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Prospective meta-analysis protocol on randomised trials of renin–angiotensin system inhibitors in patients with COVID-19: an initiative of the International Society of Hypertension

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ABSTRACT

Introduction Whether ACE inhibitors (ACEi) or angiotensin II receptor blocker (ARB) therapy should be continued, initiated or ceased in patients with 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 SARS-CoV-2.

Methods and analysis RCTs will be eligible if they compare patients with COVID-19 randomised to ACEi/ARB continuation or commencement versuss 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). Prespecified 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, preprint 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 21 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.

INTRODUCTION

Renin–angiotensin system (RAS) inhibitors, including ACE inhibitors (ACEi) and

Strengths and limitations of this study

► First prospective meta-analysis of randomised controlled trials assessing the safety and efficacy of ACE inhibitors (ACEi)/angiotensin II receptor blocker (ARBs) in adults with 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.

angiotensin II receptor blockers (ARBs), are the most widely prescribed antihypertensive 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 (CKD). However, infection with SARS-CoV-2 involves the viral spike protein attaching to the 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 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 RCTs 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 with those not on ACEi/ARBs. As primary outcome, pooled data will be used to assess all-cause mortality associated with ACEi/ARB therapy compared with those not on ACEi/ARBs stratified by age, comorbidity, 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 Reviews and Meta-Analyses 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: (1) RCTs recruiting between March 2020 and March 2021; (2) aged ≥18 years; (3) laboratory confirmed SARS-CoV-2 infection; (4) comparison of patients randomised to ACEi/ARB versus no ACEi/ARB therapy; (5) findings reported in English; (6) trial duration ≥14 days and (7) oral administration of ACEi/ARB therapies.

We will include trials that investigate continuation vs cessation of ACEi/ARB among patients currently treated with ACEi/ARB; and trials that report initiation of ACEi/ARB vs 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 deidentified data will be requested from triallists for both short-term (≤30 days) and longer-term

Table 1 Outcome grouped tabular data

	No ACEi/ARB	ACEi/ARB
Baseline characteristics		
N		
Mean age ±SD (years)		
Sex, n		
Men		
Women		
Medical history, n		
Hypertension		
Diabetes		
Chronic kidney disease		
Cardiovascular disease		
Chronic obstructive pulmonary disease		
Smoking		
Ever-smoked		
Non-smoker		
Outcomes for ≤30 days		
Total no 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, ACEi, ARB; acute kidney injury: decline in kidney function or urine output from baseline.
ACEi, ACE inhibitors; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; MeSH, medical subject headings.

