

# World Journal of *Clinical Cases*

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## Beta receptor blocker therapy for the elderly in the COVID-19 era

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### Abstract

When the coronavirus disease 2019 (COVID-19) pandemic spread globally from the Hubei region of China in December 2019, the impact on elderly people was particularly unfavorable. The mortality associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was highest in older individuals, in whom frailty and comorbidities increased susceptibility to severe forms of COVID-19. Unfortunately, in older patients, the course of COVID-19 was often characterized by significant cardiovascular complications, such as heart failure decompensation, arrhythmias, pericarditis, and myopericarditis. Ensuring that the elderly have adequate therapeutic coverage against known cardiovascular diseases and risk factors is particularly important in the COVID-19 era. Beta blockers are widely used for the treatment and prevention of cardiovascular disease. The clinical benefits of beta blockers have been confirmed in elderly patients, and in addition to their negative chronotropic effect, sympathetic inhibition and anti-inflammatory activity are theoretically of great benefit for the treatment of COVID-19 infection. Beta blockers have not been clearly shown to prevent SARS-CoV-2 infection, but there is evidence from published studies including elderly patients that beta blockers are associated with a more favorable clinical course of COVID-19 and reduced mortality. In this minireview, we summarize the most important evidence available in the literature on the usefulness of beta blocker therapy for older patients in the context of the COVID-19 pandemic.

**Key Words:** Adrenergic beta-antagonist; COVID-19; Aged; SARS-CoV-2; Cardiovascular diseases

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**Core Tip:** This minireview offers an original and innovative summary of recent studies of the usefulness of beta blocker therapy for the elderly in the coronavirus disease 2019 (COVID-19) pandemic. We discuss the pharmacologic benefits of beta blocker therapy for older subjects and report the results of early studies highlighting the favorable effects of beta blockers on elderly patients affected by COVID-19.

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## INTRODUCTION

The current coronavirus disease 2019 (COVID-19) pandemic is one of the most pressing public health problems worldwide because of excessive mortality and the economic impact on health systems[1,2]. Indeed, despite the development of several specific vaccines for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the application of stringent preventive measures to limit the transmission of the infection, COVID-19 has continued to spread in recurrent waves, with the ability of the virus to mutate rapidly[3].

The elderly, especially those who are frail and with comorbidities, are particularly vulnerable to COVID-19[4,5]. It is widely recognized that SARS-CoV-2 infection causes higher hospitalization and mortality rates in older than in younger individuals[6,7]. Initially, COVID-19 was viewed as a predominantly respiratory disease, but recent studies have shown that SARS-CoV-2 infection can also be considered a vascular disease, given that endothelial and thrombotic processes are fundamental etiopathogenic actors in the development of the disease[8]. Furthermore, COVID-19 is characterized by frequent cardiovascular complications, such as heart failure decompensation and arrhythmias[9]; indeed, cardiovascular drugs, such as heparin and antihypertensive drugs, have been investigated for their possible use in the prevention and treatment of SARS-CoV-2 infection and its complications[10,11].

Beta blockers have been used for decades for arterial hypertension, heart failure, ischemic heart disease, and arrhythmias in geriatric patients[12-14]. They may also be protective in patients with COVID-19. In this minireview, we discuss the most significant pathophysiological and clinical evidence suggestive of the usefulness of beta blockers in elderly patients during the COVID-19 pandemic, beginning with their pharmacologic properties.

