# Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and coronavirus

**Paolo Verdecchia[a], Fabio Angeli[b], and Gianpaolo Reboldi[c]**

Esler and Esler [1] recommend that angiotensin receptor blockers (ARBs) should not be discontinued until convincing data will confirm the hypothesis that the entry of SARS-CoV-2, which mainly occurs through binding to the pulmonary angiotensin-converting enzyme 2 (ACE2) receptors [2,3], is favored by the up-regulation of these receptors induced by ARBs. Several studies showed that up-regulation of ACE2 receptors is induced not only by ARBs [4–7] but also by ACE inhibitors [4]. The hypothesis that such up-regulation favors virus entry has never been proved. Correctly, Esler and Esler [1] point out that ACE2 up-regulation induced by ACE inhibitors and ARB has never been tested in the lungs, the predominant site of SARS-CoV-2 entry [2,3].

It is important to remark that available data from experimental and human studies are conflicting and some counter-intuitive findings suggest that ARBs may indeed be beneficial instead of harmful. Studies with SARS-Cov and MERS-Cov viruses showed that ACE2 receptors are 'down-regulated' following their interaction with the virus [8,9]. Of note, down-regulation of ACE2 was most prevalent in the pulmonary areas infected by virus but not in the surrounding areas [10]. ACE2 down-regulation induced by virus leads to a reduced formation of angiotensin$_{1-7}$ because of the reduced degradation of angiotensin II, with consequent accumulation of angiotensin II [9]. In animal models of pulmonary damage induced by sepsis, accumulation of angiotensin II induced inflammation, pulmonary edema and worsening of pulmonary function [11]. In these animal studies, pulmonary lesions were reduced not only by ARBs [9] but also by recombinant ACE2 [12] and angiotensin1–7 [13], suggesting that ACE2 activation contributes to limit pulmonary damage. In a recent study from China, a direct association has been found between circulating angiotensin II and the pulmonary damage in patients infected with SARS-Cov-2 virus [14]. Overall, these studies suggest that degradation of angiotensin II and production of angiotensin$_{1-7}$ through the action of ACE2 may effectively control pulmonary inflammation.

So far, clinical evidence that ARBs may limit the pulmonary damage is scanty. A large study from the US compared, using propensity score matching, 11 498 patients with pneumonitis who were treated with ACE-inhibitors or ARBs with 11 498 patients with pneumonitis and not treated with these drugs [15]. Mortality at 30 days was 13% in the total population, 30% with ACE inhibitors and 4% with ARBs [15]. ARB treatment during hospital stay was associated with a lower mortality (odds ratio 0.47; 95% confidence interval 0.30–0.72) [15]. Further clinical studies in patients infected with SARS-2-Cov are eagerly awaited.

We agree that, at present, the suggestion to withdraw ACE inhibitors or ARBs in all patients who are receiving these drugs to prevent the diffusion of SARS-CoV-2 virus is neither based on sound clinical evidence nor is it supported by solid experimental studies. Conversely, and perhaps counter-intuitively, some data suggest that ARBs could be beneficial to limit pulmonary inflammatory lesions.

## ACKNOWLEDGEMENTS

### Conflicts of interest

There are no conflicts of interest.

## REFERENCES


1. Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? *J Hypertens* 2020; 38:781–782.
2. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, *et al*. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020; doi:10.1016/j.cell.2020.02.052.
3. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS. *J Virol* 2020; 94:; pii: e00127-20.
4. 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; 111:2605–2610.
5. Gallagher PE, Ferrario CM, Tallant EA. MAP kinase/phosphatase pathway mediates the regulation of ACE2 by angiotensin peptides. *Am J Physiol Cell Physiol* 2008; 295:C1169–C1174.
6. Ishiyama Y, Gallagher PE, Averill DB, Tallant EA, Brosnihan KB, Ferrario CM. Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors. *Hypertension* 2004; 43:970–976.
7. Jessup JA, Gallagher PE, Averill DB, Brosnihan KB, Tallant EA, Chappell MC, Ferrario CM. Effect of angiotensin II blockade on a new congenic model of hypertension derived from transgenic Ren-2 rats. *Am J Physiol Heart Circ Physiol* 2006; 291:H2166–H2172.
8. Glowacka I, Bertram S, Herzog P, Pfefferle S, Steffen I, Muench MO, *et al*. Differential downregulation of ACE2 by the spike proteins of severe acute respiratory syndrome coronavirus and human coronavirus NL63. *J Virol* 2010; 84:1198–1205.
9. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, *et al*. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med* 2005; 11:875–879.
10. Matsuyama S, Nagata N, Shirato K, Kawase M, Takeda M, Taguchi F. Efficient activation of the severe acute respiratory syndrome coronavirus spike protein by the transmembrane protease TMPRSS2. *J Virol* 2010; 84:12658–12664.
11. Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, *et al*. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* 2005; 436:112–116.
12. Zou Z, Yan Y, Shu Y, Gao R, Sun Y, Li X, *et al*. Angiotensin-converting enzyme 2 protects from lethal avian influenza A H5N1 infections. *Nat Commun* 2014; 5:3594.

13. Zambelli V, Bellani G, Borsa R, Pozzi F, Grassi A, Scanziani M, *et al*. Angiotensin-(1-7) improves oxygenation, while reducing cellular infiltrate and fibrosis in experimental acute respiratory distress syndrome. *Intensive Care Med Exp* 2015; 3:44.
14. 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; 63:364–374.
15. Mortensen EM, Nakashima B, Cornell J, Copeland LA, Pugh MJ, Anzueto A, Mortensen EM. Population-based study of statins, angiotensin II receptor blockers, and angiotensin-converting enzyme inhibitors on pneumonia-related outcomes. *Clin Infect Dis* 2012; 55:1466–1473.

Journal of Hypertension 2020, 38:000–000

[a]Fondazione Umbra Cuore e Ipertensione-ONLUS and Struttura Complessa di Cardiologia, Ospedale S. Maria della Misericordia, Perugia, [b]Department of Medicine and Surgery, University of Insubria, Varese and Department of Medicine and Cardiopulmonary Rehabilitation, Maugeri Care and Research Institute and [c]Department of Medicine, University of Perugia, Italy

Correspondence to Paolo Verdecchia, MD, FESC, FACC, Fondazione Umbra Cuore e Ipertensione-ONLUS, Struttura Complessa di Cardiologia, Hospital S. Maria della Misericordia, Perugia, Italy. E-mail: verdecchiapaolo@gmail.com



DOI:10.1097/HJH.0000000000002469