Received: 16 June 2022 | Revised: 4 August 2022 | Accepted: 12 August 2022

DOI: 10.1111/dom.14835

RESEARCH LETTER

WILEY

Are angiotensin-converting enzyme inhibitors/angiotensin receptor blockers associated with reduced severe acute respiratory syndrome coronavirus 2 infections and improved outcomes, and does race matter?

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Funding information
M.J. Murdock Charitable Trust

KEYWORDS: ACE inhibitor, angiotensin receptor blocker, SARS-CoV-2

1 | BACKGROUND

By 1 December 2021, coronavirus disease 2019 (COVID-19) was responsible for more than 263 million infections and more than 5 million deaths worldwide.[1] The virus enters the cell via the cell surface angiotensin-converting enzyme-2 (ACE2) receptor.[2] The intersection between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the renin–angiotensin–aldosterone system (RAAS) and antagonists of the RAAS (angiotensin-converting enzyme inhibitors [ACEi]/angiotensin receptor blockers [ARB]) was recognized early in the pandemic based on prior insights from SARS and Middle East respiratory syndrome.[3]

ACEi/ARB have been proposed to counteract the inflammatory effects of COVID-19 infection by shifting metabolic activity toward AT2/MasR pathways and away from AT1 pathway. Conversely, potential for increased risk was suggested by upregulation of ACE2 resulting from ACEi and ARB.[4] Retrospective analyses of outcomes involving prescribed ACEi or ARB have shown either a neutral or beneficial effect.[5] Consensus exists that ACEi/ARB treatment should be continued in the presence of COVID-19 infection.[6,7]

This retrospective review is an assessment of the association between ACEi/ARB (ever vs. never) and COVID-19 infection and outcomes. This study did not explore the timing, duration or indications for treatment. In total, 6 039 403 patients with/without COVID-19 infection were categorized by ACEi or ARB and stratified by self-reported ethnicity. Rates of COVID-19 infection and secondary outcomes were compared. Because of the increased rates of COVID-19 infections and severe outcomes in African Americans (AAs),[8] this population was independently evaluated. Although Hispanic and other groups may experience outcome inequalities, AA populations differ in mean plasma renin activity, further raising the possibility that ACEi or ARB use might have a different effect in this population.[9-11]

2 | METHODS

A retrospective review of 7 938 123 health records from Providence Health System from 1 January 2020 to 15 December 2021 was conducted. A waiver of Institutional Review Board approval was received from Providence Institutional Review Board, Portland, Oregon.

Records documenting ACEi/ARB were identified. See the supporting information for inclusion/exclusion criteria and the medical diagnoses assessed. The population was further stratified by self-reported ethnicity and Social Vulnerability Index (SVI),[12] a measure of social determinants of health.

After exclusions, 6 039 403 records were evaluated for rates of COVID-19 infection and secondary outcomes. Additional data were

