PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A Prospective Meta-Analysis Protocol on Randomised Trials of Renin-Angiotensin System Inhibitors in Patients with Coronavirus Disease 2019 (COVID-19): An initiative of the International Society of Hypertension.
AUTHORS	Gnanenthiran, Sonali; Borghi, Claudio; Burger, Dylan; Charchar, Fadi; Poulter, Neil; Schlaich, Markus P.; Steckelings, Ulrike; Stergiou, George; Tomaszewski, Maciej; Unger, Thomas; Wainford, Richard; Williams, Bryan; Rodgers, Anthony; Schutte, Aletta

VERSION 1 – REVIEW

REVIEWER	Antonia Anna Lukito, MD, PhD Department of Cardiovascular, Pelita Harapan University/Siloam Hospital Lippo Village Tangerang, Indonesia
REVIEW RETURNED	23-Aug-2020

GENERAL COMMENTS	Suggestion for the authors: The reason or background to initiate an ACEi/ARB for the patient who are naive to ACEi/ARB in each trial should be described thoroughly.

REVIEWER	Andrew M. South, MD, MS Wake Forest School of Medicine, United States
REVIEW RETURNED	08-Sep-2020

GENERAL COMMENTS	Thank you for submitting this very interesting protocol that proposes to investigate an important topic. Overall, I believe that you clearly stated the rationale for the study and the objective. I have a few major concerns that need to be addressed and which will greatly improve the manuscript and proposed study. Special attention to various sources of potential bias, even for a randomized controlled trial and a meta-analysis, must be acknowledged, even if they cannot be fully mitigated. General points: 1. Please use appropriate and consistent terminology throughout, e.g., remove the hyphen from between “angiotensin-system” and “coronavirus” and “2”; and insert a hyphen between “angiotensin” and “converting”. It is “coronavirus disease 2019”. Please define the abbreviation, “ACE2”. 2. Please be consistent with the definition for RCT - clinical or controlled? 3. For authors’ initials, please be consistent with either “AS” or “AES”.

	Abstract: Overall it is written clearly and succinctly. I do not believe that your sub-group analyses (i.e., stratification) are truly sensitivity analyses, so please rephrase. See further points below about the choice of this method. Introduction: 1. I recommend that you use patient-centric language, including "patients with COVID-19" rather than "COVID-19 patients" and "kidney" rather than "renal" when referring to kidney function or kidney disease. 2. Clarify the sentence, "cornerstones of cardiovascular…", because as it is written, "such as" refers to the therapies, not the diseases. 3. Throughout the manuscript, you must make the distinction between SARS-CoV-2 infection and COVID-19; they are distinct outcomes. 4. I suggest rewriting the latter half of paragraph one so that it is more concise, flows more logically, and is more consistent with the underlying pathophysiology. Your sentence, "Animal studies have demonstrated…" belongs with the preceding sentence, "ACEi/ARB therapies may upregulate…" 5. "COVID-19 disease" is redundant; remove "disease". 6. Further qualify your statement as "with limited evidence of possible protective benefits". 7. I think it would be helpful to add a sentence to better transition from observational studies to RCTs, such as that observational studies, even rigorous ones, still have multiple sources of bias, which RCTs help mitigate. 8. Rewrite as "However, to date reliable data from randomised controlled clinical trials…" 9. Include nephrology societies as well. 10. Rewrite the sentence, "are necessary to ensure…" for clarity. 11. The sentence, "Given the uncertainty…", is out of place. Rewrite this paragraph for a more logical and concise progression. 12. I suggest that you break up the second paragraph into two paragraphs. It would be helpful to better justify your study and highlight its novelty. There are already several planned meta-analyses on this topic from international investigators. Your reasoning is too generalized; there are important distinctions among these RCTs, including the patient populations from which they are recruiting, and it's not simply "ACEi/ARB vs. no ACEi/ARB". This is a major source of numerous types of bias, not only for observational studies but also RCTs and meta-analyses. You must identify and acknowledge these limitations, because just performing a meta-analysis will not mitigate these sources of bias or even identify them. In addition, in the text and in Table 2, you should identify the specific medical conditions for which ACEi/ARB are prescribed. I.e., most RCTs are recruiting patients with hypertension. 13. I think it would be helpful if you justify your statement about bias from retrospective meta-analyses with citations. Objectives: 1. To my major point, you must be more specific about from which patient populations your included RCTs are drawing. Infection with SARS-CoV-2 and development of COVID-19 are two distinct outcomes and hence these patient populations will be different. The ongoing RCTs thus draw from several distinct groups, and you must make these distinctions a priori throughout your manuscript and your analytic plan. 2. See my comments below about your stratification plan.

