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Effect of ACE inhibitors and angiotensin receptor blockers on in-hospital mortality and length of stay in hospitalized COVID-19 patients

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is the causative agent of Coronavirus disease 2019 (COVID-19) has created a pandemic. Many patients with cardiovascular disease, hypertension, and diabetes are on angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-receptor blockers (ARB). Controversy arose when Wrapp et al. described the SARS-CoV-2 spike glycoprotein as having a higher binding affinity to the Angiotensin Converting Enzyme 2 Receptor (ACE2 receptor) in animal models [1]. This led experts to question not only the continued use of ACEi/ARB during COVID-19 infections, but also the possibility that patients on ACEi/ARB were at risk for higher rates of morbidity and mortality.

ACE2 receptors, a homolog of angiotensin I-converting enzyme (ACE) receptor, incise Angiotensin II to generate Angiotensin 1-7, which has anti-inflammatory, anti-proliferative and vasodilatory effects. This contrasts with the effects of Angiotensin II, which are cell proliferation, fibrosis, inflammation and vascular smooth muscle contraction [2]. It was then hypothesized that ACEi/ARB would decrease mortality and/or severity of the disease warranting more research.

A study of 4480 Danish patients by Fosbøl et al. found no significant association between prior use of ACEi/ARB and mortality or severity of COVID-19 disease after adjusting for demographics and comorbidities [3]. We investigated if ACEi/ARB was associated with worse outcomes in hospitalized COVID-19 patients.

To achieve our objective, we performed a retrospective cohort study of 995 COVID-19 patients admitted between March 13th, 2020 and May 15th, 2020. Exposed patients were on ACEi/ARB previously at home which were continued in the hospital while control patients had no exposure to ACEi/ARB at home or in the hospital.

We performed multiple imputation for missing data using the MICE method and Rubin's rules were applied. Analyses included the *t*-test or Mann-Whitney test for quantitative data and Chi-square or Fisher's Exact test for categorical data. An adjusted cox regression model controlled for age, body mass index (BMI), race, sex, smoking status, congestive heart failure (CHF), hypertension (HTN), chronic obstructive pulmonary disease (COPD), asthma, diabetes, coronary artery disease (CAD), cerebrovascular accident/transient ischemic attack (CVA/TIA), glomerular filtration rate (GFR), neutrophil, lymphocyte, and inflammatory markers such as ferritin, d-dimer, and C-reactive protein (CRP). Quantitative variables are reported as mean ± SD or median [IQR] for non-normally distributed data; nominal variables are reported as percentages. Significance was assessed at $p < 0.05$. All analyses were performed using STATA 13.1.

Of the 995 patients in the study, 241 were exposed to ACEi/ARB and 754 were not. ACEi/ARB patients were older, had higher percentage of former smoking, and patients with HTN, DM, CAD and CVA/TIA (Table 1).

There was no association between use of ACEi/ARB and in-hospital mortality; this finding held when analyzing intubated patients only (Table 2).

Median length of stay (LOS) for non-intubated survivors was statistically similar between the groups. Rates of intubation were also similar.

We found no association between ACEi/ARB use and in-hospital mortality in hospitalized COVID 19 patients for both unadjusted and adjusted analyses. LOS and intubation rates were also similar between the groups. Inflammatory markers at admission between the exposed group and non-exposed group were similar, implying that both groups had the same amount of inflammatory reaction to COVID-19 and ACEi/ARB did not have a role in this inflammatory pathway. Inflammatory markers, along with race and BMI, were controlled for in our analyses. Our study adds to the growing evidence that discontinuation of ACEi/ARB is not clinically indicated in COVID-19 patients after diagnosis or hospitalization and should not be restricted in the community or hospital due to the COVID-19 pandemic. The benefits of appropriate ACEi/ARB use when indicated for cardiovascular indications outweigh any potential harm in COVID-19 patients.

Disclosure

Author's contributions: H.L., N.K., A.S., G.K. conceived the study. A. S. served as the project administrator of the study. H.L., N.K., A.S., G.K. contributed to the study design. N.K. drafted the initial Introduction and Literature Review. T.K. drafted the Methods. H.L., N.K., A.S., G.K., T.K. drafted the results, discussion and conclusion and provided revisions. All authors contributed subsequent revisions of the letter. G.K and A.S. formatted the final manuscript and G.K. serves as corresponding author. All authors approved the final manuscript.

