Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Systematic review of the role of renin-angiotensin system inhibitors in late studies on Covid-19: A new challenge overcome?

Massimo Volpe a,b,⁎, Allegra Battistoni a

a Department of Clinical and Molecular Medicine, Faculty of Medicine and Psychology, Sapienza University of Rome, Italy
b IRCCS Neuromed, Pozzilli, Italy

Abstract

A role for the renin-angiotensin-aldosterone-system in Severe Acute Respiratory Syndrome-Coronavirus-2 infection and in the development of COVID-19 disease has generated remarkable concerns among physicians and patients. Even though a suggestive pathophysiological link between renin-angiotensin-aldosterone-system and the virus has been proposed, its pathogenic role remains very difficult to be defined. Although COVID-19 targets preferentially older people with high prevalence of hypertension and extensive use of renin-angiotensin-aldosterone-system inhibitors, an independent role for hypertension and its therapies is not defined. In this article, we scrutinize evidence from the most representative available studies in which the potential role of renin-angiotensin system inhibitors, specifically angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, was evaluated in the COVID-19 disease course, with regard to severity of the disease and mortality. We conclude that at this time, the overall available evidence fails to support a pathogenetic link between renin-angiotensin system inhibitors and Covid-19. Consequently, we conclude that treatment with renin-angiotensin-aldosterone-system inhibitors should not be discontinued and, therefore, these therapies should not be interrupted.

© 2020 Elsevier B.V. All rights reserved.

1. Introduction

The toll on people affected by COVID-19 has exceeded 4 million with more than 300,000 victims in over 200 states worldwide [1]. The management of this pandemic has been different across countries, but it has implied everywhere a huge deployment of health and economic resources. From the first observations, it was evident that the incidence of this disease and its severity increases with age, male sex and the presence of comorbidities [2]. Arterial hypertension is present in up to 50% of affected patients, in international case-series [3]. Therefore, it has been speculated that one of the key pathophysiological mechanisms of hypertension itself, as well as anti-hypertensive therapies, could influence the development of COVID-19. In particular, the renin-angiotensin-aldosterone system (RAAS) seems to play a crucial role, since the Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV2) uses the angiotensin converting enzyme 2 (ACE2) to enter cells [4]. On this basis, it has been initially proposed that angiotensin receptor blockers (ARB) and angiotensin converting enzyme inhibitors (ACEI), by increasing levels of ACE2 might favor SARS-CoV2 infection and therefore patients chronically treated with these therapies might present a more severe course of COVID-19. On the other hand, evidence from basic science and from pathophysiological data may suggest just the opposite since the blockade of angiotensin II is considered beneficial towards the pulmonary damage occurring during viral infections [5,6]. Indeed, the chronic assumption of ARB, may protect patients against acute lung injury by blocking the deleterious effect of angiotensin II, such as vasoconstriction of lung vessels, increased pulmonary vascular permeability, inflammation and interstitial fibrosis, as well as by decreasing the production of angiotensin II by up-regulating ACE2 which in turn increases the production of angiotensin-(1–7) which plays beneficial effect on lungs in several experimental models. (5).

2. Methods

We searched clinical papers investigating the effects of RAAS inhibitors on SARS-CoV2 infection and Covid-19 published during the last 90 days in English or at least with an abstract available in English, using as keywords “Covid 19”; “Sars-CoV-2”; “hypertension”; “angiotensin II”; “renin-angiotensin-aldosterone system”; “angiotensin converting enzyme inhibitors”; “angiotensin receptor blockers” through Pubmed, with at least 50 patients enrolled.
Table 1
Clinical trials assessing the relationship between RAS inhibitors and Covid-19 disease.

