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CLINICAL COMMENTARIES

CARDIOVASCULAR RESEARCH Onlife

COVID-19, hypertension, and RAAS blockers: the BRACE-CORONA trial

Giuseppe Mancia *

University of Milano-Bicocca, Milan, Italy

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At the beginning of the COVID-19 pandemic, the hypertension world was shaken by the evidence that, as shown in 2003 for the severe acute respiratory syndrome (SARS)-corona virus,[1] the SARS coronavirus-2 (SARS-CoV-2) virus entered the cell via an enzyme, the angiotensin-converting enzyme 2 (ACE2), which is part of the renin–angiotensin–aldosterone system (RAAS) and thus, albeit somewhat collaterally, of the mechanisms through which ACE-inhibitors, angiotensin receptor blockers and, to a lesser extent, mineralocorticoid receptor antagonists exert their therapeutic lifesaving influence in hypertension, heart failure, chronic kidney disease, and the post-myocardial infarction state. Evidence that these drugs might up-regulate ACE2 in several organs, including the lungs and the heart,[2] favoured the hypothesis, widely reported by the press, that the susceptibility to the infection, as well as its severity, might increase by their chronic use, and that thus their discontinuation might represent an appropriate defense measure against the expanding rate of the disease and its lethality.[3]

Large observational studies performed in the subsequent months have made the hypothesis of an adverse effect of pretreatment with RAAS blockers on the risk and severity of the COVID-19 infection unlikely,[4-5] offering support to the recommendations of Scientific Societies and Health-Care Organizations to continue assumption of these drugs and thus avoid the well-known increase of cardiovascular risk that follows their discontinuation. The same studies showed that pretreatment with RAAS blockers did not reduce the risk and severity of the COVID-19 infection, offering no support also to the counter-hypothesis, i.e. that, because ACE2 metabolizes angiotensin II from a powerful vasoconstrictor to a vasodilator or inactive substance, RAAS blocker pretreatment might protect against the SARS-CoV-2 virus.[6]

In more recent months, attention has shifted from the effects of RAAS-blocker-based pretreatment to those that may be associated with their administration during the infection, due to reports that the virus-related death was less common in patients in whom this treatment was continued, even when compared with use of other antihypertensive agents.[7-9] The reports were generated by uncontrolled studies, which limited their scientific strength and made their conclusion largely hypothetical. This is now no more the case, however, because the hypothesis has been tested by a trial (BRACE-CORONA) which has examined the outcome of hospitalized COVID-19 positive patients randomized to temporary suspension or continuation of ACE inhibitors or angiotensin receptor blocker treatment.

The trial involved 34 Brazilian medical sites which recruited 659 hypertensive patients defined as having a COVID-19 infection of moderate severity and elected to take, as the primary endpoint, the number of days they were alive and out-of-hospital over a 30-day period. The design was open label and the endpoint estimate was blind. As shown in the presentation of the trial at the recent virtual meeting of the European Society of Cardiology, the number of alive and out-of-hospital patients was similar between the two groups, the mean risk ratio being 0.95 (95% confidence interval 0.90–1.01, $P = 0.09$) with a between-group not significant difference of just 1.1 days. The same was true for the number of patients who died (9 in either group) which exhibited a risk ratio of 0.97 and a 95% confidence interval of 0.38–2.52 ($P = 0.95$). This justified the conclusion that the results offered no evidence that during a COVID-19 infection ACE inhibitors and angiotensin receptor blockers affect the disease outcome, in line with the previous evidence that this is the case for pretreatment with these drugs as well.

Do the results of the BRACE-CORONA trial provide a final negative answer to the hypothesis of a relationship between RAAS blockers and the SARS-CoV-2 virus? Although the BRACE-CORONA trial was correctly designed and well conducted, the trial has limitations that make confirmatory studies desirable. First, although further data may be made available in the published paper, the presentation did not include on-treatment variables, leaving without answer the possibility for the between-group outcome similarity to be driven by BP or other differences that moved to the null some direct effect of RAAS blockers on the disease severity. Second, rather than assessing the disease severity by death or need of intensive care, the trial made use of an unusual primary endpoint, i.e. patients alive and out-of-hospital, which might have been influenced by differences in dismissal criteria from hospital between medical sites. Third, although the included patients had a high prevalence of factors that are known to increase COVID-19 severity (hypertension: 100%, diabetes: >30%, obesity: >55%), mortality was so low as to prevent any meaningful analysis of an endpoint such as death as well as to use death to reliably back the primary endpoint results. Finally, the study was not planned to separately analyse the effect of ACE inhibitors and angiotensin receptor blockers, despite previous reports that during the COVID-19 infection their effect may differ[10] Because the number of patients under ACE inhibitors was much greater than that of patients under angiotensin receptor blockers, it seems unlikely that this question will be convincingly addressed by subgroup analysis.

