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REVIEW

Pharmacotherapy for hypertensive urgency and emergency in COVID-19 patients

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ABSTRACT

Introduction: Hypertension is a common chronic disorder in patients hospitalized for coronavirus disease 2019 (COVID-19). Furthermore, an exaggerated cardiovascular response with persistently raised blood pressure during hospitalization seems independently associated with in-hospital all-cause mortality, intensive care unit admission and heart failure. However, the real burden of elevated blood pressure during the acute phase of COVID-19 remains undefined.

Areas covered: The authors review the available evidence on the pharmacotherapy for the treatment of acute elevations in blood pressure (including hypertensive urgency and emergency) in COVID-19 patients.

Expert opinion: Acute elevations in blood pressure and unstable in-hospital blood pressure may be associated with organ damage and worse outcome in patients with COVID-19. In this setting, hypertensive emergencies require immediate reduction in blood pressure through intravenous treatment according to specific features and goals. Conversely, hypertensive urgencies usually require solely oral treatment. Diuretics, beta-blockers, renin-angiotensin-aldosterone system inhibitors, and calcium channel blockers may be of benefit in treating COVID-19 patients with elevated blood pressure values.

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1. Introduction

Studies in patients admitted to hospital for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection showed that comorbidities increase the risk of severe clinical outcomes [1–4].

The United States Centers for Disease Control and Prevention (CDC) released a list of well-established risk factors that have been associated with severe coronavirus disease 2019 (COVID-19) as documented in observational studies, systematic reviews and meta-analyses [5]. The list includes older age, hypertension, cancer, previous cerebrovascular disease, history of cardiovascular disease, chronic kidney disease, diabetes mellitus, and obesity. Among these, one of the most common comorbidities among COVID-19 patients is hypertension [1,2].

In a clinical study involving 5700 hospitalized COVID-19 patients from New York area in the United States, hypertension was the most common comorbidity (prevalence of 56.6%) and it was associated with an increased risk of death, intensive care unit admission, invasive ventilation, and renal replacement therapy [6]. These results have been confirmed in a meta-analysis of 7 clinical studies including 1576 COVID-19 infected patients. It showed that the most prevalent comorbidity was hypertension (21.1%, 95% confidence interval [CI]: 13.0–27.2%) [7] and that patients with hypertension were at increased risk of severe COVID-19 (odds ratio [OR]: 2.49; 95% CI: 1.98–3.12) along with a higher risk of mortality (OR: 2.42; 95% CI: 1.51–3.90) [8]. Furthermore, an exaggerated cardiovascular response with persistently elevated blood pressure (BP) and high BP variability during hospitalization are independently associated with in-hospital all-cause mortality, intensive care unit admission, and heart failure [9,10].

These findings indicate that acute elevations in BP and unstable in-hospital BP are significant predictors of worse outcome in COVID-19 [9,10].

Although hypertension seems to be linked to the pathogenesis of COVID-19 and acute elevations in BP can result in acute worsening of hypertension-mediated organ damage and more unfavorable outcome [9], the real burden of elevated BP during the acute phase of COVID-19 remains undefined. Furthermore, there are conflicting views of the epidemiology in academic literature.

The main aim of our narrative review was to summarize available evidences on the pharmacotherapy for the treatment of acute elevations of BP, including hypertensive urgency and emergency, in COVID-19 patients. For this purpose, we conducted a systematic review of clinical and experimental studies according to established methods [11,12]. Literature searches were conducted using PubMed, Scopus, EMBASE, Web of Science, and Google Scholar databases. We searched for eligible studies using research Methodology Filters [11,12]. The following research terms were used: 'COVID-19, SARS-CoV-2, blood pressure, hypertensive emergency, hypertensive urgency,