## PHARMACOLOGIC PROPERTIES OF BETA BLOCKERS

Beta blockers are widely used in cardiology and have other indications, such as headaches (migraine), glaucoma, or essential tremor[15]. As the prevalence of hypertension, heart failure, and arrhythmias is particularly high in geriatric age groups, beta blockers are often prescribed to elderly patients[16,17]. Depending on the selectivity of binding to various beta-adrenergic receptors (*i.e.*, beta-1, beta-2, or beta-3 receptor), beta blockers are classified as nonselective or beta-1-selective. Most bind to beta-1 receptors, causing their inhibition and resulting in negative chronotropic and inotropic effects that reduce cardiac work and oxygen consumption[18]. Beta blockers also protect the heart from the negative effects of excess of catecholamines secondary to sympathetic overstimulation, receptor downregulation, and desensitization, as occurs in heart failure[19,20]. Beta blockers decrease the activity of the renin-angiotensin-aldosterone system by inhibiting renal beta-1 receptors[21]. Inhibition of beta-2 receptors causes some of the adverse effects of beta blockers, such as bronchoconstriction and peripheral vasoconstriction, and inhibition of beta-3 receptors decreases lipolysis in peripheral adipose tissue[22]. Some beta blockers increase the expression and/or activity of beta-3 receptors in the heart, which improves myocardial metabolism in the failing myocardium[23]. Nonselective beta blockers, such as carvedilol, inhibit alpha-adrenergic receptors, causing vasodilation and reduced blood pressure[24]. The binding of beta blockers to adrenergic receptors starts a complex cascade of proteins involved in the genesis of cardiac remodeling, such as mitogen-activated protein kinases, Gs-adenylyl cyclase-cyclic AMP and phosphoinositide 3-kinase signaling[25]. It has been reported that beta-receptor desensitization reduces the therapeutic activity of beta blockers in the elderly and in heart failure patients[26,27]. Studies conducted in aged heart failure patients have clearly confirmed the benefits of beta blockers on relevant clinical endpoints, such as hospitalization and symptoms[28,29].



## BETA RECEPTOR BLOCKERS FOR ELDERLY IN THE CONTEXT OF COVID-19

### **Pharmacologic basis of beta blocker benefits**

There are several pharmacologic reasons why treatment with beta blockers may be of benefit for patients with SARS-CoV-2 infection. First, the entry of SARS-CoV-2 into cells involves the binding of viral spike proteins to angiotensin-converting enzyme 2 (ACE2)[30]. ACE2 is expressed in various cells, such as cardiomyocytes, endothelial cells, alveolar macrophages, and type II pneumocytes[31]. SARS-CoV-2 entry downregulates ACE2 receptors, which is followed by dysregulation of the ACE2-mediated pathway that protects against inflammation, and the adverse ACE-mediated axis[32]. Beta blockers downregulate ACE2, thereby reducing the virus' ability to attack cells[33]. However, as beta blockers reduce renin production, they may protect against SARS-CoV-2 infection by preventing the pro-inflammatory action promoted by angiotensin 2[34]. Cardiovascular complications are among the most frequent and feared COVID-19 complications, and beta blocker therapy might help prevent them or result in a milder clinical course. Beta blockers have been used to treat heart failure and arrhythmias secondary to COVID-19 infection[35,36], and treatment of myocarditis associated with COVID-19 may also benefit from the administration of beta blockers[37]. Some beta blockers, such as nebivolol, improve endothelial function by promoting nitric oxide bioavailability[38], which may be protective in diseases like COVID-19 in which endothelial dysfunction is involved[39].

Beta blockers have favorable anti-inflammatory activity that is potentially useful in preventing the cytokine storm of COVID-19[40]. In particular, beta blockers reduce interleukin-6 and decrease the activation of NOD-, LRR- and pyrin domain-containing protein 3 inflammasomes[41]. Hypoxia that occurs in the course of severe SARS-CoV-2 bronchopneumonia results in overactivation of the sympathetic nervous system, whose deleterious effects may be counteracted by beta blocker treatment[42]. Finally, beta blockers appear to limit the undesirable effects of some drugs used to treat COVID-19, such as azithromycin or hydroxychloroquine, which may promote QT prolongation and predispose to lethal arrhythmias[43].

### **Clinical evidence of beta blocker usefulness in the elderly**

With the outbreak of the COVID-19 pandemic, a concern of physicians and researchers was that certain chronically taken medications could promote SARS-CoV-2 infection or induce an unfavorable course, especially in geriatric patients[44]. However, the safety of beta blockers regarding the eventual predisposition or worse clinical course of COVID-19 was already evident from the results of early studies in the elderly. A large retrospective study in Spain of 34,936 hypertensive patients of  $70.9 \pm 11.3$  years of age verified that beta blockers are not associated with an increased risk of a subsequent diagnosis with COVID-19[45]. Other studies have ruled out the existence of any association between inpatient mortality from COVID-19 and beta blocker use, including patients in their 90s[46,47]. A meta-analysis of 53 studies of the association of antihypertensive medications with COVID-19 incidence and mortality found a neutral effect of the beta blocker class[48]. There was no association between use of beta blockers and COVID-19 incidence (odds ratio [OR]: 1.03; 95% confidence interval [CI]: 0.78–1.35) or severity (OR: 1.23; 95%CI: 0.74–2.04). However, only 3 of the 10 studies on beta blockers in the meta-analysis included patients older than 65 years of age, making it difficult to generalize the results to geriatric populations. On the other hand, there is evidence that beta blocker therapy causes clinical improvement and improved survival in patients with COVID-19, including those in older age groups [49–52]. Consistently, the benefits of beta blockers in COVID-19 infection are confirmed by the observation that discontinuation of beta blocker therapy outside the guidelines results in increased in-hospital mortality in COVID-19 patients[53].