Corresponding author. Tel: +39 347 4327142, E-mail: giuseppe.mancia@unimib.it

The above criticism does not detract from the importance and interest of the results of the BRACE-CORONA trial which deserves the praise of the medical community for providing the first controlled data in an area where so far only observational studies, with their well-known limitations, have been made available. Hopefully, this will serve as a stimulus for future controlled trials aiming at expanding on the BRACE-CORONA evidence to be designed and implemented.

Conflict of interest: none declared.

References

1. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, Choe H, Farzan M. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 2003;**426**:450–454.
2. Kreutz R, Algharably EAE, Azizi M, Dobrowolski P, Guzik T, Januszewicz A, Persu A, Prejbisz A, Riemer TG, Wang JG, Burnier M. Hypertension, the renin-angiotensin system, and the risk of lower respiratory tract infections and lung injury: implications for COVID-19. *Cardiovasc Res* 2020;**116**:1688–1699.
3. Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? *J Hypertens* 2020;**38**:781–782.
4. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-angiotensin-aldosterone system blockers and therisk of COVID-19. *N Engl J Med* 2020;**382**:2431–2440.
5. Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Iturrate E, Johnson SB, Hausvater A, Newman JD, Berger JS,Bangalore S, Katz SD, Fishman GI, Kunichoff D, Chen Y, Ogedegbe G, Hochman JS. Renin–angiotensin–aldoster-one system inhibitors and risk of COVID19. *N Engl J Med* 2020;**382**:2441–2448
6. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SN. Renin-angiotensin-aldosetrone system inhibitors in patients with COVID-19. *N Engl J Med* 2020;**382**:1653–1659.
7. Gao C, Cai Y, Zhang K, Zhou L, Zhang Y, Zhang X, Li Q, Li W, Yang S, Zhao X, Zhao Y, Wang H, Liu Y, Yin Z,Zhang R, Wang R, Yang M, Hui C, Wijns W, McEvoy JW, Soliman O, Onuma Y, Serruys PW, Tao L, Li F. Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. *Eur Heart J* 2020;**41**:2058–2066.
8. Zhang P, Zhu L, Cai J, Lei F, Qin J-J, Xie J, Liu Y-M, Zhao Y-C, Huang X, Lin L, Xia M, Chen M-M, Cheng X, Zhang X, Guo D, Peng Y, Ji Y-X, Chen J, She Z-G, Wang Y, Xu Q, Tan R, Wang H, Lin J, Luo P, Fu S, Cai H, Ye P,Xiao B, Mao W, Liu L, Yan Y, Liu M, Chen M, Zhang X-J, Wang X, Touyz RM, Xia J, Zhang B-H, Huang X, YuanY, Loomba R, Liu PP, Li H. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensinII receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. *Circ Res* 2020;**126**:1671–1681.
9. Cannata F, Chiarito M, Reimers B, Azzolini E, Ferrante G, My I, Viggiani G, Panico C, Regazzoli D, Ciccarelli M, Voza A, Aghemo A, Li H, Wang Y, Condorelli G, Stefanini GG. Continuation versus discontinuation of ACEinhibitors or angiotensin II receptor blockers in COVID-19: effects on blood pressure control and mortality. *Eur Heart J Cardiovasc Pharmacother* 2020;doi:10.1093/ehjcvp/pvaa056.
10. de Abajo FJ, Rodríguez-Martín S, Lerma V, Mejía-Abril G, Aguilar M, García-Luque A, Laredo L, Laosa O, Cen-teno-Soto GA, Ángeles Gálvez M, Puerro M, González-Rojano E, Pedraza L, de Pablo I, Abad-Santos F, Rodríguez-Mañas L, Gil M, Tobías A, Rodríguez-Miguel A, Rodríguez-Puyol D, Barreira-Hernandez D, Zubiaur P, Santos-Mo-lina E, Pintos-Sánchez E, Navares-Gómez M, Aparicio RM, García-Rosado V, Gutiérrez-Ortega C, Pérez C, AscasoA, Elvira C; MED-ACE2-COVID19 study group. Use of renin-angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. *Lancet* 2020;**395**:1705–1714.

Author

Biography: Giuseppe Mancia is Professor Emeritus at the University Milano-Bicocca and Chairman of the European Society of Hypertension (ESH) Foundation after serving for 20 years as Chairman of the Department of Internal Medicine of the Milano and Milano-Bicocca University at the San Gerardo Hospital in Monza. He has been for 20 years Chairman of the Organizing Committee of ESH meetings and is a past President of the ESH, International Society of Hypertension (ISH), European Society of Clinical Investigation, Italian Society of Hypertension, and European Society of Cardiology (ESC) Working Group on Hypertension and the Heart. He co-chaired the ESH/ESC Hypertension Guidelines Task Force in 2003, 2007, 2009, 2013, and 2018. He is an honorary member of several hypertension and cardiovascular societies and has received, for his scientific activity, many international Awards and degrees *Honoris Causa*. He is the Editor-in-Chief of the *Journal of Hypertension*. Professor Mancia's research focuses on several basic and clinical aspects of hypertension and cardiovascular disease. He has published more than 2000 articles in peer review Journals. His articles have received more than 200 000 citations (Microsoft Academics), for which he is listed as a highly cited scientist.