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COVID-19

## Drugs acting on renin angiotensin system and use in ill patients with COVID-19

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**Summary** Some concerns about the prescription of drugs acting on the renin-angiotensin system (angiotensin-converting enzyme 1 (ACE1) inhibitors, ACEi; angiotensin II type 1 receptor blockers, ARB) have emerged due to SARS COV2 and COVID-19 pandemic. These very legitimate questions are directly the consequence of the recent recognition of the fundamental role of ACE2 (angiotensin-converting enzyme 2) in COVID-19 infection. Indeed, SARS COV2 utilizes ACE2 as a membrane receptor to enter target cells. Consequently, the putative impact of drugs modulating the renin-angiotensin system on the risk of developing severe or fatal severe acute respiratory syndrome in case of COVID-19 infection emerged. As a membrane-bound enzyme (carboxypeptidase), ACE2 inactivates angiotensin II and therefore physiologically counters its effects. Due to a different structure compared with ACE1, ACE2 is insensitive to ACEi. In vitro, both ARBs and ACEi appear able to upregulate ACE2 tissue expression and activity but these results were not confirmed in Humans. The exact impact of both ARBs and ACEi on COVID-19 infection is definitively known and preliminary results are even in favor of a protective role conferred by these drugs. Due to the crucial role of ACE2, some groups support the hypothesis that a modulation of ACE2 expression could represent a valuable therapeutic target could confer protective properties against inflammatory tissue damage in COVID-19 infection.

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So, studies are currently ongoing to test the impact of elevated ACE2 membrane expression, administration of ARB and infusion of soluble ACE2. In summary, based on the currently available evidences and as recommended by several medical societies, ACEi or ARB should not be systematically discontinued because to date no safety signal was raised with the use of these drugs.

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## Abbreviations

ACE1	angiotensin-converting enzyme 1
ACE2	angiotensin-converting enzyme 2
ACEi	angiotensin-converting enzyme inhibitors
ARB	angiotensin II type 1 receptor blockers
COVID-19	coronavirus 2019 infection
MRAs	mineralocorticoid receptor antagonist
RAAS	renin-angiotensin-aldosterone system

## Introduction

Cardiovascular diseases and/or risk factors are highly prevalent in severe forms of coronavirus 2019 (COVID-19) infection [1,2]. Clinical manifestations are principally respiratory, but some patients may also show cardiovascular complications [1]. The present article reviews the current state of knowledge regarding the relation between the renin-angiotensin-aldosterone system (RAAS), particularly angiotensin-converting enzyme 2 (ACE2), and COVID-19, and between RAAS blockers and COVID-19.