Some studies have not found decreased COVID-19 severity in elderly people taking beta blockers. It cannot be excluded that this finding may have resulted from a lack of statistical power[48,54], but a retrospective study excluded the preventive efficacy of beta blockers against COVID-19 infectious risk [55]. Existence of the clinical benefits of beta blockers has been investigated in critically ill COVID-19 patients. A case-control study including 20 patients with acute respiratory distress syndrome and requiring mechanical ventilation found that infusion of the beta blocker metoprolol (15 mg daily for 3 d) improved both oxygenation and the degree of lung inflammation. The investigators argued that metoprolol acted by stunning neutrophils and abrogating exacerbated inflammation[56].

Another mechanism by which metoprolol in infusion could have ameliorated the oxygenation of critical patients with COVID 19 is hemodynamic. In fact, it has been hypothesized that metoprolol, through a reduction in cardiac output, may have consequently reduced the intrapulmonary shunts, therefore improving the ventilation-perfusion ratio[57]. Overall, the available study results exclude that beta blocker therapy may favor worsening of the course of COVID-19 and SARS-CoV-2 infection (Table 1). Conversely, some studies found that elderly patients taking beta blocker therapy had a more favorable clinical COVID-19 course. Nevertheless, the results of the available studies must be interpreted with caution because of possible bias related to small sample size and to the diverse pharmacological properties possessed by the various beta blockers.

