Severe acute respiratory syndrome coronavirus 2 and renin-angiotensin system blockers: A review and pooled analysis

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Abbreviated title: SARS-CoV-2 and RAS blockers

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Summary

A novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is causing an international outbreak of respiratory illness described as coronavirus disease 2019 (COVID-19). SARS-CoV-2 infects human cells by binding to angiotensin-converting enzyme 2. Small studies suggest that renin-angiotensin system (RAS) blockers may upregulate the expression of angiotensin-converting enzyme 2, affecting susceptibility to SARS-CoV-2. This may be of great importance considering the large number of patients worldwide who are treated with RAS blockers, and the well-proven clinical benefit of these treatments in several cardiovascular conditions. In contrast, RAS blockers have also been associated with better outcomes in pneumonia models, and may be beneficial in COVID-19. This review sought to analyse the evidence regarding RAS blockers in the context of COVID-19 and to perform a pooled analysis of the published observational studies to guide clinical decision making. A total of 21 studies were included, comprising 11,539 patients, of whom 3417 (29.6%) were treated with RAS blockers. All-cause mortality occurred in 587/3417 (17.1%) patients with RAS blocker treatment and in 982/8122 (12.1%) patients without RAS blocker treatment (odds ratio 1.00, 95% confidence interval 0.69–1.45; $P = 0.49$; $I^2 = 84\%$). As several hypotheses can be drawn from experimental analysis, we also present the ongoing randomized studies assessing the efficacy and safety of RAS blockers in patients with COVID-19. In conclusion, according to the current data and the results of the pooled analysis, there is no evidence supporting any harmful effect of RAS blockers on the course of patients with COVID-19, and it seems reasonable to recommend their continuation.

Résumé

Un nouveau coronavirus appelé severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) provoque une épidémie internationale de maladie respiratoire appelée coronavirus disease 2019 (COVID-19). Le SARS-CoV-2 infecte les cellules humaines en se liant à l'enzyme de conversion de l'angiotensine 2. Des études suggèrent que les bloqueurs du système rénine-angiotensine (SRA) peuvent augmenter l'expression de l'enzyme de conversion de l'angiotensine 2, modifiant la susceptibilité au SARS-CoV-2. Cela pourrait avoir des conséquences importantes compte-tenu du nombre de patients traités dans le monde par des bloqueurs du SRA et des avantages prouvés de ces traitements dans les maladies cardiovasculaires. D'un autre côté, les bloqueurs du SRA ont

démontré une amélioration du pronostic dans des modèles de pneumonies et pourraient être bénéfiques dans la COVID-19. Le but de cette revue est de mettre en perspective les preuves existantes concernant l'effet des bloqueurs du SRA dans le contexte de la COVID-19 et d'effectuer une méta-analyse sur les études publiées pour aider à la décision thérapeutique. Un total de 21 études ont été inclues, représentant un total de 11 539 patients, parmi lesquels 3417 (29,6 %) étaient traités par bloqueurs du SRA. La mortalité toutes causes est survenue chez 587/3417 (17,1 %) et 982/8122 (12,1 %) patients avec et sans bloqueurs du SRA respectivement (rapport de cotes 1,00, intervalle de confiance à 95 % 0,69–1,45 ; $P = 0,49$; $I^2 = 84$ %). Plusieurs études randomisées sont en cours pour évaluer l'efficacité et la sécurité des bloqueurs du SRA chez les patients infectés par COVID-19. Les données actuelles ne mettent pas en évidence d'effet délétère des bloqueurs du SRA sur l'évolution des patients atteints de COVID-19 et il parait raisonnable de recommander leur poursuite.

KEYWORDS

RAS blockers;

COVID-19

MOTS CLÉS

Bloqueurs du SRA ;

COVID-19

Abbreviations: ACE, angiotensin-converting enzyme; ACE-I, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; AT1/AT2 receptor, angiotensin II type 1/2 receptor; CI, confidence interval; COVID-19, coronavirus disease 2019; mRNA, messenger ribonucleic acid; RAS, renin-angiotensin system; RNA, ribonucleic acid; SARS, severe acute respiratory syndrome; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Background

Since December 2019, a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused an international outbreak of respiratory illness described as coronavirus disease 2019 (COVID-19). The full spectrum of COVID-19 is still being depicted [1, 2], but at least 20.5 million confirmed cases of COVID-19 and 740,000 deaths had been reported worldwide by the end of August 2020. First clinical reports from China noted that individuals with cardiovascular disease infected with SARS-CoV-2 may be at higher risk of developing severe forms of COVID-19 [1, 3-7], with increased mortality [8]. Although the baseline medications of these patients were not reported, they would probably have included a renin-angiotensin system (RAS) blocker, such as angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARBs) [9]. The main effect of these antihypertensive drugs is to reduce the angiotensin II vasoconstrictor effect [10]; they may also cause upregulation of expression of angiotensin-converting enzyme 2 (ACE2) [11]. This may be important in the context of the COVID-19 pandemic, as SARS-CoV-2 infects human cells by binding to ACE2, which acts as a co-receptor for cellular viral entry [2, 12-15]. In contrast, RAS blockers have been also associated with better outcomes in pneumonia models, and may be beneficial in COVID-19 [16-19]. International scientific societies recommend continuing these treatments based on previous trials that demonstrated a clear benefit of RAS blockers in several cardiovascular conditions and the lack of evidence against their use in the particular setting of COVID-19 [20]. Recently, several large dedicated observational studies have demonstrated an absence of association between the use of RAS blockers and the risk of infection by SARS-CoV-2 or the severity of the infection [21-30]. These studies need to be confirmed by randomized trials, but provide reassuring data for clinicians.

The aims of this review were to report the updated evidence to guide physicians' clinical decision making, to present a pooled analysis of the published observational studies evaluating all-cause mortality of patients with COVID-19 according to treatment with RAS blockers and to provide the latest information on ongoing clinical research related to RAS blocker treatments in patients with COVID-19.

Physiology and inhibitors of the RAS

The RAS regulates blood pressure and fluid and electrolyte balance [31, 32]. In response to a reduction in renal blood flow, a sympathetic nervous system stimulation or a diminution in sodium delivery to the macula densa, renin is secreted by the juxtaglomerular cells of the kidneys, converting

angiotensinogen, produced in the liver, into angiotensin I (Fig. 1). Angiotensin I, an inactive peptide, is then converted into angiotensin II by the angiotensin-converting enzyme (ACE) present on the surface of vascular endothelial cells, predominantly in the lungs. It should be noted that there are other ACE-independent pathways that produce angiotensin II: angiotensin I can be converted by chymase or chymostatin-sensitive angiotensin II-generating enzyme (CAGE) [33]; and angiotensinogen can be converted directly to angiotensin II by serine proteases, such as cathepsin-G or tissue plasminogen activator (t-PA) [34, 35]. Therefore, the plasma concentrations of angiotensin II remain normal in patients receiving chronic treatment with ACE-I [10].

