Angiotension-converting enzyme inhibitors and angiotensin-receptor blockers are not associated with increased risk of SARS-CoV-2 infection

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In a large Israeli dataset of 14,520 individuals tested for SARS-CoV-2, angiotension-converting enzyme inhibitors and angiotensin-receptor blockers were not found to be associated with increased SARS-CoV-2 infection after adjusting for major confounders. Patients on these medications should not stop their medication prophylactically.

The ongoing coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) has swept across the globe and put millions of lives at stake1. SARS-CoV-2 binds to the host cell's membrane via angiotensin converting enzyme 2 (ACE2), an enzyme that physiologically inhibits the renin–angiotensin system (RAS)[2]. Consequently, concerns were raised regarding the use of RAS inhibitors, including angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), and their potential role in increasing ACE2 expression and subsequent elevated risk of COVID-19 infection[3-6].

Currently, data from COVID-19 patients regarding the use of RAS inhibitors and infection risk are limited. The objective of this cross-sectional real-world data analysis was therefore to assess whether use of RAS inhibitors may increase the likelihood of positive results among tested members of Maccabi Health Services (MHS), a large health organization in Israel.

Using MHS database we have identified all 14,520 confirmed cases of COVID-19, defined as a positive result on real-time reverse-transcriptase– polymerase-chain-reaction (RT-PCR) assay of nasal and throat swab specimens. Criteria for testing were according to guidelines published by the Ministry of Health (Guidelines for coping with the novel coronavirus, 2020, Ministry of Health, Israel). A total of 1317 (9%) were found positive.

We collected information on demographics, the most recent document body mass index (BMI), medical conditions, lab tests results (e.g. last vitamin D and B12), and dispensed of prescribed medications, including RAS inhibitors, anytime between Jan 1st, 2020 and date of first SARS-COV-2 test.

Multivariable logistic regression model was used to assess the independent adjusted relationship between history of dispensed medication and SARS-COV-2 positivity with

adjustment to age, sex, SES, BMI, and co-morbidities. Interactions between ACEI status and age were examined and found insignificant. Assuming that the prevalence of patients treated for hypertension with ACEIs/ARBs in MHS is 10%, a minimum of 623 positive patients were required to calculate an odds ratio of 2 or above at a p-value <0.05 and a statistical power of 95%. All analyses were conducted with IBM-SPSS version 25 and R software version 3.6.

Compared to SARS-COV-19 negative cases, positive cases were significantly ($p<0.001$) more likely to be males (59.8% vs. 46.1%), older (40.6y vs. 37.0y), and reside in low socioeconomic status (SES) areas (27.9% vs. 12.7%), primarily in ultra-orthodox Jewish communities. Positive cases were also significantly ($p<0.001$) more likely to have a dispensed ARB/ACEI as compared to negative cases (9.9% vs. 6.4%, $p<0.001$). No such difference was observed for Calcium channel blockers (CCBs) ($p=0.539$), alpha blockers, beta blocker ($p=0.621$), or tamoxifen. Use of non-thiazide diuretics and HRT were less frequently observed among positive cases as compared to negative cases. Levels of vitamin D and B12 were comparable between SARS-COV-19 positive (mean=23.6±SD=8.6ng/ml and 407.5±166.7pg/ml) and negative cases (24.1±9.1 and 411.7±168.9, respectively).

In a multivariable logistic regression none of the medications of interest were found to be significantly ($p>0.1$) associated with positive SARS-CoV-2 result. Diabetes and obesity (BMI 30-35kg/m2) were associated with increased likelihood of positive result (OR=1.43; 1.09-1.87 and 1.45; 1.14-1.84) while heart failure with reduced one (0.18; 0.04-0.72) (Table 1). Comparable results were obtained when analysis was restricted to patients aged 50 or above. Non-significant ($P=0.113$) association (OR=1.19; 0.96-1.47) was calculated in the fully adjusted model when ACEIs and/or ARBS users were categorized as one group. Similar results were calculated among patients treated with both medications (OR=1.14; 0.25-5.08)

The results of this report suggest that the increased use of RAS-inhibitors among COVID-19 patients is fully explained by older age, male sex and higher prevalence of co-morbid conditions including hypertension, diabetes, heart failure, and chronic kidney disease. We also have found no indication of reduced likelihood of infection among patients who were treated with CCBs that do not affect RAS.

Curiously, in our cohort, heart failure had a protective effect. The observed reduced likelihood of infection found in our study may be due to detection bias, as shortness of breath is a common symptom of heart failure, which may have prompted testing in this population without other evidence of infection. Vitamin D has been suggested as a potential protective factor against COVID-19 infection by lowering viral replication rates and reducing concentrations of pro-inflammatory cytokines that injure the lining of the lungs, Our results show no association [7] between vitamin D levels and higher risk of COVID-19 infection.

