

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

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.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-043625
Article Type:	Protocol
Date Submitted by the Author:	09-Aug-2020
Complete List of Authors:	Gnanenthiran, Sonali; The George Institute for Global Health, ; Concord Hospital, Borghi, Claudio; S.Orsola Malpighi University Hospital, Department of Medical and Surgical Sciences Burger, Dylan; Kidney Research Centre, Ottawa Hospital Research Institute, Department of Cellular and Molecular Medicine, University of Ottawa Charchar, Fadi; Federation University Australia, Poulter, Neil; Imperial Clinical Trials Unit, Imperial College London Schlaich, Markus P.; University of Western Australia, Medical School Steckelings, Ulrike; Department of Cardiovascular and Renal Research, University of Southern Denmark Stergiou, George; Third University, Hypertension Center STRIDE-7 Tomaszewski, Maciej; Division of Medicine and Manchester Academic Health Science Centre, Manchester University NHS Foundation Trust Manchester Unger, Thomas; Maastricht University, CARIM – School for Cardiovascular Diseases Wainford, Richard; Boston University, Department of Pharmacology and Experimental Therapeutics and the Whitaker Cardiovascular Institute, Boston University School of Medicine Williams, Bryan; University College London, Institute of Cardiovascular Science; Rodgers, Anthony; The George Institute for Global Health, Sydney Medical School, University of Sydney, Schutte, Aletta; The George Institute for Global Health
Keywords:	CARDIOLOGY, COVID-19, Hypertension < CARDIOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 **A Prospective Meta-Analysis Protocol on Randomised Trials of Renin-Angiotensin-**
4
5
6 **System Inhibitors in Patients with Coronavirus Disease-19 (COVID-19):**
7
8 **An initiative of the International Society of Hypertension.**
9

10
11
12
13 Sonali R Gnanenthiran¹, Claudio Borghi², Dylan Burger³, Fadi Charchar⁴, Neil R Poulter⁵,
14 Markus Schlaich⁶, Ulrike Muscha Steckelings⁷, George S Stergiou⁸, Maciej Tomaszewski⁹,
15 Thomas Unger¹⁰, Richard D Wainford¹¹, Bryan Williams¹², Anthony Rodgers¹, Aletta E Schutte¹
16
17
18
19

- 20
21
22 1. The George Institute for Global Health, University of New South Wales, Sydney, NSW,
23 Australia
24 2. Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
25 3. Kidney Research Centre, Ottawa Hospital Research Institute, Department of Cellular and
26 Molecular Medicine, University of Ottawa, Ottawa, Canada
27 4. School of Health and Life Sciences, Federation University Australia, Ballarat, Victoria,
28 Australia
29 5. Imperial Clinical Trials Unit, Imperial College London, United Kingdom
30 6. Dobney Hypertension Centre, School of Medicine, Royal Perth Hospital Unit, University
31 of Western Australia, Perth, Australia
32 7. Department of Cardiovascular and Renal Research, University of Southern Denmark,
33 Odense, Denmark
34 8. Hypertension Center STRIDE-7, School of Medicine, Third Department of Medicine,
35 Sotiria Hospital, National and Kapodistrian University of Athens, Athens, Greece
36 9. Division of Medicine and Manchester Academic Health Science Centre, Manchester
37 University NHS Foundation Trust Manchester, United Kingdom
38 10. CARIM – School for Cardiovascular Diseases, Maastricht University, Maastricht, the
39 Netherlands
40 11. Department of Pharmacology and Experimental Therapeutics and the Whitaker
41 Cardiovascular Institute, Boston University School of Medicine, Massachusetts, USA.
42 12. Institute of Cardiovascular Science, University College London and National Institute for
43 Health Research (NIHR) University College London Hospitals Biomedical Research Centre,
44 London, United Kingdom.
45
46
47
48
49
50

51 **Address for correspondence:**

52 Professor Aletta E Schutte
53 School of Public Health and Community Medicine, University of New South Wales,
54 Kensington Campus, High Street, Sydney, NSW 2052, Australia
55 E-mail: a.schutte@unsw.edu.au; Tel: +61 450 315 918
56
57
58

59 Word count: 1843
60

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

1
2
3 results of our analysis can inform public health policy and clinical decision making regarding
4
5 ACEi/ARB use in patients with COVID-19 on a global scale.
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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.

er review only

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 disease¹⁶ 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.

1
2
3
4
5
6 International hypertension and cardiovascular societies have consistently recommended that
7
8 patients continue ACEi/ARB therapy during the COVID-19 pandemic, on the basis of the strong
9
10 and well-documented evidence on their protective effects, but identify a need for more
11
12 reliable human data.¹⁸⁻²¹ There are multiple randomised clinical trials (RCTs) in process, which
13
14 are necessary to ensure informed clinical decision making rather than relying on observational
15
16 human studies¹⁰⁻¹⁴ and inconsistent animal data.^{4 8} Most of the RCTs under way are small to
17
18 moderate in size (~40% aim to recruit less than 250 participants), with many unlikely to meet
19
20 their recruitment targets. Given the uncertainty, some trials are starting ACEi/ARB therapy
21
22 for possible benefit, while other trials are stopping the same therapy due to concerns about
23
24 harm. These are essentially the same randomisations, and so can be pooled in an ACEi/ARB
25
26 vs. no ACEi/ARB meta-analysis, with appropriate prespecification of preplanned analyses
27
28 from the two groups of trials. A prospective meta-analysis led by the International Society of
29
30 Hypertension will therefore be an ideal approach to address these limitations, as well as
31
32 promoting international collaboration. This approach entails studies to be identified,
33
34 evaluated, and determined to be eligible before the results of any included studies are known
35
36 or published, thereby avoiding some of the potential biases inherent in standard,
37
38 retrospective meta-analyses.
39
40
41
42
43
44
45
46
47
48
49

50 **OBJECTIVES**

51
52 We will therefore perform a prospective meta-analysis of RCTs recruiting COVID-19 infected
53
54 patients to assess the safety and efficacy of ACEi/ARB therapy compared to those not on
55
56 ACEi/ARBs. As primary outcome, pooled data will be used to assess all-cause mortality
57
58
59
60

1
2
3 associated with ACEi/ARB therapy compared to those not on ACEi/ARBs stratified by age, co-
4 morbidity, sex, ethnicity, and trial characteristics.
5
6
7
8
9

10 **METHODS AND ANALYSIS**

11 **Protocol Design**

12
13 For this meta-analysis, we will only include RCTs to minimise the impact of bias and
14 confounding. We herewith describe our methods as per the Preferred Reporting Items for
15 Systematic Review and Meta-Analysis for protocol (PRISMA) recommendations.²² Final
16 reporting of this study will be compliant with the main PRISMA statement.
17
18
19
20
21
22
23
24
25
26

27 **Eligibility Criteria**

28
29 For clinical trials to be eligible for inclusion, the following criteria must be met: (i) RCTs
30 recruiting between March 2020 and May 2021; (ii) aged ≥ 18 years; (iii) SARS-CoV-2 infection
31 confirmed; (iv) comparison of patients randomised to ACEi/ARB versus no ACEi/ARB therapy;
32 confirmed; (iv) comparison of patients randomised to ACEi/ARB versus no ACEi/ARB therapy;
33 (v) findings reported in English; (vi) trial duration ≥ 14 days; (viii) oral administration of
34 ACEi/ARB therapies.
35
36
37
38
39
40
41
42
43
44

45 We will include trials that investigate continuation versus cessation of ACEi/ARB among
46 patients currently treated with ACEi/ARB; and trials that report initiation of ACEi/ARB versus
47 control in those not currently treated with such therapies. Studies must contain sufficient
48 detail and be able to provide at least one outcome outlined within our data extraction form
49 (Table 1). The exclusion criteria will be at the discretion of each individual trial.
50
51
52
53
54
55
56
57
58
59
60

1
2
3 The intervention will comprise continuation or initiation of ACEi/ARB therapy. The control will
4
5 be discontinuation of current ACEi/ARB therapy, substitution with an equivalent dose of non-
6
7 ACEi/ARB therapy, placebo or usual care.
8
9

10 11 12 13 **Outcomes**

14
15 The primary outcome will be all-cause mortality at ≤ 30 days. Secondary outcomes will include
16
17 mechanical ventilation at ≤ 30 days; admission to intensive care at ≤ 30 days; myocardial
18
19 infarction at ≤ 30 days, revascularisation at ≤ 30 days, congestive cardiac failure at ≤ 30 days;
20
21 pulmonary embolism and/or deep vein thrombosis at ≤ 30 days; all-cause mortality at >1
22
23 month follow-up. Standardised grouped tabular de-identified data will be requested from
24
25 triallists for both short-term (≤ 30 days) and longer term (>1 month) follow up where available
26
27 (Table 1). Individual identifiable patient data will not be requested.
28
29
30
31
32
33
34

35 Sensitivity analyses will be performed depending on data availability, but will aim to assess
36
37 all-cause mortality at ≤ 30 days and >1 month for the following subgroups: (i) sex: male versus
38
39 female; (ii) age: <60 years versus ≥ 60 years; (iii) comorbidities: hypertension versus no
40
41 hypertension, diabetes versus no diabetes, chronic kidney disease (CKD) defined as $eGFR < 60$
42
43 $mL/min/1.73m^2$ versus no CKD, cardiovascular disease (CVD) [defined as established coronary
44
45 artery disease, heart failure, arrhythmia and/or stroke] versus no CVD, chronic obstructive
46
47 pulmonary disease versus no chronic obstructive pulmonary disease; (iv) smoking status: ever
48
49 smoked versus non-smokers; (v) hospitalisation status: hospitalised versus non-hospitalised
50
51 patients; (vi) ethnicity: White, South-East/East Asian, South Asian, African and Other; (vii) trial
52
53 type: randomised trials that investigate continuation and cessation of ACEi/ARBs among
54
55 patients currently treated with ACEi/ARBs, versus trials that investigate initiation of
56
57
58
59
60

1
2
3 ACEi/ARBs in those not currently treated with such therapies compared to control; (vii)
4
5 region: Americas, Europe, Africa, South and West Asia/Middle East, and North Asia/South-
6
7 East Asia/Oceania (viii) ACEi and ARB separately if feasible (Supplemental Tables 1 and 2).
8
9

10 11 12 13 **Search strategy and searching sources**

14
15 An electronic search of ClinicalTrial.gov was performed to identify potential ongoing trials for
16
17 inclusion in the meta-analysis. Figure 1 summarises the trial search as of July 2020 performed
18
19 using the search terms: coronavirus-19, COVID-19, SARS-CoV-2, randomised controlled trial,
20
21 ACEi and/or ARB. A total of 19 trials were identified which potentially met the eligibility
22
23 criteria (Figure 1, Table 2). Of these, 5 trials evaluated the continuation of ACEi/ARB therapies
24
25 in those already on such therapies compared to discontinuation, and 15 trials involved
26
27 initiation of ACEi/ARB therapies in those not on such therapies. Nine trials did not meet
28
29 inclusion criteria due to (a) not assessing ACEi/ARB therapies (n=4), (b) absence of a control
30
31 group (n=2), (c) use of non-oral administration of ACEi/ARB therapies (n=2), or (d) recruitment
32
33 of patients with active malignancy (n=1). We extracted information about eligible
34
35 investigators to invite them to participate in the prospective meta-analysis by contributing
36
37 tabular data. An invitation letter will be sent via email and will include details about the study
38
39 protocol, offer of authorship, identification of the time for data retrieval and confirmation of
40
41 data security.
42
43
44
45
46
47
48
49
50

