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CLINICAL RESEARCH

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

Syndrome de détresse respiratoire aigue au coronarovirus-2 et bloqueurs du système rénine angiotensine : une revue et métaanalyse des données globales

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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

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.

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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.

MOTS CLÉS
Bloqueurs du SRA ;
COVID-19

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.

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

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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 lev-

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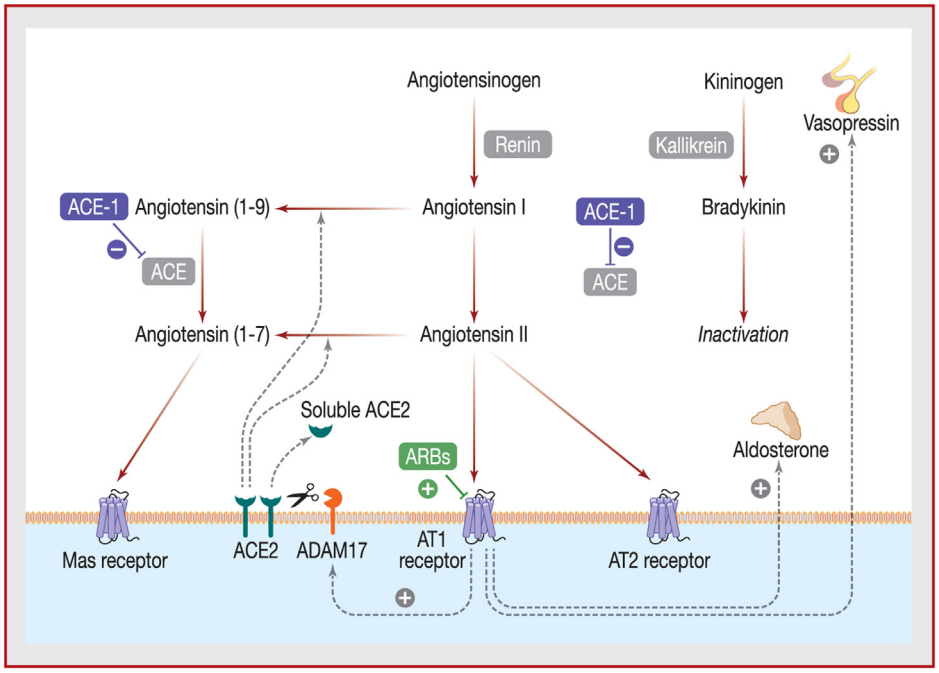

Figure 1. The renin-angiotensin system. ACE: angiotensin-converting enzyme; ACE2: angiotensin-converting enzyme 2; ACE-I: angiotensin-converting enzyme inhibitors; ADAM17: a disintegrin and metalloproteinase 17; ARBs: angiotensin II receptor blockers; AT1/AT2 receptor, angiotensin II type 1/2 receptor.

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.

els 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

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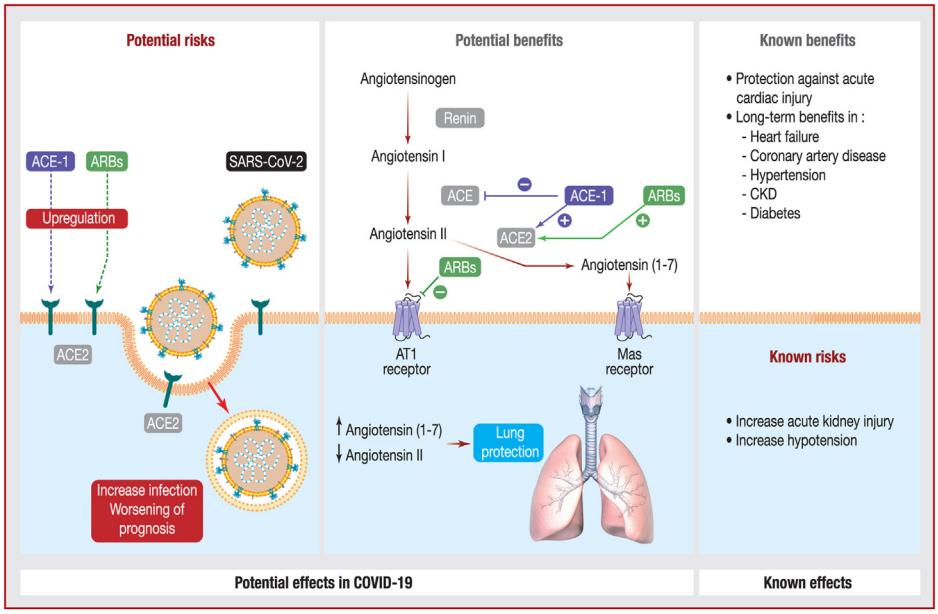

Figure 2. Potential and known effects of renin-angiotensin system blockers in the context of coronavirus disease 2019 (COVID-19). ACE: angiotensin-converting enzyme; ACE2: angiotensin-converting enzyme 2; ACE-I: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; AT1 receptor: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

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

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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) [80—109]. The main indications for ACE-I or ARBs are summarized in Table A.2 [110].

