Supplementary Material*

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* This supplementary material was provided by the authors to give readers further details on their article. The material was reviewed but not copyedited.

Supplement Table 1. Study Characteristics and Results of Trials on ARB Initiation in COVID-19

Study, Country, Period	**N**	**Population**	**Patient Characteristics** (demographics for intervention versus comparator)	**Intervention and Comparator**	**Primary Outcome Results (intervention versus comparator)**	**Mortality Results** (if mortality was a secondary outcome)
Duarte (4), Argentina, 5/14/20-10/30/20	158	Adults hospitalized with COVID-19	Mean age: 67 v 64 Male: 44 v 63% Race/ethnicity: NR HTN: 44 v 45% DM: 18 v 21% CV disease: NR	Telmisartan 80 mg twice daily for 14 days compared to standard care	CRP serum levels expressed as percentage of day 0: at day 5: -57.6 ±56.2% v 5.5 ± 122.2%; at day 8: -73.82 ± 38.41% v 13.9 ± 148.2%	30-day mortality: 3/70 (4%) v 16/71 (23%) RR = 0.19 (95% CI [0.06, 0.57])
Geriak (5), US, 3/30/20-7/4/20	31	Adults hospitalized with COVID-19 and mild to moderate hypoxia	Mean age: 59 v 55 Male: 63 v 60 Black/AA: 6 v 0% Hispanic: 75 v 87% Asian: 0 v 0% White: 6 vs 13% HTN: 44 v 33% DM: 19 v 33% CV disease: 6 v 0%	Losartan 12.5mg twice daily for 10 days (with up-titration at the decision of the treating clinician) compared to standard care	Need for ICU transfer: 1/16 (6%) v 2/15 (13%)	In-hospital mortality: 1/16 (6%) vs 1/15 (7%)
Nouri-Vaskeh (6), Iran, 4/2/20-6/30/20	80	Adults hospitalized with COVID-19 and HTN	Mean age: 67 v 60 Male: 54 v 46 Race/ethnicity: NR HTN: 100% (inclusion criteria) DM: 11 v 8% CV disease: 8 v 7%	Losartan 25mg twice daily compared to amlodipine 5mg daily for at least 14 days	30-day mortality: 2/41 (5%) v 5/39 (13%), *p* = .241	NA
Puskarich (7), US, 4/1/20-11/30/20	117	Adults presenting for SARS-CoV-2 PCR testing and found to have a positive result	Mean age: 38 v 37 Male: 43 v 58 Black/AA: 7 v 7% Hispanic: 9 v 9% Asian: 2 v 9% White: 78 v 66% HTN: 10 v 5% DM: 7 v 5% CV disease: 0 v 0%	Losartan 25mg twice daily (adjusted for renal function if needed) for 10 days v placebo	All-cause hospitalization at or before day 15: 3/58 (5%) v 1/59 (2%) Absolute difference of -3.5% (95% CI [-13.2, 4.8%]; p = 0.320) favoring placebo	No deaths among study participants

Abbreviations: CV=Cardiovascular disease; DM=Diabetes mellitus; HTN=Hypertension; N=Number of participants; NA=Not applicable; NR=NR

Supplement Table 2. Quality Assessment of Trials on ARB Initiation in COVID-19

Study	Risk of bias from randomization process	Risk of bias from deviation from intended interventions (assignment)	Risk of bias from deviation from intended interventions (adherence)	Risk of bias from missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall Risk of Bias
Duarte (4)	High Allocation sequence was random but unclear if the sequence was concealed appropriately. Baseline differences in % male, % obese, and CRP levels raise concern about a problem with the randomization process.	Some concerns Open label design in which participants and carers were aware of group. One patient in the intervention group did not receive the intervention after randomization. Study used intention-to-treat analysis.	Low Open label design in which participants and carers were aware of group. Deviations from intended interventions were balanced. Study used intention-to-treat analysis.	Low Primary outcome data available for all participants.	Low Open label design but awareness of group assignment would not have affected laboratory data or other data obtained by chart review.	High Study endpoints and some secondary outcomes were changed during the study period.	High
Geriak (5)	Some concerns The allocation sequence and whether it was concealed were not reported. Baseline differences between groups do not suggest a problem with randomization.	Some concerns Open label design in which participants and carers were aware of group. One patient in the intervention group did not receive the intervention after randomization. Study used intention-to-treat analysis.	Low Open label design in which participants and carers were aware of group. No reported deviations from intended interventions. Study used intention-to-treat analysis.	Low Primary outcome data available for all participants.	Low Open label design but awareness of group assignment would not have affected laboratory data or other data obtained by chart review.	Low Results were reported for all participants in concordance with the pre-specified analysis plan.	Some concerns

Nouri-Vaskeh (6)	Some concerns Block randomization process with use of computer-generated random number. Allocation sequence was concealed. Baseline differences in participant age between groups raises concern about a problem with the randomization process.	Low Participants and carers were probably blinded to group allocation, but blinding is not well-described. No apparent deviations from group assignment.	Some concerns Participants and carers were probably blinded to group allocation, but blinding is not well-described. Two patients in the comparator group were lost to follow-up and it is unclear whether they received the intended treatment.	Some concerns Two patients in the comparator group were lost to follow-up and were not included in final analyses.	Low Participants and carers were probably blinded to group allocation but regardless, awareness of group assignment would not have affected laboratory data or other data obtained by chart review.	Low	Some concerns
Puskarich (7)	Some concerns Block randomization process. Allocation sequence was concealed. A higher percent of males assigned to the comparator group. Otherwise, baseline differences between groups do not suggest a problem with randomization.	Low Double-blinded study. No apparent deviations from group assignment.	Low Double-blinded study. Deviations from intended interventions were balanced. Study used intention-to-treat analysis.	Low Missing data are reported, and the study assessed the potential for bias due to missing data.	Low Double-blinded study. Data obtained by chart review.	Low Results were reported for all participants in concordance with the pre-specified analysis plan.	Low

