European Journal of Heart Failure (2021) **23**, 486–488
doi:10.1002/ejhf.2098

EDITORIAL COMMENT

Renin–angiotensin–aldosterone inhibitors and COVID-19: nearing the end of a media-fuelled controversy

Daniela Tomasoni[1]*, Mark C. Petrie[2], Marianna Adamo[1], and Marco Metra[1]

[1]Cardiology and Cardiac Catheterization Laboratory, ASST Spedali Civili and Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy; and [2]British Heart Foundation Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK

This article refers to 'Association between renin–angiotensin–aldosterone system inhibitor use and COVID-19 hospitalization and death: a 1.4 million patient nationwide registry analysis' by G. Savarese *et al.*, published in this issue on pages 476–485.

From early in the coronavirus disease 2019 (COVID-19) pandemic the use of renin–angiotensin–aldosterone system inhibitors (RAASi) was flagged as a potential concern due to the key role of this system in the mechanism of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. These concerns were widely broadcast by the mainstream media and have caused anxiety amongst patients and a wide spectrum of clinicians. In this issue of the Journal, the large and careful analysis by Savarese *et al.*[1] provides further reassurance that RAASi are safe to continue in the COVID era.

SARS-CoV-2 enters host human cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor and leads to a down-regulation of ACE2. In human physiology, ACE2 is an enzyme responsible for the cleavage of angiotensin II into angiotensin 1–7, which has vasodilating, anti-inflammatory and anti-fibrotic effects. The virus-mediated down-regulation of ACE2 was postulated to possibly contribute to an exaggerated inflammatory response through the increased levels of angiotensin II.[2] As some animal studies suggested that RAASi might increase circulating levels of ACE2, speculation regarding potential harmful effects — including enhancing the risk of infection — was raised. Humans studies have, however, not consistently demonstrated high plasma levels of ACE2 in patients treated with RAASi.[3] In a large observational study of patients with heart failure (HF) ACE2 plasma levels were not elevated in patients receiving angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs).[4]

In contrast to the trumpeted possible, putative harms related to RAASi in COVID-19, the many potential beneficial effects of these agents have been highlighted. ACEi and ARBs could provide a protective action and reduce the severity of COVID-19 disease by opposing the myriad effects of angiotensin II activity[2,3] (*Figure 1*). Stopping RAASi in patients taking these drugs for their many beneficial effects (e.g. ACEi in HF) would be a major decision that could not be based on theoretical whims.

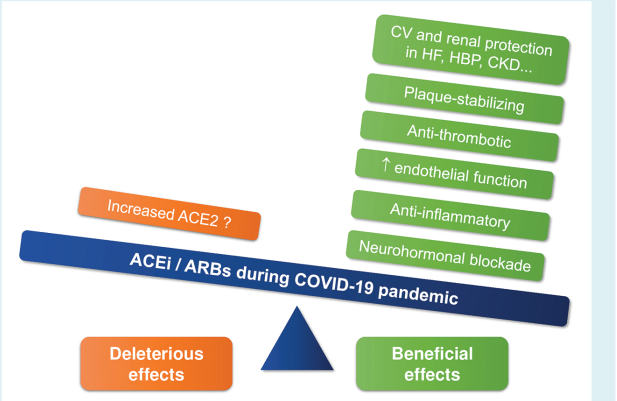

Figure 1 Deleterious and beneficial effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in COVID-19 patients. ACE2, angiotensin converting enzyme 2; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; CV, cardiovascular; HBP, high blood pressure; HF, heart failure. Adapted from Tomasoni *et al.*[2]

Many observational studies of hospital cohorts and registries have investigated the association between the use of RAASi and clinical outcomes during the COVID-19 pandemic.[2] In this issue of the Journal, Savarese *et al.*[1] reported the association between RAASi treatment and the risk of incident hospitalization or death for COVID-19 and the risk of death in COVID-19 cases.

