CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187
http://doi.org/10.5281/zenodo.3987309

Available online at: http://www.iajps.com *Review Article*

SEVERITY OF COVID-19 PATIENTS DEALING WITH ACE INHIBITORS, ARBS, HYPERTENSION, PNEUMONIA AND DIABETES-A REVIEW ARTICLE

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Article Received: June 2020 **Accepted:** July 2020 **Published:** August 2020

Abstract:
Concerns exists that angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs) increase susceptibility to coronavirus SARS CoV-2 (the viral agent that causes the disease COVID-19) and the likelihood of severe COVID-19 illness. Millions of people around the world are on treatment with ACE-inhibitors and ARBs for hypertension, heart failure, coronary artery disease, or kidney disease. Speculation about worse outcomes among patients on these medications during the COVID-19 pandemic has caused widespread anxiety among patients and their care providers. This article is based on different effects of COVID-19 on those patients with other severe diseases like hypertension, pneumonia, diabetes etc. It also explains that whether angiotensin-converting enzyme inhibitors have any bad impact on these patients if they continue to use these drugs.

Keywords: *Covid-19, SARS-COV-2, ACE inhibitors, ARBs Hypertension, Diabetes and Pneumonia.*

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Please cite this article in press Bilal Hussain et al, ***Severity of covid-19 patients dealing with ace inhibitors, arbs, hypertension, pneumonia and diabetes****. A review article****.,*** *Indo Am. J. P. Sci, 2020; 07(08).*

INTRODUCTION:

Coronaviruses are a group of enveloped viruses with non-segmented, single-stranded, and positive-sense RNA genomes. Apart from infecting a variety of economically important vertebrates (such as pigs and chickens), six coronaviruses have been known to infect human hosts and cause respiratory diseases. Among them, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) are zoonotic and highly pathogenic coronaviruses that have resulted in regional and global outbreaks. Coronaviruses possess a distinctive morphology, the name being derived from the outer fringe, or ―coronal‖ of embedded envelope protein. Members of the family Coronaviridae cause a broad spectrum of animal and human diseases. Uniquely, replication of the RNA genome proceeds through the generation of a nested set of viral mRNA molecules. Human coronavirus (HCoV) infection causes respiratory diseases with mild to severe outcomes. Angiotensin converting enzyme (ACE) inhibitors are medicines used to treat patients with high blood pressure, heart problems and other conditions. They have active ingredients whose names generally end in "pril". ACE inhibitors prevent an enzyme in the body from producing angiotensin II, a hormone that narrows blood vessels. This narrowing can cause high blood pressure and force the heart to work harder. Angiotensin II also releases other hormones that raise blood pressure. Angiotensin receptor blockers (ARBs, also known as angiotensin-II-receptor antagonists or sartans) are used to treat patients with high blood pressure and those with certain heart or kidney diseases and complications such as diabetic nephropathy. They also work by blocking the action of angiotensin II, preventing blood vessels from constricting so that blood pressure does not rise.

Types:

Coronaviruses belong to the subfamily Coronavirinae in the family Coronaviridae. Different types of human coronaviruses vary in how severe the resulting disease becomes, and how far they can spread. Doctors currently recognize seven types of coronavirus that can infect humans.

Common types:

1. 229E (alpha coronavirus)
2. NL63 (alpha coronavirus)
3. OC43 (beta coronavirus)
4. HKU1 (beta coronavirus)

Rarer strains that cause more severe complications include MERS-CoV, which causes Middle East respiratory syndrome (MERS), and SARS-CoV, the virus responsible for severe acute respiratory syndrome (SARS). In 2019, a dangerous new strain called SARS- CoV-2 started circulating, causing the disease COVID-19.

Transmission:

Limited research is available on how HCoV spreads from one person to the next. However, researchers believe that the viruses transmit via fluids in the respiratory system, such as mucus.

