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Reply to the Comment by Dr. Cure on "Should COVID-19 Concern Nephrologists? Why and to What Extent? The Emerging Impasse of Angiotensin Blockade"

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We thank Professor Erkan Cure and Professor Medine Cumhur Cure [1] for their constructive and stimulating discussion of this issue, which is of the utmost clinical importance.

The identification of angiotensin-converting enzyme 2 (ACE2) as the entry receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) gave rise to serious concerns about the possible detrimental effect of angiotensin receptor blockers (ARBs) in the outcome of the 2019 novel coronavirus disease (COVID-19), given the ability of ARBs to increase ACE2 in cardiac and renal tissues. However, as they correctly stated in their letter, "*there are no scientific data yet that ARBs increase the ACE2 level in lung tissue*."

With that caveat in mind, we collected all the clinical and preclinical evidence available that describe the possible role of ACE2 in the lungs during coronavirus infections [2]. What emerged clearly from these studies is that viral entrance is a complex multistep process, of which binding to ACE2 is merely the first [2]. They are correct in stating that "*COVID-19 passes into the cell using ACE2 as a host and causes infection*," although it is worth mentioning that at least two different routes exist for coronavirus entry into target cells [2]. In addition to ACE2-dependent endosomal entry, SARS-CoV-2 can enter alveolar cells through a cell surface non-endosomal pathway, which is ACE2 independent [3]. For this reason, the absence or reduction of ACE2 per se does not necessarily reduce the risk of infection from SARS-CoV-2. This is supported by the finding that ACE2 is strongly downregulated in the elderly patients and in patients with hypertension and diabetes who are, counterintuitively, the subjects with the greatest fatality rates for COVID-19, supporting the idea that ACE2 reduction is not sufficient to limit SARS-CoV-2 infection [2]. Again, ACE2 deletion or inhibition exacerbates viral pneumonia in mice, while ARBs ameliorated disease outcomes after coronavirus infection. Collectively, all these data signal that ACE2 has a protective effect [4].

In light of these findings, we tried to analyze three different counterintuitive scenarios in which the hypothetical increased ACE2 expression in the lungs induced by ARBs could be beneficial in COVID-19 [2]. However, we never claimed that "*ARBs could alter the ACE2 structure*." We hypothesized that, following ARB treatment, angiotensin II cannot bind to angiotensin type 1 receptor (AT_1R) and becomes more available for binding to ACE2 [2]. What previous studies demonstrated is that engagement of the catalytic domain of ACE2 by its substrate (i.e., Ang II) induces a strong conformational alteration of the

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ACE2 ectodomain, which, in turn, may interfere with the interaction with the spike protein of SARS-CoV-2 [5].

The authors' additional point that "*Angiotensin II may increase pulmonary vascular leakage, causing lung injury during COVID infection*" is well-taken. However, a large body of work demonstrates that these effects are mediated by AT_1R on endothelial cells. By blocking AT_1R, ARBs promote an increase in angiotensin II, which in turns binds to ACE2 and, to a lesser extent, AT_2R, exerting anti-inflammatory and anti-fibrotic effects [6]. In particular, angiotensin II binding to the catalytic domain of ACE2 generates angiotensin 1–7, which is beneficial during the acute respiratory distress syndrome in COVID-19, as correctly reported in the authors' Comment when they stated that "*angiotensin 1–7 intravenous or intraperitoneal administration is useful in the ARDS treatment*."

Finally, we absolutely understand the authors' concerns regarding the possibility "*that ARBs should be discontinued in COVID-19 infection*." However, this consideration is not in line with the current European Society of Hypertension and European Society of Cardiology position statements, which strongly recommend maintaining antihypertensive therapy, as there is no clinical or scientific evidence to support ARB withdrawal during COVID-19 [7, 8]. On the contrary, a recent multicenter retrospective study from China reported that, among the elderly patients, the risk of developing severe COVID-19 was significantly lower in patients who took ARBs prior to hospitalization than patients who took no drugs [9]. Notably, this protection was not observed in patients taking other antihypertensive drugs, including calcium channel blockers [9]. In a recent article, Vaduganathan and colleagues [4] clearly suggested that abrupt withdrawal or switching of antihypertensive drugs may result in clinical instability and adverse health outcomes associated with excess cardiovascular risk in high-risk COVID-19 patients. Finally, to further confirm the protective role of ARBs, a recent network-based drug repurposing study identified ARBs as a potential therapeutic option for COVID-19 [10]. Whether ARB treatment is a valuable therapeutic intervention in COVID-19 will become clear from the ongoing multicenter, double-blinded study (Identifier: NCT04312009) that has been designed to test the beneficial effect of daily losartan in COVID-19 patients requiring hospitalization [11].

Disclosure Statement

The authors have no conflicts of interest to declare.

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