

## ACE INHIBITORS AND AT1R BLOCKERS FOR COVID-2019: FRIENDS OR FOES ?

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Abbreviations : COVID-19 : coronavirus disease 2019; ACEI : ACE inhibitors; ARB : angiotensin receptor blockers; SARS: severe acute respiratory syndrome; ALI : acute lung injury ; ARDS : acute respiratory distress syndrome.

### Abstract

Human respiratory beta coronavirus are emerging causes for Public Health Emergencies of International Concern (PHEIC). SARS-CoV2 is circulating worldwide since November 2019. We review here the cardiovascular morbidity and mortality in COVID-19, and data supporting the role for dysregulation of the RAS counterregulatory axis due to binding of SARS-CoV2 S protein to ACE2 receptor. Since this counterregulatory axis provides benefits not only on the cardiovascular front but also in acute lung injury, we speculate on potential use of ACE inhibitors and AT<sub>1</sub>R blockers in critically ill COVID-19 patients, and report current evidences.

### ***Human respiratory betacoronaviruses***

Three respiratory betacoronaviruses of bat origin and various intermediate hosts have emerged in humans in China and Middle East in the last two decades, rapidly evolving into Public Health Emergencies of International Concern (PHEIC). Severe acute respiratory syndrome (SARS) was first identified in Guangdong, China in November 2002 and spread to 8096 cases in 29 countries for an overall case fatality rate (CFR) of 9.6% before WHO declared worldwide containment in July 2003, despite a few new cases in 2004. The responsible betacoronavirus was named SARS-CoV. In September 2012 the cause for the Middle-Eastern Respiratory syndrome (MERS) was identified in the MERS-CoV, and the epidemic has to date caused approximately 2500 cases with a CFR of 34%. In January 2020, following an outbreak of pneumonia in Wuhan, Chinese scientists isolated a novel betacoronavirus, which was initially named 2019-nCoV[1] and then renamed SARS-CoV2 by the International Committee on Taxonomy of Viruses (ICTV). The nosological entity was named COVID-2019[2], and the epidemic is currently ongoing worldwide.

### ***Cardiovascular morbidity and mortality in COVID-19***

COVID-19 has a far lower estimated mortality than SARS but still high morbidity, with approximately 10% of patients requiring ICU staying: up to 50% of hospitalized patients have a chronic medical illness, 80% of which are cardiovascular or cerebrovascular. Overall the CFR remains low at 2.3%, but jumps to 6% in hypertensives and 10.5% in patients with cardiovascular disease[3].

Table 1. Evidences for cardiovascular damage from published COVID-19 case series.

Reference	<i>n</i> (confirmed cases)	Cardiovascular features
Huang C et al, <i>Lancet</i> 2020, [4]	41	5 cases (12%) showed increased high-sensitivity cardiac troponin I and received a diagnosis of virus-related acute cardiac injury.
Chen N et al, <i>Lancet</i> 2020, [5]	99	40% had pre-existing cardiovascular or cerebrovascular disease.

Xiao-Wei X et al., <i>BMJ</i> 2020 [6]	62	5 (8%) with pre-existing hypertension and 1 with cerebrovascular disease. At admission, mean arterial pressure 97 mm Hg (87-106).
Wang D et al., <i>JAMA</i> 2020[7]	138	43 (32.1%) with pre-existing hypertension, 7 (5.1%) with pre-existing unspecified CV disease, and 7 (5.1) with pre-existing cerebrovascular disease. At admission median arterial pressure 90 mm Hg, normal values of mean high-sensitivity cardiac troponin I. The probability of being admitted to ICU was higher in those with hypertension and CV disease. Acute cardiac injury was a complication in 10 patients (7.2%) and shock in 12 patients (8.7%)
Yang X et al, <i>Lancet</i> 2020 [8]	710 (52 critically ill)	32 died - pre-existing chronic cardiac disease 5 (10%) Compared with survivors, non-survivors were older (65 vs 52 years), more likely to develop ARDS (81% vs 45%), and more likely to receive mechanical ventilation (94% patients vs 35%), either invasively or non-invasively. 23% had cardiac injury. Mean systolic blood pressure was 133 mmHg in survivors vs 140 in non survivors
Wu Z et al, <i>JAMA</i> 2020 [9]	44,672	CFR was elevated among those with preexisting comorbid conditions—10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension

Viral illness is a well-known destabilizing factor in chronic cardiovascular disease: e.g. it can destabilize coronary plaques through several mechanisms including systemic inflammatory responses, but we will focus here on an additional mechanism of action, namely ACE2 axis dysregulation.

