Association Between COVID-19 Mortality and ICU Admission Rates and Prior History of Angiotensin-Converting Enzyme or Angiotensin Receptor Blockers Use Among Hospitalized COVID-19 Patients with Hypertension in Michigan.

Eiman M. Elhouderi[1], Eman A. Elsawaly[1], Najlaa K. Al-Sudani[1], Irum Mahmood[1], and David M. Sengstock[1]

[1]BHSH Beaumont Health

January 30, 2023

Abstract

Abstract: Importance: There are conflicting data regarding the safety of the use of Angiotensin-converting enzyme inhibitors or Angiotensin receptor blockers (ACEI/ARBs) medications in hypertensive patients who are susceptible to COVID-19. **Objective:** Our study assesses the association between COVID-19 severity and mortality and the use of ACEI/ARBs among hospitalized patients with hypertension. **Research design, setting and participants:** This was a retrospective cohort study. Using the EPIC system of Beaumont Health, we identified 5490 patients with COVID-19 who were admitted to the eight Beaumont hospitals. After excluding subjects who have no hypertension and those with missing data, we included 2129 COVID-19 patients who have hypertension. Logistic regression and Cox proportional hazard models were used to analyze the association history of ACEI/ARBs use, ICU admission rate and COVID-19 mortality. **Exposure:** Using of ACEI/ARBs as documented in the medical records before admission to the hospitals. **Main outcome:** 30 days COVID-19 mortality and ICU admission rates . **Results:** There were 1281 subjects (60%) with prior ACEI/ARBs use and 848 subjects (40%) with no ACEI/ARBs use. There was no significant association between ICU admission and use of ACEI/ARBs (odds ratio was 0.95, 95% CI [0.76, 1.19] and p-value was 0.6). Although the unadjusted logistic regression model demonstrated a statistically significant association between history of use of ACEI/ARBs and COVID-19 mortality (odds ratio= 1.31, 95% CI [1.05, 1.66], p-value= 0.02), the adjusted logistic regression model failed to show this statistically significant association (odds ratio= 1.20, 95% CI [0.93, 1.54], p-value= 0.14). Moreover, we were not able to reveal a statistically significant association between 30 days COVID-19 survival and prior use of ACEI/ARBs in the adjusted Cox-proportional hazard model (Hazard ratio (HR) = 1.11, 95% CI [0.91, 1.40], p-value =0.14). **Conclusion:** In a large retrospective study, we conclude that there was no statistically significant association between prior history of ACEI/ARBs use and COVID-19 ICU admission rates or mortality in hypertensive patients hospitalized with COVID-19.

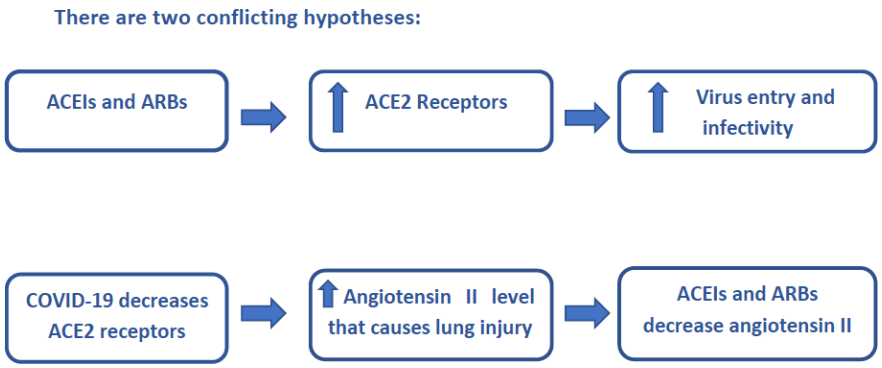
Introduction:

The number of people who got infected with COVID-19 virus were around 43.7 million and the number of deaths was around 710 thousand by October 2021 in the United States according to the Center for Disease Control and Prevention (CDC) data tracker.

