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

Marieta P. Theodorakopoulou,¹ Maria-Eleni Alexandrou,¹ Afroditi K. Boutou,² Charles J. Ferro,³ Alberto Ortiz,⁴ Pantelis Sarafidis¹

1) Department of Nephrology, Hippokration Hospital, Aristotle University of Thessaloniki, Greece; 2) Department of Respiratory Medicine, G. Papanikolaou Hospital, Thessaloniki, Greece; 3) Department of Renal Medicine, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; 4) Department of Nephrology and Hypertension, IIS-Fundacion Jimenez Diaz UAM, Madrid, Spain

Correspondence to: Pantelis Sarafidis; E-mail: psarafidis11@yahoo.gr

Running Head: RAS blockers and COVID-19
ABSTRACT

Hypertension and chronic kidney disease (CKD) are among the most common co-morbidities associated with 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 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 SARS-CoV-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 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: COVID-19, hypertension and chronic kidney disease

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the new severe acute respiratory syndrome coronavirus (SARS-CoV-2); it broke out in China at the end of 2019 and developed in a global pandemic from the year 2020 [1]. Since then, COVID-19 has been established as a major issue of public health, infecting over 200 million individuals and accounting for more than 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 hypertension, diabetes mellitus, cardiovascular disease and, above all, chronic kidney disease (CKD) [3].

Initial reports from China, Italy and the United States 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 [6]. As a consequence, early in the pandemic, a large number of observational studies associated COVID-19–related deaths to prevalent hypertension [4,5,7]. However, the role of hypertension as a risk factor for the adverse COVID-19 probably needs to be better defined, as there are 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 higher risk for COVID-19 related complications [9]. In a seminal cross-sectional study designed to delineate some of these issues, Iaccarino et al. 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 [3]. As such the association
of the presence of hypertension per se with COVID-19 severity and associated-death needs further examination.

Chronic kidney disease 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 for SARS-CoV-2 infection and COVID-19-associated mortality [10,11]. A study from the United States 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 (n=1013) had 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 aged>75 years, 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 renin-angiotensin system**

The RAS is rather the most important endocrine systems, 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 the RAS involved in BP regulation are angiotensin II (Ang II) and angiotensin 1–7 (Ang 1–7) [21]. Angiotensin II is a potent vasoconstricting agent, that increases renal sodium and water reabsorption through a direct action in proximal tubules and indirectly, through increase of aldosterone secretion, in distal tubules [22]. In addition to these actions, Ang II also has significant oxidative, inflammatory, and fibrotic actions that are involved in cardiorenal remodeling [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. Angiotensin (1–7) activates the Mas receptor 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 or not tissue injury will occur in response to different stimuli [21].

Angiotensin-converting enzyme (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 trans-membranic mono-carboxypeptidase with 806 amino acids that shares about 40% structural identity and 60% sequence similarity with ACE [24]. ACE2 is highly expressed in the heart (endothelial cells, cardiomyocytes, fibroblasts), blood vessels (endothelial
and smooth muscle cells), lungs (bronchial epithelial cells, type-2 pneumocytes, 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 angiotensin (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 do 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 COVID-19 pandemic. ACE-2 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 (S) 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 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 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 be presumably blocked by 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 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 ACE inhibitors (ACEIs) and angiotensin-receptor blockers (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] have 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 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, nor disease severity [44]. Similar observations were also made in another cohort study including 12,594 patients from USA; there was no association between the use of 5 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 with increased risk for severe COVID-19 [45]. In addition, in a multicenter cohort study including more than 1.3 million patients with hypertension from 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 (HR 0.98, 95%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. 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 [47].

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 analyzed separately, whereas ACEI use was
not significantly associated with any outcome [48]. The aforementioned meta-analysis from Baral et al. also showed that among patients with hypertension there were significant reductions in the risk of death (adjusted OR [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 [47]. 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 chronic kidney disease [49].