Supplement Table 3. Summary of Evidence for ACE/ARB Initiation in COVID-19

Outcome	Population	SOE	No. Studies (N) Study Design	Study Limitations	Directness	Consistency	Precision	Finding
Mortality	Hospitalized adults with COVID-19	Insufficient	3 RCTs	High (1 RCT); Some concerns (2 RCTs)	Direct	Inconsistent	Imprecise	1 RCT found a reduced mortality risk with telmisartan compared to usual care (RR = 0.19; 95% CI [0.06, 0.57]). 2 RCTs found no difference.
Hospitalization	Non-hospitalized adults with COVID-19	Insufficient	1 RCT	Low	Direct	Not applicable	Precise	1 RCT found that losartan compared to placebo did not reduce hospitalization risk (absolute difference in all-cause hospitalization between groups was -3.5% favoring the placebo).

Supplement Table 4. Planned or In-Progress Trials on ACEI/ARB Initiation in COVID-19 (updated 24 November 2021)

Study Title	NCT Identifier	Sponsor	Intervention	Primary Outcome(s)	Enrollment	Status	Estimated Completion Date
Randomized Controlled Trial of Losartan for Patients With COVID-19 Requiring Hospitalization. (8)	NCT04312009	University of Minnesota, US	Losartan compared to placebo	Difference in Estimated (PEEP adjusted) P/F Ratio at 7 days	205 (Actual)	Completed; last update posted August 2021	NA
Efficacy of Captopril Nebulization in COVID-19 Patients Suffering of SARS CoV-2 Pneumonia. A Randomized Phase II Study (CAPTOCOVID) (9)	NCT04355429	Assistance Publique - Hôpitaux de Paris, France	Nebulized captopril compared to standard care	14-day ventilation free survival	230 (Estimated)	Not yet recruiting; last update posted April 2020	August 2020
Telmisartan in Respiratory Failure Due to COVID-19 (STAR-COVID) (10)	NCT04510662	Abraham Edgar Gracia-Ramos, Mexico	Telmisartan 40mg compared to standard care	30-day mortality and mechanical ventilation at 14 days	60 (Estimated)	Recruiting; last update posted August 2020	April 2021
Ramipril for the Treatment of COVID-19 (RAMIC) (11)	NCT04366050	University of California, San Diego, US	Ramipril 2.5mg orally daily compared to placebo	Composite of mortality or need for ICU admission or ventilator use at 14 days	560 (Estimated)	Recruiting, last update posted January 2021	May 2021
Host Response Mediators in Coronavirus (COVID-19) Infection - Is There a Protective Effect of Losartan on Outcomes of Coronavirus	NCT04606563	University of British Columbia, Canada	Losartan (25-100mg) compared to usual care	28-day mortality	1372 (Estimated)	Recruiting; last update posted October 2020	June 2021

Infection? (ARBs CORONA II) (12)							
Pilot Clinical Trial of the Safety and Efficacy of Telmisartan for the Mitigation of Pulmonary and Cardiac Complications in COVID-19 Patients (13)	NCT04360551	University of Hawaii, US	Telmisartan 40mg compared to placebo	Maximum clinical severity of disease	40 (Estimated)	Recruiting; last update posted August 2020	June 2021
COVID MED Trial - Comparison of Therapeutics for Hospitalized Patients Infected With COVID-19 (COVIDMED) (14)	NCT04328012	Bassett Healthcare, New York, US	Losartan compared to placebo	National Institute of Allergy and Infectious Diseases COVID-19 Ordinal Severity Scale (NCOSS)	100 (Estimated)	Recruiting; last update posted February 2021	August 2021
CLARITY Controlled evaLuation of Angiotensin Receptor blockers for COVID-19 respIraTorY disease (15)	NCT04394117	The George Institute, Australia	ARB (any) compared to placebo	7-Point National Institute of Health Clinical Health Score	1500 (Estimated)	Active, not recruiting; last update posted October 2021	January 2022
Evaluation of the Potential Benefit of Renin-angiotensin System Inhibitors (RASi, ACEi/ARB) in High-risk Patients With COVID-19. (COVID-RASi) (16)	NCT04591210	Ottawa Heart Institute Research Corporation, Canada	ACEI or ARB compared to usual care	Death, mechanical ventilation, ICU admission, and major adverse cardiac events within the first 28 days of randomization	1155 (Estimated)	Recruiting; last update posted June 2021	December 2022
INvestigating TELmisartin Study (INTEL) (17)	NCT04715763	University of Hawaii, US	Telmisartan 40mg compared to placebo	Duration of hospitalization	40 (Estimated)	Recruiting; last update posted September 2021	December 2022

Angiotensin Converting Enzyme Inhibitors in Treatment of Covid 19 (18)	NCT04345406	Tanta University, Egypt	ACEIs with conventional treatment for COVID19 compared to standard care	Number of patients with virological cure	60 (Estimated)	Not yet recruiting; last update posted April 2020	December 2029