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Letter to the editor:

TO DO OR NOT TO DO: ANGIOTENSIN CONVERTING ENZYME INHIBITORS/ANGIOTENSIN RECEPTOR BLOCKER IN COVID-19 ELDERLY PATIENTS

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Dear Editor,

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative organism of coronavirus disease-19 (COVID-19) is tied to the 2020 pandemic that originally began at the end of December 2019 in Wuhan, Hubei province, China. Epidemiological studies have shown that SARS-CoV-2 is known to cause increased mortality in adults beyond the sixth decade of life; similar findings were noticed consistently across the orb; the reason for the differential clinical severity remains murky. The higher prevalence of cardiovascular disease (CVD), hypertension, and diabetes mellitus in older adults infected with COVID-19 are linked to deteriorating the prognosis. The majority of the older adults are known to be taking either angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEl/ARBs) for various aforementioned causes. SARS-CoV-2 uses its viral spike glycoprotein ectodomain to bind the angiotensin-converting enzyme 2 (ACE2) receptor to gain entry into the human cells (Walls et al, 2020). Preclinical studies have suggested that the renin-angiotensin-aldosterone system (RAAS) inhibitors may increase ACE2 expression, raising concerns regarding their safety in patients with COVID-19. This issue sparked a debate regarding the use of ACEl/ARBs because of the association between ACE2 and SARS-CoV-2. We review recent research to provide evidence-based recommendations amid Covid-19 in older adults using ACEI/ARBs.

Renin-Angiotensin System (RAS)

The initial rate-controlling step in RAS is renin. Renin is responsible for hydrolyzing angiotensinogen to angiotensin I. Angiotensin I is further converted to angiotensin II by angiotensin-converting enzyme (ACE1). Angiotensin II binds and activates angiotensin II receptor type 1, this activates downstream pro-inflammatory actions, including vasoconstriction and cell proliferation, responsible for acute lung injury seen in COVID-19 patients. ACE2 physiologically counters RAAS activation by metabolizing angiotensin II to angiotensin$_{1-7}$ and angiotensin I to angiotensin$_{1-9}$. Angiotensin$_{1-9}$ binds to the Mas receptor which leads to anti-inflammatory and vasodilation. Both ACE1 and ACE2 are members of the ACE family of dipeptidyl carboxydipeptidases (Bavishi et al., 2020). ACE2 is predominantly expressed in alveolar epithelium,

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bronchiolar epithelium, endothelium, smooth muscles of pulmonary vessels (Xie et al., 2006). ACE2 exists in two forms: a structural transmembrane protein with an extracellular domain that serves as a receptor for spike protein of SARS-CoV-2 and a soluble form that represents the circulating ACE2. Observational studies have shown that urinary ACE2 levels were substantially increased in hypertensive and diabetic patients treated with ACEI/ARBs. A study by Liu et al. showed higher angiotensin II levels in patients infected with SARS-CoV-2 that was linearly associated with viral load and lung injury (Liu et al., 2020). Based on these observations, one can contemplate the use of ACEI/ARBs can increase ACE2 expression and intensify SARS-CoV-2 entry leading to severe COVID-19 (Figure 1).