The opinions expressed in this article are not necessarily those of the Editors of the *European Journal of Heart Failure* or of the European Society of Cardiology. doi: 10.1002/ejhf.2060

*Corresponding author. Cardiology and Cardiac Catheterization Laboratory, ASST Spedali Civili and Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Piazzale Spedali Civili, 25123 Brescia, Italy. Email: danielatomasoni8@gmail.com

They included 1 387 746 patients with HF, hypertension, kidney disease, ischaemic heart disease or diabetes from the Swedish National Patient Registry. After adjusting for 45 variables, the use of ACEi/ARBs was associated with a lower risk of incident hospitalization or death for COVID-19 in the overall population [odds ratio 0.86, 95% confidence interval (CI) 0.81–0.91], and with lower mortality in the COVID-19 cohort [hazard ratio (HR) 0.89, 95% CI 0.82–0.96]. The authors are to be congratulated for testing an extensively debated hypothesis on such a large population. Their results reinforce and add to those of previous studies. The extensive adjustment was wise as there are many reasons why patients with conditions such as HF and other cardiorenal conditions may not be prescribed RAASi that may have confounded the observed outcomes.

In a smaller population in Madrid, Spain, the use of RAASi was not associated with an increased risk of COVID-19 requiring hospital admission, compared with the use of other anti-hypertensive drugs. A decrease in the risk of hospitalization was observed among patients with diabetes receiving RAASi.[5] In a population-based case–control study in the Lombardy region of Italy, 6272 patients with COVID-19 were matched to 30 759 controls. ACEi/ARB use was not associated with an increased risk of COVID-19 nor a more severe course of the disease.[6] In 1178 COVID-19 patients in Wuhan, China, there were no differences in outcomes between those receiving, or not receiving ACEi/ARBs.[7] In an Italian multicentre study, HF was an independent predictor of mortality in COVID-19 patients, with an adjusted HR of 2.25 (95% CI 1.26–4.02; $P = 0.006$). HF patients were more likely to receive RAASi, and treatment with RAASi was more prevalent in the patients who died. However, RAASi use was not associated with death on multivariable analysis.[8] A very recent meta-analysis, including 459 755 patients from 86 non-randomized observational studies, showed that ACEi/ARB treatment was not associated with a greater likelihood of COVID-19, hospitalization, intensive care unit admission, ventilation, or death among hypertensive patients.[9]

The analysis by Savarese *et al.*[1] confirmed and extended previous results using a large nationwide observational registry. Going further than previous studies, they suggested not only a neutral but also a putative protective role of ACEi/ARBs. Importantly, the authors noted that, when ARBs and ACEi were analysed separately, the association between the use of ARBs and both the lower hospitalization/mortality for COVID-19 and all-cause mortality in COVID-19 patients remained significant, while the use of ACEi was not associated with lower risk of this outcome. ARBs inhibit angiotensin II type 1 receptors which mediate the detrimental effects of angiotensin II. Thus, their effects may be particularly important when angiotensin II levels are elevated such as when ACE2 is potentially down-regulated by SARS-CoV-2 infection.

The role of mineralocorticoid receptor antagonists (MRA) in COVID-19 has been barely discussed. Savarese *et al.*[1] showed that their use was not associated with adverse outcomes after adjustment for baseline variables. The impact of MRA on ACE2 plasma and tissue concentrations, as well as on all aspects of COVID-19 disease, warrants further study.