Angiotensin II can bind with two types of receptors: mostly angiotensin II type 1 (AT1), but also angiotensin II type 2 (AT2). The AT2 receptor-mediated effects are physiologically antagonistic to those mediated by the AT1 receptor (Table 1). After binding to AT1, angiotensin II induces vasoconstriction of arterioles and secretion of aldosterone and vasopressin, leading to an increase in blood pressure, mainly through vasoconstriction, promotion of fibrosis and water and sodium reabsorption [36]. Angiotensin II may also contribute to endothelial dysfunction and enhance the oxidation and uptake of low-density lipoprotein by macrophages and endothelial cells, thus promoting atherosclerosis [36]. Conversely, when binding to AT2 receptors, angiotensin II may lead to vasodilation and natriuresis, and prevent inflammation or fibrosis [37].

Finally, ACE2, a homologue of ACE that is highly expressed in the cardiovascular, renal, testicular and gastrointestinal systems, as well as in lung cells [38-41], negatively regulates the RAS, converting angiotensin I into angiotensin (1–9) and angiotensin II into angiotensin (1–7), with potent vasodilatory, anti-inflammatory, antioxidant and antiproliferative properties that are mediated by Mas receptors [32]. Angiotensin (1–9) can then be converted to angiotensin (1–7) by ACE, which is also responsible for its degradation [42]. Deficiency in ACE2 results in reduced levels of angiotensin (1–7) and increased levels of angiotensin II, which may lead to systolic hypertension [43-46] and cardiac hypertrophy [47]. In a process called shedding, the ACE2 membrane anchor is cleaved by a metalloprotease called ADAM17 (a disintegrin and metalloproteinase 17), which is upregulated by the AT1 receptor, thus increasing ACE2 soluble levels [48, 49].

Different treatments have been developed to inhibit the RAS, with the two main targets being ACE, targeted by ACE-I, and AT1 receptors, targeted by ARBs. ACE-I bind competitively to ACE, thus preventing its fixation to angiotensin I, leading to a decrease in angiotensin II levels and,

consequently, in aldosterone and vasopressin secretion. ACE-I also increases levels of bradykinin, a potent vasodilator peptide, by inhibiting its ACE-mediated degradation. ARBs prevent the AT1 receptor-mediated effect of angiotensin II without affecting AT2 receptors, leading to vasodilation and inflammation reduction. Overall, ACE-I and ARBs lead to a reduction in aldosterone and vasopressin levels, lowering vascular resistance, increasing natriuresis and decreasing cardiac stroke work and volume.

Role of ACE2 in COVID-19 and the potential effect of RAS blockers

Potential deleterious effects

As described previously with other strains of severe acute respiratory syndrome coronavirus (SARS-CoV) [46, 50], SARS-CoV-2 infects human cells through the binding of its spike protein to ACE2, which acts as a co-receptor for cellular viral entry [2, 12-15] (Fig. 2). A cellular serine protease called transmembrane protease serine 2 (TMPRSS2) primes SARS-CoV-2 entry by proteolytic cleavage of the spike protein [12]. In an autopsy study of four patients who died of severe acute respiratory syndrome (SARS), the presence of SARS-CoV spike protein and its ribonucleic acid (RNA) were only detected in ACE2 positive cells in the lungs and other organs, highlighting that ACE2-expressing cells are the primary target in humans [51]. Animal studies have reported that RAS blockers may increase the translation and synthesis of cardiac ACE2, raising concern that RAS blockers could potentially facilitate the binding of SARS-CoV-2 to human cells [11, 52]. In a murine model, administration of lisinopril and losartan resulted in an increase in cardiac ACE2 messenger RNA (mRNA) [11]. Patients with hypertension treated with olmesartan have also been reported to present an increase in urinary secretion of ACE2, suggesting that upregulation of ACE2 by RAS blockers may also be found in humans [53]. Of note, RAS blockers act at different levels of the system, and thus may have different effects on ACE2 levels [54]. Both ACE-I and ARBs have been demonstrated to increase angiotensin (1–7) levels in animal models [11, 55]. However, ARBs have been demonstrated to increase the level of ACE2 expression in experimental models [55, 56], whereas ACE-I only lead to an increase in cardiac ACE2 mRNA, but not in cardiac ACE2 activity [11, 40]. It has been hypothesized that the increase in angiotensin II levels following therapy with ARBs (but not ACE-I), by increasing the substrate load on ACE2, is responsible for its upregulation [57]. This hypothesis is unlikely, given the number of ACE2 substrates and the low level of angiotensin II variations. It has been demonstrated in

murine neuroblastoma cells that treatment with angiotensin II is associated with an acute decrease in ACE2 activity, which was prevented by treatment with losartan, suggesting that AT1 receptor blockade potentially plays a role [58]. The less consistent effect of ACE-I on ACE2 also seems to be tissue dependent, as they have been demonstrated to increase ACE2 activity in kidneys in a murine model [59], and to increase intestinal ACE2 mRNA levels in patients treated with ACE-I compared with in those on ARBs [60]. Nevertheless, discrepancies between ACE2 mRNA levels and ACE2 activity have been reported [11, 59, 61], and the circulating and urinary levels of ACE2 are not a good indicator of the activity of the membrane-bound form. Thus, ACE-I and ARBs may have different influences on the course of SARS-CoV-2 infection. In addition, data regarding the effect of RAS blockers on ACE2 expression in lungs are lacking. It should be noted however, that SARS-CoV infection was reported in in vitro models of ACE2-negative cells, whereas some ACE2-positive cells were spared, suggesting that other receptors, co-receptors or mechanisms are involved in the interaction between cells and virus [62].

Finally, the concerns about the use of RAS blockers in the context of COVID-19 are also based on observational studies. Individuals infected with SARS-CoV-2 with a history of diabetes, hypertension or cardiovascular disease appear to have a higher risk of developing a severe form of COVID-19, with higher mortality [1, 3-7]. In the landmark Chinese cohort study (n = 1099 patients), 23.7% of the individuals with confirmed COVID-19 had hypertension, 16.2% had diabetes and 8% had ischaemic heart disease or cerebrovascular disease [4]. In another study from Wuhan, China, the most common co-morbidities of 32 non-survivors from a group of 52 patients with COVID-19 admitted to an intensive care unit were diabetes (22%) and cardiovascular disease (22%) [8]. In another Chinese case series of 187 patients with confirmed COVID-19, 35.3% had underlying cardiovascular disease, including hypertension, coronary heart disease and cardiomyopathy. The mortality rate of patients treated with RAS blockers was numerically higher compared with patients without ACE-I or ARBs (36.8% vs 25.6%, respectively), albeit not reaching statistical significance [63]. The continuation of RAS blockers could also enhance acute kidney injury, a frequent complication (3–15%) among individuals with severe COVID-19 [1, 4, 7, 64-66]. Major drawbacks of these studies were that adjusted multivariable analyses were not performed, and that confounding factors, such as age or a coexisting condition (e.g. hypertension, diabetes, obesity or chronic organ failure), can explain these results. Finally, whereas chronic medications of individuals infected with COVID-19 were not reported

in the vast majority of these observational studies [1, 4, 7, 8, 64-66], the Patient-Centered Evaluative Assessment of Cardiac Events (PEACE) study on 1.7 million adults in China recently reported that 30.1% of the Chinese adults aged 35–75 years with systemic hypertension received antihypertensive medication, with RAS blockers being the second most commonly used treatment, concerning 28.5% of patients [9].