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Table 1
Demographic and clinical characteristic comparisons.

Characteristics	ACE/ARB (n = 241 [24.2%])	Control (n = 754 [75.8%])	p-value
Age	70.1 ± 14.3	66.5 ± 18.0	0.002
Sex, % female	122 (50.6%)	389 (51.6%)	0.79
Race			0.50
African American	87 (37.9%)	286 (37.9%)	
Caucasian	128 (53.1%)	405 (53.7%)	
Other	26 (10.8%)	63 (8.4%)	
BMI	30.7 ± 8.0	30.0 ± 8.5	0.28
	Missing 8	Missing 31	
Smoking			0.042
Current or quit <6 mo.	9 (3.7%)	35 (4.6%)	
Former, quit >6 mo.	71 (29.5%)	166 (22.0%)	
Never	134 (55.6%)	427 (56.6%)	
Unknown	27 (11.2%)	126 (16.7%)	
CHF, % yes	40 (16.6%)	114 (15.1%)	0.58
HTN, % yes	226 (93.8%)	411 (54.5%)	<0.001
COPD, % yes	35 (14.5%)	108 (14.3%)	0.94
Asthma, % yes	21 (8.7%)	74 (9.8%)	0.61
Diabetes, % yes	122 (50.6%)	205 (27.2%)	<0.001
CAD, % yes	53 (22.0%)	109 (14.5%)	0.006
CVA/TIA, % yes	40 (16.6%)	83 (11.0%)	0.022
GFR Admission[a]	61 [40.5–75.5]	63 [42–82.3]	0.29
		Missing 8	
Neutrophil Admission[a]	4.7 [3.5–7.6]	5.1 [3.5–7.4]	0.30
	Missing 3	Missing 27	
Lymphocyte Admission[a]	0.9 [0.6–1.4]	0.9 [0.6–1.3]	0.59
	Missing 6	Missing 46	
Ferritin Admission[a]	441.5 [250–1019]	486.9 [245–994]	0.92
	Missing 71	Missing 250	
D-dimer Admission[a]	473 [285.3–966.5]	543 [296–1119]	0.23
	Missing 95	Missing 314	
CRP Admission[a]	9.6 [4.4–16.8]	10.0 [5–16.8]	0.41
	Missing 81	Missing 304	

[a] Median (IQR).

Table 2
In-hospital mortality, length of stay and intubation rate comparisons.

	Outcomes		
Analysis	Death	Length of stay, non-intubated survivors (p = 0.48)	% Intubated (p = 0.15)
	# of events / # of patients at risk (%)		
ACE/ARB	52/241 (21.6%)	7 days [4–10][a]	28/241 (11.6%)
Control	176/754 (23.3%)	6 days [4–10][a]	116/754 (15.4%)
Crude analysis	0.87 [0.64–1.16]		
Multivariate analysis[b]	0.77 [0.55–1.09]		
Propensity-score matched analysis[c]	0.83 [0.52–1.22]		
Intubated patients only[d]	1.14 [0.68–1.89]		

[a] Median [IQR].
[b] Hazard ratio (HR) and 95% confidence interval (CI) from a multivariate cox proportional-hazards model with adjustment for patient characteristics (Age, BMI, race, sex, smoking status, CHF, HTN, COPD, Asthma, Diabetes, CAD, CVATIA) and admission lab values (GFR, Ferritin, D dimer, Neutrophil, Lymphocyte, CRP). The analysis included 995 patients.
[c] HR [95% CI] estimates were derived using the multiply imputed matched data with 241 matched exposed and control patients in each of the 10 imputed datasets (n = 482).
[d] HR [95% CI] from a multivariable cox proportional-hazards model with adjustment for patient characteristics (Age, race, smoking status) and admission lab values (GFR, Neutrophil) including intubated patients only. The analysis included 144 patients (28 ACE/ARB and 116 control).

The authors declare they have no conflicts of interest.

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