

COMMENT



The effects of antihypertensive medications on severity and outcomes of COVID19

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A retrospective study reports in the journal that hypertensive patients with corona virus disease 2019 (COVID19) do not show any significant differences in the outcomes of COVID19 such as survival, hospital stay, ICU admission, disease severity, and invasive medical ventilation compared to the normotensive patients [1]. The participants were all hospitalized during the first wave of COVID19 from 19 February 2020 to 20 July 2020. Majority of hypertensive patients were on angiotensin receptor blockers (ARB) (53.8%). The implications of the study are multifaceted. We still do not have clear answers to important questions such as: is hypertension (HTN) associated with COVID19 outcome? Or do antihypertensive medications differ in their class effects on COVID19 outcome?

BIOCHEMICAL BASIS FOR COVID-19 HYPERTENSIVE DYSREGULATION

Biological mechanisms can explain the intense and complex relation between blood pressure (BP) and COVID19. COVID19 involves the attachment to the spike protein of the virus to the membrane bound angiotensin converting enzyme 2 (ACE2) [2]. A recent study with meta-analysis of ~130,000 public single-cell transcriptome analysis provides insight about the mechanisms of COVID19. ACE2 expressing alveolar cells are the primary cellular targets for SARS-CoV-2 infection in the lung [3]. SARS-CoV-2 receptor is abundantly expressed with components of the of the kinin-kallikrein (KKS), renin-angiotensin-aldosterone (RAAS) and coagulation systems [3]. KKS works in close connection with RAAS to regulate the BP. The KKS opposes the hypertensive effects of RAAS by releasing vasodilatory peptides of bradykinin (BK) and kallidin (KD) [4]. Peptidase kininase I cleaves BK into the active metabolite des-Arg9-bradykinin (DABK). The kinins transmit their biological effects by activating the bradykinin-1 (B1) and bradykinin-2 (B2) receptors [4].

KKS and RAAS systems are intensely involved in the pathophysiology of HTN and its complications. ACE2–SARS-CoV-2 complex alters the interaction between mediators such as BK, angiotensins, and homeostasis related factors [4]. Experimental and clinical studies prove that the mediators in these systems are tightly regulated through a close interaction with each other [4, 5].

HTN, COMORBIDITIES, AND CONFOUNDING

The pathophysiology of COVID19 involves the attachment of the spike protein of SARS-CoV-2 to the ACE2 receptor [2, 3]. ACE2 has

a pivotal role in the mechanisms related to BP control and vascular protection [4]. The binding of virus to ACE2 downregulates ACE2. Functional loss of ACE2 causes renin angiotensin aldosterone system (RAAS) activation. RAAS activation has a pivotal role in the pathophysiology of chronic complex diseases such as HTN, vascular disease, atherosclerosis, diabetes mellitus (DM), ischemic heart disease, chronic kidney disease, heart failure and many more [4, 5].

Hospitalized patients with COVID19 have significant cardiovascular co-morbidities. HTN (56.6%) and DM (33.8%) are the most commonly observed co-morbidities in patients with COVID19 [5]. Despite plausible biological theories, difficulties remain in establishing HTN as an independent risk factor in COVID19 related mortality. Conflicting reports and observational studies exist on the association of HTN and COVID19 outcome [6, 7]. Several reasons can explain the contrasting findings in observational studies. First, COVID19 is an extremely heterogenous disease [8]. COVID19 induced inflammation causes long-term complications and vascular events as a potential confounder [9]. Patient related factors such as age, ethnicity, gender and cardiovascular disease are commonly observed confounders in COVID19 patients. Furthermore, early observational studies report conflicting methodologies and mixed outcome points. We are currently facing and traversing through the large COVID19 related information. Earlier studies are mixed with confounders that can seriously affect the effect size of the associations between HTN and COVID19 outcome. In a disease with a wide spectrum of clinical phenotype from asymptomatic patients to overt sepsis, it will be difficult to establish a uniform relationship between the history of HTN and COVID19 outcome.