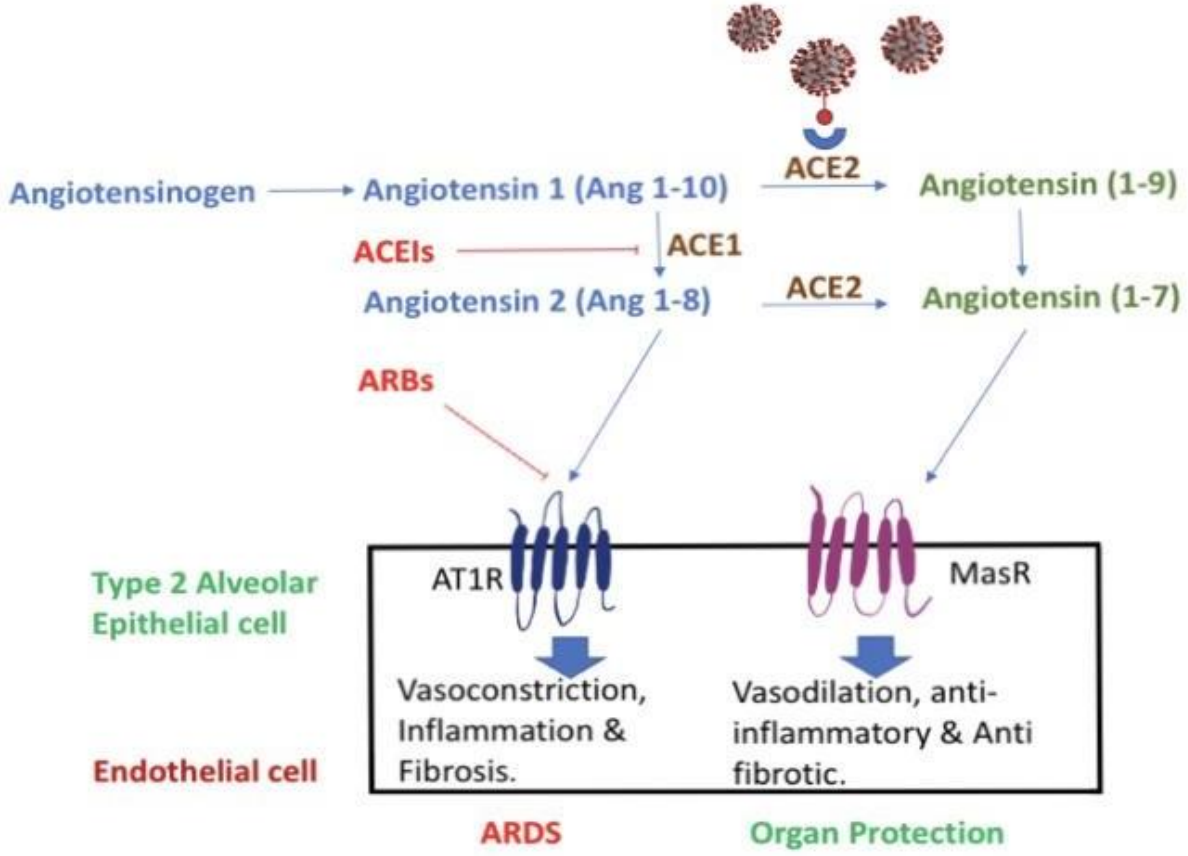

Figure 1: Schematic representation of the RAAS system and the effects of RAAS inhibitors in normal physiology and possible correlation with COVID-19 infection. ACE1 converts Angiotensin I to angiotensin II. Angiotensin II is responsible for acute lung injury and ACE2 metabolizes angiotensin II to angiotensin$_{1-7}$. ACE II acts as the receptor for viral binding for SARS-CoV-2.

Age-related changes

In an epidemiological analysis conducted in Wuhan in patients infected with COVID-19, it was observed that patients above the age of 59 years were 5.1 (4.2-6.1) times more likely to die after developing symptoms. Furthermore, the risk of symptomatic infection also increased with age (Wu et al., 2020). In fact, a retrospective cohort study identified older age as the leading risk factor for mortality in patients infected with SARS-CoV-2 (Zhou et al., 2020).

It is crucial to understand age-related alterations in ACE2 expression. Aging is associated with a decline in the ACE2 expression in the rat lungs (Xie et al., 2006). In older adults with comorbidities such as hypertension and diabetes, ACE2 is downregulated as well. This decline in ACE2 levels is followed by decreased clearance of pro-inflammatory Angiotensin II, thus explaining the higher severity of disease seen in older individuals. Moreover, binding of SARS-

CoV-2 with ACE2 for viral entry, further decreased the cell surface expression of the receptor, leading to exaggerated signaling by the Angiotensin II (AlGhatrif et al., 2020).

Paradoxically decline in ACE2 expression in older individuals could significantly lower the incidence of disease in this subset of the population as ACE2 acts as the receptor for the SARS-Co-V-2 (AlGhatrif et al., 2020). The number of cases in South Korea was the highest in the age group 20-29 years old. Interestingly, epidemiological data of SARS are the predominance of the young adult population. Cellular entry receptor is similar for both SARS-CoV-1 and SARS-CoV-2; this could be explained by reduced expression of ACE2 in older individuals (Xie et al., 2006).

A large proportion of the elderly population are on medications including ACE inhibitors and ARB's. Animal studies in the past have shown that blockade of angiotensin II synthesis with ACE inhibitor or activity with ARBs is associated with an increase in ACE2 gene expression and activity (Ferrario et al., 2005). Higher urinary ACE2 levels are seen in hypertensives treated with ARBs. This is the basis of the hypothesis that patients treated with ACEI/ARBs have augmented ACE2 activity leading to worse prognosis in COVID-19 patients. Conversely, it can be hypothesized that increased ACE2 activity would lead to increased degradation of Angiotensin II, and may prevent the deleterious effects of angiotensin II described above.

