



# Angiotensin-converting enzyme 2: a double-edged sword in COVID-19 patients with an increased risk of heart failure

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## Abstract

The coronavirus disease (COVID-19) pandemic is a global health priority. Given that cardiovascular diseases (CVD) are the leading cause of morbidity around the world and that several trials have reported severe cardiovascular damage in patients infected with SARS-CoV-2, a substantial number of COVID-19 patients with underlying cardiovascular diseases need to continue their medications in order to improve myocardial contractility and to prevent the onset of major adverse cardiovascular events (MACEs), including heart failure. Some of the current life-saving medications may actually simultaneously expose patients to a higher risk of severe COVID-19. Angiotensin-converting enzyme 2 (ACE2), a key counter regulator of the renin-angiotensin system (RAS), is the main entry gate of SARS-CoV-2 into human host cells and an established drug target to prevent heart failure. In fact, ACE inhibitors, angiotensin II receptor blockers, and mineralocorticoid antagonists may augment ACE2 levels to protect organs from angiotensin II overload. Elevated ACE2 expression on the host cell surface might facilitate viral entrance, at the same time sudden nonadherence to these medications triggers MACEs. Hence, safety issues in the use of RAS inhibitors in COVID-19 patients with cardiac dysfunction remain an unsolved dilemma and need paramount attention. Although ACE2 generally plays an adaptive role in both healthy subjects and patients with systolic and/or diastolic dysfunction, we conducted a literature appraisal on its maladaptive role. Understanding the exact role of ACE2 in COVID-19 patients at risk of heart failure is needed to safely manage RAS inhibitors in frail and non-frail critically ill patients.

**Keywords** ACE2 · Angiotensin II · RAS inhibitors · COVID-19 · Heart failure · SARS-CoV-2

## Introduction

### The outbreak of COVID-19: an unexpected Pandora's box

A few months after the emergence of the coronavirus disease (COVID-19) in China and during the outbreak peak in Italy [1], on 11 March 2020, the World Health Organization (WHO) claimed that the new viral disease was considered a pandemic. However, the global rate of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission was and is still significant in several countries including Spain, Brazil and the USA [2]. Easy human-to-human transmission of SARS-CoV-2 compared with previous coronaviruses (SARS-CoV, MERS-CoV) may be due to the fact that the infection is spread by unpredictable asymptomatic carriers [3]. In addition, the binding affinity of SARS-CoV-2 to its

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receptor on the host cell surface is 10–20-fold higher than previous  $\beta$ -coronaviruses [4].

Besides epithelial cells resident in the nasal mucosa, lower airways, lung parenchyma, conjunctiva, cornea, and enteric tube [5–7], SARS-CoV-2 can also infect arterial vascular cells [8], cardiomyocytes [8], and neural cells [9].

COVID-19 is thus a specific disease with different phenotypes from the well-known adult respiratory distress syndrome (ARDS), although acute respiratory failure and severe hypoxemia are easily identifiable in infected non-intubated and intubated patients [10]. It is conceivable that heart function and vessel patency are simultaneously impaired in patients with COVID-19 pneumonia, and the magnitude of cardiovascular damage may depend on comorbidities and co-mediations.

### Cardiovascular system vulnerability and COVID-19: an emerging relationship

Cardiovascular diseases and COVID-19 share common symptoms such as dyspnea and fatigue [11, 12], which make differential diagnosis difficult. Also, severe hypoxemia, as the ultimate pathophysiological cause of death, is detected both in heart failure and COVID-19 patients [11]. COVID-19-related hypoxemia may also possibly induce atrial fibrillation as the most common arrhythmia among hospitalized individuals [13]. Atrial fibrillation is life-threatening if it becomes refractory and runs into a detrimental cycle, especially before respiratory function returns to a normal status. This condition could deteriorate particularly in the case of hypercoagulability due to an exaggerated systemic inflammatory storm in response to viral infection [14, 15]. In fact, increasing evidence suggests that the onset of atrial fibrillation may be secondary to micro-thrombotic coronary events [16].