Secondly, HTN is often seen with other co-morbidities such as DM, coronary artery disease, congestive heart failure, atrial fibrillation, chronic renal failure, cerebrovascular diseases and chronic obstructive pulmonary disease, all of which can associate with mortality in COVID19 [5].

The phenotype of hypertensive patients widely varies among studies, populations and countries. Countries with organized health systems and primary care attain success in controlling HTN, yet countries with limited resources suffer from the complications of poorly controlled HTN [10]. Similarly, wide variability exists among countries in COVID19 outcome.

Therapies for COVID19 can also confound the association between HTN and COVID19 outcome. For instance, dexamethasone (6–12 mg per day) remains one of the few therapies proven

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to improve the outcome in patients with severe COVID19 [11]. Dexamethasone can induce HTN. Thus, patients who receive dexamethasone during their acute illness, can have medication induced HTN and concurrently suffer worse outcomes. Therefore, HTN can be a signal for the severity of COVID19 to warrant dexamethasone use. In summary, observational studies suffer from confounding effects of therapies in COVID19.

Finally, the studies come from different time periods and waves of the COVID19 pandemic. Over the last 2 years, COVID-19 phenotype has changed significantly. Vaccination, novel variants, effective therapies, and global response to pandemics have all modulated the phenotype of COVID-19. For example, in the summer of 2020, the delta variant had not yet reached global circulation. The first variants were dominant throughout the world. Therefore, the prognostic effects of HTN and other comorbidities will also change according to the globally dominant variants of SARS-CoV-2.

The adverse effects of HTN on prognosis in COVID19 were reported in several studies. The effects of resistant HTN on in-hospital mortality of 1897 patients hospitalized with COVID19 were reported in a retrospective study [6]. The definition of resistant arterial HTN was BP \geq 130/80 mmHg despite treatment with 3 antihypertensive drugs including a diuretic. The patients were divided into 3 groups: non-hypertensive, regulated HTN, and resistant HTN. Mortality of normotensive patients was significantly lower than regulated or resistant HTN groups (13.3, 27.5, and 32.1%, respectively, $p < 0.001$). Mortality was similar between the regulated and resistant HTN groups on univariate analysis. Multivariate analysis displayed that resistant HTN was independently associated with increased in-hospital mortality in COVID19. However, results were confounded by other risk factors such as age, male gender, chronic renal failure, lymphocyte, procalcitonin, creatinine, and oxygen saturation levels on admission.

Another large study of 45,418 COVID19 patients displayed that 11,950 had controlled BP, 17,025 had prehypertension, 13,173 had stage 1 HTN and 3270 had stage 2 HTN [7]. Patients with stage 1 uncontrolled BP showed lower risk of COVID19 related death compared with patients with well-controlled BP. In fact, there was an inverse relationship between recent BP control and COVID19 related mortality. As an explanation to the study findings, patients with well-controlled BP were older than the other groups.

RAAS INHIBITION

SARS-CoV-2-ACE2 interaction lead to the concerns about the use of ACE inhibitors and ARBs in infected patients with Sars-CoV-ACE2. One of the main challenges in managing COVID19 patients arises from the fact that patients present with a wide range of clinical case scenarios. Heart failure and vascular disease are common co-morbidities [5]. Such patients expect a strong benefit from RAAS blockade with ACE inhibitors and ARBs. After infection with SARS-CoV-2, patients can be completely asymptomatic or experience a mild influenza-like illness, or as in the worst-case scenario, patients can present with serious symptoms and lung injury that require hospitalization and intubation. HTN is the most common concomitant disease in hospitalized patients with COVID19 and RAAS blockers such as ACE inhibitors and ARBs are commonly used to control BP in these patients. Uniform recommendations for all patients with COVID19 will be premature in the setting of wide physiological and biological heterogeneity.