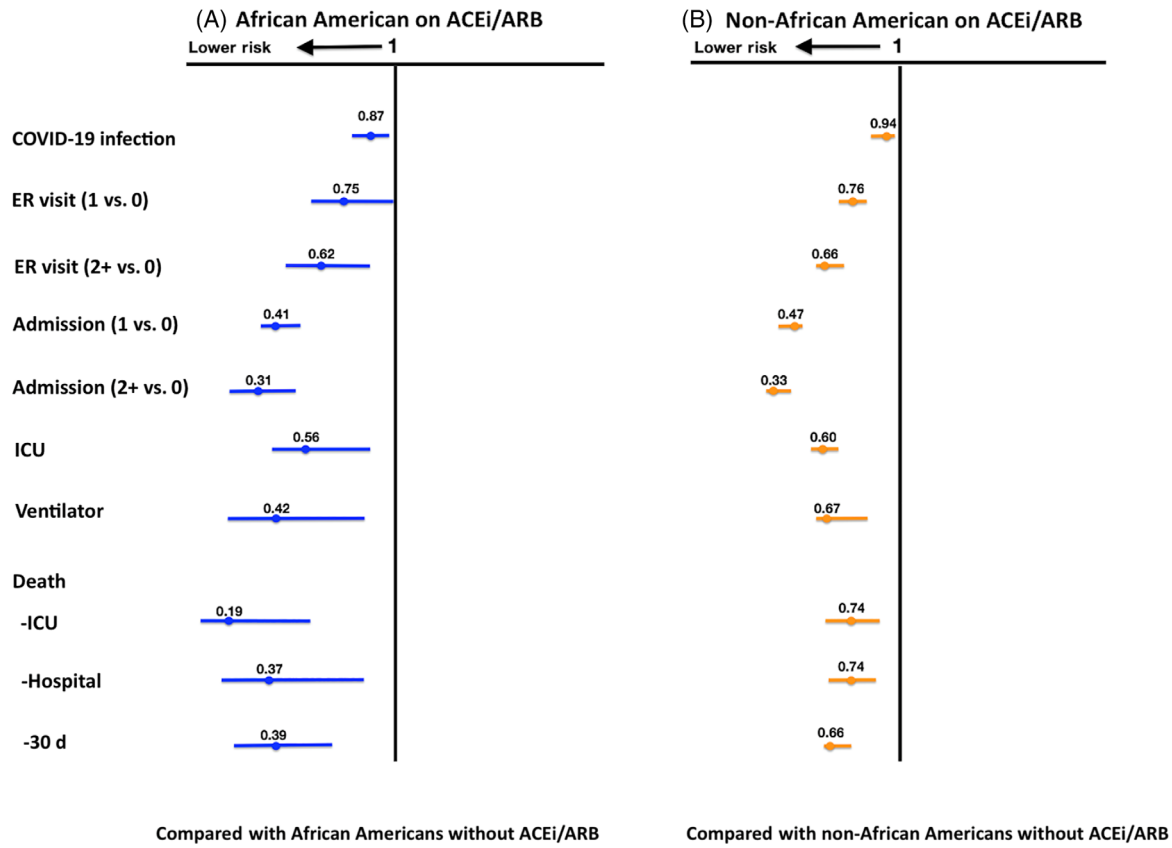

FIGURE 1 Odds ratios of COVID-19 infection and secondary outcomes in (A) African American and (B) Non-African American patients with a record of ACEi/ARB. Odds ratios of rates of COVID-19 infection and subsequent secondary outcomes in patients on ACEi/ARB are compared with a propensity-matched population without a record of ACEi/ARB. Propensity matching included demographic characteristics, medical diagnoses known to influence COVID-19 outcomes, and the SVI, an indication of social determinants of health. ACEi/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; COVID-19, coronavirus disease 2019; ER, emergency room; ICU, intensive care unit; SVI, Social Vulnerability Index

utilized for propensity matching for medical diagnoses and pharmacologic agents (Table S2). No genotype data were available.

Frequency and percentage of the primary outcome, COVID-19 diagnosis, was documented. Race comparisons were generated from paired odds ratios (ORs) with 95% confidence intervals (CIs). Propensity score matching (PSM) was based upon multivariate logistic regression including the following covariates: medication administered during admission or emergency room (ER) visit, gender, age, ethnicity, regions, SVI, colchicine, congregate living and other co-morbidities, including asthma, coronary artery disease (CAD), congestive heart failure, chronic obstructive pulmonary disease, diuretics, hypertension, type 1 diabetes and type 2 diabetes. PSM for AA versus non-AA (NAA) populations, with and without documentation of ACEi/ARB, were compared. Utilizing balanced standardized mean differences between matched populations, the calculated adjusted ORs and associated 95% CIs determined statistical significance.

Unmatched and propensity-matched AA versus NAA populations, stratified by ACEi/ARB, were used to evaluate secondary outcomes, including number of admissions, ER visits, hospital length of stay (LOS), intensive care unit (ICU) admission, ICU LOS, ventilator requirement, ventilator days, death in ICU and death during hospitalization; long-term follow-up was limited to 30-day mortality. Appropriate statistics of the clinical outcomes, including median, interquartile range, frequency and percentage, were summarized in tables and the corresponding *P* values were generated by Chi-square test or t-test on differences of median. ORs with 95% CIs comparing secondary outcomes between AA and NAA populations after PSM were represented in forest plots (Figures 1 and S1).