51
52 This search will be continuously updated, and investigators of newly reported and eligible
53
54 trials will be invited to join the collaboration. Using the Cochrane Collaboration guidelines,²³
55
56 electronic searches of MEDLINE (1996–present), EMBASE (1996–present) and the Cochrane
57
58 Central Register of Controlled Trials (most recent edition) will also be performed to identify
59
60

1
2
3 any other RCTs that meet inclusion criteria. A comprehensive search strategy using MeSH
4 terms and text words will be used. Two investigators (SG and AS) will screen the abstracts for
5
6 potential inclusion against the eligibility criteria, and screen the full texts. Reference
7
8 management software (EndNote) will be used to store identified records.
9
10
11
12
13
14

15 All provided data will be stored on a password protected server, with limited access only to
16
17 those directly involved in data analysis.
18
19
20
21
22

23 **Study Evaluation**

24
25 When conducting the prospective meta-analysis of RCTs, we will undertake a quality
26
27 assessment of each RCT using the CONSORT (CONsolidated Standards of Reporting Trials)
28
29 checklist.²⁴ Randomisation procedures, treatment allocation according to assignment,
30
31 outcomes collected and compared across groups; blinding methods; and risk of bias both at
32
33 study and outcome levels will also be assessed using the Cochrane Risk of Bias Tool.²⁵ Two
34
35 investigators (SG and AS) will independently review the articles and any disagreements will
36
37 be adjudicated by a third independent investigator (AR).
38
39
40
41
42
43
44

45 **Statistical Analysis**

46
47 Trial-specific outcome data will be pooled. For binary outcomes, risk ratios and 95% CI will be
48
49 estimated using log-binomial mixed-effects models (or odds ratios from logistic models as
50
51 required). Key results will be presented using Forest plots, and the I^2 statistic will be used to
52
53 quantify the degree of heterogeneity between studies.²⁶ A two-tailed p-value risk of 5% will
54
55 be used for hypothesis testing. A fixed effects analysis will be used unless there is significant
56
57 heterogeneity (as evidenced by $I^2 > 70\%$ and quantitatively large variation), in which case
58
59
60

1
2
3 pooling will not be performed.²⁷ Publication bias will be assessed by visual inspection of
4
5 funnel plots and formally using Egger's method to evaluate the tendency of publishing studies
6
7 with statistically significant findings.²⁸ We will use meta-regression analyses to further explore
8
9 heterogeneity of treatment effects if considerable residual heterogeneity remains after
10
11 controlling for variables. Analyses will also be stratified by the prespecified subgroup analysis
12
13 as mentioned above. In general, reporting of the findings will follow PRISMA guidelines.²² All
14
15 analyses will be conducted using Review Manager 5.3 software (Copenhagen, The Nordic
16
17 Cochrane Centre, The Cochrane Collaboration, 2014).
18
19
20
21
22
23
24

25 **Data Statement**

26
27 We will not have access to identifiable patient information. All data sharing and storage
28
29 procedures will be compliant with the Australian Data Privacy Act of 1988. All trial data will
30
31 be considered confidential and will not be provided to any third party. Data will be stored on
32
33 site at The George Institute for Global Health, King St Campus, Sydney, Australia, with strict
34
35 confidentiality and comprehensive data security.
36
37
38
39
40
41

42 **Ethics and dissemination**

43
44 All individual trials will require Ethics Committee or Institution Review Board approval. We
45
46 will publish our findings in peer-reviewed medical journals. Publications will be in the name
47
48 of the collaborative group involving all trialists who provided data. Further, we will share and
49
50 present our findings at scientific meetings and through the networks and memberships across
51
52 professional societies.
53
54
55
56
57
58

59 **Implications of the review**

1
2
3 Given the widespread use of ACE inhibitors and ARBs worldwide, guidance on the use of
4
5 ACEi/ARBs in adults with COVID-19 infection is urgently needed relying on evidence beyond
6
7 observational data. This collaborative international approach will allow dissemination of
8
9 results, which will inform public health policy and clinical decision making for ongoing
10
11 ACEi/ARBs use on an international scale. Healthcare providers and policy-makers can use the
12
13 findings to improve the clinical decision making by developing strategies and guidelines to
14
15 guide use of ACEi/ARBs in hypertension, cardiovascular disease and renal disease.
16
17
18
19
20
21
22

23 **Patient and public involvement**

24
25 Patients were not involved in the development of the research question, outcome measure
26
27 and study design.
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

REFERENCES

1. Gu Q, Burt VL, Dillon CF, Yoon S. Trends in antihypertensive medication use and blood pressure control among United States adults with hypertension: the National Health And Nutrition Examination Survey, 2001 to 2010. *Circulation* 2012 126(17):2105-14.
2. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, Choe H, Farzan M. Angiotensin-converting Enzyme 2 Is a Functional Receptor for the SARS Coronavirus. *Nature* 2003;426(6965):450-54.
3. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181:271-80.
4. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, Diz DI, Gallagher PE. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation* 2005 111(20):2605-10.
5. Igase M, Kohara K, Nagai T, Miki T and Ferrario CM. Increased expression of angiotensin converting enzyme 2 in conjunction with reduction of neointima by angiotensin II type 1 receptor blockade. *Hypertens Res* 2008;31:553-9.
6. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Resp Med* 2020;8(4):e21.
7. Sommerstein R, Grani C. Preventing a covid-19 pandemic: ACE inhibitors as a potential risk factor for fatal Covid-19. *BMJ* 2020;368:m810.
8. Ocaranza MP, Moya J, Barrientos V, Alzamora R, Hevia D, Morales C, Pinto M, Escudero N, García L, Novoa U, Ayala P, Díaz-Araya G, Godoy I, Chiong M, Lavandero S, Jalil JE, Michea L. Angiotensin-(1-9) Reverses Experimental Hypertension and Cardiovascular Damage by Inhibition of the Angiotensin Converting enzyme/Ang II Axis. *J Hypertens* 2014 32(4):771-83.
9. Sparks MA, South A, Welling P, Luther M, Cohen J, Byrd JB, Burrell L, Battle D, Tomlinson L, Bhalla V, Rheault MN, Soler MJ, Swaminathan S, Hiremath S. Sound Science Before Quick Judgement Regarding RAS Blockade in COVID-19. *Clin J Am Soc Nephrol* 2020 7(15):714-16.
10. de Abajo FJ, Rodriguez-Martin S, Lerma V, Mejía-Abril G, Aguilar M, García-Luque A, Laredo L, Laosa O, Centeno-Soto GA, Ángeles Gálvez M, Puerro M, González-Rojano E, Pedraza L, de Pablo I, Abad-Santos F, Rodríguez-Mañas L, Gil M, Tobías A, Rodríguez-Miguel A, Rodríguez-Puyol D; MED-ACE2-COVID19 study group. Use of renin-angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. *Lancet* 2020;395(10238):1705-14.
11. Jung SY, Choi JC, You SH, Kim WY. Association of renin-angiotensin-aldosterone system inhibitors with COVID-19-related outcomes in Korea: a nationwide population-based cohort study. *Clin Infect Dis* 2020;Epub ahead of print
12. Li J, Wang X, Chen J, Zhang H, Deng A. Association of Renin-Angiotensin System Inhibitors With Severity or Risk of Death in Patients With Hypertension Hospitalized for Coronavirus Disease 2019 (COVID-19) Infection in Wuhan, China. *JAMA Cardiol* 2020;epub ahead of print
13. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19. *N Engl J Med* 2020;382(25):2431-40.

14. Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Iturrate E, Johnson SB, Hausvater A, Newman JD, Berger JS, Bangalore S, Katz SD, Fishman GI, Kunichoff D, Chen Y, Ogedegbe G, Hochman JS. Renin-Angiotensin-Aldosterone System Inhibitors and Risk of Covid-19. *N Engl J Med* 2020;382(25):2441-48.
15. Zhang P, Zhu L, Cai J, Lei F, Qin J, Xie J, Liu Y, Zhao Y, et al. Association of Inpatient Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Mortality Among Patients With Hypertension Hospitalized With COVID-19. *Circ Res* 2020 126(12):1671-81.
16. Pirola CJ, Sookoian S. Estimation of Renin-Angiotensin-Aldosterone-System (RAAS)-Inhibitor Effect on COVID-19 Outcome: A Meta-analysis. *J Infect* 2020 S0163-4453(20):30329-7.
17. Felice C, Nardin C, Di Tanna GL, Grossi U, Bernardi E, Scaldaferrri L, Romagnoli M, Tonon L, Cavasin P, Novello S, Scarpa R, Farnia A, De Menis E, Rigoli R, Cinetto F, Pauletto P, Agostini C, Rattazzi M. Use of RAAS inhibitors and risk of clinical deterioration in COVID-19: results from an Italian cohort of 133 hypertensives. *Am J Hypertens* 2020; epub ahead of print
18. International Society of Hypertension. Statement on COVID-19. 2020
19. American College of Cardiology, American Heart Association and Heart Failure Society of America. Patients taking ACE-i and ARBs who contract COVID-19 should continue treatment, unless otherwise advised by their physician 2020 [Available from: <https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19> accessed May 6 2020.
20. European Society of Cardiology Council on Hypertension. Position statement of the ESC Council on Hypertension on ACE-inhibitors and angiotensin receptor blockers 2020 [Available from: [https://www.escardio.org/Councils/Council-on-Hypertension-\(CHT\)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang](https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang).
21. European Society of Hypertension. Statement on COVID-19 2020 [Available from: <https://www.eshonline.org/spotlights/esh-statement-on-covid-19/>.
22. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;21(339)
23. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.0 (updated July 2019): Cochrane, 2019.
24. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
25. Higgins JP, Altman DG, Gotzsche P, Jüni P, et al. Cochrane bias methods group; cochrane statistical methods group. the cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:1–9.
26. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21(11):1539–58.
27. Hedges LV, Vevea JL. Fixed- and random-effects models in meta-analysis. *Psychol Methods* 1998;3(4):486–504.

