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LETTER TO THE EDITOR

A Viewpoint on Angiotensin-Converting Enzyme 2, Anti-Hypertensives and Coronavirus Disease 2019 (COVID-19)

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TO THE EDITOR,

The current life-threatening pandemic outbreak of coronavirus disease 2019 (COVID-19) is hitting the whole world in terms of mortality as well as economic losses [1, 2]. It has thought to be originated from Wuhan, China, in December 2019. This outbreak has the link to Wuhan's seafood and exotic animal wholesale markets [3, 4]. As SARS-CoV-2 is highly contagious, it has now spread to every corner of the world [1,2]. According to the World Health Organization (WHO) situation report (77^{th}), updated on 6 April, 2020 there have been globally 1210956 confirmed cases and 67 594 deaths of COVID-19 [2]. This viral outbreak has now posed a global threat to healthcare systems. So many efforts are going on to find new drugs or to repurpose already existed drugs [1,5-7]. It has been found that most of the COVID-19 patients belong to cardiovascular comorbidities [8-10]. It is obvious that they qualify for antihypertensive therapy. Many of them are treating with angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) [8].

There has been considerable debate in the scientific community and health professionals about whether angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) may increase attractiveness towards the COVID-19 virus infection or not? [9-16]. One of the important concerns highlighted by these studies involving antihypertensive medications suggested that these drugs might cause increments in the abundance of SARS-CoV-2 receptor henceforth causing COVID-19 by entering into cells [17, 18]. This suggests a plausible increase in ACE2 receptors on lung and heart cells and hence offering more entry points for SARS-CoV-2 [17]. However, no strong evidence has been noted. There have been a number of commentaries published explaining both sides and still they appear on daily basis [12-16]. Herein, we tried to summaries, clinical aspects of ACEs and ARBs based on literature and commentaries to explain both the sides. A recent published article in Nature by Zhou *et al.* (2020)[19], reported that the angiotensin-converting enzyme II (ACE2) is acting as a receptor for SARS Coronavirus 2.These receptors were also acted as receptors for SARS-CoV and HCoV-NL63. Zhou *et al.* (2020), clearly wrote that "We show that 2019-nCoV (COVID-19) is able to use ACE2 proteins as an entry receptor to enter ACE2-expressing cells, but not cells that did not express ACE2, indicating that ACE2 is probably the cell receptor through which 2019-nCoV enters cells". ACE2 is aminopeptidase responsible for cleaving angiotensin I and angiotensin II into the angiotensin-(1–9) and angiotensin-(1–7) peptides [20].

Normally, ACE2 has been found to be overexpressed in clinical conditions, including heart failure, arterial hypertension, *etc.* It has also been noted that ACE2 acts as a functional receptor for SARS-CoV-2 entry. There have been several literatures supporting the role of a cardiovascular-protective ACE2–angiotensin-(1–7)–Mas receptor axis.

A recent viewpoint article published in the JAMA journal by author Majd AlGhatrif exaplains [15] correlations among aging, cardiovascular diseases, and COVID-19 patients. He clearly concluded important fact saying, "compared with young individuals, older persons with cardiovascular disorders (CVD); who already have reduced ACE2 levels will be expected to be more predisposed to exaggerated inflammation with further reduction in ACE2 expression in the context of COVID-19, manifesting with greater disease severity". One well-known Austrian scientist Prof. Josef Penninger [21], Josef Penninger noted an important relationship between RAS (the renin-angiotensin system) and ACE2. He is particularly focusing on ACE2 as a potential treatment approach. In one of the article by Mourad *et al.*, (2020), explained different effects on ACE2 levels in correlation with different administrations of RAAS inhibitors and believed that chronic treatment with ACE inhibitors has no reason to influence the course of SARS-CoV-2 infection [22]. A reply to this article has also been published by Zheng *et al.*, (2020) [23] saying that "although ACE2 has been identified as the

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functional receptor for SARS-CoV-2, the role of ACE2 in the progression of COVID-19 after SARS-CoV-2 infection is still controversial, so the benefits of aliskiren use in patients with COVID-19 needs further investigation".

Today, many healthcare societies, ' especially cardiovascular societies are urging the patients suffering from CVDs (cardiovascular diseases) not to discontinue their medications[24-26]. These healthcare societies give more stress upon statements saying that there is no sound evidence to correlate ACEs and ARBs leading risk of COVID-19 infection. It has also been noted that healthcare societies do not suggest immediate starting of ACEIs/ARBs in those patients having no settlements with clinical conditions like heart failure, diabetes, hypertension, *etc.* These statements adhere to the current state of evidences. The same conclusion has been derived from the recent article by Ankit Patel *et al.*, (2020) [24]. This article suggested that there has been no definitive evidence to suggest ACE inhibitors and ARBs worsening of COVID-19. A study published by Vaduganathan *et al.,* (2020) in the New England Journal of Medicine discussed the uncertain effects of RAAS blockers on ACE2 levels [27]. They also derived to the conclusion that ACE2 may be beneficial in COVID-19 patients with lung injury. This team also suggests that the withdrawal of RAAS inhibitors may be harmful. A very recent review published by Dr. Sanchis-Gomar and his co-authors in Mayo Clinic Proceedings[14], by analysing more than 60 articles, concluded the fact that "no studies have reported an increase in circulating ACE2 levels or expression thus far, and increased expression would not necessarily imply an increased risk of infection or disease severity". Dr. Sanchis-Gomar, studies both articles explaining that elevated levels of angiotensin II fostering acute respiratory distress syndrome (ARDS) as well as the significance of RAAS inhibitors in therapy in treating patients with COVID-19. However, the authors noted that more research in this regard is needed.

CONCLUSION

In this regard, more laboratory and clinical evidences are required in order to decide COVID-19 treatment. In conclusion to this debate, suggesting roles of antihypertensive agents and severity leading changes in ACE2 levels, may shed more light on infectivity and outcome of COVID-19. There is an urgent need to establish whether treatments with antihypertensive (ACEI's/ ARBs) need to be determined.

LIST OF ABBREVIATIONS

ACEI's	=	angiotensin-converting enzyme inhibitor
ARBs	=	angiotensin II receptor blocker
COVID-19	=	coronavirus disease 2019
SARS-CoV 2	=	The Severe Acute Respiratory Syndrome Human coronavirus 2
WHO	=	The World Health Organization

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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