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A Prospective Meta-Analysis Protocol on Randomised Trials of Renin-Angiotensin-System Inhibitors in Patients with Coronavirus Disease-19 (COVID-19): An initiative of the International Society of Hypertension.

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ABSTRACT

Introduction: Whether angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor blocker (ARB) therapy should be continued, initiated or ceased in patients with coronavirus disease-19 (COVID-19) is uncertain. Given the widespread use of ACEi/ARBs worldwide, guidance on the use of these drugs is urgently needed. This prospective meta-analysis aims to pool data from randomised controlled trials (RCTs) to assess the safety and efficacy of ACEi/ARB therapy in adults infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

Methods and Analysis: RCTs will be eligible if they compare COVID-19 patients randomised to ACEi/ARB continuation or commencements versus no ACEi/ARB therapy; study duration ≥14 days; recruitment completed between March 2020 and May 2021. The primary outcome will be all-cause mortality at ≤30 days. Secondary outcomes will include mechanical ventilation, admission to intensive care or cardiovascular events at short term follow-up (≤30 days), and all-cause mortality at longer term follow-up (>1 month). Pre-specified sensitivity analyses will assess the effect of sex; age; comorbidities; smoking status; ethnicity; country of origin on all-cause mortality. A search of ClinicalTrials.gov has been performed, which will be followed by a formal search of trial registers, pre-print servers, MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials to identify RCTs that meet inclusion criteria. To date, a search of ClinicalTrials.gov identified 19 potentially eligible trials for this meta-analysis. We will request trial investigators/sponsors to contribute standardised grouped tabular outcome data.

Ethics and dissemination: Ethics approval and informed consent will be the responsibility of the individual RCTs. Dissemination of results will occur by peer-reviewed publication. The

results of our analysis can inform public health policy and clinical decision making regarding ACEi/ARB use in patients with COVID-19 on a global scale.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- First prospective meta-analysis of randomised controlled trials assessing the safety and efficacy of ACEi/ARBs in adults with coronavirus-19 disease (COVID-19)
- This meta-analysis uses a collaborative international approach to allow pooling and dissemination of results. This has the potential to inform international public health policy and clinical decision making for ongoing ACEi/ARB use in COVID-19 patients.
- Randomised controlled trials are currently under way with some having the potential to be underpowered. Pooling of data will overcome this shortcoming.
- The completion of these trials prior to data pooling is a limitation, as is the willingness of trialists to collaborate in data sharing.

INTRODUCTION

Renin-angiotensin system (RAS) inhibitors, including angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB), are the most widely prescribed anti-hypertensive treatments globally, used by hundreds of millions of people worldwide.[1] ACEi/ARB therapy are not only first line agents for the treatment of hypertension, but are also the cornerstones of cardiovascular and renal disease therapies such as heart failure, coronary heart disease, diabetes and chronic kidney disease. However, infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (also referred to as coronavirus disease-19 [COVID-19]) involves the viral spike protein attaching to the ACE2 receptor to enter the lungs,[2] with increased binding affinity a key determinant of pathogenicity.[3] ACEi/ARB therapies may upregulate ACE2 receptor expression.[4 5] Upregulated expression of ACE2 receptors on the cell surface has been postulated to increase the risk of infection with SARS-CoV-2 and the disease severity, with subsequent life-threatening complications.[6 7] Animal studies have demonstrated that ACEi/ARB therapy can also produce increased cardiac ACE2 mRNA levels, which may promote viral cell invasion.[4 8] At the same time, data from animal studies suggest that increased ACE2 expression secondary to ACEi/ARB use might have protective benefits on cardiac, renal and pulmonary function and thus reduce the severity of COVID-19.[9]

Observational retrospective studies in humans suggest that there is no effect of RAS blockade on COVID-19 disease severity and outcome,[10-14] with limited evidence of protective benefits including reduced rates of mortality,[15] critical disease[16] and admission to intensive care.[17] However, to date reliable randomised controlled data are unavailable to guide clinical decision-making. As a result, it is uncertain whether ACEi/ARB therapy should be continued, withdrawn, or initiated in patients with COVID-19.

International hypertension and cardiovascular 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.[18-21] There are multiple randomised clinical trials (RCTs) in process, which are necessary to ensure informed clinical decision making rather than relying on observational human studies[10-14] and inconsistent animal data.[4 8] Most of the RCTs under way are small to moderate in size (~40% aim to recruit less than 250 participants), with many unlikely to meet their recruitment targets. Given the uncertainty, some trials are starting ACEi/ARB therapy for possible benefit, while other trials are stopping the same therapy due to concerns about harm. These are essentially the same randomisations, and so can be pooled in an ACEi/ARB vs. no ACEi/ARB meta-analysis, with appropriate prespecification of preplanned analyses from the two groups of trials. 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.

OBJECTIVES

We will therefore perform a prospective meta-analysis of RCTs recruiting COVID-19 infected patients to assess the safety and efficacy of ACEi/ARB therapy compared to those not on ACEi/ARBs. As primary outcome, pooled data will be used to assess all-cause mortality

associated with ACEi/ARB therapy compared to those not on ACEi/ARBs stratified by age, co-morbidity, sex, ethnicity, and trial characteristics.

METHODS AND ANALYSIS

Protocol Design

For this meta-analysis, we will only include RCTs to minimise the impact of bias and confounding. We herewith describe our methods as per the Preferred Reporting Items for Systematic Review and Meta-Analysis for protocol (PRISMA) recommendations.[22] Final reporting of this study will be compliant with the main PRISMA statement.

Eligibility Criteria

For clinical trials to be eligible for inclusion, the following criteria must be met: (i) RCTs recruiting between March 2020 and May 2021; (ii) aged ≥18 years; (iii) SARS-CoV-2 infection confirmed; (iv) comparison of patients randomised to ACEi/ARB versus no ACEi/ARB therapy; (v) findings reported in English; (vi) trial duration ≥14 days; (viii) oral administration of ACEi/ARB therapies.

We will include trials that investigate continuation versus cessation of ACEi/ARB among patients currently treated with ACEi/ARB; and trials that report initiation of ACEi/ARB versus control in those not currently treated with such therapies. Studies must contain sufficient detail and be able to provide at least one outcome outlined within our data extraction form (Table 1). The exclusion criteria will be at the discretion of each individual trial.

The intervention will comprise continuation or initiation of ACEi/ARB therapy. The control will be discontinuation of current ACEi/ARB therapy, substitution with an equivalent dose of non-ACEi/ARB therapy, placebo or usual care.

Outcomes

The primary outcome will be all-cause mortality at ≤30 days. Secondary outcomes will include mechanical ventilation at ≤30 days; admission to intensive care at ≤30 days; myocardial infarction at ≤30 days, revascularisation at ≤30 days, congestive cardiac failure at ≤30 days; pulmonary embolism and/or deep vein thrombosis at ≤30 days; all-cause mortality at >1 month follow-up. Standardised grouped tabular de-identified data will be requested from triallists for both short-term (≤30 days) and longer term (>1 month) follow up where available (Table 1). Individual identifiable patient data will not be requested.

Sensitivity analyses will be performed depending on data availability, but will aim to assess all-cause mortality at ≤30 days and >1 month for the following subgroups: (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 (Supplemental Tables 1 and 2).

Search strategy and searching sources

An electronic search of ClinicalTrial.gov was performed to identify potential ongoing trials for inclusion in the meta-analysis. Figure 1 summarises the trial search as of July 2020 performed using the search terms: coronavirus-19, COVID-19, SARS-CoV-2, randomised controlled trial, ACEi and/or ARB. A total of 19 trials were identified which potentially met the eligibility criteria (Figure 1, Table 2). Of these, 5 trials evaluated the continuation of ACEi/ARB therapies in those already on such therapies compared to discontinuation, and 15 trials involved initiation of ACEi/ARB therapies in those not on such therapies. Nine trials did not meet inclusion criteria due to (a) not assessing ACEi/ARB therapies (n=4), (b) absence of a control group (n=2), (c) use of non-oral administration of ACEi/ARB therapies (n=2), or (d) recruitment of patients with active malignancy (n=1). We extracted information about eligible investigators to invite them to participate in the prospective meta-analysis by contributing tabular data. An invitation letter will be sent via email and will include details about the study protocol, offer of authorship, identification of the time for data retrieval and confirmation of data security.

This search will be continuously updated, and investigators of newly reported and eligible trials will be invited to join the collaboration. Using the Cochrane Collaboration guidelines,[23] electronic searches of MEDLINE (1996–present), EMBASE (1996–present) and the Cochrane Central Register of Controlled Trials (most recent edition) will also be performed to identify

any other RCTs that meet inclusion criteria. A comprehensive search strategy using MeSH terms and text words will be used. Two investigators (SG and AS) will screen the abstracts for potential inclusion against the eligibility criteria, and screen the full texts. Reference management software (EndNote) will be used to store identified records.

All provided data will be stored on a password protected server, with limited access only to those directly involved in data analysis.

