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Angiotensin-Converting Enzyme 2 and Anti-Hypertensives (Angiotensin Receptor Blockers and Angiotensin Converting Enzyme Inhibitors) in Coronavirus Disease 2019 (COVID-19)

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Abstract

Coronavirus disease 2019 (abbreviated "COVID-19"), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is being defined as the worst pandemic disease of modern times. Several professional health organizations have published position papers stating that there is no evidence to change the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in the management of elevated blood pressure (BP) in the context of avoiding or treating COVID-19 infection. In this article, we review the evidence on the relationship between the Renin-Angiotensin-Aldosterone system and COVID-19 infection. In agreement with current guidelines, patients with hypertension should continue taking anti-hypertensive medications as prescribed without interruption. As ACEIs and ARBs are also used to retard the progression of chronic kidney disease (CKD), we suggest that these recommendations also apply to the use of these agents in CKD. No differences generally exist between ARBs and ACEIs in terms of efficacy in decreasing BP and improve other outcomes, such as all-cause mortality, cardiovascular mortality, myocardial infarction, heart failure, stroke, and end-stage renal disease. ACEIs are associated with cough secondary to accumulation of bradykinin and angioedema, while withdrawal rates due to adverse events are lower with ARBs. Given the equal efficacy but fewer adverse events, ARBs could potentially be a more favorable treatment option in COVID-19 patients at higher risk of developing severe forms of disease.

Keywords: Angiotensin converting enzyme; Hypertension; COVID-19; Coronavirus.

Abbreviations and Acronyms: ACE = angiotensin-converting enzyme; **ACEIs** = ACE inhibitors; **ALI** = acute lung injury; **Ang 1-7** = angiotensin 1-7; **Ang I** = Angiotensin I; **Ang II** = angiotensin II; **ARDS** = acute respiratory distress syndrome; **AT_1R** = Ang II type 1 receptor; **AT2** = type II alveolar cells; **ARBs** = angiotensin receptor blockers; **BP** = blood pressure; **COVID-19** = coronavirus disease 2019; **CV** = cardiovascular; **CVD** = cardiovascular disease; **DM** = diabetes mellitus; **HF** = heart failure; **HTN** = hypertension or hypertensive; **MasR** = Mas receptor; **RAAS** = renin-angiotensin-aldosterone system; **S** = spike; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **SIRS** = systemic inflammatory response syndrome; **TMPRSS2** = type II transmembrane serine proteases.

INTRODUCTION

The global public-health crisis triggered by coronavirus disease 2019 (abbreviated "COVID-19"), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2),[1] is being defined as the worst pandemic disease of modern times.[2, 3] According to the recent statistics from the World Health Organization, this novel coronavirus has already infected nearly 340,000 people worldwide, causing nearly 15,000 deaths.[4] Alarmingly, between 15-20% (~10-15% severe and ~3-5% critical) of SARS-CoV-2 positive individuals are likely to progress towards a severe form of disease, characterized by interstitial pneumonia, with the potential to evolve into acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), and death.[5] The high numbers of patients requiring sub-intensive or intensive care can overwhelm many health care infrastructures, even in highly developed countries.[6]

The exponential growth of the contagion around the world has contributed to heightened speculations and concerns over whether two commonly used anti-hypertensive (HTN) drugs, namely, angiotensin-converting enzyme (ACE) inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), also used for cardiovascular (CV) diseases (CVD) and chronic kidney disease (CKD), may exert either deleterious or beneficial effects in COVID-19 patients compared with other drugs used to reduce blood pressure (BP) or to treat heart failure (HF).[7]

Several professional health organizations have published position papers stating that there is no evidence to change the use of ACEIs or ARBs for the management of elevated BP in the context of avoiding or treating COVID-19 infection (Table 1). In this article, we review the evidence on the relationship between the Renin-Angiotensin-Aldosterone system (RAAS) and COVID-19 infection.

COVID-19 AND ANGIOTENSIN-CONVERTING ENZYME 2 (ACE2): ORIGIN OF THE SPECULATION

Healthcare professionals, physicians, researchers, and patients are actively debating the potential influence of ACEIs and ARBs on poor outcomes among COVID-19 patients, based mainly on the evidence that ACE2 is

a functional receptor for coronaviruses, including SARS-CoV-2.[8] This receptor is located on the surface of type II alveolar cells (AT2) and on lymphocytes, thus explaining the prevalent lung involvement (i.e., interstitial pneumonia and ARDS) and lymphopenia. Moreover, ACE2 is observed on the surface of many other cell types, such as those of the heart, kidney, liver, gastrointestinal tract (especially esophagus, stomach, colon, ileum, rectum) and bladder (Figure 1).[9-11]

Kuba et al.[12] first showed that ACE2 is essential for SARS-CoV infection, acting as its effective host receptor *in vivo*. SARS-CoV infection, through binding of viral S protein to ACE2, seems to reduce receptor expression. Injecting SARS-CoV Spike into mice induces acute lung injury (ALI) *in vivo*, which can be mitigated by blocking the RAAS. Wrapp et al.[13] have recently reported that SARS-CoV-2 binds to ACE2 with 10- to 20-fold higher affinity compared to SARS-CoV. Specifically, the S protein of SARS-CoV-2 virus binds to the catalytic domain of ACE2 inducing internalization of the virus by the cell.

In brief, the RAAS is the central regulatory system for BP control.[14] Additionally, RAAS activation plays a crucial pathogenic role in HTN, through hemodynamic actions and cytokines and intracellular signaling pathways, which ultimately promote many adverse cellular processes implicated in systemic damage.[14] In the RAAS, Angiotensin I (Ang I) is converted to angiotensin II (Ang II) by ACE. Ang II mediates vasoconstrictive, pro-inflammatory and pro-oxidative effects through agonism at Ang II type 1 receptor (AT_1R).[15] ACE2 converts Ang II to angiotensin 1-7 (Ang1-7), which finally binds to Mas receptor (MasR) and mediates many beneficial actions, including vasodilation and anti-inflammatory, anti-oxidant and anti-apoptotic effects.[15] Thus, ACE2/Ang1-7/MasR axis has opposite actions to ACE/AngII/AT_1R axis (Figure 2).

ACE2, a homologue of ACE, is an integral cell membrane protein with a catalytic domain on the extracellular surface exposed to vasoactive peptides.[16] ACE2 is a monocarboxypeptidase whose major role is converting Ang II to Ang 1–7,[16] with vasodilatory and antifibrotic actions[17] when it activates MasR.[18] Moreover, ACE2 also converts Ang I to Ang 1-9 which can be further converted by ACE into Ang 1-7. Thus, ACE2 limits the adverse vasoconstrictor and profibrotic effects of Ang II through its degradation and by counteracting its actions through the formation of Ang 1–7. The high expression of ACE2 in heart, type II

alveolar cells (AT2), capillary endothelium[19] and enterocytes,[20] demonstrates its essential role in CV and immune systems,[20] being principally involved in heart function and the development of HTN and complications of diabetes mellitus (DM).

