SYSTEMATIC REVIEW AND META-ANALYSIS

Renin-Angiotensin Aldosterone System Inhibitors and COVID-19: A Systematic Review and Meta-Analysis Revealing Critical Bias Across a Body of Observational Research

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BACKGROUND: Renin-angiotensin aldosterone system (RAAS) inhibitor—COVID-19 studies, observational in design, appear to use biased methods that can distort the interaction between RAAS inhibitor use and COVID-19 risk. This study assessed the extent of bias in that research and reevaluated RAAS inhibitor—COVID-19 associations in studies without critical risk of bias.

METHODS AND RESULTS: Searches were performed in MEDLINE, EMBASE, and CINAHL databases (December 1, 2019 to October 21, 2021) identifying studies that compared the risk of infection and/or severe COVID-19 outcomes between those using or not using RAAS inhibitors (ie, angiotensin-converting enzyme inhibitors or angiotensin II type-I receptor blockers). Weighted hazard ratios (HR) and 95% CIs were extracted and pooled in fixed-effects meta-analyses, only from studies without critical risk of bias that assessed severe COVID-19 outcomes. Of 169 relevant studies, 164 had critical risks of bias and were excluded. Ultimately, only two studies presented data relevant to the meta-analysis. In 1 351 633 people with uncomplicated hypertension using a RAAS inhibitor, calcium channel blocker, or thiazide diuretic in monotherapy, the risk of hospitalization (angiotensin-converting enzyme inhibitor: HR, 0.76; 95% CI, 0.66–0.87; \( P < 0.001 \); angiotensin II type-I receptor blockers: HR, 0.86; 95% CI, 0.77–0.97; \( P = 0.015 \)) and intubation or death (angiotensin-converting enzyme inhibitor: HR, 0.64; 95% CI, 0.48–0.85; \( P = 0.002 \); angiotensin II type-I receptor blockers: HR, 0.74; 95% CI, 0.58–0.95; \( P = 0.019 \)) with COVID-19 was lower in those using a RAAS inhibitor. However, these protective effects are probably not clinically relevant.

CONCLUSIONS: This study reveals the critical risk of bias that exists across almost an entire body of COVID-19 research, raising an important question: Were research methods and/or peer-review processes temporarily weakened during the surge of COVID-19 research or is this lack of rigor a systemic problem that also exists outside pandemic-based research?

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Since it was found that SARS-CoV-2 gains entry into human cells via angiotensin-converting enzyme (ACE) 2,1 there has been an inundation of research evaluating if the use of renin-angiotensin aldosterone system (RAAS) inhibitors increases the risk of a SARS-CoV-2 infection and/or severe COVID-19 outcomes. Those studies, predominantly observational in design, were driven by the notion that RAAS...
inhibitors, such as ACE inhibitors and or angiotensin II type-I receptor blockers (ARBs), may upregulate the expression of ACE2.2–4 As the pandemic progressed, however, it became evident that, like a lot of COVID-19 research, many RAAS inhibitor—COVID-19 studies have suffered from the speed at which they were conducted;5 often using nonrepresentative samples where the risk of selection (ie, collider) bias is increased.6 At least 52 meta-analyses have assessed associations between RAAS inhibitor use and COVID-19 risk by collating parts of that body of research.7–58 However, little attention has been paid to selection bias, or other biases for that matter, which may distort the interaction between RAAS inhibitor use and COVID-19.

Given the sheer volume of previous research, it is understandable if the appeal of additional RAAS inhibitor—COVID-19 studies may be subsiding. However, in the interest of improving the methods used in observational research and, subsequently, enhancing its value, there is an urgent need to review how the scientific community has attempted to address this issue; to what extent does bias exist across that body of RAAS inhibitor—COVID-19 research and does that bias significantly distort the interaction between RAAS inhibitor use and COVID-19 risk? Accordingly, this study retested the hypothesis that RAAS inhibitor use is associated with important, severe COVID-19 outcomes, using only data from observational studies without critical risk of bias.

METHODS

The data that support the findings of this study are available within the article. The protocol of this systematic review and meta-analysis was registered on PROSPERO (Registration number: CRD42021237859) before the study commenced and is available in full on the National Institute for Health Research International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/PROSPERO). This study was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (Table S1).

Data Sources and Searches

Systematic searches were performed in MEDLINE, EMBASE, and CINAHL databases from December 1, 2019, near to when the first case of SARS-CoV-2 was identified, until October 21, 2021. A combination of subject headings for COVID-19 and RAAS inhibitors was used (Table S2). Searches were limited to “human” studies only. A manual search of the citations included in identified reviews and articles selected for full-text retrieval was also performed.

