




## CKJ REVIEW

# Renin–angiotensin system blockers during the COVID-19 pandemic: an update for patients with hypertension and chronic kidney disease

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## ABSTRACT

Hypertension and chronic kidney disease (CKD) are among the most common comorbidities associated with coronavirus disease 2019 (COVID-19) severity and mortality risk. Renin–angiotensin system (RAS) blockers are cornerstones in the treatment of both hypertension and proteinuric CKD. In the early months of the COVID-19 pandemic, a hypothesis emerged suggesting that the use of RAS blockers may increase susceptibility for COVID-19 infection and disease severity in these populations. This hypothesis was based on the fact that angiotensin-converting enzyme 2 (ACE2), a counter regulatory component of the RAS, acts as the receptor for severe acute respiratory syndrome coronavirus 2 cell entry. Extrapolations from preliminary animal studies led to speculation that upregulation of ACE2 by RAS blockers may increase the risk of COVID-19-related adverse outcomes. However, these hypotheses were not supported by emerging evidence from observational and randomized clinical trials in humans, suggesting no such association. Herein we describe the physiological role of ACE2 as part of the RAS, discuss its central role in COVID-19 infection and present original and updated evidence from human studies on the association between RAS blockade and COVID-19 infection or related outcomes, with a particular focus on hypertension and CKD.

**Keywords:** angiotensin-converting enzyme 2, chronic kidney disease, COVID-19, hypertension, renin–angiotensin system

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2); it began in China at the end of 2019 and developed into a global pandemic in 2020 [1]. Since

then, COVID-19 has been established as a major issue of public health, infecting >200 million individuals and accounting for >4.5 million deaths worldwide, with numbers continuously rising [2]. The risk of severe COVID-19 disease and associated death increases with older age, male sex and the coexistence of various comorbid conditions, including

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hypertension, diabetes mellitus, cardiovascular disease and, above all, chronic kidney disease (CKD) [3].

Initial reports from China, Italy and the USA suggested that hypertension was the most frequent comorbidity among hospitalized COVID-19 patients [4, 5] as well as among severely ill COVID-19 individuals admitted to intensive care units (ICUs) [6]. As a consequence, early in the pandemic, a large number of observational studies associated COVID-19-related deaths with prevalent hypertension [4, 5, 7]. However, the role of hypertension as a risk factor for the adverse effects of COVID-19 probably needs to be better defined, as there are a number of factors that could confound a possible relationship between hypertension and severe COVID-19, including age and common comorbidities, i.e. cardiovascular disease, diabetes mellitus and CKD [8]. The high prevalence of hypertension overall, and particularly in the elderly, could explain a large part of the association between hypertension and COVID-19 severity, as older patients seem to be at a higher risk for COVID-19-related complications [9]. In a seminal cross-sectional study designed to delineate some of these issues, Iaccarino *et al.* [3] showed that age and comorbidities, such as coronary heart disease, heart failure, CKD and chronic obstructive pulmonary disease, were the most important determinants of death among COVID-19 patients, while hypertension and antihypertensive therapy *per se* were not associated with adverse outcomes in these individuals. As such, the association of the presence of hypertension with COVID-19 severity and associated death needs further examination.

CKD was not listed in initial reports as a risk factor for severe COVID-19; however, within a few months, underlying CKD evolved as one of the most common comorbidities conveying an increased risk of SARS-CoV-2 infection and COVID-19-associated mortality [10, 11]. A study from the USA including 5279 COVID-19 patients showed that underlying CKD was associated with hospital admission and disease severity [12]. In another study from the UK, which included data from 17 million electronic health records, CKD was also identified as a risk factor for COVID-19-related mortality [13]. Furthermore, the results from the European Renal Association (ERA) Registry [14] including 4298 patients receiving kidney replacement therapy showed that both dialysis patients ( $n=3285$ ) and kidney transplant recipients (KTRs;  $n=1013$ ) had a significantly higher 28-day mortality risk than propensity score-matched historical controls. Interestingly, the mortality risk in both end-stage kidney disease (ESKD) groups was higher in patients >75 years of age, while the presence of several comorbidities also affected outcomes, similar to observations in non-CKD populations [3].

