



Management of Hypertension in the SARS-CoV2era: Current Knowledge and Future Perspectives

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ABSTRACT:

The new SARS-CoV2 pandemic has ignited research worldwide, regarding its parameters. Hypertension, a comorbidity with high prevalence among patients with COVID-19 infection, is being extensively studied in the setting of the pandemic. Furthermore, RAAS inhibitors, drugs widely used among hypertensive patients, are on the spotlight regarding their safety during the COVID-19 era. In this review, we present current knowledge regarding both these aspects, as well as the new guidelines for the treatment of hypertensive patients during the pandemic.

Key words: covid-19, sars-cov2, hypertension, comorbidities, RAAS inhibitors

INTRODUCTION

In the light of the current SARS-CoV2pandemic, physicians and researchers around the globe are racing to decode the disease mechanisms and find a cure. Scientific data so far indicate that the COVID-19 is asystemic disease; its clinical presentation being multifactorial anddiverse. Similarly, possible complications, as well as the disease progression, are being thoroughly studied in the attempt to create clinical algorithms and guidelines for the disease.

According to Center for Disease Control and Prevention, severity of symptoms range from mild to severe, including among others, fever, fatigue, shortness of breath, muscle aches, headache, diarrhoea and in various cases severe acute respiratory syndrome.¹ Furthermore, it has been highlighted that patients with severe underlying comorbidities like diabetes mellitus, coronary artery disease and chronic obstructive pulmonary disease run a higher risk of developing severe symptoms and complications.¹ As a result, correlations between the disease and pre-existing comorbidities are being intensively studied. Among those is hypertension (HTN) and the reason behind this is two-fold. On one hand, reports indicate thatthe vast percentage of patients infected by SARS-CoV2 also have a history of hypertension, either treated or not. On the other hand, the reported involvement of the

virus to the renin-angiotensin-aldosterone system (RAAS), also contributed to the theory that HTN and COVID-19maybe associated. In this review we attempt to present current knowledge regarding a. the potential association between the two entities, b. the pharmaceutical management of HTN in the COVID era and c. the new guidelines for hypertensive patients.

COVID-19 AND HYPERTENSION

The association between the new pandemic and HTN is being thoroughly studied. HTN is reported to be among the most common comorbidities of patients hospitalised with a severe case of SARS-CoV2 infection, according to scientific data originally published from China.²China, was caused by a novel betacoronavirus, the 2019 novel coronavirus (2019-nCoV).Furthermore, studies from China and Italy report high prevalence of hypertension among deceased patients with COVID-19 infection.³⁻⁴Data also propose a higher riskof hospital admission, intensive care unit admission and mortality, due to COVID-19, in patients receiving antihypertensive treatment, compared to those that receive none.⁵epidemiological evidence is lacking. We report the results of a case-population study done in Madrid, Spain, since the outbreak of COVID-19. Methods: In this case-popula-



tion study, we consecutively selected patients aged 18 years or older with a PCR-confirmed diagnosis of COVID-19 requiring admission to hospital from seven hospitals in Madrid, who had been admitted between March 1 and March 24, 2020. As a reference group, we randomly sampled ten patients per case, individually matched for age, sex, region (ie, Madrid). In addition, SARS-CoV2 virus exploits, by using it as a binding site, angiotensin-converting enzyme 2 (ACE2) for infecting cells; an enzyme that plays a crucial role in the RAAS system and is largely expressed in the lungs.⁶ and molecular simulation reveals highly similar ternary structures. However, 2019-nCoV has a distinct loop with flexible glycyl residues replacing rigid prolyl residues in SARS-CoV. Molecular modeling revealed that 2019-nCoV RBD has a stronger interaction with angiotensin converting enzyme 2 (ACE2). Both facts have triggered wide research regarding HTN and COVID-19 infection, as any possible correlation would be of major significance. The proposed correlation between antihypertensive treatment and a higher risk of adverse events, was attributed to the fact that group of hypertensive patients have comorbidities and are older. Limitations indisputably exist in all studies. Interestingly, studies have shown that low blood pressure and blood pressure drops during the first 24 hours of hospital admission for community acquired pneumonia, may increase the risk of a complicated COVID-19 course.⁷⁻⁸ This fact may be attributed to the susceptibility of hypotensive patients to acute kidney injury and underlines the importance of haemodynamic monitoring, especially in critically ill patients.⁹ 2019, Wuhan, China, has experienced an outbreak of coronavirus disease 2019 (COVID-19).¹⁰

In a review, by European Society of Hypertension COVID-19 Task Force, it was highlighted that data supporting hypertension per se as an independent risk factor for SARS-CoV2 infection are lacking.¹¹ In addition, the International Society of Hypertension on COVID-19 stated that patients over 60 years of age represent the majority in the COVID-infection cohorts; as hypertension prevalence is higher in these age groups, it tends to be overrepresented.¹² In June 2020, researchers found a two-fold

increased risk of death from SARS-CoV2 infection for hypertensive patients.¹³ It is, however, of great importance the finding that this risk affects mostly hypertensive patients that are not on any antihypertensive treatment. In the relevant meta-analysis published, researchers also found that RAAS-inhibitors use lowered the risk of death compared to the use of other drugs.¹³ However, due to the small meta-analysis cohort number, authors suggested against the overinterpretation of this result.