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:

- published studies including patients with established COVID-19;
- comparison between RAS blockers and no RAS blockers;
- studied endpoints included all-cause mortality and;
- 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 [111—122]. 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

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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 treatment with ACEI or ARBs (control)	Combination of maximum SOFA score and death at 30 days; composite of admission to an ICU, use of mechanical ventilation or all-cause death
CORONACION trial (NCT04330300); Ireland	Recruiting	Open-label, randomized trial	2414 patients aged $\geq$ 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

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Table 2 (*Continued*)

Name (NCT number); location	Status on 08 June 2020	Design	Populations	Interventions	Primary endpoint
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

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Table 2 (*Continued*)

Name (NCT number); location	Status on 08 June 2020	Design	Populations	Interventions	Primary endpoint
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, randomized trial	4000 hospitalized patients with a confirmed diagnosis of COVID-19	Randomization in a 2:2:2:1 ratio: lopinavir/ritonavir; hydroxychloroquine; losartan; placebo	Seven-category ordinal scale at 60 days
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.

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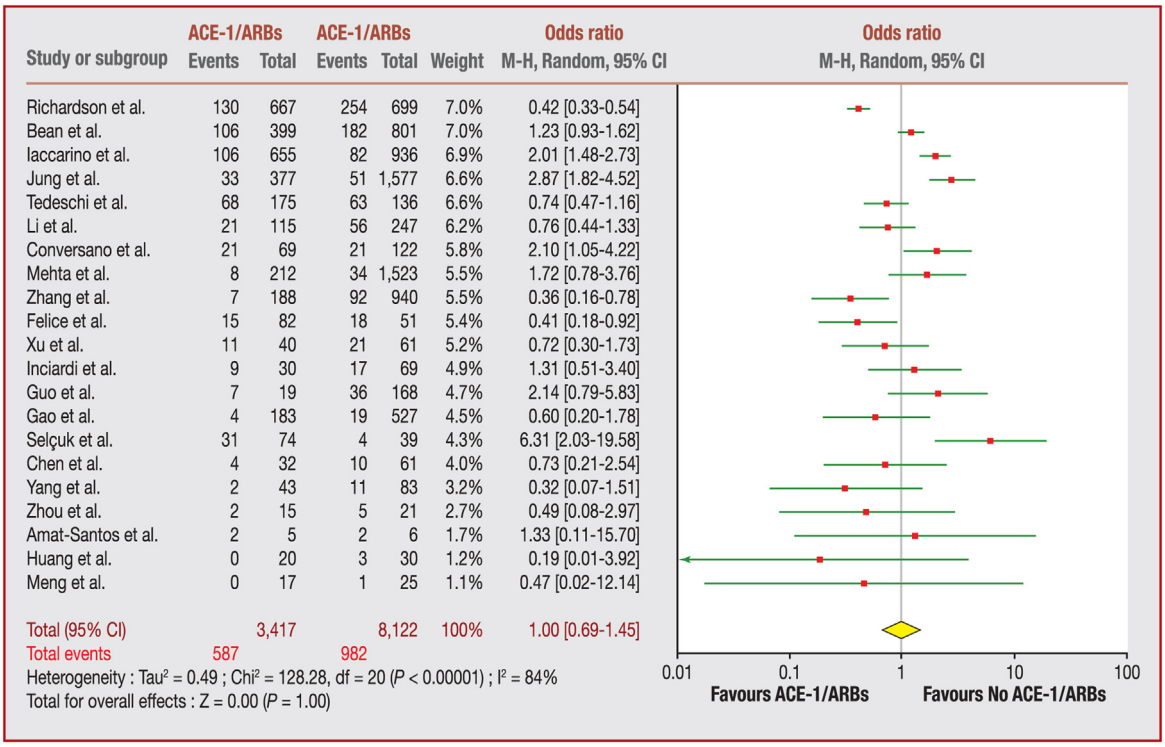

Figure 3. Impact of renin-angiotensin system blockers on all-cause mortality of patients with coronavirus disease 2019. ACE-I: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; CI: confident interval; M-H: Mantel-Haenszel.

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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The other authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2020.09.002.

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