

# Antihypertensive Drugs Therapy in Hypertension and Covid-19 Comorbidity

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## Abstract

The novel coronavirus (CoV) severe acute respiratory syndrome (SARS)-CoV-2 outbreak began at the end of 2019 in Wuhan, China, and has spread to over 200 countries. Many comorbidities have shown to be associated with the severity of the viral infection with hypertension being one of the highest rated comorbidities since loss of the ACE2 receptor due to SARS-Cov-2 infection can lead to increased blood pressure. The effects and clinical characteristics associated with the use of beta-blockers, angiotensin receptor blockers (ARB), and calcium-channel blockers (CCB) shows not to affect the outcome of covid-19, except in angiotensin converting enzyme inhibitor (ACEI) which may have negative outcomes on covid-19 infected patients. Many comorbidities have shown to be associated with the severity of the viral infection.

**Keywords:** blood pressure; comorbidity; COVID-19; renin-angiotensin system.

## INTRODUCTION

Hypertension (HTN) is a dangerous medical condition that raises the risk of disorders of the heart, brain, kidneys, and other organs (WHO, 2021). Hypertension is characterized as persistently increased blood pressure with a systolic blood pressure of 140 mmHg and/or a diastolic blood pressure of 90 mmHg (Mills et al., 2020). Globally, an estimated 1.13 billion people do have hypertension, with over 700 million people reported to with untreated hypertension (WHO, 2021). Worldwide, hypertension is the biggest avoidable risk factor for CVD and all-cause death (Stanaway et al., 2018).

Globally, the incidence of hypertension is increasing due to population aging and increased exposure to lifestyle risk factors such as bad diets (i.e. excessive salt and low potassium consumption, as well as a lack of physical exercise) (Mills, 2016). Another reason may be as a result of suboptimal outcome even with well-constructed antihypertensive treatment regimens (resistant hypertension) (Acelajado et al., 2019; Carey 2020; Moke et al., 2022). However, variations in hypertension prevalence levels are not consistent over the world. High-income countries (HICs) had a minor decline in hypertension prevalence during the last two

decades, whereas poor and middle-income countries (LMICs) saw large rises (Mills, 2016).

Antihypertensive medications are chemical substances used to prevent and treat excessive blood pressure (Jackson and Bellamy, 2015; Alawode et al., 2021). Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), diuretics, calcium channel blockers (CCBs), and beta-blockers are the most widely prescribed antihypertensive medication groups (Khalil and Zeitser, 2020; Moke et al., 2022).

The novel coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2), is a respiratory viral disease that first appeared in December 2019 in Wuhan, the capital of the Chinese province Hubei (Ruscitti et al., 2020). It is a highly contagious illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes respiratory infections and discomfort. COVID-19 possesses a wide range of clinical symptoms, from asymptomatic disease to severe pulmonary infections (Carfora et al., 2020; Omo-Aghoja et al., 2021). Various statistics on COVID-19 patients surfaced, revealing that some populations may be at higher risk than others (Booth et al., 2021; Enaohwo et al., 2021). With COVID-19 infections, patients with pre-existing

cardiac disease are among the three greatest risk categories (Chan et al., 2020).

Different comorbidities with hypertension exists, including COVID-19, and these have been reported (Schmieder and Ruilope, 2008; Noh et al., 2016, Unger et al., 2020; Batiha et al., 2021; Okonofua et al., 2021). According to preliminary findings, hypertension (HTN) is more common in critically sick, hospitalized COVID-19 patients, with total HTN rates ranging from 50 to 56 percent (Richardson et al., 2020). It was unclear if this link was causative or masked by age and other HTN-related comorbidities such as obesity, diabetes, and chronic kidney disease. Furthermore, COVID-19-affected hypertensive individuals exhibited a greater mortality risk than non-hypertensive patients (Barrera *et al.*, 2020).

Concerns about the use of angiotensin-converting enzyme inhibitors (ACEIs) in these patients arose as a result of the identification of angiotensin-converting enzyme 2 (ACE2), the monocarboxypeptidase that inactivates angiotensin II, thus, counteracts the activation of the classic renin–angiotensin–aldosterone system (RAAS), as the functional receptor for the severe acute respiratory syndrome coronavirus 2 (Vadughanathan et al., 2020). Because hypertension is a major risk factor for developing COVID-19, selecting the right medication for successful blood pressure management is critical.