OBSERVATIONAL STUDIES OF ACE INHIBITORS/ARBs AND COVID-19 OUTCOMES

Conflicting results in observational studies raise the question whether antihypertensive classes have different effects on the outcome of COVID19. The interpretation of association studies between COVID19 outcome and hypertensive medication classes requires a word of caution. Most studies display reverse causality,

because older patients with multiple comorbidities and cardiovascular disease use ACE inhibitors/ARBs. Moreover, adjustments for age and other possible confounding factors were not performed in most of the early studies. A small observational study of 247 patients assessed the relationship between COVID19 outcome and the use of ACE inhibitors or ARBs in hospitalized patients with COVID19 [12]. Primary outcome was defined as the need for intensive care unit (ICU), mechanical ventilation, or occurrence of death. The study did not display any significant relation between the primary outcomes and use of ACE inhibitors/ARBs. Prior Italian registry investigated the prognostic effects of ACE inhibitors or ARBs in 566 patients hospitalized with COVID19 [13]. RAAS blockade in fact, reduced the mortality in hospitalized patients with COVID19. The study displayed that differences existed between ARBs and ACE inhibitors in COVID19 outcome. ARBs were associated with 59 % lower risk of death in hospitalized patients COVID19, yet ACE inhibitors did not display a similar benefit.

The mechanisms for the dissimilar effects of ACE inhibitors and ARBs on COVID19 outcome, require further investigation. ACE inhibitors increase BK levels, unlike ARBs. B1 receptors are upregulated during cellular stress and inflammation [4]. Stimulation of B1 receptors by BK has been implicated in the cytokine storm of COVID19 [4]. Kininase II or ACE, inactivates the KKS by degrading kinins into inactive metabolites. ACE2 attenuates DABK mediated inflammation via B1 receptor activation by degrading DABK to BK. Therefore, the interactions between ACE, ACE2 and RAAS are critical in controlling the KKS in a state excessive inflammation such as COVID19.

Ang II on the other hand, is degraded into the smaller metabolites, the effects of which remain to be elucidated in COVID19 [4]. Increasing BK levels can contribute to the vasodilator action of ACE inhibitors and have beneficial effects in heart failure. BK is a pro-inflammatory mediator in the etiology of the inflammatory diseases. Dry cough is the common side effect of ACE inhibitors which is mediated by BK. COVID19 sets the stage for a different and heated debate. Clinical investigators put forward the idea that accumulation of BK and dysregulated BK metabolism are crucial in the pathogenesis of COVID-19 [4].

Studies tested inhibitors of cyclooxygenase pathway and BK inhibitors in COVID19 [14]. In a case control study, pharmacological inhibitors of the KKS such as icatibant (a BK receptor 2 inhibitor), and inhibitor of C1 esterase/kallikrein (iC1e/K) were tested in 30 patients with severe COVID19 [14]. Pharmacological inhibition of KKS improved lung CT scores and increased blood eosinophil counts and promoted disease recovery. Further well-designed and controlled clinical studies are required to elucidate the role of BK in COVID19. The observational study designs in COVID19 do not allow us to understand the class effects of antihypertensive medications.

RANDOMIZED INVESTIGATIONS INTO ACEI/ARB EFFECTS ON COVID-19 OUTCOMES

Several randomized clinical trials have studied the association between the use of RAAS inhibitors (ACE inhibitors or ARBs) in HTN and COVID-19 outcome (Table 1) [15–22]. Puskarich et al. investigated the efficacy of losartan in hospitalized patients with COVID19 induced lung injury in a randomized clinical trial (RCT) [15]. The initiation of oral losartan did not improve PaO₂/FIO₂ ratio at 7 days. On the other hand, Duarte et al. reported that telmisartan treated patients had a lower median time-to-discharge [16]. Death by day 30 was reduced in the telmisartan-treated group. Amat-Santos et al. studied ramipril in high-risk patients with COVID19 [17]. Ramipril had no impact on the severity of COVID-19.

Discontinuation of chronic treatment with ACE inhibitors or ARBs and COVID19 outcome has been the subject for RCTs [18–20]. In a

Table 1. Randomized trials of renin angiotensin aldosterone system inhibitors (RAASI) with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and outcomes among patients with COVID19.