As previously discussed, SARS-CoV-2 penetrates the cell through ACE2, but also necessitates type II transmembrane serine proteases (TMPRSS2) for effective priming of viral Spike (S) protein. The binding of coronavirus S protein to ACE2 triggers a conformational change in the S protein, allowing for proteolytic digestion by TMPRSS2, which enables viral and cell membrane fusion.[21] This was recently confirmed by the evidence that camostat mesylate, a protease TMPRSS2 inhibitor, blocks viral entry and may be a promising drug for SARS-CoV-2 infection.[21, 22] As ACE2 is a functional receptor for SARS- CoV-2, many healthcare professionals have begun to reconsider the safety and effects of anti-HTN therapy with ACEIs or ARBs in patients during the COVID-19 outbreak-; and, despite statements by medical organizations, they began to question whether patients with COVID-19 and HTN maintained on ACEIs or ARBs to decrease BP values (or for other conditions such as CVD and CKD) should change to another anti-HTN pharmacological agent.[23] Such considerations contributed to the current controversy.

THE USE OF ARBs OR ACEIs IN PATIENTS AT HIGH RISK OF SEVERE COVID-19: DELETERIOUS OR BENEFICIAL?

It has been hypothesized that increased levels of ACE2 may facilitate COVID-19 infection, such that administering ARBs or ACEIs might increase the risk of developing severe and fatal COVID-19.[24-26] As discussed later in this section, this premise is based in part on the findings in some, but not all, studies that ARBs and ACEIs may increase ACE2 levels. According to the most recent studies on COVID-19, it appears that HTN is one of the most important factors associated with poor prognosis at an early stage of COVID-19 infection.[27-32] HTN, however, has also been found to be associated with decreased baseline levels of ACE2 expression. Unfortunately, most of these early COVID-19 studies have not been adjusted for age or other co-morbidities. The last report on the characteristics of deceased COVID-19 positive patients in Italy officially released on March 20, 2020 by the Italian Ministry of Health through the National Institute of Health

(Istituto Superiore di Sanità; ISS) showed that the most common concurrent medical co-morbidities observed were arterial HTN (73.8%; 355 of 481), DM (33.9%; 163 of 481), ischemic cardiopathy (30.1%; 145 of 481), and atrial fibrillation (22%; 106 of 481).[33] Prior to hospitalization, 36% (173 of 481) of fatal COVID-19 patients were on treatment with ACEIs, while 16% (77 of 481) were on treatment with ARBs (odds ratio, 2.26; 95% confidence interval, 95% CI, 1.66-3.09; p<0.001). Nevertheless, these numbers are preliminary and may not precisely reflect adjusted differences in risk. It is virtually impossible to precisely identify all medical therapies before admission from medical records[33]. Moreover, patients with elevated BP on admission may be noted to have a history of chronic HTN in their medical record, and such coding may reflect provider biases from the current infectious illness. The median age of SARS-CoV-2 positive patients who died was 78.5 years (median: 80 years; range: 31-103 years; interquartile range, 73-85 years). Since HTN prevalence increases in parallel with aging, this pattern may represent the expected prevalence for the given age group. Therefore, although the number of fatal COVID-19 positive patients treated with ACEIs was more than twice the number of those treated with ARBs, one cannot definitely conclude risks or benefits of these therapies due to confounding variables of age, HTN, as well as the impact of yet unidentified comorbidities on outcome with the COVID-19 pandemic.

In a recent study, in which potential drugs targeting SARS-CoV-2 were evaluated, the authors reported that ARBs (e.g., irbesartan) may associate with some human coronaviruses-associated host proteins in the human interactome.[34] Irbesartan targets the *SLC10A1* gene (solute carrier family 10 member 1), which interacts with *C11orf74* gene, a potential transcriptional repressor that interacts with the non-structural protein 10 (NSP10) of SARS-CoV and participates in CoV replication fidelity.[35]

Crackower and co-workers[36] reported that disruption of ACE2 results in increased Ang II levels and impaired cardiac function, whereas other authors showed that ACE2 overexpression reduced left ventricular hypertrophy and myocardial fibrosis in HTN rats.[37] Lower cardiac ACE2 concentrations are observed in HTN,[37, 38] CVD associated with DM,[39] and Ang II-induced cardiac dysfunction,[40] suggesting that augmenting ACE2 could have beneficial therapeutic effects on the CV system. In numerous studies carried out in animal models, both ACEIs and ARBs may increase ACE2 expression or levels,[41-45] though other authors failed to observe such increases.[46, 47] Importantly, no studies have reported an increase in circulating ACE2 levels

and/or expression thus far[48, 49] and increased expression would not necessarily imply increased risk of infection or disease severity.

Deshotels et al.[50] investigated the compensatory reduction of ACE2 expression and activity in response to Ang II–mediated HTN. Elevated levels of Ang II decreased ACE2 activity on the cell surface via an AT_1R-dependent internalization mechanism.[50] Moreover, *in vitro* treatment of HEK293T cells with Ang II enhanced ACE2 ubiquitination also mediated by AT_1R, which ultimately stimulates ACE2 lysosomal degradation (which might prevent interaction of the SARS-Co-V2 with ACE2 catalytic site).[50] This is reported to be prevented by AT_1R antagonist losartan which may block internalization, proteolytic degradation and ubiquitination of ACE2.[50] As such, this latter pathway represents another mechanism by which ACEIs or ARBs could prevent COVID-19 viral entry. If the viral protein interaction with ACE2 is reduced in the presence of stabilized ACE2-AT_1R complexes, then ARBs could prove beneficial by stabilizing ACE2-AT_1R interaction and preventing viral protein-ACE2 interaction and internalization. Based on this mechanism of action, Gurwitz recently suggests ARBs (losartan and telmisartan) as a tentative therapy for COVID-19 patients prior to the development of ALI/acute respiratory failure.[51] However, it remains unknown whether preventing ACE2 internalization would be effective at attenuating infections by SARS coronaviruses, and further studies are urgently needed to clarify this mechanism.

Interestingly, Liu et al.[52] reported serum Ang II levels were significantly higher in COVID-19 infected than non-infected individuals and linearly associated with viral load and lung damage. It is suspected that Ang II, via pulmonary vasoconstriction leading to decrease flow and ventilation/perfusion mismatch and via increased vascular permeability and its proinflammatory and pro-oxidative properties, may induce or perpetuate ARDS in a variety of pathologies.[53] The findings by Liu et al.[52] would support the hypothesis that elevated levels of Ang II may foster ARDS in COVID-19 patients. Nevertheless, this study has important limitations as it was performed in a limited sample and, as such, require confirmation.[52]

The role of RAAS peptides in acute lung injury has been also investigated in other ARDS patients (diagnosed within 24 hours) by using a targeted metabolomics approach.[54] Ang I concentrations were significantly higher in non-survivors at study entry and at 72 hours, while ARDS survival was associated with lower Ang I levels but higher Ang 1-9 concentration (a precursor to Ang 1-7). Survivors showed a

significantly higher average Ang 1–9/Ang I and Ang 1–7/Ang I ratios, which suggests that ACE2 activity is higher in survivors than non-survivors.[54] Therefore, ACE2 activities seems to be reduced in patients who succumb from ARDS.