Study Selection, Inclusion and Exclusion Criteria

Two investigators (J. L. and F. C. T.) independently performed study selection using Covidence, an online, Cochrane approved, software designed for conducting systematic reviews.59 Discrepancies in inclusion or exclusion were solved through consultation with a third
investigator (J. S.). To address the risk of bias in all observational studies of RAAS inhibitor—COVID-19 associations, the systematic review initially identified studies that compared the risk of infection with COVID-19 and/or severe COVID-19 outcomes (eg, hospitalization, admission to an intensive care unit, intubation and/or death with COVID-19) between those using an ACE inhibitor or an ARB and those not using a RAAS inhibitor. Only data from studies on people aged ≥18 years were included. Review articles were excluded, but as stated previously, their reference lists were screened. Studies indexed to preprint servers only, which are not certified for publication, were also excluded. Finally, inclusion was limited to studies originally published in the English language or where translated copies had been made available.

Risk of Bias Assessment
Given that this review focussed on observational studies, the risk of bias assessment for each study was performed independently by J. L. and F. C. T. using the Risk of Bias in Non-Randomized Studies—of Interventions (ROBINS-I), developed by the Cochrane Bias Methods Group and the Cochrane Non-Randomized Studies Methods Group. The ROBINS-I tool includes seven domains of potential bias: (1) bias due to confounding, (2) bias in selection of participants into the study, (3) bias in the classification of interventions, (4) bias due to deviations from intended interventions, (5) bias due to missing data, (6) bias in the measurements of outcomes, and (7) bias in selection of the reported result. A study was deemed to have a low risk of bias overall if it was judged to have a low risk of bias across all domains; a moderate risk of bias overall if it was judged to have a low or moderate risk of bias across all domains; a serious risk of bias overall if it was judged to have a serious risk of bias in at least one domain, but not at a critical risk of bias in any other domain; and a critical risk of bias overall if it was judged to have a critical risk of bias in at least one domain. If there was nothing indicating a serious or critical risk of bias, but there was a lack of information to make a judgment in any of the domains, a study was deemed to have “no information” regarding its risk of bias. Discrepancies in bias classification were resolved by discussion. As recommended, any study with a critical risk of bias was excluded from the subsequent synthesis and analysis.

Outcomes
Although risk of bias was assessed in studies of the association between RAAS inhibitor use and the risk of infection, it was planned from the outset that only severe COVID-19 outcomes (eg, hospitalization, admission to an intensive care unit, intubation, death) would be evaluated by the meta-analysis. Indeed, severe outcomes are most relevant considering that they are the burden to health care systems, whereas risk of infection data have an unknown potential for bias because of changes in COVID-19 testing strategies in outpatient care and, likely, a high rate of missed cases. Severe outcomes that could be pooled from the eligible studies included hospitalization and a combination of intubation and death with COVID-19.

Data Extraction
The main characteristics of each study eligible for inclusion in the meta-analysis were summarized in duplicate by J. L. and F. C. T. into a preformatted spreadsheet. These characteristics included (1) first author names and year of publication, (2) country, (3) study design, (4) sample size, (5) comorbidities, (6) number of relevant severe COVID-19 events, and (7) the weighted estimates for each outcome of interest.

Statistical Analysis
The weighted hazard ratios (HR) and the corresponding 95% CI detailing the association between using an ACE inhibitor or an ARB in monotherapy and hospitalization, intubation, or death with COVID-19 were pooled in fixed-effects meta-analyses. Those using a RAAS inhibitor in monotherapy were compared with those using a non-RAAS inhibitor in monotherapy (ie, a calcium channel blocker or thiazide diuretic [TZD]). A fixed-effects meta-analysis was chosen as the primary analysis given the low number of studies included in the meta-analyses. Indeed, a random-effects meta-analysis may not adequately estimate the heterogeneity and weights when so few studies are available. Recognizing that there are contrasting opinions as to when it is appropriate to use either a fixed- or random-effects model, a random-effects meta-analysis was conducted as a secondary (sensitivity) analysis. Heterogeneity was quantified using the I² statistic (I²>50%) and tested using Cochran’s Q statistic (P<0.10). Publication bias was not assessed as there were fewer than 10 studies available for the analysis. A P value of <0.05 was considered statistically significant. Analyses were performed using R, version 4.0.0 (R-Core Team, Vienna, Austria).