Publication	Objective and title	N (patients)	Study period	Main conclusions
Puskarich et al. on behalf of ALPS-IP Investigators from United States [15]	Efficacy of Losartan in Hospitalized Patients With COVID19 Induced Lung Injury A Randomized Clinical Trial	205 patients	From April 2020 to February 2021	The initiation of oral losartan to hospitalized patients with COVID19 and acute lung injury did not improve PaO ₂ /FIO ₂ ratio at 7 days.
Duarte et al. from Argentina [16]	Telmisartan for treatment of COVID19 patients: An open multicenter randomized clinical trial	162 patients	From May to October 2020	Telmisartan-treated patients had a lower median time-to-discharge. Death by day 30 was reduced in the telmisartan-treated group.
Amat-Santos et al. from Spain [17]	Ramipril in High-Risk Patients With COVID19	102 patients (50 in the ramipril group and 52 in the control group)	Started on April 1, 2020. The median time of ramipril treatment was 6 months	In a high-risk population of older patients with cardiovascular disease, randomization to ramipril had no impact on the incidence or severity of COVID-19.
Bauer et al. On behalf of ACEI-COVID investigators Germany [18]	Discontinuation versus continuation of RAS inhibitors in COVID19 (ACEI-COVID): a prospective, parallel group, randomised, controlled, open-label trial	204 patients	From April 20, 2020, to January 20, 2021	Discontinuation of RAASI in COVID19 had no significant effect on the maximum severity of COVID19. There were no significant differences for mechanical ventilation and admission to intensive care unit between the groups.
Cohen et al. International study from 7 countries [19]	Continuation versus discontinuation of RAASI in patients admitted to hospital with COVID19: a prospective, randomised, open-label trial	152 patients (continuation group n = 75; discontinuation group n = 77).	From March 31 to Aug 20, 2020	Continuation compared with discontinuation of RAASI did not significantly affect the severity or the duration of hospitalisation.
Lopes et al. from Brazil [20]	Effect of Discontinuing vs Continuing ACEIs and ARBs on days alive and out of the hospital in patients admitted with mild to moderate COVID19	659 patients who were on RAASI before hospital admission	From April 9 to June 26, 2020	There were no significant differences in the mean number of days alive and out of the hospital days between the groups.
Najmeddin et al. from Iran [21]	Effects of ACEI/ARBs early outcomes of hypertensive COVID19 patients: a randomized triple-blind clinical trial	64 patients	From April to September 2020	The randomized triple-blind, multi-centric clinical trial did not show any deleterious effects of RAASI in COVID19.
Nouri Vaskeh et al. from Iran [22]	Comparison of losartan and amlodipine effects on the outcomes of patients with COVID19 and primary hypertension	82 patients	From April 2020 to June 2020	There was no difference between losartan or amlodipine in decreasing the mortality rate, hospital and intensive care unit stay.

Description of articles are listed according to location of the study, objective, time period and main conclusions. N number, HTN hypertension, PaO₂ arterial oxygen partial pressure, FIO₂ fractional inspired oxygen

Table 2. Systematic review and meta-analysis studies of the association between the use of renin-angiotensin-aldosterone system inhibitors (RAASi) with angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) and the outcomes among patients with COVID-19.

