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ORIGINAL RESEARCH

Antecedent Administration of Angiotensin-Converting Enzyme Inhibitors or Angiotensin II Receptor Antagonists and Survival After Hospitalization for COVID-19 Syndrome

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BACKGROUND: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) utilizes the angiotensin-converting enzyme-2 (ACE-2) receptor to enter human cells. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor antagonists (ARB) are associated with ACE-2 upregulation. We hypothesized that antecedent use of ACEI/ARB may be associated with mortality in coronavirus disease 2019 (COVID-19).

METHODS AND RESULTS: We used the Coracle registry, which contains data of patients hospitalized with COVID-19 in 4 regions of Italy, and restricted analyses to those ≥50 years of age. The primary outcome was in-hospital mortality. Among these 781 patients, 133 (17.0%) used an ARB and 171 (21.9%) used an ACEI. While neither sex nor smoking status differed by user groups, patients on ACEI/ARB were older and more likely to have hypertension, diabetes mellitus, and congestive heart failure. The overall mortality rate was 15.1% (118/781) and increased with age (P_{Trend}<0.0001). The crude odds ratios (ORs) for death for ACEI users and ARB users were 0.98, 95% CI, 0.60–1.60, P=0.9333, and 1.13, 95% CI, 0.67–1.91, P=0.6385, respectively. After adjusting for age, hypertension, diabetes mellitus, and congestive heart failure, antecedent ACEI administration was associated with reduced mortality (OR, 0.55; 95% CI, 0.31–0.98, P=0.0436); a similar, but weaker trend was observed for ARB administration (OR, 0.58; 95% CI, 0.32–1.07, P=0.0796).

CONCLUSIONS: In those aged ≥50 years hospitalized with COVID-19, antecedent use of ACEI was independently associated with reduced risk of inpatient death. Our findings suggest a protective role of renin-angiotensin-aldosterone system inhibition in patients with high cardiovascular risk affected by COVID-19.

Key Words: angiotensin-converting enzyme inhibitor ■ angiotensin-converting enzyme-2 ■ COVID-19 ■ hospitalization ■ mortality ■ renin-angiotensin converting enzyme inhibitor ■ SARS-CoV-2

In the midst of the coronavirus disease 2019 (COVID-19) pandemic, there has been considerable interest and speculation about the effects of prior administration of renin-angiotensin-aldosterone system (RAAS) inhibitors, given the understanding that the coronavirus family utilizes the angiotensin-converting enzyme 2 (ACE-2) receptor for entry into human somatic cells.[1,2] One line of reasoning has been that more ACE-2 receptors being available for viral entry would lead to more severe, and possibly fatal, infections. An alternative viewpoint is that

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CLINICAL PERSPECTIVE

What Is New?

- In patients hospitalized with coronavirus disease 2019 (COVID-19), antecedent use of angiotensin-converting enzyme inhibitors was associated with decreased odds of inpatient mortality, after adjusting for comorbidities.

What Are the Clinical Implications?

- Current users of renin-angiotensin-aldosterone inhibitors should continue their use during the COVID-19 pandemic.

Nonstandard Abbreviations and Acronyms

ACE-2	angiotensin-converting enzyme-2
ARB	angiotensin II receptor antagonists
ARDS	acute respiratory distress syndrome
COVID-19	coronavirus disease 2019
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

the ACE-2 receptor could be functioning in a protective manner despite facilitating viral entry, and that COVID-19 target mediated destruction and reduction of receptor density could be part of the pathogenesis of the acute respiratory distress syndrome (ARDS) associated with acute infection. By piecing together observations from preclinical models, it has been postulated that children have a relative upregulation of ACE-2 and a potentially greater pulmonary endothelial density of ACE-2 expression.[3] It is notable that the rates of symptomatic and fatal cases of COVID-19 are progressively lower at younger ages.[4] Conversely, the elderly and those who are smokers are believed to have lesser densities of ACE-2 receptors in the lungs and lower inferred levels of circulating ACE-2.[5,6] Experimental data in ARDS models suggest that ACE-2 is downregulated and some of its peptide products (Ang 1–7) are consequently diminished, and thus, vascular endothelial protection is lost in the development of ARDS.[7–9] Soluble ACE-2 has been administered experimentally and appears to lessen pathophysiological correlates of ARDS in vitro and in animal models.[10–12]