Study Evaluation

When conducting the prospective meta-analysis of RCTs, we will undertake a quality assessment of each RCT using the CONSORT (CONsolidated Standards of Reporting Trials) checklist.[24] Randomisation procedures, treatment allocation according to assignment, outcomes collected and compared across groups; blinding methods; and risk of bias both at study and outcome levels will also be assessed using the Cochrane Risk of Bias Tool.[25] Two investigators (SG and AS) will independently review the articles and any disagreements will be adjudicated by a third independent investigator (AR).

Statistical Analysis

Trial-specific outcome data will be pooled. For binary outcomes, risk ratios and 95% CI will be estimated using log-binomial mixed-effects models (or odds ratios from logistic models as required). Key results will be presented using Forest plots, and the I_2 statistic will be used to quantify the degree of heterogeneity between studies.[26] A two-tailed p-value risk of 5% will be used for hypothesis testing. A fixed effects analysis will be used unless there is significant heterogeneity (as evidenced by I^2>70% and quantitatively large variation), in which case

pooling will not be performed.[27] Publication bias will be assessed by visual inspection of funnel plots and formally using Egger's method to evaluate the tendency of publishing studies with statistically significant findings.[28] We will use meta-regression analyses to further explore heterogeneity of treatment effects if considerable residual heterogeneity remains after controlling for variables. Analyses will also be stratified by the prespecified subgroup analysis as mentioned above. In general, reporting of the findings will follow PRISMA guidelines.[22] All analyses will be conducted using Review Manager 5.3 software (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Data Statement

We will not have access to identifiable patient information. All data sharing and storage procedures will be compliant with the Australian Data Privacy Act of 1988. All trial data will be considered confidential and will not be provided to any third party. Data will be stored on site at The George Institute for Global Health, King St Campus, Sydney, Australia, with strict confidentiality and comprehensive data security.

Ethics and dissemination

All individual trials will require Ethics Committee or Institution Review Board approval. We will publish our findings in peer-reviewed medical journals. Publications will be in the name of the collaborative group involving all trialists who provided data. Further, we will share and present our findings at scientific meetings and through the networks and memberships across professional societies.

Implications of the review

Given the widespread use of ACE inhibitors and ARBs worldwide, guidance on the use of ACEi/ARBs in adults with COVID-19 infection is urgently needed relying on evidence beyond observational data. This collaborative international approach will allow dissemination of results, which will inform public health policy and clinical decision making for ongoing ACEi/ARBs use on an international scale. Healthcare providers and policy-makers can use the findings to improve the clinical decision making by developing strategies and guidelines to guide use of ACEi/ARBs in hypertension, cardiovascular disease and renal disease.

Patient and public involvement

Patients were not involved in the development of the research question, outcome measure and study design.

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Competing Interests Statement: Nil competing interests.

Figure 1: Flowchart of Trial Inclusion

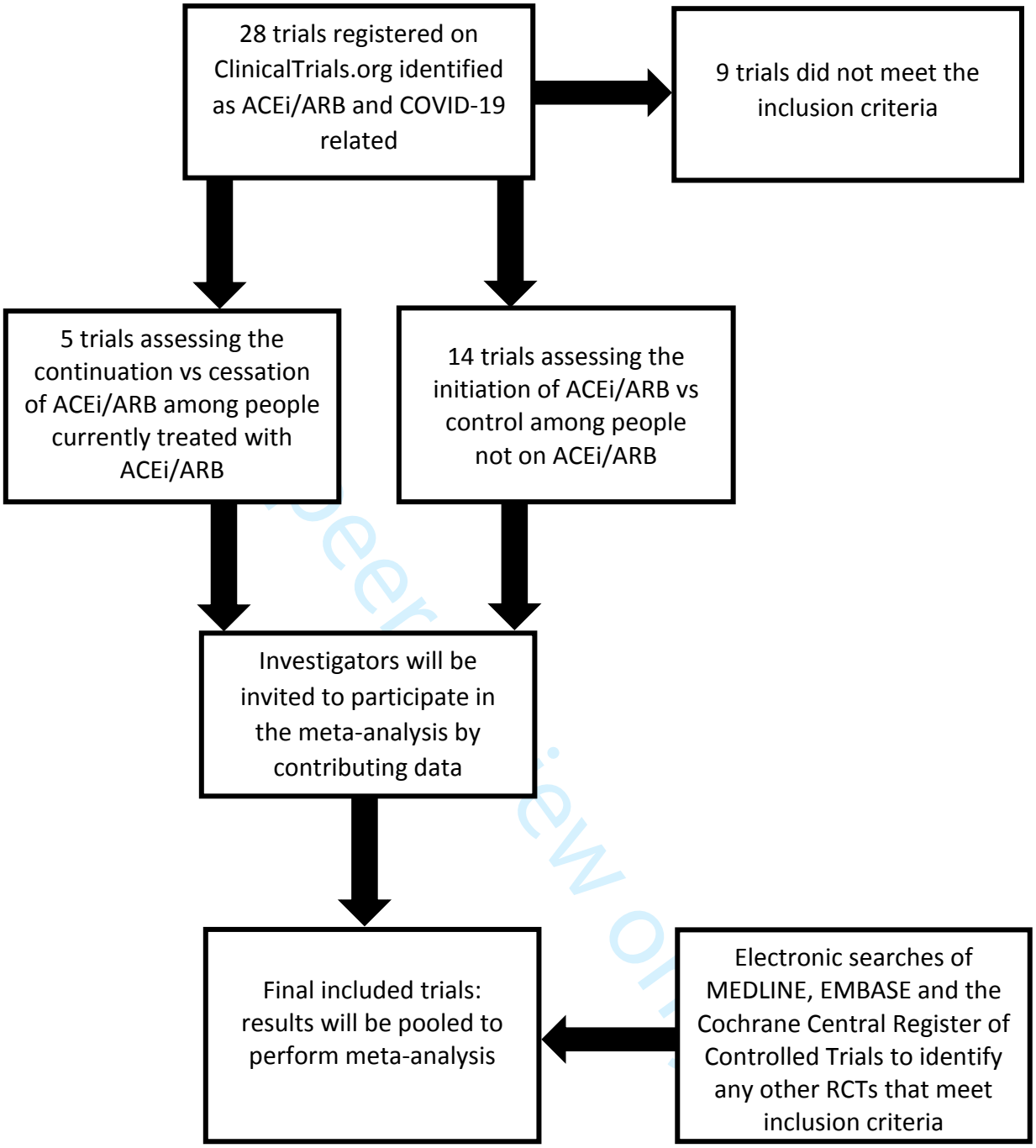

Table 1: Outcome Grouped Tabular Data

	CONTROL GROUP: NO ACEi/ARB	INTERVENTION GROUP: ACEi/ARB
BASELINE CHARACTERISTICS		
N		
Mean Age ± SD (years)		
Sex, n		
Men		
Women		
Past Medical History, n		
Hypertension		
Diabetes		
Chronic Kidney Disease		
Smoking		
Ever-smoked		
Non-smoker		
OUTCOMES FOR ≤30 DAYS		
Total number of patients in the group, n		
All-cause mortality		
Myocardial Infarction		
Congestive Cardiac Failure		
Revascularisation		
Admission to Intensive Care Unit		
Need for Mechanical ventilation		
Hospitalisation (if outpatient study)		
Pulmonary embolism/deep vein thrombosis		
OUTCOMES >1 MONTH, n		
All-cause mortality		

*N=number, SD standard deviation, ACEi angiotensin converting enzyme inhibitors, ARB angiotensin II receptor blocker

Table 2: Potential Eligible Randomised Controlled Trials of Adults with COVID-19

COUNTRY	CLINICAL TRIALS.GOV NUMBER	TREATMENT GROUP	COMPARISON GROUP	SAMPLE SIZE	INCLUSION CRITERIA	FOLLOW UP
Pennsylvania, USA	NCT04338009	Continue ACEi/ARB	Discontinue ACEi/ARB	152	18 years+ using ACEi/ARB, hospitalised	28 days
Paris, France	NCT04329195	Continue ACEi/ARB	Discontinue ACEi/ARB	554	18 years+ using ACEi/ARB, hospitalised	28 days
Sao Paulo, Brazil	NCT04364893	Continue ACEi/ARB	Discontinue ACEi/ARB	500	18 years+ using ACEi/ARB, hospitalised	30 days
Copenhagen, Denmark	NCT04351581	Continue ACEi/ARB	Discontinue ACEi/ARB	215	18 years+ using ACEi/ARB, hospitalised	30 days
Munich, Germany; Innsbruck, Austria	NCT04353596	Continue ACEi/ARB	Discontinue ACEi/ARB	208	18 years+ using ACEi/ARB,	30 days
Tanta, Egypt	NCT04345406	Captopril or enalapril	Placebo	60	18 years+, hospitalised	6 months
Vienna and Innsbruck, Austria	NCT04351724	Candesartan	Non-RAS blockade/ standard of care	500*	18 years+, hospitalised	29 days
Minnesota, USA	NCT04312009	Losartan	Placebo	200	18 years+, hospitalised	90 days
Minnesota, USA	NCT04311177	Losartan	Placebo	580	18 years+, outpatients	28 days
California, USA	NCT04340557	Losartan	Standard care	200	18 years+, mild to moderate respiratory disease with an oxygen requirement	45 days
New York, USA	NCT04328012	Losartan	Placebo	4000*	18 years+, hospitalised	60 days
s-Hertogenbosch, Arnhem, Nijmegen, Roermond, Rotterdam, Netherlands	NCT04335786	Valsartan	Placebo	651	18 years+, hospitalised	90 days
San Diego, USA	NCT04366050	Ramipril	Placebo	560	18 years+, hospitalised	14 days
Buenos Aires, Argentina	NCT04355936	Telmisartan	Standard care	400	18 years+ using ARB/ACE	90 days
Sydney, Australia	NCT04394117	ARB	Standard care	605	18 years+, SBP≥125 or SBP≥115 on non RAASI BP medications, hospitalised or high-risk features managed at home	90 days
Oyo, Nigeria; Rawalpindi, Pakistan	NCT04343001	Losartan	Standard care	10,000*	40 years+, hospitalisation	28 days
Hawaii, USA	NCT04360551	Telmisartan	Placebo	40	18 years+, outpatients	21 days
Bordeaux, France	NCT04356495	Telmisartan	Control (vitamins)	1057*	65 years+, outpatient	28 days
Strasbourg, France	NCT04359953	Telmisartan	Standard care	1600*	60 years+ if dementia or 75 years+, hospitalised	28 days

