Effects of Angiotensin II Receptor Blockers on the Risk of Mortality in Patients with COVID-19: An Updated Systematic Review and Meta-analysis of Randomized Trials

Chia Siang Kow,[1] Dinesh Sangarran Ramachandram,[2] and Syed Shahzad Hasan[3,4]

The systematic review and meta-analysis of randomized controlled trials investigating the impact of the use of renin–angiotensin system inhibitors on mortality in patients with coronavirus disease 2019 (COVID-19) performed and reported by Yin *et al.*[1] confirm the safety of these agents which certain researchers once hypothesized to cause harmful effects in this population of patients due to their potential to upregulate the expression of angiotensin-converting enzyme 2 receptors. The meta-analysis of 7 randomized trials reported no significant association between the use of renin–angiotensin system inhibitors and the risk of mortality (risk ratio = 0.84; 95% confidence interval 0.57–1.22) in patients with COVID-19. In the subgroup analysis, Yin *et al.*[1] reported that the use of angiotensin II receptor blockers (ARBs) was associated with a significant reduction in mortality (risk ratio = 0.23; 95% confidence interval 0.09–0.60) in patients with COVID-19. Although their findings indicate protective effects of ARBs, the analysis was based on only one randomized trial,[2] and hence, further evaluation is required. We, therefore, updated the systematic review to identify additional studies to confirm their findings (methods are available in Supplementary Appendix).

Our literature search yielded 718 records. After deduplication and application of the eligibility criteria, 5 relevant articles were shortlisted for inclusion through full-text examination. Of these, 2 studies were excluded due to no mortality events reported and single-arm trial, respectively. Eventually, 3 randomized trials[2–4] were included in this meta-analysis, with a total of 443 patients with COVID-19. Details of the included trials are depicted in Table 1. The regimen of ARB administered differed across the 3 trials: in the trial by Duarte *et al.*,[2] telmisartan was administered orally at a dose of 80 mg twice daily for 14 days, whereas in the 2 trials by Nouri-Vaskeh *et al.*[3] and Puskarich *et al.*,[4] losartan was administered orally at a dose of 25 and 50 mg, respectively, twice daily for 10–14 days.

The meta-analysis of three trials[2–4] revealed no significant difference in the risk of mortality with the use of ARB relative to the nonuse of ARB in patients with COVID-19. The estimated effect though indicates mortality benefits (pooled odds ratio = 0.45; 95% confidence interval 0.11–1.78, I^2 = 72%, P = 0.03, n = 443), but is without adequate evidence to reject the model hypothesis of "no significant difference" at the current sample size. Our findings indicate no protective effects of ARBs in patients with COVID-19 with the inclusion of more studies, which suggests that the previous findings by Yin *et al.*[1] may be due to chance since only one trial[2] was included in the analysis. Nevertheless, since the only one trial that investigated the use of telmisartan reported mortality benefits, it remains to be determined if the use of telmisartan was superior to the use of other ARBs such as losartan in patients with COVID-19, which was being investigated in the other 2 trials.[3,4]

Correspondence: Chia Siang Kow (chiasiang_93@hotmail.com).

[1]School of Pharmacy, International Medical University, Kuala Lumpur, Malaysia; [2]School of Pharmacy, Monash University Malaysia, Bandar Sunway, Selangor, Malaysia; [3]School of Applied Sciences, University of Huddersfield, Huddersfield, UK; [4]School of Biomedical Sciences and Pharmacy, University of Newcastle, Callaghan, Australia.

Initially submitted May 22, 2022; date of first revision May 25, 2022; accepted for publication May 30, 2022; online publication June 3, 2022.

https://doi.org/10.1093/ajh/hpac070

SUPPLEMENTARY MATERIAL

Supplementary data are available at *American Journal of Hypertension* online.

FUNDING

No external funding was used in the preparation of this manuscript.

DISCLOSURE

The authors declared no conflict of interest.

REFERENCES

1. Yin J, Wang C, Song X, Li X, Miao M. Effects of renin-angiotensin system inhibitors on mortality and disease severity of COVID-19 patients: a meta-analysis of randomized controlled trials. *Am J Hypertens* 2022; 35:462–469.
2. Duarte M, Pelorosso F, Nicolosi LN, Salgado MV, Vetulli H, Aquieri A, Azzato F, Castro M, Coyle J, Davolos I, Criado IF,

Gregori R, Mastrodonato P, Rubio MC, Sarquis S, Wahlmann F, Rothlin RP. Telmisartan for treatment of Covid-19 patients: An open multicenter randomized clinical trial. *EClinicalMedicine* 2021; 37:100962.
3. Nouri-Vaskeh M, Kalami N, Zand R, Soroureddin Z, Varshochi M, Ansarin K, Rezaee H, Taghizadieh A, Sadeghi A, Ahangari Maleki M, Esmailnajad A, Saleh P, Haghdoost M, Maleki M, Sharifi A. Comparison of losartan and amlodipine effects on the outcomes of patient with COVID-19 and primary hypertension: a randomised clinical trial. *Int J Clin Pract* 2021;75(6):e14124.
4. Puskarich MA, Ingraham NE, Merck LH, Driver BE, Wacker DA, Black LP, Jones AE, Fletcher CV, South AM, Murray TA, Lewandowski C, Farhat J, Benoit JL, Biros MH, Cherabuddi K, Chipman JG, Schacker TW, Guirgis FW, Voelker HT, Koopmeiners JS, Tignanelli CJ; Angiotensin Receptor Blocker Based Lung Protective Strategies for Inpatients With COVID-19 (ALPS-IP) Investigators. Efficacy of losartan in hospitalized patients with COVID-19-induced lung injury: a randomized clinical trial. *JAMA Netw Open* 2022 ;5(*3*):e222735.

Table 1. Characteristic of included studies

Study	Study design	Country	Number of patients	Age (median/ mean)	Regimen of ARB in the intervention group	Regimen of comparator intervention in the control group	Mortality events		Overall risk of bias[a]
							ARB users (*n*/*N*; %)	Non-ARB users (*n*/*N*; %)	
Duarte *et al*.[2]	Randomized, open-label trial	Argentina	158	ARB users = 63.8 Non-ARB users = 60.1	Telmisartan 80 mg orally twice daily for 14 days	Standard care	3/78; 3.8	16/80; 20.0	Low
Nouri-Vaskeh *et al*.[3]	Randomized, double-blind, controlled trial	Iran	80	ARB users = 67.3 Non-ARB users = 60.1	Losartan 25 mg orally twice daily for at least 14 days	Amlodipine besilate 5 mg orally per day for at least 14 days	2/41; 4.9	5/39; 12.8	Some concerns
Puskarich *et al*.[4]	Randomized, blinded, placebo-controlled trial	United States	205	ARB users = 53.8 Non-ARB users = 56.4	Losartan 50 mg orally twice daily for 10 days	Placebo	11/101; 10.9	9/104; 8.7	Low

Abbreviation: ARB, angiotensin II receptor blockers.
[a]Risk of bias was assessed using Version 2 of the Cochrane risk-of-bias tool for randomized trials.