In humans, long-standing administration of angiotensin-converting enzyme inhibitors (ACEI) and or angiotensin II receptor antagonists/blockers (ARB) leads to an upregulation of ACE-2 on the surface of vascular endothelial cells, and possibly other somatic cell lines. This may be more pronounced with ACEI since angiotensin II, the substrate for ACE-2, is diminished. By these lines of thinking, ACEI/ARB may be a "double-edged sword" with either protective or harmful effects on outcomes in older individuals and those with multiple comorbidities when hospitalized for COVID-19.[13,14] In particular, AlGhatrif and colleagues hypothesized that the increase in ACE-2 levels with RAAS inhibition is likely to be beneficial for vulnerable individuals with COVID-19 who have reduced ACE-2 expression (eg older individuals, hypertensives, and/or diabetics).[15] Several professional societies have recommended continuing ACEI/ARB in patients with COVID-19, but acknowledge a lack of data.[16,17] Hence, we sought to determine the association between ACEI/ARB use and inpatient mortality among patients with COVID-19 ≥50 years using a registry of patients with acute COVID-19 illness resulting in hospitalization in Italy.

METHODS

Data

To ensure patient confidentiality, the data used for these analyses will not be made available. We used the Coracle (epidemiology, clinical characteristics, and therapy in real life patients affected by severe acute respiratory syndrome coronavirus 2 [Sars-Cov-2]) multi-center registry, which contains data of patients hospitalized with COVID-19 from participating referral centers in the Piedmont, Lombardy, Tuscany, and Lazio regions of Italy, to perform this analysis. Patients were included in the registry if they were at least 18 years old, hospitalized with COVID-19 (confirmed using nose or throat swab testing with real-time reverse transcription polymerase chain reaction) on or after February 22, 2020, and had a known mortality or discharge status as of April 1, 2020. We chose to restrict this analysis to patients ≥50 years because of the significant increase in mortality observed at this age cutoff in previous COVID-19 publications, as well as for clinical indications of ACEI/ARB.[4] At hospital admission, patients gave written consent to data collection on the condition that the data be anonymized. This work was approved by the ethical committee of Turin (Coracle registry: epidemiology clinical characteristics and therapy in real life patients affected by SARS-CoV-2).

Statistical Analysis

The only continuous variable, age, was skewed and is presented as median [quartile 1, quartile 3]. To evaluate risk more clearly, we categorized age based on decade of life as follows: 50 to 59, 60 to 69, 70 to 79, and 80+. Categorical variables were reported as counts and proportions. Differences in characteristics between patients treated with ACEI, ARB, and those not taking ACEI/ARB were assessed via the Kruskal–Wallis

Test and Chi-Square test, respectively. We utilized the Cochran-Armitage Trend Test to assess for a trend between age group and mortality rate. We examined crude odds ratios (ORs) for death based on ACEI/ARB use, as well as adjusted ORs according to the pre-specified adjustment for age decade, history of hypertension (defined as blood pressure >140/90 mm Hg), diabetes mellitus, and congestive heart failure via multivariable logistic regression. Analyses were performed using SAS version 9.4 (Cary, NC).

RESULTS

There were 956 patient records reviewed and 175 (18.3%) were excluded because of age <50 years. Hence, 781 patients were included in this analysis. Upon admission, 477 (61.1%) patients were not using ACEI/ARB, 133 (17.0%) were using an ARB, and 171 (21.9%) were using an ACEI. While neither sex nor smoking status differed significantly by ACEI/ARB user groups, patients using ACEI/ARB tended to be older and more likely to have hypertension, diabetes mellitus, and congestive heart failure than those not using ACEI/ARB (Table). Additionally, a total of 225 (28.8%) and 107 (13.8%) patients were treated in the intensive care unit and received invasive ventilation, respectively; neither was associated with antecedent ACEI/ARB use (*P*=0.2463, *P*=0.6089).

The overall mortality rate was 15.1% (118/781) and an increasing trend with age was detected (P_{Trend}<0.0001, Figure 1). Death by specific subgroups is shown in Figure 2. Overall, the crude ORs for death for those who used ACEI and those who used ARB at admission compared to no ACEI/ARB use were 0.98 (95% CI, 0.60–1.60; *P*=0.9333) and 1.13 (95% CI, 0.67–1.91; *P*=0.6385), respectively. Among patients with diabetes mellitus, the crude ORs for death for those who used ACEI and those who used ARB at admission compared to no ACEI/ARB use were 2.05 (95% CI, 0.70–5.98; *P*=0.1884) and 2.02 (95% CI, 0.62–6.63; *P*=0.2445), respectively. Among patients

Table. Characteristics of Patients in Coracle Registry Aged ≥50 Years Hospitalized for COVID-19

