International Journal of Cardiology xxx (2020) xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Systematic review of the role of renin-angiotensin system inhibitors in late studies on Covid-19: A new challenge overcome?

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ARTICLE INFO

Article history:
Received 28 May 2020
Received in revised form 15 July 2020
Accepted 28 July 2020
Available online xxxx

Keywords:
Hypertension
Covid-19
Renin-angiotensin-aldosterone system
Angiotensin-converting enzyme inhibitors
Angiotensin receptor blockers

ABSTRACT

A role for the renin-angiotensin-aldosterone-system in Severe Acute Respiratory Syndrome-Coronavirus-2 infection and in the development of COronaVIrus Disease-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 COronaVIrus Disease-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 COronaVIrus Disease-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 speaks against any harmful role for of renin-angiotensin-aldosterone-system inhibitors in COronaVIrus Disease-19. Consequently, we conclude that treatment with renin-angiotensin-aldosterone-system inhibitors should not be discontinued and, therefore, these therapies should not be interrupted.

1. Introduction

The toll on people affected by COronaVIrus Disease-19 (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 antihypertensive 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.

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https://doi.org/10.1016/j.ijcard.2020.07.041
0167-5273/

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
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*	age, gender, diabetes, CAD, cerebrovascular disease, CKD and in-hospital medications (antiviral drug and lipid lowering drug)
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 enrolled before SARS-Cov2 spread*	NA
Li et al., China	retrospective case-control single-center, clinical data	1178 Covid-19 cases	55.5	57.7	30.7	9	No difference between patients with severe vs non-severe illness in the use of ACEI (9.2% vs 10.1%; $P = .80$), ARB (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 (19.5%vs 23.9%; $P = .42$), or the composite of ACEI/ARB (27.3% vs 33.0%; $P = .34$)	NA
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

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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
							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).	
Guo et al., China	retrospective case-control single-center, clinical data	187 Covid-19 cases	58.50	51.3	32.6	10.1	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 hospedalization	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 categorize severe vs 23.4% of ACEI/ARB group	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	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)	drugs and coexisting conditions
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.	age, sex, race, ethnic group, BMI, smoking history, history of hypertension, myocardial infarction, HF, diabetes, CKD, COPD and other classes of medication
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, $p = 0{\cdot}025$)	sex
Feng et al., China	retrospective case-control multi-center, clinical data	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	case-control 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

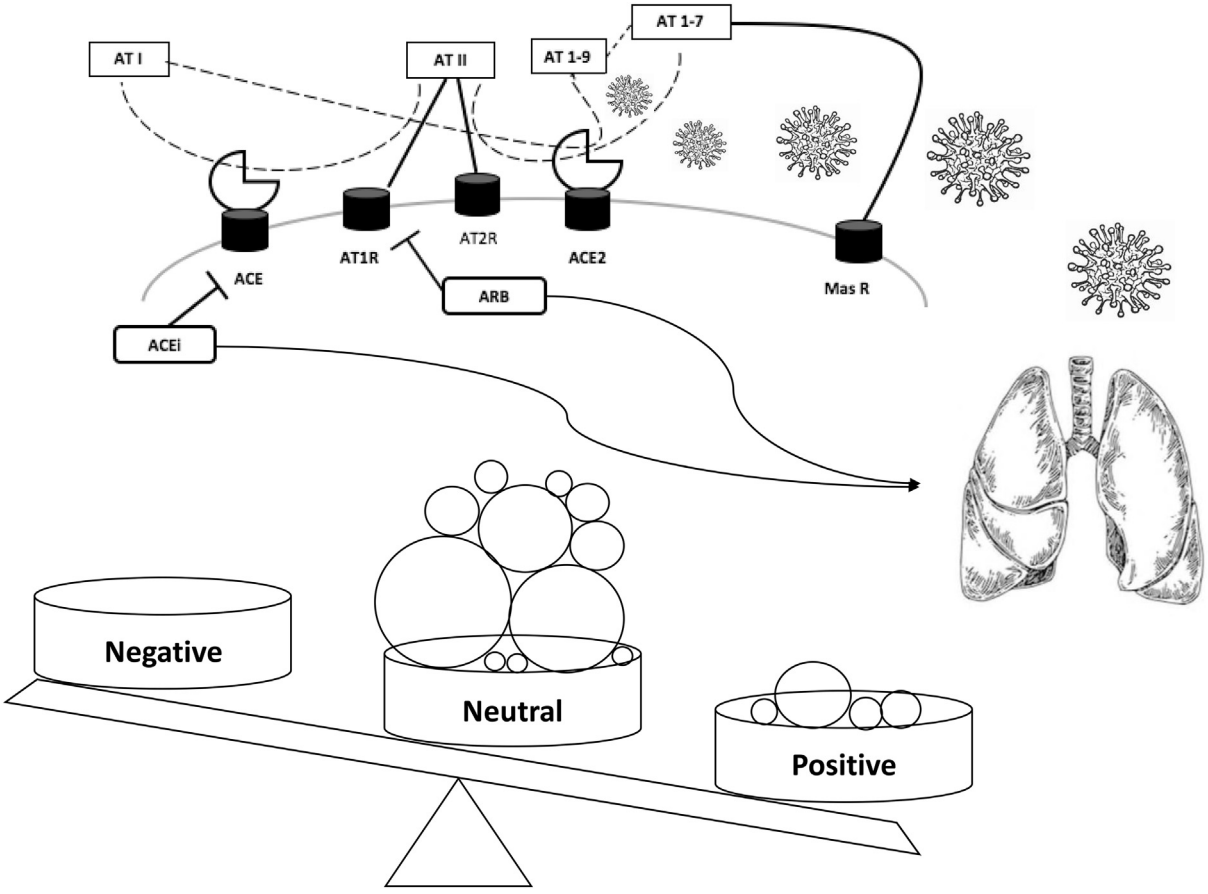

Fig. 1. Overview of current clinical evidence showing an overall neutral effect of ACEi and ARB on primary outcomes with regards to Sars-Cov2 infection and Covid-19 course. The bigger the circle, the largest is the sample enrolled in the corresponding study. ATI, angiotensin 1; ATII, angiotensin II; AT1R, type I angiotensin II receptors; AT2R, type II angiotensin II receptors; AT 1–9, angiotensin 1–9; AT 1–7, angiotensin 1–7; ACE, angiotensin converting enzyme; ACE2, angiotensin converting enzyme 2; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers.

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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 not competing interests to declare.

Acknowledgments

None.

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Please cite this article as: M. Volpe and A. Battistoni, Systematic review of the role of renin-angiotensin system inhibitors in late studies on Covid-19: A ..., International Journal of Cardiology, https://doi.org/10.1016/j.ijcard.2020.07.041