* Sample size consists of multiple trial arms including non-ACEi/ARB therapies or non-control groups

RAS, renin-angiotensin system; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BP, blood pressure

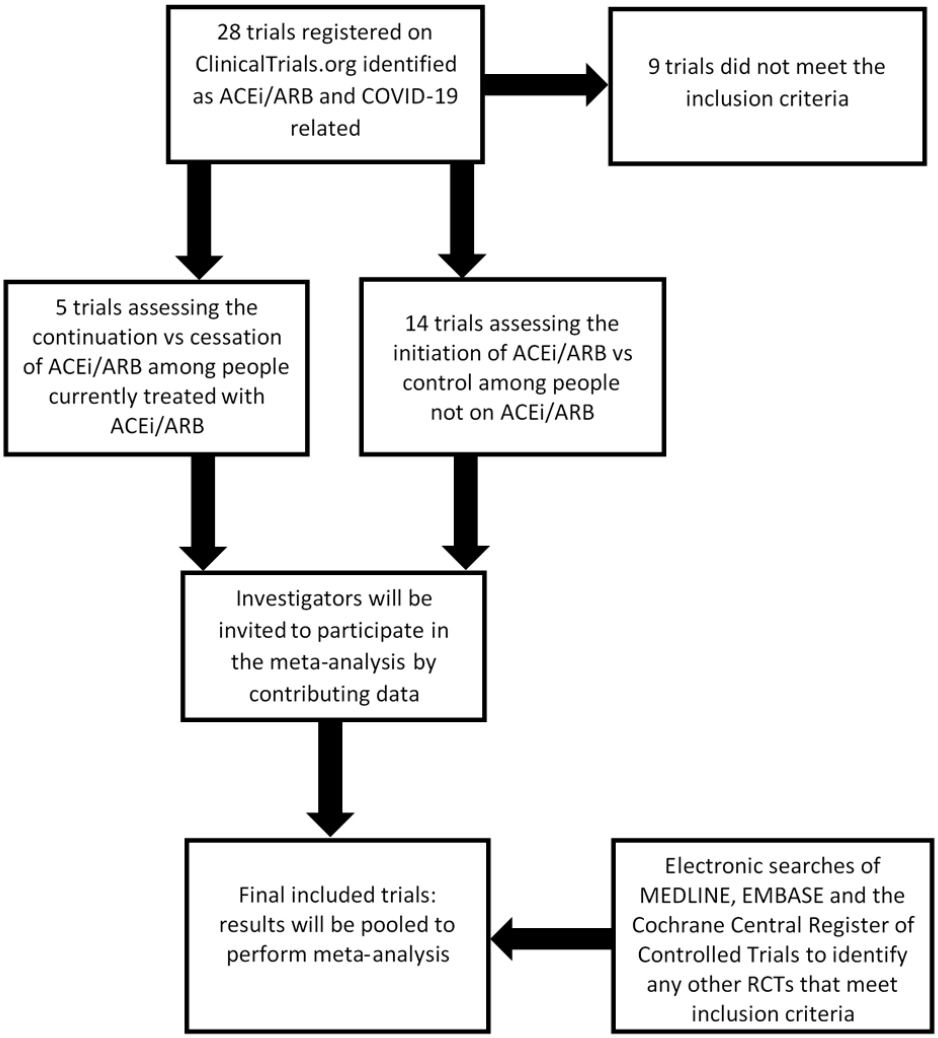

Figure 1: Flowchart of Trial Inclusion

173x208mm (144 x 144 DPI)

A Prospective Meta-Analysis Protocol on Randomised Trials of Renin-Angiotensin-System Inhibitors in Patients with Coronavirus Disease-19 (COVID-19): An initiative of the International Society of Hypertension.

Supplemental Data

Sonali R Gnanenthiran[1], Claudio Borghi[2], Dylan Burger[3], Fadi Charchar[4], Neil R Poulter[5], Markus Schlaich[6], Ulrike Muscha Steckelings[7], George S Stergiou[8], Maciej Tomaszewski[9], Thomas Unger[10], Richard D Wainford[11], Bryan Williams[12], Anthony Rodgers[1], Aletta E Schutte[1]

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12. Institute of Cardiovascular Science, University College London and National Institute for Health Research (NIHR) University College London Hospitals Biomedical Research Centre, London, United Kingdom.

Supplemental Table 1. Subgroup Analysis for All-Cause Mortality at Short Term Follow up (≤30 days)

	NO ACEi/ARB group		ACEi/ARB group	
	No. of Deaths	Total no. in subgroup	No. of Deaths	Total no. in subgroup
Sex				
Men				
Women				
Age				
<60 years				
≥60 years				
Ethnicity				
White				
South-East/East Asian				
South Asian				
African				
Other				
Comorbidities				
Hypertension				
No Hypertension				
Diabetes Mellitus				
No Diabetes Mellitus				
Chronic Kidney Disease				
No Chronic Kidney Disease				
Cardiovascular Disease				
No Cardiovascular Disease				
COPD				
No COPD				
Smoking Status				
Ever Smoked				
Non-smoker				

*ACEi angiotensin converting enzyme inhibitor, ARB angiotensin II receptor blocker, COPD chronic obstructive pulmonary disease

Supplemental Table 2: Subgroup Analysis for All-Cause Mortality at Longer Term Follow up (>1 month)

	NO ACEi/ARB group		ACEi/ARB group	
	No. of Deaths	**Total no. in subgroup**	**No. of Deaths**	**Total no. in subgroup**
Sex				
Men				
Women				
Age				
<60 years				
≥60 years				
Ethnicity				
White				
South-East/East Asian				
South Asian				
African				
Other				
Comorbidities				
Hypertension				
No Hypertension				
Diabetes Mellitus				
No Diabetes Mellitus				
Chronic Kidney Disease				
No Chronic Kidney Disease				
Cardiovascular Disease				
No Cardiovascular Disease				
COPD				
No COPD				
Smoking Status				
Ever Smoked				
Non-smoker				

*ACEi angiotensin converting enzyme inhibitor, ARB angiotensin II receptor blocker, COPD chronic obstructive pulmonary disease

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	N/A
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	16
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6-7
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	9-10
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	9-10

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10-11
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	10
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9-10
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10-11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	10-11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10-11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10-11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

A Prospective Meta-Analysis Protocol on Randomised Trials of Renin-Angiotensin-System Inhibitors in Patients with Coronavirus Disease-19 (COVID-19): An initiative of the International Society of Hypertension.

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Primary Subject Heading:	Cardiovascular medicine
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Keywords:	CARDIOLOGY, COVID-19, Hypertension < CARDIOLOGY

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A Prospective Meta-Analysis Protocol on Randomised Trials of Renin-Angiotensin System Inhibitors in Patients with Coronavirus Disease-19 (COVID-19): An initiative of the International Society of Hypertension.

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ABSTRACT

Introduction: Whether angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blocker (ARB) therapy should be continued, initiated or ceased in patients with coronavirus disease 2019 (COVID-19) is uncertain. Given the widespread use of ACEi/ARBs worldwide, guidance on the use of these drugs is urgently needed. This prospective meta-analysis aims to pool data from randomised controlled trials (RCTs) to assess the safety and efficacy of ACEi/ARB therapy in adults infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Methods and Analysis: RCTs will be eligible if they compare patients with COVID-19 randomised to ACEi/ARB continuation or commencement versus no ACEi/ARB therapy; study duration ≥14 days; recruitment completed between March 2020 and May 2021. The primary outcome will be all-cause mortality at ≤30 days. Secondary outcomes will include mechanical ventilation, admission to intensive care or cardiovascular events at short term follow-up (≤30 days), and all-cause mortality at longer term follow-up (>1 month). Pre-specified subgroup analyses will assess the effect of sex; age; comorbidities; smoking status; ethnicity; country of origin on all-cause mortality. A search of ClinicalTrials.gov has been performed, which will be followed by a formal search of trial registers, pre-print servers, MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials to identify RCTs that meet inclusion criteria. To date, a search of ClinicalTrials.gov identified 19 potentially eligible trials for this meta-analysis. We will request trial investigators/sponsors to contribute standardised grouped tabular outcome data.