Characteristic	Renin-Angiotensin-Aldosterone System Inhibition				*P* Value
	Overall (n=781)	None (n=477)	ARB (n=133)	ACEI (n=171)	
Age, y	69 [60, 78.5]	66 [58, 78]	73 [65, 80]	72 [63.7, 77]	<0.0001
Age category, y					<0.0001
50–59	194 (24.8%)	150 (31.5%)	17 (12.8%)	27 (15.8%)	
60–69	205 (26.2%)	122 (25.6%)	35 (26.3%)	48 (28.1%)	
70–79	204 (26.1%)	99 (20.8%)	46 (34.6%)	59 (34.5%)	
80+	178 (22.8%)	106 (22.2%)	35 (26.3%)	37 (21.6%)	
Sex (male)	498 (63.8%)	305 (63.9%)	83 (62.4%)	110 (64.3%)	0.9342
History of hypertension[2]	451 (57.9%)	155 (32.6%)	130 (97.7%)	166 (97.1%)	<0.0001
Obstructive lung disease[1]	84 (10.8%)	52 (10.9%)	10 (7.5%)	22 (12.9%)	0.3236
Diabetes mellitus[1]	143 (18.3%)	66 (13.8%)	31 (23.3%)	46 (27.1%)	0.0002
Smoking status[2]					0.2524
Yes	69 (8.9%)	39 (8.2%)	11 (8.3%)	19 (11.1%)	
No	655 (84.1%)	410 (86.1%)	108 (81.8%)	137 (80.1%)	
Former	55 (7.1%)	27 (5.7%)	13 (9.8%)	15 (8.8%)	
Congestive heart failure[2]	67 (8.6%)	31 (6.5%)	16 (12%)	20 (11.7%)	0.0355
Coronary artery disease (ischemia)	104 (13.3%)	46 (9.6%)	28 (21.1%)	30 (17.5%)	0.0005
Beta blocker[1]	174 (22.3%)	82 (17.2%)	42 (31.6%)	50 (29.2%)	<0.0001
Calcium channel antagonist[1]	154 (19.7%)	67 (14.1%)	40 (30.1%)	47 (27.5%)	<0.0001
Thiazide diuretic[43]	107 (14.5%)	42 (9.3%)	31 (24.6%)	34 (21.3%)	<0.0001
Loop diuretic[43]	99 (13.4%)	48 (10.6%)	26 (20.6%)	25 (15.6%)	0.0092
Intensive care unit	225 (28.8%)	130 (27.3%)	37 (27.8%)	58 (33.9%)	0.2463
Invasive ventilation[6]	107 (13.8%)	64 (13.5%)	16 (12.2%)	27 (16%)	0.6089
High flow ventilation without intubation[9]	298 (38.6%)	169 (35.9%)	54 (40.9%)	75 (44.4%)	0.1257
Oxygen low flow[9]	333 (43.1%)	214 (45.4%)	59 (44.7%)	60 (35.5%)	0.0758

Age is presented as median [quartile 1, quartile 3] and categorical variables are presented as frequency (%). The *P* value for age was calculated from the Kruskal–Wallis Test. All other *P* values were calculated using the Chi-Square test. Superscripts indicate missing data. ACEI indicates angiotensin II-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist/blocker; and COVID-19, coronavirus disease 2019.

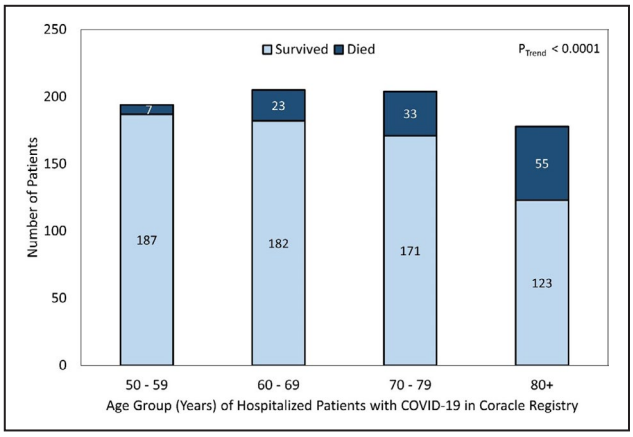

Figure 1. Frequency of survival and inpatient death of patients with coronavirus disease 2019 (COVID-19) by age group.

with hypertension, the crude ORs for death for those who used ACEI and those who used ARB at admission compared to no ACEI/ARB use were 0.49 (95% CI, 0.28–0.86; *P*=0.0125) and 0.57 (95% CI, 0.32–1.01; *P*=0.0552), respectively. Among patients with congestive heart failure, the crude OR for death for those who used ACEI at admission compared to no ACE/ARB use was 0.61 (95% CI, 0.16–2.3; *P*=0.4721); there were 0 deaths out of the 16 patients with congestive heart failure treated with ARB.