As expected, a cytokine storm might lead to erosion or rupture of undetectable atherosclerotic plaques [1] also in COVID-19 patients with coronary artery disease. In this situation, the patient will be exposed to a higher risk of acute myocardial infarction [15, 17] and acute heart failure, possibly due to the sudden formation of thrombus following plaque rupture or the spread of plaque emboli into the coronary tree. Moreover, an uncontrolled host immune response to SARS-CoV-2 infection may impair diastolic function along with the onset of heart failure with preserved ejection fraction. Therefore, the cytokine storm with the key involvement of interleukin-6 has a significant impact on the heart systolic and/or diastolic function [15, 18].

The existence of cardiovascular disorders as a comorbidity has been reported in many patients with COVID-19 [1, 15]. Among the confirmed cases of COVID-19, hypertension, myocarditis, and heart failure have been found [15] to be the most common comorbidities in hospitalized patients [12, 19]. Such patients are thus likely at a higher risk of a severe type of

COVID-19 and death compared with those without these comorbidities [15]. This clinical evidence suggests that chronic CVD makes individuals with COVID-19 more susceptible to poor outcomes.

However, there are also many reports suggesting COVID-19-induced cardiovascular injuries. In fact, clinical investigators from Wuhan [12, 20] have reported that some patients with COVID-19 showed severe heart damage. Although there are currently contrasting findings [19, 21], acute cardiac injury in terms of cardiac troponin I elevation, abnormal findings in electrocardiography and echocardiography, and arrhythmia with rapid heart rates have been diagnosed after infection with SARS-CoV-2 and could act as a risk factor of mortality. High levels of cardiac troponin I, C-reactive protein, and NT-proBNP, conventional biomarkers of acute myocardial injury, have been measured in hospitalized COVID-19 patients without concomitant CVD [1, 21, 22]. Acute myopericarditis with systolic dysfunction and ST-elevation myocardial infarction and upregulated cardiac markers have been reported anecdotally [1], and confirmatory studies are still required. In a cohort study from Wuhan, acute myocardial injury, shock, and arrhythmia were reported in about 10–20% of the studied population [19]. Cardiac dysfunction may be the result of viral infection, hypoxemia, and deterioration of an underlying undiagnosed CVD [23]. Irrespectively of a chronic CVD background or viral infection that deteriorated the cardiovascular function, these patients were at greater risk of severe heart failure and death [12, 20].

### RAS system

The renin-angiotensin system (RAS system) is a peptidergic pathway for the regulation of myocardial homeostasis [24] and vascular-related functions including blood pressure control, blood volume control, and natriuresis [25]. In the RAS system under normal conditions, renin converts angiotensinogen into angiotensin I (Ang I). The metabolism of Ang I into Ang II is performed by the angiotensin-converting enzyme (ACE), a peptidyl dipeptidase that removes C-terminal dipeptides [26]. Ang II is a biologically active hormone. It triggers several signaling pathways, which chronically lead to myocardial hypertrophy and increased fibrosis [27, 28] toward heart failure [29]. Ang II is also the molecule responsible for endothelial dysfunction, hypertension, vascular remodeling, and atherosclerosis [30, 31]. Ang II type I (AT1) receptors are those through which the proinflammatory effects of Ang II are promoted [32]. Adverse endothelial response to Ang II requires high levels of the endothelial von Willebrand factor [33].

On the other hand, bradykinin also plays a key role in cardiovascular function. Bradykinin has a vasodilation effect, increases vascular permeability, and lowers blood pressure

[34, 35]. The action of bradykinin is exerted through binding to its receptors, B1 and B2 [36]. The deleterious effects of Ang II are counterbalanced by bradykinin in normal conditions [35].

Current cardiovascular medications have long been recommended for the downregulation of Ang II and to stop the cascade of MACEs. These include ACE inhibitors, angiotensin II receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs) [37]. Translational studies have also suggested novel ways to dampen Ang II effects including gene-based therapeutic approaches [33, 38]. If no action is taken, ACE2 degrades Ang II and generates Ang 1–7 [39]. This Ang 1–7 with anti-inflammatory, antioxidant, vasodilatory, and natriuretic activities protects the cardiovascular system [39–41]. Although ACE2 exerts protective effects [39], a pilot study failed to demonstrate an improvement in the clinical outcome of patients with acute respiratory distress syndrome (ARDS) after administration of a recombinant form of human ACE2 [42]. Accordingly, continuing treatment of CVD by ACE inhibitors, ARBs, and MRAs is of the utmost importance [43], including in patients infected by SARS-CoV-2 [2].