Publication	Title	The study data	Time	Main conclusions
Baral et al. [23]	Association Between Renin-Angiotensin-Aldosterone System Inhibitors and Clinical Outcomes in Patients With COVID-19: A Systematic Review and Meta-analysis	Clinical data were pooled from 52 eligible studies (40 cohort studies, 6 case series, 4 case-control studies, 1 randomized clinical trial, and 1 cross-sectional study) enrolling 101,949 patients (26.545 (26.0%) were on ACEis or ARBs.	March, 2021	ACEis or ARBs were not associated with a higher risk of multivariable-adjusted mortality and severe adverse effects among patients with COVID-19. Patients had hypertension and multiple comorbidities. ACEis and ARBs were associated with protective benefits, among patients with hypertension and COVID-19.
Sattar et al. [24]	Safety and efficacy of renin-angiotensin-aldosterone system inhibitors in COVID-19 population	A total of 49 observational studies were included in the analysis consisting of 83,269 patients.	June, 2021	There was no association between RAASi and intensive care unit admission or worsening of clinical manifestations. Meta-regression analysis did not change the results for effect modifiers including age, sex, comorbidities, RAASi type.
Ferrari et al. [25]	Renin-Angiotensin-Aldosterone System Inhibitors in COVID-19: A Review	In total, 39 observational studies and 1 randomized trial were included.	April, 2021	The study did not identify any association between the use of RAASi and unfavorable prognosis in COVID-19.
Singh et al. [26]	Mortality and Severity in COVID-19 Patients on ACEis and ARBs —A Systematic Review, Meta-Analysis, and Meta-Regression Analysis	Meta-analyses included observational studies: 53 studies for the mortality outcome and 43 for the severity outcome.	January, 2022	The use of RAASi did not influence either the mortality or severity of COVID-19. The mortality model demonstrated that 36% of between study variations could be explained by the differences in age, gender, and proportion of heart diseases in the study populations.

recent study, 35 centers from Austria and Germany enrolled 204 patients (median age 75 years) [18]. The study demonstrated that discontinuation of RAAS blockade in COVID-19 did not impact the severity of COVID-19 [18]. There were no significant differences in the need for mechanical ventilation and admission to intensive care unit between the groups. Cohen et al. and Lopes et al. similarly reported no differences in COVID-19 outcome between the continuation and discontinuation of RAAS inhibition [19, 20].

Najmeddin et al. reported that in a RCT of 64 patients with COVID-19 requiring hospital admission, RAAS inhibition did not have any deleterious effects on COVID-19 outcome [21]. Nouri Vaskeh et al. compared losartan and amlodipine effects on the outcomes of patients with COVID-19 in 82 patients with HTN. There was no difference between losartan or amlodipine in decreasing mortality rate, hospital and ICU stay [22].

In summary, the use of ACE inhibitors and ARBs and the COVID-19 outcome have been the subject for RCTs. The studies did not show any deleterious effects of RAAS inhibition in COVID-19.

SYSTEMATIC REVIEW AND META-ANALYSIS STUDIES

Meta-analysis and systematic review studies investigate the safety and efficacy of RAAS inhibitors in COVID-19 (Table 2) [23–26]. In summary, meta-analysis of observational studies displayed that ACE inhibitors or ARBs were not associated with a higher risk of mortality or adverse effects among patients with COVID-19. In fact, some studies reported that ACE inhibitors and ARBs were associated with protective benefits in COVID-19.

Global Societies review the evidence and conclude that hypertensive patients with COVID-19 should remain on usual anti-hypertensive therapy and there is no evidence indicating that there is a need to discontinue RAAS inhibitors [27].

We should interpret the observational studies and RCTs in view of the complex pathophysiology and heterogeneity of COVID-19. Most studies suggest that presence of HTN worsens the outcome in COVID-19. The use of ACE inhibitors/ARBs are not significantly associated with the COVID-19 outcome; however, further long-term studies are needed. RCTs and observational studies support the conclusion that to continue or discontinue RAAS blockade in COVID-19 should be made after assessing the individual patient characteristics. The association studies between COVID-19 outcome and hypertensive medication classes display reverse causality. Patients who are on ACE inhibitors and ARBs are older with multiple comorbidities such as cardiovascular disease. Therefore, we need to assess the cardiometabolic risk of patients, populational characteristics, health system dynamics in COVID-19 studies before making conclusions about the association between HTN and COVID-19. A one-size-fits-all approach will leave out many patients. Vascular risk and HTN are mutual targets in COVID-19 care. Practicing personalized medicine to improve the quality of care for all hypertensive patients remains to be a global urgency in the post-COVID-19 era.

DATA AVAILABILITY

Data for the manuscript are available as open source information in the free search engines for life sciences and biomedical topics.

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All authors have read and contributed to the manuscript and the paper is not published or under review elsewhere. The author (MA) has prepared and submitted the manuscript.

COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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