Recent data showed that patients with cardiovascular diseases such as hypertension who tested positive for COVID-19 had worse outcomes. Between 2017-2018, the prevalence of hypertension was 45% among adults in the USA. Millions of hypertensive patients use angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) as the first-line treatment.

There are conflicting data regarding the use of these medications, the severity of the COVID-19 infection, and the mortality rate (Figure 1). COVID-19 virus gains entry to pulmonary cells through binding to the membrane angiotensin convertase enzyme receptor 2 (ACE-2). Hence there is a concern about using ACEI and ARBs as these medications use the same receptors. There is a debate regarding the increased risk of COVID-19 infection in patients who use ACEI and ARBs by increasing the viral entry and subsequently increasing the viral load and the mortality risk. On the other hand, studies have shown that ACEI and ARBs medications can protect against COVID-19 infection by attaching to the ACE receptors, thereby decreasing the availability of those receptors to the COVID-19 virus, leading to the deactivation of the virus and decreasing the virus load. Hence many investigators have advised the use of ACEI and ARBs medications in COVID-19-positive patients even with no history of hypertension.

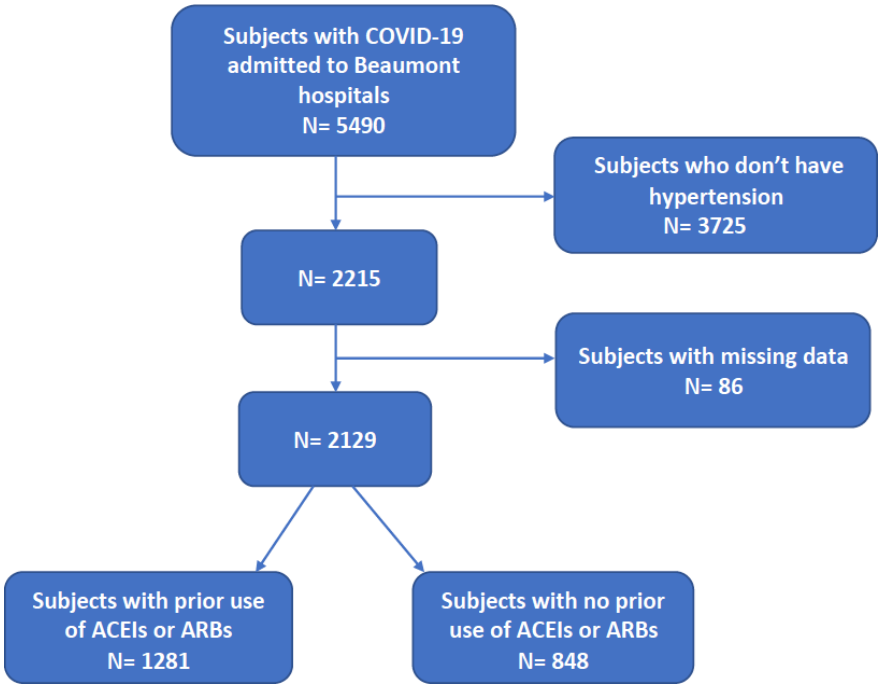
Figure 1: Two conflicting hypotheses of association between ACEI/ARB and COVID-19.



Methods:

This was a retrospective cohort study. We researched the EPIC system of the Beaumont Health system, Michigan for subjects who were admitted to the eight Beaumont hospitals and tested positive for COVID-19 from February 1st to April 30th 2020. We included only COVID-19 patients who have hypertension diagnoses in their charts. We excluded subjects with missing information on one of the possible predictor factors (BMI) (figure 2). We followed subjects for thirty days after admission. The two primary outcomes were 30 days COVID-19 mortality and ICU admission rates. We used ICU admission rate as a marker of COVID-19 severity. We defined ICU admission as admission to intensive care units or progressive care units (PCU)since the admission criteria for both units include the use of invasive or non-invasive ventilatory support or vasopressors which indicate severe disease.