- 1
2
3 28. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple,
4 graphical test. *BMJ* 1997;315:629–34.
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3 **Authors' Contributions:** SG, AR and AES were involved in the planning and writing of this
4
5 protocol. CB, DB, FC, NRP, MS, UMS, GSS, MT, TU, RDW and BW reviewed the protocol and
6
7 provided intellectual input.
8
9

10
11
12
13 **Funding Statement:** This research received no specific grant from any funding agency in the
14
15 public, commercial or not-for-profit sectors.
16
17

18
19
20 **Competing Interests Statement:** Nil competing interests.
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 1: Flowchart of Trial Inclusion

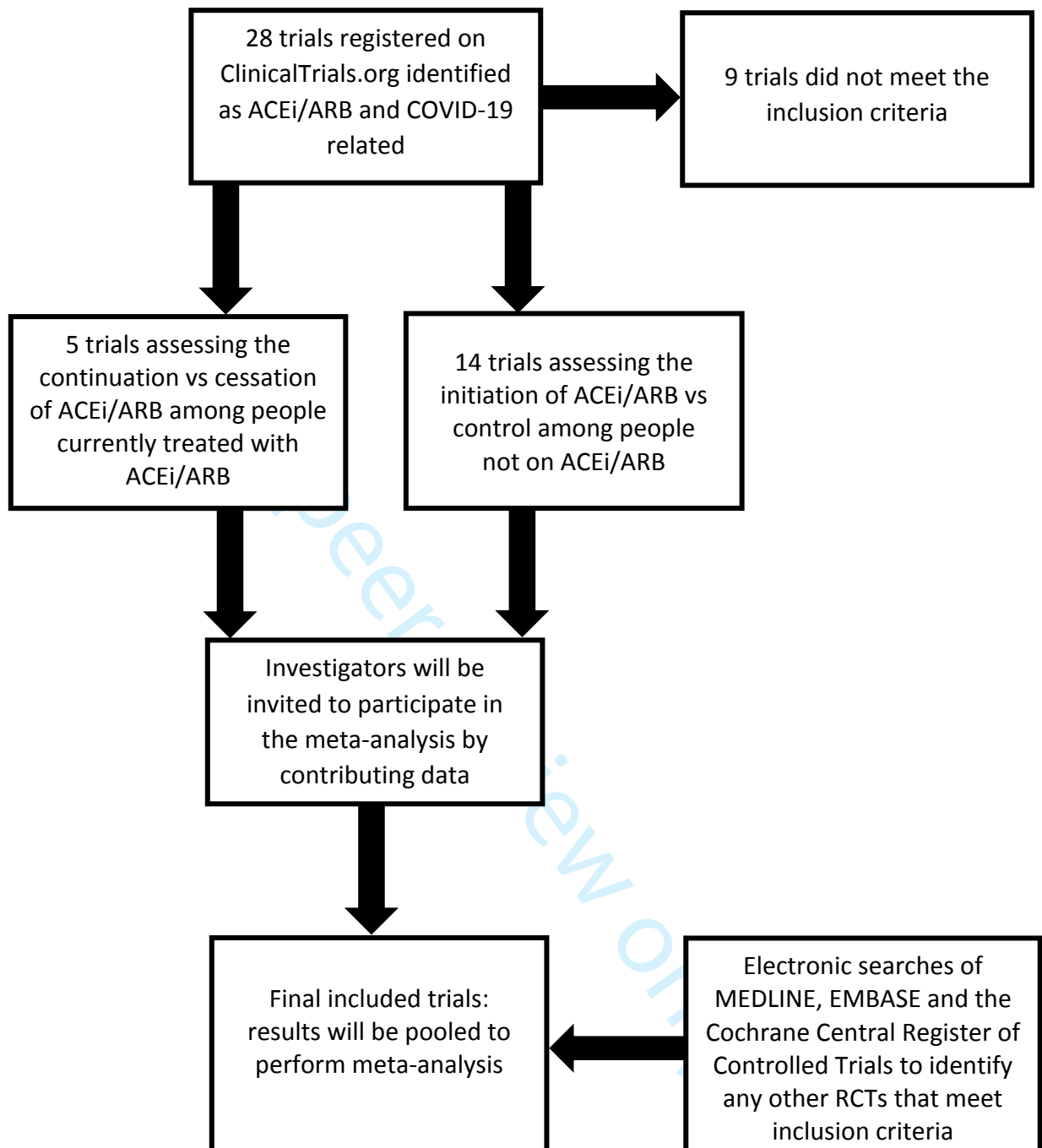


Table 1: Outcome Grouped Tabular Data

	CONTROL GROUP: NO ACEi/ARB	INTERVENTION GROUP: ACEi/ARB
BASELINE CHARACTERISTICS		
N		
Mean Age \pm 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
Cairo, 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
Eindhoven, Nijmegen, Kerkrade, 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 \geq 125 or SBP \geq 115 on non RAASI BP medications, hospitalised or high-risk features managed at home	90 days
Lagos, 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

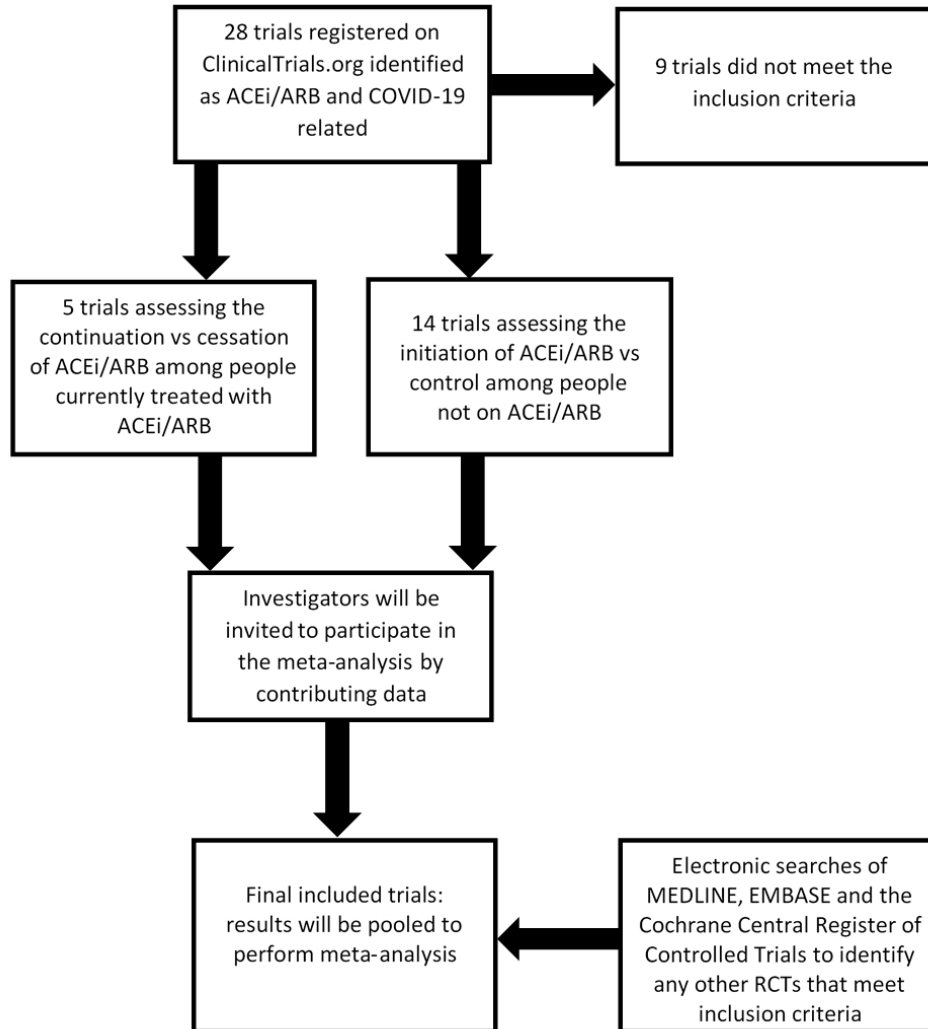


Figure 1: Flowchart of Trial Inclusion

173x208mm (144 x 144 DPI)

1
2
3 **A Prospective Meta-Analysis Protocol on Randomised Trials of Renin-Angiotensin-**
4
5
6 **System Inhibitors in Patients with Coronavirus Disease-19 (COVID-19):**
7
8 **An initiative of the International Society of Hypertension.**
9

10
11
12
13 **Supplemental Data**
14

15
16 Sonali R Gnanenthiran¹, Claudio Borghi², Dylan Burger³, Fadi Charchar⁴, Neil R Poulter⁵,
17
18 Markus Schlaich⁶, Ulrike Muscha Steckelings⁷, George S Stergiou⁸, Maciej Tomaszewski⁹,
19
20 Thomas Unger¹⁰, Richard D Wainford¹¹, Bryan Williams¹², Anthony Rodgers¹, Aletta E Schutte¹
21

- 22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
1. The George Institute for Global Health, University of New South Wales, Sydney, NSW, Australia
 2. Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
 3. Kidney Research Centre, Ottawa Hospital Research Institute, Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, Canada
 4. School of Health and Life Sciences, Federation University Australia, Ballarat, Victoria, Australia
 5. Imperial Clinical Trials Unit, Imperial College London, United Kingdom
 6. Dobney Hypertension Centre, School of Medicine, Royal Perth Hospital Unit, University of Western Australia, Perth, Australia
 7. Department of Cardiovascular and Renal Research, University of Southern Denmark, Odense, Denmark
 8. Hypertension Center STRIDE-7, School of Medicine, Third Department of Medicine, Sotiria Hospital, National and Kapodistrian University of Athens, Athens, Greece
 9. Division of Medicine and Manchester Academic Health Science Centre, Manchester University NHS Foundation Trust Manchester, United Kingdom
 10. CARIM – School for Cardiovascular Diseases, Maastricht University, Maastricht, the Netherlands
 11. Department of Pharmacology and Experimental Therapeutics and the Whitaker Cardiovascular Institute, Boston University School of Medicine, Massachusetts, USA.
 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.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-043625.R1
Article Type:	Protocol
Date Submitted by the Author:	22-Oct-2020
Complete List of Authors:	Gnanenthiran, Sonali; The George Institute for Global Health, ; Concord Hospital, Borghi, Claudio; S.Orsola Malpighi University Hospital, Department of Medical and Surgical Sciences Burger, Dylan; Kidney Research Centre, Ottawa Hospital Research Institute, Department of Cellular and Molecular Medicine, University of Ottawa Charchar, Fadi; Federation University Australia, Poulter, Neil; Imperial Clinical Trials Unit, Imperial College London Schlaich, Markus P.; University of Western Australia, Medical School Steckelings, Ulrike; Department of Cardiovascular and Renal Research, University of Southern Denmark Stergiou, George; Third University, Hypertension Center STRIDE-7 Tomaszewski, Maciej; Division of Medicine and Manchester Academic Health Science Centre, Manchester University NHS Foundation Trust Manchester Unger, Thomas; Maastricht University, CARIM – School for Cardiovascular Diseases Wainford, Richard; Boston University, Department of Pharmacology and Experimental Therapeutics and the Whitaker Cardiovascular Institute, Boston University School of Medicine Williams, Bryan; University College London, Institute of Cardiovascular Science; Rodgers, Anthony; The George Institute for Global Health, Sydney Medical School, University of Sydney, Schutte, Aletta; The George Institute for Global Health
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Infectious diseases
Keywords:	CARDIOLOGY, COVID-19, Hypertension < CARDIOLOGY