Further downstream, high levels of Ang II, which may be due to attenuated ACE2, such as that potentially caused by the SARS-CoV-2 interaction with ACE2, stimulates increased production of aldosterone. Aldosterone in turn increases ACE activity inducing further production of Ang II, leading to a potentially vicious cycle which perpetuates ARDS.[55] Moreover, aldosterone decreases expression of the MasR, minimizing the antagonizing benefits of any Ang 1-7 produced by ACE2. As such, aldosterone receptor blockers or aldosterone synthase inhibitors may have a potential role in COVID-19 therapy; however, careful evaluation of any influence on corticosteroids synthesis and signaling is required.[55]

Since SARS-CoV-2 invades alveolar epithelial cells, respiratory symptoms are often the most common reported, and is reported to be more severe in patients with CVD.[23] This might be associated with higher ACE2 levels, which has been suggested to be increased in patients maintained on RAAS inhibitors.[23] However, in a study conducted in rats by Xudong et al.,[56] ACE2 expression dramatically decreased with age in both genders, while older male rats also had lower ACE2 concentrations than did older female rats. Whether such altered profiles of ACE2 are similarly observed in humans, or if ACE2 expression is altered in disease, requires further investigation.

It has also been recently demonstrated that recombinant ACE2 administration in mice with ARDS protects from development of ALI and severe lung disease, thus strongly suggesting that ACE2 mediates a cytoprotective role in ALI;[57] whether such effects are also observed in ARDS caused by COVID-19 is unknown at this time Thus extrapolating from these and previously discussed findings, one may speculate that the administration of recombinant ACE2 or its product Ang 1-7, which directly opposes Ang II, may offer potentially beneficial effects in SARS-CoV-2-associated ARDS.[57] Moreover, specifically with SARS-CoV-2, recombinant ACE2 may serve the role as a competitive inhibitor, binding up viral particles that would otherwise bind to membrane bound ACE2, thus decreasing viral load and protecting/increasing residual endogenous membrane bound ACE2. Studies that directly administer recombinant ACE2 to mice in conjunction with those that utilize ACE2 knockout mice demonstrated that ACE2 protects murine lungs from

ARDS. Such an approach in preclinical studies of ARDS specifically due to COVID-19 is especially important and timely.

CONCLUSIONS AND POTENTIAL RECOMMENDATIONS

SARS-CoV-2 binding to ACE2 may attenuate residual ACE2 activity, further tipping the ACE/ACE2 balance to a predominant ACE/AngII/AT1 axis signaling, in which AngII may then foster pulmonary vasoconstriction, and inflammatory and oxidative organ damage, ultimately progressing towards ALI/ARDS.[53] We speculate that RAAS dysregulation may play a central role in the pathophysiology of COVID-19 associated ALI/ARDS, but definitive studies that address this issue are needed. Whether RAAS modulation may have a beneficial effect in selected patients with severe COVID-19 at risk for ALI/ARDS is entirely unknown at the present time. Moreover, the effects of other agents that may interrupt the RAAS by inhibiting renin, such as renin inhibitors and beta-blockers, would also be of interest regarding their effects on COVID-19 and attendant ALI.

In agreement with current guidelines, patients with HTN should continue taking anti-HTN medications as prescribed without interruption. Current evidence shows that RAAS inhibitors, i.e., ACEIs and ARBs, significantly reduce mortality in CVD, reduce the progression of CKD, and are the cornerstone of HF and HTN treatment. ACEIs or ARBs therapy should be maintained or initiated, as indicated, in patients with HF, HTN, or myocardial infarction, regardless of SARS-CoV-2. No differences exist between ARBs and ACEIs in terms of efficacy to decrease BP and improve other outcomes, such as all-cause mortality, CVD mortality, myocardial infarction, HF, stroke, and end-stage renal disease.[58] ACEIs are associated with cough secondary to accumulation of bradykinin and angioedema, while withdrawal rates due to adverse events are lower with ARBs.[58] Given the equal efficacy but fewer adverse events, ARBs could potentially be a more favorable treatment option in COVID-19 patients at higher risk of developing severe forms of disease (Table 2). To further evaluate the role of RAAS modulation in COVID-19, datasets should be analyzed to investigate if use of ACEIs and ARBs on admission could be associated with ALI/ARDS and/or survival/mortality in patients with DM, HTN and CVD.

Finally, the potential utility of alternative therapies, such as recombinant ACE2, Ang 1-7 peptides, angiotensin II receptor inhibitors, and potentially aldosterone synthase inhibitors, for preventing or mitigating ALI caused by viruses, is entirely unknown at the present time and requires consideration and investigation for a disease for which current care is entirely supportive.

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Figure legends

Figure 1. Localization of ACE2 protein in human organs and tissues.

Figure 2. Scheme of Renin-Angiotensin-Aldosterone system and SARS-CoV-2 infection mechanism.

Table 1. Professional societies recommendations following the statements on the issue. ✓ Recommended continuing ARBs and ACEIs. ✓ Recommended continuing angiotensin receptor neprilysin inhibitors. Adapted from N*ephJC*.[59] . Used with permission.

	Date of publication	Recommendation
European Society of Hypertension	March 12, 2020	✓
European Society of Cardiology Council on Hypertension	March 13, 2020	✓
Hypertension Canada	March 13, 2020	✓
Canadian Cardiovascular Society	March 15, 2020	✓ ✓
The Renal Association, United Kingdom	March 15, 2020	✓
International Society of Hypertension	March 16, 2020	✓
American College of Physicians	March 16, 2020	✓
Spanish Society of Hypertension	March 16, 2020	✓
American Heart Association	March 17, 2020	✓
Heart Failure Society of America	March 17, 2020	✓
American College of Cardiology	March 17, 2020	✓
European Renal Association, European Dialysis and Transplant Association	March 17, 2020	✓
High Blood Pressure Research Council of Australia	March 18, 2020	✓

Table 2. Risk factors related with worse prognosis in COVID-19 patients.

Age (>65 years)
Current smoker
Hypertension
Diabetes
Coronary heart disease
Atrial fibrillation
Chronic obstructive lung disease
Chronic kidney disease
Cancer
Obesity (BMI >30)

Angiotensin-Converting Enzyme 2 and Anti-Hypertensives (Angiotensin Receptor Blockers and Angiotensin Converting Enzyme Inhibitors) in Coronavirus Disease 2019 (COVID-19)

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Abstract

Coronavirus disease 2019 (abbreviated "COVID-19"), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is being defined as the worst pandemic disease of modern times. Several professional health organizations have published position papers stating that there is no evidence to change the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in the management of elevated blood pressure (BP) in the context of avoiding or treating COVID-19 infection. In this article, we review the evidence on the relationship between the Renin-Angiotensin-Aldosterone system and COVID-19 infection. In agreement with current guidelines, patients with hypertension should continue taking anti-hypertensive medications as prescribed without interruption. As ACEIs and ARBs are also used to retard the progression of chronic kidney disease (CKD), we suggest that these recommendations also apply to the use of these agents in CKD. No differences generally exist between ARBs and ACEIs in terms of efficacy in decreasing BP and improve other outcomes, such as all-cause mortality, cardiovascular mortality, myocardial infarction, heart failure, stroke, and end-stage renal disease. ACEIs are associated with cough secondary to accumulation of bradykinin and angioedema, while withdrawal rates due to adverse events are lower with ARBs. Given the equal efficacy but fewer adverse events, ARBs could potentially be a more favorable treatment option in COVID-19 patients at higher risk of developing severe forms of disease.

Keywords: Angiotensin converting enzyme; Hypertension; COVID-19; Coronavirus.