Bradykinin activity is largely regulated by ACE, which degrades it into an inactive form [44–46]. ACE has a much higher affinity to bradykinin than Ang I [47]. ACE inhibitors prevent the conversion of Ang I to Ang II. ACE inhibitors are also more effective in the prevention of bradykinin degradation compared with Ang II production. Consequently, use of ACE inhibitors and upcoming bradykinin signaling trigger a cascade of events such as improving vascular tone and structure, promoting thrombolysis, and enhancing vascular protection against activated platelets and leukocytes [48–51]. It is plausible that a fundamental element in the cardioprotection sequels of ACE inhibitors may contribute to bradykinin overactivation rather than a lack of Ang II [46].

ARBs inhibit the binding of Ang II to its mediator receptor (AT1). Circulating Ang II is thus trapped by ACE2 and Ang 1–7 is formed [52]. In an example of ARB therapy, a fivefold greater expression of ACE2 and increased Ang 1–7 was seen in rat models of hypertension treated with olmesartan [53, 54]. Given that the mechanism of RAS downregulation in ARBs is different from ACE inhibitors, bradykinin is not affected by ARBs [55]. This may explain the differences in blood pressure reduction and cardiovascular protection between ACE inhibitors and ARBs [46].

Regarding MRAs, the formation of Ang II is decreased by suppressing ACE activity; on the other hand, membrane ACE2 expression is promoted, and this promotion results in reduced oxidative stress and cardiovascular support [56]. In addition, the use of MRAs is an independent predictor of higher plasma ACE2 concentrations in male rather than female heart failure patients [57] (Fig. 1).

Such findings demonstrate the potential of these drugs in the downregulation of the RAS system [58]. RAS signaling is balanced by Ang II formation due to ACE activity and its binding to AT1 on the one hand and by cleavage of Ang II by ACE2 on the other [1]. ACE inhibition with or without losartan consumption has been shown to increase plasma Ang 1–7 and reduced plasma Ang II [59]. A study on the correlation between ACE and ACE2 showed that ACE2 mRNA, but not ACE2 activity, is altered by the inhibition of Ang II synthesis [59]. Conversely in another study, Ang II reduced ACE2 mRNA and ACE2 activity in cardiac myocytes [60].

In seminal studies, SARS-CoV [61] and SARS-CoV-2 [62] were reported to deregulate the RAS system and induce acute lung injury through ACE2 downregulation. However, this type of lung failure could be overwhelmed by the inhibition of AT1 receptors [63]. In fact, ACE and Ang II concentrations were reported to be high in the serum of patients with acute respiratory distress syndrome and sepsis [64, 65]. A correlation was also shown between plasma renin and Ang II with the degree of organ failure and microvascular dysfunction [64]. ACE2 therapy blunted the RAS system and was accompanied by an improvement in cardiac output, suppression of plasma cytokines, reduction in nitrotyrosine levels, refined peripheral vascular resistance, and better renal perfusion in patients at risk of right ventricular failure due to pulmonary hypertension [66]. Intriguingly, it did not significantly improve the physiological and clinical manifestations of acute respiratory distress syndrome [42]. Clinical trials on ameliorating pulmonary arterial hypertension with recombinant ACE2 are underway (NCT101884051) [66].