With the onset of the pandemic, some authors suggested that patients with hypertension or cardiovascular disease who were on renin-angiotensin system (RAS) blockers might be at higher risk of severe COVID-19 [15], based on previous evidence that SARS-CoV and SARS-CoV-2 bind to their target cells through angiotensin-converting enzyme 2 (ACE2) located in the cell membrane [16]. As RAS blockers are cornerstones in the treatment of several conditions, including hypertension, heart failure and proteinuric CKD, non-evidence-based, widespread and uncontrolled discontinuation of these drugs would have enormous consequences for cardiovascular and kidney health worldwide [17–19]. A huge number of publications related to this topic appeared and continue to be published. Thus the present work is an update on the role of ACE2 within RAS physiology, the crucial role of ACE2 in COVID-19 infection and the evidence from observational and human studies on the association of RAS blockade and COVID-19 infection and associated complications in patients with hypertension and CKD.

## ROLE OF ACE2 IN THE RAS

The RAS is the most important endocrine system, participating in the regulation of numerous physiological systems. Among others, it plays a key role in the control of blood pressure (BP) by regulating vascular tone and fluid and electrolyte balance [20]. The main components of the RAS involved in BP regulation are angiotensin II (Ang II) and angiotensin 1-7 (Ang 1-7) [21]. Ang II is a potent vasoconstricting agent that increases renal sodium and water reabsorption through direct action in the proximal tubules and indirectly through an increase of aldosterone secretion in the distal tubules [22]. In addition to these actions, Ang II also has significant oxidative, inflammatory and fibrotic actions that are involved in cardiorenal remodelling [22]. The above main effects of Ang II take place through binding to the angiotensin II type 1 receptor (AT1R) and subsequent activation of several signal transduction pathways [22]. On the other hand, the Ang 1-7/ACE2 cascade, known as the non-classic RAS, acts as an endogenous counter regulatory arm to the Ang II/ACE axis. Ang 1-7 activates the Mas receptor (MasR) to promote vasodilation and exert antioxidant, anti-inflammatory and antifibrotic functions [21]. Components of both RAS pathways are co-expressed in the majority of human tissues, having paracrine and autocrine functions independent of their systemic effects; the balance between these axes determines whether tissue injury will occur in response to different stimuli [21].

ACE is a metalloprotease converting the decapeptide Ang I into octapeptide Ang II, the main mediator of the classic RAS [23]. ACE2 is the pivotal enzyme of the non-classic RAS; it is a transmembrane monocarboxypeptidase with 806 amino acids, which shares ~40% structural identity and 60% sequence similarity with ACE [24]. ACE2 is highly expressed in the heart (endothelial cells, cardiomyocytes and fibroblasts), blood vessels (endothelial and smooth muscle cells), lungs (bronchial epithelial cells, type 2 pneumocytes and macrophages), kidney (tubular epithelial cells) and the gut (intestinal epithelial cells) and plays an important role in several cardiovascular and immune pathways [21]. Among multiple functions, the most significant role of ACE2 is the conversion of Ang I to Ang 1-9 and Ang II to Ang 1-7, promoting systemic vasodilatory and anti-inflammatory effects [21] (Figure 1). Due to structural differences in the binding sites of ACE and ACE2, the pharmacological class of ACE inhibitors (ACEIs) does not inhibit the activity of ACE2 [25].

## ROLE OF RAS BLOCKERS IN COVID-19: PRELIMINARY HYPOTHESES

The potential association between COVID-19 and RAS was hypothesized early in the course of the COVID-19 pandemic. ACE2 acts as the cell membrane receptor for some strains of coronaviruses, including SARS-CoV and SARS-CoV-2, mediating the entrance of the virus into the cells by binding the spike protein [26]. Binding of the N-terminal portion of the viral protein unit S1 to a pocket of the ACE2, along with S protein cleavage between the S1 and S2 units by transmembrane serine protease 2 (TMPRSS2), facilitates virus entry into cells, viral RNA release and replication and cell-to-cell transmission [27].