3 | RESULTS

After exclusion criteria, 6 039 403 patients were identified, of whom 283 717 self-identified as AA. There was an increased OR of COVID-19 infection (1.18 [1.12, 1.23]; $P < .0001$) in AAs compared with a matched NAA population (Table S2).

In matched same-race populations with ACEi/ARB versus no ACEi/ARB, the AA OR of COVID-19 infection was reduced (0.87 [0.78, 0.98]; $P = .0201$). Similarly, in the NAA population, ACEi/ARB were associated with a reduced OR of COVID-19 infection (0.94 [0.91, 0.97]; $P < .0001$) (Table **S1**). The reduction in the OR for COVID-19 infections was similar in the AA and NAA populations ($P > .05$).

TABLE 1 Rates of COVID-19 infection based upon ACEi/ARB status and race

		Non-African American						African American				
		without ACEi/ARB n = 9499		with ACEi/ARB n = 9499				without ACEi/ARB n = 598		with ACEi/ARB n = 598		
		Obs #	%	Obs #	%	*P* value		Obs #	%	Obs #	%	*P* value
Number of admissions	0	5889	(62)	7526	(79)	**<.0001**	0	364	(61)	480	(80)	**<.0001**
	1	2505	(26)	1501	(16)		1	166	(28)	90	(15)	
	2+	1105	(12)	472	(5)		2+	68	(11)	28	(5)	
LOS if admit ICU	Median (IQR)	7	(4,15)	6	(3,13)	0.143	Median (IQR)	9	(4,16)	8	(3,13)	0.329
	No	8534	(90)	8896	(94)	**<.0001**	No	537	(90)	562	(94)	**.009**
	Yes	965	(10)	603	(6)		Yes	61	(1)	36	(6)	
ICU days if had ICU stay	Median (IQR)	3.7	(2, 9)	3.7	(2, 1)	0.976	Median (IQR)	2.8	(1, 9)	2.9	(1, 11)	0.966
Ventilator	No	9098	(96)	9226	(97)	**<.0001**	No	568	(95)	585	(98)	**.01**
	Yes	401	(4.2)	273	(2.9)		Yes	30	(6)	13	(2.2)	
Ventilator days	Median (IQR)	5.7	(2,13)	5.5	(2,13)	0.718	Median (IQR)	6.1	(2, 10)	8.5	(8,15)	0.58
Deceased 30 d after discharge	No	8813	(93)	9037	(95)	**<.0001**	No	552	(92)	579	(97)	**.001**
	Yes	686	(7.2)	462	(4.9)		Yes	46	(7.7)	19	(3.2)	
Expired in ICU	No	9262	(98)	9322	(98)	**.003**	No	577	(96)	594	(99)	**.002**
	Yes	237	(2.5)	177	(1.9)		Yes	21	(3.5)	4	(0.7)	
Expired in hospital with ICU stay	No	9199	(97)	9276	(98)	**.001**	No	572	(96)	588	(98)	**.009**
	Yes	300	(3.2)	223	(2.4)		Yes	26	(4.4)	10	(1.7)	
ER visit	0	3205	(34)	3979	(42)	**<.0001**	0	200	(33)	255	(43)	**.002**
	1	2917	(31)	2766	(29)		1	182	(30)	173	(29)	
	2+	3377	(36)	2754	(29)		2+	216	(36)	170	(28)	

Note: Rates of COVID-19 infection are compared between unmatched and propensity matched African and non-African American patients with and without documented ACEi/ARB. *p*-values of statistical significance are in bold.

Abbreviations: ACEi/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; COVID-19, coronavirus disease 2019; ER, emergency room; ICU, intensive care unit; LOS, length of stay.

Without ACEi/ARB and comparing AAs to NAAs, AAs showed an increased OR of COVID-19 infection (1.25 [1.18, 1.32]; $P < .0001$). With ACEi/ARB, no difference in OR was observed (1.03 [0.94, 1.12]; $P = .56$) (Table **S1**).

