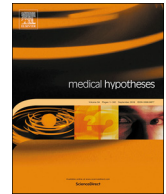




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## The puzzle of sharing bio-molecular targets between coronaviruses and mediators of the cardiovascular system in humans: Looking for plausible hypotheses



The emerging of SARS-CoV-2 and COVID-19 pandemia with a high mortality rate in older subjects with one or more known cardiovascular comorbidities [1] has prompted the question of “sharing bio-molecular targets” between coronaviruses and Renin Angiotensin Aldosterone System (RAAS), a system that is involved, at multiple levels, in the control of the cardiovascular function and, also, is a favorite drug target in cardiovascular diseases [2]. Indeed during treatment with Angiotensin-Converting Enzyme inhibitors (ACEi) and Angiotensin Receptor Blockers (ARBs) the known up-regulation of ACE2/Ang 1-7/MasR axes might be very useful to treat arterial blood pressure, ischemic heart disease and heart failure but, at the same time, detrimental since during COVID-19 it might open the route to SARS-CoV-2 that have been proven to use the ACE2 as functional receptor to enter the human cells [3]. This evidence at the bimolecular level has generated several commentary-style articles that claim it is more prudent to replace ACEi/ARBs during COVID-19 [2,4–6]. The main scientific societies have taken a critical position towards any therapeutic change in the absence of supporting data [7] and this is dictated by prudence. Nonetheless it should be said that switching can be done safely in arterial hypertension if the new drug is 1-well tolerated and a 2-good blood pressure control is achieved thus, during COVID-19, this switch, is again, a prudent position if we exclude to switch-off ACEi/ARBs in subjects with ischemic heart disease and heart failure [8] where we have no other valid therapeutic choices. Nonetheless a recent report claims that ACE2 is highly expressed in subjects with heart failure indicating a susceptibility to SARS-CoV-2 infection in these subjects [9] questioning, again, the idea of maintaining such therapy, even in people with heart failure.

This preamble clearly highlights the problem that is *coronaviruses competition with drugs targeting RAAS*, but the coin has two sides, and we don't know, till now, whether ACEi/ARBs might be detrimental or useful, thus the question is a little bit more complex and it seems necessary to produce sustainable hypotheses.

### On the reasons of sharing.

- It is a “coincidence due to the spread-over-species and ancient-phylogeny” of Renin-Angiotensin System” [2]. This hypothesis is sustainable as RAAS is very diffuse over species and ACE2 expression in the airways makes it a possible target, but to prove.
- It is the consequence of the widespread use of drugs that increase ACE2 expression. This hypothesis is sustainable, exposing targets, especially in the airways where ACE2 is significantly expressed [10], may have facilitated the pathway to the coronavirus that, as any RNA viruses, exhibit a high mutation rate which guarantees the selection of efficient clones capable of infecting the host, but, again, to prove.
- It is a spillover from a laboratory. Leaving aside conspiracies on biological war, as we know, in the late nineties, developing strategies were aimed at modulating SRA at a genetic level, by using

modified viruses targeting ACE2 to treat arterial hypertension and, more recently, to manipulate coronaviruses to better understand its virulence, are these strategies at the origin of the spillover? In a Correspondence to Nature Medicine Kristian G. Andersen et al. [11], states no with the phrase that I quote “It is improbable that SARS-CoV-2 emerged through laboratory manipulation of a related SARS-CoV-like coronavirus”. But “improbable” does not help us to remove all doubts, since we have learned the Popper's lesson: “one theory is scientific to the extent that can be disproved”. Again, to prove.

### On the effects of sharing.

- Is the high mortality rate for elderly subjects with the coexistence of comorbidities, among which high blood pressure is present in more than 70%, related to the use of ACEi/ARBs? This is in theory possible but to prove. In the Italian subset of data from the Italian Health Institute [12] the use of ACEi/ARBs is documented in 52% and, obviously, not in 49%, thus, this is not a proof, we need more data and we asked Dr. Wei-jie Guan, the Author of one of the first report on COVID-19 in China [1], and he replied by email “*In our study, we did not record the use of ARBs given the urgency of data extraction. We do, however, believe that there is a need to investigate the association between the use of ACEi or ARB and the clinical outcomes of Covid-19. In fact, we are planning to conduct a clinical trial on recombinant ACE in patients with Covid-19.*” Finally, we have also data supporting potentials benefit of ACEi/ARBs on target organ damage [13] since RAAS is involved in the cytokine cascade and in the response to damage [14,15] thus we cannot exclude that the advantages outweigh the disadvantage.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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