



Commentary to Angiotensin-Converting-Enzyme 2 and Renin–Angiotensin System Inhibitors in COVID-19: An Update

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“Your Serene Highness.....”

The passage of time has revealed to everyone the truths that I previously set forth....”

Galileo Galilei

Letter to Christine de Lorraine, Grand Duchess of Tuscany, 1615

Studies on angiotensin-converting enzyme (ACE) 2 receptor have accumulated over the last 20 years since its discovery and stimulated the understanding of the renin–angiotensin–aldosterone system (RAAS) role in physiology and disease [1–3]. While the RAAS system has always attracted the attention of basic, applied, and clinical researchers, ACE2 made only basic researchers fall in love with it. In contrast, clinicians remained substantially skeptic or unaware in front of ACE2 and its possible role in human disease until the arrival of *Rhinolophus hipposideros* (commonly known as “horseshoe bats”) and the spillover of its viruses to humans [4, 5]. Indeed, *Rhinolophus affinis* is generally believed to represent the natural reservoir host for the progenitor of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [6]. Thus, until COVID-19 pandemic, relatively few researchers were well aware of the role of ACE2 as a fundamental regulator of the RAAS and a protective agent in heart failure, systemic and pulmonary hypertension, coronary heart disease, and diabetes mellitus [7].

Clinical and experimental studies support a protective cardiometabolic role for ACE2, and its activation has been suggested by a few studies as a potential therapeutic target in cardiovascular disease, including systemic arterial hypertension, although this has yet to be proven clinically [8, 9].

In contrast to the above, floods of studies investigated the role of ACE2 as the functional receptor of SARS-CoV-2 [1–4]. Despite sharing a very close evolutionary

relationship with SARS-CoV [10], i.e. the coronavirus that is responsible for SARS, the receptor-binding domain of SARS-CoV-2 differs in several key amino acid residues. Unfortunately, this diversity demonstrated to be detrimental, allowing for stronger binding affinity with the human ACE2 receptor and thereby probably favoring the large diffusion of SARS-CoV-2. In addition, it is also likely that the loss of ACE2 function that occurs after the binding by SARS-CoV-2 is followed by further damage, depriving cells of the protective effect of the enzyme [1–4, 10]. Concordant with this, ACE2 and the angiotensin II type 2 receptor protected mice from severe acute lung injury induced by acid aspiration or sepsis [11]. Interestingly, other RAAS components, including ACE, angiotensin II, and the angiotensin II type 1 receptor exerted the opposite effect and favored lung oedema in the same experiment. Thus, ACE-deficient mice manifested with modest lung injury, while recombinant ACE2 protected mice from severe acute lung injury [11]. More recently, clinical-grade human recombinant soluble ACE2 (hrsACE2) was able to reduce SARS-CoV-2 growth in Vero E6 cells by a factor of 1000–5000 [12], indicating that further investigation on hrsACE2 is needed in the hypothesis that hrsACE2—or monoclonal antibodies against ACE2—might represent an effective therapy against COVID-19 [12].

Despite the consistent bulk of data, during the early pandemic phase ACE2 was mainly considered as the virus gateway to entry into the host cells and the enemy to fight. Consequently, since the selective blockade of either synthesis or activity of angiotensin II by ACE-inhibitors and/or angiotensin II type 1 receptors blockers modestly increased cardiac ACE2 gene expression and cardiac ACE2 activity [13], various scientific papers, social networks and the lay press pointed an accusing finger at ACE-inhibitors and angiotensin II type 1 receptors blockers. The Italian Society of Hypertension [5], as well as the European Society of Hypertension and other National/International societies promptly engaged in a campaign to demonstrate that the controversy did not

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rely on solid foundations and invited patients to continue therapies based on RAAS inhibitors. Since then, several studies, including an ad hoc study by the Italian Society of Hypertension [14], clearly demonstrated that age and multimorbidity, but not antihypertensive drugs acting on the RAAS, predicted either intensive care unit access or death. Therefore, the time is arrived to make some considerations on the effective role of ACE2 in human diseases and COVID-19.

In the current issue of this Journal [15], an exhaustive review has the merit to focus on ACE2 and its Janus-faced behavior during the pandemic. As authors correctly pointed out, no data support the hypothesis that the use of RAAS inhibitors increases susceptibility to COVID-19 infection, its severity and/or the related mortality. The authors conclude that the available clinical data do not justify the discontinuation of therapies based on RAAS inhibitors due to the pandemic.

This conclusion relies on a review of the evidence, which should be the sound approach to the study of any human disease. We know from history the damage that derives from bending to dogmas. When Galileo Galilei turned his brilliant eyes to the stars and found Copernicus was right, he was a well-funded and celebrated teacher at the University of Pisa and Padua, but he was forced to abjure in favor of the geocentric model. We do not think that web surfers, many of whom influence the public opinion, are in bad faith when expanding upon scientific matters. Simply, they do not follow the seventh Wittgenstein's proposition (*Wovon man nicht sprechen kann, darüber muß man schweigen: whereof one cannot speak, thereof one must be silent*).