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Article highlights

- Among established risk factors associated with severe coronavirus disease 2019 (COVID-19), hypertension is one of the most common comorbidities.
- Acute elevations in blood pressure and unstable in-hospital blood pressure may be associated with in-hospital mortality, intensive care unit admission and heart failure, with acute end-organ damage and a worse outcome in these patients.
- The pathophysiologic mechanisms involved in the acute target-organ dysfunction during a severe elevation of blood pressure are still undefined.
- The direct invasion of endothelial cells by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) promotes cell injury, microvascular inflammation, endothelial exocytosis, and endothelitis. Furthermore, some observations support a direct effect of SARS-CoV -2 invasion on the homeostatic regulation of the vascular system and blood pressure as mediated by the interaction with angiotensin-converting enzyme 2 (ACE2) receptors.
- For hypertensive emergencies in COVID-19, the site of organ damage mostly drives the choice of blood pressure-lowering drugs, target blood pressure, and timeframe by which reduction in blood pressure should achieved.
- In hypertensive urgencies, blood pressure should be reduced over a period of hours to days, usually requiring oral drug administration. Among common blood pressure lowering drugs, beta-blockers, renin-angiotensin-aldosterone system inhibitors, and calcium channel blockers could offer benefits in treating COVID-19 patients.

high blood pressure, hypertension, blood pressure lowering-drugs.'

2. Definition of hypertensive urgencies and emergencies

According to current Guidelines [13], hypertensive emergencies are defined as the development of marked elevation in BP values associated with signs or symptoms of acute hypertension-mediated target-organ damages [13]. They require immediate, but careful, reduction in BP to promote regression of organ damage or to limit its extension [13–15]. Key target organs of hypertensive emergencies are the heart, brain, large arteries, kidneys, and retina [13]. Target-organ damages include cardiac ischemia, advanced retinopathy (as defined by the presence of flame-shaped hemorrhages, cotton wool spots, or papilledema), hypertensive encephalopathy, acute stroke (ischemic or hemorrhagic), acute cardiogenic pulmonary edema, acute aortic disease, eclampsia and severe pre-eclampsia/HELLP syndrome (Hemolysis, Elevated Liver enzymes and Low Platelets), acute hypertensive nephrosclerosis, and thrombotic microangiopathy (Coombs-negative hemolysis and thrombocytopenia in the absence of another plausible cause) [13,16–20].

Conversely, elevated BP (systolic pressure ≥ 180 mmHg and/or diastolic pressure ≥ 120 mmHg) without acute end-organ injury is defined as severe asymptomatic hypertension or hypertensive urgency [13]. This entity often occurs among patients who have been non-adherent with their chronic antihypertensive drug regimen [20].

3. Mechanisms

The common pathophysiologic scenario involved in the acute target-organ dysfunction during a severe elevation of BP is not clearly understood [20]. The initial steps in this disease process is the failure of normal autoregulation, the release of humoral vasoconstrictors from the wall of a stressed vessel, and an abrupt rise in systemic vascular resistance [21–23]. More specifically, acute and marked elevation in BP overwhelms the autoregulation of the endothelial control of vascular tone, leading to endothelial damage with vascular permeability, recruitment of inflammatory mediators, and activation of the coagulation cascade (activation of platelets, and deposition of fibrin) [21–23]. The cycle of further vascular injury and autoregulatory dysfunction promotes hypoperfusion (end-organ ischemia) with subsequent target-organ dysfunction [21–23].

The above picture is further complicated in patients with COVID-19. The direct invasion of endothelial cells by SARS-CoV -2 promotes cell injury, microvascular inflammation, endothelial exocytosis, and endothelitis [24,25] leading to acute respiratory distress syndrome (ARDS) [24,25]. Excessive production of pro-inflammatory cytokines leads to ARDS aggravation and widespread tissue damage resulting in multi-organ failure [26–29]. Furthermore, some observations support a direct effect of SARS-CoV-2 invasion on the homeostatic regulation of the vascular system and BP [30–33].