### ***ACE2 as a viral receptor and its implications in metabolism***

The human receptor for the viral Spike (S) protein S1 subunit of SARS-CoV was identified in the catalytic domain of angiotensin-converting enzyme II (ACE2) [10], although vimentin-S protein interaction is also required for cell entry[11]. In 2005 ACE2 was also identified as the receptor for the other less invasive alphacoronavirus HCoV-NL63[12], albeit with far lower affinity. Similarly, Zhou *et al* identified ACE2 as the cell receptor of SARS-CoV2 [13], with higher affinity than SARS-CoV [14, 15]. Single-cell RNA sequencing (scRNA-Seq) technique and single-cell transcriptomes identified high ACE2 expression in apical surface of type II alveolar cells (AT2) of lung [16-19], esophagus upper and stratified epithelial cells, absorptive enterocytes from ileum and colon[18], cholangiocytes [20], myocardial cells, endothelium of coronary and

intrarenal vessels [21], kidney proximal tubule cells, bladder urothelial cells[16], and tongue epithelium [22].

ACE2 is a type I transmembrane protein, with an extracellular *N*-terminal domain containing the active terminal monocarboxypeptidase site (that degrades Ang I into a Ang<sub>1-9</sub> and Ang II into Ang<sub>1-7</sub>) and a short intracellular C-terminal tail [23]. The renin-angiotensin system (RAS) counter-regulatory axis (ACE2-Ang<sub>1-7</sub>-Mas receptor) opposes the classical arm (ACE-Ang II-AT<sub>1</sub> receptor) actions, presenting anti-inflammatory, anti-oxidative, and anti-fibrotic effects. Ang<sub>1-7</sub> is a biologically active peptide exerting a wide array of actions, many of which are opposite to those attributed to Ang II. Taken together, the cardioprotective effects of ACE2 can be attributed to degradation of Ang I to Ang<sub>1-9</sub> (limiting the availability of substrate for ACE action), degradation of Ang II (limiting its detrimental effects), and generation of Ang<sub>1-7</sub> (exerting its cardioprotective effects) [24].

S protein from SARS-CoV, but not HNL63-CoV, induces TNF- $\alpha$ -converting enzyme (TACE)/ADAM17-dependent shedding of the ACE2 ectodomain [25, 26], which is inhibited by calmodulin under physiological circumstances[27]. The TACE inhibitor TAPI-2 blocks both the SARS-CoV S protein-induced shedding of ACE2, and TNF- $\alpha$  production in lung tissues [28]. TMPRSS2 was found to compete with the metalloprotease ADAM17 for ACE2 processing, but only cleavage by TMPRSS2 resulted in augmented SARS-S-driven entry [29]. Binding of SARS-S to ACE2 triggers subtle conformational rearrangements in SARS-S, which are believed to increase the sensitivity of the S protein to proteolytic digest at the border between the S1 and S2 subunits [30]. Cleavage of the S protein by host cell proteases is essential for viral infectivity, and the responsible enzymes constitute potential targets for intervention. Collectively, these results indicate that TMPRSS2 and potentially related proteases promote SARS-CoV entry by 2 separate mechanisms: ACE2 cleavage, which might promote viral uptake, and SARS-S cleavage, which activates the S protein for membrane fusion. Soluble ACE2 would be enzymatically active but is saturated by SARS-CoV2 S protein: despite acting as a decoy receptor, it only partially inhibits virus entry into target cells [31].

Notably, injection of SARS-CoV S protein into mice worsens acute lung failure *in vivo* that can be attenuated by blocking the RAS axis with AT<sub>1</sub>R blockers [32].

Intriguingly, mortality from SARS-CoV and SARS-CoV2 is significantly higher in males than females: despite lower estrogens[33] or higher smoking could be simple explanations, an alternative stays with ACE2 gene being located on X-chromosome, making an eventual recessive infection-predisposing polymorphisms [34, 35] silenced in females. Receptor polymorphisms affecting coronavirus entry has already been proven for

MERS-CoV[36]. A number of ACE2 variants with a potential impact on protein stability have been identified. Among these, 3 missense changes, p.Asn720Asp, p.Lys26Arg, p.Gly211Arg (MAF 0.002 to 0.015), which have never been reported in the Eastern Asia population, were predicted to interfere with protein cleavage and stabilization. Rare truncating variants likely interfering with the internalization process and one missense variant, p.Trp69Cys, predicted to interfere with 2019-nCov spike protein binding were also observed.