Common symptoms include:

1. Fever
2. Breathlessness
3. Cough
4. It may take 2–14 days for a person to notice symptoms after infection.

Corona virus life cycle Steps:

1. Attachment and entry
2. Replicate protein expression
3. Replication and transcription
4. Assembly and release.

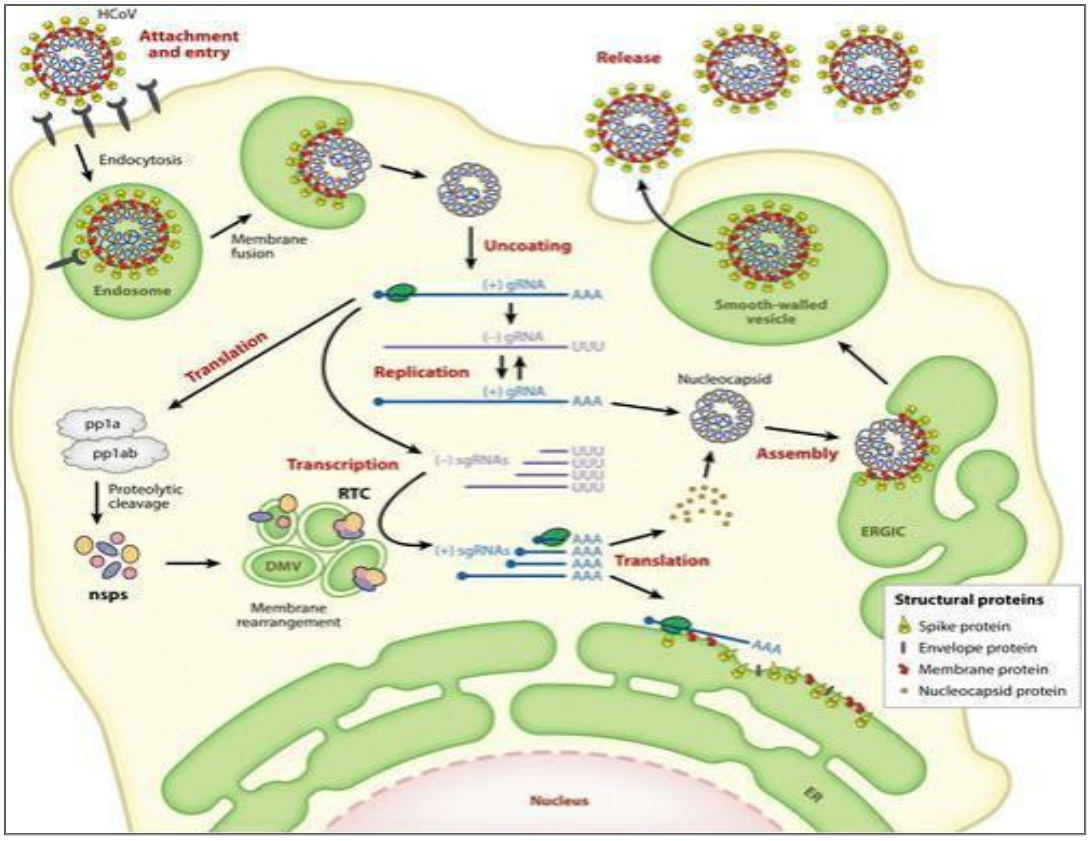

Figure 1 Life Cycle of Corona Virus

Epidemiology:

In December 2019, many pneumonia cases that were clustered in Wuhan city were reported and searches for the source have shown Huanan Seafood Market as the origin. The first case of the COVID-19 epidemic was discovered with unexplained pneumonia on December 12, 2019, and 27 viral pneumonia cases with seven being severe, were officially announced on December 31, 2019. Etiologic in-visitations have been performed in patients who applied to the hospital due to similar viral histories of these patients has strengthened the likelihood of an infection transmitted from animals to humans. On January 22, 2020, novel CoV has been declared be originated from wild bats and belonged to Group 2 of beta-coronavirus that contains Severe Acute Respiratory Syndrome Associated Coronavirus (SARS-CoV).Although COVID-19 and SARS-CoV belong to the same beta corona virus subgroup, similarity at genome level is only 70%, and the novel group has been found to show genetic differences from SARS-CoV. Similar to the SARS epidemic, this outbreak has occurred during the Spring Festival in China, which is the most famous traditional festival in China, during which nearly 3 billion people travel countrywide.