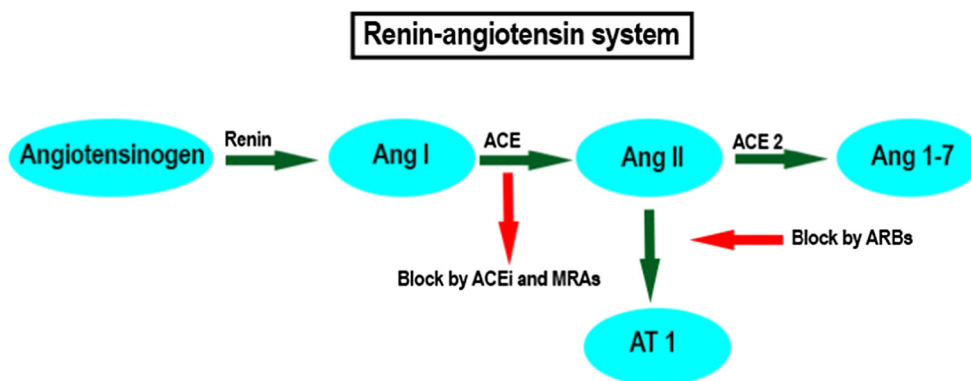
## ACE2

ACE2 is predominantly found in several organs including the bronchus, lung parenchyma, heart, endothelium, kidneys, duodenum, and small intestine. It is a type I integral membrane glycoprotein [67, 68]. There are both membrane-bound and soluble forms of ACE2 in the body [61, 69]. Although a 42% homology was shown in residues between ACE and ACE2, ACE inhibitors had no antagonistic activity on ACE2 [70, 71]. The prominent role of ACE2 in regulating cardiovascular function has been established in genetic deletion studies [72]. In an ACE2 knock out mouse model, the infusion of Ang II and recombinant ACE2 attenuated Ang II-related myocardial hypertrophy and fibrosis as well as improving diastolic function [73].

To date, the genomic sequence (up to 76%), the entry receptor, and mechanism of entry to the host cell have been found to be similar between SARS-CoV and SARS-CoV-2. It is likely that the deployment of host machinery, virus propagation, and further viral infection will be common between the two strains [74]. However, it has not been clarified

**Fig. 1** RAS system and targets of conventional RAS inhibitors.

Ang I, angiotensin I; ACE, angiotensin-converting enzyme; Ang II, angiotensin II; Ang 1–7, angiotensin 1–7; ACEi, ACE inhibitors; MRAs, mineralocorticoid receptor agonists; ARBs, angiotensin II receptor blockers; AT1, Ang II type I receptors



whether they have a similar biological activity [69]. Given that both  $\square$ -coronaviruses (SARS-CoV-2 and SARS-CoV) use ACE2 for invading the host cells, we cannot exclude that their spectrum of target cells are also similar [69]. SARS-CoV-2 infectivity, pathogenesis, and host range are mainly determined by its mechanism of receptor recognition [75, 76]. Shedding light into the virus-receptor interplay is also beneficial for development of vaccines and neutralizing monoclonal antibodies as an efficient remedy [77].

Virus binding is mediated by the activated SARS-CoV-2 surface unit (S1) of its spike protein (S) [61, 69]. In fact, a serine protease (TMPRSS2) cleaves the S protein in an acid-dependent manner at the S1/S2 sites, preparing the environment for S2 to make a fusion between viral and cellular membranes. Eventually the virus reaches the cytosol of the host cell [69]. The receptor binding domain (RBD), which contains a core and a receptor binding motif (RBM), of the spike protein is the main player in the interaction with ACE2 [78, 79].

In one very interesting study, the structural basis of receptor recognition by SARS-CoV-2 was demonstrated via the crystallization technique [77]. The findings showed that a larger binding interface and more connection surfaces are present in SARS-CoV-2 than SARS-CoV. Conformation of the loops in the ACE2-binding ridge is notably different between these two strains in the way that more contacts are formed by SARS-CoV-2 with ACE2, which in turn facilitates receptor binding. Specific structural features in the ACE2-binding ridge at RBM of the SARS-CoV-2 as well as hot spot-stabilizing residues at the RBM-ACE2 interface increase the binding affinity. It also seems that these changes augment its animal to human transmission. Overall, it was concluded that SARS-CoV-2 has been equipped with strategies to better recognize ACE2 and make a stronger connection [77].

Binding of the virus to the ACE2 changes the activity of the tumor necrosis factor  $\alpha$ -converting enzyme and promotes ACE2 ectodomain cleavage [2, 74]. Ectodomain release triggers one of the important manifestations of COVID-19, called the cytokine storm. This storm involves an array of biochemical cytokines including interleukin 2, interleukin 7, interleukin 10, granulocyte colony stimulating factor, interferon

gamma-induced protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1- $\alpha$ , and tumor necrosis factor- $\alpha$  [12]. The downregulation of ACE2 is one of the consequences of this release, which has been observed in acute lung injury [80] and post myocardial infarction [81]. This injury may be due to an excess of Ang II. Interestingly, the activity of plasma ACE2 correlated with a reduced left ventricular ejection fraction and adverse clinical outcomes [82].

