PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association of outpatient use of renin-angiotensin-aldosterone system blockers on outcomes of acute respiratory illness during the COVID-19 pandemic: a cohort study
AUTHORS	Jeffery, Molly; Oliveira J. e Silva, Lucas; Bellolio, Fernanda; Garovic, Vesna D.; Dempsey, Timothy; Limper, Andrew; Cummins, Nathan

VERSION 1 – REVIEW

REVIEWER	Diendere, Gisele Clinical Epidemiology of the Lady Davis Institute for Medical Research, Centre of Excellence in Thrombosis and Anticoagulation Care (CETAC)
REVIEW RETURNED	04-Feb-2022

GENERAL COMMENTS	1. Is the research question or study objective clearly defined? 2. Is the abstract accurate, balanced and complete? 9. Do the results address the research question or objective?. Is the research question or study objective clearly defined? Dear authors, thank you very much for submitting this article for review. Differential effects of outpatient use of ACE inhibitors and angiotensin receptor blockers on outcomes of acute respiratory illness during the COVID-19 pandemic: a cohort study I think you can delete the term 'differential effect' in the title as it does not align with your objectives (Evaluate the associations between patients taking ACE inhibitors (ACEis) and angiotensin receptor blockers (ARBs) and their clinical outcomes after an acute viral respiratory illness (AVRI) due to COVID-19), nor evaluated in the results and conclusion sections. 5. Are research ethics (e.g. participant consent, ethics approval) addressed appropriately? Please describe the ethics approval. 6. Are the outcomes clearly defined? The measure of death could involve information biases. Other co-morbidities (such as a number of diseases, medical history, etc.) were not taken into account. 7. If statistics are used are they appropriate and described fully? All confounding factors were not taken into account. 8. Are the references up-to-date and appropriate?

	Please include any new reference that was published in 2022. 12. Are the study limitations discussed adequately? Please note confounding factors (previous COVID infection, previous hospitalization, duration of treatment, etc.) were not included.

REVIEWER	Lee, Sukhyang Ajou Univ
REVIEW RETURNED	07-Feb-2022

GENERAL COMMENTS	1. It is hard to control the bias with the retrospective cohort study out of claims data. How did you keep the patient through the study period of 2017 to 2020 with the continuation of medication and the high medication possession rate which are not clear in the text? 2. The regression model and linear probability model were used in the analysis to have some meaningful interpretation of the results. There are still gaps between the statistical data and the theoretical/biological relationship of RAS inhibitors and COVID-19. Would you suggest a future study direction? 3. Patients with RAS inhibitors than other HTN meds may have a higher risk of clinical outcomes in this study. Authors have controlled with adjustment in analysis, but I am not sure the adjustment was performed enough. In discussion, hope to mention this more clearly.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1 Comments:
“Dear authors, thank you very much for submitting this article for review.

Differential effects of outpatient use of ACE inhibitors and angiotensin receptor blockers on outcomes of acute respiratory illness during the COVID-19 pandemic: a cohort study

I think you can delete the term 'differential effect' in the title as it does not align with your objectives (Evaluate the associations between patients taking ACE inhibitors (ACEis) and angiotensin receptor blockers (ARBs) and their clinical outcomes after an acute viral respiratory illness (AVRI) due to COVID-19), nor evaluated in the results and conclusion sections.”
Answer: Thank you for your comment. We changed the title as recommended.

5. Are research ethics (e.g. participant consent, ethics approval) addressed appropriately?
Please describe the ethics approval.
Answer: We added a statement in the Methods to clarify that this study was deemed exempt by the Institutional Review Board given its retrospective nature and use of de-identified administrative claims.

6. Are the outcomes clearly defined?
The measure of death could involve information biases. Other co-morbidities (such as a number of diseases, medical history, etc.) were not taken into account.
Answer: When evaluating the outcome of death, we did take into account the presence of multiple comorbidities as it is described in the subheading “Hypertension and comorbidities” in the Methods. All analyses were adjusted for potential confounders. The primary analysis takes into account all differences in comorbidities between groups. Details are available in the Supplementary Material.