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60





I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 **A Prospective Meta-Analysis Protocol on Randomised Trials of Renin-Angiotensin**
4
5
6 **System Inhibitors in Patients with Coronavirus Disease-19 (COVID-19):**
7
8 **An initiative of the International Society of Hypertension.**
9

10
11
12
13 Sonali R Gnanenthiran¹, Claudio Borghi², Dylan Burger³, Fadi Charchar⁴, Neil R Poulter⁵,
14 Markus Schlaich⁶, Ulrike Muscha Steckelings⁷, George S Stergiou⁸, Maciej Tomaszewski⁹,
15 Thomas Unger¹⁰, Richard D Wainford¹¹, Bryan Williams¹², Anthony Rodgers¹, Aletta E Schutte¹
16
17
18
19

- 20
21
22 1. The George Institute for Global Health; University of New South Wales, Sydney, NSW,
23 Australia
24 2. Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
25 3. Kidney Research Centre, Ottawa Hospital Research Institute, Department of Cellular and
26 Molecular Medicine, University of Ottawa, Ottawa, Canada
27 4. School of Health and Life Sciences, Federation University Australia, Ballarat, Victoria,
28 Australia
29 5. Imperial Clinical Trials Unit, Imperial College London, United Kingdom
30 6. Dobney Hypertension Centre, School of Medicine, Royal Perth Hospital Unit, University
31 of Western Australia, Perth, Australia
32 7. Department of Cardiovascular and Renal Research, University of Southern Denmark,
33 Odense, Denmark
34 8. Hypertension Center STRIDE-7, School of Medicine, Third Department of Medicine,
35 Sotiria Hospital, National and Kapodistrian University of Athens, Athens, Greece
36 9. Division of Medicine and Manchester Academic Health Science Centre, Manchester
37 University NHS Foundation Trust Manchester, United Kingdom
38 10. CARIM – School for Cardiovascular Diseases, Maastricht University, Maastricht, the
39 Netherlands
40 11. Department of Pharmacology and Experimental Therapeutics and the Whitaker
41 Cardiovascular Institute, Boston University School of Medicine, Massachusetts, USA.
42 12. Institute of Cardiovascular Science, University College London and National Institute for
43 Health Research (NIHR) University College London Hospitals Biomedical Research Centre,
44 London, United Kingdom.
45
46
47
48
49
50

51 **Address for correspondence:**

52 Professor Aletta E Schutte
53 School of Population Health, University of New South Wales, Kensington Campus, High
54 Street, Sydney, NSW 2052, Australia
55 E-mail: a.schutte@unsw.edu.au; Tel: +61 450 315 918
56
57

58 Word count: 2032
59
60

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

1
2
3 results of our analysis can inform public health policy and clinical decision making regarding
4
5 ACEi/ARB use in patients with COVID-19 on a global scale.
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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.

review only

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 disease¹⁵ 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

1
2
3 data from randomised controlled clinical trials are unavailable to guide clinical decision-
4 making. As a result, it is uncertain whether ACEi/ARB therapy should be continued,
5
6 withdrawn, or initiated in patients with COVID-19.
7
8
9

10
11
12 International hypertension, cardiovascular and nephrology societies have consistently
13 recommended that patients continue ACEi/ARB therapy during the COVID-19 pandemic, on
14 the basis of the strong and well-documented evidence on their protective effects, but identify
15 a need for more reliable human data.¹⁹⁻²³ There are multiple RCTs in process, which will better
16 inform clinical decision making rather than relying on observational human studies¹⁰⁻¹⁴ and
17 inconsistent animal data.^{4 6} Most of the RCTs under way are small to moderate in size (~40%
18 aim to recruit less than 250 participants), with many unlikely to meet their recruitment
19 targets. These trials are also unlikely to be powered to answer questions regarding subgroup
20 populations, including whether there is utility of ACEi/ARB therapy in patients with COVID-19
21 with concomitant hypertension, cardiovascular or renal disease. Given the uncertainty of
22 ACEi/ARB use in those with COVID-19, some trials are starting ACEi/ARB therapy for possible
23 benefit, while other trials are stopping the same therapy due to concerns about harm. These
24 RCTs are not completely free from bias, but nevertheless represent a higher quality of
25 evidence than observational studies. A prospective meta-analysis led by the International
26 Society of Hypertension will therefore be an ideal approach to address these limitations, as
27 well as promoting international collaboration. This approach entails studies to be identified,
28 evaluated, and determined to be eligible before the results of any included studies are known
29 or published, thereby avoiding some of the potential biases inherent in standard,
30 retrospective meta-analyses.
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 randomisations, and so can be pooled in an ACEi/ARB vs. no ACEi/ARB meta-analysis, with
4 appropriate prespecification of preplanned analyses from the two groups of trials. Studies
5
6 must contain sufficient detail and be able to provide at least one outcome outlined within our
7
8 data extraction form (Table 1) and be reported using an intention to treat basis. The exclusion
9
10
11
12
13 criteria will be at the discretion of each individual trial.
14
15
16
17

18 The intervention will comprise continuation or initiation of ACEi/ARB therapy. The control will
19
20 be discontinuation of current ACEi/ARB therapy, substitution with an equivalent dose of non-
21
22 ACEi/ARB therapy, placebo or usual care.
23
24
25
26
27

28 **Outcomes**

29
30 The primary outcome will be all-cause mortality at ≤ 30 days. Secondary outcomes will include
31
32 mechanical ventilation at ≤ 30 days; admission to intensive care at ≤ 30 days; myocardial
33
34 infarction at ≤ 30 days, revascularisation at ≤ 30 days, congestive cardiac failure at ≤ 30 days;
35
36 pulmonary embolism and/or deep vein thrombosis at ≤ 30 days, hospitalisation at ≤ 30 days
37
38 and acute kidney injury at ≤ 30 days; all-cause mortality at >1 month follow-up. Standardised
39
40 grouped tabular de-identified data will be requested from trialists for both short-term (≤ 30
41
42 days) and longer term (>1 month) follow up where available (Table 1). Individual identifiable
43
44 patient data will not be requested.
45
46
47
48
49
50
51

52 There is heterogeneity in trial inclusion criteria, which may affect the meta-analysis findings
53
54 and be a source of bias. Therefore, subgroup analyses will be performed depending on data
55
56 availability, but will aim to assess all-cause mortality at ≤ 30 days and >1 month for the
57
58 following subgroups: (i) sex: male versus female; (ii) age: <60 years versus ≥ 60 years; (iii)
59
60

1
2
3 comorbidities: hypertension versus no hypertension, diabetes versus no diabetes, chronic
4 kidney disease (CKD) defined as eGFR<60 mL/min/1.73m² versus no CKD, cardiovascular
5 disease (CVD) [defined as established coronary artery disease, heart failure, arrhythmia and/or
6 stroke] versus no CVD, chronic obstructive pulmonary disease versus no chronic obstructive
7 pulmonary disease; (iv) smoking status: ever smoked versus non-smokers; (v) hospitalisation
8 status: hospitalised versus non-hospitalised patients; (vi) ethnicity: White, South-East/East
9 Asian, South Asian, African and Other; (vii) trial type: randomised trials that investigate
10 continuation and cessation of ACEi/ARBs among patients currently treated with ACEi/ARBs,
11 versus trials that investigate initiation of ACEi/ARBs in those not currently treated with such
12 therapies compared to control; (viii) region: Americas, Europe, Africa, South and West
13 Asia/Middle East, and North Asia/South-East Asia/Oceania; (ix) ACEi and ARB separately if
14 feasible as pooling ACEi and ARB together does not account for within-class differences.; (x)
15 follow-up period: final short term follow-up 14 days compared to final follow-up at 28-30
16 days; (x) asymptomatic vs symptomatic clinical status (Supplemental Tables 1 and 2).

Search strategy and searching sources

17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42 An electronic search of ClinicalTrial.gov was performed to identify potential ongoing trials for
43 inclusion in the meta-analysis. Figure 1 summarises the trial search as of July 2020 performed
44 using the search terms: coronavirus 2019, COVID-19, SARS-CoV-2, randomised controlled
45 trial, ACEi and/or ARB. A total of 19 trials were identified which potentially met the eligibility
46 criteria (Figure 1, Table 2). Of these, 5 trials evaluated the continuation of ACEi/ARB therapies
47 in those already on such therapies compared to discontinuation, and 14 trials involved
48 initiation of ACEi/ARB therapies in those not on such therapies. Nine trials did not meet
49 inclusion criteria due to (a) not assessing ACEi/ARB therapies (n=4), (b) absence of a control
50
51
52
53
54
55
56
57
58
59
60

1
2
3 group (n=2), (c) use of non-oral administration of ACEi/ARB therapies (n=2), or (d) recruitment
4
5 of patients with active malignancy (n=1). We extracted information about eligible
6
7 investigators to invite them to participate in the prospective meta-analysis by contributing
8
9 tabular data. An invitation letter will be sent via email and will include details about the study
10
11 protocol, offer of authorship, identification of the time for data retrieval and confirmation of
12
13 data security.
14
15
16
17
18
19

20 This search will be continuously updated, and investigators of newly reported and eligible
21
22 trials will be invited to join the collaboration. Using the Cochrane Collaboration guidelines,²⁵
23
24 electronic searches of MEDLINE (1996–present), EMBASE (1996–present) and the Cochrane
25
26 Central Register of Controlled Trials (most recent edition) will also be performed to identify
27
28 any other RCTs that meet inclusion criteria in March 2021. A comprehensive search strategy
29
30 using MeSH terms and text words will be used (Supplemental Table 3). Two investigators (SG
31
32 and AES) will screen the abstracts for potential inclusion against the eligibility criteria, and
33
34 screen the full texts. Reference management software (EndNote) will be used to store
35
36 identified records.
37
38
39
40
41
42
43
44

45 All provided data will be stored on a password protected server, with limited access only to
46
47 those directly involved in data analysis.
48
49
50

51 **Study Evaluation**

52 A quality assessment of each RCT will be performed independently by two authors (SRG, AES),
53
54 with disagreements resolved by discussion. This will include evaluation of allocation
55
56 sequence, allocation concealment, blinding, loss to follow-up, and completeness of outcome
57
58
59
60

1
2
3 reporting.²⁵ Randomisation procedures, treatment allocation according to assignment,
4
5 outcomes collected and compared across groups; blinding methods; and risk of bias both at
6
7 study and outcome levels will also be assessed using the Cochrane Risk of Bias Tool.²⁶ Two
8
9 investigators (SG and AES) will independently review the articles and any disagreements will
10
11 be adjudicated by a third independent investigator (AR).
12
13
14
15
16
17

