Dangers of ACE inhibitor and ARB usage in COVID-19: evaluating the evidence

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Abstract

Background: Concerns have been raised regarding the safety of Angiotensin Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) in patients with COVID-19, based on the hypothesis that such medications may raise expression of ACE2, the receptor for SARS-CoV-2.

Methods: We conducted a literature review of studies (n=12) in experimental animals and human subjects (n=11) and evaluated the evidence regarding the impact of administration of ACEIs and ARBs on ACE2 expression. We prioritized studies that assessed ACE2 protein expression data, measured directly or inferred from ACE2 activity assays.

Results: The findings in animals are inconsistent with respect to an increase in ACE2 expression in response to treatment with ACEIs or ARBs. Control/sham animals show little to no effect in the plurality of studies. Those 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.

Conclusion: Available evidence, in particular, data from human studies, does not support the hypothesis that ACEI/ARB use increases ACE2 expression and the risk of complications from COVID-19. We conclude that patients being treated with ACEIs and ARBs should continue their use for approved indications.

There has been much recent debate regarding the use of ACE inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) in COVID-19 patients [1-5], thus prompting concern among patients and health care providers. The basis of this concern involves whether ACEIs/ARBs increase expression of ACE2, the primary cellular receptor for the SARS-CoV-2 virus and thereby may increase severity of the infection. Here, we review key literature regarding this possibility by assessing studies conducted in experimental animals (primarily rats) and humans. We focus our discussion on studies for which ACE2 protein data are available, as tissue ACE2 mRNA expression appears to only weakly correlate with protein expression, as shown from data in the Human Protein Atlas [6] (*proteinatlas.org*), results from human renal samples [7] and animal studies discussed below (e.g. [8,9]) .

We focused our assessment on studies that evaluated ACE2 levels in tissues/cells involved in infection by SARS-CoV-1 or SARS-CoV-2. Data from 12 animal studies are summarized in **Table 1**, which shows the effect of ACEI/ARB use on ACE2 protein expression/activity in animals (primarily in rats). We used conversion factors based on the principles of allometric scaling to evaluate doses in animals relative to their use in humans [10]. For studies in which this was relevant, we used the HED (Human Equivalent Dose, assuming a 60 kg human [10]) for doses of ACEI/ARBs. We obtained recommended doses for humans using approved labelling from the Food and Drug Administration (FDA) website (fda.gov). These recommended human doses are provided in **Table 2**. For most of the drugs, the maximum doses indicated in **Table 2** are seldom achieved in humans, such that treatment of animals with equivalent (or larger) doses, (especially in models of acute dosing, as in refs [15] and [19] discussed in **Table 1**) raise concern about their relevance to ACEI/ARB administration to patients, including in the setting of COVID-19.

In summary, 3 studies [8,11,19] in animals reported an increase in all treatment groups, of ACE2 protein expression/activity with ACEI/ARB treatment but in one such study,[8] combined ARB/ACEI treatment did not show this effect. The other two studies reported relatively small effects (< 40% increase in ACE2 protein expression in control/sham animals). All of these studies used high doses of ACEIs/ARBs, as noted above. By contrast, 6 studies [9, 12, 14, 16, 17, 20] found little or no change in ACE2 expression with ACEI/ARB treatment. In 3 studies [13, 15, 19], treatment with ACEI/ARB had no effect or a decrease in ACE2 protein expression/activity in

control/sham animals; increased ACE2 expression was only observed following experimental exposure, such as lung injury, MI, etc. In nearly all studies that reported an increase in ACE2, doses of ACEIs/ARBs used were greater than equivalent doses typically administered to patients. We identified only one study [13] in which ACEI/ARB use increased ACE2 protein expression at doses typical of human use, albeit these changes only occurred after exposure to acute injury (subtotal nephrectomy). Overall, the studies with experimental animals do not provide consistent evidence for an effect of ARB/ACEI administration on ACE2 protein expression, especially in contexts that model drug administration in humans.

Evidence of changes in ACE2 protein in human subjects/patients (**Table 3**) are derived from studies that assessed ACE2 protein concentration or enzymatic activity in urine or serum/plasma. Of the 10 studies summarized in **Table 3**, 7 showed no effect of ARB/ACEI use on ACE2 protein levels. One study [26] documented a small increase in serum ACE2 attributable to use of ACEIs among Type-1 diabetic patients but found no effect from use of ARBs. Another study [23] found a slightly larger proportional *decrease* in urinary ACE2 in patients with Type-2 diabetes using ACEIs/ARBs, but did not distinguish between effects from use of ACEIs or ARBs. In one study [22] the investigators observed that subjects using the ARB Olmesartan had increased ACE2 levels, but several other ARBs and ACEIs had no effect. Besides these quantitative data, other results regarding ACE2 protein expression, generated from immunohistochemical analysis in kidneys [31], indicated no ACEI-dependent effect. Together, these results imply a lack of association between ACE2 protein expression and the use of ARBs or ACEIs and support the idea that ACEIs/ARBs are unlikely to raise ACE2 and be harmful in the context of COVID-19 infection.