COVID-19 and major disorders:

People of any age with certain underlying medical conditions are at increased risk for severe illness from COVID-19:

People of any age with the following conditions are at increased risk of severe illness from COVID-19:

- Chronic kidney disease
- COPD (chronic obstructive pulmonary disease)
- Immunocompromised state (weakened immune system) from solid organ transplant
- Obesity (body mass index [BMI] of 30 or higher)
- Serious heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
- Sickle cell disease
- Type 2 diabetes mellitus

Children who are medically complex, who have neurologic, genetic, metabolic conditions, or who have congenital heart disease are at higher risk for severe illness from COVID-19 than other children.

COVID-19 is a new disease. Currently there are limited data and information about the impact of underlying medical conditions and whether they increase the risk for severe illness from COVID-19. Based on what we know at this time, people with the following conditions might be at an increased risk for severe illness from COVID-19:

- Asthma (moderate-to-severe)
- Cerebrovascular disease (affects blood vessels and blood supply to the brain)
- Cystic fibrosis
- Hypertension or high blood pressure
- Immunocompromised state (weakened immune system) from blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of other immune weakening medicines
- Neurologic conditions, such as dementia
- Liver disease
- Pregnancy
- Pulmonary fibrosis (having damaged or scarred lung tissues)
- Smoking
- Thalassemia (a type of blood disorder)
- Type 1 diabetes mellitus

A case shows the severity of pneumonia caused to develop coronavirus pneumonia. A 27-year-old Indian man, with known type 2 diabetes, presented with a 5-day history of gradually progressive, moderate severity, generalized abdominal pain. He did not have any fever, sore throat, myalgias, influenza-like symptoms or shortness of breath. Physical examination revealed a patient in distress due to abdominal pain. There was mild generalized abdominal tenderness, but no guarding, rigidity or rebound. The chest examination showed coarse bibasal crackles. Initial work-up revealed normocytic anaemia, thrombocytopaenia and non-elevated inflammatory markers. Two repeated samples confirmed asymptomatic hyponatraemia. Liver enzymes, renal function and the endocrine panel were unremarkable. syndrome of inappropriate antidiuretic hormone secretion (SIADH) was the probable cause of hyponatremia. Then patient developed high-grade fever. He was placed under isolation and screened for viral respiratory infections. The patient turned out to be positive for COVID-19. Differential diagnosis given the patient's chief complaint of abdominal pain with diarrhea; gastroenteritis was the initial working diagnosis. There was no food intake from outside and no sick contacts. Viral pneumonia was another diagnostic possibility for which a viral panel was sent, which included SARS-CoV-2 PCR, which eventually came back positive and hence confirmed the diagnosis of the novel coronavirus pneumonia.

Effects or Actions of ACE Inhibitors on Covid-19 patients:

ACE inhibitors and ARBs are used for treating patients with high blood pressure, heart problems or kidney disease. Concerns exists that angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs) increase susceptibility to coronavirus SARS CoV-2 and the likelihood of severe COVID- 19 illness. These concerns are based on considerations of biological plausibility, and the observation that there is an overrepresentation of patients with hypertension and other cardiovascular comorbidities among patients with COVID-19 who have poor outcomes. 3 Millions of people around the world are on treatment with ACE-Is and ARBs for hypertension, heart failure, coronary artery disease, or kidney disease. Speculation about worse outcomes among patients on these medications during the COVID-19 pandemic has caused widespread anxiety among patients and their care providers. On the other hand, the harms of indiscriminate withdrawal of these medications on cardiovascular outcomes are well documented. There is also widespread speculation about the potential benefits of ACE-inhibitors and ARBs, based on biological plausibility arguments and animal data and small clinical studies on patients with other viral respiratory infections. Recent observational studies of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have not shown an effect of these medicines on the risk of becoming infected with severe acute respiratory syndrome coronavirus 2 (the virus causing COVID-19) and do not indicate a negative impact on the outcome for patients with COVID-19 disease. The report from one hospital in Wuhan found that among patients with hypertension hospitalized with the COVID-19 virus, there was no difference in disease severity or death rate in patients taking ACE inhibitors or ARBs and those not taking such medications. The study adds to another recent report in a larger number of COVID-19 patients from nine Chinese hospitals that suggested a beneficial effect of ACE inhibitors or ARBs on mortality. ACE inhibitor/ARB therapy had a lower rate of severe disease and a trend toward a lower level of IL-6 in peripheral blood. In addition, patients on ACE inhibitor/ARB therapy had increased CD3+ and CD8+ T-cell counts in peripheral blood and decreased peak viral load compared with other antihypertensive drugs. And a preliminary study from the UK, which has not yet been peer reviewed, found that treatment with ACE inhibitors was associated with a reduced