Certainty of the Evidence Assessment
The Grading of Recommendations Assessment, Development and Evaluation (GRADE) was performed in duplicate by J. L. and F. C. T. to provide an assessment of the quality of (ie, certainty of) the evidence produced by the meta-analyses. The GRADE’s official software package, GRADEpro Guideline Development Tool (McMaster University and Evidence Prime Inc.), was used to summarize the findings of the meta-analyses.
RESULTS

Study Selection and Risk of Bias Analysis

The systematic search identified 169 observational studies that assessed the associations between RAAS inhibitor use and the risk of contracting a SARS-CoV-2 infection and/or experiencing severe COVID-19 outcomes (Figure 1). Of those 169 studies, 164 had critical risks of bias and were excluded from the meta-analysis (Figure 2). Among these 164 studies, critical biases were most commonly due to confounding bias (n=157), selection bias (n=146), and bias due to deviations from the intended interventions (n=67). The risk of bias in the classification of the interventions, the measurement of the outcomes, and the selection of the reported result was predominantly low across the entire body of research. Notably, a substantial number of studies failed to provide information about how missing data were handled (n=90) or if important con-interventions (ie, other antihypertensive therapies) were addressed (n=60).

Of the five studies without critical risks of bias, two studies assessed only the association between RAAS inhibitor use and risk of infection (a nonsevere outcome that does not burden health care systems) and, as planned, were not included in the subsequent data synthesis. A third study without critical bias had eligible data in its secondary analysis, but the event rates for the relevant outcomes were not available; and, thus, it could not be pooled in the meta-analysis.

Study Characteristics

Two nationwide studies, one each from France and Sweden, could be included in the meta-analysis (Table 1). Although the study from France also completed analyses on those using a combination of antihypertensive therapies, the meta-analysis considered only outcomes commonly assessed in each study and, thus, included data from all French (n=1 186 987) and Swedish (n=164 655) residents with uncomplicated hypertension who used either an ACE inhibitor, ARB, calcium channel blocker, or TZD in monotherapy (Note: data for French citizens using a TZD in monotherapy were not available). Given that as-treated data were available only in the study from Sweden, only intention-to-treat data were used in the meta-analysis. Both studies excluded those with known cardiovascular and/or kidney diseases in order to limit confounding bias. The follow-up period was similar in both the French and Swedish studies, running from February...
likely driven by the low number of events in the study. The heterogeneity in each mortality analysis was most relevant, that the risk of hospitalization, intubation, or death varies little between those using a RAAS inhibitor and those using a calcium channel blocker or TZD (Table 2). Although the meta-analyses were based on observational studies, certainty in the evidence for each outcome began with a high rating because of the use of the ROBINS-I. There were no reasons to downgrade the certainty of the evidence for each of the hospitalization outcomes. However, given that only
one of two studies provided intubation data in the intubation or death outcomes, certainty of the evidence for these outcomes was downgraded by one level to a moderate rating owing to serious indirectness in the outcomes between studies.

**DISCUSSION**

This study reveals that current policy regarding the safety of using RAAS inhibitors during the ongoing COVID-19 pandemic is based almost entirely on a body of research that has severe limitations due to critical risk of bias. However, when only studies without critical risk of bias were pooled, results were consistent with the majority of that body of research; indicating that RAAS inhibitor use does not increase the risk of severe COVID-19 outcomes.

Critical risk of bias was most often attributed to confounding bias and/or selection bias, found in 164 of 169 observational studies relevant to this meta-analysis. Confounding bias was introduced mainly by the inclusion of people with preexisting cardiovascular and kidney diseases, confounding factors that are inherently uncontrollable when aiming to isolate the effect of RAAS inhibitor use on COVID-19 outcomes. Selection bias was introduced by the inclusion of samples restricted to people who were tested for/tested positive to a SARS-CoV-2 infection and/or who had been hospitalized due to COVID-19; sampling strategies that form cohorts unrepresentative of the general population.

These biases have the potential to create a spurious within-sample association between two variables, so called collider bias (eg, in the context of RAAS inhibitor—COVID-19 studies: frailty due to cardiovascular disease, with a high likelihood of being prescribed a RAAS inhibitor; and frailty due to an adverse COVID-19 course), that affects the probability of being included in the sample (eg, being hospitalized). To minimize such biases in the context of RAAS inhibitor—COVID-19 observational research, a primary prevention sample of yet uninfected people using RAAS inhibitors or a relevant comparator drug class needs to be studied in order to isolate the interaction between RAAS inhibitor use and COVID-19, not in those already affected by the virus.