This review briefly discusses the drug therapy with antihypertensive drugs in hypertensive patients with COVID-19 comorbidity. Articles used for this review ranged from 2008 to 2022, and over 100 articles were obtained following literature search, amongst which 64 were adapted for this article. Other articles whose scope were not applicable to the review were excluded. The articles were retrieved following searches using search engines and databases including Medline, Elsevier, Medscape, eMedicine, Google, PubMed, and others.

## CORONA VIRUS DISEASE 2019 (COVID-19)

The novel coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2), is a respiratory viral disease that first appeared in December 2019 in Wuhan, the capital of the Chinese province Hubei (Ruscitti et al., 2020). It is a highly contagious illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes respiratory infections and discomfort.

Corona Virus Disease 2019 (COVID-19) is an RNA virus with a crown-like appearance under an electron microscope due to glycoprotein spikes on its envelope (Malik, 2020). COVID-19 possesses a wide range of clinical symptoms, from asymptomatic disease to severe pulmonary infections (Carfora et al., 2020; Omo-Aghoja et al., 2021). It is not the first time that a coronavirus has caused an epidemic, as an outbreak of coronaviruses (CoVs) with severe acute respiratory syndrome (SARS)-

CoV began in the Chinese province of Guangdong in November 2019, while on September 2012, the Middle East respiratory syndrome (MERS)-CoV appeared (Lu et al., 2020).

The coronaviruses (CoVs) are classified into four genera: (a)  $\alpha$ -coronavirus (alphaCoV), (b)  $\beta$ -coronavirus (betaCoV), (c)  $\delta$ -coronavirus (deltaCoV), and (d)  $\gamma$ -coronavirus (gammaCoV), which are most likely found in birds (Pal et al., 2020). The origin of the virus is natural and zoonotic in nature. The clinical severity of the disease is varies from displaying no symptom to being very fatal, as its medical features and risk factors are so inconstant (Phan, 2020).

## Molecular Structure of Corona Virus

Coronaviruses are enclosed positive strand RNA viruses with the biggest known RNA genomes (30–32 kb), a 5'-cap structure, and a 3'-poly-A tail. The production of polyprotein 1a/1ab (pp1a/pp1ab) in the host begins with viral RNA (Lei et al., 2018). Transcription is carried out by the replication-transcription complex (RCT), which is structured in double-membrane vesicles, and by the synthesis of subgenomic RNAs (sgRNAs). It is worth noting that transcription termination occurs at transcription regulatory sequences, which are positioned between the so-called open reading frames (ORFs), which serve as templates for the creation of subgenomic mRNAs (Letko et al., 2020).

At least six ORFs can be found in the atypical CoV genome. Among these, a frameshift between ORF1a and ORF1b directs the synthesis of both pp1a and pp1ab polypeptides, which are then processed by a virally encoded chymotrypsin-like protease (3CLpro) or main protease (Mpro), as well as one or two papain-like proteases for the synthesis of 16 non-structural proteins (nsps) (Letko et al., 2020). Other ORFs, in addition to ORF1a and ORF1b, encode structural proteins such as spike, membrane, envelope, and nucleocapsid proteins, as well as auxiliary proteic chains (Lei et al., 2020). Different CoVs have unique structural and auxiliary proteins that are translated by specialized sgRNAs. The role of the nsps and structural proteins is linked to the pathophysiology and virulence processes of CoVs, and hence to SARS-CoV-2. Among the structural proteins' activities, the envelope plays a critical role in virus pathogenicity by promoting viral assembly and release (Yadav et al., 2021).

## PREVALENCE OF HYPERTENSION IN PEOPLE WITH COVID-19

- Prevalence of hypertension in people with COVID-19 was 25.4% in Africa, 31% in China, 49% in Italy, 21% in India, 32% in Oman, and 10% in Iran (Cook, 2020).
- The prevalence of hypertension in patients with COVID-19 was 4.7%, and 24.37% of COVID-19

related deaths occurred in individuals in Iran (Moftakhar *et al.*, 2021).