	Methods: 1. As I have noted, excluding observational studies lessens but does not minimize bias; please acknowledge. 2. Please be more specific regarding criteria for determining SARS-CoV-2 infection. 3. Please note the limitation of assuming ACEi and ARB are the same, as well as not accounting for within-class differences. 4. Your discretionary exclusion criteria present a potential loophole to introduce/enhance bias. Please note this limitation and consider a few of your own criteria to apply. 5. I strongly suggest requiring a minimum follow-up period such as 28 or 30 days. It would introduce bias to include studies which only go for 14 or 28 days, while allowing for up to 30 days for the rest. 6. Throughout the manuscript, you have not discussed or accounted for the underlying indication for medication treatment, i.e., the majority of these studies are recruiting patients with hypertension. This is a source of potential bias and limits generalizability, even for an RCT or meta-analysis. Please acknowledge and address. 7. I am pleased that you will account for cessation/continuation vs. de novo treatment. However, caution must be taken by assuming that discontinuation of one's ACEi/ARB is equivalent to a control group. In those RCTs, this is in fact the intervention. Again, this introduces potential for bias, but you do not address this possibility. 8. I strongly suggest assessing the secondary outcome, acute kidney injury. This is a very relevant end point in this context, and, combined with hypotension and hyperkalemia, are major indications to stop ACEi/ARB and thus are causes of a participant leaving the RCT or switching to your "control" designation. 9. Similarly, can you address intention to treat? I suspect this will be a major consideration in these RCTs. 10. Please define abbreviations at first use of the full term (e.g., CKD, and, in the "Implications of the review" section, be consistent when abbreviating ACE inhibitors). 11. As I have mentioned, you are not performing sensitivity analyses but rather just stratifying your results. This implies that you are considering these factors (e.g., age) to be effect-modifying factors rather than confounding factors, mediators, etc. You should acknowledge this as a source of bias, even for RCTs and meta-analyses. If this is your approach, will you be objectively assessing for effect modification, for instance estimating interaction terms? 12. Please be more specific about how you are defining your covariates. Will you make the distinction between patient-reported conditions vs. trial-confirmed diagnoses? For example, how will CKD actually be defined? Only by patient report, or will the trial have to measure creatinine and estimate GFR? Similar with CVD. For smoking status, what about current-smoking status? 13. Can you provide a citation to justify your ethnicity groups? Many of these values are better classified as race rather than ethnicity. What would a patient who identifies as African-American be classified as? Patients who identify as Hispanic? Similarly, justify the classification of geographic region with a citation. 14. You should list hospitalization as a secondary outcome in the Methods, rather than only in Table 1. 15. Please clarify - 5 continuation trials + 15 initiation trials sums to 20, not 19. 16. For the statistical analysis, please state when you will use logistic regression models. Can you provide more detail about the meta-regression? 17. Please remove "risk" from the sentence, "A two-tailed p-value

	risk of 5%". 18. Can you be more clear about whether you are estimating effect sizes using multivariable models and if so, how will you determine which potentially confounding factors to include, and how will you incorporate them? References: 1. Ensure that all references are formatted properly and consistently, according to journal guidelines. For example, several citations are missing the semicolon between year and volume (see ref. #1 and 4). 2. Be consistent with capitalization of article titles; use either sentence case or title case (see ref. #2). 3. Remove "and" from author lists (see ref. #5). 4. Please confirm that ref. #8 is an appropriate choice. 5. Please provide DOI for e-published studies (e.g., ref. #11). 6. Be consistent with length of listed author names and use of 'et al'. 7. For web pages, please close the "available from" brackets and consistently report access dates (see ref. 19-21). 8. Ref. 18 is incomplete. Tables/Figures/Supplemental Material: 1. Figure 1: Should the bottom-right panel instead point to the "Investigators will be invited" panel? Or will additionally identified study authors not be invited? 2. Table 1: As I stated earlier, it is inappropriate and misleading to label these groups as "Control" and "Intervention". It appears this table is incomplete - you are missing CVD and COPD from the Past Medical History section. Please be complete and thorough. Will investigators report treatment failure or assignment switch? Shouldn't this be included in Table 1? 3. Table 2 is nice but is too busy. Please make it more concise and visually appealing. 4. Supplementary tables - Is there a reason that you did not list each subgroup that you mention in the Methods?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

The reason or background to initiate an ACEi/ARB for the patient who are naive to ACEi/ARB in each trial should be described thoroughly.