Ultimately, only five observational studies used bias-minimized study designs, two of which could be included in the meta-analysis. The conclusion from this research, that RAAS inhibitor use does not increase the risk of severe COVID-19 outcomes, is consistent with the eight randomized controlled trials that have evaluated RAAS inhibitor—COVID-19 associations thus far. Although the 164 studies with critical biases cannot isolate the interaction between RAAS inhibitor use and COVID-19, the value of that research should not be discounted entirely. Indeed, those studies combined contributed to a detailed characterization of the population who experienced a severe COVID-19 disease course, identifying the people (eg, elderly people, people with comorbidities) who need more attention or greater protection (eg, prioritized vaccination) during the ongoing pandemic.

The exclusion of people with preexisting cardiovascular and kidney diseases from the studies pooled in the meta-analyses is likely to prompt questions about the limitations of this study: Do these findings apply to those with such comorbidities? Would these findings

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**Table 1. Main Characteristics of the Studies Included in the Meta-Analysis**

| Study            | Country | Study period                     | Population* | Comorbidities                                                                 | Hospitalization with COVID-19 | Intubation or death with COVID-19† |
|------------------|---------|----------------------------------|-------------|-------------------------------------------------------------------------------|------------------------------|-----------------------------------|
| Loader et al, 2021 | Sweden  | January 1, 2020–June 23, 2020    | All residents in Sweden (n=164 655) uncomplicated hypertension using, in monotherapy, an ACE inhibitor (n=47 998) ARB (n=68 239) CCB or TZD (n=48 418) | Those with preexisting cardiovascular disease and kidney diseases were excluded | ACE inhibitor (n=94) ARB (n=135) CCB or TZD (n=107) | ACE inhibitor (n=16) ARB (n=19) CCB or TZD (n=26) |
| Semenzato et al, 2021 | France | February 15, 2020–June 7, 2020   | All residents in France (n=1 186 987) uncomplicated hypertension using, in monotherapy, an ACE inhibitor (n=353 236) ARB (n=582 031) CCB (n=251 720) | Those with diabetes, cardiovascular disease, chronic respiratory disease, and/or chronic renal failure in the 5 years before the study were excluded | ACE inhibitor (n=340) ARB (n=690) CCB (n=384) | ACE inhibitor (n=72) ARB (n=148) CCB (n=99) |

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II type-I receptor blocker; CCB, calcium channel blocker; and TZD, thiazide diuretic.

*Although only data for treatment by monotherapy are presented in the table, it should be noted that Semenzato et al. (2021) also conducted analyses on those in combination therapy.

†Intubation was only an outcome in the study by Semenzato et al. (2021), meaning only deaths were recorded in Loader et al. (2021).
not be more relevant if the analyses include those with comorbidities, those who are more at risk of severe a COVID-19 disease course? Indeed, it is unknown whether the findings of this meta-analysis extend to those with underlying comorbidities, the proportion of the population who are most at risk of severe COVID-19 outcomes and who represent the majority of people using RAAS inhibitors. Although it is important that this limitation is acknowledged, the fact remains that people with preexisting cardiovascular and kidney diseases could introduce confounding so intractable that statistical methods will not be able to control for this bias, necessitating the exclusion of those people to isolate any interaction between RAAS inhibitors and COVID-19. This methodological consideration represents an effort to produce observational research that, as best as possible, emulates a randomized controlled trial, a methodological principle.

Figure 3. Forest plots for each outcome assessed in the fixed-effects meta-analyses. Presented are the associations between (A) the use of an ACE inhibitor in monotherapy and hospitalization, (B) the use of an ACE inhibitor in monotherapy and intubation or death, (C) the use of an ARB in monotherapy and hospitalization and (D) the use of an ARB in monotherapy and intubation or death. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II type-I receptor blocker; CCB, calcium channel blocker; HR, hazard ratio; and TZD, thiazide diuretic.
### Table 2. Summary of Findings Including the Certainty of the Evidence