Figure 2: Patient Flow Chart:



Statistical analysis:

We compared the baseline characteristics between subjects who had a history of use of ACEI/ARB those who didn't use these medications using the chi-square test and t-test (Table1). First, we performed a simple logistic regression analysis to study the association between ICU admission rates and the use of ACEI/ARBs. We then used a multivariate logistic regression model to adjust for possible confounders including age, sex, race, BMI, COPD, asthma, use of aldosterone antagonists, heart failure, DM, and ESRD. Using the same methods, we studied the association between COVID-19 mortality and the use of ACEI/ARB. We used a Cox proportional hazards model to study the association between the use of ACEI/ARB and 30 days-COVID-19 survival. We censored the time to the event to 30 days. We first performed a univariate model and then performed a multivariate-adjusted model. We adjusted for the same possible confounders as those mentioned above.

R studio was used to analyze the data and a p-value of [?]0.05 was considered statistically significant.

Results:

We identified 5490 patients with COVID-19 who were admitted to the hospital. After excluding subjects with no hypertension and those with missing data, we included 2129 COVID-19 patients who had hypertension. Table 1 reveals the baseline subject characteristics of the two groups (a group that has a history of ACEI/ARB use and a group with no history of ACEI/ARBs use. Both groups are similar in terms of sex, BMI, and use of steroid during hospitalization. There were more patients with DM, heart failure, ESRD, asthma, and COPD in the ACEI/ARB group than in the non-ACE/ARB group. A total of 532 (25%) patients were admitted to ICU or PCU (319 subjects (25%) from ACEI/ARB group and 213 (25%) subjects from non-ACEI/ARB group). There was no statistically significant difference in ICU admission rates between the ACEI/ARB and no ACEI/ARB groups in both adjusted (odds ratio= 1.02, 95% CI [0.04, 0.22], p-value= 0.7) and unadjusted models (odds ratio= 0.95, 95% CI [0.76,1.19], p-value= 0.6) (Table 2).

Table 1: Baseline patients characteristics.

Variables	ACEI or ARBs N= 1281, 60%,	NO ACEI or ARB N= 848, 40%	P value
Age	68 (14)	66 (15)	0.007
Sex (F)	649 (50%)	442 (52%)	0.5
BMI	32.1 (8.3)	31.8 (8.8)	0.4
Race	White=526 (41%) African= 680 (53%) Other= 75 (5%)	White=272 (32%) African= 525 (61%) Other= 51 (6%)	0.0001
Asthma	176 (14%)	91 (10%)	0.04
COPD	125 (10%)	49 (6%)	0.001
HF	186 (16%)	83 (10%)	0.001
DM	628 (49%)	285 (33%)	<0.001
ESRD	76 (5%)	33 (4%)	0.03
Steroid use	627 (49%)	438 (52%)	0.2
Aldosterone antagonist	128 (84%)	23 (15%)	<0.01

Abbreviation: HF, heart failure; DM, diabetes mellitus; BMI, body mass index.*We used N (%) for categorical variables and mean (SD) for continuous variables. COPD

Table 2: Adjusted logistic regression model exploring the association between the use of ACEI/ARBs and ICU admission rates.

	Odds ratio	95 % CI	P value
ACEI[a]	1.02	(0.04, 0.22)	0.7
Age	1.01	(1.002, 1.02)	0.01
Sex (F)	0.89	(0.72, 1.08)	0.23
BMI	0.99	(0.98, 1.01)	0.4
Race (African American)	1.32	(1.06, 1.64)	0.01
Asthma	0.67	(0.48, 0.92)	0.01
COPD	1.08	(0.75, 1.54)	0.6
HF	1.22	(0.90, 1.66)	0.2
DM	1.43	(1.18, 1.75)	<0.01
ESRD	2.45	(1.62, 3.80)	<0.01
Steroid use	3.45	(2.83, 4.24)	<0.01
Aldosterone antagonist	1.02	(0.69, 1.49)	0.9

[a] Adjusted for age, sex, BMI, race, asthma, COVPD, HF, DM,ESRD Aldosterone antagonist and steroid use.