Previous data from animal studies have shown that RAS blockers might upregulate tissue activity or ACE2 expression in the heart, lung and kidneys [28–32]. However, it was also proposed that soluble ACE2 may behave as a decoy receptor for SARS-CoV-2, limiting viral binding to cell membrane ACE2 (Figure 2). Indeed, the combination of soluble ACE2 and remdesivir markedly improved their therapeutic windows

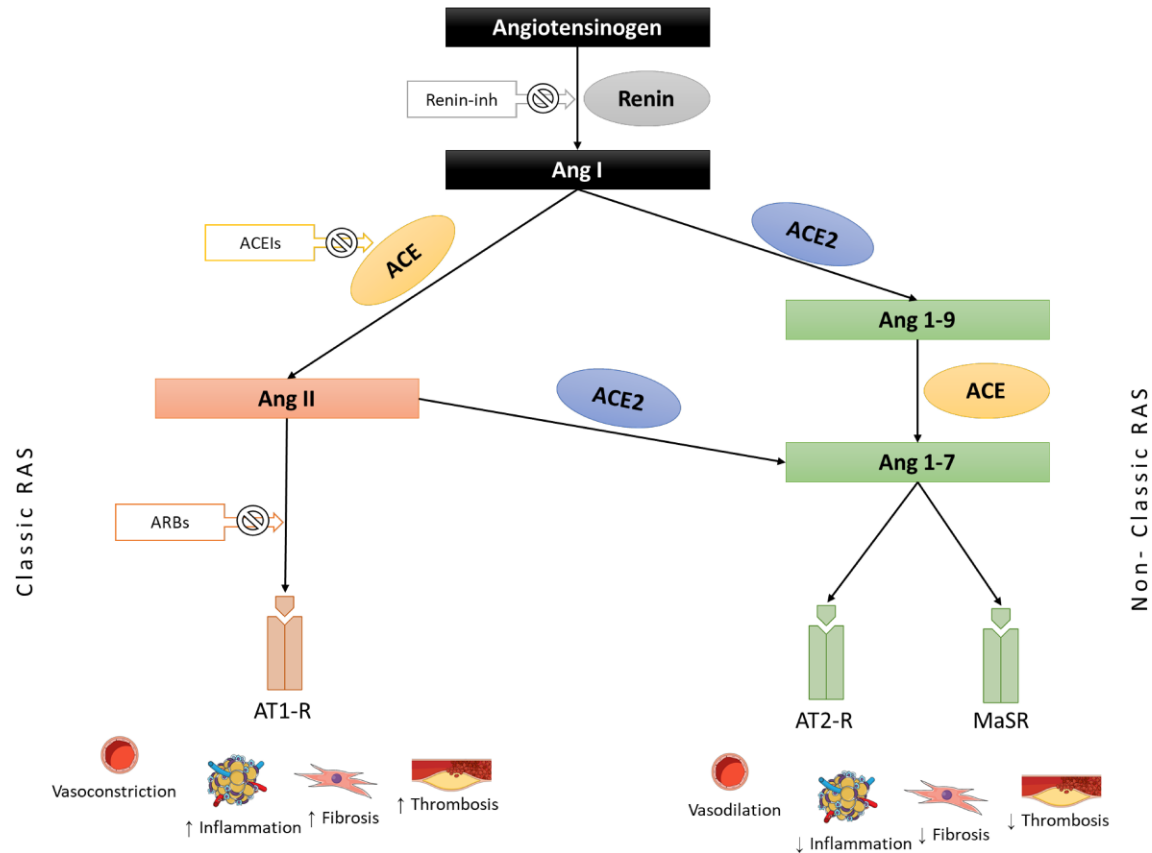


FIGURE 1: The role of ACE and ACE2 in classic and non-classic RAS pathways.