risk of rapidly deteriorating severe COVID-19 disease. The new report from Wuhan, China, gives modest reassurance that the use of ACE inhibitors or ARBs in hypertensive patients with COVID-19 disease does not increase the risk of clinical deterioration or death.

CONCLUSION:

The preliminary study from the UK, found that treatment with ACE inhibitors was associated with a reduced risk of rapidly deteriorating severe COVID-19 disease. The evidence that ARBs increase ACE-2 is not consistent — the data come from animal studies and varies between agents and organs. It is not possible to make a blank statement on this. And there is no evidence at all that ARBs increase coronavirus entry by increasing ACE-2 expression. This is pure speculation. There is an evidence from animal studies that ACE inhibitors/ARBs are protective in pulmonary infections. Putting it all together we conclude that ACE inhibitors/ARBs should not be discontinued based on current available evidence. This is not just relevant to hypertension patients. ACE inhibitors/ARBs are also the mainstay of treatment in heart failure, chronic kidney disease, and diabetic nephropathy. If these patients stop taking these drugs this will cause huge harm. Because we don't have any data that these drugs enhance infectivity, we see no reason to discontinue them. We do not change a beneficial treatment regimen based on speculation from an animal model. The data is just not there to change treatment patterns, period. EMA therefore reiterates its previous advice that patients should continue to use ACE inhibitors or ARBs as advised by their doctors. Patients with questions or concerns about their treatment should consult a healthcare professional. EMA and the EU regulatory network will continue monitoring available and emerging data on the use of medicines during the ongoing COVID-19 pandemic and are working with other regulators and relevant European and international organizations to provide reliable advice on the safe use of medicines.

DISCUSSION:

Novel coronavirus belongs to a group of severe acute respiratory syndrome-related coronaviruses. It originated in Wuhan, Hubei Province, China, in December 2019 and was declared a pandemic by WHO on 11 March 2020. The most common clinical features are fever, dry cough, myalgia, anorexia and dyspnoea. Gastrointestinal symptoms such as diarrhea, abdominal pain and vomiting have been previously seen with acute viral respiratory infections and reported recently as rare manifestations of COVID-19. The confirmation of a suspected case relies on SARS-CoV-2 RNA detection via PCR. Watery diarrhea is present in SARS-CoV-1 infection secondary to virus replication within the intestinal cells. The presence of gastrointestinal symptoms in coronavirus infection (SARS-CoV-1 and SARS-CoV-2) can be linked to the distribution of ACE-2 receptor, which is present in lung alveolar type 2 cells, as well as in enterocytes. Acute hyponatraemia is present in atypical pneumonia, especially Legionella. The underlying mechanism is the syndrome of inappropriate antidiuretic hormone (ADH) secretion. There is a rapidly accumulating body of knowledge regarding the epidemiology, pathophysiology, clinical manifestations, infection control and management of COVID-19. Like any other RNA virus, SARS-CoV-2 attacks the host cell, and penetrates and enters the nucleus for replication. The virus has an affinity to ACE-2 as binding receptors. This affinity is the probable reason that the lungs are the most commonly affected organs. The response of the host organ can be from minimal symptoms to organ failure. Another common disease phenomenon observed and reported is a hypercoagulable state, which can be explained by the expression of ACE-2 enzymes by the endothelium. Similarly, the gastrointestinal tract also expresses ACE-2, leading to a viral attack of the system. There is ongoing research to understand the pathophysiology of COVID-19 infection. In a recent report on a case series of 1178 patients hospitalized with COVID-19 at the Central Hospital of Wuhan, Hubei, China. Patients were a median age of 55 years, and 46% were men. They had an overall inhospital mortality rate of 11%. Of the 1178 patients, 362 had a diagnosis of hypertension. These patients were older (median age, 66 years) and had a greater prevalence of chronic diseases. Patients with hypertension also had more severe manifestations of COVID-19 compared to those without hypertension, including higher rates of acute respiratory distress syndrome and inhospital mortality. Of the 362 patients with hypertension, 31.8% were taking ACE inhibitors or ARBs. Apart from a greater prevalence of coronary artery disease, patients taking ACE inhibitors or ARBs had similar comorbidities to those not taking these medications, and also similar laboratory profile results including blood counts, inflammatory markers, renal and liver function tests, and cardiac biomarkers, although those taking ACE inhibitors/ARBs had higher levels of alkaline phosphatase. The most commonly used antihypertensive drugs were calcium blockers. The percentage of patients with hypertension taking any drug or drug combination did not differ between those with severe and nonsevere infections and between those who survived and those who died. Specifically, regarding ACE inhibitors/ARBs, there was no difference between those with severe versus nonsevere