This study has some limitations. The analysis does not report outcomes for patients who were taking RAASi for different reasons (e.g. HF or hypertension or chronic kidney disease). The pros and cons of RAASi may vary markedly in different patient populations. The, use of RAASi was defined at the index date and data about their discontinuation are not available. Given the initial theoretical concerns regarding the role of RAASi and the possible lower tolerability of these agents in COVID-19 patients, some physicians could have discontinued RAASi.[10] The authors have acknowledged that their observational study cannot take the place of randomized trials of continuing vs. stopping RAASi during COVID-19. The recently presented ARBs and ACEi and adverse outcomes in patients with COVID-19 BRACE-CORONA trial (NCT04364893) enrolled 659 participants in Brazil with a confirmed diagnosis of COVID-19. Eligible patients using ACEi/ARBs were randomized to either treatment continuation or discontinuation for 30 days. Discontinuation of ACEi/ARBs did not provide benefit in terms of days alive and out of hospital, all-cause mortality, cardiovascular death and complications (i.e. stroke or transient ischaemic attack, myocardial infarction, new or worsening HF).[11] These results have recently been confirmed in the randomized Elimination or Prolongation of ACEi and ARBs in Coronavirus Disease 2019 (REPLACE COVID) trial (NCT04338009).[12]

Another limitation of the study by Savarese *et al.* was the lack of data regarding ethnicity, although the authors assumed that black population was small as few were born in non-European countries. A prospective cohort study, including more than 8 million participants in England reported that ACEi treatment was associated with a lower risk of COVID-19 in the white population (adjusted HR 0.66, 95% CI 0.63–0.70) but a higher risk in black Africans (adjusted HR 1.31, 95% CI 1.08–1.59). Similar results were observed with ARBs (adjusted HR 1.24, 95% CI 0.99–1.58 for black Africans, and adjusted HR 0.56, 95% CI 0.52–0.62 for the white population).[13] The impact of ethnicity could not be explored in the study by Savarese *et al.* but it is worthy of consideration in future studies.

In conclusion, treatment with RAASi in the setting of the COVID-19 pandemic was not associated with worse outcome in this large Swedish observational study. These data add to the similar, reassuring message from many other observational studies and one small randomized trial. The major angst delivered by the mainstream media on the basis of a largely theoretical concern can almost be put to bed.

Conflict of interest: M.C.P. has received research funding from Boehringer Ingelheim, Roche, SQ Innovations, AstraZeneca, Novartis, Novo Nordisk, Medtronic, Boston Scientific, Pharmacosmos and consultancy and endpoint committees payments for Boehringer Ingelheim, Novartis, AstraZeneca, Novo Nordisk, Abbvie, Bayer, Takeda, Cardiorentis, Pharmacosmos, Simens. M.C.P. is supported by the British Heart Foundation (BHF) Centre of Research Excellence Award (RE/13/5/30177 and RE/18/6/34217+). M.M. reports personal fees from Actelion, Amgen, AstraZeneca, Abbott Vascular, Bayer, Servier, Edwards Therapeutics, Livanova, Novartis, Vifor pharma, WindTree Therapeutics, for participation to clinical trials' committees or advisory boards or lectures in the last 3 years outside the submitted work. All other authors have nothing to disclose.