Several mechanisms have been suggested to explain the greater risk for COVID-19 among patients with diabetes and obesity. These include higher affinity cellular binding and a more efficient host viral entry, diminished viral clearance, reduced T cell function, and a greater susceptibility to hyper-inflammation and cytokine storm due to the infection[8]. They may also have a greater prevalence of underlying diseases that increase the risk of COVID-19 such as cardiovascular disease. In addition, these patients are more likely to develop severe COVID-19 symptoms and consequently to seek testing.

In conclusion, we found that patients with co-morbid medical conditions, predominantly diabetes are at increased risk for COVID-19. Our data support current recommendations [9, 10]that patients on ACEIs or ARBs should not stop their medication prophylactically. Further research is needed regarding outcome of COVID-19 patients treated with these drugs.

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The authors have nothing to declare

Conflict of interest

The authors have no conflict of interests

Author contribution

GC and VS were responsible for the study conception. GC and AN drafted the manuscript. NY was responsible for data collection and analysis. All authors contributed to interpretation of results.

References

1. World Health Organozation. Coronavirus disease (COVID-19) Pandemic. [cited; Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019
2. Li W, Moore M, Vasilieva N. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003; **426**: 450-4.
3. Fang L, Karakiulakis G, M. R. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. 2020.
4. Sommerstein R, Gräni C. Preventing a COVID-19 pandemic: ACE inhibitors as a potential risk factor for fatal COVID-19. . BMJ. 2020; **368**: m810-m.
5. Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? . J Hypertens 2020.
6. Diaz J. Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19. J Travel Med 2020.
7. Grant WB, Lahore H, McDonnell S, Baggerly C, French C, Aliano J, et al. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. Nutrients. 2020.
8. Ryan P, Caplice N. Is Adipose Tissue a Reservoir for Viral Spread, Immune Activation and Cytokine Amplification in COVID-19. Obesity. 2020; **In Press**.
9. Danser A, Epstein M, Batlle D. Renin-Angiotensin System Blockers and the COVID-19 Pandemic. Hypertension. 2020; **120**.
10. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19. New England Journal of Medicine. 2020.

Table 1: Multivariable logistic regression for positive SARS-CoV-2 tests among 14520 tested

	SARS-CoV-2		OR*	95%CI	P value	OR**	95%CI	P value
	Positive n = 1317	**Negative n = 13,203**						
Sex, female, n (%)	529 (40.2%)	7111 (46.1%)	0.57	0.51-0.64	<0.001	0.58	0.52-0.65	<0.001
Age (years), mean (SD)	40.6 (19.1)	37.0 (19.1)	1.01	1.00-1.01	<0.001	1.01	1.00-1.01	<0.001
BMI (kg/m^2)[a], % >25	602 (45.7%)	7550 (52.6%)	1 (ref)			1 (ref)		
25-30	383 (29.1%)	3264 (24.7%)	1.15	1.00-1.33	0.055	1.14	0.99-1.32	0.076
30-35	186 (14.1%)	1319 (10%)	1.41	1.17-1.69	<0.001	1.38	1.14-1.66	0.001
>35	68 (5.2%)	602 (4.6%)	1.17	0.90-1.54	0.245	1.16	0.88-1.52	0.302
HF, n (%)	2 (0.2%)	73 (0.6%)	0.18	0.04-0.74	0.017	0.18	0.04-0.72	0.016
DM, n (%)	115 (8.7%)	642 (4.9%)	1.42	1.14-1.78	0.002	1.45	1.14-1.84	0.003
CKD, n (%)	104 (7.9%)	823 (6.2%)	0.91	0.72-1.16	0.445	0.90	0.70-1.16	0.424
Hypertension, n (%)	185 (14%)	1445 (10.9%)	0.96	0.79-1.16	0.674	0.81	0.64-1.03	0.082
ARB, n (%)	76 (5.8%)	527 (4%)	1.28	0.95-1.73	0.105	1.29	0.93-1.79	0.129
ACEI, n (%)	56 (4.3%)	332 (2.5%)	1.08	0.83-1.41	0.548	1.18	0.87-1.61	0.285

[a] Most recent record (data were missing for 8% of the study population). HF Heart failure; IHD Ischemic heart diseases; DM Diabetes Mellitus; CKD Chronic kidney disease
*Adjusted for age-and-sex **Adjusted for age, sex, hypertension, diabetes, BMI, and HF status