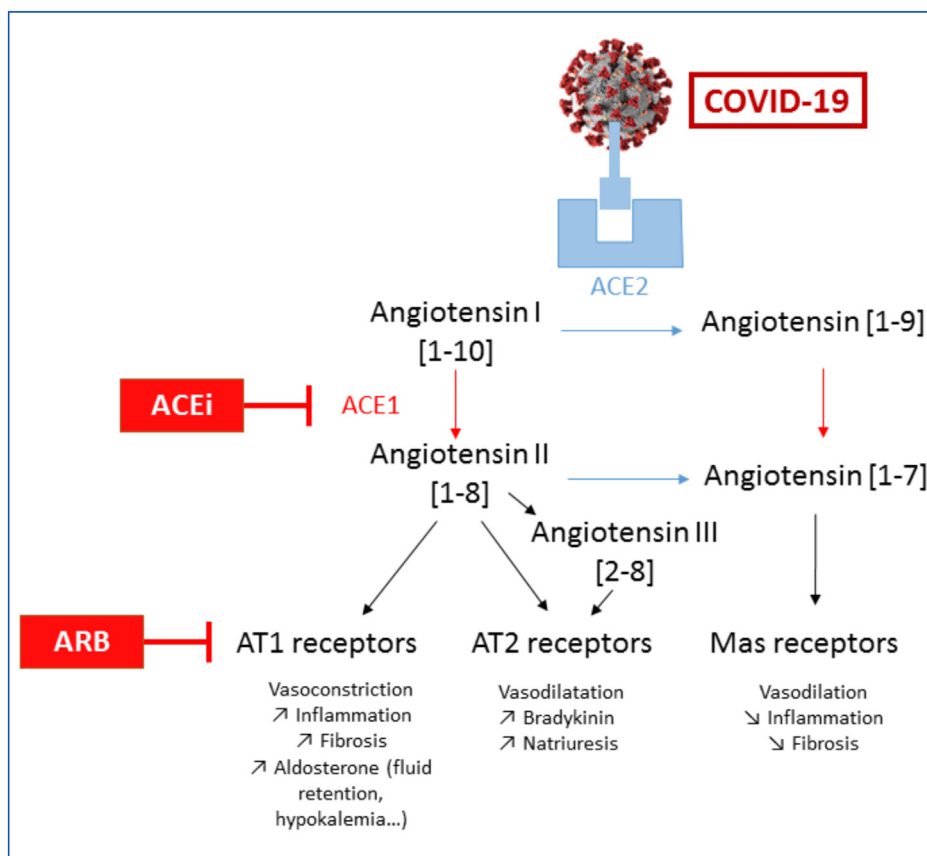
## ACE2 and COVID-19

In human physiology, peptides are degraded by a limited number of non-specific extracellular enzymes known as peptidases or proteases. These are membrane proteins, the active sites of which face the extracellular space. Endopeptidases cut within the peptide chain, while exopeptidases release C- or N-terminal amino acids. Angiotensin-converting enzymes are exopeptidases (carboxypeptidases), relatively specific to the amino acids surrounding the cut site, although these may be common to several peptides. Angiotensin-converting enzyme 2 (ACE2) is an enzyme (carboxypeptidase) mainly located in the membrane cell, circulating forms remaining largely underrepresented; ACE2 is homologous to the angiotensin-converting enzyme (formerly simply known as ACE but now better denoted ACE1) first described in 2000 [3,4]. ACE2 acts as a deactivator of angiotensin II (also known as angiotensin-(1-8), an active peptide causing vasoconstriction, pro-fibrosis, pro-inflammation action, stimulating aldosterone secretion by binding to the AT1 receptor), converting it into angiotensin-(1-7), an active peptide with opposite properties to angiotensin II [5]. Several in vitro

studies showed that angiotensin-(1-7), by binding to the Mas receptor, induced vasodilatation and showed anti-fibrosis and anti-inflammatory properties (Fig. 1) [6].

Angiotensin II is also deactivated by an aminopeptidase which converts it into angiotensin III, which induces vasodilatation and increases natriuresis and bradykinin by preferential binding to AT2 receptors with 30-fold greater affinity than for AT1 receptors [7,8]. ACE2 also converts angiotensin 1 (also known as angiotensin-(1-10)) into angiotensin-(1-9), of unknown action, which is further converted into angiotensin-(1-7) by ACE1. The RAAS includes both an "activator" system including the classical and historical angiotensin II/ACE1/AT1R/aldosterone pathway, and an "inhibitor" system including the angiotensin-(1-7)/ACE2/MasR pathway, the latter able both to deactivate angiotensin II and counter its effects. The pharmacology of the angiotensin-(1-7)/ACE2/MasR pathway, in contrast to the angiotensin II/ACE1/AT1R/aldosterone pathway, has been little explored, but some in vitro studies showed beneficial cardiovascular impact when activated, possibly involving GMPc-elevation [8–12]. ACE2 has also been reported to interact with the angiotensin-1 receptor AT1R, targeted by angiotensin II receptor blockers (ARB). ARBs counter AT1R-mediated effects of angiotensin II, thus stimulating angiotensin II liberation; in response to this increase in angiotensin II, they thus increase ACE2 expression [9]. Moreover, ACE2 via the Mas receptors, can hetero-oligomerize with the AT1 receptor and by so doing inhibit the actions of angiotensin II and therefore play a pivotal role in angiotensin II regulation [10]. ACE2 seems to be expressed by the cells of various organs, including heart, brain, kidney, vessels, digestive tract, testicles, adipose tissues, and lung [11–15].

Specific to the SARS CoV2 virus, the SARS-coronavirus spikes (surface glycoprotein) utilize ACE2 as a membrane receptor and the cellular protease TMPRSS2 to enter target cells [16,17]. As a membrane enzyme with an extracellular domain, ACE2 seems to provide the entry into the human cells of SARS CoV2/COVID-19, and therefore acts as a receptor for this coronavirus (Fig. 1) [11,17]. Precise identification of the SARS CoV2 spike glycoproteins and their ACE2 binding site shows the latter to be identical to that of SARS CoV [18], despite the two viruses being distinct and showing no more than 80% homology. The spike protein on the viral surface of SARS-CoV-2 has been shown to bind to ACE2 with 10–20 times the affinity of SARS-CoV-1, the coronavirus responsible for the SARS outbreak in 2003 [19,20]. The higher ACE2 affinity of SARS-CoV-2 may explain the ease of human-to-human transmission in the current pandemic. This spike



**Figure 1.** General view of the renin-angiotensin-aldosterone system in the context of COVID-19 infection. ACE1: angiotensin-converting enzyme 1; ACE2: angiotensin-converting enzyme 2; ARB: angiotensin II receptor blocker; ACEi: angiotensin-converting enzyme inhibitor.

protein activation by TMPRSS2 proteases followed by SARS-CoV-2 binding to the extracellular domain of membrane ACE2 explains how the virus binds to and penetrates the cell (Fig. 1 in reference [5]). Conversely, circulating soluble ACE2, while it can bind to SARS-CoV-2, is unable to induce cell infection. Experimentally, antibodies targeting SARS-CoV-2 seem also to block SARS-CoV-2 binding to ACE2, suggesting possible therapeutic strategies, notably by repositioning certain protease inhibitors [21].