Potential beneficial effects

Hypotheses regarding the facilitating role of RAS blockers in SARS-CoV-2 infection should be analysed cautiously because they come from non-randomized trials with many confounding factors or from small in vitro or animal studies. In contrast, RAS blockers may also have several beneficial effects in patients with COVID-19. ACE2 has been shown to reduce inflammation [46] and RAS blockers have been associated, in animal studies, with a reduction in severe lung injury in the setting of viral pneumonias [16-19]. The binding of the SARS-CoV-2 spike protein to ACE2 leads to ACE2 downregulation in the infected cells, leading to an increased effect of angiotensin II, which induces pulmonary vasoconstriction and increases pulmonary vascular permeability by overstimulation of AT1 receptor, thus promoting lung injury [17, 18, 67]. Interestingly, high levels of plasma angiotensin II were reported in patients with COVID-19, and were associated with total viral load and degree of lung injury [68]. Therefore, AT1 receptor blockade, by increasing ACE2 expression and angiotensin (1–7) production and reducing angiotensin II deleterious effects, could have the potential to prevent lung injury [16, 19, 69].

Recently, dedicated observational studies have reported reassuring findings. In a Chinese cohort enrolling 1128 adult patients with hypertension (including 188 patients taking ACE-I or ARBs) and hospitalized for COVID-19, RAS blockers were independently associated with a reduction in the 28-day all-cause mortality rate compared with other antihypertensive drugs (adjusted hazard ratio 0.42, 95% confidence interval [CI] 0.19–0.92; $P = 0.03$) [29]. In another study from the Wuhan region, among 1178 patients, 30.7% were hypertensive, of whom 31.8% were taking ACE-I or ARBs. No association was found between the use of RAS blockers and the severity of COVID-19 or the fatality rate [23]. An Italian case-control study among 6272 patients with SARS-CoV-2 infection demonstrated that cases were more likely to be treated with ACE-I or ARBs than controls, but also with other antihypertensive drugs, because of a higher prevalence of cardiovascular disease, and that RAS

blockers did not affect the susceptibility to COVID-19 or its severity [24]. In a third large observational study in New York, among 12,594 patients tested for COVID-19, 5894 (46.8%) had a positive test, 1002 (17.0%) had a severe form and 4357 (34.6%) were hypertensive, of whom 634 (24.6%) had a severe illness. Previous treatment with RAS blockers was not associated with a higher risk of testing positive for COVID-19 or of a severe form of the disease [27]. In another study, among 1705 patients with SARS-CoV-2 infection, eight deaths occurred in the ACE-I/ARBs group (3.8%) and 34 in the control group (2.1%) [25]. Finally, a UK study involving 1200 patients with COVID-19 reported a lower rate of death or transfer to a critical illness unit among those treated with ACE-I or ARBs (odds ratio 0.63, 95% CI 0.47–0.84; $P < 0.01$) [21].

Finally, RAS blocker treatment is beneficial in case of heart failure, type 1 or 2 myocardial infarction or myocarditis, which are common complications of COVID-19, where the presence of acute cardiac injury has been reported in up to 10% of patients [6, 7]. In an autopsy study of patients who died from SARS infection, viral RNA was present in heart samples from 35% of the patients, and was associated with marked reductions in ACE2 protein expression [70]. In one murine model, ACE2 deficiency was associated with adverse left ventricular remodelling after myocardial infarction by potentiation of angiotensin II effects [71]. As a result, it may be hypothesized that although the heart may be particularly affected by SARS-CoV strains, discontinuation of RAS blockers in patients with COVID-10 could render them even more vulnerable to early and late complications.

Value of RAS blockers in patients without COVID-19

Any potential risk associated with ACE-I should also be balanced by the well-described adverse impact of discontinuing RAS blockers in individual patients with systemic hypertension or established cardiovascular disease [72-75]. In the Get With The Guidelines Heart Failure (GWTG-HF) registry, discontinuation of RAS blockers among patients hospitalized for acute heart failure with reduced ejection fraction was associated with high rates of mortality or readmission after discharge [73]. The Withdrawal of Pharmacological Treatment for Heart Failure in Patients with Recovered Dilated Cardiomyopathy (TRED-HF) trial demonstrated clinical worsening 6 months after withdrawal of heart failure medications (including RAS blockers) among patients with recovered dilated cardiomyopathy [74]. In a study including African Americans with heart failure with reduced ejection fraction, RAS blocker dose reduction or discontinuation was associated with a longer median length of hospital stay

[76]. In a study evaluating ACE-I treatment following myocardial infarction, a high incidence of ischaemia-related events occurred after ACE-I withdrawal, suggesting a rebound phenomenon [77]. In a study evaluating haemodynamic and hormonal responses to captopril therapy among seven patients, captopril withdrawal resulted in abrupt increases in circulating angiotensin II levels, arterial pressure, pulse rate and plasma norepinephrine, but without a decrease in cardiac function [78].

RAS blockers have also demonstrated some benefits in several conditions in major clinical trials (Table A.1). The main indications for ACE-I or ARBs are summarized in Table A.2.

Pooled analysis

We conducted a pooled analysis to evaluate the effect of ACE-I/ARBs on all-cause mortality in patients with established COVID-19. Searches of PubMed and Embase Central databases were carried out from December 2019 until July 2020. Predefined search terms were: 'COVID-19' OR 'severe acute respiratory syndrome coronavirus 2' OR 'coronavirus' OR 'SARS-CoV-2' OR 'coronavirus disease 2019' OR '2019-nCOV' OR 'novel coronavirus' AND 'renin-angiotensin system' OR 'angiotensin-converting enzyme inhibitors' OR 'angiotensin receptor blockers' OR 'RAS blockers' OR 'RAAS blockers' OR 'ACE inhibitors' OR 'ACEI' OR 'ARB'. Selection was done by two independent reviewers (M. K. and A.F.). Inclusion criteria were defined as follows: (1) published studies including patients with established COVID-19; (2) comparison between RAS blockers and no RAS blockers; (3) studied endpoints included all-cause mortality; and (4) articles written in English. Exclusion criteria were duplicate reports or unpublished studies. Extraction of data on study design and clinical outcomes was performed independently by two reviewers, and discrepancies were resolved by consensus. The endpoint of interest was all-cause mortality at the longest available follow-up. RAS blocker treatment was defined as the administration of ACE-I or ARBs before or during COVID-19. Odds ratios and 95% CIs were estimated using Mantel-Haenszel random-effects models according to DerSimonian and Laird. A fixed-effect model is also reported in Fig. A.1. A P value < 0.05 was considered as statistically significant. Analyses were conducted using Review Manager (RevMan), version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark).

A total of 21 studies were included, comprising a total of 11,539 patients, of whom 3417 (29.6%) were treated with RAS blockers (Fig. A.2). The main characteristics of the included studies are detailed in Table A.3. All-cause mortality occurred in 587/3417 (17.1%) and 982/8122 (12.1%) patients

with and without RAS blocker treatment, respectively (odds ratio 1.00, 95% CI 0.69–1.45; $P = 0.49$; $I^2 = 84\%$) (Fig. 3). Consistent results were found using a fixed-effect model (Fig. A.1).