In unadjusted analyses, neither ACEI nor ARB significantly changed the odds of death compared to no ACEI/ARB use (Figure 3). However, after adjusting for age decade, hypertension, diabetes mellitus, and congestive heart failure, ACEI decreased the odds of death by ≈45% (OR, 0.553; 95% CI, 0.311–0.983; *P*=0.0436). The large shift in ORs is primarily attributed to the adjustment for hypertension. Specifically, although only 57.9% of the patients in this analysis were hypertensive, they accounted for 74.6% of the deaths. Further, the mortality rates for patients with hypertension were 15.1%, 16.9%, and 26.5% for ACEI users, ARB users, and no RAASi users, respectively. ARB use did not significantly change the odds of death compared to patients using neither ACEI nor ARB, under the same adjustment (OR, 0.586; 95% CI, 0.322–1.065; *P*=0.0796). The Hosmer-Lemeshow test yielded a *P* value of 0.8093, indicating the model fit the data well. Additionally, the area under the receiver operating characteristic curve was 0.737, indicating that the model had good ability to discriminate inpatient mortality from survival.

DISCUSSION

We found that among individuals aged ≥50 years hospitalized with COVID-19 infection, that antecedent ACEI administration was associated with a considerably reduced case fatality rate after adjusting for age, hypertension, diabetes mellitus, and heart failure. Because of the predisposition of these comorbidities to mortality, only after adjustment did the protective effect of ACEI usage become apparent. Because it is common that hypotension and likely withdrawal of ACEI (or ARB) occurred in the sequence of events before death in COVID-19 infections, we would infer it is the antecedent chronic use and not the acute administration of these agents that had an effect.

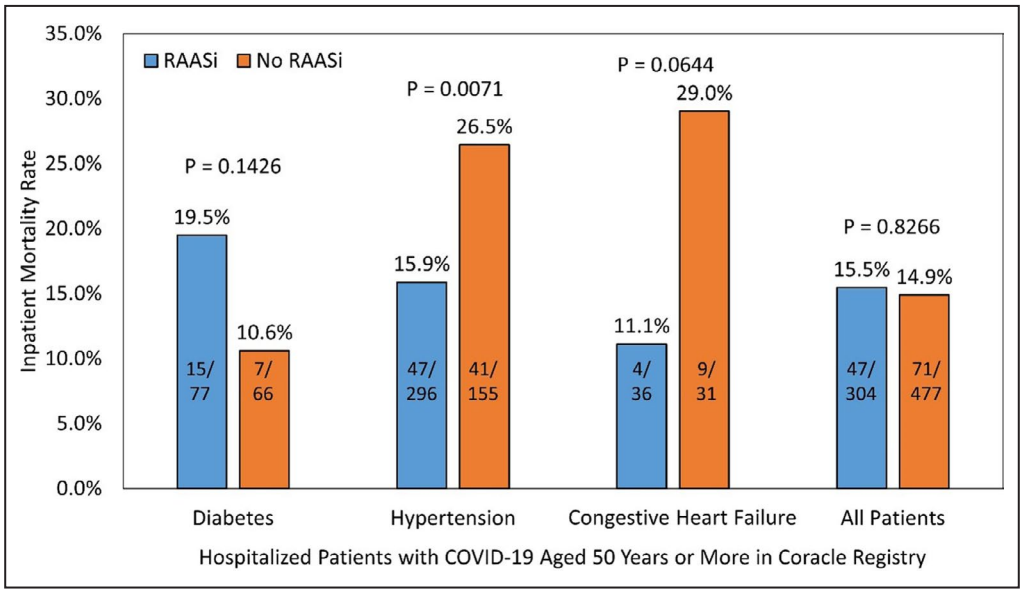

Figure 2. Inpatient mortality rates by renin-angiotensin-aldosterone system inhibitor use before admission for coronavirus disease 2019 (COVID-19).
RAASi indicates renin-angiotensin-aldosterone system inhibitor.