Despite the fact that RAS-blockers are among the most frequently described medication in patients with CKD, data about the effects of RAS-blockers in COVID-19 severity particularly in this population are scarce. The European Renal Association COVID-19 database (ERACODA) is a European multicenter database aiming to investigate the course and outcome of COVID-19 in patients on dialysis and kidney transplant recipients (KTRs) [50]. In a recent sub-analysis 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 (hemodialysis patients: aHR 1.04; 95% CI, 0.73 to 1.47; KTRs: aHR 1.12; 95% CI, 0.69 to 1.83). Similarly, RAS-blockers discontinuation during COVID-19 disease was not associated with mortality in both dialysis patients and KTRs (hemodialysis patients: aHR 1.52; 95% CI, 0.51 to 4.56; KTRs: aHR 1.36; 95% CI, 0.40 to 4.58). Finally, no significant associations between treatment with RAS-blockers and COVID-19 severity outcomes (i.e. hospitalization, ICU admission, ventilator support) were again 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 Blockers of Angiotensin Receptor and Angiotensin-Converting Enzyme inhibitors suspension in hospitalized patients with coronavirus infection (BRACE-CORONA) trial, 659 hospitalized COVID-19 patients were randomized in 1:1 ratio either to continuation or discontinuation of ACEi/ARB therapy for 1 month. Among baseline characteristics 40.4% of participants were females; 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 Coronavirus Disease 2019 (REPLACE COVID) trial including 152 hypertensive patients (45.0% females; mean age 62±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 vs 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 again 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 discontinuation vs 33% in the continuation group; p=0.05).

More recently, the results of the Stopping ACE-inhibitors in Covid-19 (ACEI-COVID) trial have been published. This was a randomized, controlled, multicenter, 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 participants were older (mean age 72±11 years) than the two aforementioned trials; 33% had diabetes, 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 2 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 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±9.9 years) showed that the primary outcome (i.e. hospitalization/ICU length of stay) was not different between patients with continuation of RAS blockers or patients in which RAS blockers were substituted with a calcium channel blocker [55]. It has to 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 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 a RAS blocker during COVID-19 infection may have beneficial effects on disease severity and outcomes. As of this writing, there are 2 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±17.1 years, 19.0% diabetes) who were not on ACE inhibitor or ARB treatment at baseline, Duarte et al. showed a significant reduction in inflammatory markers such as C-reactive protein levels by adding telmisartan on existing standard of care treatment compared to 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 (RAMIC) trial 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 (NCT04366050). Similarly, 2 other trials are investigating the effects of losartan (NCT04312009) 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.

**Conclusions**

RAS blockade represents a cornerstone of the treatment for 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 do 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 the group of patients with CKD.