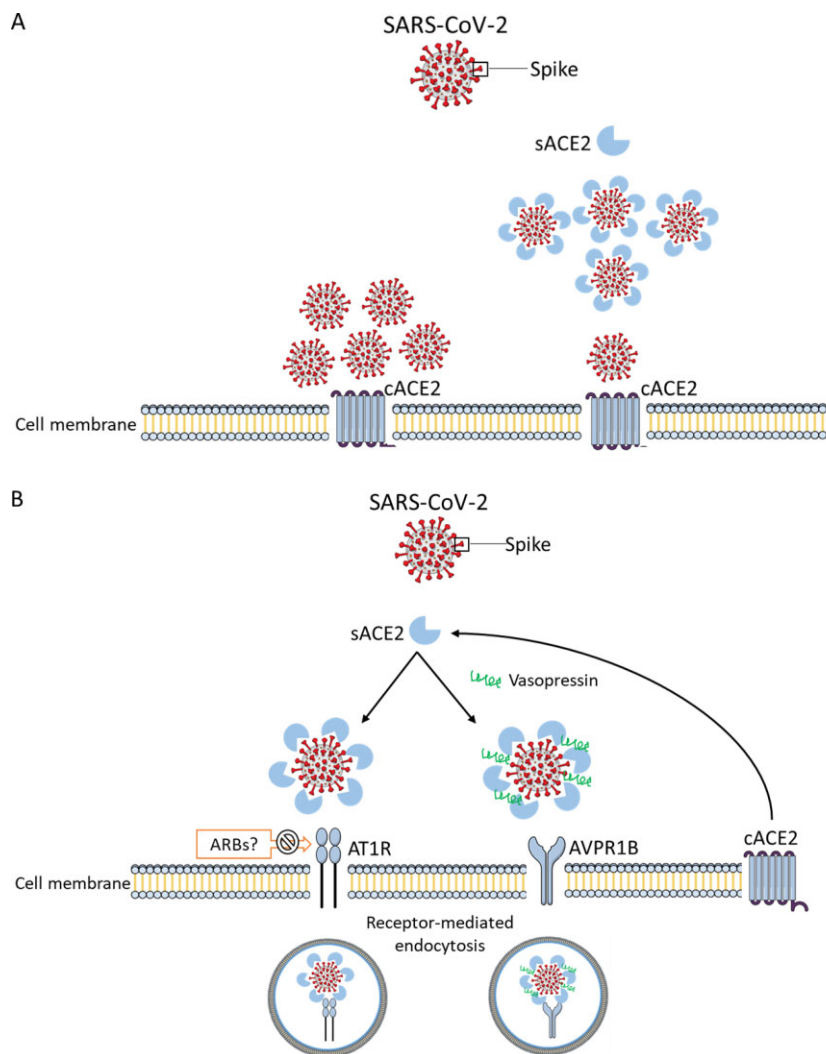
against SARS-CoV-2 in *in vitro* and animal models [33, 34]. To this end, clinical trials of soluble ACE2 for COVID-19 are ongoing (e.g. NCT05065645), although initial phase 2 trials did not meet the primary endpoint (NCT04335136). In this regard, most, if not all, clinical studies addressing the impact of RAS blockade on ACE2 studied soluble ACE2 (which may limit SARS-CoV-2 infection) rather than cell membrane ACE2 (that may potentially favor SARS-CoV-2 infection). They described multiple determinants of soluble ACE2, including both therapeutic agents and underlying conditions. Thus, in some studies, RAS blockade was associated with lower soluble ACE2 [35] while in others there was no association [36, 37]. A final glimpse of the complexity of the system and the need for results of actual clinical trials rather than relying on predictions from preclinical models came for the realization that SARS-CoV-2 forms aggregates, through the spike protein, with soluble ACE2 or soluble ACE2-vasopressin to enter cells via receptor-mediated endocytosis using AT1R or arginine vasopressin receptor 1B (AVPR1B), respectively [38]. Entry using AT1R would presumably be blocked by angiotensin-receptor blockers (ARBs) (Figure 2).

In any case, given that increased cell membrane ACE2 in response to RAS blockade, as observed in animals, could theoretically increase the chance of virus entry into organs through an increase of the potential entry sites [39], there was initially much concern about the role of RAS blockers on ACE2 expression and hence susceptibility to COVID-19 infection [40]. On the other hand, some authors have also proposed that ACEIs and ARBs could have a beneficial effect in COVID-19 [41]. More specifically, it has been suggested that either by diminishing

production of Ang II with the use of an ACEI or by blocking the Ang II-AT1R binding with the use of an ARB, there could be an enhanced generation of Ang 1-7 by ACE2 and activation of the MasR, which could attenuate lung inflammation and fibrosis [42]. Finally, Cohen et al. [42] previously proposed a third hypothesis, i.e. that ACEIs could be harmful and ARBs are neutral in COVID-19 severity, as ACEIs block bradykinin breakdown, thus increased bradykinin and its active metabolite DABK binds to the B2/B1 receptor, respectively, leading to increased lung inflammation [43]. On the other hand, ARBs do not take part in the bradykinin cascade and thus they do not precipitate further bradykinin-mediated lung injury [42]. Moreover, as indicated above, they may block virus entry via AT1R [38].