Thanks for this comment. Based on the inclusion criteria of trials into this meta-analysis, the reason to initiate an ACEi/ARB in patients who are naive to ACEi/ARB in each trial is to assess the safety and efficacy of therapy in those with COVID-19 infection. In our main paper where we present our meta-analysis results, we will report the inclusion criteria of each trial in the supplement.

Reviewer: 2

Thank you for submitting this very interesting protocol that proposes to investigate an important topic. Overall, I believe that you clearly stated the rationale for the study and the objective. I have a few major concerns that need to be addressed and which will greatly improve the manuscript and proposed study. Special attention to various sources of potential bias, even for a randomized controlled trial and a meta-analysis, must be acknowledged, even if they cannot be fully mitigated.

General points:

1. Please use appropriate and consistent terminology throughout, e.g., remove the hyphen from between “angiotensin-system” and “coronavirus” and “2”; and insert a hyphen between “angiotensin” and “converting”. It is “coronavirus disease 2019”. Please define the abbreviation, “ACE2”.

Thank you for your comments. We have made the requested changes.

2. Please be consistent with the definition for RCT - clinical or controlled?

Thank you for your comments. We have used ‘controlled’ throughout.

3. For authors’ initials, please be consistent with either “AS” or “AES”.

Thank you for your comments. We have made the requested changes.

Abstract:
Overall it is written clearly and succinctly. I do not believe that your sub-group analyses (i.e., stratification) are truly sensitivity analyses, so please rephrase. See further points below about the choice of this method.

Thank you for this point. We have addressed this as follows:
“Pre-specified subgroup analyses will assess the effect of sex; age; comorbidities; smoking status; ethnicity; country of origin on all-cause mortality.” (page 2, paragraph 2, line 7)

Introduction:
1. I recommend that you use patient-centric language, including “patients with COVID-19” rather than “COVID-19 patients” and “kidney” rather than “renal” when referring to kidney function or kidney disease.

We have made the requested changes.

2. Clarify the sentence, “cornerstones of cardiovascular…”, because as it is written, “such as” refers to the therapies, not the diseases.

We have amended this to “ACEi/ARB therapy are not only first line agents for the treatment of hypertension, but are also the cornerstones of treating cardiovascular and kidney disease such as heart failure, coronary heart disease, diabetes and chronic kidney disease.” (page 5, paragraph 1, lines 5-6)

3. Throughout the manuscript, you must make the distinction between SARS-CoV-2 infection and COVID-19; they are distinct outcomes.

This is a good point. We have ensured throughout the manuscript that these terms are used correctly – referring to either the infection or the disease, as appropriate.

4. I suggest rewriting the latter half of paragraph one so that it is more concise, flows more logically, and is more consistent with the underlying pathophysiology. Your sentence, “Animal studies have demonstrated…” belongs with the preceding sentence, “ACEi/ARB therapies may upregulate…”

Thank you for your comment. We have amended this to:
‘’Animal studies have demonstrated that ACEi/ARB therapy may upregulate ACE2 receptor expression and produce increased cardiac ACE2 mRNA levels, which may promote viral cell invasion.’’ (page 5, paragraph 1, lines 12-14)

5. “COVID-19 disease” is redundant; remove “disease”.

We have made the requested change.

6. Further qualify your statement as “with limited evidence of possible protective benefits”.

We have amended this to:

''Observational retrospective studies in humans suggest that there is no adverse effect of RAS blockade on COVID-19 severity and outcome, but there may be possible protective benefits including reduced rates of mortality, critical disease and admission to intensive care.'' (page 5, paragraph 2, lines 1-3)

7. I think it would be helpful to add a sentence to better transition from observational studies to RCTs, such as that observational studies, even rigorous ones, still have multiple sources of bias, which RCTs help mitigate.