Ethics and dissemination: Ethics approval and informed consent will be the responsibility of the individual RCTs. Dissemination of results will occur by peer-reviewed publication. The

results of our analysis can inform public health policy and clinical decision making regarding ACEi/ARB use in patients with COVID-19 on a global scale.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- First prospective meta-analysis of randomised controlled trials assessing the safety and efficacy of ACEi/ARBs in adults with coronavirus 2019 disease (COVID-19).
- This meta-analysis uses a collaborative international approach to allow pooling and dissemination of results. This has the potential to inform international public health policy and clinical decision making for ongoing ACEi/ARB use in patients with COVID-19.
- Randomised controlled trials are currently under way with some having the potential to be underpowered. Pooling of data will overcome this shortcoming.
- The completion of these trials prior to data pooling is a limitation, as is the willingness of trialists to collaborate in data sharing.

INTRODUCTION

Renin-angiotensin system (RAS) inhibitors, including angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB), are the most widely prescribed anti-hypertensive treatments globally, used by hundreds of millions of people worldwide.[1] 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. However, infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) involves the viral spike protein attaching to the angiotensin-converting enzyme 2 (ACE2) receptor to enter the lungs,[2] with increased binding affinity a key determinant of pathogenicity.[3] Animal studies have demonstrated that ACEi/ARB therapy may upregulate ACE2 receptor expression[4 5] and produce increased cardiac ACE2 mRNA levels, which may promote viral cell invasion.[4 6] Upregulated expression of ACE2 receptors on the cell surface has been postulated to increase the risk of infection with SARS-CoV-2 and the disease severity, with subsequent life-threatening complications.[7 8] At the same time, data from animal studies suggest that increased ACE2 expression secondary to ACEi/ARB use might have protective benefits on cardiac, kidney and pulmonary function and thus reduce the severity of coronavirus disease 2019 (COVID-19).[9]

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,[10-16] but there may be possible protective benefits including reduced rates of mortality,[17] critical disease[15] and admission to intensive care.[18] Observational studies, even rigorous ones, can still have multiple sources of bias, and thus are insufficient for sound clinical decision making. Randomised controlled trials (RCTs) are needed to mitigate this risk. However, to date reliable

data from randomised controlled clinical trials are unavailable to guide clinical decision-making. As a result, it is uncertain whether ACEi/ARB therapy should be continued, withdrawn, or initiated in patients with COVID-19.

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.[19-23] There are multiple RCTs in process, which will better inform clinical decision making rather than relying on observational human studies[10-14] and inconsistent animal data.[4 6] Most of the RCTs under way are small to moderate in size (~40% aim to recruit less than 250 participants), with many unlikely to meet their recruitment targets. These trials are also unlikely to be powered to answer questions regarding subgroup populations, including whether there is utility of ACEi/ARB therapy in patients with COVID-19 with concomitant hypertension, cardiovascular or renal disease. 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. These RCTs are not completely free from bias, but nevertheless represent a higher quality of evidence than observational studies. 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.

OBJECTIVES

We will therefore perform a prospective meta-analysis of RCTs recruiting patients with COVID-19 to assess the safety and efficacy of ACEi/ARB therapy compared to those not on ACEi/ARBs. As primary outcome, pooled data will be used to assess all-cause mortality associated with ACEi/ARB therapy compared to those not on ACEi/ARBs stratified by age, co-morbidity, sex, ethnicity, and trial characteristics.

METHODS AND ANALYSIS

Protocol Design

For this meta-analysis, we will only include RCTs to minimise the impact of bias and confounding. We herewith describe our methods as per the Preferred Reporting Items for Systematic Review and Meta-Analysis for protocol (PRISMA) recommendations.[24] Final reporting of this study will be compliant with the main PRISMA statement.

Eligibility Criteria

For clinical trials to be eligible for inclusion, the following criteria must be met: (i) RCTs recruiting between March 2020 and March 2021; (ii) aged ≥18 years; (iii) laboratory confirmed SARS-CoV-2 infection; (iv) comparison of patients randomised to ACEi/ARB versus no ACEi/ARB therapy; (v) findings reported in English; (vi) trial duration ≥14 days; (viii) oral administration of ACEi/ARB therapies.

We will include trials that investigate continuation versus cessation of ACEi/ARB among patients currently treated with ACEi/ARB; and trials that report initiation of ACEi/ARB versus control in those not currently treated with such therapies. These are essentially the same

randomisations, and so can be pooled in an ACEi/ARB vs. no ACEi/ARB meta-analysis, with appropriate prespecification of preplanned analyses from the two groups of trials. 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. The exclusion criteria will be at the discretion of each individual trial.

The intervention will comprise continuation or initiation of ACEi/ARB therapy. The control will be discontinuation of current ACEi/ARB therapy, substitution with an equivalent dose of non-ACEi/ARB therapy, placebo or usual care.

Outcomes

The primary outcome will be all-cause mortality at ≤30 days. Secondary outcomes will include mechanical ventilation at ≤30 days; admission to intensive care at ≤30 days; myocardial infarction at ≤30 days, revascularisation at ≤30 days, congestive cardiac failure at ≤30 days; pulmonary embolism and/or deep vein thrombosis at ≤30 days, hospitalisation at ≤30 days and acute kidney injury at ≤30 days; all-cause mortality at >1 month follow-up. Standardised grouped tabular de-identified data will be requested from triallists for both short-term (≤30 days) and longer term (>1 month) follow up where available (Table 1). Individual identifiable patient data will not be requested.

There is 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, but will aim to assess all-cause mortality at ≤30 days and >1 month for the following subgroups: (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 within-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 1 and 2).

Search strategy and searching sources

An electronic search of ClinicalTrial.gov was performed to identify potential ongoing trials for inclusion in the meta-analysis. Figure 1 summarises the trial search as of July 2020 performed using the search terms: coronavirus 2019, COVID-19, SARS-CoV-2, randomised controlled trial, ACEi and/or ARB. A total of 19 trials were identified which potentially met the eligibility criteria (Figure 1, Table 2). Of these, 5 trials evaluated the continuation of ACEi/ARB therapies in those already on such therapies compared to discontinuation, and 14 trials involved initiation of ACEi/ARB therapies in those not on such therapies. Nine trials did not meet inclusion criteria due to (a) not assessing ACEi/ARB therapies (n=4), (b) absence of a control

group (n=2), (c) use of non-oral administration of ACEi/ARB therapies (n=2), or (d) recruitment of patients with active malignancy (n=1). We extracted information about eligible investigators to invite them to participate in the prospective meta-analysis by contributing tabular data. An invitation letter will be sent via email and will include details about the study protocol, offer of authorship, identification of the time for data retrieval and confirmation of data security.

This search will be continuously updated, and investigators of newly reported and eligible trials will be invited to join the collaboration. Using the Cochrane Collaboration guidelines,[25] electronic searches of MEDLINE (1996–present), EMBASE (1996–present) and the Cochrane Central Register of Controlled Trials (most recent edition) will also be performed to identify any other RCTs that meet inclusion criteria in March 2021. A comprehensive search strategy using MeSH terms and text words will be used (Supplemental Table 3). Two investigators (SG and AES) will screen the abstracts for potential inclusion against the eligibility criteria, and screen the full texts. Reference management software (EndNote) will be used to store identified records.

All provided data will be stored on a password protected server, with limited access only to those directly involved in data analysis.

Study Evaluation

A quality assessment of each RCT will be performed independently by two authors (SRG, AES), with disagreements resolved by discussion. This will include evaluation of allocation sequence, allocation concealment, blinding, loss to follow-up, and completeness of outcome

reporting.[25] Randomisation procedures, treatment allocation according to assignment, outcomes collected and compared across groups; blinding methods; and risk of bias both at study and outcome levels will also be assessed using the Cochrane Risk of Bias Tool.[26] Two investigators (SG and AES) will independently review the articles and any disagreements will be adjudicated by a third independent investigator (AR).

Statistical Analysis

Trial-specific outcome data will be pooled. For binary outcomes, risk ratios and 95% CI will be estimated using log-binomial mixed-effects models (or odds ratios from logistic models as required). Key results will be presented using Forest plots, and the I_2 statistic will be used to quantify the degree of heterogeneity between studies.[27] A two-tailed p-value of 5% will be used for hypothesis testing. A fixed effects analysis will be used unless there is significant heterogeneity (as evidenced by I^2>70% and quantitatively large variation), in which case pooling will not be performed.[28] Publication bias will be assessed by visual inspection of funnel plots and formally using Egger's method to evaluate the tendency of publishing studies with statistically significant findings.[29] We will use meta-regression analyses to further explore heterogeneity of treatment effects if considerable residual heterogeneity remains after controlling for variables. Analyses will also be stratified by the prespecified subgroup analysis as mentioned above. In general, reporting of the findings will follow PRISMA guidelines.[24] All analyses will be conducted using Review Manager 5.3 software (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Data Statement

We will not have access to identifiable patient information. All data sharing and storage procedures will be compliant with the Australian Data Privacy Act of 1988. All trial data will be considered confidential and will not be provided to any third party. Data will be stored on site at The George Institute for Global Health, King St Campus, Sydney, Australia, with strict confidentiality and comprehensive data security.