illness in the use of ACE inhibitors, ARBs, or the composite of ACE inhibitors or ARBs. Similarly, there were no differences in non-survivors and survivors in the use of ACE inhibitors, ARBs, or the composite of ACE inhibitors or ARBs. The frequency of severe illness and death also did not differ between those treated with and without ACE inhibitors/ARBs in patients with hypertension and other various chronic conditions including coronary heart disease, cerebrovascular disease, diabetes, neurological disease, and chronic renal disease. These data confirm previous reports showing that patients with hypertension have more severe illness and higher mortality rates associated with COVID-19 than those without hypertension. But the data provide some reassurance that ACE inhibitors/ARBs are not associated with the progression or outcome of COVID-19 hospitalizations in patients with hypertension. It also notes that these results support the recommendations from almost all major cardiovascular societies that patients do not discontinue ACE inhibitors or ARBs because of worries about COVID-19. However, the authors do point out some limitations of their study, which include a small number of patients with hypertension taking ACE inhibitors or ARBs and the fact that a nonsevere disease course was still severe enough to require hospitalization. In addition, it was not clear whether ACE inhibitor/ARB treatment at baseline was maintained throughout hospitalization for all patients. This was also an observational comparison and may be biased by differences in patients taking versus not taking ACE inhibitors or ARBs at the time of hospitalization. The authors also highlight the finding that patients with hypertension had three times the mortality rate of all other patients hospitalized with COVID-19. Hypertension combined with cardiovascular and cerebrovascular disease, diabetes, and chronic kidney disease would predispose patients to an increased risk of severity and mortality of COVID-19. Therefore, patients with these underlying conditions who develop COVID-19 require particularly intensive surveillance and care. Meanwhile, other information has surfaced suggesting that ACE inhibitors and ARBs may actually be beneficial in patients with COVID-19 infection by reducing the risk or severity of viral pneumonia, with some authors even suggesting that that these drugs may have potential as treatments for patients with the infection. COVID-19 uses the ACE-2 receptor to gain access into cells. COVID-19 is able to use ACE-2 proteins as an entry receptor to enter ACE-2 expressing cells, but not cells that did not express ACE-2, indicating that ACE-2 is probably the cell receptor through which COVID-19 enters cells. The crux of the controversy is that use of ACE inhibitors and ARBs may increase expression of ACE-2, which leads to the hypothesis that these drugs may increase patient susceptibility to the virus. The expression of ACE-2 is substantially increased in patients with type 1 or type 2 diabetes, who are treated with ACE inhibitors and angiotensin II type-I receptor blockers (ARBs). Hypertension is also treated with ACE inhibitors and ARBs, which results in an upregulation of ACE-2. ACE-2 can also be increased by thiazolidinediones and ibuprofen. Consequently, the increased expression of ACE-2 would facilitate infection with COVID-19. We therefore hypothesize that diabetes and hypertension treatment with ACE-2 stimulating drugs increases the risk of developing severe and fatal COVID-19.

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