We have amended this to:
''Observational studies, even rigorous ones, can still have multiple sources of bias, and thus randomised controlled trials (RCTs) are needed to mitigate this risk.'' (page 6, paragraph 1, lines 1-4)

8. Rewrite as "However, to date reliable data from randomised controlled clinical trials…"

We have amended this to:
''However, reliable data from randomised controlled clinical trials are unavailable to guide clinical decision-making.'' (page 6, paragraph 1, lines 4-6)

9. Include nephrology societies as well.

Thank you for your comment. We have included nephrology societies as well and amended the text to:
"International hypertension, cardiovascular and nephrology societies have consistently recommended that patients continue ACEi/ARB therapy during the COVID-19 pandemic, on the basis of the strong and well-documented evidence on their protective effects, but identify a need for more reliable human data" (page 6, paragraph 2, lines 1-2)

10. Rewrite the sentence, "are necessary to ensure…" for clarity.

We have amended this to: "There are multiple RCTs in process, which will better inform clinical decision making rather than relying on observational human studies" (page 6, paragraph 2, lines 4-6)

11. The sentence, "Given the uncertainty…", is out of place. Rewrite this paragraph for a more logical and concise progression.

We have amended the wording and flow of the paragraph.
'Given the uncertainty of ACEi/ARB use in those with COVID-19, some trials are starting ACEi/ARB therapy for possible benefit, while other trials are stopping the same therapy due to concerns about harm. A prospective meta-analysis led by the International Society of Hypertension will therefore be an ideal approach to address these limitations, as well as promoting international collaboration. This approach entails studies to be identified, evaluated, and determined to be eligible before the results of any included studies are known or published, thereby avoiding some of the potential biases inherent in standard, retrospective meta-analyses.'' (page 6, paragraph 2, lines 11-20)

12. There are already several planned meta-analyses on this topic from international investigators. Your reasoning is too generalized; there are important distinctions among these RCTs, including the patient populations from which they are recruiting, and it's not simply "ACEi/ARB vs. no ACEi/ARB". This is a major source of numerous types of bias, not only for observational studies but also RCTs and meta-analyses. You must identify and acknowledge these limitations, because just performing a meta-analysis will not mitigate these sources of bias or even identify them. In addition, in the text and in Table 2, you should identify the specific medical conditions for which ACEi/ARB are prescribed. I.e., most RCTs are recruiting patients with hypertension.

Thank you for your comments. The inclusion criteria of the trials unfortunately do not discriminate between those on ACEi/ARB therapy for hypertension, cardiovascular or renal disease, but we intend to perform subgroup analyses as stated in Supplemental Tables 1 and 2 if this data is available.

13. I think it would be helpful if you justify your statement about bias from retrospective meta-analyses with citations.

Thank you for your comments. We have amended the manuscript to
"Observational retrospective studies in humans and meta-analyses of these studies suggest that there is no adverse effect of RAS blockade on COVID-19 severity and outcome, but there may be possible protective benefits including reduced rates of mortality, critical disease and admission to intensive care. Observational studies, even rigorous ones, can still have multiple sources of bias, and thus are insufficient for sound clinical decision making." (page 5, paragraph 2, lines 1-3)

Objectives:
1. To my major point, you must be more specific about from which patient populations your included RCTs are drawing. Infection with SARS-CoV-2 and development of COVID-19 are two distinct outcomes and hence these patient populations will be different. The ongoing RCTs thus draw from several distinct groups, and you must make these distinctions a priori throughout your manuscript and your analytic plan.

We agree that the patient population is a very important aspect in this context. However, in the main meta-analyses, all trials will be grouped together. The trials unfortunately do not all clearly discriminate between SARS-CoV-2 infection and development of COVID-19, but currently all trials include symptomatic patients (mostly hospitalised patients) suggesting actual development of COVID-19. If this data is available, we will perform a subgroup analysis to differentiate asymptomatic and symptomatic clinical status. Similarly, the trials also do not discriminate between those on ACEi/ARB therapy for hypertension, cardiovascular or renal disease, but we intend to perform subgroup analyses as stated in Supplemental Tables 1 and 2.