A total of 391 patients (18%) passed away within thirty days of admission (256 (20%) subjects from the ACEI/ARB group and 135 (16%) subjects from the non-ACEI/ARB group.

Although there was a statistically significant difference in the COVID-19 mortality rates between the two groups in the unadjusted logistic regression model (odds ratio= 1.31, 95% CI[1.01,1.54], p-value= 0.03), the difference in the odd of COVID-19 mortality between the two groups was not statistically significant in the adjusted model (odds ratio= 1.20, 95% [(0.93, 1.54)], p-value= 0.14) (Table 3).

Table 3: Adjusted logistic regression model exploring the association between the use of ACEI/ARBs and COVID-19 mortality.

	Odds ratio	95 % CI	P value
ACEI[a]	1.20	(0.93, 1.54)	0.14
Age	1.06	(1.05, 1.07)	<0.01
Sex (F)	0.85	(0.65, 1.07)	0.16
BMI	1.01	(0.98, 1.023)	0.47
Race (African American)	0.84	(0.66, 1.1)	0.23
Asthma	0.93	(0.62, 1.37)	0.74
COPD	1.07	(0.72, 1.57)	0.72
HF	1.19	(0.85, 1.66)	0.28
DM	1.30	(1.02, 1.66)	0.03
ESRD	1.30	(0.75, 2.17)	0.32
Steroid use	2.82	(2.20, 3.64)	<0.01
Aldosterone Antagonist	1.03	(0.64, 1.60)	0.9

[a] Adjusted for age, sex, BMI, race, asthma, COVPD, HF, DM,ESRD Aldosterone antagonist and steroid use.

The Kaplan-Meier curve illustrated that ACEI/ARBs were associated with increased COVID-19 mortality (Figure 3). Similarly, the unadjusted Cox proportional hazard model showed that the use of ACEI/ARBs was associated with an increase in COVID-19 mortality (HR= 1.25, 95% CI[1.01, 1.54), p-value= 0.03). However, we failed to find a statistically significant association between the history of ACEI/ARB use and 30 days-COVID-19 survival in the adjusted Cox proportional hazard model (Table 4).

Figure 3: Kaplan-Meier curve demonstrating the association between the use of ACEI/ARBS and COVID-19 mortality.