If membrane-bound ACE2 on the host cell surface decreases due to ectodomain release following SARS-CoV-2 entry, the concentration of circulating ACE2 will be increased without interruption in viral propagation. In this case, the membrane-bound ACE2 is predicted to downregulate with its downstream signaling pathways, which provokes systemic inflammation and injures a multitude of organs. The use of RAS downregulators including ACE inhibitors, ARBs, and MRAs would thus be beneficial by over expressing the ACE2 and reducing the endogenous Ang II. This would lead to compensatory anti-inflammatory, antifibrotic, and anti-thrombotic consequences [2, 83].

The origin of the association between ACE2, membrane-bound or circulating, and the severity of tissue damage ultimately lies in the extent of upregulation of systemic inflammatory response [2, 83]. Soluble ACE2 also has the potential to regulate systemic Ang II. Recombinant ACE2 converts endogenous Ang II into Ang 1–7 [42, 66]. In a mouse model of acute lung injury by lipopolysaccharide, inflammation and lung injury were observed following ACE2 downregulation. The infusion of transfected cells with ACE2 improved lung function. Lung injury also improved when these mice were treated with ACE inhibitors and ARBs [63].

Ectodomain release is another challenge regarding the detection and eradication of SARS-CoV-2 by the immune cells. When this virus invades the host cell and ectodomain is released, the amount of ACE2 at the surface of the host cell decreases. Following transcription of the spike protein, S1 fuses directly to the membrane of neighboring cells through the formation of multinucleated syncytia and culminates the propagation of SARS-CoV-2.

As the virus hides in these syncytia, the neutralizing antibodies are not able to detect them [84].

ACE2 appears to play a paradoxical role in COVID-19 patients with CVD (Fig. 2). It protects the cardiovascular system from harm due to hypertension, myocardial fibrosis, myocardial hypertrophy, arrhythmia, atherosclerosis, and sodium retention. In contrast, ACE2 is highly expressed upon the use of RAS system inhibitors which unfortunately might provide more entry gates (ACE2) for SARS-CoV-2 [85] following S1 cleavage. As ACE inhibitors, ARBs, and MRAs are administered for hypertension, heart failure, and ischemic heart disease, close monitoring of such patients is advisable when they are infected with COVID-19. Overall, due to the anti-inflammatory, antifibrotic, and antithrombotic consequences of potentially upregulated-ACE2, this protein could be targeted as a therapy by contributing to the improvement in clinical outcomes of COVID-19 patients [86]. To date, there is no evidence supporting the discontinuation of their chronic administration [87].

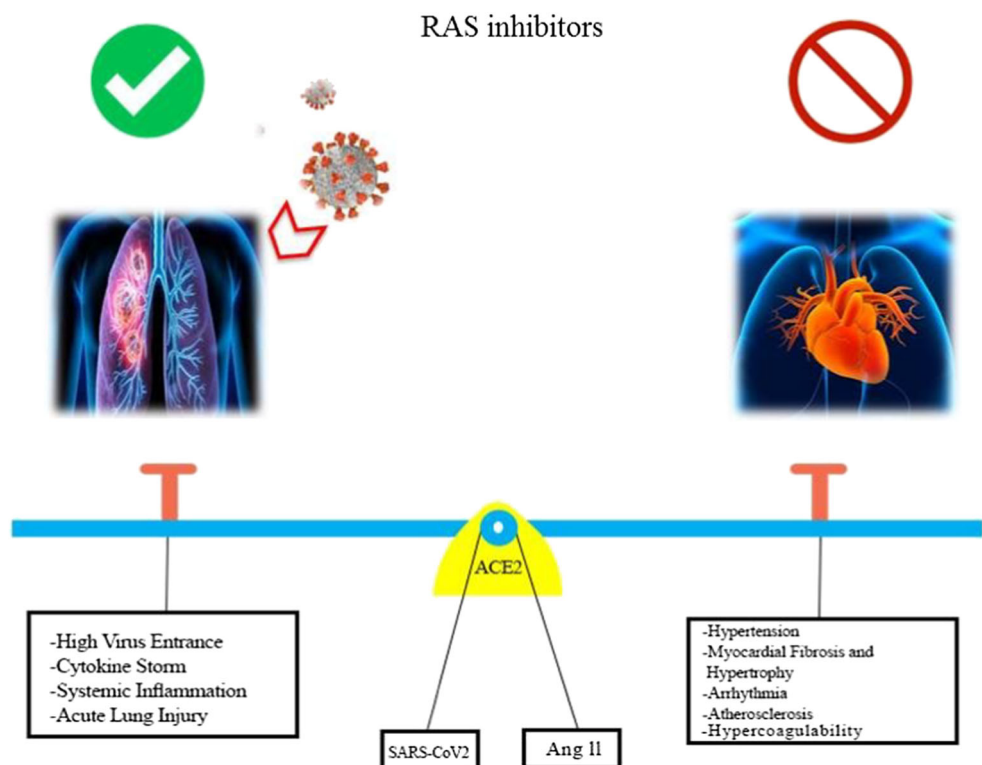
There are several clinical trials regarding the effect of RAS inhibitors in COVID-19 patients (Table 1). NCT04318301 and NCT04318418 are the ongoing clinical trials on the effects of RAS inhibition and ACE2 overexpression in patients infected with SARS-CoV-2. In line with these, the effects of losartan (an ARB) in hospitalized and ambulatory COVID-19 patients are being investigated in other trials (NCT04312009, NCT04311177). Perhaps the most interesting studies on