What would constitute strong, supportive evidence for the hypothesis that ACEI/ARB usage is a risk factor in the setting of SARS-CoV2 infection? Findings to help support that hypothesis would include: 1) Replication of a prominent effect in multiple animal studies and models; 2) Evidence that tissues with low expression of ACE2 have prominent increases in its expression and activity following ACEI/ARB treatment; 3) Data documenting that increases in ACE2 expression in response to ACEI/ARB treatment enhance the ability of the SARS-CoV-2 virus to infect cells; 4) Findings from human studies of statistically significant relationships between ACEI/ARB usage and ACE2 expression/activity; 5) Epidemiological data showing that COVID-19 patients administered ACEIs/ARBs have increased morbidity and mortality, ideally with a dose-response relationship for such outcomes.

How well do the available data provide such evidence? 1) The hypothesis that ACE2 expression increases with ACEI/ARB use is not supported by the plurality of available data from animal studies. 2) There is no available evidence for *de novo* expression of ACE2 expression in response to ACEIs/ARBs in tissues with low expression. 3) The affinity of SARS-CoV-2 for ACE2 is very high, ~4-fold greater than SARS-CoV-1 [32]. It is unclear if small or modest perturbations in ACE2 expression impact the infectivity of SARS-COV-2. Moreover, ACE2 levels may decrease with age [33,34] and diabetes [35], yet elderly/diabetic subjects are more vulnerable than younger individuals to COVID-19 [36]. Modest changes in ACE2 expression may not meaningfully impact on the high infectivity of SARS-CoV-2 in host tissues. 4) Data from human studies suggest that treatment with ACEIs/ARBs produces little or no effect on urinary or circulating ACE2 levels. As a caveat, changes in ACE2 levels in serum or urine may not reflect changes in tissue. 5) Epidemiological studies have not assessed outcomes in matched groups of patients infected with SARS-CoV-2, who have or have not been taking ACEIs/ARBs.

Based on the data summarized above, we conclude that current evidence, especially from human studies (**Table 3**), does not support the idea that treatment with ACEIs or ARBS produces pathophysiologically relevant increases in ACE2 protein abundance. The hypothesis that the use of these drugs increases SARS-CoV-2 virus infectivity and/or severity of COVID-19 is therefore not supported by the available evidence. It would thus seem prudent for patients to continue receiving these medications, as recently recommended by multiple health associations[2].

(1091 words without/ 1295 including the abstract)

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Table 1. Studies in animals that have assessed ACE2 protein expression in response to ACEI/ARB treatment.

Source	Study Details	Effect of ACEI / ARB on ACE2
Ferrario et al. [8]	Lewis rats were treated with losartan (an ARB) or lisinopril (an ACEI) 10 mg/kg/day (HED = 96.8 mg/day), for 20 days. ACE2 activity was measured in membranes from the renal cortex.	Lisinopril or Losartan treatment were both associated with increases in ACE2 activity but used in combination, did not produce this effect.
Ocaranza et al. [11]	Sprague Dawley (SD) rats were used in a myocardial infarction model, via coronary ligation. The ACEI Enalapril (10 mg/kg/day; HED = 96.8 mg/day) was administered for 8 weeks post- surgery. Plasma ACE2 activity was measured.	Enalapril increased plasma ACE2 by ~14% and ~36% in sham and MI animals, respectively.
Hamming et al. [12]	Renal ACE2 activity was assayed in Wistar rats, controls or on low sodium diet along with lisinopril (75 g/l) in drinking water for 3 weeks.	Renal ACE2 activity was unchanged with ACEI treatment in either group
Velkoska et al. [13]	ACE2 activity was assessed in kidneys from SD rats with subtotal nephrectomy and given ramipril (ACE, 1 mg/kg/day; HED = 9.68 mg/day) for 10 days.	ACE2 activity in renal cortex and medulla was unchanged by ACEI treatment In control rats and increased ~50% with nephrectomy.
Han et al. [14]	. ACE2 protein expression in lungs was measured in SD rats with cigarette smoke-induced lung damage. Rats were treated with losartan (10 or 30mg/kg/day [HED = 96.8 or 290 mg/day]) for 6 months.	ACE2 expression was unchanged in control rats by either dose of losartan. Animals exposed to cigarette smoke had reduced ACE2, which losartan treatment restored.
Wösten-van Asperen et al. [15]	SD rats were used in a LPS-induced model of Acute Respiratory Distress Syndrome (ARDS). Rats were given losartan (2.5 mg/kg/h during 4h of ventilation [HED = 96.8 mg]),. ACE2 protein expression in the lung was measured 24h after inducing ARDS with LPS.	Losartan administration decreased ACE2 activity in control animals (unclear if/how statistics were performed). After induction of ARDS, ACE2 levels decreased and were restored to normal by losartan.
Burrell et al. [16]	ACE2 activity and protein expression were assayed in tissues from SD rats 28 days after subtotal nephrectomy and which received ramipril (an ACEI, 1 mg/kg/day (HED = 9.68 mg/day)	Ramipril had no effect on ACE2 in cardiac or renal (cortex or medullary) tissue. ACE2 activity was reduced in renal cortex by nephrectomy; ramipril restored ACE2 activity to control levels.
Burchill et al. [17]	ACE2 protein expression was assessed in cardiac tissue in a Myocardial Infarction (MI) model in SD rats. Ramipril (1 mg/kg/day, HED = 9.68 mg/day) and Valsartan (ARB, 10 mg/kg/day; HED = 96.8 mg/day) were given for 28 days post-coronary artery ligation.	ACE2 expression was not altered but may have decreased in viable myocardium border or infarct zones, (unclear statistical analysis).
Yang et al. [9]	Spontaneously Hypertensive rats were treated with enalapril (15 mg/kg/day; HED = 145.2 mg/day) for 4 weeks. Cardiac ACE2 protein expression was measured.	ACE2 mRNA expression was increased but ACE2 protein expression did not change with ACEI treatment
Zhang et al. [18]	. Cardiac ACE2 protein was assayed from SD rats with cardiac remodeling from aortic constriction and treated with losartan (30 mg/kg/day; HED = 290.3 mg/day) or enalapril (20 mg/kg/day; HED = 193.5 mg/day) for 20 days, starting 4 days after surgery.	ACE2 cardiac protein expression was increased (~3-fold) with both drugs in rats with cardiac remodeling; data were not provided for animals with sham surgery.
Li et al. [19]	SD rats underwent LPS-stimulated lung injury. Simultaneous with intravenous injection of LPS, animals were administered captopril (50 mg/kg [HED = 483.9 mg]). After 8h, samples were collected and ACE2 protein expression was measured in the lung.	ACE2 protein expression was elevated in the lung, in control rats (~35%) and those with LPS-induced lung injury (~ 2-fold).
Wang et al. [20]	Pigs were used to study effects of ACEIs on cardiac arrest and resuscitation. Enalapril (0.2 mg/kg; HED = 10.9 mg) was perfused for 30 min, followed by surgery. Myocardial ACE2 protein expression was assayed in samples collected 6h post- surgery.	Compared to saline-infused controls, enalapril did not increase ACE2 levels; enalapril was not administered to sham rats.