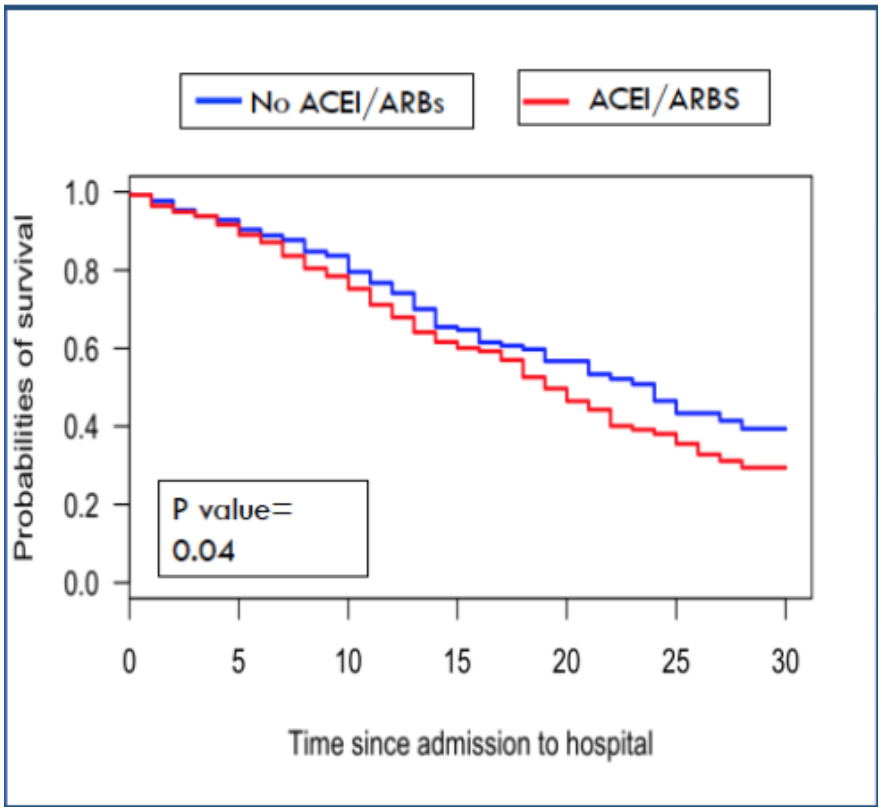


Table 4: Adjusted proportional hazard model illustrating the association between the use of ACEI/ARB and COVID-19 mortality.

	Odd ratio	95 % CI	P value
ACEI	1.12	(0.91, 1.40)	0.14
Age	1.04	(1.037, 1.05)	< 0.01
Sex (F)	0.90	(0.73, 1.11)	0.34
BMI	0.99	(0.98, 1.01)	0.72
Race (African American)	0.83	(0.67, 1.03)	0.83
Asthma	1.01	(0.72, 1.40)	0.97
COPD	1.20	(0.87, 1.66)	0.24
HF	0.95	(0.72, 1.25)	0.73
DM	1.15	(0.94, 1.41)	0.16
ESRD	0.87	(0.55, 1.37)	0.56
Steroid use	1.01	(0.83, 1.31)	0.69
Aldosterone antagonist use	1.09	(0.75, 1.58)	0.63

The COX proportional hazard model showed no significant association between ACEI/ARB use and the time to ICU admission in both the unadjusted (HR=0.9, 95% CI [0.8, 1.1], p-value= 0.5) and adjusted models (HR= 0.9, 95% CI[0.79, 1.11], p-value= 0.5) (Table 5).

Table 5: Adjusted proportional hazard model illustrating the association between the use of ACEI/ARB ICU admission rates.

	Hazard ratio	95 % CI	P-value
ACEI	0.9	(0.79, 1.11)	0.5
Age	1.01	(0.99, 1.01)	0.1
Sex (F)	1.06	(0.90, 1.25)	0.4
BMI	0.99	(0.98, 1.00)	0.2
Race (African)	1.02	(0.86, 1.22)	0.7
Asthma	0.8	(0.67, 1.16)	0.4
COPD	1.07	(0.80, 1.43)	0.6
HF	1.01	(0.79, 1.28)	0.9
DM	0.98	(0.83, 1.16)	0.8
ESRD	1.09	(0.80, 1.49)	0.5
Steroid use	0.65	(0.55, 0.78)	<0.01
Aldosterone Antagonist	0.9	(0.73, 1.35)	0.9

Discussion:

Among patients who were hospitalized for COVID-19, this study showed no significant association between prior use of ACEI/ARBs and COVID-19 mortality or severity as evident by ICU admission rate after adjusting for baseline characteristics, comorbidities, and steroid use, using the adjusted logistic regression model and Cox-proportional hazard model.

The mean BMI in our study population was high (32). Eighty percent of the patients had BMI equal or higher than 25. This finding correlates with the findings of other studies on the association between BMI and COVID-19 hospitalization rates.

Some studies have suggested that ACEI/ARB may increase viral entry, with concerns that these drugs could increase the risk of developing severe outcome with COVID-19

However, to date, there is insufficient data the association between prior use of ACEI/ARBs associated and an increased risk of COVID-19 severity. A retrospective cohort study was conducted in two Saudi public specialty hospitals, included 354 patients with COVID-19 (in which 146 were ACEI/ARB users and 208 were non-ACEI/ARB users) after controlling for confounders, using multivariate logistic regression and sensitivity analyses using propensity score matching (PSM) and inverse propensity score weighting (IPSW) for high-risk patient subsets. The ACEI/ARB group had an eight-fold higher risk of developing critical or severe COVID-19 (OR = 8.25, 95%CI = 3.32–20.53); a nearly 7-fold higher risk of intensive care unit (ICU) admission (OR = 6.76, 95%CI = 2.88–15.89) and a nearly 5-fold higher risk of requiring noninvasive ventilation (OR = 4.77,95%CI = 2.15–10.55). Concluding that ACEI/ARBs use was associated with a higher risk of severe COVID-19 disease. However, this study had a small sample size, some variables were overlooked including the use of steroids, and the results showed a wide confidence interval.