| Outcomes                                      | Anticipated absolute effects* (95% CI) | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) | Comments                                                                 |
|-----------------------------------------------|---------------------------------------|--------------------------|-------------------------------|-----------------------------------|--------------------------------------------------------------------------|
| ACE inhibitor use and the risk of hospitalization with COVID-19 | 164 per 100 000 (108–142)             | HR 0.76 (0.66–0.87)      | 701 372 (2 observational studies) | ⬤⬤⬤⬤ HIGH                    | The risk of hospitalization with COVID-19 differs little between those using an ACE inhibitor and those using a CCB or TZD in monotherapy |
| ACE inhibitor use and the risk of intubation or death with COVID-19 | 42 per 100 000 (20–35)                 | HR 0.64 (0.48–0.85)      | 701 372 (2 observational studies) | ⬤⬤⬤⬤ MODERATE†,‡,§          | The risk of intubation or death with COVID-19 differs little between those using an ACE inhibitor and those using a CCB or TZD in monotherapy |
| ARB use and the risk of hospitalization with COVID-19 | 164 per 100 000 (126–159)             | HR 0.86 (0.77–0.97)      | 950 408 (2 observational studies) | ⬤⬤⬤⬤ HIGH                    | The risk of hospitalization with COVID-19 differs little between those using an ARB and those using a CCB or TZD in monotherapy  |
| ARB use and the risk of intubation or death with COVID-19 | 42 per 100 000 (24–40)                 | HR 0.74 (0.58–0.95)      | 950 408 (2 observational studies) | ⬤⬤⬤⬤ MODERATE†,‡,§          | The risk of intubation or death with COVID-19 differs little between those using an ARB and those using a CCB or TZD in monotherapy  |

GRADE Working Group grades of evidence—High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II type-1 receptor blocker; CCB, calcium channel blocker; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HR, hazard ratio; and TZD, thiazide diuretic.

*The risk in users of an ACE inhibitor or an ARB (and its 95% CI) is based on the assumed risk in the users of a CCB or TZD and the relative effect of the intervention (and its 95% CI).

**Explanations**

1. A composite outcome of intubation and death was used in the meta-analysis, but intubation data were not available in Loader et al. (2021), resulting in the certainty of the evidence being downgraded by one level due to serious indirectness.
2. Point estimates vary greatly between each study, but the importance of this is questionable when considering the weighting of each study and does not decrease certainty in the evidence.
3. Heterogeneity is most likely explained by the low number of deaths in Loader et al. (2021).
that seems to have been overlooked in many drug-safety and effectiveness studies during the COVID-19 pandemic, not only those pertaining to RAAS inhibitors. Other potential limitations must also be addressed. This meta-analysis did not conduct an analysis including people on combination therapy with antihypertensive drugs. However, given the results from the nationwide study in France, it would appear that these findings based on monotherapy data could be extended to those on combination therapy. Owing to data availability, only intention-to-treat data were used in the analysis and variations in the prescribed RAAS inhibitor dose were not addressed by the meta-analysis. Thus, it is unclear how an as-treated analysis would affect the findings. However, the nationwide study from Sweden indicated that there is not much variation in the estimates between an intention-to-treat and an as-treated analysis. Finally, both studies in the meta-analysis (like most RAAS inhibitor—COVID-19 research) covered only the first wave of the pandemic, where event rates were relatively low compared with subsequent waves, and when early variants of the virus existed, possibly limiting the data in terms of their relevance to the evolving COVID-19 situation.

This study was not the first systematic review and meta-analysis to assess the associations between RAAS inhibitor use and COVID-19 outcomes. As of December 2021, at least 52 meta-analyses had been conducted, each of which pooled studies that have a critical risk of bias. Critical biases limit confidence in the evidence produced by these meta-analyses as much as they do in each of the studies that they were based on. Current guidelines from the Cochrane Collaboration instruct that these meta-analyses should not have been conducted, that studies with critical risk of bias should not be synthesized. However, only six of the 52 previous meta-analyses followed current guidelines and used the ROBINS-I to assess risk of bias. It is unclear as to why the authors of five of those six studies did not identify any critical risks of bias and proceeded with their meta-analyses. One meta-analysis, however, deviated from the guidelines, establishing their own unstandardized scoring system for the ROBINS-I.

Of the other 46 meta-analyses, only 18 referred to having completed a risk of bias assessment. Whether they recognized it or not, 34 studies used the Newcastle-Ottawa Scale for assessing the risk of bias. The Newcastle-Ottawa Scale, which has not been recommended by the Cochrane Collaboration since well before the COVID-19 pandemic (in a now archived version of the guidelines), provides a quality score where a higher value is interpreted as a lower risk of bias. Although this scale might detect a critical risk of bias in one domain, a study may still be deemed to be of high quality overall and, thus, have a low risk of bias overall because of strengths in other domains; essentially allowing for an important, potentially association-distorting bias(es) to go overlooked and explaining why some studies proceeded with their meta-analyses. In contrast, the ROBINS-I recognises that a critical risk of bias needs to exist in only one domain to limit confidence in an entire study and to provide reason for it to be excluded from a data synthesis. The Cochrane Collaboration’s transition from the Newcastle-Ottawa Scale to the ROBINS-I further reflects the need for more rigor in the design of observational research.