Table 2. FDA-recommended doses of the ACEIs/ARBs discussed in **Table 1**.

Drug	Typical initial daily adult dose	Maximum daily adult dose
Losartan	50 mg	100 mg
Enalapril	5 mg	40 mg
Lisinopril	10 mg	40 mg
Ramipril	2.5 mg	20 mg
Captopril	50 mg	450 mg
Valsartan	80 mg	320 mg

Table 3: Studies in humans of the relationship between ACE1/ARB use and ACE2 protein expression. Entries are ordered chronologically, first for studies in urine and then for studies in circulating ACE2.

Source	Details of Study	Effect of ACEI / ARB on ACE2
Mizuiri et al., [21]	Urinary ACE2 protein levels were measured in 190 patients with chronic kidney disease and 36 healthy subjects.	No significant difference in urinary ACE2 was observed in response to treatment with ACEI and ARB
Furuhashi et al., [22]	Urinary ACE2 protein concentration was assayed in 617 subjects, including 101 subjects who did not use any medication and 100 hypertensives treated with various drugs.	Enalapril, losartan, valsartan, candesartan, valsartan and telmisartan had no effect. Olmesartan increased urinary ACE2.
Liang et al., [23]	Urinary ACE2 protein concentration was assessed in 132 Type-2 Diabetic patients and 34 healthy volunteers.	Patients with hypertension had a ~40% decrease in urinary ACE2 if treated with inhibitors of renin-angiotensin signaling, compared to hypertensive patients not taking such medications.
Mariana et al., [24]	Urinary ACE2 protein levels were measured via ELISA in 75 patients with Type-2 diabetes	Use of ARBs or ACEIs had no effect on urinary ACE2 levels
Epelman et al., [25]	Plasma ACE2 activity was assayed from 228 patients with heart failure.	No association was found between ACEI/ARB use and ACE2 levels.
Soro-Paavonen et al., [26]	Serum ACE2 activity was measured in 859 patients with Type-1 Diabetes and 99 healthy control subjects.	ACE2 was increased ~10 to 20% (higher in women) In diabetics using ACEIs, No association was found between ARB usage and ACE2 levels.
Ortiz-Perez et al.[27]	Serum ACE2 activity was assayed in 95 patients with ST-elevation myocardial infarction and 22 control subjects.	No association was found between ACEI use and ACE2 levels. ARB usage was not discussed.
Uri et al., [28]	Serum ACE2 activity was assayed in 141 healthy subjects, 239 hypertensive patients, and 188 patients with heart failure of different types.	Logistic regression analysis showed that ACEI and ARB usage had no association with ACE2 levels
Walters et al., [29]	Plasma ACE2 activity was assessed in 25 control subjects and 88 patients with atrial fibrillation.	No association was found between ACE2 levels and ACEI/ARB use.
Ramchand et al., [30]	Plasma ACE2 activity was measured in 79 patients with obstructive coronary artery disease.	ACE2 levels had no association with use of ACEIs or ARBs