This analysis had several limitations. First, almost all the studies included in the pooled analysis were observational. Second, the populations were heterogenous, as some studies included all patients treated with RAS blockers, whereas others included only patients with hypertension or diabetes. Third, this analysis was not conducted using patient-level data. Nevertheless, these results support the current international society recommendation to continue ACE-I or ARBs during the COVID-19 pandemic [20].

Ongoing trials and studies

It remains crucial to prospectively determine the effect of RAS blocker continuation or discontinuation on outcomes in patients infected with SARS-CoV-2. Several scientific societies have wisely advised not to stop such treatments in patients with an underlying indication, in the setting of COVID-19 [20]. Despite the considerable challenge of running a randomized controlled trial during a major health crisis, several upcoming or already ongoing studies will assess the efficacy and safety of RAS blockers in patients with COVID-19 (Table 2 and Fig. A.3). Some of these projects are evaluating a strategy of adding a RAS blocker to naïve patients, and testing, therefore, the hypothesis that RAS blockers have a beneficial effect on COVID-19, whereas others are testing the opposite strategy of transient discontinuation of RAS blockers in chronically treated patients with COVID-19.

Conclusions

There is a great deal of interest in the potential role of the RAS and RAS blockers in the development of SARS-CoV-2 infection. This review and the results of the pooled analysis of observational studies support the continuation of RAS blockers during the COVID-19 pandemic. Despite the major challenges of conducting randomized trials during the COVID-19 pandemic, several ongoing prospective studies will provide evidence with respect to the safety and efficacy of RAS blocker treatment in this setting. Before the results of these studies, and based on large cohort analysis and this pooled analysis, it is reasonable to recommend continuing RAS blockers.

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References

[1] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.

[2] Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270-3.

[3] Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020;8:e21.

[4] Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708-20.

[5] Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol 2020;109:531-8.

[6] Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020;17:259-60.

[7] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.

[8] Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475-81.

[9] Lu J, Lu Y, Wang X, et al. Prevalence, awareness, treatment, and control of hypertension in China: data from 1.7 million adults in a population-based screening study (China PEACE Million Persons Project). Lancet 2017;390:2549-58.

[10] Nakamura T, Kawachi K, Saito Y, et al. Effects of ARB or ACE-inhibitor administration on plasma levels of aldosterone and adiponectin in hypertension. Int Heart J 2009;50:501-12.

[11] Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation 2005;111:2605-10.

[12] Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020;181:271-80 e8.

[13] Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395:565-74.

[14] Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. J Virol 2020;94.

[15] Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science 2020;367:1444-8.

[16] Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev Res 2020;81:537-40.

[17] Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 2005;436:112-6.

[18] Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 2005;11:875-9.

[19] Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med 2020;46:586-90.

[20] HFSA/ACC/AHA Statement Addresses Concerns Re: Using RAAS Antagonists in COVID-19. Available at: https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19.

[21] Bean DM, Kraljevic Z, Searle T, et al. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are not associated with severe COVID-19 infection in a multi-site UK acute hospital trust. Eur J Heart Fail 2020;22:967-74.

[22] Conversano A, Melillo F, Napolano A, et al. Renin-Angiotensin-Aldosterone System Inhibitors and Outcome in Patients With SARS-CoV-2 Pneumonia. A Case Series Study. Hypertension 2020;76:e10–e2.

[23] Li J, Wang X, Chen J, Zhang H, Deng A. Association of Renin-Angiotensin System Inhibitors With Severity or Risk of Death in Patients With Hypertension Hospitalized for Coronavirus Disease 2019 (COVID-19) Infection in Wuhan, China. JAMA Cardiol 2020;5:825-30.

[24] Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19. N Engl J Med 2020;382:2431-40.

[25] Mehta N, Kalra A, Nowacki AS, et al. Association of Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Testing Positive for Coronavirus Disease 2019 (COVID-19). JAMA Cardiol 2020.

[26] Meng J, Xiao G, Zhang J, et al. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. Emerg Microbes Infect 2020;9:757-60.

[27] Reynolds HR, Adhikari S, Pulgarin C, et al. Renin-Angiotensin-Aldosterone System Inhibitors and Risk of Covid-19. N Engl J Med 2020;382:2441-8.

[28] Yang G, Tan Z, Zhou L, et al. Effects of Angiotensin II Receptor Blockers and ACE (Angiotensin-Converting Enzyme) Inhibitors on Virus Infection, Inflammatory Status, and Clinical Outcomes in Patients With COVID-19 and Hypertension: A Single-Center Retrospective Study. Hypertension 2020;76:51-8.

[29] Zhang P, Zhu L, Cai J, et al. Association of Inpatient Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Mortality Among Patients With Hypertension Hospitalized With COVID-19. Circ Res 2020;126:1671-81.

[30] Zhou X, Zhu J, Xu T. Clinical characteristics of coronavirus disease 2019 (COVID-19) patients with hypertension on renin-angiotensin system inhibitors. Clin Exp Hypertens 2020;42:656-60.

[31] Nehme A, Zouein FA, Zayeri ZD, Zibara K. An Update on the Tissue Renin Angiotensin System and Its Role in Physiology and Pathology. J Cardiovasc Dev Dis 2019;6:14.

[32] Santos RAS, Oudit GY, Verano-Braga T, Canta G, Steckelings UM, Bader M. The renin-angiotensin system: going beyond the classical paradigms. Am J Physiol Heart Circ Physiol 2019;316:H958-H70.

[33] Hollenberg NK, Fisher ND, Price DA. Pathways for angiotensin II generation in intact human tissue: evidence from comparative pharmacological interruption of the renin system. Hypertension 1998;32:387-92.

[34] Belova LA. Angiotensin II-generating enzymes. Biochemistry (Mosc) 2000;65:1337-45.

[35] Dzau VJ. Multiple pathways of angiotensin production in the blood vessel wall: evidence, possibilities and hypotheses. J Hypertens 1989;7:933-6.

[36] Papademetriou V. The potential role of AT(1)-receptor blockade in the prevention and reversal of atherosclerosis. J Hum Hypertens 2002;16 Suppl 3:S34-41.

[37] Matavelli LC, Siragy HM. AT2 receptor activities and pathophysiological implications. J Cardiovasc Pharmacol 2015;65:226-32.

[38] Donoghue M, Hsieh F, Baronas E, et al. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. Circ Res 2000;87:E1-9.

[39] Harmer D, Gilbert M, Borman R, Clark KL. Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. FEBS Lett 2002;532:107-10.

[40] Tipnis SR, Hooper NM, Hyde R, Karran E, Christie G, Turner AJ. A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase. J Biol Chem 2000;275:33238-43.

[41] Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med 2020;14:185-92.

[42] Rice GI, Thomas DA, Grant PJ, Turner AJ, Hooper NM. Evaluation of angiotensin-converting enzyme (ACE), its homologue ACE2 and neprilysin in angiotensin peptide metabolism. Biochem J 2004;383:45-51.

[43] Thomas MC, Pickering RJ, Tsorotes D, et al. Genetic Ace2 deficiency accentuates vascular inflammation and atherosclerosis in the ApoE knockout mouse. Circ Res 2010;107:888-97.