Ethics and dissemination

All individual trials will require Ethics Committee or Institution Review Board approval. We will publish our findings in peer-reviewed medical journals. Publications will be in the name of the collaborative group involving all trialists who provided data. Further, we will share and present our findings at scientific meetings and through the networks and memberships across professional societies.

Implications of the review

Given the widespread use of ACEi and ARBs worldwide, guidance on the use of ACEi/ARBs in adults with COVID-19 is urgently needed, relying on evidence beyond observational data. This collaborative international approach will allow dissemination of results, which will inform public health policy and clinical decision making for ongoing ACEi/ARBs use on an international scale. Healthcare providers and policy-makers can use the findings to improve the clinical decision making by developing strategies and guidelines to guide use of ACEi/ARBs in hypertension, cardiovascular disease and kidney disease.

Patient and public involvement

Patients were not involved in the development of the research question, outcome measure and study design.

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Figure 1: Flowchart of Trial Inclusion

Table 1: Outcome Grouped Tabular Data

	NO ACEi/ARB	ACEi/ARB
BASELINE CHARACTERISTICS		
N		
Mean Age ± SD (years)		
Sex, n		
Men		
Women		
Past Medical History, n		
Hypertension		
Diabetes		
Chronic Kidney Disease		
Cardiovascular disease		
Chronic obstructive pulmonary disease		
Smoking		
Ever-smoked		
Non-smoker		
OUTCOMES FOR ≤30 DAYS		
Total number of patients in the group, n		
All-cause mortality		
Myocardial Infarction		
Congestive Cardiac Failure		
Revascularisation		
Admission to Intensive Care Unit		
Need for Mechanical ventilation		
Hospitalisation (if outpatient study)		
Pulmonary embolism/deep vein thrombosis		
Acute kidney injury		
OUTCOMES >1 MONTH, n		
All-cause mortality		

*N=number, SD standard deviation, ACEi angiotensin-converting enzyme inhibitors, ARB angiotensin II receptor blocker; acute kidney injury: decline in renal function or urine output from baseline.

Table 2: Potential Eligible Randomised Controlled Trials of Adults with COVID-19

COUNTRY	CLINICAL TRIALS.GOV NUMBER	TREATMENT GROUP	COMPARISON GROUP	SAMPLE SIZE	FOLLOW UP
Pennsylvania, USA	NCT04338009	Continue ACEi/ARB	Discontinue ACEi/ARB	152	28 days
Paris, France	NCT04329195	Continue ACEi/ARB	Discontinue ACEi/ARB	554	28 days
Sao Paulo, Brazil	NCT04364893	Continue ACEi/ARB	Discontinue ACEi/ARB	500	30 days
Copenhagen, Denmark	NCT04351581	Continue ACEi/ARB	Discontinue ACEi/ARB	215	30 days
Munich, Germany; Innsbruck, Austria	NCT04353596	Continue ACEi/ARB	Discontinue ACEi/ARB	208	30 days
Tanta, Egypt	NCT04345406	Captopril or enalapril	Placebo	60	6 months
Vienna and Innsbruck, Austria	NCT04351724	Candesartan	Non-RAS blockade/ standard of care	500*	29 days
Minnesota, USA	NCT04312009	Losartan	Placebo	200	90 days
Minnesota, USA	NCT04311177	Losartan	Placebo	580	28 days
California, USA	NCT04340557	Losartan	Standard care	200	45 days
New York, USA	NCT04328012	Losartan	Placebo	4000*	60 days
's-Hertogenbosch, Arnhem, Nijmegen, Roermond, Rotterdam, Netherlands	NCT04335786	Valsartan	Placebo	651	90 days
San Diego, USA	NCT04366050	Ramipril	Placebo	560	14 days
Buenos Aires, Argentina	NCT04355936	Telmisartan	Standard care	400	90 days
Sydney, Australia	NCT04394117	ARB	Standard care	605	90 days
Oyo, Nigeria; Rawalpindi, Pakistan	NCT04343001	Losartan	Standard care	10,000*	28 days
Hawaii, USA	NCT04360551	Telmisartan	Placebo	40	21 days
Bordeaux, France	NCT04356495	Telmisartan	Control (vitamins)	1057*	28 days
Strasbourg, France	NCT04359953	Telmisartan	Standard care	1600*	28 days

* Sample size consists of multiple trial arms including non-ACEi/ARB therapies or non-control groups

RAS, renin-angiotensin system; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BP, blood pressure

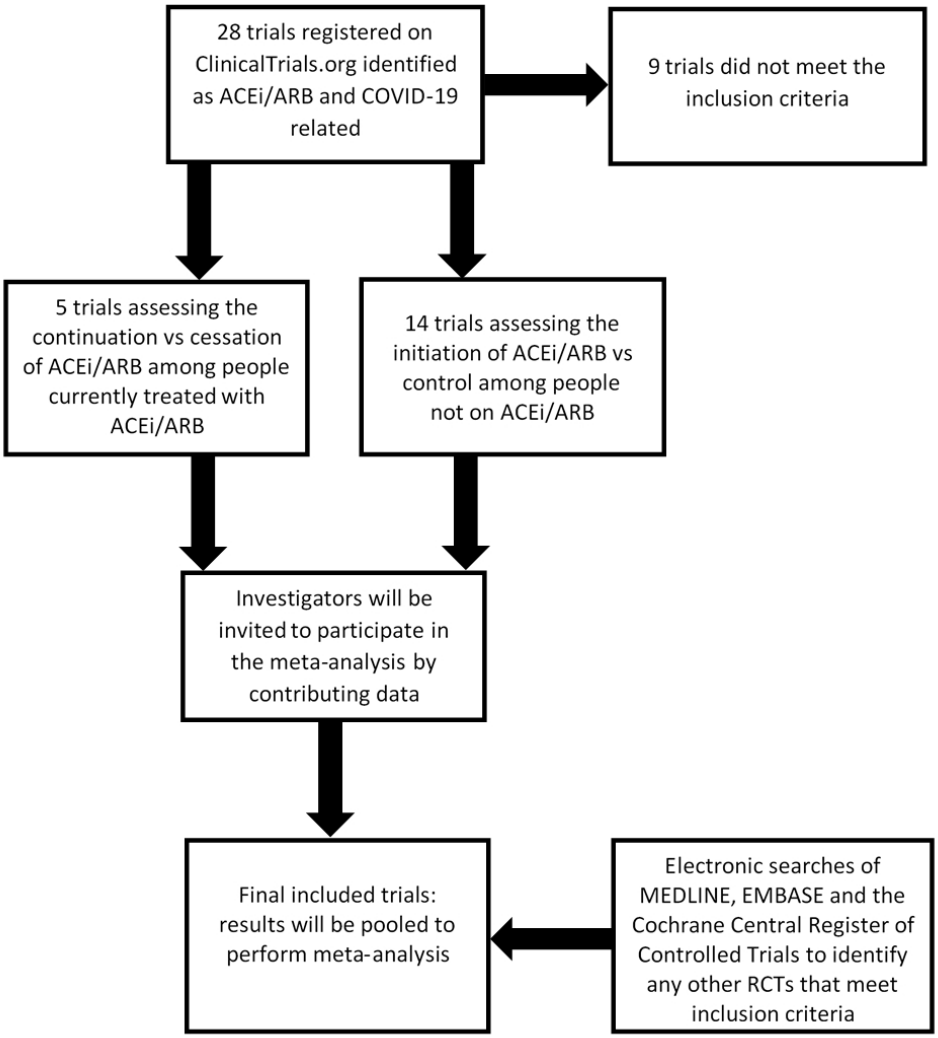

Figure 1: Flowchart of Trial Inclusion

173x208mm (144 x 144 DPI)

A Prospective Meta-Analysis Protocol on Randomised Trials of Renin-Angiotensin-System Inhibitors in Patients with Coronavirus Disease-19 (COVID-19): An initiative of the International Society of Hypertension.

