INVITED PAPER

An ISH-led prospective meta-analysis on RCTs of RAAS inhibitors in COVID-19 patients: A call for collaboration

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With 2020 came COVID-19. Already early on in the pandemic the go-to antihypertensive therapy, namely renin-angiotensin aldosterone system (RAAS) inhibitors, came under fire. This includes angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB). The COVID-19 pandemic has drawn attention to these first line therapies due to the fact that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects respiratory epithelial cells via attachment to the angiotensin-converting enzyme 2 (ACE2) receptor. With millions of patients using ACEi/ARB therapy on a daily basis, there was overall anxiety on whether therapy should be continued, initiated or ceased in patients with COVID-19.

Animal studies: These studies have shown that ACEi/ARB therapy may upregulate ACE2 receptor expression and produce increased cardiac ACE2 mRNA levels.^{1,2} Upregulated expression of surface ACE2 receptors has been postulated to promote viral cell invasion, increase the risk of SARS-CoV-2 infection and increase disease severity, with consequent life-threatening complications.^{3,4} At the same time, other animal studies suggest that increased ACE2 expression secondary to ACEi/ARB use might have protective effects on cardiac, kidney and pulmonary function and thus reduce the severity of COVID-19.⁵

Observational retrospective human studies: Observational studies in humans and meta-analyses of these studies suggest that there is no adverse effect of RAS blockade on COVID-19

severity and outcome⁶, but there may be possible protective benefits including reduced rates of mortality,⁷ critical disease⁸ and admission to intensive care.⁹ Observational studies can still have multiple sources of bias, and RCTs are needed to mitigate this risk.

Randomised controlled trials: To date reliable data from large robust RCTs are unavailable to guide clinical decision-making. Preliminary results from the BRACE-CORONA randomised trial¹⁰ presented at the European Society of Cardiology conference 2020 suggested that all-cause mortality at 30 days was equivalent in those continuing ACEi/ARBs compared to those who had therapy suspended (HR 0.97, 95%CI 0.38-2.52, p=0.95). However, the trial did not assess benefit in those acutely initiated on ACEi/ARBs, nor did it assess longer-term outcomes. There are multiple other RCTs in process, which will better inform clinical decision making rather than relying on observational human studies and inconsistent animal data. Most of the RCTs under way are small to moderate in size. It is still difficult to know whether these trials are powered to answer questions regarding subgroup populations, including whether there is utility of ACEi/ARB therapy in patients with COVID-19 with concomitant hypertension, cardiovascular or kidney disease.

Current recommendations: International hypertension and cardiovascular societies have recommended that patients continue ACEi/ARB therapy during the COVID-19 pandemic, on the

basis of the strong and well-documented evidence on their protective cardiovascular effects, but identified a need for more reliable human data.^{11, 12, 13, 14}

A prospective meta-analysis of RCTs: Given the uncertainty of ACEi/ARB use in those with COVID-19, several RCTs started ACEi/ARB therapy for possible benefit, while other trials are stopping the same therapy due to concerns about harm. A prospective meta-analysis led by the *International Society of Hypertension* will therefore be an ideal approach to address these limitations, as well as promoting international collaboration. This approach entails studies to be identified, evaluated, and determined to be eligible before the results of any included studies are known or published, thereby avoiding some of the potential biases inherent in standard, retrospective meta-analyses.

The ISH will therefore be leading a prospective meta-analysis pooling data from RCTs to investigate the safety and efficacy of these RAAS inhibitors.

We are including 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.

A detailed protocol of our approach has been published in *BMJ Open*.¹⁵

For clinical trials to be eligible for inclusion, the trials must meet the criteria listed in **Box 1**.

Box 1: Eligibility Criteria for Meta-Analysis

- RCTs recruiting between March 2020 and March 2021
- Aged ≥ 18 years
- Laboratory confirmed SARS-CoV-2 infection
- Comparison of patients randomised to ACEi/ARB versus no ACEi/ARB therapy
- Findings reported in English
- Trial duration ≥ 14 days
- 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. The exclusion criteria will be at the discretion of each individual trial.

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

An electronic search of **ClinicalTrials.gov** was performed to identify potential ongoing trials for inclusion in the meta-analysis. This search will be continuously updated, and investigators of newly reported and eligible trials will be invited to join the collaboration. Electronic searches of MEDLINE (1996–present), EMBASE (1996–present) and the Cochrane Central Register of Controlled Trials will also be performed to identify any other RCTs that meet inclusion criteria in March 2021. We emailed invitations including details about the study protocol, offer of authorship, identification of the time for data retrieval and confirmation of data security. Thus far, the following trials have already agreed to be involved in the meta-analysis, including sites in the United States of America, Austria, Brazil, Denmark, France, Germany and the Netherlands:

- ⊙ Stopping ACE-inhibitors in COVID 19 (ACEi-COVID): Innsbruck, Austria; Munich, Germany.
- ⊙ Austrian CoronaVirus Adaptive Clinical Trial (ACOVACT): Innsbruck and Vienna, Austria.
- ⊙ Outpatient Treatment of Elderly People with Symptomatic SARS-CoV-2 Infection: a Multi-arm, Multi-stage RCT to Assess the Efficacy and Safety of Several Experimental Treatments to Decrease the Risk of Hospitalization or Death (COVERAGE): Bordeaux, France.

- ⊙ A Double blind, Placebo-controlled RCT with Valsartan for Prevention of Acute Respiratory distress Syndrome in hospitalised patients with SARS-COV-2 Infection Disease (PRAETORIAN-COVID): 's-Hertogenbosch, Arnhem, Nijmegen, Roermond, Rotterdam, the Netherlands.
- ⊙ Effects of Discontinuing Renin-angiotensin System Inhibitors in Patients With COVID-19 (RASCOVID-19): Copenhagen, Denmark.
- ⊙ RCT of Losartan for Patients With COVID-19 requiring Hospitalization: Minnesota, USA.
- ⊙ RCT of Losartan for Patients With COVID-19 not requiring Hospitalization: Minnesota, USA.
- ⊙ RCT of ACEIs in Treatment of COVID-19: Tanta, Egypt.
- ⊙ Elimination or Prolongation of ACE Inhibitors and ARB in Coronavirus Disease 2019 (REPLACECOVID): Pennsylvania, USA.
- ⊙ Pilot Clinical Trial of the Safety and Efficacy of Telmisartan for the Mitigation of Pulmonary and Cardiac Complications in COVID-19 Patients: Hawaii, USA.
- ⊙ Switch of Renin-Angiotensin System Inhibitors in Patients With Covid-19 (SWITCH-COVID): São Paulo, Brazil.

Given the widespread use of RAAS inhibitors worldwide, clear guidance based on evidence from RCTs on the use of ACEi/ARBs in adults with COVID-19 is still outstanding. We trust that this international collaboration will give clear direction to inform public health policy and clinical decision making on RAAS inhibition therapy in COVID-19 patients.

We continue to openly invite other eligible trialists to collaborate with us. Please get in touch at a.schutte@unsw.edu.au

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