[44] Tikellis C, Bialkowski K, Pete J, et al. ACE2 deficiency modifies renoprotection afforded by ACE inhibition in experimental diabetes. Diabetes 2008;57:1018-25.

[45] Tikellis C, Thomas MC. Angiotensin-Converting Enzyme 2 (ACE2) Is a Key Modulator of the Renin Angiotensin System in Health and Disease. Int J Pept 2012;2012:256294.

[46] Turner AJ, Hiscox JA, Hooper NM. ACE2: from vasopeptidase to SARS virus receptor. Trends Pharmacol Sci 2004;25:291-4.

[47] Oudit GY, Kassiri Z, Patel MP, et al. Angiotensin II-mediated oxidative stress and inflammation mediate the age-dependent cardiomyopathy in ACE2 null mice. Cardiovasc Res 2007;75:29-39.

[48] Lambert DW, Yarski M, Warner FJ, et al. Tumor necrosis factor-alpha convertase (ADAM17) mediates regulated ectodomain shedding of the severe-acute respiratory syndrome-coronavirus (SARS-CoV) receptor, angiotensin-converting enzyme-2 (ACE2). J Biol Chem 2005;280:30113-9.

[49] Xu J, Sriramula S, Xia H, et al. Clinical Relevance and Role of Neuronal AT1 Receptors in ADAM17-Mediated ACE2 Shedding in Neurogenic Hypertension. Circ Res 2017;121:43-55.

[50] Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003;426:450-4.

[51] He L, Ding Y, Zhang Q, et al. Expression of elevated levels of pro-inflammatory cytokines in SARS-CoV-infected ACE2+ cells in SARS patients: relation to the acute lung injury and pathogenesis of SARS. J Pathol 2006;210:288-97.

[52] Kreutz R, Algharably EAE, Azizi M, et al. Hypertension, the renin-angiotensin system, and the risk of lower respiratory tract infections and lung injury: implications for COVID-19. Cardiovasc Res 2020;116:1688-99.

[53] Furuhashi M, Moniwa N, Mita T, et al. Urinary angiotensin-converting enzyme 2 in hypertensive patients may be increased by olmesartan, an angiotensin II receptor blocker. Am J Hypertens 2015;28:15-21.

[54] Mourad JJ, Levy BI. Interaction between RAAS inhibitors and ACE2 in the context of COVID-19. Nat Rev Cardiol 2020;17:313.

[55] Ishiyama Y, Gallagher PE, Averill DB, Tallant EA, Brosnihan KB, Ferrario CM. Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors. Hypertension 2004;43:970-6.

[56] Zhong JC, Ye JY, Jin HY, et al. Telmisartan attenuates aortic hypertrophy in hypertensive rats by the modulation of ACE2 and profilin-1 expression. Regul Pept 2011;166:90-7.

[57] Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? J Hypertens 2020;38:781-2.

[58] Deshotels MR, Xia H, Sriramula S, Lazartigues E, Filipeanu CM. Angiotensin II mediates angiotensin converting enzyme type 2 internalization and degradation through an angiotensin II type I receptor-dependent mechanism. Hypertension 2014;64:1368-75.

[59] Ferrario CM, Jessup J, Gallagher PE, et al. Effects of renin-angiotensin system blockade on renal angiotensin-(1-7) forming enzymes and receptors. Kidney Int 2005;68:2189-96.

[60] Vuille-dit-Bille RN, Camargo SM, Emmenegger L, et al. Human intestine luminal ACE2 and amino acid transporter expression increased by ACE-inhibitors. Amino Acids 2015;47:693-705.

[61] Wang G, Lai FM, Lai KB, et al. Discrepancy between intrarenal messenger RNA and protein expression of ACE and ACE2 in human diabetic nephropathy. Am J Nephrol 2009;29:524-31.

[62] Gu J, Korteweg C. Pathology and pathogenesis of severe acute respiratory syndrome. Am J Pathol 2007;170:1136-47.

[63] Guo T, Fan Y, Chen M, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). JAMA Cardiol 2020;5:811-8.

[64] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-13.

[65] Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020;323:1061-9.

[66] Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 2020;180:934-43.

[67] Haga S, Yamamoto N, Nakai-Murakami C, et al. Modulation of TNF-alpha-converting enzyme by the spike protein of SARS-CoV and ACE2 induces TNF-alpha production and facilitates viral entry. Proc Natl Acad Sci U S A 2008;105:7809-14.

[68] Liu Y, Yang Y, Zhang C, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci 2020;63:364-74.

[69] Kuster GM, Pfister O, Burkard T, et al. SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19? Eur Heart J 2020;41:1801-3.

[70] Oudit GY, Kassiri Z, Jiang C, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Invest 2009;39:618-25.

[71] Kassiri Z, Zhong J, Guo D, et al. Loss of angiotensin-converting enzyme 2 accelerates maladaptive left ventricular remodeling in response to myocardial infarction. Circ Heart Fail 2009;2:446-55.

[72] Bhagat AA, Greene SJ, Vaduganathan M, Fonarow GC, Butler J. Initiation, Continuation, Switching, and Withdrawal of Heart Failure Medical Therapies During Hospitalization. JACC Heart Fail 2019;7:1-12.

[73] Gilstrap LG, Fonarow GC, Desai AS, et al. Initiation, Continuation, or Withdrawal of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers and Outcomes in Patients Hospitalized With Heart Failure With Reduced Ejection Fraction. J Am Heart Assoc 2017;6.

[74] Halliday BP, Wassall R, Lota AS, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. Lancet 2019;393:61-73.

[75] Pflugfelder PW, Baird MG, Tonkon MJ, DiBianco R, Pitt B. Clinical consequences of angiotensin-converting enzyme inhibitor withdrawal in chronic heart failure: a double-blind, placebo-controlled study of quinapril. The Quinapril Heart Failure Trial Investigators. J Am Coll Cardiol 1993;22:1557-63.

[76] Kane JA, Kim JK, Haidry SA, Salciccioli L, Lazar J. Discontinuation/Dose Reduction of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers during Acute Decompensated Heart Failure in African-American Patients with Reduced Left-Ventricular Ejection Fraction. Cardiology 2017;137:121-5.

[77] van den Heuvel AF, van Gilst WH, van Veldhuisen DJ, de Vries RJ, Dunselman PH, Kingma JH. Long-term anti-ischemic effects of angiotensin-converting enzyme inhibition in patients after myocardial infarction. The Captopril and Thrombolysis Study (CATS) Investigators. J Am Coll Cardiol 1997;30:400-5.

[78] Nicholls MG, Ikram H, Espiner EA, Maslowski AH, Scandrett MS, Penman T. Hemodynamic and hormonal responses during captopril therapy for heart failure: acute, chronic and withdrawal studies. Am J Cardiol 1982;49:1497-501.

[79] Weber MA. Interrupting the renin-angiotensin system: the role of angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists in the treatment of hypertension. Am J Hypertens 1999;12:189S-94S.

[80] CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429-35.

[81] The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.

[82] The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327:685-91.

[83] Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. Circulation 1999;100:2312-8.