| Author, Region | Study design, source of data | Sample (n° of patients) | Mean age (years) | Female (%) | Hypertension (%) | ACEi/ARB therapy (% of total) | Outcomes | Pre-specified adjustments |
|----------------|-----------------------------|-------------------------|------------------|------------|-----------------|-----------------------------|----------|-------------------------|
| Yudong et al., China | retrospective case-control single-center, N/A | 112 Covid-19 cases | 62 | 52.6 | 82.14 | 19.64 | No significant difference in the proportion of ACEi/ARB medication between critical patients affected by Covid-19 and the general group nor between Covid-19 non-survivors and survivors | NA |
| Bean et al., United Kingdom | retrospective case-control multicenter, electronic health records | 205 Covid-19 cases | 63 | 48 | 51.2 | NA | ACEi were associated with a reduced risk of death or transfer to a critical care unit for organ support within 7-days of symptom onset. (OR 0.29, 95% CI 0.10–0.75; p < .01) | age, gender, hypertension, diabetes, CAD, HF |
| Tedeschi et al., Italy | retrospective case-control single center, clinical data | 609 Covid-19 cases | 68 | 32 | 51 | ACEi 16 ARB 12 | Chronic use of RAASi (aHR 0.97, 95% CI 0.68–1.39; p = .88) was not associated in-hospital mortality. | age, gender, presence of cardiovascular comorbidities, COPD, age, gender, diabetes, CAD, cerebrovascular disease, CKD and in-hospital medications (antiviral drug and lipid lowering drug) |
| Zhang et al., China | retrospective case-control multicenter, clinical data | 3430 Covid-19 cases | 57 | 51.2 | 32.8 | 5 | *Risk of 28-day all-cause mortality was lower in the ACEi/ARB hypertensive group versus the non-ACEi/ARB hypertensive group (aHR 0.37, 95% CI 0.15–0.89; P = .03) Secondary: The incidence of septic shock was lower in the ACEi/ARB hypertensive group versus the non-ACEi/ARB hypertensive group (aHR 0.36, 95% CI 0.16–0.84; P = .01) | * Analysis conducted in 174 hypertensive patients treated with ARB/ACEI matched 1:2 to 544 hypertensive patients treated with non-ACEi/ARB |
| Yang et al., China | retrospective case-control single center, electronic health records and clinical data | 251 Covid-19 cases (126 hypertensive age- and sex-matched with 125 non-hypertensive) | 66 | 51 | 50 | 17% | *The frequency of ARB/ACEI usage in hypertensive with or without Covid-19 were comparable. Among hypertensive Covid-19 + patients, those receiving either ARB/ACEI or non-ARB/ACEI had comparable blood pressure levels. ARB/ACEI group had significantly lower concentrations of hs-CRP (p = .049) and procalcitonin (PCT, p = .008). | * Analysis conducted with a control groups of 1942 COVID - hypertensive patients enrolled before SARS-CoV2 spread |
| Li et al., China | retrospective case-control single-center, clinical data | 1178 Covid-19 cases | 55.5 | 57.7 | 30.7 | 9 | No differences between non-survivors and survivors in use of ACEi (9.1% vs 10.1%; P = .80), ARBs (24.9% vs 21.2%; P = .40), or the composite of ACEi/ARB (32.9%vs 30.7%; P = .65) | No differences between non-survivors and survivors in use of ACEi (9.1% vs 9.8%; P = .85), ARBs (10.5%vs 23.9%; P = .42), or the composite of ACEi/ARB (27.3% vs 33.0%; P = .34) |
| Mehta et al., United States | retrospective case-control single center, electronic health records | 18,472 tested for Covid-19 | 49 | 60 | 39.5 | 12.5 -ACEi 7.2 -ARB 5.3 | The Covid-19 test positivity rate was 8.6% in patients taking ACEI compared with 9.5% in patients not taking ACEi (overlap propensity score-weighted OR: 0.89; 95% CI 0.72–1.10) Secondary: Among patients with Covid-19 positive test those taking ACEI were more frequently admitted to the hospital (OR, 1.84; | age, sex, and presence of hypertension, diabetes, CAD, HF, COPD |

(continued on next page)
Table 1 (continued)