HYPERTENSION DRUGS

Aforementioned scientific data regarding SARS-CoV2 infection, triggered speculation and extensive research around the safety of RAAS-inhibitors, during the pandemic. Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), both widely prescribed RAAS-inhibitors highly recommended for the treatment of hypertension worldwide, were speculated to increase the risk of contracting and disease and predispose towards the severe manifestation of the infection. Largely, this theory was based on the mechanism of action of both drugs, which are thought to increase ACE2 levels in the lungs, thus making the respiratory tract more vulnerable to the virus.¹⁴ The theory has not been supported by scientific data. In a study of 1139 patients, on RAAS inhibitors treatment, admitted to the hospital due to COVID-19 infection, ACEIs and ARBs use was not associated with a higher risk of hospital admission or severe complications, defined as clinical manifestations leading to intensive care unit admission or death. Interestingly, results were unbiased by age, sex and prior cardiovascular risk.⁵ epidemiological evidence is lacking. We report the results of a case-population study done in Madrid, Spain, since the outbreak of COVID-19. Methods: In this case-population study, we consecutively selected patients aged 18 years or older with a PCR-confirmed diagnosis of COVID-19 requiring admission to hospital from seven hospitals in Madrid, who had been admitted between March 1 and March



24, 2020. As a reference group, we randomly sampled ten patients per case, individually matched for age, sex, region (ie, Madrid). Furthermore, no differences regarding the main outcome were found when ACEIs and ARBs were compared.⁵epidemiological evidence is lacking. We report the results of a case-population study done in Madrid, Spain, since the outbreak of COVID-19. Methods: In this case-population study, we consecutively selected patients aged 18 years or older with a PCR-confirmed diagnosis of COVID-19 requiring admission to hospital from seven hospitals in Madrid, who had been admitted between March 1 and March 24, 2020. As a reference group, we randomly sampled ten patients per case, individually matched for age, sex, region (ie, Madrid). In favour of those outcomes was data derived from similar studies as well. A higher prevalence of ACEIs and ARBs use among COVID-19 patients was noticed, possibly due to higher prevalence of cardiovascular disease. However, that study concluded that both categories do not correlate to the risk of COVID-19 disease.¹⁵2020, were matched to 30,759 beneficiaries of the Regional Health Service (controls Reynolds et al. also concluded that the five categories of antihypertensive drugs (ACEIs, ARBs, beta-blockers, calcium-channel blockers, thiazide diuretics) neither increase the risk of severe viral infection nor predispose to a positive COVID-19 test.¹⁶Interestingly enough, RAAS inhibitors have been found to lower the risk of adverse outcomes deriving from a COVID-19 infection, in diabetic patients, when compared to other hypertensive drugs.⁵epidemiological evidence is lacking. We report the results of a case-population study done in Madrid, Spain, since the outbreak of COVID-19. Methods: In this case-population study, we consecutively selected patients aged 18 years or older with a PCR-confirmed diagnosis of COVID-19 requiring admission to hospital from seven hospitals in Madrid, who had been admitted between March 1 and March 24, 2020. As a reference group, we randomly sampled ten patients per case, individually matched for age, sex, region (ie, Madrid). On the other hand, while supporting the safety of ACEIs

and ARBs in the setting of SARS-CoV2 infection, a recently published study proposed a possible benefit of ACEIs use over ARBs use regarding mortality; authors cautioned against overinterpretation though, due to potential unmeasured confounding.¹⁷However, studies have proposed a possible protective effect of RAAS inhibitors over other hypertensive drugs, regarding COVID-19 complications and mortality.¹⁸⁻¹⁹ Conclusively, observational studies so far have concluded that there is no direct correlation between RAAS-inhibitors use and an increased COVID-19 risk or an increased risk of complications and mortality.^{5,15-16,20} Larger, randomized studies could elucidate, confirm or discard evidence that has derived so far.

CURRENT GUIDELINES

Raised concern regarding management of hypertensive patients during the pandemic period has been the main concern of both patients and physicians. The Council on Hypertension of the European Society highlighted in a position statement March 2020, that there is no evidence from current data, that supports the seizure, either as precaution or as treatment of the viral infection, of well tolerated ACEIs and ARBs use by stable hypertensive patients in the COVID-19 era and in the absence of not COVID-related indications.²¹ In a review, published on April 2020, European Society of Hypertension COVID-19 Task Force reviewed available evidence and concluded that RAAS blockers do not have an adverse effect on the COVID-19 infection and highlighted that their discontinuation is not indicated in stable patients.¹¹

Similarly, the International Society of Hypertension underlined the lack of evidence supporting the seizure of RAAS inhibitors in the COVID-19 era, highlighting that there are no data supporting that this class of medication increases the susceptibility to the virus or the risk of possible complications.¹² However, it is important that scientific data and studies derive constantly. As a result, guidelines, including contemporary and new evidence, may change in the attempt to reflect available data

and in the service of providing the best possible advice to physicians regarding the management of patients.

CONCLUSION

During the unprecedented conditions of the ongoing pandemic, researchers are sprinting to elucidate its aspects. Due to its high prevalence and associated cardiovascular risk, hypertension has been on the spotlight of ongoing research. Evidence so far suggest that it does not increase the risk of contracting the virus nor of development of COVID-19 related complications; recent data suggest an increase in mortality risk for hypertensive patients, especially those not under hypertensive treatment. The theory proposing a risk deriving from RAAS-inhibitors use in the COVID-19 era has not been scientifically proven. Guidelines so far, advise against the discontinuation of this class of drugs as a precaution or treatment of SARS-CoV2 infection, as the cardiovascular benefit that RAAS inhibitors offer is of great importance. Further research is well expected.

Abbreviations

ACEI: angiotensin converting enzyme inhibitor

ARB: angiotensin receptor blocker

HTN: hypertension

RAAS: renin-angiotensin-aldosterone system

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