Abbreviations and Acronyms: **ACE** = angiotensin-converting enzyme; **ACEIs** = ACE inhibitors; **ALI** = acute lung injury; **Ang 1-7** = angiotensin 1-7; **Ang I** = Angiotensin I; **Ang II** = angiotensin II; **ARDS** = acute respiratory distress syndrome; **AT_1R** = Ang II type 1 receptor; **AT2** = type II alveolar cells; **ARBs** = angiotensin receptor blockers; **BP** = blood pressure; **COVID-19** = coronavirus disease 2019; **CV** = cardiovascular; **CVD** = cardiovascular disease; **DM** = diabetes mellitus; **HF** = heart failure; **HTN** = hypertension or hypertensive; **MasR** = Mas receptor; **RAAS** = renin-angiotensin-aldosterone system; **S** = spike; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **SIRS** = systemic inflammatory response syndrome; **TMPRSS2** = type II transmembrane serine proteases.

INTRODUCTION

The global public-health crisis triggered by coronavirus disease 2019 (abbreviated "COVID-19"), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2),[1] is being defined as the worst pandemic disease of modern times.[2, 3] According to the recent statistics from the World Health Organization, this novel coronavirus has already infected nearly 340,000 people worldwide, causing nearly 15,000 deaths.[4] Alarmingly, between 15-20% (~10-15% severe and ~3-5% critical) of SARS-CoV-2 positive individuals are likely to progress towards a severe form of disease, characterized by interstitial pneumonia, with the potential to evolve into acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), and death.[5] The high numbers of patients requiring sub-intensive or intensive care can overwhelm many health care infrastructures, even in highly developed countries.[6]

The exponential growth of the contagion around the world has contributed to heightened speculations and concerns over whether two commonly used anti-hypertensive (HTN) drugs, namely, angiotensin-converting enzyme (ACE) inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), also used for cardiovascular (CV) diseases (CVD) and chronic kidney disease (CKD), may exert either deleterious or beneficial effects in COVID-19 patients compared with other drugs used to reduce blood pressure (BP) or to treat heart failure (HF).[7]

Several professional health organizations have published position papers stating that there is no evidence to change the use of ACEIs or ARBs for the management of elevated BP in the context of avoiding or treating COVID-19 infection (Table 1). In this article, we review the evidence on the relationship between the Renin-Angiotensin-Aldosterone system (RAAS) and COVID-19 infection.

COVID-19 AND ANGIOTENSIN-CONVERTING ENZYME 2 (ACE2): ORIGIN OF THE SPECULATION

Healthcare professionals, physicians, researchers, and patients are actively debating the potential influence of ACEIs and ARBs on poor outcomes among COVID-19 patients, based mainly on the evidence that ACE2 is

a functional receptor for coronaviruses, including SARS-CoV-2.[8] This receptor is located on the surface of type II alveolar cells (AT2) and on lymphocytes, thus explaining the prevalent lung involvement (i.e., interstitial pneumonia and ARDS) and lymphopenia. Moreover, ACE2 is observed on the surface of many other cell types, such as those of the heart, kidney, liver, gastrointestinal tract (especially esophagus, stomach, colon, ileum, rectum) and bladder (Figure 1).[9-11]

Kuba et al.[12] first showed that ACE2 is essential for SARS-CoV infection, acting as its effective host receptor *in vivo*. SARS-CoV infection, through binding of viral S protein to ACE2, seems to reduce receptor expression. Injecting SARS-CoV Spike into mice induces acute lung injury (ALI) *in vivo*, which can be mitigated by blocking the RAAS. Wrapp et al.[13] have recently reported that SARS-CoV-2 binds to ACE2 with 10- to 20-fold higher affinity compared to SARS-CoV. Specifically, the S protein of SARS-CoV-2 virus binds to the catalytic domain of ACE2 inducing internalization of the virus by the cell.

In brief, the RAAS is the central regulatory system for BP control.[14] Additionally, RAAS activation plays a crucial pathogenic role in HTN, through hemodynamic actions and cytokines and intracellular signaling pathways, which ultimately promote many adverse cellular processes implicated in systemic damage.[14] In the RAAS, Angiotensin I (Ang I) is converted to angiotensin II (Ang II) by ACE. Ang II mediates vasoconstrictive, pro-inflammatory and pro-oxidative effects through agonism at Ang II type 1 receptor (AT_1R).[15] ACE2 converts Ang II to angiotensin 1-7 (Ang1-7), which finally binds to Mas receptor (MasR) and mediates many beneficial actions, including vasodilation and anti-inflammatory, anti-oxidant and anti-apoptotic effects.[15] Thus, ACE2/Ang1-7/MasR axis has opposite actions to ACE/AngII/AT_1R axis (Figure 2).

ACE2, a homologue of ACE, is an integral cell membrane protein with a catalytic domain on the extracellular surface exposed to vasoactive peptides.[16] ACE2 is a monocarboxypeptidase whose major role is converting Ang II to Ang 1–7,[16] with vasodilatory and antifibrotic actions[17] when it activates MasR.[18] Moreover, ACE2 also converts Ang I to Ang 1-9 which can be further converted by ACE into Ang 1-7. Thus, ACE2 limits the adverse vasoconstrictor and profibrotic effects of Ang II through its degradation and by counteracting its actions through the formation of Ang 1–7. The high expression of ACE2 in heart, type II

alveolar cells (AT2), capillary endothelium[19] and enterocytes,[20] demonstrates its essential role in CV and immune systems,[20] being principally involved in heart function and the development of HTN and complications of diabetes mellitus (DM).

As previously discussed, SARS-CoV-2 penetrates the cell through ACE2, but also necessitates type II transmembrane serine proteases (TMPRSS2) for effective priming of viral Spike (S) protein. The binding of coronavirus S protein to ACE2 triggers a conformational change in the S protein, allowing for proteolytic digestion by TMPRSS2, which enables viral and cell membrane fusion.[21] This was recently confirmed by the evidence that camostat mesylate, a protease TMPRSS2 inhibitor, blocks viral entry and may be a promising drug for SARS-CoV-2 infection.[21, 22] As ACE2 is a functional receptor for SARS- CoV-2, many healthcare professionals have begun to reconsider the safety and effects of anti-HTN therapy with ACEIs or ARBs in patients during the COVID-19 outbreak-; and, despite statements by medical organizations, they began to question whether patients with COVID-19 and HTN maintained on ACEIs or ARBs to decrease BP values (or for other conditions such as CVD and CKD) should change to another anti-HTN pharmacological agent.[23] Such considerations contributed to the current controversy.

THE USE OF ARBs OR ACEIs IN PATIENTS AT HIGH RISK OF SEVERE COVID-19: DELETERIOUS OR BENEFICIAL?