## ROLE OF RAS BLOCKERS IN COVID-19: OBSERVATIONAL STUDIES

In contrast to the above hypotheses, observational studies published in mid-2020 demonstrated that the use of RAS blockers is not associated with a higher risk of COVID-19 infection and disease severity, including mortality [44, 45]. In a population-based case-control study in Italy, the use of RAS blockers was more common among COVID-19 patients than among controls, but was not associated with COVID-19 infection or disease severity [44]. Similar observations were also made in another cohort study including 12 594 patients from the USA; there was no association between the use of five



**FIGURE 2:** The potential roles of soluble ACE2 (sACE2) in COVID-19 infection. (A) sACE2 may behave as a decoy receptor for SARS-CoV-2, limiting viral binding to cell membrane ACE2 (cACE2). (B) SARS-CoV-2 forms aggregates, through the spike protein, with sACE2 or sACE2-vasopressin to enter cells via AT1R or AVPR1B.

different classes of antihypertensive treatment (ACEIs, ARBs, beta blockers, calcium-channel blockers or thiazide diuretics) and an increased likelihood of a positive test for COVID-19 or an increased risk for severe COVID-19 [45]. In addition, in a multicentre cohort study including >1.3 million patients with hypertension from the USA and Spain showed that there was no association between COVID-19 diagnosis and exposure to ACEI/ARB therapy versus calcium-channel blockers/thiazide therapy [hazard ratio [HR] 0.98 [95% confidence interval (CI) 0.84–1.14]], as well as no significant difference between RAS blockers and calcium-channel blockers/thiazides for risk of COVID-19 hospitalization, acute respiratory distress syndrome, acute kidney injury or sepsis across all comparisons [46]. Finally, in a meta-analysis from Baral et al. [47] including 52 studies with a total of 101 949 COVID-19 patients, treatment with ACEIs or ARBs was not associated with a higher risk of multivariable-adjusted mortality and severe adverse events.

Of note, there are also some studies indicating a protective effect of RAS blockers in COVID-19-related outcomes. For example, in a large cohort of 1.4 million patients with different diseases (hypertension, heart failure, diabetes mellitus, CKD) in Sweden,

the use of RAS blockers was associated with a significantly lower risk of COVID-19-related hospitalization and death [48]. A similar association was observed when ARB use was analysed separately, whereas ACEI use was not significantly associated with any outcome [48]. The aforementioned meta-analysis from Baral et al. [47] also showed that among patients with hypertension there were significant reductions in the risk of death [adjusted odds ratio (aOR) 0.57 (95% CI 0.43–0.76)] and severe adverse events [aOR 0.68 (95% CI 0.53–0.88)] in patients receiving ACEIs or ARBs. Similarly, a recent properly designed meta-analysis of 30 observational studies with 17 281 patients accounting for confounders during data synthesis showed that treatment with RAS blockers was associated with significantly decreased mortality in hospitalized patients with COVID-19 after adjusting for age, sex, cardiovascular disease, hypertension, diabetes and CKD [49].

Despite the fact that RAS blockers are among the most frequently described medications in patients with CKD, data about the effects of RAS blockers in COVID-19 severity, particularly in this population, are scarce. The ERA COVID-19 database (ERACODA) is a European multicentre database aiming to investigate the course and outcome of COVID-19 in patients

on dialysis and KTRs [50]. In a recent subanalysis of ERACODA including 1052 dialysis patients and 459 KTRs, Soler *et al.* [51] demonstrated that there was no association between treatment with RAS blockers and 28-day mortality in both crude and adjusted models [haemodialysis patients: adjusted HR (aHR) 1.04 (95% CI 0.73–1.47); KTRs: aHR 1.12 (95% CI 0.69–1.83)]. Similarly, discontinuation of RAS blockers during COVID-19 disease was not associated with mortality in both dialysis patients and KTRs [haemodialysis patients: aHR 1.52 (95% CI 0.51–4.56); KTRs: aHR 1.36 (95% CI 0.40–4.58)]. Finally, no significant associations between treatment with RAS blockers and COVID-19 severity outcomes (i.e. hospitalization, ICU admission, ventilator support) were observed [51]. Similar results were obtained across both subgroups when ACEIs and ARBs were studied separately [51].