18 **Statistical Analysis**

19
20 Trial-specific outcome data will be pooled. For binary outcomes, risk ratios and 95% CI will be
21
22 estimated using log-binomial mixed-effects models (or odds ratios from logistic models as
23
24 required). Key results will be presented using Forest plots, and the I^2 statistic will be used to
25
26 quantify the degree of heterogeneity between studies.²⁷ A two-tailed p-value of 5% will be
27
28 used for hypothesis testing. A fixed effects analysis will be used unless there is significant
29
30 heterogeneity (as evidenced by $I^2 > 70\%$ and quantitatively large variation), in which case
31
32 pooling will not be performed.²⁸ Publication bias will be assessed by visual inspection of
33
34 funnel plots and formally using Egger's method to evaluate the tendency of publishing studies
35
36 with statistically significant findings.²⁹ We will use meta-regression analyses to further explore
37
38 heterogeneity of treatment effects if considerable residual heterogeneity remains after
39
40 controlling for variables. Analyses will also be stratified by the prespecified subgroup analysis
41
42 as mentioned above. In general, reporting of the findings will follow PRISMA guidelines.²⁴ All
43
44 analyses will be conducted using Review Manager 5.3 software (Copenhagen, The Nordic
45
46 Cochrane Centre, The Cochrane Collaboration, 2014).
47
48
49
50
51
52
53
54
55
56

57 **Data Statement**

58
59
60

1
2
3 We will not have access to identifiable patient information. All data sharing and storage
4
5 procedures will be compliant with the Australian Data Privacy Act of 1988. All trial data will
6
7 be considered confidential and will not be provided to any third party. Data will be stored on
8
9 site at The George Institute for Global Health, King St Campus, Sydney, Australia, with strict
10
11 confidentiality and comprehensive data security.
12
13
14
15
16
17

18 **Ethics and dissemination**

19
20 All individual trials will require Ethics Committee or Institution Review Board approval. We
21
22 will publish our findings in peer-reviewed medical journals. Publications will be in the name
23
24 of the collaborative group involving all trialists who provided data. Further, we will share and
25
26 present our findings at scientific meetings and through the networks and memberships across
27
28 professional societies.
29
30
31
32
33
34

35 **Implications of the review**

36
37 Given the widespread use of ACEi and ARBs worldwide, guidance on the use of ACEi/ARBs in
38
39 adults with COVID-19 is urgently needed, relying on evidence beyond observational data. This
40
41 collaborative international approach will allow dissemination of results, which will inform
42
43 public health policy and clinical decision making for ongoing ACEi/ARBs use on an
44
45 international scale. Healthcare providers and policy-makers can use the findings to improve
46
47 the clinical decision making by developing strategies and guidelines to guide use of ACEi/ARBs
48
49 in hypertension, cardiovascular disease and kidney disease.
50
51
52
53
54
55
56

57 **Patient and public involvement**

1
2
3 Patients were not involved in the development of the research question, outcome measure
4
5 and study design.
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
REFERENCES

1. Gu Q, Burt VL, Dillon CF, Yoon S. Trends in antihypertensive medication use and blood pressure control among United States adults with hypertension: the National Health And Nutrition Examination Survey, 2001 to 2010. *Circulation* 2012;126(17):2105-14.
2. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, Choe H, Farzan M. Angiotensin-converting enzyme 2 is a functional receptor for the SARS Coronavirus. *Nature* 2003;426(6965):450-54.
3. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181(2):271-80.
4. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, Diz DI, Gallagher PE. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation* 2005;111(20):2605-10.
5. Igase M, Kohara K, Nagai T, Miki T, Ferrario CM. Increased expression of angiotensin converting enzyme 2 in conjunction with reduction of neointima by angiotensin II type 1 receptor blockade. *Hypertens Res* 2008;31(3):553-9.
6. Ocaranza MP, Moya J, Barrientos V, Alzamora R, Hevia D, Morales C, Pinto M, Escudero N, García L, Novoa U, Ayala P, Díaz-Araya G, Godoy I, Chiong M, Lavandero S, Jalil JE, Michea L. Angiotensin-(1-9) reverses experimental hypertension and cardiovascular damage by inhibition of the angiotensin converting enzyme/Ang II Axis. *J Hypertens* 2014;32(4):771-83.

- 1
2
3 7. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at
4
5 increased risk for COVID-19 infection? *Lancet Resp Med* 2020;8(4):e21.
6
7
- 8 8. Sommerstein R, Grani C. Preventing a COVID-19 pandemic: ACE inhibitors as a potential risk
9
10 factor for fatal COVID-19. *BMJ* 2020;368:m810.
11
12
- 13 9. Sparks MA, South A, Welling P, Luther M, Cohen J, Byrd JB, Burrell L, Batlle D, Tomlinson L,
14
15 Bhalla V, Rheault MN, Soler MJ, Swaminathan S, Hiremath S. Sound science before
16
17 quick judgement regarding RAS blockade in COVID-19. *Clin J Am Soc Nephrol* 2020;
18
19 7(15):714-16.
20
21
- 22 10. de Abajo FJ, Rodriguez-Martin S, Lerma V, Mejía-Abril G, Aguilar M, García-Luque A,
23
24 Laredo L, Laosa O, Centeno-Soto GA, Ángeles Gálvez M, Puerro M, González-Rojano E,
25
26 Pedraza L, de Pablo I, Abad-Santos F, Rodríguez-Mañas L, Gil M, Tobías A, Rodríguez-
27
28 Miguel A, Rodríguez-Puyol D; MED-ACE2-COVID19 study group. Use of renin-
29
30 angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission
31
32 to hospital: a case-population study. *Lancet* 2020;395(10238):1705-14.
33
34
35
36
- 37 11. Jung SY, Choi JC, You SH, Kim WY. Association of renin-angiotensin-aldosterone system
38
39 inhibitors with COVID-19-related outcomes in Korea: a nationwide population-based
40
41 cohort study. *Clin Infect Dis* 2020;Epub ahead of print. DOI 10.1093/cid/ciaa624
42
43
44
- 45 12. Li J, Wang X, Chen J, Zhang H, Deng A. Association of renin-angiotensin system inhibitors
46
47 with severity or risk of death in patients with hypertension hospitalized for
48
49 coronavirus disease 2019 (COVID-19) infection in Wuhan, China. *JAMA Cardiol* 2020;
50
51 5(7):825-830.
52
53
- 54 13. Mancia G, Rea F, Ludergrani M, Apolone G, Corrao G. Renin-angiotensin-aldosterone
55
56 system blockers and the risk of COVID-19. *N Engl J Med* 2020;382(25):2431-40.
57
58
59
60

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
14. Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Iturrate E, Johnson SB, Hausvater A, Newman JD, Berger JS, Bangalore S, Katz SD, Fishman GI, Kunichoff D, Chen Y, Ogedegbe G, Hochman JS. Renin-angiotensin-aldosterone system inhibitors and risk of COVID-19. *N Engl J Med* 2020;382(25):2441-48.
 15. Pirola CJ, Sookoian S. Estimation of Renin-Angiotensin-Aldosterone-System (RAAS)-Inhibitor Effect on COVID-19 Outcome: A Meta-analysis. *J Infect* 2020;S0163-4453(20):30329-7.
 16. Guo X, Zhu Y, Hong Y. Decreased Mortality of COVID-19 With Renin-Angiotensin-Aldosterone System Inhibitors Therapy in Patients With Hypertension: A Meta-Analysis. *Hypertension* 2020;76(2):e13-e14.
 17. Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie J, Liu YM, Zhao YC, Huang X, Lin L, Xia M, Chen MM, Cheng X, Zhang X, Guo D, Peng Y, Ji YX, Chen J, She ZG, Wang Y, Xu Q, Tan R, Wang H, Lin J, Luo P, Fu S, Cai H, Ye P, Xiao B, Mao W, Liu L, Yan Y, Liu M, Chen M, Zhang XJ, Wang X, Touyz RM, Xia J, Zhang BH, Huang X, Yuan Y, Loomba R, Liu PP, Li H. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. *Circ Res* 2020;126(12):1671-81.
 18. Felice C, Nardin C, Di Tanna GL, Grossi U, Bernardi E, Scaldaferrri L, Romagnoli M, Tonon L, Cavasin P, Novello S, Scarpa R, Farnia A, De Menis E, Rigoli R, Cinetto F, Pauletto P, Agostini C, Rattazzi M. Use of RAAS inhibitors and risk of clinical deterioration in COVID-19: results from an Italian cohort of 133 hypertensives. *Am J Hypertens* 2020; epub ahead of print. DOI 10.1093/ajh/hpaa096

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
19. International Society of Hypertension. Statement on COVID-19. 2020. [Available from: <https://ish-world.com/news/a/A-statement-from-the-International-Society-of-Hypertension-on-COVID-19>. Accessed May 6, 2020]
 20. American College of Cardiology, American Heart Association and Heart Failure Society of America. Patients taking ACE-i and ARBs who contract COVID-19 should continue treatment, unless otherwise advised by their physician 2020. [Available from: <https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19>. Accessed May 6, 2020]
 21. European Society of Cardiology Council on Hypertension. Position statement of the ESC Council on Hypertension on ACE-inhibitors and angiotensin receptor blockers 2020 [Available from: [https://www.escardio.org/Councils/Council-on-Hypertension-\(CHT\)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang](https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang). Accessed May 6, 2020]
 22. European Society of Hypertension. Statement on COVID-19 2020. [Available from: <https://www.eshonline.org/spotlights/esh-statement-on-covid-19>. Accessed May 6, 2020]
 23. The Renal Association. UK position statement on COVID-19 and ACE Inhibitor/Angiotensin Receptor Blocker use, 2020. [Available from: <https://renal.org/covid-19/ra-resources-renal-professionals/renal-association-uk-position-statement-covid-19-ace-inhibitorangiotensin-receptor-blocker-use>. Accessed Oct 6, 2020]
 24. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic

1
2
3 reviews and meta-analyses of studies that evaluate healthcare interventions:
4 explanation and elaboration. *BMJ* 2009;21(339)
5
6
7

- 8 25. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane
9 Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019):
10 Cochrane, 2019.
11
12
13
14
15 26. Higgins JP, Altman DG, Gotzsche P, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks
16 L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The
17 cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ*
18 2011;343:1–9.
19
20
21
22
23
24
25 27. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*
26 2002;21(11):1539–58.
27
28
29
30 28. Hedges LV, Vevea JL. Fixed- and random-effects models in meta-analysis. *Psychol Methods*
31 1998;3(4):486–504.
32
33
34
35 29. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a
36 simple, graphical test. *BMJ* 1997;315(7109):629–34.
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **Authors' Contributions:** SG, AR and AES were involved in the planning and writing of this
4
5 protocol. CB, DB, FC, NRP, MS, UMS, GSS, MT, TU, RDW and BW reviewed the protocol
6
7 and provided intellectual input.
8
9

10
11
12
13 **Funding Statement:** This research received no specific grant from any funding agency in the
14
15 public, commercial or not-for-profit sectors.
16
17

18
19
20 **Competing Interests Statement:** Nil competing interests.
21
22

23
24
25 **Acknowledgements:** Stella Galanis, NSW Health librarian
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **Figure 1: Flowchart of Trial Inclusion**
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Table 1: Outcome Grouped Tabular Data

	NO ACEi/ARB	ACEi/ARB
BASELINE CHARACTERISTICS		
N		
Mean Age \pm 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