It has been hypothesized that increased levels of ACE2 may facilitate COVID-19 infection, such that administering ARBs or ACEIs might increase the risk of developing severe and fatal COVID-19.[24-26] As discussed later in this section, this premise is based in part on the findings in some, but not all, studies that ARBs and ACEIs may increase ACE2 levels. According to the most recent studies on COVID-19, it appears that HTN is one of the most important factors associated with poor prognosis at an early stage of COVID-19 infection.[27-32] HTN, however, has also been found to be associated with decreased baseline levels of ACE2 expression. Unfortunately, most of these early COVID-19 studies have not been adjusted for age or other co-morbidities. The last report on the characteristics of deceased COVID-19 positive patients in Italy officially released on March 20, 2020 by the Italian Ministry of Health through the National Institute of Health

(Istituto Superiore di Sanità; ISS) showed that the most common concurrent medical co-morbidities observed were arterial HTN (73.8%; 355 of 481), DM (33.9%; 163 of 481), ischemic cardiopathy (30.1%; 145 of 481), and atrial fibrillation (22%; 106 of 481).[33] Prior to hospitalization, 36% (173 of 481) of fatal COVID-19 patients were on treatment with ACEIs, while 16% (77 of 481) were on treatment with ARBs (odds ratio, 2.26; 95% confidence interval, 95% CI, 1.66-3.09; p<0.001). Nevertheless, these numbers are preliminary and may not precisely reflect adjusted differences in risk. It is virtually impossible to precisely identify all medical therapies before admission from medical records[33]. Moreover, patients with elevated BP on admission may be noted to have a history of chronic HTN in their medical record, and such coding may reflect provider biases from the current infectious illness. The median age of SARS-CoV-2 positive patients who died was 78.5 years (median: 80 years; range: 31-103 years; interquartile range, 73-85 years). Since HTN prevalence increases in parallel with aging, this pattern may represent the expected prevalence for the given age group. Therefore, although the number of fatal COVID-19 positive patients treated with ACEIs was more than twice the number of those treated with ARBs, one cannot definitely conclude risks or benefits of these therapies due to confounding variables of age, HTN, as well as the impact of yet unidentified comorbidities on outcome with the COVID-19 pandemic.

In a recent study, in which potential drugs targeting SARS-CoV-2 were evaluated, the authors reported that ARBs (e.g., irbesartan) may associate with some human coronaviruses-associated host proteins in the human interactome.[34] Irbesartan targets the *SLC10A1* gene (solute carrier family 10 member 1), which interacts with *C11orf74* gene, a potential transcriptional repressor that interacts with the non-structural protein 10 (NSP10) of SARS-CoV and participates in CoV replication fidelity.[35]

Crackower and co-workers[36] reported that disruption of ACE2 results in increased Ang II levels and impaired cardiac function, whereas other authors showed that ACE2 overexpression reduced left ventricular hypertrophy and myocardial fibrosis in HTN rats.[37] Lower cardiac ACE2 concentrations are observed in HTN,[37, 38] CVD associated with DM,[39] and Ang II-induced cardiac dysfunction,[40] suggesting that augmenting ACE2 could have beneficial therapeutic effects on the CV system. In numerous studies carried out in animal models, both ACEIs and ARBs may increase ACE2 expression or levels,[41-45] though other authors failed to observe such increases.[46, 47] Importantly, no studies have reported an increase in circulating ACE2 levels

and/or expression thus far[48, 49] and increased expression would not necessarily imply increased risk of infection or disease severity.

Deshotels et al.[50] investigated the compensatory reduction of ACE2 expression and activity in response to Ang II–mediated HTN. Elevated levels of Ang II decreased ACE2 activity on the cell surface via an AT_1R-dependent internalization mechanism.[50] Moreover, *in vitro* treatment of HEK293T cells with Ang II enhanced ACE2 ubiquitination also mediated by AT_1R, which ultimately stimulates ACE2 lysosomal degradation (which might prevent interaction of the SARS-Co-V2 with ACE2 catalytic site).[50] This is reported to be prevented by AT_1R antagonist losartan which may block internalization, proteolytic degradation and ubiquitination of ACE2.[50] As such, this latter pathway represents another mechanism by which ACEIs or ARBs could prevent COVID-19 viral entry. If the viral protein interaction with ACE2 is reduced in the presence of stabilized ACE2-AT_1R complexes, then ARBs could prove beneficial by stabilizing ACE2-AT_1R interaction and preventing viral protein-ACE2 interaction and internalization. Based on this mechanism of action, Gurwitz recently suggests ARBs (losartan and telmisartan) as a tentative therapy for COVID-19 patients prior to the development of ALI/acute respiratory failure.[51] However, it remains unknown whether preventing ACE2 internalization would be effective at attenuating infections by SARS coronaviruses, and further studies are urgently needed to clarify this mechanism.

Interestingly, Liu et al.[52] reported serum Ang II levels were significantly higher in COVID-19 infected than non-infected individuals and linearly associated with viral load and lung damage. It is suspected that Ang II, via pulmonary vasoconstriction leading to decrease flow and ventilation/perfusion mismatch and via increased vascular permeability and its proinflammatory and pro-oxidative properties, may induce or perpetuate ARDS in a variety of pathologies.[53] The findings by Liu et al.[52] would support the hypothesis that elevated levels of Ang II may foster ARDS in COVID-19 patients. Nevertheless, this study has important limitations as it was performed in a limited sample and, as such, require confirmation.[52]

The role of RAAS peptides in acute lung injury has been also investigated in other ARDS patients (diagnosed within 24 hours) by using a targeted metabolomics approach.[54] Ang I concentrations were significantly higher in non-survivors at study entry and at 72 hours, while ARDS survival was associated with lower Ang I levels but higher Ang 1-9 concentration (a precursor to Ang 1-7). Survivors showed a

significantly higher average Ang 1–9/Ang I and Ang 1–7/Ang I ratios, which suggests that ACE2 activity is higher in survivors than non-survivors.[54] Therefore, ACE2 activities seems to be reduced in patients who succumb from ARDS.

Further downstream, high levels of Ang II, which may be due to attenuated ACE2, such as that potentially caused by the SARS-CoV-2 interaction with ACE2, stimulates increased production of aldosterone. Aldosterone in turn increases ACE activity inducing further production of Ang II, leading to a potentially vicious cycle which perpetuates ARDS.[55] Moreover, aldosterone decreases expression of the MasR, minimizing the antagonizing benefits of any Ang 1-7 produced by ACE2. As such, aldosterone receptor blockers or aldosterone synthase inhibitors may have a potential role in COVID-19 therapy; however, careful evaluation of any influence on corticosteroids synthesis and signaling is required.[55]

Since SARS-CoV-2 invades alveolar epithelial cells, respiratory symptoms are often the most common reported, and is reported to be more severe in patients with CVD.[23] This might be associated with higher ACE2 levels, which has been suggested to be increased in patients maintained on RAAS inhibitors.[23] However, in a study conducted in rats by Xudong et al.,[56] ACE2 expression dramatically decreased with age in both genders, while older male rats also had lower ACE2 concentrations than did older female rats. Whether such altered profiles of ACE2 are similarly observed in humans, or if ACE2 expression is altered in disease, requires further investigation.

It has also been recently demonstrated that recombinant ACE2 administration in mice with ARDS protects from development of ALI and severe lung disease, thus strongly suggesting that ACE2 mediates a cytoprotective role in ALI;[57] whether such effects are also observed in ARDS caused by COVID-19 is unknown at this time Thus extrapolating from these and previously discussed findings, one may speculate that the administration of recombinant ACE2 or its product Ang 1-7, which directly opposes Ang II, may offer potentially beneficial effects in SARS-CoV-2-associated ARDS.[57] Moreover, specifically with SARS-CoV-2, recombinant ACE2 may serve the role as a competitive inhibitor, binding up viral particles that would otherwise bind to membrane bound ACE2, thus decreasing viral load and protecting/increasing residual endogenous membrane bound ACE2. Studies that directly administer recombinant ACE2 to mice in conjunction with those that utilize ACE2 knockout mice demonstrated that ACE2 protects murine lungs from

ARDS. Such an approach in preclinical studies of ARDS specifically due to COVID-19 is especially important and timely.