The angiotensin-converting-enzyme-2 (ACE_2) is a catalytic enzyme which is recognized as the receptor for the entry point for the SARS-CoV-2 virus on host cells [34,35]. At the same time, ACE_2 receptors play a key role in the modulation of the balance between vasoconstriction and vasodilatation, and in the regulation of the cardiovascular and renal function [30–32,36].

Indeed, ACE_2 receptors are regulators of the renin-angiotensin-aldosterone-system (RAAS) by catalyzing the cleavage of angiotensin I into angiotensin$_{1\text{-}9}$, and angiotensin II into the vasodilator angiotensin$_{1\text{-}7}$. Angiotensin II is a potent vasoconstrictor, a stimulant of aldosterone release, and a promoter of adverse reactions including hypercoagulability, endothelial dysfunction, enhanced inflammation, and increased oxidative stress. On the contrary, angiotensin$_{1,7}$ exerts several protective cardiovascular effects by the inhibition of angiotensin II–induced signaling, vasodilatation, sympathetic modulation, and restoration of endothelial function [30,31]. Remarkably, the interaction between ACE_2 and SARS-CoV-2 is associated with the phenomenon of ACE_2 downregulation, with internalization of ACE_2 receptors into cells [37,38] and consequent substantial loss of ACE_2 receptor enzymatic activity from the external site of the membrane. These mechanisms lead to less angiotensin II inactivation and less generation of antiotensin$_{1\text{-}7}$ (imbalance between angiotensin II overactivity and angiotensin$_{1\text{-}7}$ deficiency) which may trigger inflammation, thrombosis, and, notably, a rise in BP (Figure 1) [30–32].

4. Pharmacotherapy of hypertensive emergencies

There are only few data on the treatment of these conditions during the acute phase of COVID-19. A case report has been reported of a primi mother with COVID-19 who presented with