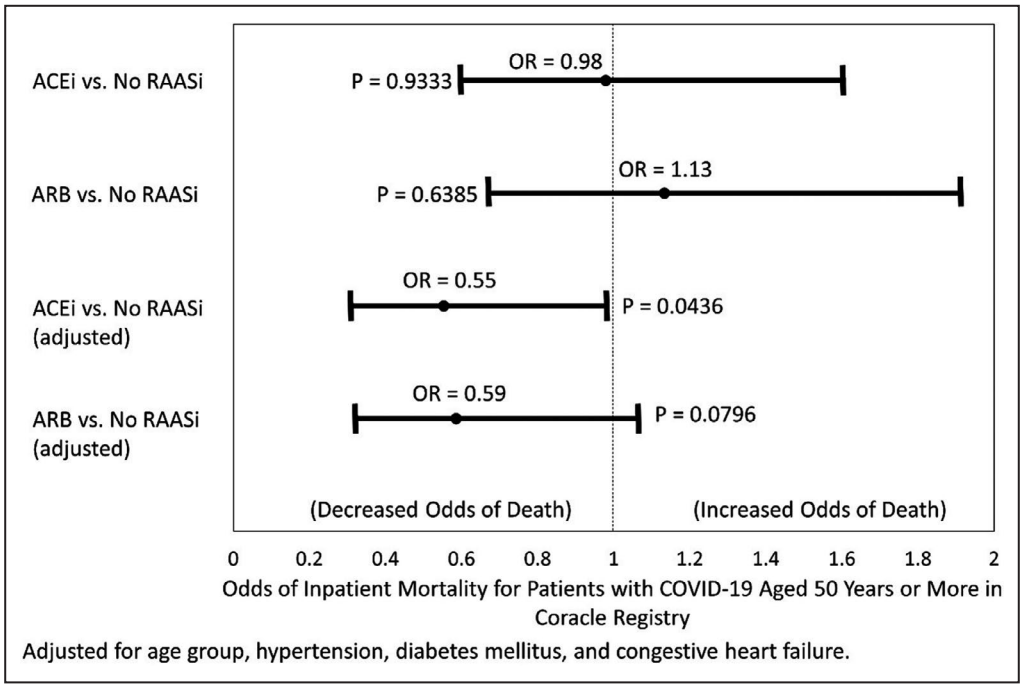

Figure 3. Forest plot of odds ratios for death pertaining to renin-angiotensin-aldosterone system inhibitor use.
ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist/blocker; COVID-19, coronavirus disease 2019; and RAASi, renin-angiotensin-aldosterone system inhibitor.

Our findings are in line with Lui, who reported on 46 patients over age 65 with hypertension hospitalized with COVID-19, that both ACEI and ARB were associated with unadjusted reduced odds for mortality, but the point estimates were unstable and only ARB use had an adjusted *P* value of 0.046.[18] The finding is reassuring in that in older individuals with common and compelling indications for ACEI/ARB use, including chronic kidney disease and heart failure, there was no excessive risk of mortality with previous chronic administration and this supports most professional societies that have advised that patients on ACEI/ARB be continued on therapy in the setting of COVID-19.[19]

Our study raises many questions for the current COVID-19 pandemic. Could chronic ACEI/ARB use be protective against initial infection or reduce the severity of COVID-19 pneumonia? Large population studies including the large fraction of patients with COVID-19 who shelter at home and are not hospitalized will need to be performed. Would administration of ACEI/ARB in hospital be protective against the development of ARDS? For this question, daily ACEI/ARB administration is needed or, preferably, a randomized trial recruiting hospitalized subjects. Finally, do these data suggest, along with the body of information on ACE-2 and COVID-19, that therapeutic upregulation of ACE-2 or soluble ACE-2 be a therapeutic strategy suitable for other agents or possibly recombinant ACE-2?

Our study has all the limitations of retrospective observational cohort studies performed with limited information in the setting of a critical pandemic. We lacked clarity on the primary indication of ACEI/ARB prescription, dose, duration, and tolerability with respect blood pressure and azotemia. We did not have information on the choice of ACEI versus ARB and whether ARB treated patients were more likely to be ACEI intolerant. Additionally, other variables of interest, such as body mass index, or measures of ACE-2 activity or its genetic determinants, were not available for study. Further, the relatively small sample size could have hindered the ability to detect an association between antecedent ARB administration and inpatient mortality, as its point estimate was similar to that of ACEI's; an adjusted pooled analysis comparing patients taking either ACEI or ARB against those taking neither ACEI nor ARB revealed significance (OR, 0.568; 95% CI, 0.347–0.928; *P*=0.0239). Lastly, our data may have limited generalizability attributable to the relatively homogeneous nature of the Italian population studied. Despite these limitations, the Coracle registry provides a representation of patients from regions of Italy that experienced high levels of viral spread, as well as those that were less affected, likely attributable to lockdown.

In summary, antecedent use of ACEI in patients aged 50 and older who were hospitalized with COVID-19 was associated with a reduced risk of mortality after adjustment for common indications for ACEI/ARB

administration. Future research is urgently needed for a better understanding on how the renin angiotensin system and its related pharmacological therapies influence the frequency, severity, and outcomes related to COVID-19 infection.

ARTICLE INFORMATION

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Disclosures

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