CONCLUSIONS AND POTENTIAL RECOMMENDATIONS

SARS-CoV-2 binding to ACE2 may attenuate residual ACE2 activity, further tipping the ACE/ACE2 balance to a predominant ACE/AngII/AT1 axis signaling, in which AngII may then foster pulmonary vasoconstriction, and inflammatory and oxidative organ damage, ultimately progressing towards ALI/ARDS.[53] We speculate that RAAS dysregulation may play a central role in the pathophysiology of COVID-19 associated ALI/ARDS, but definitive studies that address this issue are needed. Whether RAAS modulation may have a beneficial effect in selected patients with severe COVID-19 at risk for ALI/ARDS is entirely unknown at the present time. Moreover, the effects of other agents that may interrupt the RAAS by inhibiting renin, such as renin inhibitors and beta-blockers, would also be of interest regarding their effects on COVID-19 and attendant ALI.

In agreement with current guidelines, patients with HTN should continue taking anti-HTN medications as prescribed without interruption. Current evidence shows that RAAS inhibitors, i.e., ACEIs and ARBs, significantly reduce mortality in CVD, reduce the progression of CKD, and are the cornerstone of HF and HTN treatment. ACEIs or ARBs therapy should be maintained or initiated, as indicated, in patients with HF, HTN, or myocardial infarction, regardless of SARS-CoV-2. No differences exist between ARBs and ACEIs in terms of efficacy to decrease BP and improve other outcomes, such as all-cause mortality, CVD mortality, myocardial infarction, HF, stroke, and end-stage renal disease.[58] ACEIs are associated with cough secondary to accumulation of bradykinin and angioedema, while withdrawal rates due to adverse events are lower with ARBs.[58] Given the equal efficacy but fewer adverse events, ARBs could potentially be a more favorable treatment option in COVID-19 patients at higher risk of developing severe forms of disease (Table 2). To further evaluate the role of RAAS modulation in COVID-19, datasets should be analyzed to investigate if use of ACEIs and ARBs on admission could be associated with ALI/ARDS and/or survival/mortality in patients with DM, HTN and CVD.

Finally, the potential utility of alternative therapies, such as recombinant ACE2, Ang 1-7 peptides, angiotensin II receptor inhibitors, and potentially aldosterone synthase inhibitors, for preventing or mitigating ALI caused by viruses, is entirely unknown at the present time and requires consideration and investigation for a disease for which current care is entirely supportive.

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Figure legends

Figure 1. Localization of ACE2 protein in human organs and tissues.

Figure 2. Scheme of Renin-Angiotensin-Aldosterone system and SARS-CoV-2 infection mechanism.

Table 1. Professional societies recommendations following the statements on the issue. ✓ Recommended continuing ARBs and ACEIs. ✓ Recommended continuing angiotensin receptor neprilysin inhibitors. Adapted from N*ephJC*.[59] . Used with permission.

	Date of publication	Recommendation
European Society of Hypertension	March 12, 2020	✓
European Society of Cardiology Council on Hypertension	March 13, 2020	✓
Hypertension Canada	March 13, 2020	✓
Canadian Cardiovascular Society	March 15, 2020	✓ ✓
The Renal Association, United Kingdom	March 15, 2020	✓
International Society of Hypertension	March 16, 2020	✓
American College of Physicians	March 16, 2020	✓
Spanish Society of Hypertension	March 16, 2020	✓
American Heart Association	March 17, 2020	✓
Heart Failure Society of America	March 17, 2020	✓
American College of Cardiology	March 17, 2020	✓
European Renal Association, European Dialysis and Transplant Association	March 17, 2020	✓
High Blood Pressure Research Council of Australia	March 18, 2020	✓

Table 2. Risk factors related with worse prognosis in COVID-19 patients.

Age (>65 years)
Current smoker
Hypertension
Diabetes
Coronary heart disease
Atrial fibrillation
Chronic obstructive lung disease
Chronic kidney disease
Cancer
Obesity (BMI >30)

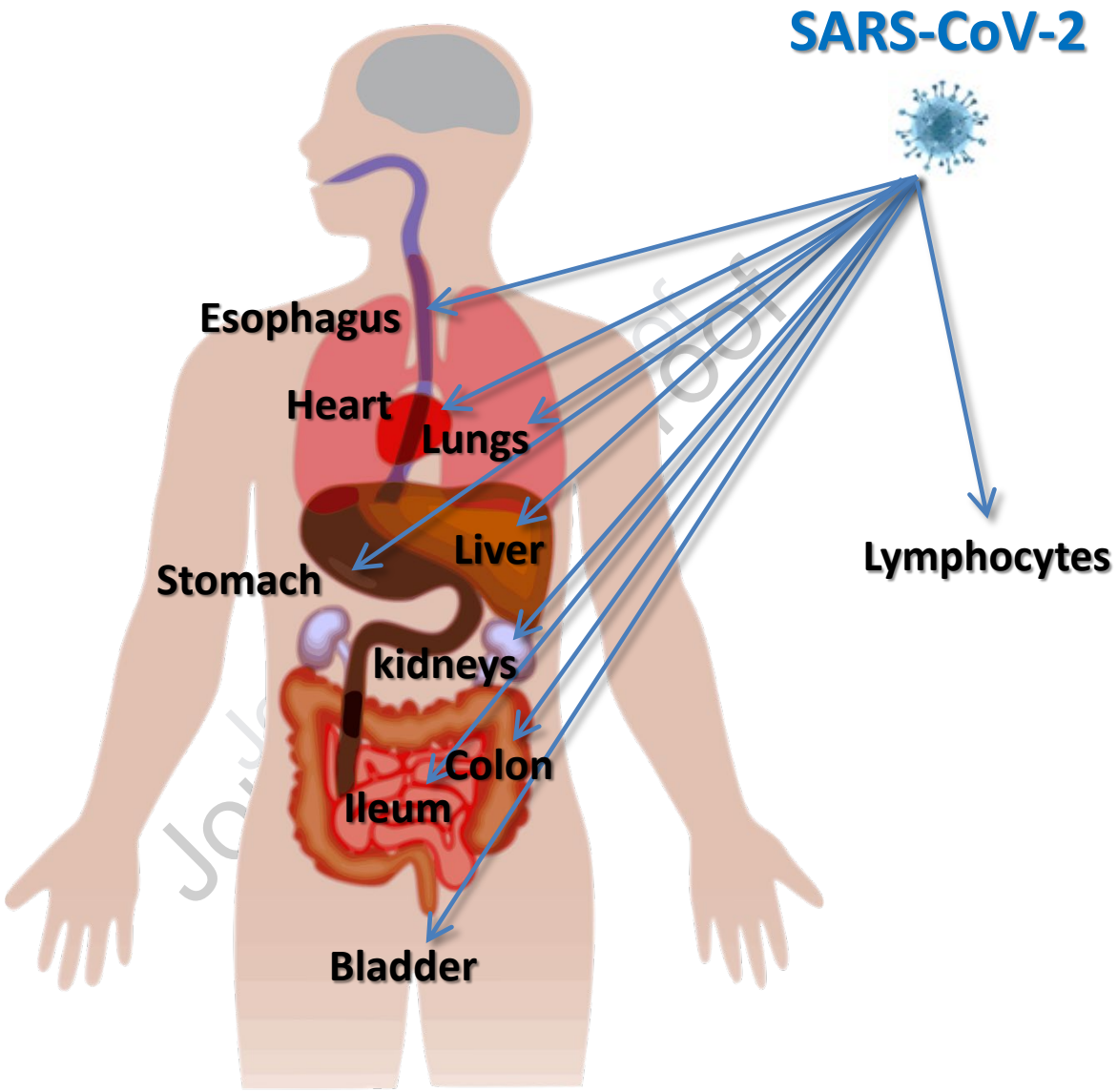

SARS-CoV-2
Esophagus
Heart
Lungs
Liver
Stomach
kidneys
Colon
Ileum
Bladder
Lymphocytes