Supplemental Data

Sonali R Gnanenthiran[1], Claudio Borghi[2], Dylan Burger[3], Fadi Charchar[4], Neil R Poulter[5], Markus Schlaich[6], Ulrike Muscha Steckelings[7], George S Stergiou[8], Maciej Tomaszewski[9], Thomas Unger[10], Richard D Wainford[11], Bryan Williams[12], Anthony Rodgers[1], Aletta E Schutte[1]

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9. Division of Medicine and Manchester Academic Health Science Centre, Manchester University NHS Foundation Trust Manchester, United Kingdom
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Supplemental Table 1. Subgroup Analysis for All-Cause Mortality at Short Term Follow up (≤30 days)

	NO ACEi/ARB group		ACEi/ARB group	
	No. of Deaths	Total no. in subgroup	No. of Deaths	Total no. in subgroup
Sex				
Men				
Women				
Age				
<60 years				
≥60 years				
Ethnicity				
White				
South-East/East Asian				
South Asian				
African				
Other				
Comorbidities				
Hypertension				
No Hypertension				
Diabetes Mellitus				
No Diabetes Mellitus				
Chronic Kidney Disease				
No Chronic Kidney Disease				
Cardiovascular Disease				
No Cardiovascular Disease				
COPD				
No COPD				
Smoking Status				
Ever Smoked				
Non-smoker				

*ACEi angiotensin converting enzyme inhibitor, ARB angiotensin II receptor blocker, COPD chronic obstructive pulmonary disease

Supplemental Table 2: Subgroup Analysis for All-Cause Mortality at Longer Term Follow up (>1 month)

	NO ACEi/ARB group		ACEi/ARB group	
	No. of Deaths	**Total no. in subgroup**	**No. of Deaths**	**Total no. in subgroup**
Sex				
Men				
Women				
Age				
<60 years				
≥60 years				
Ethnicity				
White				
South-East/East Asian				
South Asian				
African				
Other				
Comorbidities				
Hypertension				
No Hypertension				
Diabetes Mellitus				
No Diabetes Mellitus				
Chronic Kidney Disease				
No Chronic Kidney Disease				
Cardiovascular Disease				
No Cardiovascular Disease				
COPD				
No COPD				
Smoking Status				
Ever Smoked				
Non-smoker				

*ACEi angiotensin converting enzyme inhibitor, ARB angiotensin II receptor blocker, COPD chronic obstructive pulmonary disease

Supplemental Table 3: Search Strategy

MEDLINE	EMBASE®	Cochrane Central Register of Controlled Trials
1. exp angiotensin receptor antagonist/ 2. "angiotensin converting enzyme inhibitor*".mp. 3. "angiotensin II receptor blocker*".mp. 4. "ACEi".ti,ab,kw. 5. "ARB".ti,ab,kw. 6. 1 or 2 or 3 or 4 or 5 7. "COVID-19".mp. 8. "coronavirus-19".mp. 9. "severe acute respiratory syndrome coronavirus 2".mp. 10. "2019-nCoV".mp. 11. "SARS-CoV-2".mp. 12. "COV-2".mp. 13. "SARS coronavirus".mp. 14. 12 and 13 15. 7 or 8 or 9 or 10 or 11 or 14 16. 6 and 15 17. "randomized controlled trial"/ 18. "randomized controlled trial (topic)"/ 19. 17 or 18 20. 16 and 19	1. exp angiotensin receptor antagonist/ (91561) 2. "angiotensin converting enzyme inhibitor*".mp. (22027) 3. "angiotensin II receptor blocker*".mp. (5419) 4. "ACEi".ti,ab,kw. (8009) 5. "ARB".ti,ab,kw. (10521) 6. 1 or 2 or 3 or 4 or 5 (109156) 7. "COVID-19".mp. (49866) 8. "coronavirus-19".mp. (109) 9. "severe acute respiratory syndrome coronavirus 2".mp. (16979) 10. "2019-nCoV".mp. (1158) 11. "SARS-CoV-2".mp. (16860) 12. "COV-2".mp. (16934) 13. "SARS coronavirus".mp. (6360) 14. 12 and 13 (1045) 15. 7 or 8 or 9 or 10 or 11 or 14 (54626) 16. 6 and 15 (737) 17. "randomized controlled trial"/ (578979) 18. "randomized controlled trial (topic)"/ (187582) 19. 17 or 18 (762956) 20. 16 and 19 (30) 21. (randomi?ed and trial).mp. (928533) 22. 20 and 21 (30)	1. covid-19 OR coronavirus 19 OR coronavirus disease : in Title, Abstract 2. angiotensin receptor antagonist OR angiotensin converting enzyme inhibitor OR angiotensin II receptor blockers OR ACEi OR ARB : in Title, Abstract, Keyword 3. 1 AND 2 4. COVID in All Text 5. 3 AND 4 6. randomized control* trial* or RCT or OR "controlled clinical trial" OR clinical trial as topic 7. 5 AND 6

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	N/A
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	16
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6-7
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	9-10
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	9-10

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10-11
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	10
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9-10
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10-11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	10-11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10-11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10-11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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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.

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Infectious diseases, Global health
Keywords:	CARDIOLOGY, COVID-19, Hypertension < CARDIOLOGY

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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.

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ABSTRACT

Introduction: Whether angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blocker (ARB) therapy should be continued, initiated or ceased in patients with coronavirus disease 2019 (COVID-19) is uncertain. Given the widespread use of ACEi/ARBs worldwide, guidance on the use of these drugs is urgently needed. This prospective meta-analysis aims to pool data from randomised controlled trials (RCTs) to assess the safety and efficacy of ACEi/ARB therapy in adults infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Methods and Analysis: RCTs will be eligible if they compare patients with COVID-19 randomised to ACEi/ARB continuation or commencement versus no ACEi/ARB therapy; study duration ≥14 days; recruitment completed between March 2020 and May 2021. The primary outcome will be all-cause mortality at ≤30 days. Secondary outcomes will include mechanical ventilation, admission to intensive care or cardiovascular events at short term follow-up (≤30 days), and all-cause mortality at longer term follow-up (>1 month). Pre-specified subgroup analyses will assess the effect of sex; age; comorbidities; smoking status; ethnicity; country of origin on all-cause mortality. A search of ClinicalTrials.gov has been performed, which will be followed by a formal search of trial registers, pre-print servers, MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials to identify RCTs that meet inclusion criteria. To date, a search of ClinicalTrials.gov identified 19 potentially eligible trials for this meta-analysis. We will request trial investigators/sponsors to contribute standardised grouped tabular outcome data.

Ethics and dissemination: Ethics approval and informed consent will be the responsibility of the individual RCTs. Dissemination of results will occur by peer-reviewed publication. The

results of our analysis can inform public health policy and clinical decision making regarding ACEi/ARB use in patients with COVID-19 on a global scale.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- First prospective meta-analysis of randomised controlled trials assessing the safety and efficacy of ACEi/ARBs in adults with coronavirus 2019 disease (COVID-19).
- This meta-analysis uses a collaborative international approach to allow pooling and dissemination of results. This has the potential to inform international public health policy and clinical decision making for ongoing ACEi/ARB use in patients with COVID-19.
- Randomised controlled trials are currently under way with some having the potential to be underpowered. Pooling of data will overcome this shortcoming.
- The completion of these trials prior to data pooling is a limitation, as is the willingness of trialists to collaborate in data sharing.

INTRODUCTION

Renin-angiotensin system (RAS) inhibitors, including angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB), are the most widely prescribed anti-hypertensive treatments globally, used by hundreds of millions of people worldwide.[1] 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. However, infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) involves the viral spike protein attaching to the angiotensin-converting enzyme 2 (ACE2) receptor to infect epithelial cells in the respiratory tract,[2] with increased binding affinity a key determinant of pathogenicity.[3] Animal studies have demonstrated that ACEi/ARB therapy may upregulate ACE2 receptor expression[4] [5] and produce increased cardiac ACE2 mRNA levels, which may promote viral cell invasion.[4] [6] Upregulated expression of ACE2 receptors on the cell surface has been postulated to increase the risk of infection with SARS-CoV-2 and the disease severity, with subsequent life-threatening complications.[7] [8] At the same time, data from animal studies suggest that increased ACE2 expression secondary to ACEi/ARB use might have protective benefits on cardiac, kidney and pulmonary function and thus reduce the severity of coronavirus disease 2019 (COVID-19).[9]

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,[10-16] but there may be possible protective benefits including reduced rates of mortality,[17] critical disease[15] and admission to intensive care.[18] Observational studies, even rigorous ones, can still have multiple sources of bias, and thus more robust evidence is needed for sound clinical

decision making. Randomised controlled trials (RCTs) are needed to mitigate this risk. However, to date reliable data from randomised controlled clinical trials are unavailable to guide clinical decision-making. As a result, it is uncertain whether ACEi/ARB therapy should be continued, withdrawn, or initiated in patients with COVID-19.

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.[19-23] There are multiple RCTs in process, which will better inform clinical decision making rather than relying on observational human studies[10-14] and inconsistent animal data.[4 6] Most of the RCTs under way are small to moderate in size (~40% aim to recruit less than 250 participants), with many unlikely to meet their recruitment targets. These trials are also unlikely to be powered to answer questions regarding subgroup populations, including whether there is utility of ACEi/ARB therapy in patients with COVID-19 with concomitant hypertension, cardiovascular or kidney disease. 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. These RCTs are not completely free from bias, but nevertheless represent a higher quality of evidence than observational studies. 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.

OBJECTIVES

We will therefore perform a prospective meta-analysis of RCTs recruiting patients with COVID-19 to assess the safety and efficacy of ACEi/ARB therapy compared to those not on ACEi/ARBs. As primary outcome, pooled data will be used to assess all-cause mortality associated with ACEi/ARB therapy compared to those not on ACEi/ARBs stratified by age, co-morbidity, sex, ethnicity, and trial characteristics.

