

Hypertension and COVID-19

Ernesto L. Schiffrin,^{1,✉} John M. Flack,² Sadayoshi Ito,³ Paul Muntner,⁴ and R. Clinton Webb⁵

The world is currently suffering from the outbreak of a pandemic caused by the severe acute respiratory syndrome coronavirus SARS-CoV-2 that causes the disease called COVID-19, first reported in Wuhan, Hubei Province, China on 31 December 2019.¹ As of 29 March 2020, there have been 732,153 confirmed cases of COVID-19 reported worldwide, with 34,686 deaths.² The clinical and epidemiological features of COVID-19 have been repeatedly published in the last few weeks. Interestingly, specific comorbidities associated with increased risk of infection and worse outcomes with development of increased severity of lung injury and mortality have been reported. The most common comorbidities in one report were hypertension (30%), diabetes (19%), and coronary heart disease (8%).³ Another report showed that the most frequent comorbidities in patients with COVID-19 who developed the acute respiratory distress syndrome were hypertension (27%), diabetes (19%), and cardiovascular disease (6%).⁴ The frequency with which

COVID-19 patients are hypertensive is not entirely surprising nor does it necessarily imply a causal relationship between hypertension and COVID-19 or its severity, since hypertension is exceedingly frequent in the elderly, and older people appear to be at particular risk of being infected with SARS-CoV-2 virus and of experiencing severe forms and complications of COVID-19.

It is unclear whether uncontrolled blood pressure is a risk factor for acquiring COVID-19, or whether controlled blood pressure among patients with hypertension is or is not less of a risk factor. However, several organizations have already stressed the fact that blood pressure control remains an important consideration in order to reduce disease burden, even if it has no effect on susceptibility to the SARS-CoV-2 viral infection.⁵ Nevertheless, the fact that hypertension, and other forms of cardiovascular disease also found frequently in COVID-19 patients, are often treated with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), and that SARS-CoV-2, the virus causing COVID-19, binds to ACE2 in the lung to enter cells,^{6,7} has raised questions regarding the possibility that these agents could either be beneficial or actually nefarious in patients treated with them with respect to susceptibility to acquire COVID-19 or in relation to its outcome. It has been shown that ACE inhibitors and ARBs increase ACE2,^{8,9} which could theoretically increase the binding of SARS-Cov-2 to the lung and its pathophysiological effects leading to greater lung injury. However, ACE2 has actually been shown to protect from lung injury in experimental studies.¹⁰ ACE2 forms angiotensin 1–7 from angiotensin II, and thus reduces the inflammatory action of angiotensin II, and increases the potential for the anti-inflammatory effects of angiotensin 1–7. Accordingly, by reducing either

formation of angiotensin II in the case of ACE inhibitors, or by antagonizing the action of angiotensin II by blocking angiotensin AT₁ receptors in the case of ARBs,^{11,12} these agents could actually contribute to reduce inflammation systemically and particularly in the lung, heart, and kidney. Thus, ACE inhibitors and ARBs could diminish the potential for development of either acute respiratory distress syndrome, myocarditis or acute kidney injury, which can occur in COVID-19 patients. In fact, ARBs have been suggested as a treatment for COVID-19 and its complications.¹³ Increased soluble ACE2 in the circulation could bind SARS-CoV-2, reducing its ability to injure the lungs and other ACE2 bearing organs.¹⁴ Using recombinant ACE2 could be a therapeutic approach in COVID-19 to reducing viral load by binding circulating SARS-CoV-2 viral particles and reducing their potential attachment to tissue ACE2. None of these possibilities have however been demonstrated in patients yet.

In conclusion, there is as yet no evidence that hypertension is related to outcomes of COVID-19, or that ACE inhibitor or ARB use is harmful, or for that matter beneficial, during the COVID-19 pandemic. Use of these agents should be maintained for the control of blood pressure, and they should not be discontinued, at least on the basis of current evidence at this time.

Correspondence: Ernesto L. Schiffrin (ernesto.schiffrin@mcgill.ca, <http://ladydavis.ca/en/ernestoschiffrin>).

¹Lady Davis Institute for Medical Research, and Department of Medicine, Sir Mortimer B. Davis-Jewish General Hospital, McGill University, Montreal, Quebec, Canada; ²Department of Internal Medicine, Southern Illinois University School of Medicine, Springfield, Illinois, USA; ³Division of Nephrology, Endocrinology and Hypertension, Tohoku University, Sendai, Japan; ⁴Department of Epidemiology, University of Alabama, Birmingham, Alabama, USA; ⁵Department of Cell Biology and Anatomy, and Cardiovascular Translational Research Centre, University of South Carolina, Columbia, South Carolina, USA.

Initially submitted March 30, 2020; online publication April 6, 2020.

doi:10.1093/ajh/hpaa057

© American Journal of Hypertension, Ltd 2020. All rights reserved. For Permissions, please email: journals.permissions@oup.com

REFERENCES

- Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020; 382:727–733.
- Coronavirus COVID-19 Global Cases by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University. <https://gisanddata.maps.arcgis.com>

- [com/apps/opsdashboard/index.html#/bda7594740fd402994](https://www.cdc.gov/apps/opsdashboard/index.html#/bda7594740fd402994). Accessed 30 March 2020.
3. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical Course and Risk Factors for Mortality of Adult Inpatients With COVID-19 in Wuhan, China: A Retrospective Cohort Study. *Lancet*. 2020; 395:1054–1062.
 4. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020, published online 13 March (doi:10.1001/jamainternmed.2020.0994).
 5. HFSA/ACC/AHA Statement Addresses Concerns Re: Using RAAS Antagonists in COVID-19. https://professional.heart.org/professional/ScienceNews/UCM_505836_HFSAACCAHA-statement-addresses-concerns-re-using-RAAS-antagonists-in-COVID-19.jsp. Accessed 29 March 2020.
 6. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *J Virol* 2020; 94:e00127-20.
 7. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu N-H, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020; 181:1–10.
 8. 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; 111:2605–2610.
 9. Furuhashi M, Moniwa N, Mita T, Fuseya T, Ishimura S, Ohno K, Shibata S, Tanaka M, Watanabe Y, Akasaka H, Ohnishi H, Yoshida H, Takizawa H, Saitoh S, Ura N, Shimamoto K, Miura T. Urinary angiotensin-converting enzyme 2 in hypertensive patients may be increased by olmesartan, an angiotensin II receptor blocker. *Am J Hypertens* 2015; 28:15–21.
 10. 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; 436:112–116.
 11. Phadke M, Saunik S. Rapid response: use of angiotensin receptor blockers such as Telmisartan, Losartan in nCoV Wuhan Corona Virus infections—novel mode of treatment. Response to the emerging novel coronavirus outbreak. *Br Med J* 2020; 368:m406.
 12. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol*, published online 5 March 2020 (doi:10.1038/s41569-020-0360-5).
 13. Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Drug Dev Res* 2020, published online 4 March; doi: 10.1002/ddr.21656.
 14. Battle D, Wysocki J, Satchell K. Soluble angiotensin-converting enzyme 2: a potential approach for coronavirus infection therapy? *Clin Sci (Lond)* 2020; 134:543–545.