## ROLE OF RAS BLOCKERS IN COVID-19: CLINICAL TRIALS

Despite the importance of the studies described above, these works inevitably carry some limitations inherent to their observational design, including selection bias, collider and time-dependent bias and confounding [42], therefore these findings should be considered as hypothesis-generating, requiring confirmation by randomized controlled trials (RCTs). As of this writing, only a few RCTs investigating the association of RAS blocker use and the course and prognosis of COVID-19 disease have been published (Table 1). In the Angiotensin Receptor Blockers and Angiotensin-converting Enzyme Inhibitors and Adverse Outcomes in Patients with COVID-19 trial (BRACE-CORONA; NCT04364893), 659 hospitalized COVID-19 patients were randomized in a 1:1 ratio either to continuation or discontinuation of ACEI/ARB therapy for 1 month. Among baseline characteristics, 40.4% of participants were females, the median age was 55.1 years, 31.9% had diabetes and 4.6% had coronary heart disease; however, the study excluded patients with decompensated heart failure 1 year prior to enrollment. RAS blocker discontinuation was not associated with beneficial effects for the primary outcome [mean between-group difference in days alive and out of hospital:  $-1.10$  (95% CI  $-2.30$ – $0.13$ )], suggesting that withdrawal of RAS blockers in hospitalized COVID-19 patients does not alter the short-term prognosis of the disease [52]. A study characteristic that might limit the generalizability of these findings is the reasonable exclusion of patients with contraindications to discontinue therapy with RAS blockers (i.e. patients with heart failure). Consistent with the above, the results from the Randomized Elimination or ProLongation of Angiotensin Converting Enzyme inhibitors and angiotensin receptor blockers in COVID-19 (REPLACE COVID) trial including 152 hypertensive patients (45.0% females, mean age  $62 \pm 12$  years, 52.0% diabetes, 12% coronary heart disease) hospitalized for COVID-19 infection also suggested that there were no significant differences between RAS blocker continuation versus discontinuation in the incidence of the combined primary endpoint (time to death, duration of mechanical ventilation, time on renal replacement or vasopressor therapy and multiorgan dysfunction during hospitalization) [53]. Limitations of the study included the exclusion of patients with contraindications to discontinue RAS blockers (e.g. heart failure with reduced ejection fraction, nephrotic range proteinuria, etc.), as well as an imbalance in the use of ACEIs across the assigned groups at baseline (49% in the discontinuation versus 33% in the continuation group;  $P = 0.05$ ).

More recently, the results of the Stopping ACE-inhibitors in Covid-19 trial (ACEI-COVID; NCT04353596) have been published.

This was a randomized, controlled, multicentre, open-label trial that randomly assigned 204 COVID-19 patients on chronic treatment with an ACEI/ARB to continuation or discontinuation of RAS blockers for 30 days [54]. Participants of the ACEI-COVID trial were older (mean age  $72 \pm 11$  years) than the two aforementioned trials, 33% had diabetes and 22% had coronary heart disease. Patients with severe heart failure (ejection fraction  $<30\%$ , New York Heart Association class 3–4) were again excluded. The primary endpoint was the maximal Sequential Organ Failure Assessment (SOFA) score within 30 days and was not significantly different between the two arms [54]. Among the secondary endpoints, the area under the SOFA score and mean SOFA score were significantly lower in the discontinuation than in the continuation group, suggesting that the discontinuation of RAS blockers in COVID-19 may lead to a faster and better recovery [54]. Nonetheless, these observations should be considered again as hypothesis-generating, as the primary result of the study was considered to be neutral. Finally, another recently published prospective, blinded, randomized clinical trial in Iran in 64 patients with hypertension (53.1% females, mean age  $66.3 \pm 9.9$  years) showed that the primary outcome (i.e. hospitalization/ICU length of stay) was not different between patients with the continuation of RAS blockers or patients in which RAS blockers were substituted with a calcium channel blocker [55]. It should be noted that the conclusions of the later trial, as well as other trials of relevant size, may be limited by inadequate study power, whereas the findings of the larger studies in the field (i.e. the BRACE-CORONA trial) are more solid. Overall, the aforementioned trials showed that treatment with RAS blockers does not seem to affect outcomes in hospitalized patients with COVID-19. These findings are aligned with the existing observational data and support the general recommendations produced by several national and international scientific organizations and societies to continue the use of antihypertensive medications in general and ACEIs/ARBs in particular in patients with COVID-19 infections [56, 57].