Figure 1

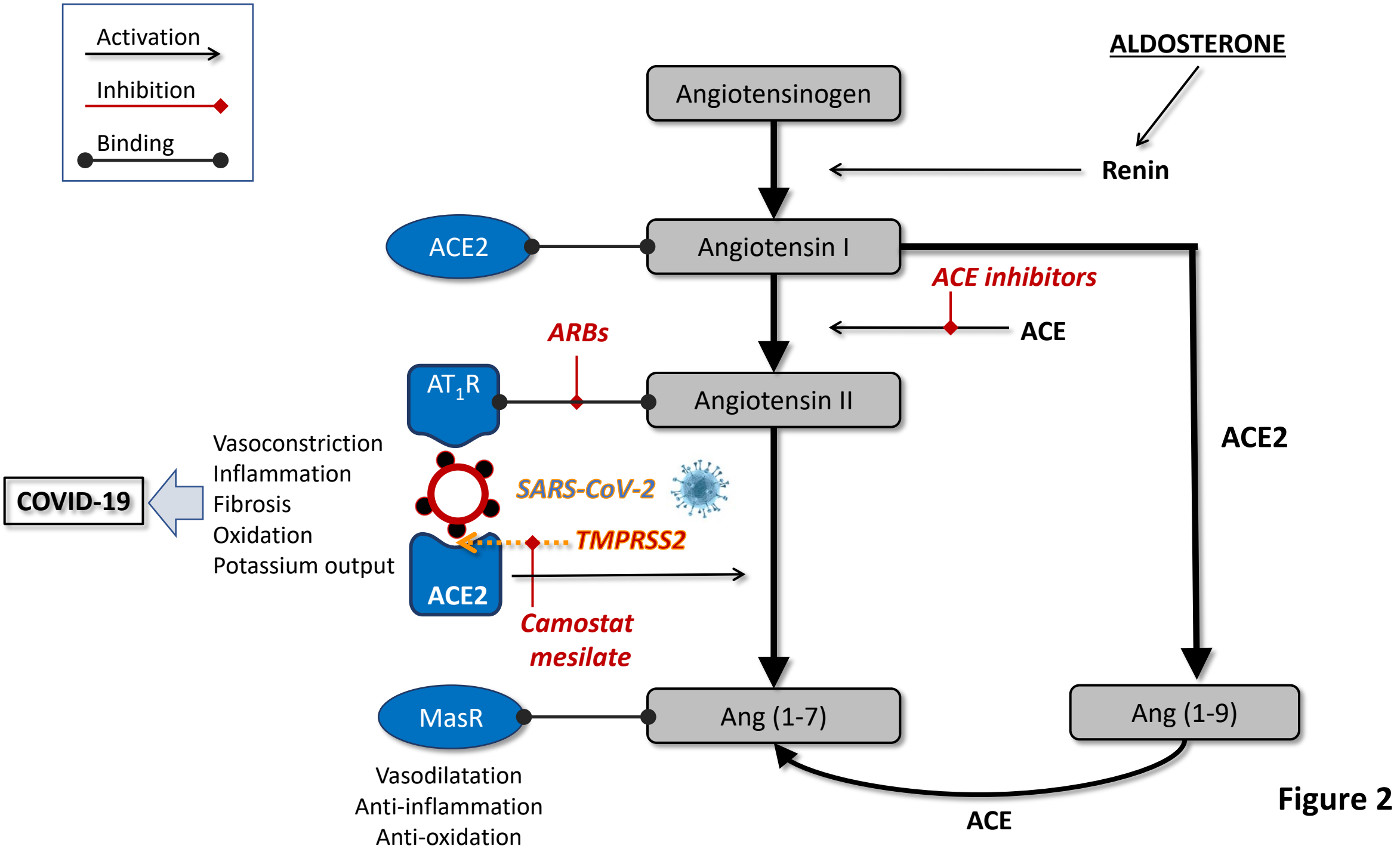
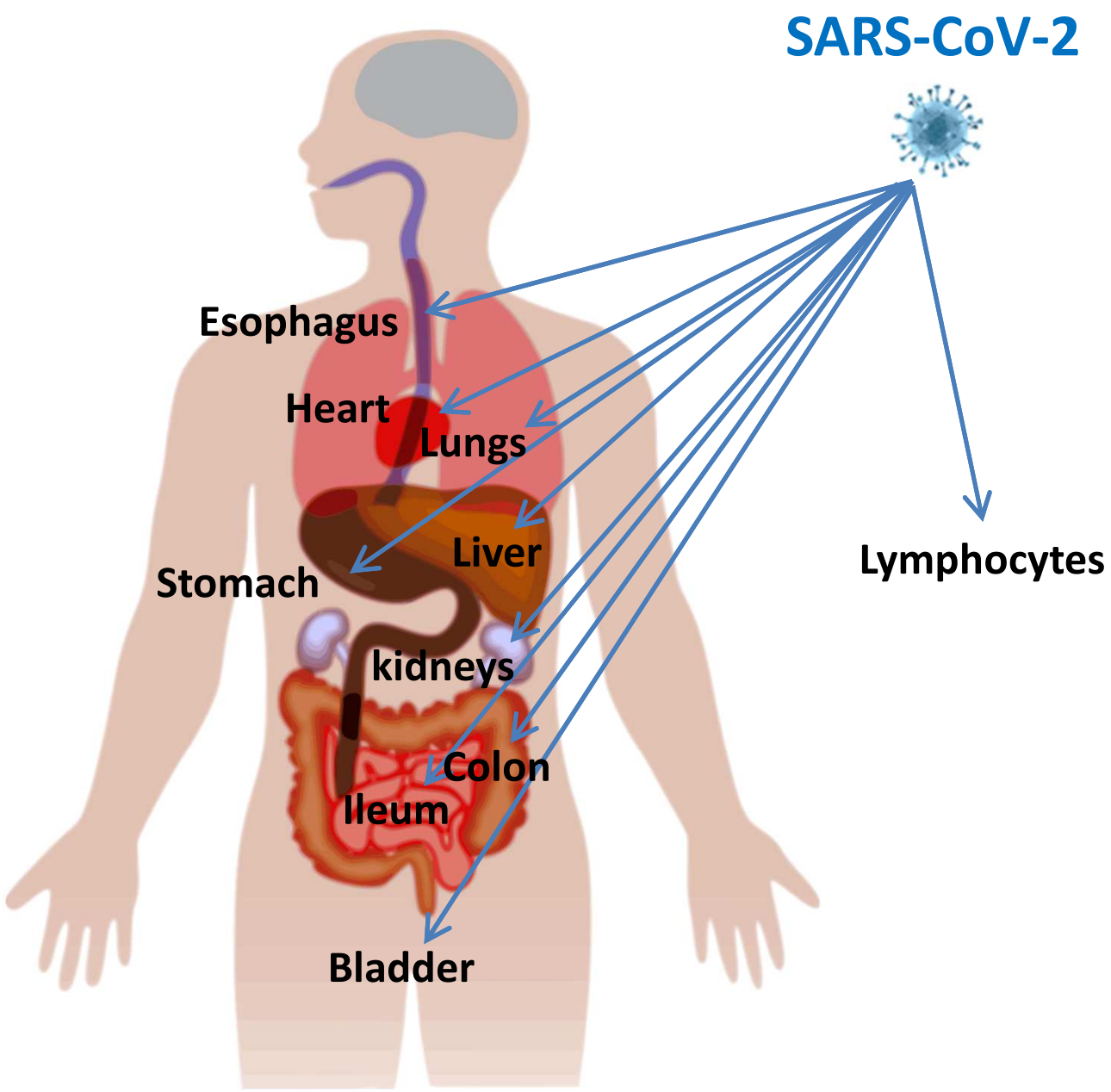
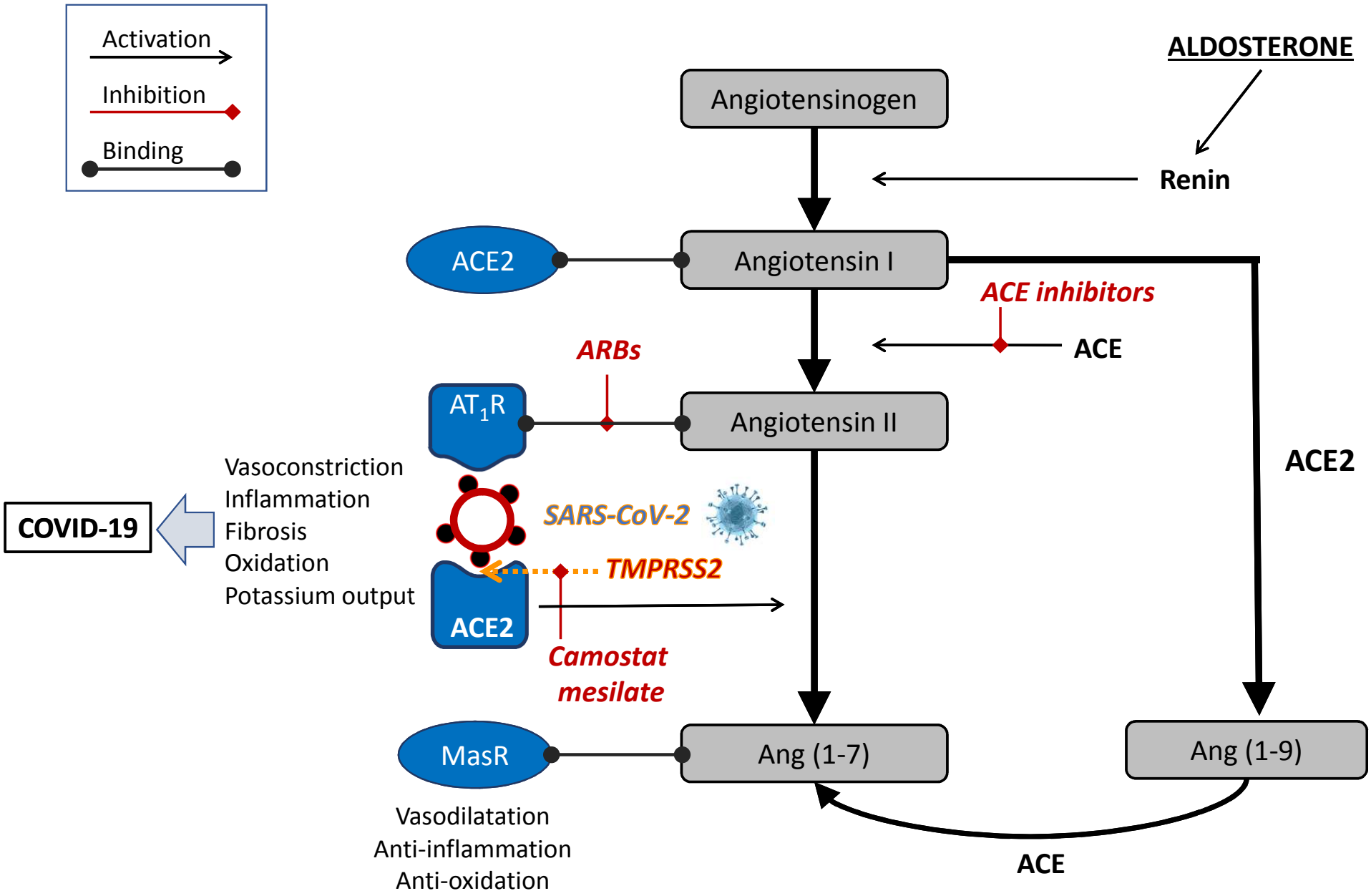