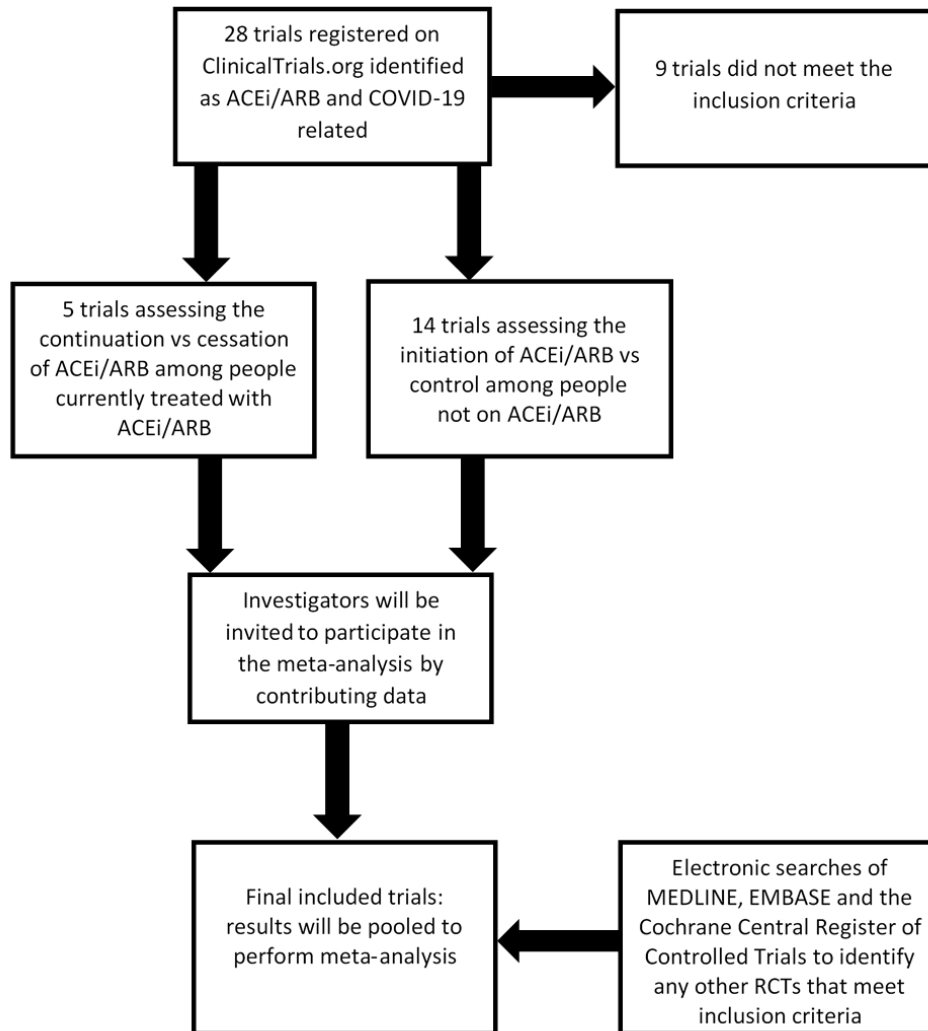


Figure 1: Flowchart of Trial Inclusion

173x208mm (144 x 144 DPI)

1
2
3 **A Prospective Meta-Analysis Protocol on Randomised Trials of Renin-Angiotensin-**
4
5
6 **System Inhibitors in Patients with Coronavirus Disease-19 (COVID-19):**
7
8 **An initiative of the International Society of Hypertension.**
9

10
11
12
13 **Supplemental Data**
14

15
16 Sonali R Gnanenthiran¹, Claudio Borghi², Dylan Burger³, Fadi Charchar⁴, Neil R Poulter⁵,
17 Markus Schlaich⁶, Ulrike Muscha Steckelings⁷, George S Stergiou⁸, Maciej Tomaszewski⁹,
18 Thomas Unger¹⁰, Richard D Wainford¹¹, Bryan Williams¹², Anthony Rodgers¹, Aletta E Schutte¹
19
20
21

- 22
23
24 1. The George Institute for Global Health, University of New South Wales, Sydney, NSW,
25 Australia
26 2. Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
27 3. Kidney Research Centre, Ottawa Hospital Research Institute, Department of Cellular and
28 Molecular Medicine, University of Ottawa, Ottawa, Canada
29 4. School of Health and Life Sciences, Federation University Australia, Ballarat, Victoria,
30 Australia
31 5. Imperial Clinical Trials Unit, Imperial College London, United Kingdom
32 6. Dobney Hypertension Centre, School of Medicine, Royal Perth Hospital Unit, University
33 of Western Australia, Perth, Australia
34 7. Department of Cardiovascular and Renal Research, University of Southern Denmark,
35 Odense, Denmark
36 8. Hypertension Center STRIDE-7, School of Medicine, Third Department of Medicine,
37 Sotiria Hospital, National and Kapodistrian University of Athens, Athens, Greece
38 9. Division of Medicine and Manchester Academic Health Science Centre, Manchester
39 University NHS Foundation Trust Manchester, United Kingdom
40 10. CARIM – School for Cardiovascular Diseases, Maastricht University, Maastricht, the
41 Netherlands
42 11. Department of Pharmacology and Experimental Therapeutics and the Whitaker
43 Cardiovascular Institute, Boston University School of Medicine, Massachusetts, USA.
44 12. Institute of Cardiovascular Science, University College London and National Institute for
45 Health Research (NIHR) University College London Hospitals Biomedical Research Centre,
46 London, United Kingdom.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

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-2019 (COVID-19): An initiative of the International Society of Hypertension.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-043625.R2
Article Type:	Protocol
Date Submitted by the Author:	24-Dec-2020
Complete List of Authors:	Gnanenthiran, Sonali; The George Institute for Global Health, ; Concord Hospital, Borghi, Claudio; S.Orsola Malpighi University Hospital, Department of Medical and Surgical Sciences Burger, Dylan; Kidney Research Centre, Ottawa Hospital Research Institute, Department of Cellular and Molecular Medicine, University of Ottawa Charchar, Fadi; Federation University Australia, Poulter, Neil; Imperial Clinical Trials Unit, Imperial College London Schlaich, Markus P.; University of Western Australia, Medical School Steckelings, Ulrike; Department of Cardiovascular and Renal Research, University of Southern Denmark Stergiou, George; Third University, Hypertension Center STRIDE-7 Tomaszewski, Maciej; Division of Medicine and Manchester Academic Health Science Centre, Manchester University NHS Foundation Trust Manchester Unger, Thomas; Maastricht University, CARIM – School for Cardiovascular Diseases Wainford, Richard; Boston University, Department of Pharmacology and Experimental Therapeutics and the Whitaker Cardiovascular Institute, Boston University School of Medicine Williams, Bryan; University College London, Institute of Cardiovascular Science; Rodgers, Anthony; The George Institute for Global Health, Sydney Medical School, University of Sydney, Schutte, Aletta; The George Institute for Global Health
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Infectious diseases, Global health
Keywords:	CARDIOLOGY, COVID-19, Hypertension < CARDIOLOGY

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60





I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 **A Prospective Meta-Analysis Protocol on Randomised Trials of Renin-Angiotensin**
4
5
6 **System Inhibitors in Patients with Coronavirus Disease 2019 (COVID-19):**

7
8 **An initiative of the International Society of Hypertension.**
9

10
11
12
13 Sonali R Gnanenthiran¹, Claudio Borghi², Dylan Burger³, Fadi Charchar⁴, Neil R Poulter⁵,
14 Markus Schlaich⁶, Ulrike Muscha Steckelings⁷, George S Stergiou⁸, Maciej Tomaszewski⁹,
15 Thomas Unger¹⁰, Richard D Wainford¹¹, Bryan Williams¹², Anthony Rodgers¹, Aletta E Schutte¹
16
17
18
19

- 20
21
22 1. The George Institute for Global Health; University of New South Wales, Sydney, NSW,
23 Australia
24 2. Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
25 3. Kidney Research Centre, Ottawa Hospital Research Institute, Department of Cellular and
26 Molecular Medicine, University of Ottawa, Ottawa, Canada
27 4. School of Health and Life Sciences, Federation University Australia, Ballarat, Victoria,
28 Australia
29 5. Imperial Clinical Trials Unit, Imperial College London, United Kingdom
30 6. Dobney Hypertension Centre, School of Medicine, Royal Perth Hospital Unit, University
31 of Western Australia, Perth, Australia
32 7. Department of Cardiovascular and Renal Research, University of Southern Denmark,
33 Odense, Denmark
34 8. Hypertension Center STRIDE-7, School of Medicine, Third Department of Medicine,
35 Sotiria Hospital, National and Kapodistrian University of Athens, Athens, Greece
36 9. Division of Medicine and Manchester Academic Health Science Centre, Manchester
37 University NHS Foundation Trust Manchester, United Kingdom
38 10. CARIM – School for Cardiovascular Diseases, Maastricht University, Maastricht, the
39 Netherlands
40 11. Department of Pharmacology and Experimental Therapeutics and the Whitaker
41 Cardiovascular Institute, Boston University School of Medicine, Massachusetts, USA.
42 12. Institute of Cardiovascular Science, University College London and National Institute for
43 Health Research (NIHR) University College London Hospitals Biomedical Research Centre,
44 London, United Kingdom.
45
46
47
48
49
50

51 **Address for correspondence:**

52 Professor Aletta E Schutte
53 School of Population Health, University of New South Wales, Kensington Campus, High
54 Street, Sydney, NSW 2052, Australia
55 E-mail: a.schutte@unsw.edu.au; Tel: +61 450 315 918
56
57

58 Word count: 2223
59
60

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

1
2
3 results of our analysis can inform public health policy and clinical decision making regarding
4
5 ACEi/ARB use in patients with COVID-19 on a global scale.
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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.

review only

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 expression⁴ 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 disease¹⁵ 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

1
2
3 decision making. Randomised controlled trials (RCTs) are needed to mitigate this risk.
4
5
6 However, to date reliable data from randomised controlled clinical trials are unavailable to
7
8 guide clinical decision-making. As a result, it is uncertain whether ACEi/ARB therapy should
9
10 be continued, withdrawn, or initiated in patients with COVID-19.
11
12
13