The above trials provide important evidence on the effects of discontinuation of RAS blockade in COVID-19-infected patients. However, they did not assess all the relevant questions in the field, i.e. whether treatment with RAS blockers increases the propensity of infection with SARS-CoV-2 infection or whether the above neutral results are also present in specific patient groups, such as individuals with ESKD. Another important question is whether initiation of an RAS blocker during COVID-19 infection may have beneficial effects on disease severity and outcomes. As of this writing, there are two studies that tried to address this issue (Table 2). In a parallel-group, randomized, superiority trial including 158 hospitalized COVID-19 patients (46.8% females, mean age  $65.3 \pm 17.1$  years, 19.0% diabetes) who were not on ACEI or ARB treatment at baseline, Duarte *et al.* [58] showed a significant reduction in inflammatory markers such as C-reactive protein levels by adding telmisartan on existing standard-of-care treatment compared with standard-of-care treatment alone [58]. In contrast, a placebo-controlled randomized clinical trial testing the efficacy of adding losartan on ACEI/ARB-naïve outpatients with COVID-19 ( $n = 117$  patients, 49.5% females, median age 38 years, 5.9% diabetes) was terminated early because of the low likelihood of treatment effect [59]. The currently ongoing Ramipril for the Treatment of COVID-19 trial (RAMIC; NCT04366050) is investigating the potential benefits of ramipril over placebo in improving survival, reducing ICU admissions and the use of mechanical ventilation support in 560 patients hospitalized for severe COVID-19. Similarly, two other trials are investigating the effects of losartan (NCT04312009)

Table 1. Studies investigating the effects of discontinuation of RAS blockers during COVID-19 infection on disease severity and outcomes

Study	Location	Study design	Participants	Primary outcome	Secondary outcomes	Results
BRACE-CORONA trial [52]	Brazil	Multicentre, registry-based, open-label, parallel-group randomized clinical trial with blinded endpoint assessment	n = 659 hospitalized patients [median age 55.1 years (IQR 46.1–65.0)]	Number of days alive and out of the hospital through 30 days	Death (during the 30-day follow-up period), CV death, COVID-19 progression	Primary outcome: no difference [discontinuation: 21.9 ± 8.0 versus continuation group: 22.9 ± 7.1 days] Secondary outcomes: no differences in death, CV death, COVID-19 progression
REPLACE COVID trial [53]	USA, Canada, Mexico, Sweden, Peru, Bolivia, and Argentina	Prospective, randomized, open-label, parallel-group trial	n = 152 hospitalized patients (age 62 ± 12 years)	A global rank score (time to death, duration of MV, time on renal replacement or vasopressor therapy and multi-organ dysfunction during the hospitalization)	All-cause death, length in-hospital stay, length of ICU stay, invasive MV or ECMO, AUC of the SOFA score	Primary outcome: no differences [discontinuation: median rank 81 (IQR 38–117) versus continuation: 73 (40–110); $\beta$ -coefficient 8 (95% CI 13–29)] Secondary outcomes: no differences between the two arms in all outcomes studied.
ACEI-COVID trial [54]	Austria and Germany	Parallel group, randomized, controlled, open-label trial	n = 204 hospitalized patients [median age 75 years (IQR 66–80)]	Maximum SOFA score within 30 days, where death was scored with the maximum achievable SOFA score	Area under the death-adjusted SOFA score (AUCSOFA), mean SOFA score, ICU admission, MV and death	Primary outcome: no difference [discontinuation: median SOFA score 0 (0–2) versus continuation: 1 (0–3); P = 0.12] Secondary outcomes: ↓ AUCSOFA, ↓ mean SOFA score, ↓ death and organ dysfunction at 30 days in discontinuation group. No significant differences for MV and ICU admission
Najmeddin et al. [55]	Iran	Prospective, parallel-group, triple-blind, randomized trial	n = 64 hospitalized patients (age 66.3 ± 9.9 years)	Length of stay in hospitals and ICU	Need for MV, non-invasive ventilation, readmission, and COVID-19 symptoms after discharge	Primary outcome: no difference [hospitalization length: discontinuation 4.0 (IQR 2.0–5.0) versus continuation 4.0 days (2.0–8.0); P = 1.000, ICU stay length: 4.0 days (IQR 2.0–5.0) versus 7.0 (3.5–11.2); P = 0.691] Secondary outcomes: no differences between the two arms in all outcomes studied

AUC, area under the curve; CV, cardiovascular; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; MV, mechanical ventilation; SOFA, Sequential Organ Failure Assessment.

