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LETTER TO THE EDITOR

Combination Therapy with CCBs and RAS Inhibitors to Counteract Endothelial Dysfunction in COVID-19

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After the breakthrough discovery that the SARS-CoV-2 utilizes angiotensin-converting enzyme 2 (ACE-2) receptor for cellular entry, several researchers warned about the use of renin-angiotensin system (RAS) inhibitors (ACE inhibitors and angiotensin type II receptor blockers [ARBs]) due to their potential to enhance the expression of ACE-2, while proposing calcium channel blockers (CCBs) to replace the use of RAS inhibitors in patients with coronavirus disease 2019 (COVID-19) [1]. Since then, there has been a growing interest to investigate the efficacy of CCBs in patients with COVID-19 [2].

Nevertheless, the recently reported randomized controlled trial by Nouri-Vakesh et al. [3] seems to hamper further investigations on the therapeutic potential of CCBs in COVID-19. The randomized trial [3], which aimed to compare the effects between losartan and amlodipine in patients with COVID-19 and primary hypertension, reported no significant difference in mortality rate, length of hospital stay, and requirement for intubation between the two treatment arms. Although with no safety concerns, the randomized trial [3] has also reported no clinical benefits with the use of CCBs or even RAS inhibitors in patients with COVID-19.

The findings from the randomized trial [3] are in contrary to the observational evidence [4, 5] that the use of CCBs in patients with COVID-19 could be associated with mortality benefits. A systematic review and meta-analysis [5] of observational studies reported that the use of CCBs in patients with COVID-19 was significantly associated with lower odds of mortality (odds ratio = 0.65, 95% confidence interval 0.49–0.86) and lower odds of severe disease (odds ratio = 0.61, 95% confidence interval 0.44–0.84) compared with non-use of CCBs. While the calcium channels blocking effects of CCBs in the lungs and vascular system may mitigate the inflammatory effects of COVID-19, it seems that such an effect is inadequate to provide mortality benefits [2]. The same occurs with the use of RAS inhibitors in patients with COVID-19, in which the observational evidence [6] reported positive effects, but the randomized trials [7] reported neutral effects.

Therefore, instead of administering CCBs alone or RAS inhibitors alone to patients with COVID-19, it might be better to combine the two agents. The combination of CCBs and RAS inhibitors has synergistic effects that improve endothelial function, reduce oxidative stress, and suppress inflammatory responses, especially in the arterial vasculature [8]. Several clinical trials in patients with hypertension have demonstrated the efficacy of such combination therapy; most notably the landmark ACCOMPLISH trial [9], which randomized patients to combination therapy with benazepril plus either amlodipine or hydrochlorothiazide and reported that the primary endpoint, which was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac death or coronary revascularization, achieved significantly less often in the benazepril-amlodipine group (hazard ratio: 0.80; 95% confidence interval 0.72–0.90).

Therefore, we believe that instead of investigating the use of CCBs alone (or RAS inhibitors alone) to patients with COVID-19, the combination therapy with CCBs and RAS inhibitors which can potentially counteract the endothelial activation and dysfunction involved in COVID-19 pathogenesis should be further investigated, preferably in randomized trials, to undertand its clinical implications in patients with COVID-19.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

References

1. 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):217–21.
2. Safizadeh F, Nguyen TNM, Brenner H, Schöttker B. Association of Renin-Angiotensin-Aldosterone System inhibition with Covid-19 hospitalization and all-cause mortality in the UK Biobank [published online ahead of print, 2021 Dec 22]. Br J Clin Pharmacol. 2021. https://doi.org/10.1111/bcp.15192.
3. Nouri-Vaskeh M, Kalami N, Zand R, et al. 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. Kow CS, Ramachandram DS, Hasan SS. Calcium channel blockers and the risk of all-cause mortality and severe illness in patients with COVID-19. J Cardiovasc Pharmacol. 2021. https://doi.org/10.1097/FJC.0000000000001144.
5. Kow CS, Ramachandram DS, Hasan SS. Clinical outcomes of hypertensive patients with COVID-19 receiving calcium channel blockers: a systematic review and meta-analysis [published online ahead of print, 2021 Nov 9]. Hypertens Res. 2021;1–4.
6. Hasan SS, Kow CS, Hadi MA, Zaidi STR, Merchant HA. Mortality and disease severity among COVID-19 patients receiving renin-angiotensin system inhibitors: a systematic review and meta-analysis. Am J Cardiovasc Drugs. 2020;20(6):571–90.
7. Kow CS, Ming LC, Hasan SS. Renin-angiotensin system inhibitor use and the risk of mortality in hospitalized patients with COVID-19: a meta-analysis of randomized controlled trials. Hypertens Res. 2021;44(8):1042–5.
8. Mizuno Y, Jacob RF, Mason RP. Effects of calcium channel and renin-angiotensin system blockade on intravascular and neurohormonal mechanisms of hypertensive vascular disease. Am J Hypertens. 2008;21(10):1076–85.
9. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med. 2008;359(23):2417–28.