14
15 International hypertension, cardiovascular and nephrology societies have consistently
16
17 recommended that patients continue ACEi/ARB therapy during the COVID-19 pandemic, on
18
19 the basis of the strong and well-documented evidence on their protective effects, but identify
20
21 a need for more reliable human data.¹⁹⁻²³ There are multiple RCTs in process, which will better
22
23 inform clinical decision making rather than relying on observational human studies¹⁰⁻¹⁴ and
24
25 inconsistent animal data.^{4 6} Most of the RCTs under way are small to moderate in size (~40%
26
27 aim to recruit less than 250 participants), with many unlikely to meet their recruitment
28
29 targets. These trials are also unlikely to be powered to answer questions regarding subgroup
30
31 populations, including whether there is utility of ACEi/ARB therapy in patients with COVID-19
32
33 with concomitant hypertension, cardiovascular or kidney disease. Given the uncertainty
34
35 of ACEi/ARB use in those with COVID-19, some trials are starting ACEi/ARB therapy for
36
37 possible benefit, while other trials are stopping the same therapy due to concerns about
38
39 harm. These RCTs are not completely free from bias, but nevertheless represent a higher
40
41 quality of evidence than observational studies. A prospective meta-analysis led by the
42
43 International Society of Hypertension will therefore be an ideal approach to address these
44
45 limitations, as well as promoting international collaboration. This approach entails studies to
46
47 be identified, evaluated, and determined to be eligible before the results of any included
48
49 studies are known or published, thereby avoiding some of the potential biases inherent in
50
51 standard, retrospective meta-analyses.
52
53
54
55
56
57
58
59
60

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

1
2
3 control in those not currently treated with such therapies. These will be pooled in an
4
5 ACEi/ARB vs. no ACEi/ARB meta-analysis, with appropriate prespecification of preplanned
6
7 sensitivity analyses from the two groups of trials given the fundamental differences. Studies
8
9 must contain sufficient detail and be able to provide at least one outcome outlined within our
10
11 data extraction form (Table 1) and be reported using an intention to treat basis. If an RCT
12
13 consists of multiple arms, we will include only the relevant arms. The exclusion criteria will be
14
15 at the discretion of each individual trial.
16
17
18
19
20
21
22

23 The intervention will comprise continuation or initiation of ACEi/ARB therapy. The control will
24
25 be discontinuation of current ACEi/ARB therapy, substitution with an equivalent dose of non-
26
27 ACEi/ARB therapy, placebo or usual care.
28
29
30
31
32

33 **Outcomes**

34
35 The primary outcome will be all-cause mortality at ≤ 30 days. Secondary outcomes will include
36
37 mechanical ventilation at ≤ 30 days; admission to intensive care at ≤ 30 days; myocardial
38
39 infarction at ≤ 30 days, revascularisation at ≤ 30 days, congestive cardiac failure at ≤ 30 days;
40
41 pulmonary embolism and/or deep vein thrombosis at ≤ 30 days, hospitalisation at ≤ 30 days
42
43 and acute kidney injury (defined as per each individual RCT) at ≤ 30 days; all-cause mortality
44
45 at >1 month follow-up. Standardised grouped tabular de-identified data will be requested
46
47 from triallists for both short-term (≤ 30 days) and longer term (>1 month) follow up where
48
49 available (Table 1). Individual identifiable patient data will not be requested.
50
51
52
53
54
55
56

57 **Search strategy and searching sources**

58
59
60

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

17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40 This search will be continuously updated, and investigators of newly reported and eligible
41 trials will be invited to join the collaboration. Using the Cochrane Collaboration guidelines,²⁵
42 electronic searches of MEDLINE (1996–present), EMBASE (1996–present) and the Cochrane
43 Central Register of Controlled Trials (most recent edition) will also be performed to identify
44 any other RCTs that meet inclusion criteria in March 2021. A comprehensive search strategy
45 using MeSH terms and text words will be used (Supplemental Table 1). Two investigators (SG
46 and AES) will screen the abstracts for potential inclusion against the eligibility criteria, and
47 screen the full texts. Reference management software (EndNote) will be used to store
48 identified records.

1
2
3
4
5
6 All provided data will be stored on a password protected server, with limited access only to
7
8 those directly involved in data analysis.
9

10 11 12 13 **Study Evaluation**

14
15 A quality assessment of each RCT will be performed independently by two authors (SRG, AES),
16
17 with disagreements resolved by discussion. This will include evaluation of allocation
18
19 sequence, allocation concealment, blinding, loss to follow-up, and completeness of outcome
20
21 reporting.²⁵ Randomisation procedures, treatment allocation according to assignment,
22
23 outcomes collected and compared across groups; blinding methods; and risk of bias both at
24
25 study and outcome levels will also be assessed using the Cochrane Risk of Bias Tool.²⁶ Two
26
27 investigators (SG and AES) will independently review the articles and any disagreements will
28
29 be adjudicated by a third independent investigator (AR).
30
31
32
33
34
35
36
37
38
39

40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 **Statistical Analysis**

60
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

1
2
3
4 investigated in a sensitivity analysis by dropping each study at a time. Publication bias will be
5
6
7 assessed by visual inspection of funnel plots and formally using Egger's method to evaluate
8
9 the tendency of publishing studies with statistically significant findings.²⁹ We will use meta-
10
11 regression analyses to further explore heterogeneity of treatment effects if considerable
12
13 residual heterogeneity remains after controlling for variables. Analyses will also be stratified
14
15 by the prespecified subgroup analysis as mentioned below. In general, reporting of the
16
17 findings will follow PRISMA guidelines.²⁴ All analyses will be conducted using Review Manager
18
19 5.3 software (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).
20
21
22

23
24
25
26 There is potential heterogeneity in trial inclusion criteria, which may affect the meta-analysis
27
28 findings and be a source of bias. Therefore, subgroup analyses will be performed depending
29
30 on data availability to explore differences in effects by partitioning by study-level categorical
31
32 covariates. We will aim to assess all-cause mortality at ≤ 30 days and >1 month based on the
33
34 following stratifications: (i) sex: male versus female; (ii) age: <60 years versus ≥ 60 years; (iii)
35
36 comorbidities: hypertension versus no hypertension, diabetes versus no diabetes, chronic
37
38 kidney disease (CKD) defined as $eGFR < 60$ mL/min/1.73m² versus no CKD, cardiovascular
39
40 disease (CVD) [defined as established coronary artery disease, heart failure, arrhythmia and/or
41
42 stroke] versus no CVD, chronic obstructive pulmonary disease versus no chronic obstructive
43
44 pulmonary disease; (iv) smoking status: ever smoked versus non-smokers; (v) hospitalisation
45
46 status: hospitalised versus non-hospitalised patients; (vi) ethnicity: White, South-East/East
47
48 Asian, South Asian, African and Other; (vii) trial type: randomised trials that investigate
49
50 continuation and cessation of ACEi/ARBs among patients currently treated with ACEi/ARBs,
51
52 versus trials that investigate initiation of ACEi/ARBs in those not currently treated with such
53
54
55
56
57
58
59
60

1
2
3 therapies compared to control; (vii) region: Americas, Europe, Africa, South and West
4
5 Asia/Middle East, and North Asia/South-East Asia/Oceania; (viii) ACEi and ARB separately if
6
7 feasible as pooling ACEi and ARB together does not account for between-class differences.;
8
9
10 (ix) follow-up period: final short term follow-up 14 days compared to final follow-up at 28-30
11
12 days; (x) asymptomatic vs symptomatic clinical status (Supplemental Tables 2 and 3).
13
14
15
16
17

18 **Data Statement**

19
20 We will not have access to identifiable patient information. All data sharing and storage
21
22 procedures will be compliant with the Australian Data Privacy Act of 1988. All trial data will
23
24 be considered confidential and will not be provided to any third party. Data will be stored on
25
26 site at The George Institute for Global Health, King St Campus, Sydney, Australia, with strict
27
28 confidentiality and comprehensive data security.
29
30
31
32
33
34

35 **Limitations**

36
37 Limitations of our meta-analysis reflect the limitations of the included RCTs, and are outside
38
39 the control of our planned analyses. We have attempted to be inclusive as possible and aim
40
41 to perform subgroup analyses given the trials are mostly small and may not be powered for
42
43 such analyses. Key limitations include the relatively short follow-up duration of included trials
44
45 (most ≤ 30 days), which prevent robust assessment of long-term outcomes such as
46
47 cardiovascular events and overall mortality. Additionally, the majority of patients on
48
49 ACEi/ARBs will likely be on such therapy to treat hypertension (although this has not been
50
51 specified in the inclusion trials of the eligible RCTs) and the generalisability of our findings to
52
53 cardiac failure and renal disease may be uncertain if there are insufficient numbers.
54
55
56
57
58
59
60

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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
REFERENCES

1. Gu Q, Burt VL, Dillon CF, Yoon S. Trends in antihypertensive medication use and blood pressure control among United States adults with hypertension: the National Health And Nutrition Examination Survey, 2001 to 2010. *Circulation* 2012;126(17):2105-14.
2. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, Choe H, Farzan M. Angiotensin-converting enzyme 2 is a functional receptor for the SARS Coronavirus. *Nature* 2003;426(6965):450-54.
3. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181(2):271-80.
4. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, Diz DI, Gallagher PE. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation* 2005;111(20):2605-10.
5. Igase M, Kohara K, Nagai T, Miki T, Ferrario CM. Increased expression of angiotensin converting enzyme 2 in conjunction with reduction of neointima by angiotensin II type 1 receptor blockade. *Hypertens Res* 2008;31(3):553-9.
6. Ocaranza MP, Moya J, Barrientos V, Alzamora R, Hevia D, Morales C, Pinto M, Escudero N, García L, Novoa U, Ayala P, Díaz-Araya G, Godoy I, Chiong M, Lavandero S, Jalil JE, Michea L. Angiotensin-(1-9) reverses experimental hypertension and cardiovascular damage by inhibition of the angiotensin converting enzyme/Ang II Axis. *J Hypertens* 2014;32(4):771-83.

- 1
2
3 7. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at
4
5 increased risk for COVID-19 infection? *Lancet Resp Med* 2020;8(4):e21.
6
7
- 8 8. Sommerstein R, Grani C. Preventing a COVID-19 pandemic: ACE inhibitors as a potential risk
9
10 factor for fatal COVID-19. *BMJ* 2020;368:m810.
11
12
- 13 9. Sparks MA, South A, Welling P, Luther M, Cohen J, Byrd JB, Burrell L, Batlle D, Tomlinson L,
14
15 Bhalla V, Rheault MN, Soler MJ, Swaminathan S, Hiremath S. Sound science before
16
17 quick judgement regarding RAS blockade in COVID-19. *Clin J Am Soc Nephrol* 2020;
18
19 7(15):714-16.
20
21
- 22 10. de Abajo FJ, Rodriguez-Martin S, Lerma V, Mejía-Abril G, Aguilar M, García-Luque A,
23
24 Laredo L, Laosa O, Centeno-Soto GA, Ángeles Gálvez M, Puerro M, González-Rojano E,
25
26 Pedraza L, de Pablo I, Abad-Santos F, Rodríguez-Mañas L, Gil M, Tobías A, Rodríguez-
27
28 Miguel A, Rodríguez-Puyol D; MED-ACE2-COVID19 study group. Use of renin-
29
30 angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission
31
32 to hospital: a case-population study. *Lancet* 2020;395(10238):1705-14.
33
34
35
36
- 37 11. Jung SY, Choi JC, You SH, Kim WY. Association of renin-angiotensin-aldosterone system
38
39 inhibitors with COVID-19-related outcomes in Korea: a nationwide population-based
40
41 cohort study. *Clin Infect Dis* 2020;Epub ahead of print. DOI 10.1093/cid/ciaa624
42
43
44
- 45 12. Li J, Wang X, Chen J, Zhang H, Deng A. Association of renin-angiotensin system inhibitors
46
47 with severity or risk of death in patients with hypertension hospitalized for
48
49 coronavirus disease 2019 (COVID-19) infection in Wuhan, China. *JAMA Cardiol* 2020;
50
51 5(7):825-830.
52
53
- 54 13. Mancia G, Rea F, Ludergrani M, Apolone G, Corrao G. Renin-angiotensin-aldosterone
55
56 system blockers and the risk of COVID-19. *N Engl J Med* 2020;382(25):2431-40.
57
58
59
60