Three meta-analyses acknowledged use of a risk of bias assessment tool that is integrated into the GRADE. This tool, by admission of its creators, was not as comprehensive as other methods available at the time (Note: created long before the development for the ROBINS-I); and like the Newcastle-Ottawa Scale, it also overlooks important sources of bias. Only eight out of 52 meta-analyses used the GRADE to summarize their findings and determine the certainty of their evidence; a process that is crucial in being able to properly interpret the clinical importance of findings from a meta-analysis (eg, as demonstrated in this study: the difference between concluding a protective effect and no effect). Collectively, this poor methodology demonstrates a lack of knowledge around the current guidelines for systematic reviews and meta-analyses, among authors, reviewers, and journal editors alike.

**CONCLUSIONS**

Despite wavering interest, additional studies related to COVID-19 risk are inevitable, emphasizing the urgent need for this present systematic review and meta-analysis. Indeed, to improve future research, the inadequate methodologies used by almost an entire body of observational research, as well as by the meta-analyses that collated those studies, needed to be highlighted. If further RAAS—COVID-19 observational studies are to be conducted, it would be interesting if they extended follow-up to include subsequent waves of the pandemic, where event rates were substantially higher and when new variants of COVID-19 exist(ed); evaluating if associations change over time with variations in infection rates and in the virus. That research must address the methodological issues (eg, confounding bias and selection bias) identified in most previous studies in order to, as best as possible, isolate the interaction between RAAS inhibitor use and COVID-19. Researchers should also recognize that the methodological principles needed to improve RAAS—COVID-19 studies extend to other drug safety and effectiveness studies; methodological approaches that are crucial to enhancing the scientific value of observational research.
In summary, this study presents data that, fortunately, support directives from health authorities early in the pandemic, that antihypertensive therapies could be continued safely as per normal. However, it is not certain whether the effect estimates would remain consistent throughout subsequent waves of the pandemic or whether the findings are applicable to those with underlying comorbidities. Most significantly, this study reveals the extent of bias in RAAS inhibitor—COVID-19 studies, showing how wrong things can go when there is carelessness in research; that poorly designed studies continue, with little question, to direct subsequent research and health policies alike. This raises an important question: Have research methods and/ or peer review processes been temporarily weakened during the surge of COVID-19 research, potentially because of a desire to be the first published or to be the first to publish, or is this lack of rigor a systemic problem that also exists outside pandemic-based research?

**ARTICLE INFORMATION**

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Author contributions: Dr Jordan Loader developed the concept and the design of the study. Dr Loader and Miss Frances Taylor were responsible for acquisition of the data. Dr Loader and Dr Erik Lampa were responsible for data analysis. All authors in addition to Professor Johan Sundström, contributed to the interpretation of the data and to the production of the article. All authors approved the final version of the article.

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**Disclosures**

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**Supplemental Material**

Data S1
Tables S1–S2
Figure S1

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Supplemental Material
Supplemental Methods

Assessment of the certainty in the evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) was performed in duplicate by J.L. and F.C.T. to provide an assessment of the quality of (i.e., certainty of the) evidence produced by the meta-analyses. The GRADE rates the certainty of the evidence as high, moderate, low, or very low. The evidence from a meta-analysis including studies that are observational in design usually begin with a low-quality rating. However, when using the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I), evidence can begin with a high-quality rating as it comprehensively addresses potential confounding and selection biases. Thereafter, certainty in the evidence can be downgraded due to: 1) study limitations; 2) inconsistency of results; 3) indirectness of evidence; 4) imprecision; and/or 5) reporting bias. The quality of evidence can be upgraded again if there is: 1) a large magnitude of effect; 2) a dose-response gradient; and/or 3) if plausible biases would decrease the magnitude of an apparent treatment effect. The highest rating that can be given to a body of evidence is high-quality, indicating a high level of certainty in the evidence.
Table S1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.