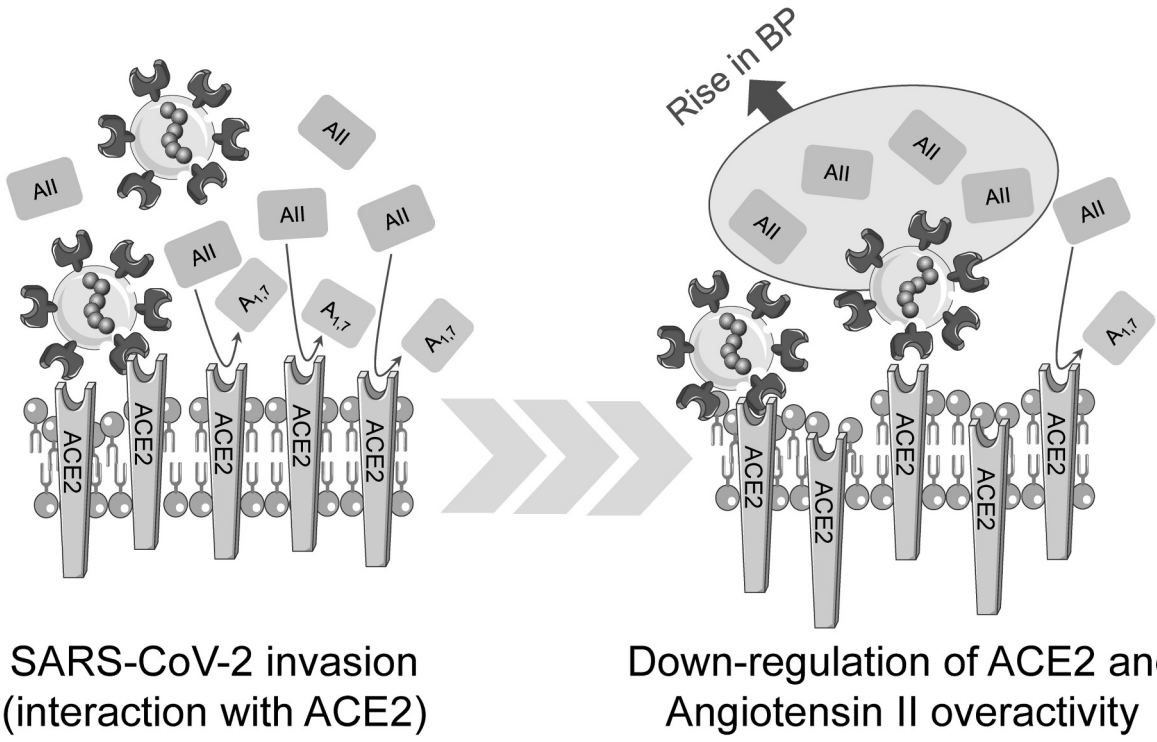

Figure 1. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) interaction with angiotensin converting enzyme 2 (ACE2) receptors. After the invasion of SARS-CoV-2, the binding to membranal ACE2 is associated with the phenomenon of downregulation and progressive loss of catalytic activities. The process leads to a marked imbalance between angiotensin II overactivity and angiotensin$_{1-7}$ deficiency, triggering rise in BP (see text for details).

diarrhea and very high BP and evolved toward placental abruption [39].

In this setting, we strongly recommend to follow the indications from current Guidelines for the treatment of hypertensive emergencies [13]. As depicted in Table 1, the type of target organ damage is the main determinant of the choice of BP-lowering drugs, target BP, and timeframe by which reduction in BP should achieved [13].

For most hypertensive emergencies, mean arterial pressure (MAP) should be reduced gradually (by approximately 10 to 20% in the first hour and by a further 5 to 15% over the next 23 hours) [40]. The target is to reduce systolic BP <180 mmHg and diastolic BP <120 mmHg for the first hour. In the next 23 hours, systolic/diastolic BP should be reduced to <160/110 mmHg [40].

However some exceptions to gradual BP lowering over the first day include the acute phase of an ischemic stroke [41], aortic dissection [42], and intracerebral hemorrhage [43].

An example of hypertensive emergency (acute cardiac injury with elevated values of systolic BP) during the acute phase of COVID-19 is depicted in Figure 2. Specifically, a 70-year old white man, hospitalized for COVID-19 pneumonia, developed after 3 days from admission a hypertensive emergency with Non-ST-Elevation Myocardial Infarction (NSTEMI). Treatments with infusion of nitroglycerin and labetalol were used to lower heart rate and BP values with consequent normalization of electrocardiographic examination. A RAAS blocker (telmisartan 80 mg once daily) was also added during hospitalization to attain BP target.

Table 1. Types of acute hypertension-mediated organ damage, target BP, time line and first line treatments (see text for details).

Hypertensive emergency	Lowering BP strategy		
	Timeline	Target BP	First line treatments
Malignant hypertension	Several hours	MAP −20% to −25%	Labetalol Nicardipine
Hypertensive encephalopathy	Immediate	MAP −20% to −25%	Labetalol Nicardipine
Acute hemorrhagic stroke	Immediate	SBP < 180 mmHg (and >130 mmHg)	Labetalol Nicardipine
Acute ischemic stroke°	1 hour	MAP −15%	Labetalol Nicardipine
Acute coronary event	Immediate	SBP < 140 mmHg	Labetalol Nitroglycerin
Acute cardiogenic pulmonary edema	Immediate	SBP < 140 mmHg	Nitroglycerin Nitroprusside
Acute aortic disease	Immediate	SBP < 120 mmHg and HR < 60 bpm	Nicardipine Mitroglycerine Nitroprusside Esmolol
Eclampsia and severe pre-eclampsia/HELLP	Immediate	SBP < 160 mmHg and DBP < 105 bpm	Labetalol Nicardipine Magnesium sulphate

DBP = diastolic blood pressure; HELLP = hemolysis, elevated liver enzymes and low platelets; MAP = mean arterial pressure; SBP = systolic blood pressure.
° = acute ischemic stroke with indication for thrombolytic therapy and SBP>185 mmHg or DBP>110 mmHg; acute ischemic stroke and SBP >220 mmHg or DBP > 120 mmHg; acute hemorrhagic stroke and SBP > 180 mmHg.

