Do the meta-analyses provide a clean bill of health to the use of renin-angiotensin system inhibitors in COVID-19?

Chia Siang Kow [1], Syed Shahzad Hasan [2]

Affiliations

[1]School of Postgraduate Studies, International Medical University, Kuala Lumpur, Malaysia.
[2]Department of Pharmacy, University of Huddersfield, Huddersfield, United Kingdom

Correspondence to:

Kow Chia Siang
International Medical University, Kuala Lumpur, Malaysia
Email ID: chiasiang_93@hotmail.com

Dear editor,

We agree with de Feria et al. [1] which commented that current observational studies on the effects of renin-angiotensin system (RAS) inhibitors use in coronavirus disease 2019 (COVID-19) are with marked limitations. In fact, we are aware of the publication of few systematic reviews and meta-analyses [2-8] which included these observational studies with questionable quality to determine the association between renin-angiotensin system (RAS) inhibitors use, including angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), and mortality/severity of COVID-19. Therefore, we demand caution when adopting the findings from these meta-analyses. **Table 1** summarizes the characteristics of systematic reviews and meta-analyses investigating on the use of ACEIs/ARBs on COVID-19 mortality and/or severity.

Firstly, these systematic reviews and meta-analyses suffer from a common methodological flaw where the authors pooled mostly the unadjusted odds ratio in their meta-analyses to determine the risk of mortality or severe/critical illness from COVID-19, especially when the adjusted odds ratios were not provided in the included original studies. The pooling of unadjusted estimates can be misleading, since there are many factors that could influence the clinical outcomes of patients with COVID-19. Without adjustment of the covariates or covariables which could modify the association between RAS inhibitors use and mortality/severity of COVID-19, the true effect on the use of RAS inhibitors in COVID-19 cannot be revealed even through a meta-analysis.

Secondly, some of these systematic reviews and meta-analyses included studies or only involved findings on COVID-19 patients with concurrent hypertension. Selective inclusion of only hypertensive individuals may not reflect the association between RAS inhibitors use and mortality/severity of COVID-19 since RAS inhibitors are also prescribed for indications other than hypertension, including congestive heart failure, diabetic nephropathy, coronary artery disease, acute coronary syndrome, Raynaud phenomenon, amongst others. Patients with these conditions too need long-term usage of RAS inhibitors, where increased expression of ACE2 receptor, which is the hypothesized pathological

mechanism leading to worse outcomes among COVID-19 patients receiving RAS inhibitors, could also occur in the users of RAS inhibitors for indications other than hypertension [9].

Thirdly, at least half of the studies pooled in these systematic reviews and meta-analyses (**Table 1**) are originated from China. This presented another source of selection bias since patient outcomes may be different across continents or even across different countries, as demonstrated in the wide interval of case fatality rates of COVID-19 among countries. In fact, while all studies from China reported either no difference or significant reduced risk of mortality and/or severe/critical disease from COVID-19 among users of ACEIs/ARBs compared to non-users, a single-center study [10] from France reported otherwise, in which hospitalized patients with COVID-19 receiving RAS inhibitors at baseline had significantly increased odds of being admitted to an intensive care unit or death before admission to an intensive care unit (odds ratio 1.73, 95% confidence interval 1.02–2.93). Therefore, there may be regional differences in the clinical outcomes from COVID-19 among patients receiving ACEIs/ARBs which the currently available systematic reviews and meta-analysis failed to address.

We agree with de Feria et al. [1] that only through randomized controlled trials that a cause-and-effect relationship can be established. Nevertheless, future retrospective or prospective studies should adjust for covariates or covariables in their analysis to provide more clarity on the association between RAS inhibitors use and clinical outcomes of COVID-19.