On the other hand, a prospective cohort study in England involving 8.28 million participants showed reduced risk of COVID-19 positive disease requiring hospitalization. This study is limited by unavailability of standard systematic strategy for COVID-19 testing in the UK and restricting the COVID-19 testing to only hospitalized patients by UK health policy during the period of the study.

Despite that, a meta-analysis including 13 studies conducted in 2020 showed that ACEI/ARB use was not associated with an increased risk of all-cause mortality or severe disease due to COVID-19. Among these 13 studies, 11 studies that reported odds ratio showed the thebACEI/ARB group had a significantly lower risk of all-cause mortality than non-ACEI/ARB group regardless of confounders of adjustment for confounders. This meta-analysis was limited by inconsistencies in the definition of severe diseases and in inclusion criteria that were inconsistent across the studies.

In addition to this meta-analysis, an open randomized controlled trial in Brazil including 659 hospitalized patients with mild to moderate COVID-19 showed no effect of discontinuation of ACEIs or ARBs on COVID-

19 mortality. However, this study explored a different question than our study. The two proposed two conflicting hypotheses state that ARBs and ACEIs either increase ACE2 expression, allowing virus entry into the cell and, therefore, increasing SARS-COV2 infectivity and severity or coronavirus downregulates ACE2 receptors causing an elevation of angiotensin II, which may lead to lung injury. Based on this, prior use of ACEI/ARB would affect the COVID-19 infectivity, severity or mortality or than the use of ACEIs/ARBs after establishment COVID-19.

Another study conducted in New York in the March of 2020 showed a reduced length of hospital stay in patients admitted with COVID-19 who used ACEI/ARB in the hospital, most of whom belonged to ethnic minorities. This limitations of this study include the disproportionate size of the control vs. treatment group and the fact that study only considered the ACEIARB during the hospitalization. The results were not significant for the other primary outcome or the secondary outcomes.

We have a large high-quality database of hospitalized COVID-19 patients at our hospitals. Our study is observational and we were able to reduce the confounding effect by adjusting a wide range of confounders recorded in electronic medical records including age, race, BMI, and other comorbidities. Our sample was representative and was restricted to a group of patients with hypertensive. Another great strength of our study is the inclusion of a diverse group of patients as the eight hospitals are spread out over the Southeast Michigan region where a majority of Michigan's population resides and comprises of Caucasians, African Americans, and Arabs. The limitations of our study include, the retrospective nature of the study, the inability to specify the chronicity of ACEI/ARB use based on the available data, overlooking of unknown confounders and finally, and performing the study during the early months of COVID-19 pandemic where little information about the treatment and disease was available.

At this stage, there is insufficient clinical evidence for either, thus we still need further studies. Until further data are available, we should continue using ACEI and ARB to treat cardiovascular disease in patients with COVID-19 given the significant cardiovascular benefits of ACEI/ARBs. In addition, the sudden withdrawal of ACEI/ARBs in those patients may result in adverse outcomes.

Conclusion:

In a large retrospective study, we concluded that there was no statistically significant association between prior history of ACEI/ARB use and COVID-19 ICU admission rates or mortality in patients hospitalized with COVID-19.

References:

Acknowledgments:

Janice Weinberg, ScD, MS, Director of the Master of Science in Clinical Research at the Boston University School of Medicine, USA.

Aisha Elhouderi, MEng, Loughborough University, UK.

Mostafa Hoderi, B.Eng., Texas A&M University, USA.