- Hypertension was the most prevalent reported comorbidity in COVID-19 patients in Wuhan; the reported prevalence rates ranged from 15.0% to 36.5% (Haung *et al.*, 2020).
- The prevalence of hypertension was also higher in COVID-19 deceased patients; 34.0% vs. those who were discharged alive; 28.0% (Leiva *et al.*, 2020).
- Along with the increased risk of infection and worsened outcomes among hypertensives, there is a growing concern that some medications used in the treatment may influence mortality in patients with COVID-19 (Patel and Verma, 2020).
- Studies have reported that COVID-19 deaths were mostly among people with comorbidities (99%), the majority of these were hypertensive (Guan *et al.*, 2020; Osibogun *et al.*, 2021).
- In Nigeria, the prevalence of hypertension, the most common comorbidity of COVID-19, was 17.8% followed by diabetes (7.2%) and asthma (2.0%) (Abayomi *et al.*, 2021).
- In Nigeria, overall mortality was 4.2% while mortality among the hypertensives was 13.7%. Severe symptoms and mortality were significantly higher among the hypertensives and survival rates were significantly lowered by the presence of additional comorbidity to 50% (Abayomi *et al.*, 2021).
- Studies have shown that hypertension imposes on those who suffer from it an increased risk of getting infected with COVID-19, experiencing worse symptomatology and complications and a 2-fold risk of dying from the infection (Cancarevic and Malik, 2020; Abayomi *et al.*, 2021).

### SOME ANTI-HYPERTENSIVE DRUGS IN THE TREATMENT OF HYPERTENSIVE PATIENTS WITH COVID-19 COMORBIDITY

Anti-hypertensive medications are a type of medication used to treat hypertension (high blood pressure) (Ettihad *et al.*, 2016). Antihypertensive treatment aims to avoid high blood pressure problems such as stroke and myocardial infarction. Evidence shows that lowering blood pressure by 5 mmHg can reduce the risk of stroke by 34%, ischemic heart disease by 21%, and the chance of dementia, heart failure, and cardiovascular disease death by 34% (Nelson, 2010).

There are several kinds of anti-hypertensives, each of which works in a different way to reduce blood pressure. Thiazide diuretics, calcium channel blockers, ACE inhibitors, angiotensin II receptor antagonists (ARBs), and beta blockers are among the most significant and extensively used drugs (Armstrong, 2014; Ettihad *et al.*, 2016).

### Beta-adrenoreceptor blockers

Beta-blockers lower blood pressure by preventing catecholamines from binding to beta-adrenergic receptors, resulting in coronary and peripheral artery vasodilation (Farzam and Jan, 2020). Beta-adrenoreceptor blockers reduce blood pressure via decreasing cardiac output, heart rate, renin release, and adrenergic nerve system effects (Farzam and Jan, 2020). They improve outcomes after an acute myocardial infarction and in patients with heart failure who have a low left ventricular ejection fraction, but in the absence of these comorbidities, beta-adrenoreceptor blockers are inferior to other first-line antihypertensives in terms of reducing CVD morbidity and mortality (Wysonse *et al.*, 2017). This impact has been related to lower aortic blood pressure and negative effects on body weight and glucose metabolism with beta-adrenoreceptor blockage (Frishman *et al.*, 2011).

Vasanthakumar's study suggested that using beta-blockers to treat COVID-19 could provide numerous benefits, including reducing SARS-CoV-2 cell entry via downregulation of the angiotensin-converting enzyme 2 (ACE-2), reducing the expression of proinflammatory cytokines, and reducing complications such as pulmonary embolism, ARDS, and septic shock (Vasanthakumar, 2020). A research found that beta-blockers had no effect on the severity of COVID-19 (Bauer *et al.*, 2021). Another study found that using beta-blockers greatly lowered the chance of severe consequences (Kjeldsen *et al.*, 2021). Patients on beta-blockers had a decreased risk of testing positive for COVID-19 (Reynold *et al.*, 2020).