Declarations of interest: None

References

1. de Feria A, Ortega-Legaspi JM. ACE inhibitors/ARB use and COVID-19. Time to change practice or keep gathering data? [published online ahead of print, 2020 Jul 4]. Clin Infect Dis. 2020;ciaa819.
2. Grover A, Oberoi M. A systematic review and meta-analysis to evaluate the clinical outcomes in COVID-19 patients on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [published online ahead of print, 2020 Jun 15]. Eur Heart J Cardiovasc Pharmacother. 2020;pvaa064.
3. 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.
4. Pirola CJ, Sookoian S. Estimation of Renin-Angiotensin-Aldosterone-System (RAAS)-Inhibitor effect on COVID-19 outcome: A Meta-analysis. J Infect. 2020;81(2):276-281.
5. Zhang X, Yu J, Pan LY, Jiang HY. ACEI/ARB use and risk of infection or severity or mortality of COVID-19: A systematic review and meta-analysis. Pharmacol Res. 2020;158:104927.
6. Greco A, Buccheri S, D'Arrigo P, et al. Outcomes of renin-angiotensin-aldosterone system blockers in patients with COVID-19: a systematic review and meta-analysis [published online ahead of print, 2020 Jul 16]. Eur Heart J Cardiovasc Pharmacother. 2020;pvaa074.
7. Usman MS, Siddiqi TJ, Khan MS, et al. A Meta-analysis of the Relationship Between Renin-Angiotensin-Aldosterone System Inhibitors and COVID-19 [published online ahead of print, 2020 Jun 2]. Am J Cardiol. 2020;S0002-9149(20)30548-8.
8. Pranata R, Permana H, Huang I, et al. The use of renin angiotensin system inhibitor on mortality in patients with coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis [published online ahead of print, 2020 Jun 27]. Diabetes Metab Syndr. 2020;14(5):983-990.
9. Kow CS, Zaidi STR, Hasan SS. Cardiovascular Disease and Use of Renin-Angiotensin System Inhibitors in COVID-19. Am J Cardiovasc Drugs. 2020;20(3):217–221.
10. Liabeuf S, Moragny J, Bennis Y, et al. Association between renin-angiotensin system inhibitors and COVID-19 complications [published online ahead of print, 2020 Jun 12]. Eur Heart J Cardiovasc Pharmacother. 2020;pvaa062.

Table 1: Characteristics of systematic reviews and meta-analysis on the use of ACEIs/ARBs on COVID-19 mortality and/or severity

Study	No. of studies included	No of RCTs included	Population	Effect size (mortality)	Effect size (severity)	Retracted study included	No. of Chinese studies pooled
Grover et al. [2]	16	0	Mixed population of HTN & other CDs	OR = 0.86, 95% CI = 0.53–1.41 **(adjusted effect size from 1 study out of 6 studies pooled)**	OR = 0.81, 95% CI = 0.41–1.58 **(adjusted effect size from 1 study out of 4 studies pooled)**	Yes	4/6 (66.7%) for mortality analysis; 4/4 (100%) for severity analysis
Guo et al. [3]	9	0	HTN	OR = 0.57, 95 % CI = 0.38–0.84 **(unadjusted effect size from 6 studies pooled)**	OR = 0.71, 95 % CI = 0.46–1.08 **(unadjusted effect size from 6 studies pooled)**	No	6/6 (100%) for mortality analysis; 5/6 (83.3%) for severity analysis
Pirolaa et al. [4]	16	0	Mixed population of HTN & other CDs	OR: 0.768, 95% CI: 0.651-0.907 for death and/or critical disease **(unadjusted effect size from 16 studies pooled)**		Yes	8/16 (50%)
Zhang et al. [5]	12	0	Mixed population of HTN & other CDs	OR = 0.91, 95 % CI = 0.51–1.61 **(adjusted effect size from 4 studies out of 8 studies pooled)**	OR = 0.98, 95 % CI = 0.87–1.09 **(unadjusted effect size from 8 studies pooled)**	Yes	5/8 (62.5%) for mortality analysis; 5/7 (71.4%) for severity analysis
Greco et al. [6]	13	1	Mixed population of HTN & other CDs	OR = 0.95, 95% CI, 0.57–1.58 **(unadjusted effect size from 13 studies pooled)**	N/A	No	8/13 (61.5%)

Usman et al. [7]	5	0	HTN	OR = 0.74, 95% CI = 0.31–1.58 **(unadjusted effect size from 5 studies pooled)**	N/A	No	5/5 (100%)
Pranata et al. [8]	15	0	Mixed population of HTN & other CDs	OR = 0.73, 95% CI = 0.38–1.40 (**adjusted effect size from 3 studies out of 11 studies pooled)**	OR = 1.03, 95 % CI = 0.73–1.45 **(adjusted effect size from 1 study out of 9 studies pooled)**	No	7/11 (63.6%) for mortality analysis; 7/9 (77.8%) for severity analysis