Activation
Inhibition
Binding
ALDOSTERONE
Angiotensinogen
Renin
ACE2
Angiotensin I
ACE inhibitors
ACE
ARBs
AT1R
Angiotensin II
ACE2
Vasoconstriction
Inflammation
Fibrosis
Oxidation
Potassium output
COVID-19
SARS-CoV-2
TMPRSS2
ACE2
Camostat mesilate
MasR
Ang (1-7)
Ang (1-9)
Vasodilatation
Anti-inflammation
Anti-oxidation
ACE

Figure 2


SARS-CoV-2
Esophagus
Heart
Lungs
Liver
Stomach
kidneys
Colon
Ileum
Bladder
Lymphocytes


Activation
Inhibition
Binding
ALDOSTERONE
Angiotensinogen
Renin
ACE2
Angiotensin I
ACE inhibitors
ACE
ARBs
AT1R
Angiotensin II
ACE2
Vasoconstriction
Inflammation
Fibrosis
Oxidation
Potassium output
COVID-19
SARS-CoV-2
TMPRSS2
ACE2
Camostat mesilate
MasR
Ang (1-7)
Ang (1-9)
Vasodilatation
Anti-inflammation
Anti-oxidation
ACE

Fabian Sanchis
Fri 3/27/2020 4:10 PM

- Wentz, Margaret R. (Peg);
- Nath, Karl A., M.D.

+4 others

Hi Peg,

Here is the permission to use table 1 (see below). The authors would prefer we cite it as:

Sparks MA, Hiremath S et al. "The Coronavirus Conundrum: ACE2 and Hypertension Edition" NephJC http://www.nephjc.com/news/covidace2 *with access date*

Access date: whenever you access it as the document is being updated daily or so

Let me know if this is ok and do not hesitate to contact me if you need anything else.

Best regards,

Fabian

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De: Nephrology JC <nephrologyjc@gmail.com>
Fecha: viernes, 27 de marzo de 2020, 13:57
Para: Fabian Sanchis <fabian.sanchis@uv.es>
Asunto: Re: Permission to used an adapted version of a table of your website

Hi Fabian
Please go ahead
We would prefer you cite it as

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NephJC http://www.nephjc.com/news/covidace2 *with access date*

Access date: whenever you access it as the document is being updated daily or so

Swapnil

On Mar 27, 2020, at 11:31 AM, Fabian Sanchis <fabian.sanchis@uv.es> wrote:

Dear Sir or Madam,

I'm planning to publish a manuscript on ACE inhibitors use in COVID-19 and I would like to ask if I could use your table (PDF #1 attached) on professional societies statements on the topic. I've simplified and adapted it (see also my table, PDF #2 attached). Obviously, your website will be also cited.

Please let me know at your earlier convenience.

With my best wishes,

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<#1 Table.pdf>
<#2 Table.pdf>