There have been prior animal studies that have concluded that ACEI (Captopril) have had protective effects on oleic acid-induced acute lung injury in rats (He et al., 2007). In 2017, Kim et al., in their retrospective study concluded that RAAS inhibitors may have protective effects in ARDS in humans as well (Kim et al., 2017). In another meta-analysis of 37 studies - ACE inhibitors but not ARB's were associated with reduced risk of pneumonia (Caldeira et al., 2012).

Evidence

There is limited evidence available to date. A retrospective study done in China by Li et al. showed no association with disease severity in hypertensive patients taking ACEI/ARBs (Li et al., 2020). Another retrospective cohort study done by Mehta et al. (2020) concluded with no association between ACEI and ARB use and COVID-19 positivity.

Please refer to Table 1 for all the investigations that were completed to date and their conclusions.

Conclusion

There is no sufficient evidence at this time to stop ACEI/ARBs in older adults. Most societies recommend continuing these medications when patients already on them. Moreover, they do not recommend initiating ACE inhibitors/ARBs in COVID-19 patients unless another clinical indication (like hypertension, diabetes). Based on available studies and society guidelines one should not hold ACEI/ARBs at this time. Much larger studies are needed for addressing this matter to provide evidence-based recommendations in the near future. We recommend continuation of renin-angiotensin system inhibitors safely in COVID-19 infected patients which are concordant with international society recommendations.

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Table 1: Studies that we reviewed about the use of ACEI/ARB in COVID patients

Study name	Date Published	Study type	Location	Results	Conclusion
Mehta et al.	May 5, 2020	Retrospective cohort study	Cleveland Clinic Health System, Ohio and Florida	Out of a total of 18,472 patients tested for COVID-19, 12.4 % were taking ACE inhibitor/ARB. From 1,735 out of 18,472 (9.4 %) patients who were tested positive, 24.3 % were admitted to the hospital, 9.3 % were admitted to intensive care, 6.4 % required mechanical ventilation.	No association between ACE inhibitor/ ARB use and COVID-19 test positivity
Mehra et al.	May 1, 2020	Observational study	169 hospitals in Asia, Europe, North America	Of the 8,910 patients with COVID-19, 5.8 % died in the hospital. Factors associated with increased risk of in-patient death were age > 65 years, CAD, heart failure, cardiac arrhythmia, COPD and current smoking. No increased risk of in-hospital death associated with the use of ACE inhibitors or the use of ARBs.	The study did not confirm the potentially harmful association of ACE inhibitors or ARBs with in-hospital death in COVID-19 patients.
Reynolds et al.	May 1, 2020; updated on May 6, 2020	Observational study	New York University Langone health	Out of 12,594 patients who were tested for COVID-19, 46.8 % were tested positive, 17 % of these patients had severe disease. History of hypertension was found in 34.6 % of total patients and 59.1 % of patients with hypertension had a positive result.	No substantial increase in the likelihood of a positive test for COVID-19 or in the severity of the disease in patients previously treated with ACE inhibitors/ARBs/beta blockers/calcium channel blockers/thiazide diuretics
Mancia et al.	May 1, 2020	Case control study	Lombardy, Italy	Use of ACE inhibitors (23.9 % in cases vs 21.4 % in controls) and ARBs (22.2 % in cases vs 19.2 % in controls) was more common amongst case patients than control. Use of ACE inhibitors or ARBs did not show any association with COVID-19 amongst case patients.	Use of ACE inhibitors and ARBs were more frequent among patients with COVID-19, however, no evidence that ACE inhibitors or ARBs affected the risk of COVID-19.
Zhang et al.	April 17, 2020	Retrospective multi-center study	Hubei, China	Out of 1,128 hospitalized patients diagnosed with COVID-19, 188 patients were taking ACE inhibitors/ ARBs and 940 were not. The all-cause mortality was lower in the ACE inhibitor/ARB group versus the non ACE inhibitor/ARB group.	Amongst hospitalized COVID-19 patients, in-patient ACE inhibitor/ARB was associated with lower risk of all-cause mortality compared to non-users.

Study name	Date Published	Study type	Location	Results	Conclusion
Lopes et al.	January 19, 2021	Randomized clinical trial	Brazil	Among 659 patients who were using ACEIs or ARB, in 334 patients it was discontinued and continued in 325. There was no difference in deaths or duration of stay in hospital.	Amongst COVID-19 hospitalized patients with mild to moderate infection use of ACEIs or ARBs does not affect duration of hospital stay hence can be continued if its very indicated.
Cohen et al.	March, 2021	Randomized clinical trial	USA, Canada, Mexico, Sweden, Peru, Bolivia, and Argentina	Out of the 152 participants, ACEIs or ARB were continued in 75 participants and discontinued in the rest. Similar results were seen in ICU/ventilators requirement and death in both groups. No differences were seen in vitals and laboratory results in both groups during follow-up.	Continuation and discontinuation of ACE inhibitor/ARB in COVID-19 hospitalized patients had identical effects on acute outcomes. Continuation of these in accordance with international society recommendation is advised.