COVID-19 individuals with comorbid CVD are those that examine the continuation or withdrawal of RAS inhibitors (NCT04330300, NCT04329195). Also, NCT04287686 is an ongoing trial on recombinant ACE2 therapy in these patients. To date, the role of ACE2 in improving or intensifying COVID-19 patients with CVD remains a mystery.

Of utmost importance in COVID-19 patients with underlying CVD is whether or not the use of ACE inhibitors, ARBs, or MRAs should be continued as these agents increase the expression of ACE2 and facilitate viral entry and infection [53, 56, 81, 88, 89]. Several cardiology societies such as the American College of Cardiology, the American Heart Association, the Heart Failure Society of America [90], the European Society of Cardiology [91], and the Italian Society of Cardiovascular Researchers [1] have issued statements emphasizing the continuation of RAS antagonists in CVD patients with COVID-19 due to the lack of data on increased susceptibility to COVID-19 by ACE2 over activation.

Any discussion on the management of COVID-19 patients with underlying CVD must therefore address the issue of ACE2. If possible, it is better to identify the most effective RAS system inhibitors based on an evaluation of the related risks and benefits in COVID-19 patients. The role of ACE2 in simultaneous COVID-19 infection and cardiovascular disorders urgently needs more in-depth investigations, which could lead to more effective treatments for such patients.

**Fig. 2** Seesaw role of ACE2 in using (left) or misusing (right) RAS inhibitors in COVID-19 patients, which in both cases is accompanied by adverse consequences especially on the pulmonary and cardiovascular systems, respectively. ACE2, angiotensin-converting enzyme II; RAS, renin-angiotensin system; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2



**Table 1** Clinical trials investigating the association of RAS inhibitors with health outcomes in COVID-19 patients. *RAS*, renin-angiotensin system; *ACEi*, angiotensin-converting enzyme inhibitors; *ARBs*, angiotensin II receptor blockers; *DRI*, direct renin inhibitor