METHODS AND ANALYSIS

Protocol Design

For this meta-analysis, we will only include RCTs to minimise the impact of bias and confounding. We herewith describe our methods as per the Preferred Reporting Items for Systematic Review and Meta-Analysis for protocol (PRISMA) recommendations.[24] Final reporting of this study will be compliant with the main PRISMA statement.

Eligibility Criteria

For clinical trials to be eligible for inclusion, the following criteria must be met: (i) RCTs recruiting between March 2020 and March 2021; (ii) aged ≥18 years; (iii) laboratory confirmed SARS-CoV-2 infection; (iv) comparison of patients randomised to ACEi/ARB versus no ACEi/ARB therapy; (v) findings reported in English; (vi) trial duration ≥14 days; (viii) oral administration of ACEi/ARB therapies.

We will include trials that investigate continuation versus cessation of ACEi/ARB among patients currently treated with ACEi/ARB; and trials that report initiation of ACEi/ARB versus

control in those not currently treated with such therapies. 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. 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. If an RCT consists of multiple arms, we will include only the relevant arms. The exclusion criteria will be at the discretion of each individual trial.

The intervention will comprise continuation or initiation of ACEi/ARB therapy. The control will be discontinuation of current ACEi/ARB therapy, substitution with an equivalent dose of non-ACEi/ARB therapy, placebo or usual care.

Outcomes

The primary outcome will be all-cause mortality at ≤30 days. Secondary outcomes will include mechanical ventilation at ≤30 days; admission to intensive care at ≤30 days; myocardial infarction at ≤30 days, revascularisation at ≤30 days, congestive cardiac failure at ≤30 days; pulmonary embolism and/or deep vein thrombosis at ≤30 days, hospitalisation at ≤30 days and acute kidney injury (defined as per each individual RCT) at ≤30 days; all-cause mortality at >1 month follow-up. Standardised grouped tabular de-identified data will be requested from triallists for both short-term (≤30 days) and longer term (>1 month) follow up where available (Table 1). Individual identifiable patient data will not be requested.

Search strategy and searching sources

An electronic search of ClinicalTrial.gov was performed to identify potential ongoing trials for inclusion in the meta-analysis. Figure 1 summarises the trial search as of August 2020 performed using the search terms: coronavirus 2019, COVID-19, SARS-CoV-2, randomised controlled trial, ACEi and/or ARB. A total of 21 trials were identified which potentially met the eligibility criteria (Figure 1, Table 2). Of these, 5 trials evaluated the continuation of ACEi/ARB therapies in those already on such therapies compared to discontinuation, and 14 trials involved initiation of ACEi/ARB therapies in those not on such therapies. Eleven trials did not meet inclusion criteria due to (a) not assessing ACEi/ARB therapies (n=6), (b) absence of a control group (n=2), (c) use of non-oral administration of ACEi/ARB therapies (n=2), or (d) recruitment of patients with active malignancy (n=1). We extracted information about eligible investigators to invite them to participate in the prospective meta-analysis by contributing tabular data. An invitation letter will be sent via email and will include details about the study protocol, offer of authorship, identification of the time for data retrieval and confirmation of data security.

This search will be continuously updated, and investigators of newly reported and eligible trials will be invited to join the collaboration. Using the Cochrane Collaboration guidelines,[25] electronic searches of MEDLINE (1996–present), EMBASE (1996–present) and the Cochrane Central Register of Controlled Trials (most recent edition) will also be performed to identify any other RCTs that meet inclusion criteria in March 2021. A comprehensive search strategy using MeSH terms and text words will be used (Supplemental Table 1). Two investigators (SG and AES) will screen the abstracts for potential inclusion against the eligibility criteria, and screen the full texts. Reference management software (EndNote) will be used to store identified records.

All provided data will be stored on a password protected server, with limited access only to those directly involved in data analysis.

Study Evaluation

A quality assessment of each RCT will be performed independently by two authors (SRG, AES), with disagreements resolved by discussion. This will include evaluation of allocation sequence, allocation concealment, blinding, loss to follow-up, and completeness of outcome reporting.[25] Randomisation procedures, treatment allocation according to assignment, outcomes collected and compared across groups; blinding methods; and risk of bias both at study and outcome levels will also be assessed using the Cochrane Risk of Bias Tool.[26] Two investigators (SG and AES) will independently review the articles and any disagreements will be adjudicated by a third independent investigator (AR).

Statistical Analysis

Trial-specific outcome data will be pooled. For binary outcomes, risk ratios and 95% CI will be estimated using log-binomial mixed-effects models (or odds ratios from logistic models as required). Key results will be presented using Forest plots, and the I_2 statistic will be used to quantify the degree of heterogeneity between studies.[27] A two-tailed p-value of 5% will be used for hypothesis testing. A fixed effects analysis will be used unless there is significant heterogeneity (as evidenced by I^2>70% and quantitatively large variation), in which case pooling will not be performed.[28] 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. Publication bias will be assessed by visual inspection of funnel plots and formally using Egger's method to evaluate the tendency of publishing studies with statistically significant findings.[29] We will use meta-regression analyses to further explore heterogeneity of treatment effects if considerable residual heterogeneity remains after controlling for variables. Analyses will also be stratified by the prespecified subgroup analysis as mentioned below. In general, reporting of the findings will follow PRISMA guidelines.[24] All analyses will be conducted using Review Manager 5.3 software (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

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).

Data Statement

We will not have access to identifiable patient information. All data sharing and storage procedures will be compliant with the Australian Data Privacy Act of 1988. All trial data will be considered confidential and will not be provided to any third party. Data will be stored on site at The George Institute for Global Health, King St Campus, Sydney, Australia, with strict confidentiality and comprehensive data security.

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 follow-up duration of included trials (most ≤30 days), which prevent 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.

Ethics and dissemination

All individual trials will require Ethics Committee or Institution Review Board approval. We will publish our findings in peer-reviewed medical journals. Publications will be in the name of the collaborative group involving all trialists who provided data. Further, we will share and present our findings at scientific meetings and through the networks and memberships across professional societies.

Implications of the review

Given the widespread use of ACEi and ARBs worldwide, guidance on the use of ACEi/ARBs in adults with COVID-19 is urgently needed, relying on evidence beyond observational data. This collaborative international approach will allow dissemination of results, which will inform public health policy and clinical decision making for ongoing ACEi/ARBs use on an international scale. Healthcare providers and policy-makers can use the findings to improve the clinical decision making by developing strategies and guidelines to guide use of ACEi/ARBs in hypertension, cardiovascular disease and kidney disease.

Patient and public involvement

Patients were not involved in the development of the research question, outcome measure and study design.

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Competing Interests Statement: Nil competing interests.

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Figure 1: Flowchart of Trial Inclusion

Table 1: Outcome Grouped Tabular Data

	NO ACEi/ARB	ACEi/ARB
BASELINE CHARACTERISTICS		
N		
Mean Age ± SD (years)		
Sex, n		
Men		
Women		
Past Medical History, n		
Hypertension		
Diabetes		
Chronic Kidney Disease		
Cardiovascular disease		
Chronic obstructive pulmonary disease		
Smoking		
Ever-smoked		
Non-smoker		
OUTCOMES FOR ≤30 DAYS		
Total number of patients in the group, n		
All-cause mortality		
Myocardial Infarction		
Congestive Cardiac Failure		
Revascularisation		
Admission to Intensive Care Unit		
Need for Mechanical ventilation		
Hospitalisation (if outpatient study)		
Pulmonary embolism/deep vein thrombosis		
Acute kidney injury		
OUTCOMES >1 MONTH, n		
All-cause mortality		

*N=number, SD standard deviation, ACEi angiotensin-converting enzyme inhibitors, ARB angiotensin II receptor blocker; acute kidney injury: decline in kidney function or urine output from baseline.