| Author, Region | Study design, source of data | Sample (n° of patients) | Mean age (years) | Female (%) | Hypertension (%) | ACEi/ARB therapy (% of total) | Outcomes | Pre-specified adjustments |
|----------------|----------------------------|------------------------|------------------|------------|-----------------|-----------------------------|----------|--------------------------|
| Guo et al., China | retrospective case-control single-center, clinical data records during hospitalization | 187 Covid-19 cases | 58.50 | 51.3 | 32.6 | 10.1 | 95% CI 1.22–2.79); and to an ICU (OR, 1.77; 95% CI 1.07–2.92). Among patients with Covid-19 positive test those taking ARB were more frequently admitted to the hospital (OR, 1.61; 95% CI 1.04–2.50). The mortality of those treated with or without use of ACEi/ARB did not show a significant difference in outcome | NA |
| Meng et al., China | retrospective case-control single center, electronic records during hospitalization | 417 Covid-19 cases | 64.5 | 42.9 | 12.2 | 4 | The median number of days from the onset of symptoms to hospital admission was 2.0 in the non-ACEi/ARB group and 3.0 in the ACEi/ARB group. The median number of days from symptom onset to hospital discharge was 16 days in the non-ACEi/ARB group and 20 days in the ACEi/ARB group. During hospitalization 48% of non-ACEi/ARB group was categorized severe vs 23.4% of ACEi/ARB group. Use of ARB or ACEi did not show any association with Covid-19 among cases for ARB (aOR,0.95; 95% CI, 0.86–1.05) and for ACEI (0.96; 95% CI, 0.87–1.07) or among patients who had a severe or fatal course of the disease for ARB (aOR,0.83; 95% CI, 0.63–1.10 and for ACEI (aOR 0.91; 95% CI 0.69–1.21) | NA |
| Mancia et al., Italy | population-based case-control study retrospective multicenter, regional databases of health care | 6272 Covid-19 cases matched for sex, age, and municipality of residence to 30,759 controls | 68 | 37 | NA | -ACEI 23.9 | -ARB 22.2 | drugs and coexisting conditions | age, sex, race, ethnic group, BMI, smoking history, history of hypertension, myocardial infarction, HF, diabetes, CKD, COPD and other classes of medication |
| Reynolds et al. | retrospective case-control single center, electronic health records | 12,594 Covid-19 cases | 49 | 58.5 | 34.6 | -ACEI 8.3 | -ARB 10.5 | No positive association for ACEI and ARB, for either a Covid-19 positive test result or severe illness in both overall population and hypertensive ones. | |
| Liu et al., China | case-control retrospective multi center, clinical data | 78 Covid-19 cases | 65.2 | 44.9 | 100 | -ACEI 3.8 | -ARB 24.3 | No difference in disease severity in patients taking ACEI or ARB. Among the elderly (age > 65) Covid-19 patients with hypertension, the risk of severe Covid-19 was significantly decreased in patients who took ARB drugs prior to hospitalization compared to patients who took no drugs (OR = 0.343, 95% CI 0.128–0.916, p = 0.025) | |
| Feng et al., China | retrospective case-control multi-center, clinical data case-control | 476 Covid-19 cases | 53 | 44.1 | 23.7 | -ACEI 7.1 | -ARB 23.9 | The Covid-19 moderate group had a higher percentage of patients receiving either ARB or ACEI/ARB than severe and critical groups | NA |
| De Abajo, Spain | population based retrospective multicenter, electronic health records | 1139 Covid-19 cases each matched to ten controls for age, sex, region, and date of admission to hospital | 69.1 | 39 | 50 | -ACEI 19 | -ARB 15 | No increased risk of hospital admission for Covid-19 in the RAASi group (OR 0.94;95% CI 0.77–1.15) nor with ACEI (aOR 0.80, 0.64–1.00) or ARB (aOR 1.10, 0.88–1.37) A decreased risk of Covid-19 requiring admission to hospital was found among patients with diabetes who were users of RASI (aOR 0.53; 95% CI 0.34–0.80) | age, sex, history of hypertension, diabetes, dyslipidaemia, CAD, AF, HF, thromboembolic disease, cerebrovascular accident, asthma, COPD, CKD, cancer. |
| Zhou, China | case-control retrospective single center, electronic health records | 110 Covid-19 cases | 57.7 | 45.5 | 32.7 | 13.6 | No difference in lymphocyte counts, crude cure rate, crude mortality rate, onset time, and length of hospital in the ACEI/ARB group | age, sex, hospitalization time, time from onset to hospital admission |

ACEi, angiotensin converting enzyme inhibitors; AF, atrial fibrillation; aHR, adjusted hazard ratio; ARB, angiotensin receptor blockers; aOR, adjusted odds ratio; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; COPD, chronic obstructive lung disease; CKD, chronic kidney disease; HF, heart failure; ICU, intensive care unit; NA, not applicable; OR, odds ratio; RAASi, renin angiotensin aldosterone system inhibitors.
3. Results

Through the search, we retrieved sixteen eligible studies. All of them were retrospective case-reports, totally involving more than 50,000 Covid-19 cases. Four studies investigated the risk of develop Sars-Cov-2 infection [7–10], whereas others investigated the severity of the Covid-19 and death rate according to exposure to RAAS inhibitors. Most studies showed a neutral effect for ACEi/ARB on the primary outcome [7–18], whereas six trials retrieved a protective effect for ACEi/ARB on primary or secondary outcomes [15,16,19–22]; one study retrieved an increased risk in two secondary outcomes for patients taking ACEi/ARB [8]. Lately one study by Mehra et al. [15] has been retracted because all the authors were not granted access to the raw data and the raw data could not be made available to a third-party auditor. Results are summarized on Table 1.