**Table 1 Studies on beta blocker therapy and coronavirus disease 2019 in elderly patients**

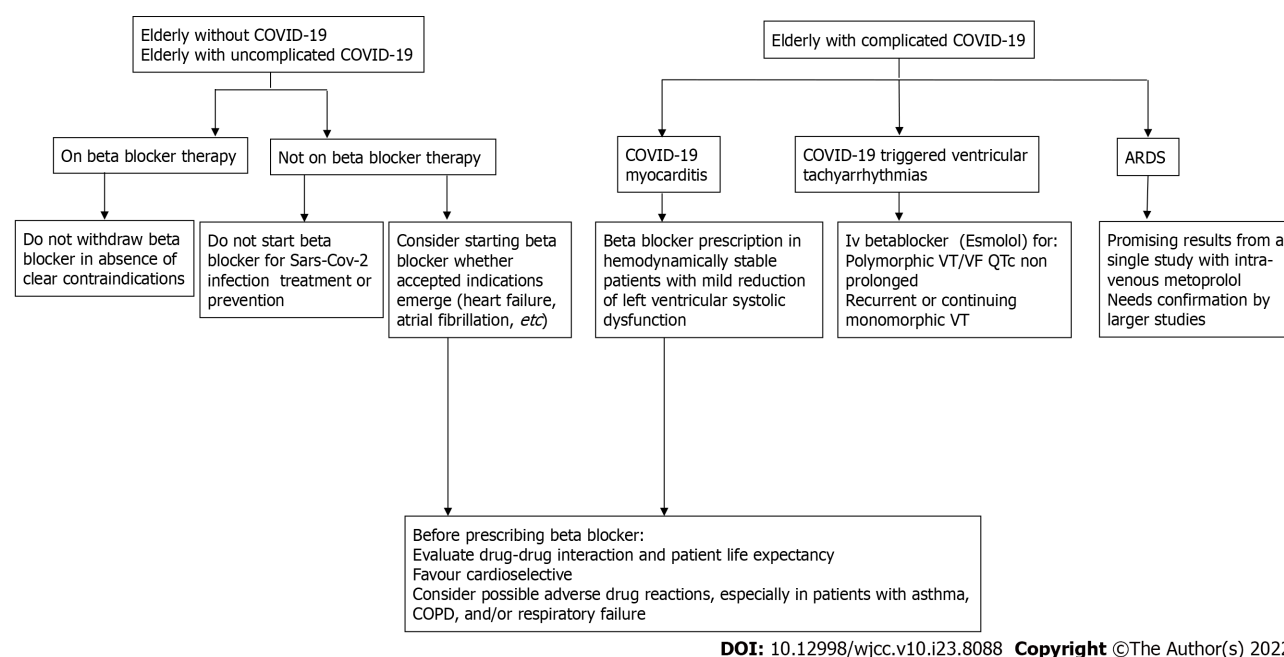
Ref.	Study type	Study aim	Subjects	Study findings
Yan F <i>et al</i> [49], 2020	Multicenter retrospective	Examine association between clinical outcomes with the use of antihypertensive drugs	665 hypertensive COVID-19 patients (mean age: 64.6 ± 11.8 yr)	Reduced dyspnea in BB users; improved clinical indices
Rey JR <i>et al</i> [53], 2020	Prospective	Study cardiovascular outcomes in patients with COVID-19 and a prior diagnosis of heart failure	3080 hospitalized COVID-19 patients (mean age: 62.3 ± 20.3 yr)	↑ in-hospital mortality associated to withdrawal of BB (HR: 4.15; 95%CI: 1.61–10.71)
Liu Y <i>et al</i> [54], 2020	Retrospective	Association between antihypertensive use and disease severity of COVID-19 patients	46 elderly hypertensive COVID-19 patients (> 65 yr in age)	BB use not associated to less disease severity (OR: 0.49; 95%CI: 0.2–1.98)
Saifi Said E <i>et al</i> [51], 2021	Retrospective	Examine factors associated with survival in older people with COVID-19	34 inpatients with COVID-19 (90 yr in age)	Better survival in patients treated with BB <i>vs</i> non-treated ( <i>P</i> = 0.008 by Kaplan-Meier analysis)
Couchana L <i>et al</i> [52], 2021	Retrospective multicenter cohort study	Investigate association between antihypertensive agent use and in-hospital mortality	8078 patients hospitalized for COVID-19 (median age: 75.4 yr)	↓Risk of mortality in BB users (aOR: 0.80; 95%CI: 0.67–0.95)
Clemente-Moragón A <i>et al</i> [56], 2021	Pilot randomized controlled trial	Evaluate the effects of intravenous metoprolol on lung inflammation and oxygenation	20 COVID-19 patients with ARDS (median age: 60 yr)	Intravenous metoprolol reduced lung inflammation, improved oxygenation, and was safe
Blanc F <i>et al</i> [55], 2021	Retrospective case-control	Find a pharmacological preventive treatment of COVID-19 in elderly patients	89 COVID-19 patients (mean age: 84.4 yr) compared with 90 non-COVID-19 patients (mean age: 83.8 yr); 40.78% on BB therapy	taking BB does not reduce risk of COVID-19 infection (OR: 1.28; 95%CI: 0.71–2.31, <i>P</i> = 0.7909)
Vrillon A <i>et al</i> [47], 2020	Prospective cohort	Describe clinical features and outcome of COVID-19 elderly inpatients	76 COVID-19 inpatients (median age: 90 yr)	No difference in BB therapy between survivors <i>vs</i> non-survivors ( <i>P</i> = 0.796)
Vila-Corcoles A <i>et al</i> [45], 2020	Population-based retrospective cohort	Investigate relationships between antihypertensive drug use and COVID-19 infection	34,936 ambulatory hypertensive adults (> 50 yr of age; mean age: 70.9 ± 11.3 yr)	Receiving BB did not significantly alter the risk of PCR-confirmed COVID-19 (HR: 0.97; 95%CI: 0.68–1.37, <i>P</i> = 0.844)
Polverino F <i>et al</i> [46], 2020	Nationwide observational retrospective	Whether hypertension medications may increase the risk of death	3179 COVID-19 inpatients (58% of patients ≥ 65 yr of age)	Hypertension medication does not significantly increase COVID-19-related deaths in an older population (OR: 0.85; 95%CI: 0.65–1.12, <i>P</i> = 0.244)

aOR: Adjusted odds ratio; ARDS: Acute respiratory distress syndrome; BB: Beta blocker; CI: Confidence interval; COVID: Coronavirus 2019 disease; HR: Hazard ratio; OR: Odds ratio.