Table 2: Potential Eligible Randomised Controlled Trials of Adults with COVID-19

COUNTRY	CLINICAL TRIALS.GOV NUMBER	TREATMENT GROUP	COMPARISON GROUP	SAMPLE SIZE	FOLLOW UP
Pennsylvania, USA	NCT04338009	Continue ACEi/ARB	Discontinue ACEi/ARB	152	28 days
Paris, France	NCT04329195	Continue ACEi/ARB	Discontinue ACEi/ARB	554	28 days
São Paulo, Brazil	NCT04364893	Continue ACEi/ARB	Discontinue ACEi/ARB	500	30 days
Copenhagen, Denmark	NCT04351581	Continue ACEi/ARB	Discontinue ACEi/ARB	215	30 days
Munich, Germany; Innsbruck, Austria	NCT04353596	Continue ACEi/ARB	Discontinue ACEi/ARB	208	30 days
São Paulo, Brazil	NCT04493359	Continue ACEi/ARB	Discontinue ACEi/ARB	240	30 days
Tanta, Egypt	NCT04345406	Captopril or enalapril	Placebo	60	6 months
Vienna and Innsbruck, Austria	NCT04351724	Candesartan	Non-RAS blockade/ standard of care	500*	29 days
Minnesota, USA	NCT04312009	Losartan	Placebo	200	90 days
Minnesota, USA	NCT04311177	Losartan	Placebo	580	28 days
California, USA	NCT04340557	Losartan	Standard care	200	45 days
New York, USA	NCT04328012	Losartan	Placebo	4000*	60 days
's-Hertogenbosch, Arnhem, Nijmegen, Roermond, Rotterdam, Netherlands	NCT04335786	Valsartan	Placebo	651	90 days
San Diego, USA	NCT04366050	Ramipril	Placebo	560	14 days
Buenos Aires, Argentina	NCT04355936	Telmisartan	Standard care	400	90 days
Sydney, Australia	NCT04394117	ARB	Standard care	605	90 days
Oyo, Nigeria; Rawalpindi, Pakistan	NCT04343001	Losartan	Standard care	10,000*	28 days
Hawaii, USA	NCT04360551	Telmisartan	Placebo	40	21 days
Bordeaux, France	NCT04356495	Telmisartan	Control (vitamins)	1057*	28 days
Strasbourg, France	NCT04359953	Telmisartan	Standard care	1600*	28 days
Zumpango, Estado De Mexico, Mexico	NCT04510662	Telmisartan	Standard care	60	30 days

* Sample size consists of multiple trial arms including non-ACEi/ARB therapies or non-control groups

RAS, renin-angiotensin system; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers

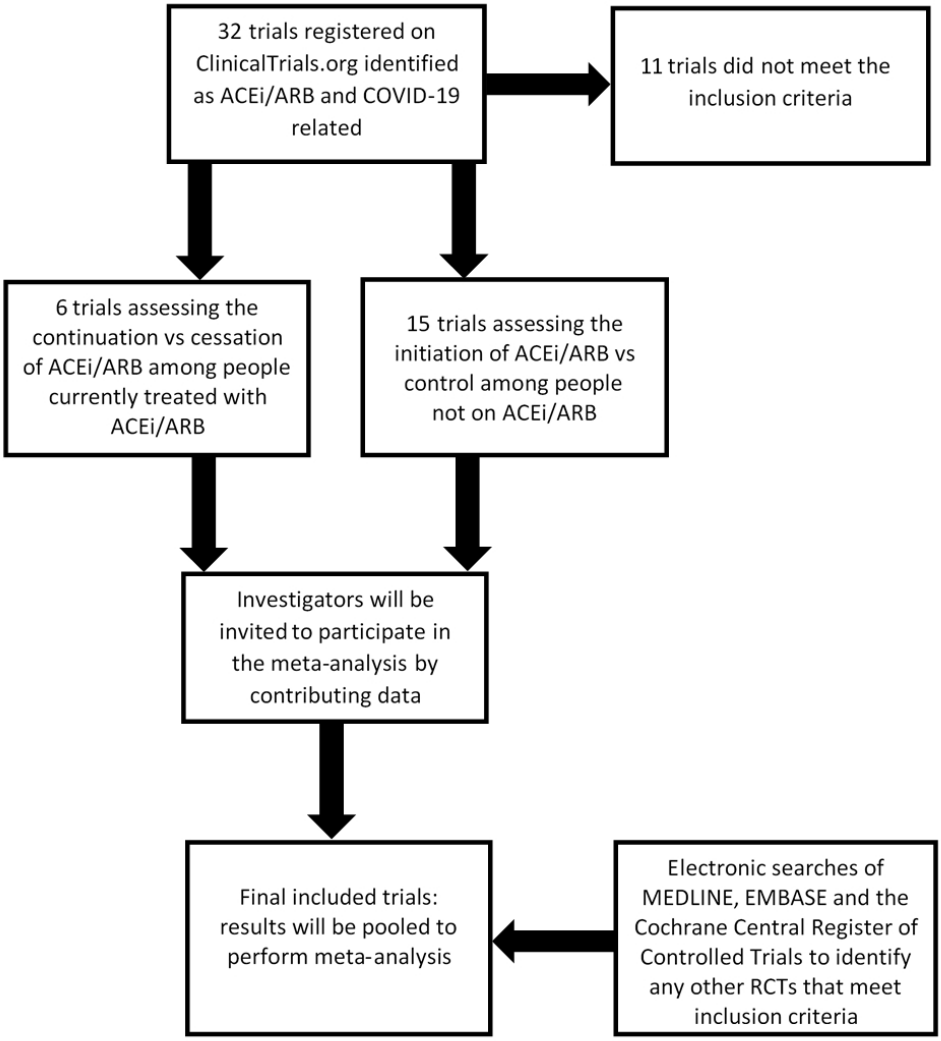

Figure 1: Flowchart of Trial Inclusion

173x188mm (144 x 144 DPI)

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.

Supplemental Data

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Supplemental Table 1: Search Strategy

MEDLINE	EMBASE®	Cochrane Central Register of Controlled Trials
1. exp angiotensin receptor antagonist/ 2. "angiotensin converting enzyme inhibitor*".mp. 3. "angiotensin II receptor blocker*".mp. 4. "ACEi".ti,ab,kw. 5. "ARB".ti,ab,kw. 6. 1 or 2 or 3 or 4 or 5 7. "COVID-19".mp. 8. "coronavirus-19".mp. 9. "severe acute respiratory syndrome coronavirus 2".mp. 10. "2019-nCoV".mp. 11. "SARS-CoV-2".mp. 12. "COV-2".mp. 13. "SARS coronavirus".mp. 14. 12 and 13 15. 7 or 8 or 9 or 10 or 11 or 14 16. 6 and 15 17. "randomized controlled trial"/ 18. "randomized controlled trial (topic)"/ 19. 17 or 18 20. 16 and 19	1. exp angiotensin receptor antagonist/ (91561) 2. "angiotensin converting enzyme inhibitor*".mp. (22027) 3. "angiotensin II receptor blocker*".mp. (5419) 4. "ACEi".ti,ab,kw. (8009) 5. "ARB".ti,ab,kw. (10521) 6. 1 or 2 or 3 or 4 or 5 (109156) 7. "COVID-19".mp. (49866) 8. "coronavirus-19".mp. (109) 9. "severe acute respiratory syndrome coronavirus 2".mp. (16979) 10. "2019-nCoV".mp. (1158) 11. "SARS-CoV-2".mp. (16860) 12. "COV-2".mp. (16934) 13. "SARS coronavirus".mp. (6360) 14. 12 and 13 (1045) 15. 7 or 8 or 9 or 10 or 11 or 14 (54626) 16. 6 and 15 (737) 17. "randomized controlled trial"/ (578979) 18. "randomized controlled trial (topic)"/ (187582) 19. 17 or 18 (762956) 20. 16 and 19 (30) 21. (randomi?ed and trial).mp. (928533) 22. 20 and 21 (30)	1. covid-19 OR coronavirus 19 OR coronavirus disease : in Title, Abstract 2. angiotensin receptor antagonist OR angiotensin converting enzyme inhibitor OR angiotensin II receptor blockers OR ACEi OR ARB : in Title, Abstract, Keyword 3. 1 AND 2 4. COVID in All Text 5. 3 AND 4 6. randomized control* trial* or RCT or OR "controlled clinical trial" OR clinical trial as topic 7. 5 AND 6

Supplemental Table 2. Subgroup Analysis for All-Cause Mortality at Short Term Follow up (≤30 days)

	NO ACEi/ARB group		ACEi/ARB group	
	No. of Deaths	**Total no. in subgroup**	**No. of Deaths**	**Total no. in subgroup**
Sex				
Men				
Women				
Age				
<60 years				
≥60 years				
Ethnicity				
White				
South-East/East Asian				
South Asian				
African				
Other				
Comorbidities				
Hypertension				
No Hypertension				
Diabetes Mellitus				
No Diabetes Mellitus				
Chronic Kidney Disease				
No Chronic Kidney Disease				
Cardiovascular Disease				
No Cardiovascular Disease				
COPD				
No COPD				
Smoking Status				
Ever Smoked				
Non-smoker				

*ACEi angiotensin-converting enzyme inhibitor, ARB angiotensin II receptor blocker, COPD chronic obstructive pulmonary disease

Supplemental Table 3: Subgroup Analysis for All-Cause Mortality at Longer Term Follow up (>1 month)

	NO ACEi/ARB group		ACEi/ARB group	
	No. of Deaths	**Total no. in subgroup**	**No. of Deaths**	**Total no. in subgroup**
Sex				
Men				
Women				
Age				
<60 years				
≥60 years				
Ethnicity				
White				
South-East/East Asian				
South Asian				
African				
Other				
Comorbidities				
Hypertension				
No Hypertension				
Diabetes Mellitus				
No Diabetes Mellitus				
Chronic Kidney Disease				
No Chronic Kidney Disease				
Cardiovascular Disease				
No Cardiovascular Disease				
COPD				
No COPD				
Smoking Status				
Ever Smoked				
Non-smoker				

*ACEi angiotensin-converting enzyme inhibitor, ARB angiotensin II receptor blocker, COPD chronic obstructive pulmonary disease

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	N/A
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	16
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6-7
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	9-10
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	9-10

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10-11
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	10
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9-10
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10-11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	10-11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10-11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10-11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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