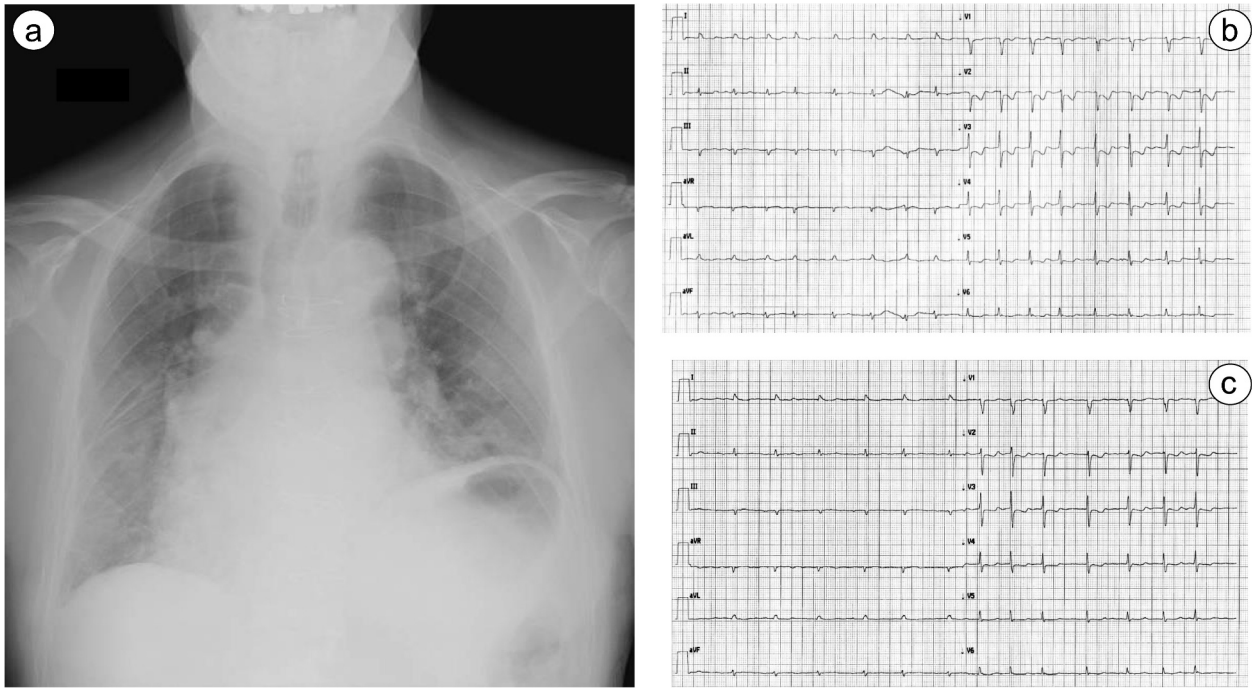

Figure 2. A 70-year old white man, with a history of coronary artery bypass graft, hospitalized for COVID-19 pneumonia. At admission, he reported fever and cough. Anteroposterior chest radiograph showed vague hazy densities and lung opacities (a). During hospitalization, he developed a hypertensive emergency (systolic blood pressure > 200 mmHg) with acute ischemic heart disease (b) and elevated high-sensitivity troponin I levels. Treatment with infusion of nitroglycerin and labetalol lowered heart rate and BP values with consequent normalization of electrocardiographic examination (c).

5. Pharmacotherapy of hypertensive urgencies

In hypertensive urgencies, BP should be reduced over a period of hours to days with slower reductions in elderly patients to avoid and increased risk of cerebral or myocardial ischemia resulting from excessively rapid reduction of BP [13].

Systolic/diastolic BP should usually be lowered to <160/<100 mmHg and MAP should not be lowered by more than 25 to 30% over the first two to four hours [13,20]. In the long-term, BP should be reduced further according to current Guidelines [44,45].

