertension	1.35 (1.11–1.64)	1.07 (0.86–1.34)	0.531
Heart failure	1.29 (0.92–1.81)	1.09 (0.78–1.54)	0.606
Ischemic heart disease	1.25 (0.95–1.64)	1.00 (0.76–1.33)	0.977
Diabetes mellitus	1.29 (1.03–1.60)	1.15 (0.92–1.43)	0.299
Maximum AKI stage			
Regular ACE inhibitors/ARBs	1.20 (0.98–1.48)	0.97 (0.78–1.22)	0.809
Age, years*	1.04 (0.99–1.09)	1.01 (0.95–1.06)	0.939
Male sex	1.28 (1.07–1.53)	1.20 (1.00–1.43)	0.053
Hypertension	1.38 (1.15–1.65)	1.29 (1.06–1.58)	0.012
Heart failure	1.12 (0.82–1.53)	0.96 (0.70–1.31)	0.791
Ischemic heart disease	1.35 (1.05–1.72)	1.20 (0.93–1.55)	0.164
Diabetes mellitus	1.62 (1.33–1.98)	1.52 (1.24–1.86)	<0.001
Maximum CRP (mg/L)§			
Regular ACE inhibitors/ARBs	1.46 (1.16–1.85)	1.34 (1.04–1.73)	0.024
Age, years*	1.00 (0.94–1.06)	0.97 (0.92–1.04)	0.401
Male sex	1.41 (1.15–1.72)	1.36 (1.11–1.67)	0.003
Hypertension	1.27 (1.04–1.55)	1.14 (0.91–1.43)	0.261
Heart failure	1.06 (0.75–1.50)	0.98 (0.69–1.40)	0.906
Ischemic heart disease	1.12 (0.85–1.48)	1.02 (0.76–1.36)	0.903
Diabetes mellitus	1.34 (1.07–1.69)	1.22 (0.97–1.54)	0.089

AKI = acute kidney injury; CRP = C-reactive protein; NEWS-2 = National Early Warning Score 2.

* OR for 10 years' increase.

† OR for 5 point increase.

‡ OR for 5 L/min increase.

§ OR for 100 mg/L increase.

of worsened outcomes in COVID-19. The proportion of doses omitted in the hospital was significantly associated with increased mortality (OR of 9.59 [95% CI, 2.55–36.09]; $P < 0.001$), maximum NEWS-2 score (OR of 1.66 [95% CI, 1.27–2.17] for a 5 point increase; $P < 0.001$), maximum oxygen requirements (OR of 3.00 [95% CI, 1.83–4.91] for a 5 L/min increase; $P < 0.001$), and maximum CRP concentration (OR of 1.83 [95% CI, 1.06–3.17] for a 100 mg/L increase; $P = 0.030$) (Table IV). The observed effects remained similar when patients who had all of their ACE inhibitor/ARB doses omitted were excluded from the analysis, implying that sporadic omission may affect clinical outcomes (Table V).

DISCUSSION

Summary of Key Findings

Within our cohort of 612 patients hospitalized with COVID-19, mortality was increased in those who were elderly, male, and who had significant comorbidities. Patients who required greater supplemental oxygen, exhibited higher NEWS-2 scores, and who were admitted to the ICU were also at higher risk of death. Our subpopulation of 151 patients taking ACE inhibitors/ARBs was more likely to be elderly and to have comorbidities associated with ACE inhibitor/ARB prescription than the remainder of our cohort. Outcomes were broadly poorer in this subgroup in unadjusted studies.

After adjusting for age, sex, and comorbidities, the relationships between ACE inhibitor/ARB use and indicators of morbidity diminished but remained significant. Mortality, however, in adjusted studies did not exhibit a significant relationship with ACE inhibitor/ARB use. Strikingly, lower inpatient provision of ACE inhibitors/ARBs was highly predictive of worsened outcomes in COVID-19. Markedly significant associations were observed between the proportion of ACE inhibitor/ARB doses omitted during acute COVID-19 illness and mortality, maximum NEWS-2, and maximum oxygen requirements. These associations remained after adjustment for hypotension, AKI, ICU admission, and palliation.