7. If statistics are used are they appropriate and described fully? All confounding factors were not taken into account.

Answer: All analyses were adjusted for known potential confounders. The primary analysis takes into account all differences in comorbidities between groups, for example. Details are available in the Supplementary Material.

8. Are the references up-to-date and appropriate?
Please include any new reference that was published in 2022.
Answer: Thank you for the suggestion. We have added citations in the discussion for recent studies of the same question and highlighted the differences between findings and approach.

12. Are the study limitations discussed adequately?
Please note confounding factors (previous COVID infection, previous hospitalization, duration of treatment, etc.) were not included.
Answer: We added a statement in the Limitations to clarify that residual confounding is still a possibility given the lack of adjustment for variables not available in our dataset such as duration of treatment, for example. Nevertheless, we clarified that our analyses were adjusted for the most important confounders such as age and presence of comorbidities, as detailed in the Methods and Supplementary Materials.

Reviewer #2 Comments:
"1. It is hard to control the bias with the retrospective cohort study out of claims data.
How did you keep the patient through the study period of 2017 to 2020 with the continuation of medication and the high medication possession rate which are not clear in the text?"
Answer: We agree that there could be a potential for bias by requiring patients to have continuous enrollment for the entire study period. Our approach was to require continuous enrollment only for the 6-month period prior to the AVRI episode (see Study design and participants section in Methods, page 9).
We did not specify a medication possession rate. We only required a fill for an ACEi or ARB in the 90 days before the AVRI episode started (see Hypertension medications section in Methods, page 10). This time limit is because many people taking medications for chronic conditions fill 90 days' worth of medication at a time.

"2. The regression model and linear probability model were used in the analysis to have some meaningful interpretation of the results. There are still gaps between the statistical data and the theoretical/biological relationship of RAS inhibitors and COVID-19. Would you suggest a future study direction?"
Answer: Two recent RCTs have answered the key clinical question on whether ACEis/ARBs should be discontinued in patients hospitalized with COVID-19: there is no evidence that they discontinuing ACEis/ARBs improves outcomes. At this time, we believe with a disease as complex as COVID-19, such with multiple immuno pathophysiologic processes occurring simultaneously, that a simplistic model of just drug – receptor – virus is now obviously grossly inadequate to account for medication effects in the natural and clinical history of infection. Further teasing out the theoretical/biological relationship is likely a question only answerable with basic science, with a limited role for further prospective clinical studies.

RCT citations:
Cohen JB, Hanff TC, William P, et al. Continuation versus discontinuation of renin–angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial. The Lancet Respiratory Medicine 2021;9(3):275-84. doi: 10.1016/S2213-2600(20)30558-0

Lopes RD, Macedo AVS, Silva PGMdBE, et al. Effect of Discontinuing vs Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on Days Alive and Out of the Hospital in Patients Admitted With COVID-19: A Randomized Clinical Trial. JAMA 2021;325(3):254-64. doi: 10.1001/JAMA.2020.25864

"3. Patients with RAS inhibitors than other HTN meds may have a higher risk of clinical outcomes in this study. Authors have controlled with adjustment in analysis, but I am not sure the adjustment was performed enough. In discussion, hope to mention this more clearly."
Answer: Thank you for your comment. We added a statement in the Limitations to clarify about the possibility of residual confounding.

VERSION 2 – REVIEW

REVIEWER	Lee, Sukhyang Ajou Univ
REVIEW RETURNED	03-May-2022

GENERAL COMMENTS	For the observational study using the data warehouse, confounding factors such as co-morbidities would give change in results of the study without control. The patients with RASi might have more comorbidities. In this study, the distribution of comorbidity was comparable among the groups with the RAS inhibitors and without the RAS inhibitors. The clinical outcomes presented the coefficient estimates and risk ratio of marginal effects. The interpretation would be more clinically oriented for the parameters. The design of the study was appropriate to compare 3 years with 2017/18 baseline, the medication groups of HTN medication.