In the context of COVID-19, the management of hypertensive patients and the choice of antihypertensive medications deserve specific consideration. Several effective BP-lowering drugs (including beta-blockers, diuretics, RAAS blockers, and calcium channel blockers) have been evaluated in COVID-19 patients. Taken together, the results of clinical studies suggest that some drug classes might offer specific benefits in COVID-19 patients with hypertension.

5.1. Diuretics

Only a retrospective study in 971 hypertensive patients specifically evaluated the use of diuretics and its association with various outcomes of COVID-19 [46]. In logistic regression model adjusted by propensity score, the use of diuretics was associated with higher risk of cardiac injury (OR = 2.65, 95% CI: 1.25–5.62, p = 0.011) vs. non-users of diuretics [46]. The basic mechanisms of such adverse reaction remain substantially unclear.

5.2. Calcium-channel-blockers

Zhang and coworkers reported that a panel of nine clinically approved channel blockers (benidipine, amlodipine, cilnidipine, nicardipine, nifedipine, isradipine, nimodipine, nisoldipine, and felodipine) may inhibit the post-entry replication events of SARS-CoV-2 in vitro, among which benidipine, amlodipine, cilnidipine, and nicardipine showed more significant inhibition effect [47].

These agents, when combined with chloroquine, provided an enhancement of the anti-SARS-CoV-2 efficacy [47]. The same Authors analyzed retrospective data of hospitalized COVID-19 patients with hypertension. They revealed that therapy with amlodipine was associated with a decreased rate of all-cause mortality [47].

Similarly, a retrospective review was conducted on calcium-channel-blockers use in hospitalized COVID-19 patients to evaluate the potential effects on survival and progression of disease leading to intubation and mechanical ventilation [48]. Patients treated with a calcium-channel-blocker were more likely to survive than those not treated with a calcium-channel-blocker. Furthermore, patients treated with calcium-channel-blockers were also significantly less likely to undergo intubation and mechanical ventilation [48].

Such results were not confirmed by a clinical trial in hospitalized patients with COVID-19 and primary hypertension in which 80 patients were randomized to losartan (25 mg, twice a day) or amlodipine (5 mg per day). The main outcomes were 30-day mortality rate and length of hospital stay [49]. The length of hospital stay in losartan and amlodipine groups was 4.57 and 7.30 days, respectively (p = 0.085). The length of ICU admission in losartan and amlodipine group was 7.13

Table 2. Observational studies in COVID-19 patients treated or not treated with ACE-inhibitors or angiotensin II receptor blockers. Reproduced from ref [30]. with permission of Wolters Kluwer Health.

Study	Number of patients	Ref.	Main results
Peng et al	112	[60]	The proportion of patients treated with ACEIs/ARBs did not differ between survivors and nonsurvivors, as well as between those with or without severe illness.
Zhang et al	1,128	[58]	Treatment with ACEIs/ARBs was associated with lower risk of all-cause death (unadjusted mortality for ACEIs/ARBs group vs non-ACEIs/ARBs group: 3.7% vs 9.8%; P = 0.01). In a multivariable analysis, the risk for all-cause death was lower in the ACEIs/ARBs group vs the non-ACEIs/ARBs group (adjusted HR, 0.42 [95% CI, 0.19–0.92]; P = 0.03)
Richardson et al.	5,700	[6]	Death rate during hospitalization did not differ significantly between patients treated or not treated with ACEIs/ARBs before hospitalization (31.4% vs 26.7%).
Li et al.	1,178	[61]	Treatment with ACEIs/ARBs did not differ between patients with severe vs non severe illness (32.9% vs 30.7%; P = 0.645), as well between non survivors and survivors (27.3% vs 33.0%; P = 0.34)
Yang et al.	251	[62]	Treatment with ACEIs/ARBs was associated with a not significant lower proportion of critical illness (9.3% vs 22.9%; P = 0.061) and death (4.7% vs 13.3%; P = 0.216).
Mancia et al.	37,031	[63]	Treatment with ACEIs/ARBs was not associated with an increased risk of severe or fatal course of the disease (adjusted OR, 0.83 [0.63–1.10] for ARBs and 0.91 [0.69–1.21] for ACEIs).
Mehra et al.	8,910	[59]	Treatment with ACEIs, but not with ARBs, was associated with a significantly lower risk of in-hospital death (2.1% vs 6.1%; OR, 0.33 [0.20–0.54]).
Reynolds et al.	12,594	[64]	Treatment with ACEIs/ARBs was not associated with an increased likelihood of COVID-19 test positivity (58.1% vs 57.7%) or with the risk of severe illness (24.8% vs 24.9%).
Mehta et al.	18,472	[65]	Treatment with ACEIs/ARBs was not associated with an increased likelihood of COVID-19 test positivity (OR, 0.97 [0.81–1.15]).
Conversano et al.	191	[66]	Age, heart failure, and chronic kidney disease, but not treatment with ACEIs/ARBS, were associated with an increased risk of death.