Comparisons With the Literature

A large number of studies have examined the impact of long-term ACE inhibitor/ARB prescription on outcomes in COVID-19. Several meta-analyses have concluded that antecedent ACE inhibitor/ARB prescription did not predispose to worsened outcomes in COVID-19.[6–8] Others concluded that prior ACE inhibitor/ARB use reduced the risk of mortality and ICU admission, and decreased length of stay.[9–14] There is a theoretical basis for both deleterious and protective effects of these agents in SARS-CoV-2 infection.[22] Notably, however, there is no substantial clinical evidence that ACE inhibitor/ARB use worsens outcomes in COVID-19 compared with outcomes in appropriately matched control subjects.

To date, the one peer-reviewed publication examining the effects of in-hospital ACE inhibitor/ARB provision on COVID-19 illness concurs with our findings. Lam et al[15] found that total omission of ACE inhibitors/ARBs in patients with hypertension and SARS-CoV-2 infection is associated with similarly significant ($P < 0.001$) increases in mortality and ICU admission. These effects were adjusted for AKI and hypotension, although the definition of the latter was not defined. We expand on these findings by showing that similarly firm associations are seen for nonhypertensive patients taking ACE inhibitors/ARBs, that they are robust to adjustment for ICU admission and palliation, and that partial omission of these agents might also incur morbidity. The first randomized controlled trials concerning this topic are ongoing, the results of which will be the next important step in clarifying the role of ACE inhibitors/ARBs in acute COVID-19 illness.[23–27]

Regular ACE inhibitor/ARB use in the present study was associated with worsened indicators of morbidity. It is possible that this finding is attributable to the large number of our patients who had their ACE inhibitors/ARBs omitted during admission, an intervention that we found to be strongly associated with poorer outcomes. The average proportion of pre-palliative ACE inhibitor/ARB doses received in our cohort was 36.5%. Furthermore, 42.3% of patients taking regular ACE inhibitors/ARBs received no doses during their admission. Trials reporting 100% inpatient provision of ACE inhibitors/ARBs show significant protective benefits associated with their use.[9] We propose that the mixed picture painted in the wider literature regarding ACE inhibitors/ARBs in COVID-19 is in part due to lack of standardization to provision of these medications during the acute illness. A limitation of studies examining only antecedent use may be in confounding the significant morbidity associated with discontinuing these

Table IV. Adjusted effects of inpatient angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) omission on clinical outcomes. Column 2 describes the adjusted relationships between each variable and the outcome measure when entered into multivariate linear and logistic regressions with all parameters listed. Column 3 presents the significance (α) of the adjusted associations. Odds ratios for ACE inhibitor/ARB omission were calculated as the likelihood of a unit increase (as below) in each parameter for every 10% decrease in inpatient ACE inhibitor/ARB provision.

Outcome Variable	Adjusted Odds Ratio (95% CI)	*P*
Mortality		
% of ACE inhibitor/ARB doses omitted	9.59 (2.55–36.09)	<0.001
Age, years*	2.68 (1.60–4.48)	<0.001
Male sex	0.91 (0.37–2.27)	0.846
Hypertension	0.60 (0.16–2.19)	0.440
Heart failure	3.00 (0.85–10.57)	0.087
Ischemic heart disease	0.87 (0.27–2.75)	0.809
Diabetes mellitus	1.22 (0.47–3.13)	0.680
Intensive care admission	16.44 (3.21–84.11)	<0.001
Acute kidney injury	1.43 (0.91–2.26)	0.125
Hypotension	0.98 (0.93–1.03)	0.511
Maximum NEWS-2†		
% of ACE inhibitors/ARBs dose omitted	1.66 (1.27–2.17)	<0.001
Age, years*	1.08 (0.99–1.18)	0.076
Male sex	0.96 (0.78–1.17)	0.670
Hypertension	1.01 (0.77–1.32)	0.949
Heart failure	1.12 (0.84–1.50)	0.440
Ischemic heart disease	0.90 (0.70–1.16)	0.421
Diabetes mellitus	1.03 (0.84–1.25)	0.792
Intensive care admission	1.06 (0.79–1.43)	0.701
Acute kidney injury	1.13 (1.02–1.24)	0.016
Inpatient hypotension	1.01 (1.00–1.02)	0.081
Maximum oxygen (L/min)‡		
% of ACE inhibitor/ARB doses omitted	3.00 (1.83–4.91)	<0.001
Age, years*	1.12 (0.95–1.32)	0.189
Male sex	1.23 (0.85–1.78)	0.275
Hypertension	0.83 (0.50–1.36)	0.448
Heart failure	1.26 (0.73–2.17)	0.402
Ischemic heart disease	0.94 (0.59–1.50)	0.797
Diabetes mellitus	1.03 (0.71–1.49)	0.883
Intensive care admission	3.11 (1.79–5.41)	<0.001
Acute kidney injury	1.14 (0.95–1.36)	0.166
Inpatient hypotension	1.00 (0.98–1.02)	0.933
Maximum CRP (mg/L)§		
% of ACE inhibitor/ARB doses omitted	1.83 (1.06–3.17)	0.030
Age, years*	1.05 (0.87–1.26)	0.609
Male sex	1.12 (0.74–1.69)	0.587
Hypertension	1.49 (0.86–2.60)	0.154
Heart failure	1.26 (0.69–2.30)	0.454
Ischemic heart disease	0.76 (0.45–1.27)	0.291