Consequently, ACE2, being the cell entry receptor for SARS-CoV-2, establishes the link between COVID-19 and the RAAS. Some *in vitro* studies reported a positive correlation between membrane expression and/or tissue activity of ACE2 and risk of COVID-19 infection [22]. Moreover, by binding to ACE2, the virus induces a downregulation of ACE2 tissue activity in the infected cells, thus assumed to aggravate COVID-19-induced inflammation in organs such as lungs and also reducing the SARS-CoV-2 infection of other tissues [23]. An *in vitro* study reported decreased ACE2 membrane expression levels in mouse lung following SARS-CoV administration, concomitant with respiratory impairment [11]. Administration of ARB (losartan) improved respiratory function, maybe by restoring ACE2 membrane expression and tissue activity and allowing angiotensin II to bind to pulmonary AT1 receptor thus decreasing the risk of lung injury.

Thus, ACE2 membrane expression levels and/or tissue activity may influence onset of COVID-19 infection and

thus the risk of developing more severe inflammatory tissue injuries. Likewise, in a recent retrospective study of 175 Chinese COVID-19 patients requiring hospital admission, 62% showed hypokalemia, which the authors explained by altered angiotensin II deactivation by a shift in ACE1/ACE2 balance (reduced ACE2 tissue activity under COVID-19) in favor of ACE1, thus inducing aldosterone synthesis and hypokalemia occurrence (Fig. 1) [24]. In line with this hypothesis, the role of mineralocorticoid receptor antagonists must be examined because of their ability to correct hypokalemia but also to increase angiotensin II levels that might play a protective as well as a deleterious role in lung injury.

Therefore, ACE2 and particularly its membrane expression and tissue activity appear to be a key player in COVID-19 infection. The exact roles, however, are complex and may be deleterious in the contamination phase, as ACE2 acts as a receptor to COVID-19 (and severity may correlate with membrane expression and tissue activity) [25,26] while being beneficial in the inflammatory lesion phase [5,27]. Many questions remain unanswered to date. To our knowledge, there are no pharmacologic ACE2 activators or inhibitors available to date in humans while some ACE2 activators are currently used for *in vitro* experiments and/or for veterinary use, including xanthenone and diminazene aceturate, an antiparasitic drug [28]. ACE2 activators have demonstrated *in vitro* interesting antifibrotic and anti-inflammatory properties that could represent a valuable

therapeutic option in SARS-COV2 infection in humans [29]. Some groups suggested using circulating soluble ACE2 to capture as many viruses as possible in plasma, restricting their fixation on cell-membrane ACE2 and thus limiting cell infection. In vitro studies showed that genetically engineered recombinant soluble ACE2 could be a useful therapeutic option [17,30]. Moreover, soluble ACE2 might favor the angiotensin-(1-7)/ACE2/MasR pathway over the angiotensin II/ACE/AT1R/aldosterone pathway, preventing or treating severe inflammatory tissue lesions [11]. Human recombinant soluble ACE2 is an FDA-approved treatment since 2013, with a 2017 phase-II trial in acute respiratory distress syndrome [31], which would allow rapid transfer to COVID-19 application. A dedicated clinical trial must start soon (NCT04287686). Angiotensin II is also hypothesized to confer protection in COVID-19 infection. As angiotensin II represents the major substrate of ACE2, it may compete with the SARS-CoV-2 for the ACE2 receptor (Fig. 1).

## RAAS inhibitors and COVID-19

Angiotensin-converting enzyme inhibitors (ACEi) principally inhibit ACE1, thus blocking angiotensin II release. (Fig. 1); ACE2 is insensitive to ACEis [32,33]. ACEi, like ARB, are widely prescribed as maintenance therapy in several chronic cardiovascular diseases, including arterial hypertension, heart failure and diabetic nephropathy. In vitro models free of COVID-19 reported that ACEi and ARB treatment increased membrane expression of ACE2, especially in the heart [13,34,35] but the few available human studies performed in healthy subjects (COVID-19-free) did not confirm these observations [36–39]. It should also be noted that circulating ACE2 levels may not be in line with membrane expression and tissue activity (the latter possibly varying depending on the tissue). Some in vitro studies reported very low levels of circulating ACE2 despite high membrane (and thus tissue) expression [40]. There is also no evidence on the impact of ACEi/ARB on pulmonary expression of ACE2, notably in the context of COVID-19.