[84] Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303-10.

[85] Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet 2003;362:772-6.

[86] McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet 2003;362:767-71.

[87] Cohn JN, Tognoni G, Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345:1667-75.

[88] Cleland JG, Tendera M, Adamus J, et al. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 2006;27:2338-45.

[89] Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359:2456-67.

[90] Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777-81.

[91] The EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet 2003;362:782-8.

[92] The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000;342:145-53.

[93] Braunwald E, Domanski MJ, Fowler SE, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. N Engl J Med 2004;351:2058-68.

[94] Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 1992;327:669-77.

[95] ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. Lancet 1995;345:669-85.

[96] Swedberg K, Held P, Kjekshus J, Rasmussen K, Ryden L, Wedel H. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. Results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). N Engl J Med 1992;327:678-84.

[97] The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet 1993;342:821-8.

[98] Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med 1995;333:1670-6.

[99] The PREAMI Investigators. Effects of angiotensin-converting enzyme inhibition with perindopril on left ventricular remodeling and clinical outcome: results of the randomized Perindopril and Remodeling in Elderly with Acute Myocardial Infarction (PREAMI) Study. Arch Intern Med 2006;166:659-66.

[100] Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 2003;349:1893-906.

[101] Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. Lancet 1999;353:611-6.

[102] Hansson L, Lindholm LH, Ekbom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. Lancet 1999;354:1751-6.

[103] The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002;288:2981-97.

[104] Lindholm LH, Ibsen H, Dahlof B, et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359:1004-10.

[105] Niskanen L, Hedner T, Hansson L, Lanke J, Niklason A, CAPPP Study Group. Reduced cardiovascular morbidity and mortality in hypertensive diabetic patients on first-line therapy with an ACE inhibitor compared with a diuretic/beta-blocker-based treatment regimen: a subanalysis of the Captopril Prevention Project. Diabetes Care 2001;24:2091-6.

[106] Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. Lancet 2000;355:253-9.

[107] Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-60.

[108] Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861-9.

[109] The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. Lancet 1997;349:1857-63.

[110] Halperin JL, Levine GN, Al-Khatib SM, et al. Further Evolution of the ACC/AHA Clinical Practice Guideline Recommendation Classification System: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2016;133:1426-8.

[111] Amat-Santos IJ, Santos-Martinez S, Lopez-Otero D, et al. Ramipril in High-Risk Patients With COVID-19. J Am Coll Cardiol 2020;76:268-76.

[112] Chen Y, Yang D, Cheng B, et al. Clinical Characteristics and Outcomes of Patients With Diabetes and COVID-19 in Association With Glucose-Lowering Medication. Diabetes Care 2020;43:1399-407.

[113] Felice C, Nardin C, Di Tanna GL, et al. Use of RAAS inhibitors and risk of clinical deterioration in COVID-19: results from an Italian cohort of 133 hypertensives. Am J Hypertens 2020.

[114] Gao C, Cai Y, Zhang K, et al. Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. Eur Heart J 2020;41:2058-66.

[115] Huang Z, Cao J, Yao Y, et al. The effect of RAS blockers on the clinical characteristics of COVID-19 patients with hypertension. Ann Transl Med 2020;8:430.

[116] Iaccarino G, Grassi G, Borghi C, et al. Age and Multimorbidity Predict Death Among COVID-19 Patients: Results of the SARS-RAS Study of the Italian Society of Hypertension. Hypertension 2020;76:366-72.

[117] Inciardi RM, Adamo M, Lupi L, et al. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy. Eur Heart J 2020;41:1821-9.

[118] Jung SY, Choi JC, You SH, Kim WY. Association of renin-angiotensin-aldosterone system inhibitors with COVID-19-related outcomes in Korea: a nationwide population-based cohort study. Clin Infect Dis 2020.

[119] Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA 2020;323:2052-9.

[120] Selcuk M, Cinar T, Keskin M, et al. Is the use of ACE inb/ARBs associated with higher in-hospital mortality in Covid-19 pneumonia patients? Clin Exp Hypertens 2020;42:738-42.

[121] Tedeschi S, Giannella M, Bartoletti M, et al. Clinical Impact of Renin-angiotensin System Inhibitors on In-hospital Mortality of Patients With Hypertension Hospitalized for Coronavirus Disease 2019. Clin Infect Dis 2020;71:899-901.

[122] Xu J, Huang C, Fan G, et al. Use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in context of COVID-19 outbreak: a retrospective analysis. Front Med 2020.

Figure legends

Figure 1. The renin-angiotensin system. ACE: angiotensin-converting enzyme; ACE2: angiotensin-converting enzyme 2; ACE-I: angiotensin-converting enzyme inhibitors; ADAM17: a disintegrin and metalloproteinase 17; ARBs: angiotensin II receptor blockers; AT1/AT2 receptor, angiotensin II type 1/2 receptor.

Figure 2. Potential and known effects of renin-angiotensin system blockers in the context of coronavirus disease 2019 (COVID-19). ACE: angiotensin-converting enzyme; ACE2: angiotensin-converting enzyme 2; ACE-I: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; AT1 receptor: angiotensin II type 1 receptor; CKD: chronic kidney disease; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Figure 3. Impact of renin-angiotensin system blockers on all-cause mortality of patients with coronavirus disease 2019. ACE-I: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; CI: confident interval; M-H: Mantel-Haenszel.

Table 1 Main effects of angiotensin II on angiotensin II type 1 and 2 receptors and of angiotensin (1–7) on angiotensin II type 2 and Mas receptors [79].

Effects of angiotensin II on AT1 receptors	Arteriole vasoconstriction (direct and indirect)
	Vascular wall growth effects
	Secretion of aldosterone by adrenals: sodium and water reabsorption; potassium and H^+ excretion
	Secretion of vasopressin by the pituitary gland: water reabsorption; vasoconstriction
	Stimulus for thirst by stimulating the central nervous system
Effects of angiotensin II on AT2 receptors	Arteriole vasodilation
	Cellular growth inhibition
	Apoptosis
Effects of angiotensin (1–7) on AT2 and Mas receptors	Arteriole vasodilation
	Anti-inflammatory
	Antioxidant
	Production of nitric oxide and prostanoids

AT1/AT2 receptor: angiotensin II type 1/2 receptor; H^+: hydrogen ion.

Table 2 Ongoing trials and studies on the renin-angiotensin system and coronavirus disease 2019.

