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 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 (5), 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 (6), 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 v 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%) v 1/15 (7%)
Freilich (4),US, study end 5/27/21 (start NR)	14	Adults hospitalized with COVID-19	Mean age: 64 v 62 Male: 67 v 60% White: 100 v 100% HTN: NR DM: 22 v 25% CV disease: 22 v 80%	Losartan 25mg twice daily compared to placebo (3 participants) or lopinavir 400mg/ritonavir 100mg twice daily (2 participants) for 5-14 days	Slopes of change for COVID-19 Ordinal Severity Score[a]: losartan vs. combined control (p = 0.4), losartan v placebo-only control (p = .05) (trend favoring placebo)	60-day mortality: 4/9 (44%) v 1/5 (20%), p = .9
Jardine (2), India and Australia, 5/3/20-11/13/21	787	Adults with COVID-19 in the inpatient setting (71%) and outpatient setting (29%)	Mean age: 49 v 49 Male: 254 v 251 Southern Asian: 99 v 99% White: 1 v 1% HTN: 24 v 31% DM: 23 v 27% CV disease: 3 v 3%	Telmisartan at a starting dose of 40mg daily vs placebo (in India) or an ARB at the discretion of the treating team vs usual care (in Australia)	WHO scale score at day 14: adjusted[b] odds ratio = 1.51 (95% credible interval 1.02 to 2.23) and WHO scale score at day 28: adjusted[b] odds ratio = 1.02 (95% credible interval 0.55 to 1.87)	28-day mortality: 10/378 (3%) v 6/377 (2%); OR 1.74 (95% credible interval 0.62 to 5.25)

Nouri-Vaskeh (7), 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 (3), US, 4/1/20-2/28/21	205	Adults hospitalized with COVID-19	Mean age: 54 v 56 Male: 59 v 61% Black/AA: 37 v 39% Hispanic: 20 v 22% Asian: 7 v 2% White: 35 v 45% HTN: 35 v 44% DM: 19 v 25% CAD: 3 v 7%	Losartan 50mg twice daily or placebo for 10 days or until hospital discharge	Imputed arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2:FiO2) ratio at 7 days: difference, −24.8 [95% CI (−55.6, 6.1), p = .12]	28-day mortality: 11/101 (11%) v 9/104 (9%)
Puskarich (8), US, 4/1/20-11/30/20	117	Adults presenting for SARS-CoV-2 PCR testing in the outpatient setting 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 = .320] favoring placebo	No deaths among study participants

Bold = Newly included study in Update Alert 10

Notes:

[a] COVID-19 Ordinal Severity Score: 1) Death; 2) Hospitalized-on mechanical ventilation/ extracorporeal membrane oxygenation; 3) Hospitalized-on non-invasive ventilation; 4) Hospitalized-requiring oxygen; 5) Hospitalized-not requiring oxygen; 6) Not hospitalized-with limitations; 7) Not hospitalized-without limitations.

[b] Adjusted for age, sex, co-morbidities, hypertension, and oxygen requirement.

Abbreviations: CV=Cardiovascular disease; DM=Diabetes mellitus; HTN=Hypertension; N=Number of participants; NA=Not applicable; NR=NR; v = versus; OR= odds ratio; RR=relative risk.

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 (5)	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 (6)	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
Freilich (4)	Some concerns. Block randomization process. Allocation sequence was	Low Double-blinded study. No apparent deviations from group assignment.	Low Double-blinded study. No reported deviations from	Low Primary outcome data available for all participants.	Low Double-blinded study. Data obtained by chart review.	Low Results were reported for all participants in concordance	Low

	concealed. A higher percent of participants in the control group had heart disease and other co-morbidities. Otherwise, baseline differences between groups do not suggest a problem with randomization.	Study used intention-to-treat analysis.	intended interventions. Study used intention-to-treat analysis.			with the pre-specified analysis plan.	
Jardine (2)	Low Block randomization process. Allocation sequence was concealed. Baseline differences between groups do not suggest a problem with randomization.	Low Double-blinded study. No apparent deviations from group assignment. Study used intention-to-treat analysis.	Low Double-blinded study. No reported deviations from intended interventions. Study used intention-to-treat analysis.	Low Missing data are reported, and the study used statistical techniques to account for 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

Nouri-Vaskeh (7)	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 (3)	Some concerns Block randomization process. Allocation sequence was concealed. Percentages of participants with co-morbidities was generally higher in the control group. Otherwise, baseline differences between groups do not suggest a problem with randomization.	Low Double-blinded study. No apparent deviations from group assignment. Study used intention-to-treat analysis.	Low Double-blinded study. Deviations from intended interventions were balanced. Study used intention-to-treat analysis.	Low Missing data are reported, and the study used statistical techniques to account for 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

Puskarich (8)	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. Study used intention-to-treat analysis.	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

Bold = Newly included study in Update Alert 10

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

Outcome	Population	SOE	No. Studies (N) Study Design	Study Limitations	Directness	Consistency	Precision	Finding
Mortality	Adults with COVID-19	Moderate	7 RCTs	High (1 RCT); Some concerns (2 RCTs); Low (4 RCTs)	Direct	Mostly consistent	Imprecise	6 RCTs found no difference. 1 RCT found a reduced mortality risk with telmisartan compared to usual care [RR = 0.19; 95% CI (0.06, 0.57)].
Disease severity	Adults hospitalized with COVID-19	Moderate	3 RCTs	Some concerns (1 RCT); Low (2 RCTs)	Direct	Consistent	Precise	2 RCTs found no difference in severity scores and 1 RCT found no difference in need for intensive care.
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. Active Trials on ACEI/ARB Initiation in COVID-19 (updated 2 February 2023)

Study Title	NCT Identifier	Sponsor	Intervention	Primary Outcome(s)	Enrollment	Status	Estimated Completion Date
Evaluation of the Potential Benefit of Renin-angiotensin System Inhibitors (RASi, ACEi/ARB) in High-risk Patients With COVID-19. The COVID-RASi Trial (18)	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 January 2023	April 2023
Angiotensin Converting Enzyme Inhibitors in Treatment of Covid 19 (19)	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