2. See my comments below about your stratification plan.

Methods:
1. As I have noted, excluding observational studies lessens but does not minimize bias; please acknowledge.

This is indeed true. We have included this on page 6, paragraph 2, lines 15-16.
"These RCTs are not completely free from bias, but nevertheless represent a higher quality of evidence than observational studies."

2. Please be more specific regarding criteria for determining SARS-CoV-2 infection.

Criteria for determining SARS-CoV-2 infection is dependent on the trial, with some trials stating diagnosis of " SARS-CoV-2 on any biological sample with any detection method" or just ''verified COVID-19' or 'laboratory confirmed infection with SARS-CoV-2'. We have amended our inclusion criteria to best reflect this
"(iii) laboratory confirmed SARS-CoV-2 infection" (page 7, paragraph 4, line 3)

3. Please note the limitation of assuming ACEi and ARB are the same, as well as not accounting for within-class differences.

We agree with this, and aim to perform an analysis looking at ACEi vs ARB therapy if feasible.
We have amended the text to
''viii) ACEi and ARB separately if feasible as pooling ACEi and ARB together does not account for within-class differences.'' (page 9, paragraph 2, line 16)

4. Your discretionary exclusion criteria present a potential loophole to introduce/enhance bias. Please note this limitation and consider a few of your own criteria to apply.

We prefer to be inclusive and perform subgroup analyses given the trials are mostly small and unlikely to meet recruitment targets. We certainly note that this is a limitation. Once we have gained access to the data from trials contributing data, we will be very critical in how data from all trials are included and compared in the total and sub group analyses.

5. I strongly suggest requiring a minimum follow-up period such as 28 or 30 days. It would introduce bias to include studies which only go for 14 or 28 days, while allowing for up to 30 days for the rest.

The minimum follow-up period in the short term has been specified to 14-30 days dependent on data availability in order to be inclusive. However, a sensitivity analysis will be performed in those trials who only have final follow up of only 14 days. Again, this is a measure to be as inclusive as possible, but keeping the option open to be highly critical on whether to inclde the data if numbers are very low.

6. Throughout the manuscript, you have not discussed or accounted for the underlying indication for medication treatment, i.e., the majority of these studies are recruiting patients with hypertension. This is a source of potential bias and limits generalizability, even for an RCT or meta-analysis. Please acknowledge and address.

As mentioned above, the trials do not discriminate between those on ACEi/ARB therapy for hypertension, cardiovascular or renal disease, but we intend to perform subgroup analyses of as stated in Supplemental Tables 1 and 2 in order to differentiate between the groups. This is certainly a limitation of the trials under way and we have acknowledged this.
"There is heterogeneity in trial inclusion criteria, which may affect the meta-analysis findings and cause bias." (page 9, paragraph 2, lines 1-2)

7. I am pleased that you will account for cessation/continuation vs. de novo treatment. However, caution must be taken by assuming that discontinuation of one's ACEi/ARB is equivalent to a control group. In those RCTs, this is in fact the intervention. Again, this introduces potential for bias, but you do not address this possibility.

Yes, we agree that this can include bias. As stated, we will analyse these trials separately in the subgroup analysis
"vii) trial type: randomised trials that investigate continuation and cessation of ACEi/ARBs among patients currently treated with ACEi/ARBs, versus trials that investigate initiation of ACEi/ARBs in those not currently treated with such therapies compared to control" (page 9, paragraph 2, line 11)

8. I strongly suggest assessing the secondary outcome, acute kidney injury. This is a very relevant end point in this context, and, combined with hypotension and hyperkalemia, are major indications to stop ACEi/ARB and thus are causes of a participant leaving the RCT or switching to your "control" designation.

Thank you for your thoughtful comments. We have added this as a secondary outcome.

9. Similarly, can you address intention to treat? I suspect this will be a major consideration in these RCTs.

Randomised trials are generally performed on an intention to treat basis, and the meta-analysis will also reflect this.
"Studies must contain sufficient detail and be able to provide at least one outcome outlined within our data extraction form (Table 1) and be reported using an intention to treat basis." (page 8, paragraph 2, line 7)

10. Please define abbreviations at first use of the full term (e.g., CKD, and, in the "Implications of the review" section, be consistent when abbreviating ACE inhibitors).

We have amended this.