Some groups suggested that increased angiotensin II expression may underlie a “compensatory” response by increasing ACE2 expression [41]. Therefore, by acting at different levels of the system, RAAS inhibitors may result in heterogeneous effects on the peptides and enzymes involved. Whereas ARBs and mineralocorticoid receptor antagonists (MRAs) have been shown to increase membrane ACE2 expression levels and activity in various in vitro and clinical models [42,43], impact of ACEi administration are more debated [4,13,44,45] since findings in animals are inconsistent [46]. In humans, some groups speculated that only ARBs could induce ACE2 levels elevation, as ACEis inhibit angiotensin II release [9] and to date human studies do not allow to draw definitive conclusions [46]. Moreover, ARBs, by blocking AT1 receptors, may favor conversion of angiotensin II into angiotensin III, enhancing the benefit of AT2 receptor activation (Fig. 1). Importantly, cardiovascular diseases themselves, and notably ischemic cardiopathy, heart failure, arterial hypertension and diabetes, were associated with increased ACE2 membrane expression levels and tissue activity in non-COVID-19 animal models, independently of ACEi/ARB administration [2,47–49]. The

clinical situation (infection contracted, not yet contracted, patient with or without cardiovascular history and COVID-19 infection) probably plays a major role. Some studies reported high levels of ACEi/ARB in COVID-19 cases, and especially in severe forms requiring hospital or ICU admission, although it should be noticed that arterial hypertension is very common in the general population, especially in the elderly, for which ACEi/ARB is prescribed in 25–30% of cases [5]. Thus the positive or negative impact of ACEi/ARB in COVID-19 in humans remains unknown and appears complex [50], possibly even depending on clinical stage (viral contamination phase versus tissue inflammation phase) [51,52]. Studies of this question are forthcoming (NCT04330300). Early data extracted from a retrospective cohort performed in China are in favor of a protective impact on overall mortality of ACEis/ARBs but these results must be considered with caution because of the presence of several potential confounders factors not included in analyses [53]. In line with in vitro results, it is suggested that ARBs but not ACEis may confer protection in COVID-19 infection by preventing onset of severe tissue lesions [25,54]; two clinical trials of losartan (ARB) in COVID-19, with or without hospital admission, are due to be launched (NCT04312009 and NCT04311177).

Thus, many scientific societies, including the French Society of Arterial Hypertension (SFHTA) [55] and European Society of Cardiology [56], and many publications [5,56,57] advise against stopping maintenance treatments in an attempt to “prevent” COVID-19 infection, especially as imbalance in blood pressure and heart failure may be deleterious. There remains the difficult and unanswered question of long-course ACEi/ARB therapy in case of COVID-19 infection, especially when severe. An individual and personalized attitude seems essential, considering clinical presentation and severity (hemodynamic, respiratory and renal failure, blood pressure, etc.), and the indications for ACEi or ARB (non-complicated hypertension, heart failure with impaired LVEF, etc.). It should also be noticed that the effects of ACEi and of ARB in COVID-19 infection are unknown, and that the two may not be the same. Guidelines may be rapidly revised in the light of incoming data from ongoing clinical trials, especially concerning ARB.

Other antihypertensive and cardiovascular drugs such as dihydropyridines [58–60], the combination sacubitril-valsartan [61], thiazide diuretics [62] and mineralocorticoid receptor antagonists [42,63,64] affected in vitro ACE2 tissue expression. Regarding beta-blockers, we retrieved a single in vitro study, reporting no impact of atenolol on aortic tissue expression of ACE2 [65]. We found no studies of the impact of loop diuretics on tissue expression of ACE2, although impact is physiologically conceivable.

## Conclusion and perspectives

The present theoretical concerns around ACE2, ACEi/ARB and COVID-19 require more detailed and dedicated human studies. It now seems clear that ACE2 is the key point for SARS COV2 cell-entry, and it therefore represents a reasonable pharmacological target. Reducing ACE2 membrane activity and tissue expression, especially in the lung, to prevent infection or reduce severity in patients not or not yet experiencing inflammatory lesions may represent

a valuable option. To prevent onset of severe inflammatory tissue lesions, especially in the lung, on the other hand, the angiotensin-(1-7)/ACE2/MasR pathway should be favored to the angiotensin II/ACE/AT1R/aldosterone pathway in order to increase ACE2 membrane expression and/or tissue activity as pharmacological and therapeutic target (e.g., by ARBs). All these questions are currently unresolved and are being scrupulously investigated in ongoing trials.

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## Disclosure of interest

The authors declare that they have no competing interest.

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