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Table IV. (*continued*)

Outcome Variable	Adjusted Odds Ratio (95% CI)	*P*
Diabetes mellitus	1.13 (0.75–1.70)	0.56
Intensive care admission	3.41 (1.84–6.30)	<0.001
Acute kidney injury	1.44 (1.18–1.76)	<0.001
Inpatient hypotension	1.01 (0.99–1.03)	0.345

CRP = C-reactive protein; NEWS-2 = National Early Warning Score 2.
* OR for 10 years' increase.
† OR for 5 point increase.
‡ OR for 5 L/min increase.
§ OR for 100 mg/L increase.

medications with the overall effect, thus masking potential benefits.

LIMITATIONS

The findings of the present study were derived retrospectively from purely observational data and thus suffer from the same limitations as all retrospective cohorts. It was not possible to perform a sample size calculation at the start of data collection; however, the strength of our findings suggests this was adequate. Our population size was comparable to the wider literature, with subgroups reaching acceptable sizes. A selection bias toward moderate to severe cases of COVID-19 was introduced by our inclusion criteria. Unfortunately, no reliable data were available for body mass index; raised body mass index is associated with increased mortality in patients with COVID-19.[28] Medication adherence before admission was not feasible to collect and represents a potential source of bias.

Our major finding that omission of ACE inhibitors/ARBs in the hospital is associated with greater morbidity and mortality must be placed under strict scrutiny. Undeniably, the decision to suspend ACE inhibitors/ARBs is often associated with clinical sequelae that correlate with morbidity. We believe our attempts to control for these factors were appropriate. Adjustments for both AKI and hypotension were for either event at any point in admission, irrespective of their timing in relation to ACE inhibitor/ARB omission, and hence may represent an overcorrection. Furthermore, adjustment of the days ACE inhibitors/ARBs were required was conducted with conservative parameters to prevent misleading reductions in the proportions of inpatient ACE inhibitor/ARB provision. These adjustments were based, however, on assumptions made about the timing of doses taken at home and palliative decisions.

IMPLICATIONS FOR PRACTICE

Our finding that omission of ACE inhibitors/ARBs in the hospital is associated with greater morbidity and mortality in COVID-19 prompts greater attention to these agents during the acute illness. The cause for omission in this period was infrequently specified. Some doses were missed due to delayed prescription on admission, improper stock of medications, and patients refusing doses. In cases in which reasoning was documented, suspension was often related to AKI. Several omissions were coordinated with a significant drop in blood pressure. Unfortunately, in the majority of cases, the reasoning behind suspension was unclear from electronic documentation.

Five patients in our cohort had their ACE inhibitors/ARBs suspended in the absence of AKI and remained persistently hypertensive during admission. Two of these patients received treatment with an alternative antihypertensive agent, and 3 were left untreated. Although it is unclear whether there was other reasoning behind suspension, these patients likely represent a subgroup that would have benefited from continuation of their ACE inhibitors/ARBs.

Clearly, in clinical practice there will be instances in which omission of ACE inhibitors/ARBs will be necessary in patients admitted with COVID-19. It is, however, well understood that improper management of ACE inhibitor/ARB cessation and reintroduction can

Table V. Adjusted effects of inpatient angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) omission on clinical outcomes excluding patients who received no doses. Column 2 describes the adjusted relationships between each variable and the outcome measure when entered into multivariate linear and logistic regressions with all parameters listed. Column 3 presents the significance (α) of the adjusted associations. Odds ratios for ACE inhibitor/ARB omission were calculated as the likelihood of a unit increase (as below) in each parameter for every 10% decrease in inpatient ACE inhibitor/ARB provision.