11. As I have mentioned, you are not performing sensitivity analyses but rather just stratifying your results. This implies that you are considering these factors (e.g., age) to be effect-modifying factors rather than confounding factors, mediators, etc. You should acknowledge this as a source of bias, even for RCTs and meta-analyses. If this is your approach, will you be objectively assessing for effect modification, for instance estimating interaction terms?

We have rephrased our wording to describe our stratification as 'subgroup analysis'. The analysis of effect modification and interaction terms will not be possible in this meta-analysis as we will only be obtaining grouped data rather than individual patient data.

12. Please be more specific about how you are defining your covariates. Will you make the distinction between patient-reported conditions vs. trial-confirmed diagnoses? For example, how will CKD actually be defined? Only by patient report, or will the trial have to measure creatinine and estimate GFR? Similar with CVD. For smoking status, what about current-smoking status?

These terms will reflect the individual trials and will be part of our assessment of trial methodology quality. Trials with patient reported conditions vs trial confirmed diagnosis will be given a lower rating and thus have a lower weighting in the meta-analyses as is standard meta-analysis practice.

13. Can you provide a citation to justify your ethnicity groups? Many of these values are better classified as race rather than ethnicity. What would a patient who identifies as African-American be classified as? Patients who identify as Hispanic? Similarly, justify the classification of geographic region with a citation.

The ethnic groups will be classified as done and reported within each trial – likely based on the patient's self-identification of ethnicity or race. Trial investigators will judge participants according to these terms and data will be provided if available.

14. You should list hospitalization as a secondary outcome in the Methods, rather than only in Table 1.

Thank you, we have amended this.

15. Please clarify - 5 continuation trials + 15 initiation trials sums to 20, not 19.

Thank you, we have amended this.

16. For the statistical analysis, please state when you will use logistic regression models. Can you provide more detail about the meta-regression?

We are not using individual patient data and will not be able to perform standard logistic regression. We will require each trialist to report and submit tabular data to us as per Table 1, Supplemental Tables 1 and 2. The metaregression performed will depend on the findings of the initial meta-analysis and if there is considerable residual heterogeneity.

17. Please remove "risk" from the sentence, "A two-tailed p-value risk of 5%".

Thank you, we have amended this.

18. Can you be more clear about whether you are estimating effect sizes using multivariable models and if so, how will you determine which potentially confounding factors to include, and how will you incorporate them?

We will not use individual patient data and will not be able to perform this.

References:
1. Ensure that all references are formatted properly and consistently, according to journal guidelines. For example, several citations are missing the semicolon between year and volume (see ref. #1 and 4).

Thank you. We have amended this.

2. Be consistent with capitalization of article titles; use either sentence case or title case (see ref. #2).

Thank you. We have amended this.

3. Remove “and” from author lists (see ref. #5).
Thank you. We have amended this.

4. Please confirm that ref. #8 is an appropriate choice.

Yes.

5. Please provide DOI for e-published studies (e.g., ref. #11).

Thank you. We have amended this.

6. Be consistent with length of listed author names and use of ‘et al’.

Thank you. We have amended this.

7. For web pages, please close the “available from” brackets and consistently report access dates (see ref. 19-21).

Thank you. We have amended this.

8. Ref. 18 is incomplete.

Thank you. We have amended this.

Tables/Figures/Supplemental Material:
1. Figure 1: Should the bottom-right panel instead point to the “Investigators will be invited” panel? Or will additionally identified study authors not be invited?

Additionally identified trial authors whose main paper is already published will not be invited to be authors unless supplemental data is provided.

2. Table 1: As I stated earlier, it is inappropriate and misleading to label these groups as “Control” and “Intervention”. It appears this table is incomplete - you are missing CVD and COPD from the Past Medical History section. Please be complete and thorough. Will investigators report treatment failure or assignment switch? Shouldn’t this be included in Table 1?

Thank you. We have amended this. Trials will be reported on an intention to treat basis as per standard RCT practice. Treatment failure and assignment switch will not be specifically recorded and rather be analysed according to intention to treat.

3. Table 2 is nice but is too busy. Please make it more concise and visually appealing.

We have simplified this table.

4. Supplementary tables - Is there a reason that you did not list each subgroup that you mention in the Methods?

The supplemental tables merely list data that is requested from the trial investigators. The other subgroup analysis that are not listed are at a trial level (e.g. trial type and hospitalisation status) and thus this is not needed from the investigators.