COVID-19 = Coronavirus infectious disease-2019; CVD = cardiovascular disease; ACEIs = Angiotensin converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; HR = hazard ratio; OR = Odds Ratio.

and 7.15 days, respectively (p = 0.994). The 30-day mortality was also similar between the two arms (p = 0.241) [49].

5.3. Beta-blockers

It has been suggested that the use of beta-blockers might reduce the SARS-CoV-2 invasion through a direct effect on ACE_2 expression (downregulation) [50]. Furthermore, potential protective mechanisms of beta-adrenergic receptor blocker treatment in COVID-19 include the reduction of interleukin-6 (IL-6), pro-inflammatory cytokines, and hyper-coagulation state [50]. Nonetheless, the use of beta-blockers was not associated with a lower likelihood of a positive test among 12,594 patients tested for COVID-19 [51].

A collaborative Dutch/German study investigating 1134 patients hospitalized for Covid-19 showed that beta-blocker treatment significantly reduced the risk of major outcome [52].

Similarly, a multicenter retrospective study including 2190 patients with COVID-19 indicated that beta-blockers might be beneficial, even after adjustment for age, gender, baseline BP, and coexisting medical conditions [53].

5.4. ACE-inhibitors and angiotensin receptor blockers

RAAS-blockers may up-regulate ACE_2 [54]. Thus, an increased risk of SARS-CoV-2 infection during treatment with these agents has been hypothesized [54]. However, the position held by Scientific Societies and experts in the area is that discontinuation of RAAS-blockers is not supported by evidence and, conversely, might be unsafe [55–57].

A systematic review from our group showed that available studies do not show any signal of harm associated with ACE-inhibitors or angiotensin-receptor-blockers (ARBs) in patients with COVID-19 (Table 2) [30]. Interestingly, a study conducted in hypertensive patients hospitalized for COVID-19, mortality at 28 days was lower among patients taking ACE-inhibitors or ARBs than among patients not receiving these drugs (3.7% vs. 9.8%; p = 0.01) [58]. Moreover, Mehra and coworkers, demonstrated that treatment with ACE-inhibitors, but not with ARBs, was associated with a significantly lower risk of in-hospital death (2.1% vs. 6.1%; OR 0.33, 95% CI: 0.20 to 0.54) [59].

A meta-analysis including a total of 1808 patients with hypertension and COVID-19 recruited in 6 studies showed that the administration of ACE-inhibitors or ARBs had positive effect on reducing D-dimer and the number of people with fever [67].

More recently, a systematic review and meta-analysis of 52 studies including 101,949 patients with COVID-19 evaluated the outcome among who did and did not receive ACE-inhibitors or ARBs [68]. After multivariable adjustment, the Authors demonstrated a significantly decreased risk of mortality and severe adverse events among patients who received ACE-inhibitors or ARBs compared with patients who did not [68]. Of note, subgroup analysis showed that patients with hypertension had a significant decrease in the risk of death and severe adverse outcomes among patients receiving ACE-inhibitors or ARBs (in both unadjusted and adjusted models) [68].