Conflict of interest

The authors declare no competing interests.

REFERENCES

AlGhatrif M, Cingolani O, Lakatta EG. The dilemma of Coronavirus Disease 2019, aging, and cardiovascular disease: Insights from cardiovascular aging science. JAMA Cardiol. 2020;5:747-8. doi: 10.1001/jamacardio.2020.1329.

Bavishi C, Maddox TM, Messerli FH. Coronavirus Disease 2019 (COVID-19) infection and renin angiotensin system blockers. JAMA Cardiol. 2020;5:745-7. doi: 10.1001/jamacardio.2020.1282.

Caldeira D, Alarcão J, Vaz-Carneiro A, Costa J. Risk of pneumonia associated with use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers: Systematic review and meta-analysis. BMJ. 2012;345:e4260. doi: 10.1136/bmj.e4260.

Cohen JB, Hanff TC, William P, Sweitzer N, Rosado-Santander NR, Medina C, et al. Continuation versus discontinuation of renin-angiotensin system inhibitors in patients admitted to hospital with COVID-19: A prospective, randomised, open-label trial. Lancet Respir Med. 2021;9:275-84. doi: 10.1016/S2213-2600(20)30558-0.

Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation. 2005;111:2605-10. doi: 10.1161/CIRCULATIONAHA.104.510461.

He X, Han B, Mura M, Xia S, Wang S, Ma T, et al. Angiotensin-converting enzyme inhibitor captopril prevents oleic acid-induced severe acute lung injury in rats. Shock. 2007;28:106-11. doi: 10.1097/SHK.0b013e3180310f3a.

Kim J, Choi SM, Lee J, Park YS, Lee CH, Yim JJ, et al. Effect of renin-angiotensin system blockage in patients with acute respiratory distress syndrome: A retrospective case control study. Korean J Crit Care Med. 2017;32:154-63. doi: 10.4266/kjccm.2016.00976.

Li J, Wang X, Chen J, Zhang H, Deng A. Association of renin-angiotensin system inhibitors with severity or risk of death in patients with hypertension hospitalized for Coronavirus Disease 2019 (COVID-19) infection in Wuhan, China. JAMA Cardiol. 2020;5:825-30. doi: 10.1001/jamacardio.2020.1624. Erratum in: JAMA Cardiol. 2020;5(8):968.

Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci. 2020;63:364-74. doi: 10.1007/s11427-020-1643-8.

Lopes RD, Macedo AVS, de Barros E Silva PGM, Moll-Bernardes RJ, Dos Santos TM, et al. Effect of discontinuing vs continuing angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on days alive and out of the hospital in patients admitted with COVID-19: A randomized clinical trial. JAMA. 2021;325:254-64. doi: 10.1001/jama.2020.25864.

Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-angiotensin-aldosterone system blockers and the risk of Covid-19. N Engl J Med. 2020;382:2431-40. doi: 10.1056/NEJMoa2006923.

Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med. 2020;382(25):e102. doi: 10.1056/NEJMoa2007621.

Mehta N, Kalra A, Nowacki AS, Anjewierden S, Han Z, Bhat P, et al. Association of use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with testing positive for Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020;5:1020-6. doi: 10.1001/jamacardio.2020.1855.

Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Iturrate E, Johnson SB, et al. Renin-angiotensin-aldosterone system inhibitors and risk of Covid-19. N Engl J Med. 2020;382:2441-8. doi: 10.1056/NEJMoa2008975.

Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. 2020;181:281-92.e6. doi: 10.1016/j.cell.2020.02.058.

Wu JT, Leung K, Bushman M, Kishore N, Niehus R, de Salazar PM, et al. Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China. Nat Med. 2020;26:506-10. doi: 10.1038/s41591-020-0822-7.

Xie X, Chen J, Wang X, Zhang F, Liu Y. Age- and gender-related difference of ACE2 expression in rat lung. Life Sci. 2006;78:2166-71. doi: 10.1016/j.lfs.2005.09.038.

Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie J, et al. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res. 2020;126:1671-81. doi: 10.1161/CIRCRESAHA.120.317134.

Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet. 2020;395(10229):1054-62. doi:10.1016/S0140-6736(20)30566-3.