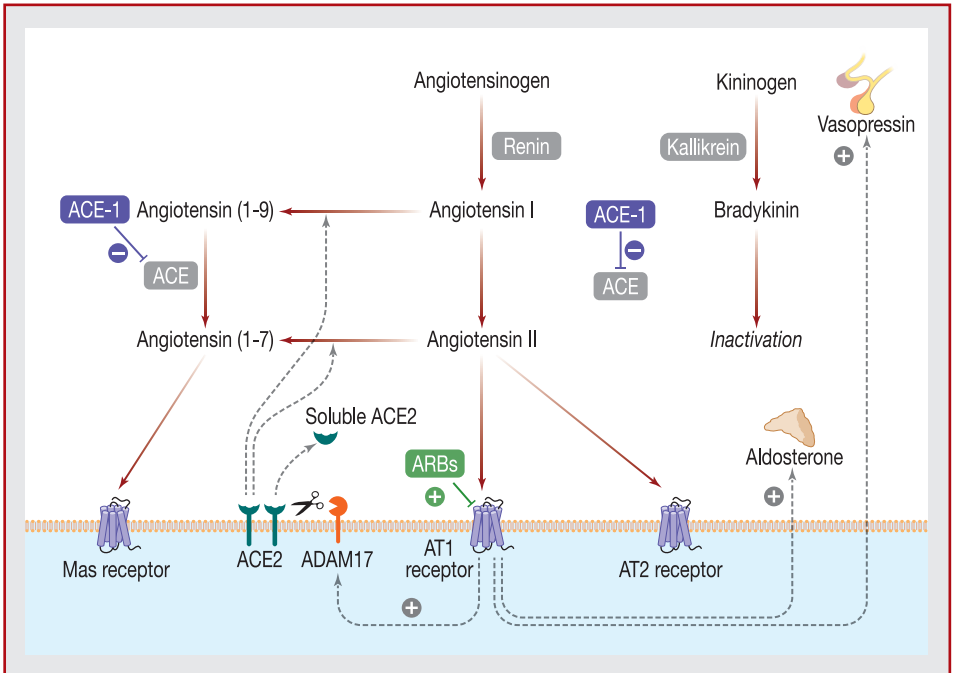
Name (NCT number); location	Status on 08 June 2020	Design	Populations	Interventions	Primary endpoint
AÇORES-2 trial (NCT04329195); France	Recruiting	Multicentre, open-label, randomized trial	554 hospitalized patients with confirmed COVID-19 and on chronic therapy with RAS blockers	Randomization in a 1:1 ratio: discontinuation of RAS blockers (experimental); continuation of RAS blockers (control)	Time to clinical improvement from day 0 to day 28, defined as an improvement of two points on a seven-category ordinal scale or live discharge from hospital, whichever comes first
BRACE-CORONA (NCT04364893); Brazil	Recruiting	Open-label, randomized trial	500 hospitalized patients with confirmed COVID-19 and treated with ACE-I/ARBs	Randomization in a 1:1 ratio: maintenance of ACE-I/ARBs; suspension of ACE-I/ARBs	Days alive and outside the hospital at 30 days
RASCOVID-19 (NCT04351581); Denmark	Recruiting	Single-blind, randomized trial	215 hospitalized patients with confirmed COVID-19 and treated with RAS-inhibiting therapy	Randomization in a 1:1 ratio: continuation of ACE-I/ARBs (experimental); discontinuation of ACE-I/ARBs (control)	Days alive and out of hospital within 14 days after recruitment
ACEI-COVID (NCT04353596); Austria	Recruiting	Multicentre, open-label, randomized trial	208 patients with confirmed COVID-19 and chronic therapy with ACE-I/ARBs	Randomization in a 1:1 ratio: stopping/replacing ACEI/ARB (experimental); further	Combination of maximum SOFA score and death at 30 days; composite of admission to an ICU, use of mechanical

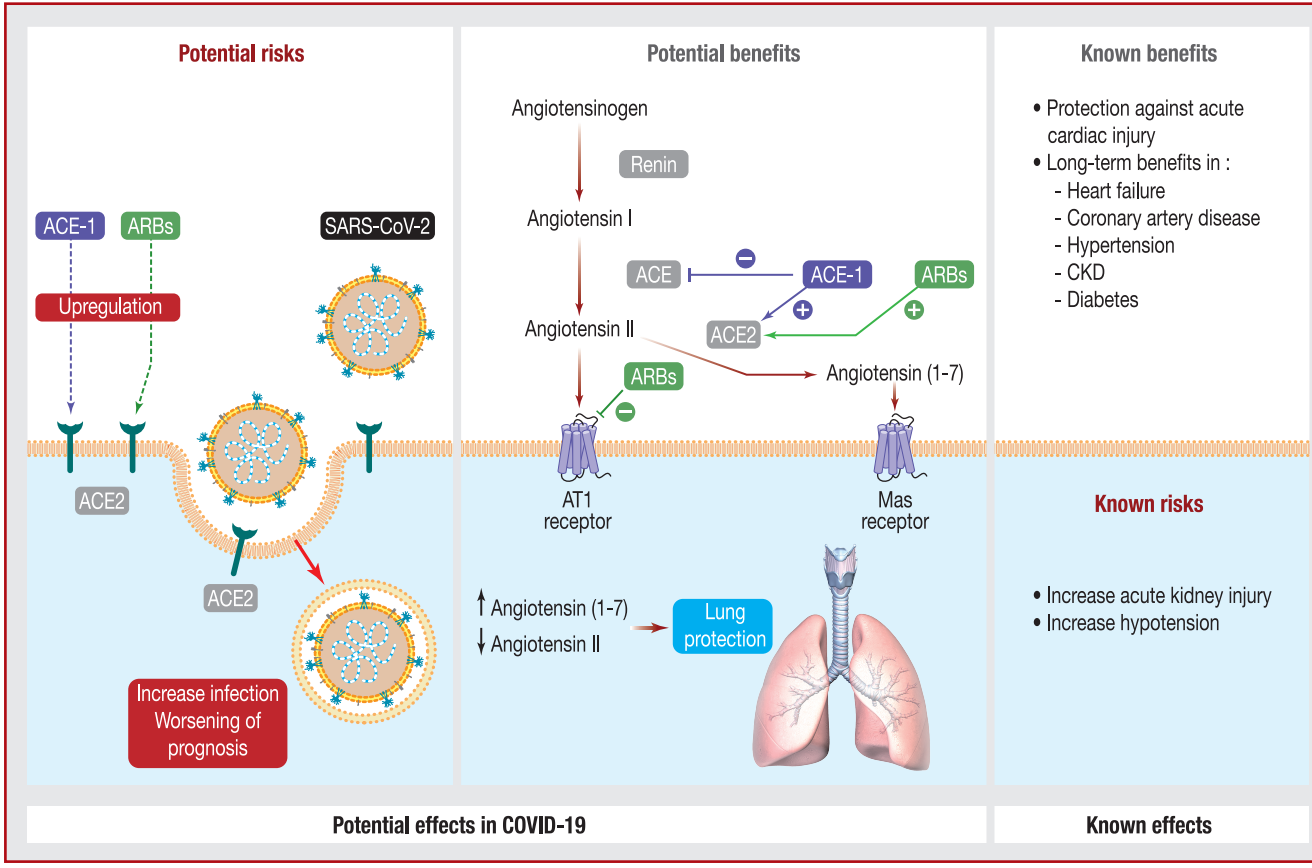
				treatment with ACEI or ARBs (control)	ventilation or all-cause death
CORONACION trial (NCT04330300); Ireland	Recruiting	Open-label, randomized trial	2414 patients aged ≥ 60 years with primary hypertension who are already taking ACE-I/ARBs and are COVID-19 naïve	Two groups: continue ACE-I/ARBs; alternative antihypertensive medication (thiazide, calcium channel blockers)	Number of COVID-19-positive participants who die, require intubation in ICU or require hospitalization for non-invasive ventilation
REPLACECOVID (NCT04338009); USA	Enrolling by invitation	Single-blind, randomized trial	152 hospitalized patients with COVID-19 suspicion and use of ACE-I/ARBs before admission	Two groups: discontinuation of ACE-I/ARBs (experimental); continuation of ACE-I/ARBs (control)	Global rank score that ranks patient outcomes according to four factors: (1) time to death; (2) number of days supported by invasive mechanical ventilation or extracorporeal membrane oxygenation; (3) number of days supported by renal replacement therapy or pressor/inotropic therapy; and (4) a modified SOFA score
Losartan for patients with COVID-19 not requiring hospitalization (NCT04311177); USA	Recruiting	Multicentre, double-blind randomized trial	516 patients with COVID-19 not requiring hospitalization	Randomization in a 1:1 ratio: losartan; placebo	Rate of hospital admission at 28 days