Secondary outcomes were significantly improved in COVID-19–positive AAs with ACEi/ARB compared with a same race-matched population without ACEi/ARB (n = 598), for ER visits ($P = .002$), hospital admission ($P < .0001$), ICU admission ($P = .009$), ventilator requirement ($P = .01$), death in ICU ($P = .002$), hospitalized death after ICU ($P = .009$) and death at 30 days ($P = .001$) (Table 1, Figure 1). Similar associations in improved secondary outcomes were found in COVID-19–positive NAAs with ACEi/ARB compared with a same race-matched population, including ER visits ($P < .0001$), hospital admission ($P < .0001$), ICU admission ($P = .001$), ventilator requirement ($P < .0001$), death in ICU ($P = .003$), death in hospital after ICU ($P = .001$) and death at 30 days ($P < .0001$) (Table 1, Figure 1).

When comparing an AA group without ACEi/ARB (n = 234 799) to a matched subset of the NAA group (n = 4 692 795), an increased rate of COVID-19 infection was observed (OR 1.25 [1.18, 1.32]) (Table **S1**). COVID-19–positive AA patients without ACEi/ARB (n = 2964) experienced increased ER visits ($P < .0001$), hospital admissions ($P = .011$), ICU death ($P = .038$) and hospital death after ICU ($P = .039$) (Table S3).

AA patients with ACEi/ARB (n = 48 918) experienced an equivalent risk of COVID-19 infection compared with the matched NAA population. Among COVID-19–positive patients in this group (n = 331), ER visits, hospital admissions, death in the ICU and hospitalization after ICU were also equivalent (Figure S1, Table S4).

4 | CONCLUSIONS

The results show: (i) an association between a reduced risk of COVID-19 infection/complications and ACEi/ARB (documented by electronic health

record) regardless of race; (ii) an increased risk of COVID-19 infection/complications in the AA population when compared with a propensity-matched NAA population; (iii) a reduction in the risk of COVID-19 infection in AAs treated with ACEi/ARB that was similar to that in NAAs. If the beneficial effect of ACEi/ARB treatment on COVID-19 infection/outcomes is validated, this could have a substantial impact on mitigating the clinical course of COVID-19 infection.[10] The majority (>70%) of the current study population was not receiving ACEi/ARB (Table 1). This retrospective study provides no method by which to identify a population to initiate ACEi/ARB treatment prospectively and says nothing about initiating ACEi/ARB treatment after COVID-19 infection occurs. However, prospective studies based upon RAAS markers may answer this question.

While a strength of the current study is the population size spanning five states, these data represent associations and cannot be used to establish causal relationships. However, the COVID-19–positive subset was significantly smaller, and vaccination status, subsets of CAD and renal function were not included in matching. Plasma renin activity measurements were not available, and any speculation regarding the role of plasma renin activity, ACEi/ARB use and outcomes would require prospective evaluation.

Independent of race, ACEi/ARB showed a reduced risk of COVID-19 infection and adverse clinical outcomes. The AA subgroup without ACEi or ARB showed an increased risk of COVID-19 infection, morbidity and mortality compared with a matched NAA population. An equivalent risk of COVID-19 infection and secondary outcomes were identified in AAs with ACEi or ARB treatment when compared with a similarly matched NAA population.

AUTHOR CONTRIBUTIONS

All the named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, had full access to the compiled data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. Authors JA and RR participated in the study design. JA, RR, RD contributed to the concept and design of the post hoc analyses. DR was responsible for data collection and contributed to data selection criteria. SC was responsible for biostatistical analysis as well as writing and editing the description of statistical analysis. JA, RR and RD participated in the interpretation of the data, the writing, reviewing and editing of the manuscript, and all authors had final responsibility for approving the published version.

FUNDING INFORMATION

Murdoch Charitable Trust supported the contribution of the data analyst DR.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14835.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Armato J, DeFronzo RA, Chiu S-T, Rider D, Ruby R. Are angiotensin-converting enzyme inhibitors/angiotensin receptor blockers associated with reduced severe acute respiratory syndrome coronavirus 2 infections and improved outcomes, and does race matter? *Diabetes Obes Metab*. 2022;1-4. doi:10.1111/dom.14835