**CONFLICT OF INTEREST STATEMENT**

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REFERENCES


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

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Study design</th>
<th>Participants</th>
<th>Primary outcome</th>
<th>Secondary outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRACE-CORONA trial [52]</td>
<td>Brazil</td>
<td>Multicenter, registry-based, open-label, parallel-group randomized clinical trial with blinded end-point assessment</td>
<td>N=659 hospitalized patients (median age 55.1 years, IQR [46.1-65.0])</td>
<td>Number of days alive and out of the hospital through 30 days.</td>
<td>Death (during the 30-day follow-up period), CV death, COVID-19 progression.</td>
<td>Primary outcome: No difference (discontinuation: 21.9±8.0 vs continuation group: 22.9±7.1 days). Secondary outcomes: No differences in death, CV death, COVID-19 progression.</td>
</tr>
<tr>
<td>REPLACE COVID trial [53]</td>
<td>USA, Canada, Mexico, Sweden, Peru, Bolivia, and Argentina</td>
<td>Prospective, randomized, open-label, parallel-group trial</td>
<td>N=152 hospitalized patients (age 62±12 years)</td>
<td>A global rank score (time to death, duration of MV, time on renal replacement or vasopressor therapy, and multiorgan dysfunction during the hospitalization)</td>
<td>All-cause death, length in-hospital stay, length of ICU stay, invasive MV or ECMO, AUC of the SOFA score</td>
<td>Primary outcome: No differences (discontinuation: median rank 81 [IQR 38-117] vs continuation: 73 [40-110]; β-coefficient 8 [95% CI -13 to 29]). Secondary outcomes: No differences between the two arms in all outcomes studied.</td>
</tr>
<tr>
<td>ACEI-COVID trial [54]</td>
<td>Austria and Germany</td>
<td>Parallel group, randomized, controlled, open-label trial</td>
<td>N=204 hospitalized patients (median age 75 years [IQR 66–80])</td>
<td>Maximum SOFA score within 30 days, where death was scored with the maximum achievable SOFA score.</td>
<td>Area under the death-adjusted SOFA score (AUCSOFA), mean SOFA score, ICU admission, MV, and death</td>
<td>Primary outcome: No difference (discontinuation: median SOFA score 0 [0–2] vs 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.</td>
</tr>
<tr>
<td>Najmeddin et al. [55]</td>
<td>Iran</td>
<td>Prospective, parallel-group, triple-blind, randomized trial</td>
<td>N=64 hospitalized patients (age 66.3 ± 9.9 years)</td>
<td>Length of stay in hospitals and ICU</td>
<td>Need for MV, non-invasive ventilation, readmission, and COVID-19 symptoms after discharge</td>
<td>Primary outcome: no difference (hospitalization length: discontinuation: 4.0 [2.0-5.0] vs continuation 4.0 [2.0-8.0]; p=1.000, ICU stay length: 4.0 [2.0-5.0] vs 7.0 [3.5-11.2]; p=0.691). Secondary outcomes: no differences between the two arms in all outcomes studied.</td>
</tr>
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Abbreviations: AUC, area under the curve; CV, cardiovascular; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; MV, mechanical ventilation; SOFA, Sequential Organ Failure Assessment;
Table 2. Published and ongoing studies investigating the effects of initiation of a renin-angiotensin system blocker during COVID-19 infection on disease severity and outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Study design</th>
<th>Participants</th>
<th>Primary outcome</th>
<th>Secondary outcomes</th>
<th>Results</th>
</tr>
</thead>
</table>
| Duarte et al. [58]   | Argentina| Randomized, open label, parallel group, controlled superiority trial (intervention: p.o.s 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] | USA      | Randomized, double-blind, parallel group, placebo controlled trial (intervention: p.o.s 25 mg Losartan twice daily for 10 days) | N=117 COVID-19 outpatients | All-cause hospitalization within 15 days | Functional status, dyspnea, 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% vs 1.7%, p=0.32), adverse events, and viral loads. |
| RAMIC study          | USA      | Randomized, double-blind, parallel group, placebo controlled trial (intervention: p.o.s 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: p.o.s 25 mg Losartan twice daily for 7 days) | N=205 hospitalized COVID-19 patients | Difference in Estimated (PEEP adjusted) PaO2/FiO2 Ratio at 7 days | Hypotension, AKI, SOFA score, SpO2/FiO2 ratio, all-cause mortality, ICU admission/length of stay, length of hospitalization, respiratory failure, viral load | - |
| NCT04345887          | Turkey   | Parallel group, placebo controlled trial (intervention: p.o.s 200 mg Spironolactone once daily for 5 days) | N=60 COVID-19 patients admitted in ICU. | Difference in PaO2/FiO2 Ratio at 5 days | Difference in SOFA score at 5 days | - |

Abbreviations: AKI, acute kidney injury; CRP, C-reactive protein; ICU, intensive care unit; IQR, interquartile range; PEEP, Positive end-expiratory pressure; SOFA, Sequential Organ Failure Assessment;
**Figure 1.** The role of angiotensin converting enzyme (ACE) and ACE2 in classic and non-classic renin-angiotensin system (RAS) pathways.
Figure 2. The potential roles of soluble angiotensin converting enzyme-2 (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 angiotensin II type 1 receptor (AT1R) or arginine vasopressin receptor 1B (AVPR1B)