The interesting, exhaustive review by Shukla and Banerjee confirms that we must not support scientocracy but science, whose role in defining the correct approach to any disease cannot represent the only driver in clinical decisions but cannot be denied in favor of hasty conclusions and/or media hype.

The bias against RAAS inhibitors made us run the risk of interrupting life-saving therapies based on ACE-inhibitors and angiotensin II type 1 receptors blockers. We do believe that only a critical, scientific approach can dismantle prejudice and pave the way to unbiased information. Cardiovascular diseases still represent a global burden and even increased their lethality during the pandemic [16]. A better knowledge of the RAAS role in human disease is one of the main ways to improve cardiovascular prevention during the COVID-19 era.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest

References

1. Wang K, Gheblawi M, Oudit GY. Angiotensin converting enzyme 2: a double-edged sword. *Circulation*. 2020;142:426–8.
2. Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong JC, Turner AJ, Raizada MK, Grant MB. Oudit GY angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. *Circ Res*. 2020;126(10):1456–74.
3. Mai F, Del Pinto R, Ferri C. COVID-19 and cardiovascular diseases. *J Cardiol*. 2020;76(5):453–8.
4. Castelli V, Cimini A, Ferri C. Cytokine storm in COVID-19: “when you come out of the storm, you won't be the same person who walked in.” *Front Immunol*. 2020;11:2132.
5. Iaccarino G, Borghi C, Cicero AFG, Ferri C, Minuz P, Muiesan ML, Mulatero P, Mulè G, Pucci G, Salvetti M, Savoia C, Sechi LA, Volpe M, Grassi G. Renin-angiotensin system inhibition in cardiovascular patients at the time of COVID19: much ado for nothing? A statement of activity from the directors of the board and the scientific directors of the Italian society of hypertension. *High Blood Press Cardiovasc Prev*. 2020;27(2):105–8.
6. Ye Z-W, Yuan S, Yuen K-S, Fung S-Y, Chan C-P, Jin D-Y. Zoonotic origins of human coronaviruses. *Int J Biol Sci*. 2020;16:1686–97.
7. Cheng H, Wang Y, Wang GQ. Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. *J Med Virol*. 2020;92(7):726–30.
8. Shenoy V, Kwon KC, Rathinasabapathy A, Lin S, Jin G, Song C, Shil P, Nair A, Qi Y, Li Q, et al. Oral delivery of angiotensin-converting enzyme 2 and angiotensin-(1–7) bioencapsulated in plant cells attenuates pulmonary hypertension. *Hypertension*. 2014;64:1248–59.
9. Basu R, Poglitsch M, Yogasundaram H, Thomas J, Rowe BH, Oudit GY. Roles of angiotensin peptides and recombinant human ACE2 in heart failure. *J Am CollCardiol*. 2017;69:805–19.
10. Shang J, Wan Y, Luo C, Ye G, Geng Q, Auerbach A, Li F. Cell entry mechanisms of SARS-CoV-2. *Proc Natl Acad Sci*. 2020;117(21):11727–34.
11. Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, Yang P, Sarao R, Wada T, Leong-Poi H, Crackower MA, Fukamizu A, Hui CC, Hein L, Uhlig S, Slutsky AS, Jiang C, Penninger JM. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature*. 2005;436(7047):112–6.
12. Monteil V, Kwon H, Prado P, Hagelkrüys A, Wimmer RA, Stahl M, Leopoldi A, Garreta E, Hurtado Del Pozo C, Prosper F, Romero JP, Wirnsberger G, Zhang H, Slutsky AS, Conder R, Montserrat N, Mirazimi A, Penninger JM. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. *Cell*. 2020;181(4):905–913.e7.
13. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, Diz DI, Gallagher PE. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation*. 2005;111(20):2605–10.
14. Iaccarino G, Grassi G, Borghi C, Ferri C, Salvetti M, Volpe M, SARS-RAS Investigators. Age and multimorbidity predict death among COVID-19 patients: results of the SARS-RAS study of the Italian society of hypertension. *Hypertension*. 2020;76(2):366–72.
15. Shukla A, Banerjee M. Angiotensin-converting-enzyme 2 and renin-angiotensin system inhibitors in COVID-19: an update. *High Blood Press Cardiovasc Prev*. 2021;28(2):129–39. <https://doi.org/10.1007/s40292-021-00439-9>.
16. Del Pinto R, Ferri C, Mammarella L, Abballe S, Dell'Anna S, Cicogna S, Grassi D, Sacco S, Desideri G. Increased cardiovascular death rates in a COVID-19 low prevalence area. *J Clin Hypertens*. 2020;22(10):1932–5.