Supplemental Material

Data S1.

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.[1] 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

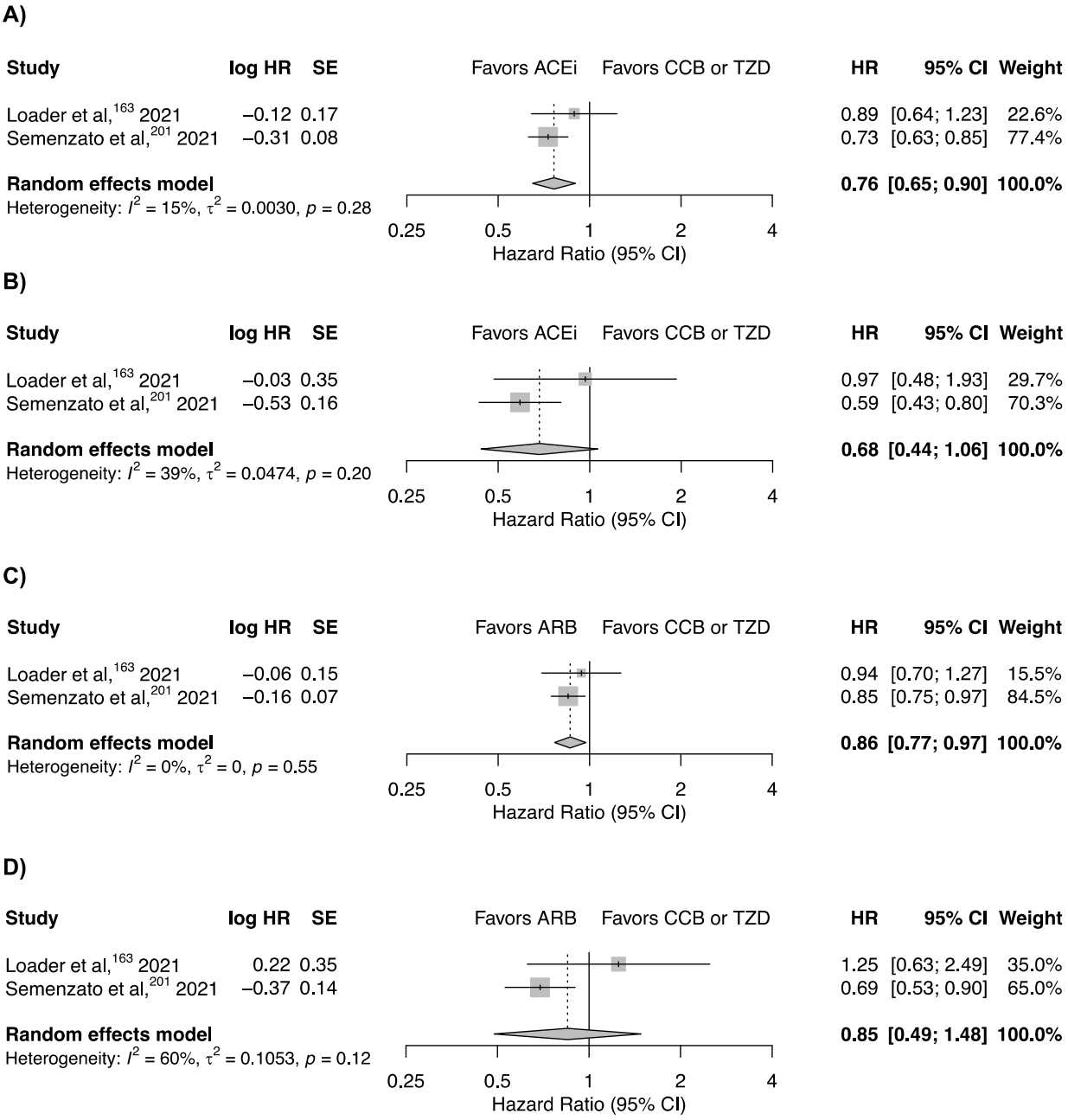
Section and Topic	Item #	Checklist item	Location where item is reported
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Not applicable
	13c	Describe any methods used to tabulate or visually display 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
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not applicable
Certainty assessment	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 other materials	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 ”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 ”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.



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 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.