Outcome Variable	Adjusted Odds Ratio (95% CI)	*P*
Mortality		
% of ACE inhibitor/ARB doses omitted	1.34 (1.09–1.65)	0.006
Age, years*	2.23 (1.10–4.52)	0.027
Male sex	1.15 (0.33–3.95)	0.829
Hypertension	2.81 (0.47–16.78)	0.258
Heart failure	2.44 (0.53–11.26)	0.252
Ischemic heart disease	1.56 (0.35–6.94)	0.557
Diabetes mellitus	1.08 (0.32–3.66)	0.904
Intensive care admission	3.33 (0.30–36.91)	0.327
Acute kidney injury	1.53 (0.78–3.00)	0.211
Hypotension	1.01 (0.93–1.10)	0.773
Maximum NEWS-2†		
% of ACE inhibitor/ARB doses omitted	1.05 (1.01–1.10)	0.019
Age, years*	1.09 (0.95–1.25)	0.215
Male sex	1.01 (0.77–1.32)	0.936
Hypertension	1.09 (0.77–1.55)	0.625
Heart failure	1.02 (0.71–1.47)	0.907
Ischemic heart disease	0.89 (0.65–1.22)	0.463
Diabetes mellitus	0.87 (0.67–1.13)	0.278
Intensive care admission	1.16 (0.70–1.90)	0.562
Acute kidney injury	1.26 (1.09–1.45)	0.002
Inpatient hypotension	1.02 (1.00–1.04)	0.033
Maximum oxygen, L/min‡		
% of ACE inhibitor/ARB doses omitted	1.15 (1.06–1.24)	0.001
Age, years*	1.14 (0.89–1.45)	0.310
Male sex	1.11 (0.68–1.81)	0.669
Hypertension	1.28 (0.67–2.45)	0.448
Heart failure	1.88 (0.97–3.64)	0.062
Ischemic heart disease	0.87 (0.49–1.57)	0.646
Diabetes mellitus	0.83 (0.51–1.34)	0.444
Intensive care admission	2.93 (1.18–7.31)	0.022
Acute kidney injury	1.33 (1.03–1.73)	0.031
Inpatient hypotension	1.00 (0.96–1.03)	0.841
Maximum CRP (mg/L)§		
% of ACE inhibitor/ARB doses omitted	1.08 (0.99–1.17)	0.069
Age, years*	1.13 (0.87–1.47)	0.368
Male sex	0.87 (0.51–1.46)	0.585
Hypertension	1.90 (0.95–3.79)	0.068
Heart failure	1.28 (0.63–2.60)	0.482

(*continued on next page*)

Table V. (*continued*)

Outcome Variable	Adjusted Odds Ratio (95% CI)	*P*
Ischemic heart disease	0.72 (0.39–1.35)	0.303
Diabetes mellitus	1.05 (0.63–1.75)	0.841
Intensive care admission	3.27 (1.24–8.66)	0.018
Acute kidney injury	1.61 (1.22–2.13)	0.001
Inpatient hypotension	1.00 (0.96–1.04)	0.963

CRP = C-reactive protein; NEWS-2 = National Early Warning Score 2.
* OR for 10 years' increase.
† OR for 5 point increase.
‡ OR for 5 L/min increase.
§ OR for 100 mg/L increase.

cause harm.[29,30] Practically speaking, we believe that our findings warrant active monitoring of decisions to suspend ACE inhibitors/ARBs in patients with COVID-19 and prompt reintroduction of these agents in the absence of a clear contraindication.

CONCLUSIONS

We show here that lower inpatient provision of ACE inhibitors/ARBs is highly predictive of worsened outcomes in COVID-19 in patients established on this therapy. These associations remained after adjustment for common clinical indications for suspension of ACE inhibitors/ARBs in the hospital, namely hypotension, AKI, ICU admission, and palliation. The evolving view of ACE inhibitors/ARBs in COVID-19 favors these agents as protective against morbidity and mortality. We propose that the lack of clarity on the subject may relate to an absence of adjustment for inpatient provision in other studies and confounding the associated morbidity of discontinuing these medications with the overall effect. Our findings prompt active monitoring of decisions to suspend ACE inhibitors/ARBs in patients with COVID-19 and timely reintroduction of these agents in the absence of a clear contraindication.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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