### Concerns for beta blockers use

The safety and benefits of beta blocker therapy for treating COVID-19 in elderly patients have been confirmed by various studies, but others have generated important warnings about the use of beta blockers. A recent retrospective observational study including 298 patients of 58.33 ± 15.52 years of age and with 93 who were ≥ 65 years of age reported that beta blocker therapy was paradoxically associated with increased mortality[58]. However, the authors of the study hypothesized that the concurrent use of other drugs may have confounded the results. In addition, it is also unclear whether previous beta blocker therapy may adversely affect the convalescence of elderly people with COVID-19. A study of 115 patients over 68 years of age with severe COVID-19 found that those with prior beta blocker use had worse lung diffusion of carbon monoxide (commonly known as DLCO) during convalescence (OR: 3.93; 95%CI: 1.05–14.76; *P* = 0.042)[59]. Those taking renin-angiotensin-aldosterone inhibitors tended to have better DLCO levels.

In some clinical settings in geriatric medicine, such as the management of patients with comorbidities or low life expectancy, the use of beta blockers should be carefully evaluated on a case-by-case basis. A recent systematic review demonstrated that beta blockers were a class of drugs, that if inappropriately used, could adversely affect the prognosis of COVID-19[60]. The review considered drugs with potential negative impact on respiratory diseases, such as asthma, chronic obstructive pulmonary disease and respiratory failure, and therefore expressed a preference for the use of selective beta blockers in the COVID-19 scenario. Finally, it is worth noting that expert opinion recommends the decision to introduce a new drug in elderly subjects, including drugs with antihypertensive effects such as beta blockers, should be based on the expected risk-benefit ratio, especially in patients with comorbidities and reduced life expectancy[61].



**Figure 1 Beta blocker therapy for the elderly in the coronavirus disease 2019 scenario.** ARDS: Acute respiratory distress syndrome; COPD: Chronic obstructive pulmonary disease; COVID-19: Coronavirus disease 2019; Iv: Intravenous.

### Actual strategies and future perspectives for beta blocker use

Some strategies for beta blocker use in relation to COVID-19-induced pathologies have already been codified and described in specific guidelines. It is the case of myocarditis that complicates COVID-19 infection. In fact, for COVID-19 myocarditis, beta blockers are recommended in hemodynamically stable subjects with slight reduction of left ventricular function and in stable patients who have had supraventricular arrhythmias[62]. In addition, intravenous administration of a beta blocker (in particular the ultrashort acting Esmolol) has been included in flow charts for the treatment of ventricular tachyarrhythmias triggered by COVID 19 infection[63].

Certainly, promising prospects for the use of beta blockers include the areas of hypertensive urgencies and emergencies in the course of COVID-19 and the treatment of post-COVID autonomic dysfunction[64,65]. On the other hand, strategies for the preventive use of beta blockers, such as the pre-treatment of frail elderly people, are not currently applicable. Indeed, evidence from specific, large clinical trials is lacking. Unfortunately, the design and conduction of these studies appear very problematic for the difficulties of having control groups during pandemic waves, and discriminating the effect of beta blocker from those of other drugs[66].

## CONCLUSION

The available evidence confirms a relevant role for beta blockers for the elderly in the COVID-19 era (Figure 1). There is strong evidence that their discontinuation for fear that they may facilitate the onset of SARS-CoV-2 virus infection is unjustified and COVID-19 should not be a contraindication. By contrast, many studies conducted in geriatric patients found that those with COVID-19 who took beta blockers had less severe infections and better survival. That finding can be interpreted in the light of the pharmacology of the drugs. As discussed, in addition to their primary anti-arrhythmic and anti-ischemic activities, beta blockers also have anti-inflammatory activity and counteract sympathetic hyperactivity that counteract COVID-19 pathogenesis. Some beta blockers (*i.e.*, nebivolol) may produce additional benefits against COVID-19 by increasing nitric oxide bioavailability. Future large studies in elderly patients should clarify the clinical usefulness of beta blocker therapy for the treatment of COVID-19 and the reduction of the risk of fatal complications. Further research is also desirable to investigate the prophylactic use of beta blockers in individuals at risk of contracting severe disease, such as the frail elderly. Finally, future studies should also clarify whether the use of beta blockers in patients already infected with SARS-CoV-2 can reduce post-acute COVID-19 symptomatology and long-term COVID symptoms.

## FOOTNOTES

**Author contributions:** Santillo E performed the majority of the writing, prepared the figure and table, designed the outline, and coordinated the writing of the paper; Migale M performed the data acquisition and initial writing, and provided input in subsequent drafts of the paper; both authors have read and approved the final manuscript.

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