6. Conclusion

Despite the association of severe COVID-19 with hypertension and the potential importance of hypertensive urgencies and emergencies [69] in this setting, the burden of this condition remains undefined. Recent data from observational studies clearly showed that an elevated BP and a high BP variability during hospitalization for COVID-19 are independently associated with a worse outcome [5,6]. Thus, the use of antihypertensive drugs and their potential impact on outcome in

COVID-19 patients remain a key point. Despite conflicting views in the literature, hypertensive emergencies should be treated according to current Guidelines in the setting of COVID-19 [13]. However, the peculiar mechanisms potentially involved in the pathogenesis of BP elevation in patients with COVID-19 may support the preferential use of RAAS-blockers, beta-blockers, and calcium channel blockers for the treatment of elevated BP during the acute phase of the disease.

7. Expert opinion

Observational studies investigating characteristics of hospitalized patients for SARS-CoV-2 infection have found that the presence of hypertension increases the risk of severe clinical outcomes [1,2]. Acute elevations in BP and uncontrolled in-hospital BP are significant predictors of organ damage and worse outcome in these patients [9]. In particular, hypertension is associated with a more frequent admission to intensive care units, worsening heart failure and mortality in patients hospitalized for COVID-19 [9,10].

Unfortunately, the real burden of elevated BP during the acute phase of COVID-19 remains undefined. Being the evidence still scanty, results of clinical studies focused on the role of different BP-lowering drugs need to be interpreted with caution.

According to current Guidelines [13], only the COVID-19 patients with hypertensive emergencies require a prompt reduction in their markedly elevated BP. Thus, hypertensive emergencies should be treated with intravenous drug administration according to specific features and treatment goals [13]. Conversely, hypertensive urgencies usually require oral drug administration. BP-lowering treatment should be individualized to each patient based on the type and extent of end-organ damage and degree of BP elevation [13].

Some mechanistic studies suggest that RAAS blockers, calcium channel blockers and beta-blockers might be preferred as antihypertensive drugs in patients with COVID-19. Indeed, these drugs have been associated with inhibition of invasion [50] and post-entry replication [47] of SARS-CoV-2, reduction of the cytokines storm [50] and enhancement of the RAAS protective pathway during the infection [70–72]. However, according to available clinical data, there is no final evidence that these drugs are associated with a better outcome.

In particular, some authors theorized that the up-regulation of ACE_2 receptors caused by ACE-inhibitors and ARBs might favor the viral invasion [54,73]. However, several large studies conducted so far did not show any signal of harm associated with ACE-inhibitors or ARBs in patients with COVID-19 [30].

There is growing evidence that the blunted ACE_2 activity resulting from downregulation of these receptors after viral entry and the resulting imbalance between angiotensin II and $angiotensin_{1-7}$ may play an important role in conditioning inflammatory, thromboembolic and hemodynamic processes in patients with COVID-19 [30,31,36]. Following this line of evidence, by enhancing ACE2 expression [74–77] and limiting the effects of unopposed angiotensin II on the heart, lungs, and vasculature, RAAS blockers could theoretically play a protective role in patients with COVID-19 infection [30,31,70,71].

As stated above, calcium-channel-blockers and beta-blockers might have a role in COVID-19 patients [53]. In a multicenter study conducted in patients hospitalized for laboratory-confirmed COVID-19, the clinical outcome of patients with COVID-19 was better in patients treated with ARBs, beta-blockers, and calcium-channel blockers [53]. Conversely, diuretics might be particularly detrimental in patients treated with mechanical ventilation at increased positive end expiratory pressure [50,78]. Diuretics could be also associated with a higher risk of cardiac injury [46].

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Declaration of interest

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