VERSION 2 – REVIEW

REVIEWER	Andrew M. South, MD, MS Department of Pediatrics, Section of Nephrology, Wake Forest School of Medicine, USA
REVIEW RETURNED	12-Nov-2020

GENERAL COMMENTS	Thank you for your revised manuscript. You were moderately receptive to my prior comments. I believe that the manuscript is acceptable for publication, pending resolution of a few outstanding and necessary edits as documented below. Best of luck with your endeavor - I look forward to seeing the results. In the title, please use the appropriate term, "coronavirus disease 2019", as you have in the rest of the manuscript. In the first paragraph of the Introduction, please remove the hyphen preceding the "2" and use the term, "severe acute respiratory syndrome coronavirus 2", as previously requested. Please be more specific with the sentence "to enter the lungs" and replace with something like "to infect epithelial cells in the respiratory tract". Delete "ACEi/ARB therapies". Introduction, second paragraph: data from observational studies are not necessarily "insufficient for sound clinical decision making", so please rephrase. Introduction, third paragraph: change "renal" to "kidney". Methods: "These are essentially the same randomisations" is not accurate enough and does not address adequately my prior comment. Please rephrase and temper your language to acknowledge that they are fundamentally distinct. For example, as has been demonstrated in human and experimental studies, duration of ACEi/ARB therapy (i.e., acute vs. chronic) has a significant effect on potential alterations to ACE2 expression. This is an example of why it is important to have an adequate understanding of the complex nature of the renin-angiotensin system and specifically the ACE2/angiotensin-(1-7) pathway. Methods: "pooling ACEi and ARB together does not account for within-class differences" should be changed to "between-class differences"; ACEi and ARB are separate drug classes. Within-class differences would, for example, be lisinopril vs. enalapril. Methods: the statistical analysis section remains brief; I suggest providing sufficient detail as previously requested. It is important to acknowledge adequately the limitations of the RCTs and thus of your meta-analysis, especially if you cannot mitigate those limitations that are out of your control. Please briefly acknowledge those limitations and potential sources of bias that I mentioned in my previous review. Table 1: please replace "renal" with "kidney" in the footnote. The definition of AKI you provided is inadequate; I suggest either defining it yourself via established guidelines (i.e., KDIGO), or simply stating that you will report the definition of each individual RCT, as this is your preferred method for outcome and covariate determination. Table 2: you can remove "BP, blood pressure" from the footnote, as I do not see that you use this abbreviation in the table. Supplemental files: please make the previously requested edits to these files too. For example, adding the hyphen to "angiotensin-converting".

VERSION 2 – AUTHOR RESPONSE

Reviewer 2:

Thank you for your revised manuscript. You were moderately receptive to my prior comments. I believe that the manuscript is acceptable for publication, pending resolution of a few outstanding and

necessary edits as documented below. Best of luck with your endeavor - I look forward to seeing the results.

In the title, please use the appropriate term, "coronavirus disease 2019", as you have in the rest of the manuscript.

Thank you for your comments. We have amended the title as requested.

In the first paragraph of the Introduction, please remove the hyphen preceding the "2" and use the term, "severe acute respiratory syndrome coronavirus 2", as previously requested.

We have changed the introduction as requested

Please be more specific with the sentence "to enter the lungs" and replace with something like "to infect epithelial cells in the respiratory tract".

We have changed the sentence as requested

Introduction, second paragraph: data from observational studies are not necessarily "insufficient for sound clinical decision making", so please rephrase.

We have rephrased this to:
''Observational studies, even rigorous ones, can still have multiple sources of bias, and thus more robust evidence is needed for sound clinical decision making'' (page 5, paragraph 2, line 5)

Introduction, third paragraph: change "renal" to "kidney".

We have made the required change as requested

Methods: "These are essentially the same randomisations" is not accurate enough and does not address adequately my prior comment. Please rephrase and temper your language to acknowledge that they are fundamentally distinct. For example, as has been demonstrated in human and experimental studies, duration of ACEi/ARB therapy (i.e., acute vs. chronic) has a significant effect on potential alterations to ACE2 expression. This is an example of why it is important to have an adequate understanding of the complex nature of the renin-angiotensin system and specifically the ACE2/angiotensin-(1-7) pathway.