Identifier	Status	Model	Aim	Population size
NCT04318418	Not yet recruiting	Observational Case-control	Association of ACEi or ARBs to severe COVID-19	5000
NCT04364893	Recruiting	Interventional	Suspension of ACEi or ARB on the length of hospital stay and mortality	500
NCT04374695	Not yet recruiting	Observational Case-control	Relationship of ACEi and ARBs with COVID-19 infection and severity	700
NCT04357535	Terminated	Observational	Association of ACEi or ARBs with prognosis of patients with COVID-19	17
NCT04331574	Recruiting	Observational	Effects of chronic intake of RAS inhibitors on the prevalence and severity of the clinical manifestation of COVID-19	2000
NCT04338009	Enrolling by invitation	Interventional	Clinical impact of continuation vs. discontinuation of ACEi and ARBs on outcomes in patients hospitalized with COVID-19	152
NCT04330300	Recruiting	Interventional	Switch to an alternative blood pressure medication or continue with the ACEi/ARB in hypertensive patients	2414
NCT04345406	Not yet recruiting	Interventional	Investigation of ACEi in treatment of COVID-19	60
NCT04353596	Recruiting	Interventional Case-control	The association of stopping chronic ACEi/ARB therapy in SARS-CoV-2-infected patients with outcomes	208
NCT04374110	Recruiting	Observational	Monitoring of drug safety and the occurrence of complications during hospitalization in patients with cardiovascular diseases with COVID-19	1000
NCT04371289	Not yet recruiting	Observational	Investigation of cardiovascular risk in COVID-19 patients during acute disease and at short-term follow-up	5500
NCT04351581	Recruiting	Interventional	Investigate whether to continue or discontinue treatment with ACEi or ARBs in hospitalized patients with COVID-19	215
NCT04345406	Not yet recruiting	Interventional	The effect of ACEi in the treatment of COVID-19	60
NCT04329195	Recruiting	Interventional	Determining whether RAS blockers should be discontinued or not in patients with COVID-19	554
NCT04338009	Enrolling by invitation	Interventional	Assessing the clinical impact of continuation vs. discontinuation of ACEi and ARBs on the outcomes in patients hospitalized with COVID-19	152
NCT04367883	Recruiting	Observational	Evaluation of influenza vaccination and treatment with ACEi and RAIII in the evolution of SARS-COVID-19 infection	2574
NCT04364984	Recruiting	Observational	Monitoring hypertensive patients receiving ARBs or DRI or ACEi with COVID-19 infection	10
NCT04353596	Recruiting	Interventional	Stopping ACEi in patients with COVID-19 to improve outcomes	208
NCT04318418	Not yet recruiting	Observational Case-control	The effect of treating COVID-19 patients with ARB or ACEi compared with treatment without these medications	5000
NCT04356417	Not yet recruiting	Observational	The effect of synthetic antimalarial and anti-hypertensive drugs on preventing serious COVID-19 infections	6,000,000
NCT04394117	Not yet recruiting	Interventional	Effectiveness of ARBs on improving the outcomes of COVID-19 patients	605
NCT04340557	Recruiting	Interventional	Investigation of ARBs on progression to acute respiratory distress syndrome with SARS-CoV-2 infection	100
NCT04337190	Recruiting	Observational	Determining ACE2 level and activity in patients with SARS-CoV-2 infection admitted to ICU	100
NCT04335786	Recruiting	Interventional	Investigation of valsartan for prevention of acute respiratory distress syndrome in hospitalized patients with COVID-19	651
NCT04337008	Recruiting	Interventional	Effectiveness of RAS blocker treatments in patients with COVID-19	50
NCT04287686	Withdrawn	Interventional	Recombinant human angiotensin-converting enzyme 2 as a treatment for patients with COVID-19	0

## Conclusions

The extent of ACE2 expression on the cell surface would seem to play a regulatory role in managing COVID-19 patients with a CVD background or heart failure. As the entry of SARS-CoV-2 into the host cells mainly requires ACE2, the

use of inhibitors, which results in the overexpression of ACE2, may increase the susceptibility to a higher virus load. This additional load can then lead to a dose-dependent inflammatory response and possibly viral-induced cardiovascular damage following impairment of cross-talk between resident cardiac cells [92].

On the other hand, the discontinuation of RAS system inhibitors strongly promotes cardiovascular dysfunction due to excess Ang II, which in turn has an unfavorable impact on the cardiovascular system especially in critically ill coronavirus patients whose gas exchange between alveolar spaces and capillaries is seriously impaired and who need extra backup from the heart apparatus [93]. Unraveling how to halt viral binding to hot spots without impairing ACE2 activity could provide new avenues for protection against both Ang II and SARS-CoV-2-induced cardiovascular injury.

**Code availability** Not applicable.

**Authors' contributions** I.R.-J. and V.L. designed and managed the project. The other authors contributed equally. All authors discussed and commented on the manuscript, provided critical feedback, and helped shape the final version of the manuscript.

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**Data availability** Not applicable.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethics approval** Not applicable.

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