Losartan for patients with COVID-19 requiring hospitalization (NCT04312009); USA	Recruiting	Multicentre, double-blind randomized trial	200 patients with COVID-19 requiring hospitalization	Randomization in a 1:1 ratio: losartan; placebo	SOFA score at 28 days
Do Angiotensin Receptor Blockers Mitigate Progression to Acute Respiratory Distress Syndrome With SARS-CoV-2 Infection (NCT04340557); USA	Recruiting	Open-label, randomized trial	200 hospitalized patients with confirmed COVID-19 and oxygen requirement of at least 2 L/min	Two groups: losartan; standard of care	Number of subjects requiring transfer into ICU for mechanical ventilation because of respiratory failure at 45 days
PRAETORIAN-COVID trial (NCT04335786); Netherlands	Recruiting	Double-blind, randomized trial	651 hospitalized adult patients infected with SARS-CoV-2	Two groups: valsartan; placebo	First occurrence of ICU admission, mechanical ventilation or death
Telmisartan for Treatment of COVID-19 Patients (NCT04355936); Argentina	Recruiting	Open-label, randomized trial	400 patients with confirmed COVID-19	Two groups: telmisartan; standard care	Serum C-reactive protein concentrations at days 1, 8 and 15
Study of Open Label Losartan in COVID-19 (NCT04335123); USA	Recruiting	Open-label, phase 1 clinical trial	50 patients with COVID-19 and respiratory failure	One group: losartan	Number of participants with treatment-related adverse events at day 14
COVID-MED trial (NCT04328012); USA	Recruiting	Multicentre, double-blind,	4000 hospitalized patients with a confirmed diagnosis of	Randomization in a 2:2:2:1 ratio: lopinavir/ritonavir;	Seven-category ordinal scale at 60 days

		randomized trial	COVID-19	hydroxychloroquine; losartan; placebo	
SARS-RAS trial (NCT04331574); Italy	Recruiting	Multicentre, observational study	2000 hospitalized patients with certified diagnosis of COVID-19	One group: patients with COVID-19	Numbers of patients with COVID-19 enrolled who use ACE-I/ARBs as antihypertensive agents; numbers of patients with COVID-19 enrolled with no symptoms, moderate symptoms or severe symptoms of pneumonia who also used ACE-I/ARBs as antihypertensive agents
APN01-COVID-19 trial (NCT04335136); Austria	Recruiting	Double-blind, randomized trial	200 hospitalized patients with confirmed COVID-19	Two groups: recombinant human ACE2; placebo	All cause-death or invasive mechanical ventilation up to 28 days or hospital discharge

ACE-I: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; ACE2: angiotensin-converting enzyme 2; COVID-19: coronavirus disease 2019; ICU: intensive care unit; NCT number: ClinicalTrials.gov identifier; RAS: renin-angiotensin system; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SOFA: sepsis-related organ failure assessment.


Angiotensinogen
Renin
Angiotensin I
ACE-1
Angiotensin (1-9)
ACE
Angiotensin (1-7)
Angiotensin II
ACE-1
ACE
Kininogen
Kallikrein
Bradykinin
Inactivation
Vasopressin
Soluble ACE2
ARBs
Aldosterone
Mas receptor
ACE2
ADAM17
AT1 receptor
AT2 receptor


Potential risks
ACE-1
ARBs
SARS-CoV-2
Upregulation
ACE2
ACE2
Increase infection
Worsening of
prognosis
Potential benefits
Angiotensinogen
Renin
Angiotensin I
ACE
ACE-1
ARBs
ACE2
Angiotensin II
Angiotensin (1-7)
ARBs
AT1
receptor
Mas
receptor
Angiotensin (1-7)
Angiotensin II
Lung
protection
Known benefits
• Protection against acute cardiac injury
• Long-term benefits in :
- Heart failure
- Coronary artery disease
- Hypertension
- CKD
- Diabetes
Known risks
• Increase acute kidney injury
• Increase hypotension
Potential effects in COVID-19
Known effects

Study or subgroup	ACE-1/ARBs Events	ACE-1/ARBs Total	ACE-1/ARBs Events	ACE-1/ARBs Total	Weight	Odds ratio M-H, Random, 95% CI
Richardson et al.	130	667	254	699	7.0%	0.42 [0.33-0.54]
Bean et al.	106	399	182	801	7.0%	1.23 [0.93-1.62]
Iaccarino et al.	106	655	82	936	6.9%	2.01 [1.48-2.73]
Jung et al.	33	377	51	1,577	6.6%	2.87 [1.82-4.52]
Tedeschi et al.	68	175	63	136	6.6%	0.74 [0.47-1.16]
Li et al.	21	115	56	247	6.2%	0.76 [0.44-1.33]
Conversano et al.	21	69	21	122	5.8%	2.10 [1.05-4.22]
Mehta et al.	8	212	34	1,523	5.5%	1.72 [0.78-3.76]
Zhang et al.	7	188	92	940	5.5%	0.36 [0.16-0.78]
Felice et al.	15	82	18	51	5.4%	0.41 [0.18-0.92]
Xu et al.	11	40	21	61	5.2%	0.72 [0.30-1.73]
Inciardi et al.	9	30	17	69	4.9%	1.31 [0.51-3.40]
Guo et al.	7	19	36	168	4.7%	2.14 [0.79-5.83]
Gao et al.	4	183	19	527	4.5%	0.60 [0.20-1.78]
Selçuk et al.	31	74	4	39	4.3%	6.31 [2.03-19.58]
Chen et al.	4	32	10	61	4.0%	0.73 [0.21-2.54]
Yang et al.	2	43	11	83	3.2%	0.32 [0.07-1.51]
Zhou et al.	2	15	5	21	2.7%	0.49 [0.08-2.97]
Amat-Santos et al.	2	5	2	6	1.7%	1.33 [0.11-15.70]
Huang et al.	0	20	3	30	1.2%	0.19 [0.01-3.92]
Meng et al.	0	17	1	25	1.1%	0.47 [0.02-12.14]
Total (95% CI)		3,417		8,122	100%	1.00 [0.69-1.45]
Total events	587		982			

Heterogeneity : Tau^2 = 0.49 ; Chi^2 = 128.28, df = 20 (P < 0.00001) ; I^2 = 84%

Total for overall effects : Z = 0.00 (P = 1.00)