We have amended this to:
These will be pooled in an ACEi/ARB vs. no ACEi/ARB meta-analysis, with appropriate prespecification of preplanned sensitivity analyses from the two groups of trials given the fundamental differences. (page 8, paragraph 1, lines 1-4)

Methods: "pooling ACEi and ARB together does not account for within-class differences" should be changed to "between-class differences"; ACEi and ARB are separate drug classes. Within-class differences would, for example, be lisinopril vs. enalapril.

We have made the required change as requested

Methods: the statistical analysis section remains brief; I suggest providing sufficient detail as previously requested.

We have added further detail as requested
'If heterogeneity is found, we will attempt to determine potential reasons by examining characteristics of individual trials. Potential outliers will be investigated in a sensitivity analysis by dropping each study at a time.' (page 11, paragraph 3, lines 8-10)

'There is potential heterogeneity in trial inclusion criteria, which may affect the meta-analysis findings and be a source of bias. Therefore, subgroup analyses will be performed depending on data availability to explore differences in effects by partitioning by study-level categorical covariates. We will aim to assess all-cause mortality at ≤30 days and >1 month based on the following stratifications:

(i) sex: male versus female; (ii) age: <60 years versus ≥60 years; (iii) comorbidities: hypertension versus no hypertension, diabetes versus no diabetes, chronic kidney disease (CKD) defined as eGFR<60 mL/min/1.73m^2 versus no CKD, cardiovascular disease (CVD) [defined as established coronary artery disease, heart failure, arrythmia and/or stroke] versus no CVD, chronic obstructive pulmonary disease versus no chronic obstructive pulmonary disease; (iv) smoking status: ever smoked versus non-smokers; (v) hospitalisation status: hospitalised versus non-hospitalised patients; (vi) ethnicity: White, South-East/East Asian, South Asian, African and Other; (vii) trial type: randomised trials that investigate continuation and cessation of ACEi/ARBs among patients currently treated with ACEi/ARBs, versus trials that investigate initiation of ACEi/ARBs in those not currently treated with such therapies compared to control; (vii) region: Americas, Europe, Africa, South and West Asia/Middle East, and North Asia/South-East Asia/Oceania; (viii) ACEi and ARB separately if feasible as pooling ACEi and ARB together does not account for between-class differences.; (ix) follow-up period: final short term follow-up 14 days compared to final follow-up at 28-30 days; (x) asymptomatic vs symptomatic clinical status (Supplemental Tables 2 and 3).' (page 12, paragraph 2, lines 1-16)

It is important to acknowledge adequately the limitations of the RCTs and thus of your meta-analysis, especially if you cannot mitigate those limitations that are out of your control. Please briefly acknowledge those limitations and potential sources of bias that I mentioned in my previous review.

Thank you for your comments. We have added the following to the manuscript:
''Limitations
Limitations of our meta-analysis reflect the limitations of the included RCTs, and are outside the control of our planned analyses. We have attempted to be inclusive as possible and aim to perform subgroup analyses given the trials are mostly small and may not be powered for such analyses. Key limitations include the relatively short duration of included trials (most ≤30 days), which prevented robust assessment of long-term outcomes such as cardiovascular events and overall mortality. Additionally, the majority of patients on ACEi/ARBs will likely be on such therapy to treat hypertension (although this has not been specified in the inclusion trials of the eligible RCTs) and the generalisability of our findings to cardiac failure and renal disease may be uncertain if there are insufficient numbers.'' (page 12, paragraph 3, lines 1-10)

Table 1: please replace "renal" with "kidney" in the footnote. The definition of AKI you provided is inadequate; I suggest either defining it yourself via established guidelines (i.e., KDIGO), or simply stating that you will report the definition of each individual RCT, as this is your preferred method for outcome and covariate determination.

We have made the required change as requested. Yes, acute kidney injury will be defined as per each individual RCT. The manuscript has been amended to reflect this. (page 8, paragraph 3, line 6)

Table 2: you can remove "BP, blood pressure" from the footnote, as I do not see that you use this abbreviation in the table.

We have made the required change as requested

Supplemental files: please make the previously requested edits to these files too. For example, adding the hyphen to "angiotensin-converting".

We have made the changes as requested.