4. Discussion

Most studies available so far have been carried out in China, in relatively small population samples [7,11,14,16,21]. Across studies the definition of SARS-Cov2 infection is variable: in most cases, it is performed according to microbiology [8,9,12,13,17,20–22], in one case only on chest computed tomography [20]; whereas there is great variability in the definition of hypertension which is based on anamnestic data or on the blood pressure values found during hospitalization [7,8,10,13,17]. There is also variability in reporting the therapeutic regimen and its adherence from anamnestic data [17–20] as well as prescription on hospital admission [17–21]. In this regards, Mancia’s and De Abajo’s recent works provide more detailed information on hypertension and its treatment [9–17]. In most studies, it is not explained whether hospitalized patients maintained their home therapy or not, nor it is stated whether blood pressure control was comparable in all groups of therapies [20]. Based on the results made available across all studies, it appears that hypertension, whose prevalence increases with ageing, is frequently associated with SARS-Cov2 infection, as well as with the development of a severe form of Covid-19 and with death, with one exception [19]. Whenever analyzed, it appears that hypertensive patients on ACEi/ARB regimen at home are usually older and affected by more comorbidities [8,13,18], e.g. ischemic heart disease, heart failure and diabetes, chronic kidney disease and obesity which have not been consistently considered in multivariate analyses for outcomes, especially in earlier studies, but they might have heavily influenced retrieved outcomes. In spite of this heterogeneity of reports, we retrieved data from sixteen studies which globally showed no association between a chronic therapeutic regimen with ARB/ACEi and the infection by SARS-Cov2 [7,9,17], nor the development of more severe forms of Covid-19 or an increase in mortality in hospitalized patients [9–14,16,19–21], except one single report, in which among patients with affected by COVID-19 those taking ACEI were more frequently admitted to the hospital and to an intensive care unit as well as those taking ARB were more frequently admitted to the hospital [8].

5. Conclusions

The potential harm caused by ARB/ACEi therapy with regard to Covid-19 has obviously generated a significant public concern, needed
to be addressed as early as possible by the scientific community. At this time, the efforts to collect data and clinical observations during a pandemic health emergency have resulted in a highly prevalent neutrality of RAS blockers towards susceptibility to Covid-19 and its outcomes (Fig. 1). The simple suspect generated by a hypothetical mechanistic correlation with Covid-19 is outweighed by the widely-documented benefit of these drugs for preserving health in several clinical conditions. For this reason, and based on the current survey, it is not recommended to withdraw ACEi/ARB from chronic therapy. Nonetheless, there may still be the need to perform randomized controlled trials which would provide more definitive answers. In addition, large and homogeneous population samples could enable to verify the contributing role of parameters such as the duration of hypertension, the presence of cardio-metabolic comorbidities, the regimens undertaken (specifically ACEi and ARB individually and in combination therapy [17]). The adherence to anti-hypertensive therapy before admission, the changes needed during the admission and the follow-up post discharge would be also important to record. This is not the first big challenge for ACEi and ARB (e.g. the suspect of causing different tumors for both or to increase the risk of myocardial infarction for ARB) and therefore, in view of the worldwide diffusion of their therapeutic use, also in this case the highest level of attention is required to reassure physicians and patients.

Author statement

AB This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation*.

MV This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation*.

AB and MV have no COI to disclose and have not received any funding.

AB and MV have no competing interests to declare.

Acknowledgments

None.

References

[1] https://www.who.int/emergencies/diseases/novel-coronavirus-2019. (Accessed 13 May 2020).

[2] T.J. Guzik, S.A. Mohiddin, A. Dimarco, et al., COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options, Cardiovasc. Res. 116 (10) (2020) 1666–1687, https://doi.org/10.1093/cvr/cva1106.

[3] S. Richardson, J.S. Hirsch, M. Narasimhan, J.M. Crawford, T. McGinn, K.W. Davidson, the Northwell COVID-19 Research Consortium, Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area, JAMA 323 (20) (2020) 2052–2059, https://doi.org/10.1001/jama.2020.6775.

[4] M. Vaduganathan, O. Vardeny, T. Michel, J.J.V. McMurray, M.A. Pfeffer, S.D. Solomon, Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19, N. Engl. J. Med. 382 (2020) 1653–1659.

[5] A. Battistoni, M. Volpe, Might renin-angiotensin system blockers play a role in the COVID-19 pandemic? Eur. Heart J. Cardiovasc. Pharmacother. 6 (4) (2020) 248–251, https://doi.org/10.1093/ehjcvp/puaa030.