### ***Therapeutic opportunities targeting the RAS system in COVID-19***

ACE2 is highly expressed in patients with hypertension, diabetes, and chronic obstructive lung disease, compared to control individuals[37, 38].

To date candidate drugs targeting SARS-CoV2 include small chemicals (such as the RNA-dependent RNA polymerase inhibitors remdesivir (GS-5734) and favipiravir (T-705)) and neutralizing antibodies (either monoclonal [39] or convalescent blood products [40]). Unfortunately no such candidate has been tested in phase III clinical trials yet. On the contrary of what has happened with DPP-IV inhibitors for MERS-CoV [41], no drug with previous clinical indications is available for prescription. Nevertheless, supportive therapy with immunomodulators such as the TLR9 suppressor hydroxychloroquine [42] or the anti-IL-6 antibody tocilizumab [43] can offer treatment opportunities for improving prognosis in COVID-19 patients .

Deployment of ACE inhibitors (ACEI) or angiotensin-receptor blockers (ARB) could be of benefit in order to reduce cardiovascular mortality in elderlies, provided such therapies are tailored to individual patients. Additionally, the RAS axes has also been implicated in the regulation of inflammation, proliferation and fibrosis in acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), with ACE2 having protective effects in different etiologies[44], including respiratory viruses (e.g. influenza virus A(H<sub>5</sub>N<sub>1</sub>) [45] or A(H<sub>7</sub>N<sub>9</sub>) [46]). Similar benefits can be achieved by direct administration of the downstream product, Ang<sub>1-7</sub>.

The ARB losartan and olmesartan, commonly applied for reducing blood pressure in hypertensive patients, increase cardiac [47, 48] and renal [49] ACE2 expression in animal models. Accordingly, higher urinary ACE2 levels are found in hypertensive patients treated with olmesartan[50]. Similarly, the ACE-inhibitor lisinopril increases mRNA expression of cardiac ACE2[48]. Taken together, these observations suggest that chronic ACE or AT<sub>1</sub>R blockade results in ACE2 upregulation, which would discourage usage. However, binding of the SARS-CoV spike protein to ACE2 leads to ACE2 downregulation, which in turn results in excessive production of angiotensin by the related enzyme ACE, while less ACE2 is capable of converting it to the vasodilator heptapeptide angiotensin 1–7. This in turn contributes to lung injury, as angiotensin-stimulated

AT<sub>1</sub>R results in increased pulmonary vascular permeability, thereby mediating increased lung pathology [32]. Therefore, higher ACE2 expression following chronically medicating SARS-CoV-2 infected patients with ARB, while seemingly paradoxical [51, 52], may protect them against acute lung injury rather than putting them at higher risk to develop SARS. Nevertheless, studies that report increases in ACE2 expression tend to involve acute injury models and/or higher doses than typically administered to patients. Data from human studies overwhelmingly imply that administration of ACEIs/ARBs does not increase ACE2 expression[53].

Accordingly, among 511 COVID-19 patients aged >65 years with hypertension, the risk of severe COVID-19 was significantly decreased (OR=0.343) in patients who took ARB prior to hospitalization compared to patients who took no anti-hypertensive drugs [54].

In another series of 126 COVID-19 patients, However, ARBs/ACEIs group had significantly lower concentrations of CRP and procalcitonin, as well as less severe disease or mortality [55].

Finally, in a multicenter retrospective series of 564 Chinese patient, hypertension without receiving ACEI/ARB therapy was an independent risk factor (odds ratio [OR], 2.07; 95% CI, 1.07 to 4.00) for developing severe pneumonia irrespective of age [56].

In a multicenter UK trial on 53 patients, a lower rate of death or transfer to a critical care unit within 7 days in patients on an ACEI was reported compared to patients not on ACEI (OR 0.29) [57].

Discordant data have also been reported. In a case series of 274 patients from Wuhan, Patients with hypertension who had previously taken ACEI/ARB have a statistically nonsignificant tendency to develop severe pneumonia (P = 0.064)[58].

As suggested by other authors, this may be accounted for by two complementary mechanisms: blocking the excessive angiotensin-mediated AT<sub>1</sub>R activation caused by the viral infection, as well as upregulating ACE2, thereby reducing angiotensin production by ACE and increasing the production of the vasodilator angiotensin 1–7[51].