| Section and Topic | Item # | Checklist item                                                                                                                                                                                                 | Location where item is reported |
|-------------------|--------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| **TITLE**         |        |                                                                                                                                                                                                                   |                                 |
| Title             | 1      | Identify the report as a systematic review.                                                                                                                                                                             | Page 1                          |
| **ABSTRACT**      |        |                                                                                                                                                                                                                   |                                 |
| Abstract          | 2      | See the PRISMA 2020 for Abstracts checklist.                                                                                                                                                                         | Pages 2-4                       |
| **INTRODUCTION**  |        |                                                                                                                                                                                                                   |                                 |
| Rationale         | 3      | Describe the rationale for the review in the context of existing knowledge.                                                                                                                                           | Page 7                          |
| Objectives        | 4      | Provide an explicit statement of the objective(s) or question(s) the review addresses.                                                                                                                                  | Pages 7-8                       |
| **METHODS**       |        |                                                                                                                                                                                                                   |                                 |
| Eligibility criteria | 5  | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.                                                                                                            | Page 9                          |
| Information sources | 6   | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | Page 8                          |
| Search strategy   | 7      | Present the full search strategies for all databases, registers and websites, including any filters and limits used.                                                                                                   | Page 8 and Table S2             |
| Selection process | 8      | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | Page 9                          |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | Page 11                         |
| Data items        | 10a    | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | Pages 10-11                     |
|                   | 10b    | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.                                      | Pages 10-11                     |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Pages 9-10                      |
| Effect measures   | 12     | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.                                                                                     | Pages 11-12                     |
| Synthesis methods | 13a    | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | Pages 9-11                      |
| Section and Topic | Item # | Checklist item                                                                                                                                                                                                 | Location where Item is reported                  |
|-------------------|--------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|
|                   | 13b    | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.         | Not applicable                                  |
|                   | 13c    | Describe any methods used to tabulate or visually display results of individual studies and syntheses.                                                                                                         | Page 11                                         |
|                   | 13d    | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | Page 11                                         |
|                   | 13e    | Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).                                                                         | Not applicable                                  |
|                   | 13f    | Describe any sensitivity analyses conducted to assess robustness of the synthesized results.                                                                                                                   | Page 11                                         |
|                   |        |                                                                                                                                                                                                                |                                                 |
|                   | 14     | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).                                                                                          | Not applicable                                  |
|                   | 15     | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.                                                                                                         | Page 12 and Supplemental Methods                |
| RESULTS           |        |                                                                                                                                                                                                                |                                                 |
| Study selection   | 16a    | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | Figure 1                                        |
|                   | 16b    | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.                                                                                 | Page 13                                         |
| Study characteristics | 17   | Cite each included study and present its characteristics.                                                                                                                                                     | Page 13 and Table 1                             |
| Risk of bias in studies | 18   | Present assessments of risk of bias for each included study.                                                                                                                                                   | Figure 2                                        |
| Results of individual studies | 19   | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Page 13, Figure 3 and Figure S1                |
| Results of syntheses | 20a  | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.                                                                                                       | Page 12-13, Table 1 and Figure 2               |
|                   | 20b    | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | Page 14, Figure 3 and Figure S1                |
|                   | 20c    | Present results of all investigations of possible causes of heterogeneity among study results.                                                                                                                   | Page 14                                         |
|                   | 20d    | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.                                                                                                    | Figure S1                                       |
| Section and Topic                  | Item # | Checklist item                                                                                                                                                                                                 | Location where Item is reported |
|-----------------------------------|--------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Reporting biases                  | 21     | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.                                                                                           | Not applicable                   |
| Certainty of evidence             | 22     | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.                                                                                                              | Page 14, Table 2                |
| **DISCUSSION**                    |        |                                                                                                                                                                                                            |                                  |
| Discussion                        | 23a    | Provide a general interpretation of the results in the context of other evidence.                                                                                                                             | Pages 17                        |
|                                  | 23b    | Discuss any limitations of the evidence included in the review.                                                                                                                                             | Pages 17-18                     |
|                                  | 23c    | Discuss any limitations of the review processes used.                                                                                                                                                         | Pages 17-18                     |
|                                  | 23d    | Discuss implications of the results for practice, policy, and future research.                                                                                                                                | Pages 20-21                     |
| **OTHER INFORMATION**             |        |                                                                                                                                                                                                            |                                  |
| Registration and protocol         | 24a    | Provide registration information for the review, including register name and registration number, or state that the review was not registered.                                                                 | Page 4 and 8                    |
|                                  | 24b    | Indicate where the review protocol can be accessed, or state that a protocol was not prepared.                                                                                                               | Page 8                          |
|                                  | 24c    | Describe and explain any amendments to information provided at registration or in the protocol.                                                                                                             | Not applicable                   |
| Support                           | 25     | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.                                                                                | Page 22                         |
| Competing interests               | 26     | Declare any competing interests of review authors.                                                                                                                                                            | Page 22                         |
| Availability of data, code and    | 27     | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | Not applicable                   |
Table S2. Search strategy used in MEDLINE, EMBASE and CINAHL databases between December 1st, 2019, and October 21st, 2021.