Table 2. Published and ongoing studies investigating the effects of initiation of a RAS blocker during COVID-19 infection on disease severity and outcomes

Study	Location	Study design	Participants	Primary outcome	Secondary outcomes	Results
Duarte et al. [58] (NCT04355936)	Argentina	Randomized, open label, parallel group, controlled superiority trial (intervention: p.os 80 mg telmisartan twice daily for 10 days on top of standard care)	n = 158 hospitalized COVID-19 patients	CRP plasma levels at day 5 and 8 after randomization	Time to discharge within 15 days, admission to ICU and death at 15 and 30 days	Primary outcome: ↓ Day 5 and Day 8 CRP levels in telmisartan group (P = 0.038/<0.001, respectively) Secondary outcomes: ↓ median time-to-discharge, ↓ death rate by day 30, ↓ composite outcome of ICU, mechanical ventilation or death at days 15 and 30 in telmisartan group
Puskarich et al. [59] (NCT04311177)	USA	Randomized, double-blind, parallel group, placebo controlled trial (intervention: oral 25 mg losartan twice daily for 10 days)	n = 117 COVID-19 outpatients	All-cause hospitalization within 15 days	Functional status, dyspnoea, temperature and viral load	The trial was terminated early due to reduced hospitalization rate and reduced likelihood of clinically important treatment effect. No significant difference between losartan and placebo for the primary outcome (5.2% versus 1.7%, P = 0.32), adverse events and viral loads
RAMIC study (NCT04366050)	USA	Randomized, double-blind, parallel group, placebo controlled trial (intervention: oral 2.5 mg ramipril once daily for 14 days)	n = 560 COVID-19 patients hospitalized or in emergency department	Composite outcome of mortality or need for ICU admission or ventilator use within 14 days	-	-
NCT04312009	USA	Randomized, double-blind, parallel group, placebo controlled trial (intervention: oral 25 mg losartan twice daily for 7 days)	n = 205 hospitalized COVID-19 patients	Difference in Estimated (PEEP-adjusted) PaO <sub>2</sub> :FiO <sub>2</sub> ratio at 7 days	Hypotension, AKI, SOFA score, SpO <sub>2</sub> :FiO <sub>2</sub> ratio, all-cause mortality, ICU admission/length of stay, length of hospitalization, respiratory failure and viral load	-
NCT04345887	Turkey	Parallel group, placebo controlled trial (intervention: oral 200 mg Spironolactone once daily for 5 days)	n = 60 COVID-19 patients admitted in ICU	Difference in PaO <sub>2</sub> /FiO <sub>2</sub> ratio at 5 days	Difference in SOFA score at 5 days	-

AKI, acute kidney injury; CRP, C-reactive protein; IQR, interquartile range; PEEP, positive end-expiratory pressure; SOFA, Sequential Organ Failure Assessment.

and spironolactone (NCT04345887) in hospitalized COVID-19 patients. Hopefully these ongoing clinical trials, as well as the future meta-analyses of randomized trials, will elucidate the optimal use of RAS blockers in patients with COVID-19.

## CONCLUSION

RAS blockade represents a cornerstone in the treatment of patients with hypertension, cardiovascular disease and CKD. At the beginning of the COVID-19 pandemic, the use of ACEIs and ARBs in COVID-19-infected patients was questioned due to the fact that cell membrane ACE2 is the main entry point of SARS-CoV-2 into cells and background studies have shown that it is upregulated during ACEIs/ARBs treatment. Observational studies suggested that there is no higher risk from continuing ACEIs/ARBs in COVID-19 patients already receiving these medications, while their use may also confer a benefit through organ protection. Subsequent randomized trials have demonstrated that RAS blockers are safe, as their discontinuation does not appear to alter outcomes. As a result, several scientific societies have recommended against discontinuation of RAS blockers in patients with or at risk of COVID-19 infection. Ongoing randomized trials are expected to offer detailed information on whether initiation of RAS blockers during COVID-19 infection may confer benefits. As of this writing, more observational studies and clinical trials are needed to specifically examine the safety of continuing RAS blockade during COVID-19 disease in CKD patients.

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