[6] A.H. Danser, M. Epstein, D. Battle, Renin-angiotensin system blockers and the COVID-19 pandemic: at present there is no evidence to abandon renin-angiotensin system blockers, Hypertension 75 (6) (2020) 1382–1385, https://doi.org/10.1161/HYPERTENSIONAHA.120.15082.

[7] G. Yang, Z. Tan, L. Zhou, et al., Effects of ARBs and ACEIs on virus infection, inflammatory status and clinical outcomes in COVID-19 patients with hypertension: a single center retrospective study, Hypertension 76 (1) (2020) 51–58, https://doi.org/10.1161/HYPERTENSIONAHA.120.15143.

[8] N. Mehta, A. Kalra, A.S. Nowacki, et al., Association of use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with testing positive for coronavirus disease 2019 (COVID-19), JAMA Cardiol. (2020) e2018555, https://doi.org/10.1001/jamacardio.2020.1855.

[9] G. Mancia, F. Rea, M. Ludergnani, G. Apolone, G. Corrao, Renin-angiotensin-aldosterone system blockers and the risk of Covid-19, N. Engl. J. Med. 382 (25) (2020) 2431–2440, https://doi.org/10.1056/NEJMoa2006923.

[10] H.R. Reynolds, S. Adhikari, C. Pulgarin, et al., Renin-angiotensin-aldosterone system inhibitors and risk of Covid-19, N. Engl. J. Med. 382 (25) (2020) 2441–2448, https://doi.org/10.1056/NEJMoa2008975.

[11] Y.D. Peng, K. Meng, H.Q. Guan, et al., Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV, Zhonghua Xin Xue Guan Bing Za Zhi 48 (2020), e004.

[12] S. Tedeschi, M. Giannella, M. Bartoletti, et al., Clinical impact of renin-angiotensin system inhibitors on in-hospital mortality of patients with hypertension hospitalized for COVID-19, Clin. Infect. Dis. 71 (15) (2020) 899–901, https://doi.org/10.1093/cid/ciaa492.

[13] J. Li, X. Wang, J. Chen, H. Zhang, A. Deng, 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. 5 (7) (2020) 1–6, https://doi.org/10.1001/jamacardio.2020.1624.

[14] T. Guo, Y. Fan, M. Chen, et al., Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19), JAMA Cardiol. 5 (7) (2020) 1–8, https://doi.org/10.1001/jamacardio.2020.1017.

[15] M.R. Mehra, S.S. Desai, S. Kuy, T.D. Henry, A.N. Patel, Cardiovascular disease, drug therapy, and mortality in Covid-19, N. Engl. J. Med. 382 (25) (2020) e102, https://doi.org/10.1056/NEJMoa2007621.

[16] Y. Liu, F. Huang, J. Xu, et al., Anti-hypertensive Angiotensin II Receptor Blockers Associated to Mitigation of Disease Severity in Elderly COVID-19 Patients, 2020https://doi.org/10.1101/2020.03.20.20039586.

[17] 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 395 (10238) (2020) 1705–1714, https://doi.org/10.1016/S0140-6736(20)31030-8.

[18] X. Zhou, J. Zhu, T. Xu, Clinical characteristics of coronavirus disease 2019 (COVID-19) patients with hypertension on renin–angiotensin system inhibitors, Clin. Exp. Hypertens. 42 (7) (2020) 656–660, https://doi.org/10.1080/10641963.2020.1764018.

[19] D. Bean, Z. Kraljevic, T. Searle, et al., Treatment with ACE-Inhibitors is Associated with Less Severe Disease with SARS-Covid-19 Infection in a Multi-site UK Acute Hospital Trust, 2020 https://doi.org/10.1164/RCCM.202004-0785OR.

[20] P. Zhang, L. Zhu, J. Cai, et al., Association of Inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19, Circ. Res. 126 (12) (2020) 1671–1681, https://doi.org/10.1161/CIRCRESAHA.120.317134.

[21] J. Meng, G. Xiao, J. Zhang, et al., Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. Clinical impact of renin-angiotensin system inhibitors on in-hospital mortality of patients with hypertension hospitalized for COVID-19, Emerg. Microb. Infect. 9 (2020) 757–760.

[22] Y. Feng, Y. Ling, T. Bai, et al., COVID-19 with different severity: a multi-center study of clinical features, Am. J. Respir. Crit. Care Med. 201 (11) (2020) 1380–1388, https://doi.org/10.1164/rccm.202002-0445OC.