(>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, RCT, ACEi and/or ARB. A total of 21 trials were identified which potentially met the eligibility criteria (figure 1, table 2). Of these, five trials evaluated the continuation of ACEi/ARB therapies in those already on such therapies compared with 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 (1) not assessing ACEi/ARB therapies (n=6), (2) absence of a control group (n=2), (3) use of non-oral administration of ACEi/ARB therapies (n=2) or (4) 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 (online supplemental table 1). Two investigators (SRG 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 and AES), with disagreements resolved by discussion. This will include evaluation of allocation sequence, allocation concealment, blinding, lost 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 (SRG 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 ORs 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
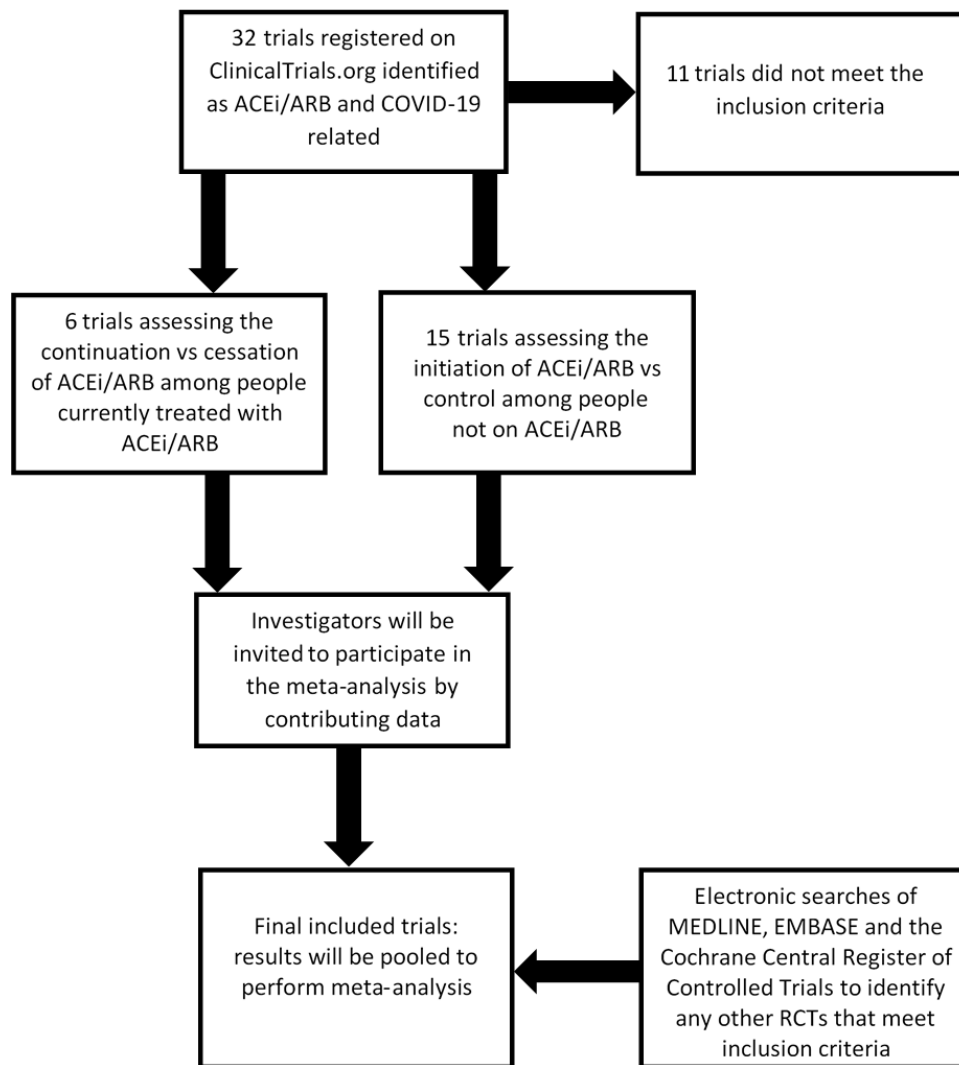
Figure 1 Flow chart of trial inclusion. ACEi, ACE inhibitors; ARB, angiotensin II receptor blocker; RCTs, randomised controlled trials.

heterogeneity (as evidenced by I²>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 V.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: (1) sex: male versus female; (2) age: <60 years versus ≥60 years; (3) comorbidities: hypertension vs no hypertension, diabetes versus no diabetes, CKD defined as eGFR <60 mL/min/1.73 m² 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; (4) smoking status: ever smoked versus non-smokers; (5) hospitalisation status: hospitalised versus non-hospitalised patients; (6) ethnicity: white, South-East/East Asian, South Asian, African and Other; (7) 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 with control; (8) region:

Table 2 Potential eligible randomised controlled trials of adults with COVID-19

Country	Clinical Trials.gov no	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.
ACEi, ACE inhibitors; ARB, angiotensin II receptor blockers; RAS, renin–angiotensin system.

Americas, Europe, Africa, South and West Asia/Middle East, and North Asia/South-East Asia/Oceania; (9) ACEi and ARB separately if feasible as pooling ACEi and ARB together does not account for between-class differences; (10) follow-up period: final short-term follow-up 14 days compared with final follow-up at 28–30 days and (11) asymptomatic versus symptomatic clinical status (online 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, CVD 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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