### Calcium Channel Blockers (CCBs).

Calcium channel blockers (CCBs) inhibit calcium entry into cells by binding to L-type voltage-gated calcium channels found in organs such as the heart and vascular smooth muscle (McKeever and Hamilton, 2020). A drop in the intracellular concentration of calcium causes smooth muscle cell relaxation and, as a result, a fall in blood pressure (Kuo and Ehrlich, 2022). Headaches, flushing, palpitations, peripheral edema, hypotension, atrioventricular block, constipation, and nausea are the most common side effects associated with this category (Solanki *et al.*, 2021). Calcium channel blockers, particularly verapamil, inhibit cardiac calcium channels, which can lower heart rate and cardiac contractility (Elliott and Ram, 2011).

According to reports, CCBs can reduce SARS-CoV-2 multiplication (Zhang *et al.*, 2020; Loas *et al.*, 2022). Amlodipine besylate was observed to decrease the risk of death in hypertension individuals (Zhang *et al.*, 2020). Another research found that nifedipine and amlodipine significantly lowered the mortality rate as well as the risk of intubation and mechanical ventilation in elderly COVID-19 patients (Solaimanzadeh, 2020). One research observed no significant changes in the administration of amlodipine in COVID-19 patients with

primary hypertension in terms of mortality and length of hospital and intensive care unit (ICU) stay (Nouri-Vaskeh et al., 2021).

### Angiotensin Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs)

The renin-angiotensin-aldosterone system (RAAS) inhibitors, such as ACE inhibitors and ARBs, are among the most often prescribed blood pressure medications (Wang et al., 2020). ACE medications reduce blood pressure by inhibiting the angiotensin-converting enzyme, resulting in less angiotensin II production and vasodilation. The mechanism of action of ARBs is to prevent angiotensin II from attaching to angiotensin-1 (AT1) receptors (Khalil and Zeitsler, 2020). The most serious side effects of this class include hyperkalemia, renal failure, coughing, and first-dose hypotension.

There is growing concern about the use of antihypertensives in COVID-19 patients, owing to the fact that angiotensin-converting enzyme 2 (ACE2), a negative regulator of the renin-angiotensin-aldosterone system (RAAS), is a co-receptor for viral entry into human cells by SARS-CoV-2 (Hui, 2020). ACE cleaves angiotensin I to produce angiotensin II, whereas ACE2 converts angiotensin II to angiotensin III (Zou, 2014). ACE2 plays an important role in maintaining blood pressure homeostasis, fluid and salt balance by counteracting the impact of ACE (Forrester, 2018).

ACE inhibitors and ARBs may increase the expression of ACE-2, a cellular receptor for SARS-CoV-2. These medications, on the other hand, have been found to protect against acute lung damage (Guo et al., 2020).

Concerns have been raised about the use of angiotensin-converting enzyme inhibitors (ACEIs) in patients following the identification of angiotensin-converting enzyme 2 (ACE2), a monocarboxypeptidase that inactivates angiotensin II and thus counteracts the activation of the classic renin-angiotensin-aldosterone system (RAAS), as the functional receptor for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) (Vadughanathan et al., 2020). As a result, discontinuing ACEIs or ARBs may result in poorer results than continuing to use them in individuals with COVID-19. Most of the world's professional societies either recommend or strongly encourage continuing ACEIs/ARBs in COVID-19 infected patients (Hoffman et al., 2020).

The novel coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2), is a respiratory illness that causes respiratory distress among other symptoms. One of the major comorbidities of COVID-19 is hypertension, which is defined by persistently high blood pressure. The use of several anti-hypertensive classes, including as beta-blockers, calcium channel blockers, diuretics, and angiotensin converting enzyme inhibitors (ACEI), to treat hypertension in patients with Covid-19 may have

side effects on the patients. While other antihypertensive classes have no to beneficial effects, ACEI have been demonstrated in multiple studies to be a source of worry since they may potentially enhance COVID-19 symptoms and promote viral entry into the cell.

### CONCLUSION

Most anti-hypertensive drugs have no detrimental impact on the outcome of COVID-19 therapy, and a few classes have favorable benefits in alleviating symptoms in patients infected with COVID-19. ACEIs are the only class of anti-hypertensive that may have an influence on the result of COVID-19 among the anti-hypertensive classes evaluated. More studies and clinical trial are recommended to be carried out with more common anti-hypertensive to evaluate the potential effects on COVID-19.

**Competing Interests:** The authors declare that there are no competing interests.

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