Following the SARS-CoV epidemic, ACEI were suggested as SARS therapeutics [59, 60]. Incidentally, in the context of the human immunodeficiency viruses (HIV), it has been demonstrated that higher expression levels of the HIV binding sites CCR5 and CD4 protect from, rather than increase, HIV virulence. Michel et al. reported that HIV employs its early gene Nef product for avoiding superinfection during the viral-entry step by downregulating CCR5. This Nef-mediated downregulation enhances the endocytosis rate of both CCR5 and CD4, which in turn facilitates efficient replication and spread of HIV, thereby promoting AIDS pathogenesis[61].

Both SARS and COVID-19 cases are normotensive at admission [62]: while SARS patients developed hypotension during staying at hospital (which is for sure a contraindication to ACEI or ARB administration), this has not been reported yet for COVID-19 patients. Whether this is due to higher affinity of S protein of SARS-CoV2 for ACE2 remains to be cleared, but at least do not pose hurdles to testing in COVID-19.

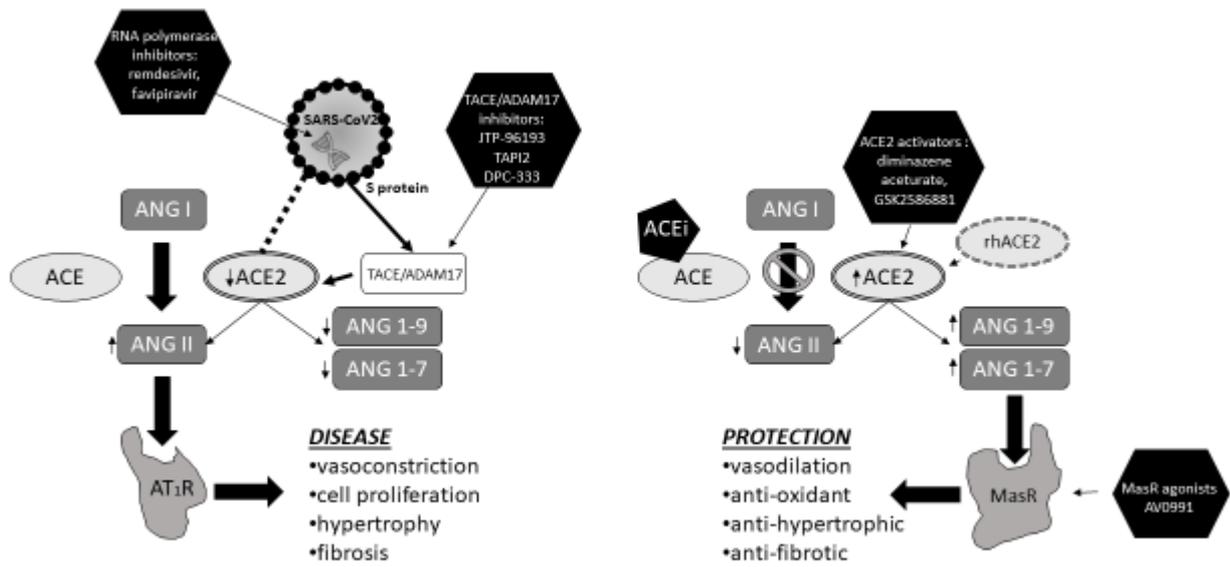
Figure 1 summarizes potential intervention points for currently approved or preclinical chemicals targeting the classical or counterregulatory RAS axes.

Of interest, a phase II clinical trial of recombinant human ACE2 (rhACE2) GSK2586881 in ARDS showed that ATII levels decreased rapidly, whereas angiotensin-(1–7) and angiotensin-(1–5) levels increased and remained elevated for 48 hours [63]. Surfactant protein D concentrations were increased, whereas there was a trend for a decrease in interleukin-6 concentrations in rhACE2-treated subjects compared with placebo. The study was unfortunately not powered to detect changes in acute physiology or clinical outcomes[63].

The low toxicity profile of ACEI and ARB encourages interventional randomized clinical trials in critically ill COVID-19 patients, escalating dose to previously treated patients and introducing ACEI to previously untreated patients [64].

We declare that we have no conflict of interest related to this manuscript.

Figure 1. Potential intervention points in RAS axes in COVID-19. Hexagons represent chemicals that can upregulate ACE2 axis or downregulate ACE axis.



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