References

1. Savarese G, Benson L, Sundström J, Lund LH. Association between renin-angiotensin-aldosterone system inhibitor use and COVID-19 hospitalization and death: a 1.4 million patient nationwide registry analysis. *Eur J Heart Fail* 2021;**23**:476–485.
2. Tomasoni D, Italia L, Adamo M, Inciardi RM, Lombardi CM, Solomon SD, Metra M. COVID-19 and heart failure: from infection to inflammation and angiotensin II stimulation. Searching for evidence from a new disease. *Eur J Heart Fail* 2020;**22**:957–966.
3. Vaduganathan M, Vardeny O, Michel T, McMurray JJ, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. *N Engl J Med* 2020;**382**:1653–1659.
4. Sama IE, Ravera A, Santema BT, van Goor H, Ter Maaten JM, Cleland JG, Rienstra M, Friedrich AW, Samani NJ, Ng LL, Dickstein K, Lang CC, Filippatos G, Anker SD, Ponikowski P, Metra M, van Veldhuisen DJ, Voors AA. Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin-angiotensin-aldosterone inhibitors. *Eur Heart J* 2020;**41**:1810–1817.
5. de Abajo FJ, Rodríguez-Martín S, Lerma V, Mejía-Abril G, Aguilar M, García-Luque A, Laredo L, Laosa O, Centeno-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; 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.
6. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-angiotensin-aldosterone system blockers and the risk of Covid-19. *N Engl J Med* 2020;**382**:2431–2440.
7. Li J, Wang X, Chen J, Zhang H, Deng A. Association of renin-angiotensin system inhibitors with severity or risk of death in patients with hypertension hospitalized for coronavirus disease 2019 (COVID-19) infection in Wuhan, China. *JAMA Cardiol* 2020;**5**:825–830.
8. Tomasoni D, Inciardi RM, Lombardi CM, Tedino C, Agostoni P, Ameri P, Barbieri L, Bellasi A, Camporotondo R, Canale C, Carubelli V, Carugo S, Catagnano F, Dalla Vecchia LA, Danzi GB, Di Pasquale M, Gaudenzi M, Giovinazzo S, Gnecchi M, Iorio A, La Rovere MT, Leonardi S, Maccagni G, Mapelli M, Margonato D, Merlo M, Monzo L, Mortara A, Nuzzi V, Piepoli M, Porto I, Pozzi A, Sarullo F, Sinagra G, Volterrani M, Zaccone G, Guazzi M, Senni M, Metra M. Impact of heart failure on the clinical course and outcomes of patients hospitalized for COVID-19. Results of the Cardio-COVID-Italy multicentre study. *Eur J Heart Fail* 2020;**22**:2238–2247.
9. Lee MM, Docherty KF, Sattar N, Mehta N, Kalra A, Nowacki AS, Solomon SD, Vaduganathan M, Petrie MC, Jhund PS, McMurray JJ. Renin-angiotensin system blockers, risk of SARS-CoV-2 infection and outcomes from CoViD-19: systematic review and meta-analysis. *Eur Heart J Cardiovasc Pharmacother* 2020 Dec 18. https://doi.org/10.1093/ehjcvp/pvaa138 [Epub ahead of print].
10. Zhang Y, Coats AJ, Zheng Z, Adamo M, Ambrosio G, Anker SD, Butler J, Xu D, Mao J, Khan MS, Bai L, Mebazaa A, Ponikowski P, Tang Q, Ruschitzka F, Seferovic P, Tschöpe C, Zhang S, Gao C, Zhou S, Senni M, Zhang J, Metra M. Management of heart failure patients with COVID-19: a joint position paper of the Chinese Heart Failure Association & National Heart Failure Committee and the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020;**22**:941–956.
11. Mancia G. COVID-19, hypertension, and RAAS blockers: the BRACE-CORONA trial. *Cardiovasc Res* 2020;**116**:e198–e199.
12. Cohen JB, Hanff TC, William P, Sweitzer N, Rosado-Santander NR, Medina C, Rodriguez-Mori JE, Renna N, Chang TI, Corrales-Medina V, Andrade-Villanueva JF, Barbagelata A, Cristodulo-Cortez R, Díaz-Cucho OA, Spaak J, Alfonso CE, Valdivia-Vega R, Villavicencio-Carranza M, Ayala-García RJ, Castro-Callirgos CA, González-Hernández LA, Bernales-Salas EF, Coacalla-Guerra JC, Salinas-Herrera CD, Nicolosi L, Basconcel M, Byrd JB, Sharkoski T, Bendezú-Huasasquiche LE, Chittams J, Edmonston DL, Vasquez CR, Chirinos JA. Continuation versus discontinuation of renin-angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial. *Lancet Respir Med*. 2021;**9**:275–284.
13. Hippisley-Cox J, Young D, Coupland C, Channon KM, Tan PS, Harrison DA, Rowan K, Aveyard P, Pavord ID, Watkinson PJ. Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: cohort study including 8.3 million people. *Heart* 2020;**106**:1503–1511.