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
14. Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Iturrate E, Johnson SB, Hausvater A, Newman JD, Berger JS, Bangalore S, Katz SD, Fishman GI, Kunichoff D, Chen Y, Ogedegbe G, Hochman JS. Renin-angiotensin-aldosterone system inhibitors and risk of COVID-19. *N Engl J Med* 2020;382(25):2441-48.
15. Pirola CJ, Sookoian S. Estimation of Renin-Angiotensin-Aldosterone-System (RAAS)-Inhibitor Effect on COVID-19 Outcome: A Meta-analysis. *J Infect* 2020;S0163-4453(20):30329-7.
16. Guo X, Zhu Y, Hong Y. Decreased Mortality of COVID-19 With Renin-Angiotensin-Aldosterone System Inhibitors Therapy in Patients With Hypertension: A Meta-Analysis. *Hypertension* 2020;76(2):e13-e14.
17. Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie J, Liu YM, Zhao YC, Huang X, Lin L, Xia M, Chen MM, Cheng X, Zhang X, Guo D, Peng Y, Ji YX, Chen J, She ZG, Wang Y, Xu Q, Tan R, Wang H, Lin J, Luo P, Fu S, Cai H, Ye P, Xiao B, Mao W, Liu L, Yan Y, Liu M, Chen M, Zhang XJ, Wang X, Touyz RM, Xia J, Zhang BH, Huang X, Yuan Y, Loomba R, Liu PP, Li H. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. *Circ Res* 2020;126(12):1671-81.
18. Felice C, Nardin C, Di Tanna GL, Grossi U, Bernardi E, Scaldaferrri L, Romagnoli M, Tonon L, Cavasin P, Novello S, Scarpa R, Farnia A, De Menis E, Rigoli R, Cinetto F, Pauletto P, Agostini C, Rattazzi M. Use of RAAS inhibitors and risk of clinical deterioration in COVID-19: results from an Italian cohort of 133 hypertensives. *Am J Hypertens* 2020; epub ahead of print. DOI 10.1093/ajh/hpaa096

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
19. International Society of Hypertension. Statement on COVID-19. 2020. [Available from: <https://ish-world.com/news/a/A-statement-from-the-International-Society-of-Hypertension-on-COVID-19>. Accessed May 6, 2020]
 20. American College of Cardiology, American Heart Association and Heart Failure Society of America. Patients taking ACE-i and ARBs who contract COVID-19 should continue treatment, unless otherwise advised by their physician 2020. [Available from: <https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19>. Accessed May 6, 2020]
 21. European Society of Cardiology Council on Hypertension. Position statement of the ESC Council on Hypertension on ACE-inhibitors and angiotensin receptor blockers 2020 [Available from: [https://www.escardio.org/Councils/Council-on-Hypertension-\(CHT\)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang](https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang). Accessed May 6, 2020]
 22. European Society of Hypertension. Statement on COVID-19 2020. [Available from: <https://www.eshonline.org/spotlights/esh-statement-on-covid-19>. Accessed May 6, 2020]
 23. The Renal Association. UK position statement on COVID-19 and ACE Inhibitor/Angiotensin Receptor Blocker use, 2020. [Available from: <https://renal.org/covid-19/ra-resources-renal-professionals/renal-association-uk-position-statement-covid-19-ace-inhibitorangiotensin-receptor-blocker-use>. Accessed Oct 6, 2020]
 24. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic

1
2
3 reviews and meta-analyses of studies that evaluate healthcare interventions:
4 explanation and elaboration. *BMJ* 2009;21(339)
5
6
7

- 8 25. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane
9 Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019):
10 Cochrane, 2019.
11
12
13
14
15 26. Higgins JP, Altman DG, Gotzsche P, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks
16 L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The
17 cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ*
18 2011;343:1–9.
19
20
21
22
23
24
25 27. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*
26 2002;21(11):1539–58.
27
28
29
30 28. Hedges LV, Vevea JL. Fixed- and random-effects models in meta-analysis. *Psychol Methods*
31 1998;3(4):486–504.
32
33
34
35 29. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a
36 simple, graphical test. *BMJ* 1997;315(7109):629–34.
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **Authors' Contributions:** SG, AR and AES were involved in the planning and writing of this
4
5 protocol. CB, DB, FC, NRP, MS, UMS, GSS, MT, TU, RDW and BW reviewed the protocol
6
7 and provided intellectual input.
8
9

10
11
12
13 **Funding Statement:** This research received no specific grant from any funding agency in the
14
15 public, commercial or not-for-profit sectors.
16
17

18
19
20 **Competing Interests Statement:** Nil competing interests.
21
22

23
24
25 **Acknowledgements:** Stella Galanis, NSW Health librarian
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **Figure 1: Flowchart of Trial Inclusion**
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Table 1: Outcome Grouped Tabular Data

	NO ACEi/ARB	ACEi/ARB
BASELINE CHARACTERISTICS		
N		
Mean Age \pm 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

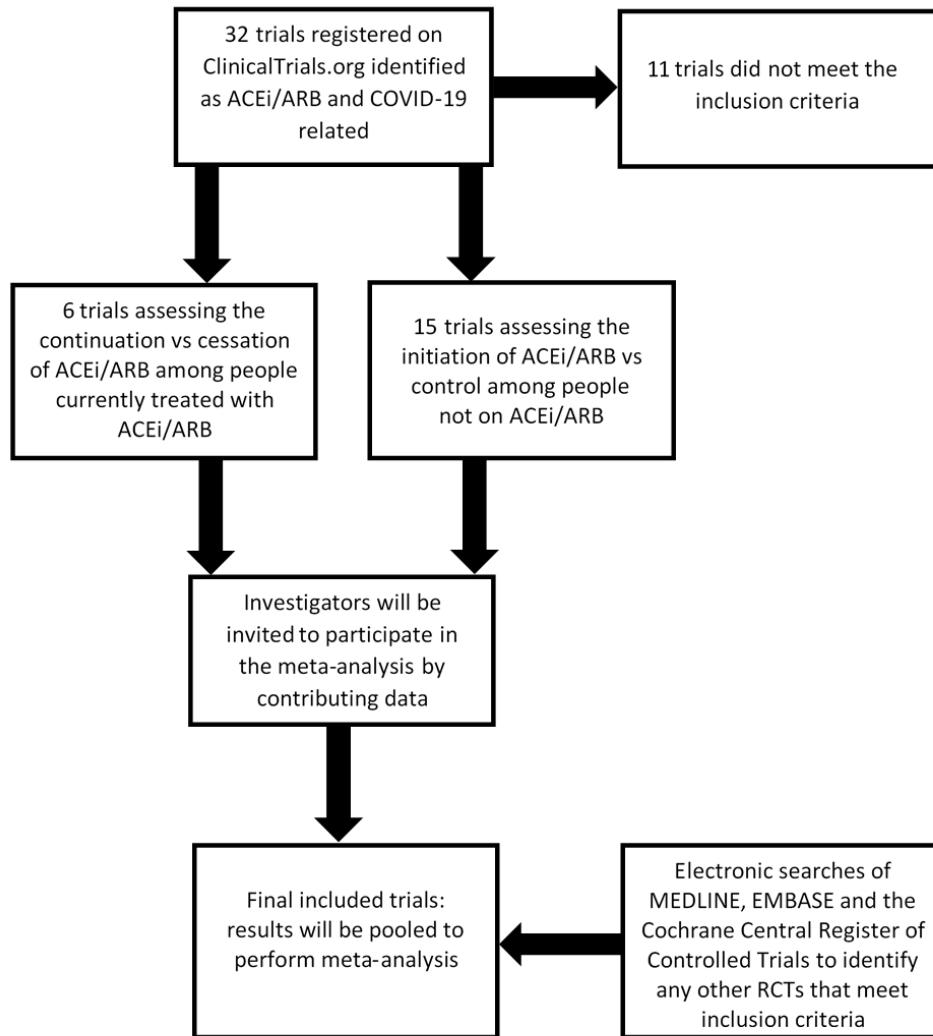


Figure 1: Flowchart of Trial Inclusion

173x188mm (144 x 144 DPI)

1
2
3 **A Prospective Meta-Analysis Protocol on Randomised Trials of Renin-Angiotensin-**
4
5
6 **System Inhibitors in Patients with Coronavirus Disease-2019 (COVID-19):**
7
8 **An initiative of the International Society of Hypertension.**
9

10
11
12
13 **Supplemental Data**
14

15
16 Sonali R Gnanenthiran¹, Claudio Borghi², Dylan Burger³, Fadi Charchar⁴, Neil R Poulter⁵,
17
18 Markus Schlaich⁶, Ulrike Muscha Steckelings⁷, George S Stergiou⁸, Maciej Tomaszewski⁹,
19
20 Thomas Unger¹⁰, Richard D Wainford¹¹, Bryan Williams¹², Anthony Rodgers¹, Aletta E Schutte¹
21

- 22
23
24 1. The George Institute for Global Health, University of New South Wales, Sydney, NSW,
25 Australia
26
27 2. Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
28
29 3. Kidney Research Centre, Ottawa Hospital Research Institute, Department of Cellular and
30 Molecular Medicine, University of Ottawa, Ottawa, Canada
31
32 4. School of Health and Life Sciences, Federation University Australia, Ballarat, Victoria,
33 Australia
34
35 5. Imperial Clinical Trials Unit, Imperial College London, United Kingdom
36
37 6. Dobney Hypertension Centre, School of Medicine, Royal Perth Hospital Unit, University
38 of Western Australia, Perth, Australia
39
40 7. Department of Cardiovascular and Renal Research, University of Southern Denmark,
41 Odense, Denmark
42
43 8. Hypertension Center STRIDE-7, School of Medicine, Third Department of Medicine,
44 Sotiria Hospital, National and Kapodistrian University of Athens, Athens, Greece
45
46 9. Division of Medicine and Manchester Academic Health Science Centre, Manchester
47 University NHS Foundation Trust Manchester, United Kingdom
48
49 10. CARIM – School for Cardiovascular Diseases, Maastricht University, Maastricht, the
50 Netherlands
51
52 11. Department of Pharmacology and Experimental Therapeutics and the Whitaker
53 Cardiovascular Institute, Boston University School of Medicine, Massachusetts, USA.
54
55 12. Institute of Cardiovascular Science, University College London and National Institute for
56 Health Research (NIHR) University College London Hospitals Biomedical Research Centre,
57 London, United Kingdom.
58
59
60

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.**

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.