| Search terms used in each database |  |
|-----------------------------------|--|
| 1. "coronavirus disease 2019" OR "covid-19" OR "severe acute respiratory syndrome coronavirus 2" OR "SARS-CoV-2" OR "coronavirus 2" (TITLE) |  |
| 2. "coronavirus disease 2019" OR "covid-19" OR "severe acute respiratory syndrome coronavirus 2" OR "SARS-CoV-2" OR "coronavirus 2" (ABSTRACT) |  |
| 3. 1. OR 2. |  |
| 4. "renin-angiotensin aldosterone system" OR "renin-angiotensin-aldosterone system" OR "renin-angiotensin system" OR "RAAS" OR "RAS" OR "RAASi" OR "angiotensin converting enzyme inhibitors" OR "ACE inhibitors" OR "angiotensin II receptor blockers" OR "ARBs" OR "ARB" (TITLE) |  |
| 5. "renin-angiotensin aldosterone system" OR "renin-angiotensin-aldosterone system" OR "renin angiotensin system" OR "RAAS" OR "RAS" OR "RAASi" OR "angiotensin converting enzyme inhibitors" OR "ACE inhibitors" OR "angiotensin II receptor blockers" OR "ARBs" OR "ARB" (ABSTRACT) |  |
| 6. 4. OR 5. |  |
| 7. 3. AND 6. |  |
| 8. Limit 7. to human studies only |  |
Figure S1. Forest plots for the random effects meta-analyses.

A) Present are the associations between A) the use of an ACE inhibitor in monotherapy and hospitalization, B) the use of an ACE inhibitor in monotherapy and intubation or death, C) the use of an ARB in monotherapy and hospitalization and D) the use of an ARB in monotherapy and intubation or death. ACEi denotes angiotensin-converting enzyme inhibitor; ARB, angiotensin II type-I receptor blocker; CCB, calcium channel blocker; CI, confidence interval; HR, hazard ratio; SE, standard error; TZD, thiazide diuretic.

| Study                          | log HR | SE  | Favors ACEi | Favors CCB or TZD | HR         | 95% CI          | Weight |
|-------------------------------|--------|-----|-------------|-------------------|------------|-----------------|--------|
| Loader et al, 2021            | -0.12  | 0.17|             |                   | 0.89       | [0.64; 1.23]    | 22.6%  |
| Semenzato et al, 2021         | -0.31  | 0.08|             |                   | 0.73       | [0.63; 0.85]    | 77.4%  |

**Random effects model**
Heterogeneity: $I^2 = 15\%$, $t^2 = 0.0030$, $p = 0.28$

| Study                          | log HR | SE  | Favors ACEi | Favors CCB or TZD | HR         | 95% CI          | Weight |
|-------------------------------|--------|-----|-------------|-------------------|------------|-----------------|--------|
| Loader et al, 2021            | -0.03  | 0.35|             |                   | 0.97       | [0.48; 1.93]    | 29.7%  |
| Semenzato et al, 2021         | -0.53  | 0.16|             |                   | 0.59       | [0.43; 0.80]    | 70.3%  |

**Random effects model**
Heterogeneity: $I^2 = 39\%$, $t^2 = 0.0474$, $p = 0.20$

| Study                          | log HR | SE  | Favors ARB  | Favors CCB or TZD | HR         | 95% CI          | Weight |
|-------------------------------|--------|-----|-------------|-------------------|------------|-----------------|--------|
| Loader et al, 2021            | -0.06  | 0.15|             |                   | 0.94       | [0.70; 1.27]    | 15.5%  |
| Semenzato et al, 2021         | -0.16  | 0.07|             |                   | 0.85       | [0.75; 0.97]    | 84.5%  |

**Random effects model**
Heterogeneity: $I^2 = 0\%$, $t^2 = 0$, $p = 0.55$

| Study                          | log HR | SE  | Favors ARB  | Favors CCB or TZD | HR         | 95% CI          | Weight |
|-------------------------------|--------|-----|-------------|-------------------|------------|-----------------|--------|
| Loader et al, 2021            | 0.22   | 0.35|             |                   | 1.25       | [0.63; 2.49]    | 35.0%  |
| Semenzato et al, 2021         | -0.37  | 0.14|             |                   | 0.69       | [0.53; 0.90]    | 65.0%  |

**Random effects model**
Heterogeneity: $I^2 = 60\%$, $t^2 = 0.1053$, $p = 0.12$