

Binding of SARS-CoV-2 and angiotensin-converting enzyme 2: clinical implications

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The emergence and consequent impact of COVID-19 has led to clinicians and academics looking for evidence, with clinical controversies to parallel socio-economical and political ones.

A key clinical controversy has been whether the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) might be detrimental or beneficial in COVID-19. This is a widely prescribed class of drugs with a strong evidence base in hypertension and cardiovascular risk reduction. Individuals have proposed stopping such drugs due to concern over up-regulation of the ACE2 receptor acting as the SARS-CoV-2 entry point; others paradoxically suggest prescribing this class of drugs to counteract a dysregulated angiotensin–aldosterone system. We therefore explore the links between the renin–angiotensin–aldosterone system (RAAS) and the ACE2 receptor specifically; expanding on the observation that hypertension is prevalent among those diagnosed with COVID-19.

SARS-Cov2 virus: the pathogen responsible for COVID-19. The SARS-Cov2 virus achieves cell entry through an S (spike) high-affinity protein binding to the catalytic domain of the ACE2 receptor;¹ pneumocytes are particularly vulnerable.

ACE2: the RAAS is well characterized in hypertension, heart failure, and beyond. ACE converts angiotensin I (Ang I) to Ang II, predominantly in the lungs. The effects of Ang II are dependent on receptor binding: AT1 receptor binding stimulates the classical effects of Ang II, ranging from increased oxidative stress, through to vasoconstriction; in principle, AT2 receptor regulates opposing effects. ACE2 is an enzyme attached to cell membranes in the lungs, endothelium, and heart, as well as the kidneys. Its main pharmacological effect is to lower blood pressure by catalysing the cleavage of Ang I to Ang 1-9 and of Ang II to Ang 1-7 (vasodilatory, anti-inflammatory activity). ACE2 has additional affinity for other vasoactive substrates, including apelin-13 and bradykinin. Soluble ACE2 has also been described, cleaved from the cell surface but with a preserved catalytic activity. A sex difference exists, with men displaying higher ACE2 levels.^{2,3} Circulating levels are low in good health, but rise in heart failure, atrial fibrillation, and kidney disease:

- In 79 patients with obstructive coronary artery disease (59% on an ACE inhibitor/ARB), the 10-year MACE (major adverse cardiovascular events) rate was higher in those with higher plasma ACE2 activity at baseline ($P = 0.035$); ACE2 remained an independent predictor in

multivariable analysis [hazard ratio (HR) 2.4, 95% confidence interval (CI) 1.2–4.7].²

- Hospitalization due to heart failure in the same cohort was associated with higher ACE2 with a HR of 1.0 (95% CI 1.4–11.5, $P = 0.009$).²
- Post-operative ACE2 levels following orthopaedic surgery in 187 patients were significantly greater in patients with a subsequent in-hospital cardiac event (25.3 vs. 39.5 pmol/mL/min, $P = 0.012$), though this did not remain significant in multivariate analysis.⁴
- In 103 participants, increased ACE2 activity was associated with hypertension, impaired left ventricular systolic function, and older age; atrial fibrillation ($P = 0.04$) and vascular disease ($P < 0.01$) were independent predictors of plasma ACE2 activity.³ ACE inhibitor/ARB use was reported in 28% of controls, 36% of paroxysmal AF, and 55% of persistent AF participants.

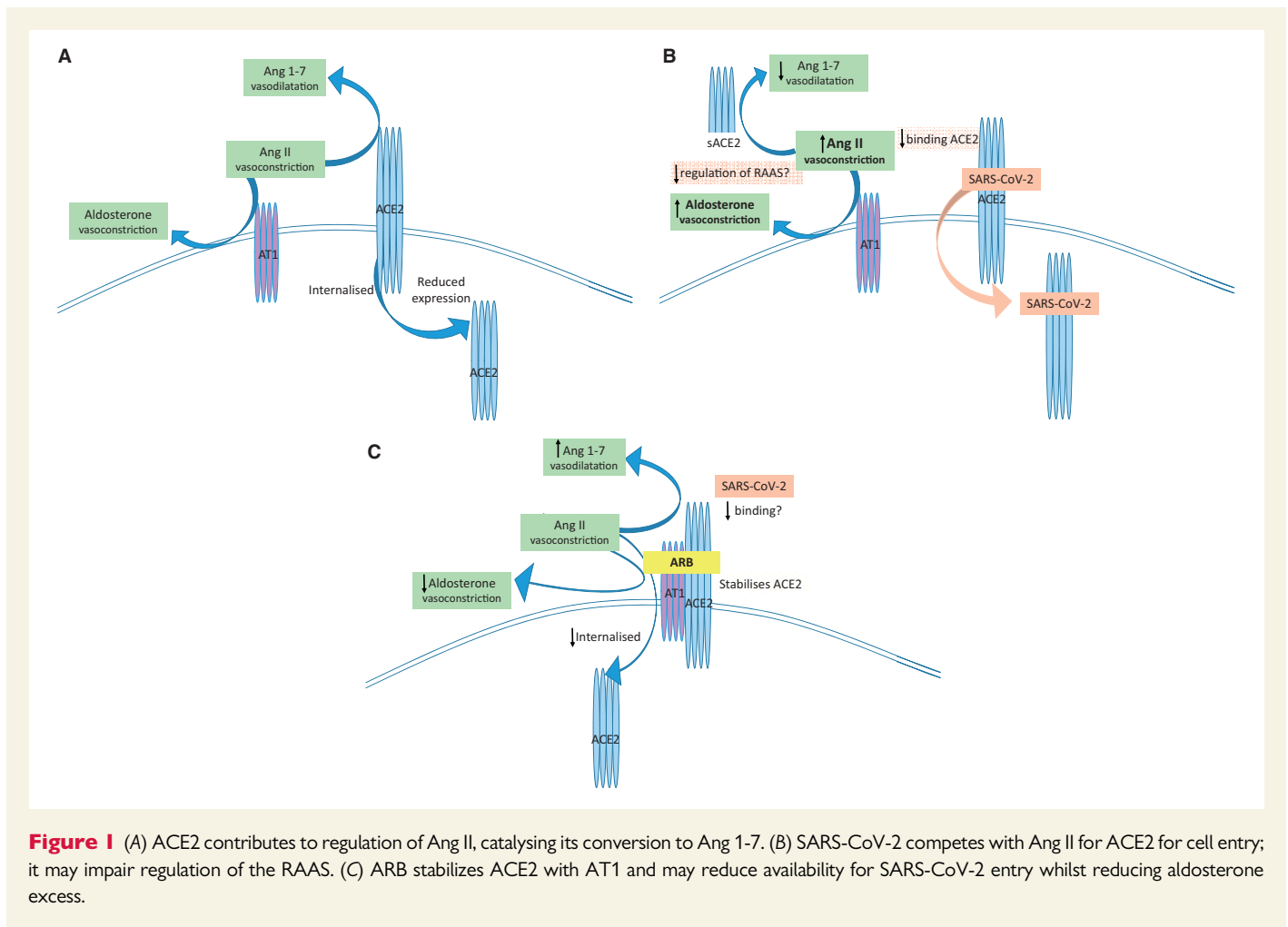
Differing rates of ACE inhibitor/ARB use between groups is important considering the aforementioned effect on membrane-bound ACE2, and a largely unknown effect on soluble ACE2.

Is ACE2 up-regulated by ACE inhibitor/ARB use, and does this facilitate COVID-19 cell entry and increase severity of infection?:

The concept of the up-regulation of ACE2 arises from animal studies; with rats demonstrating reduced plasma Ang II, increased ACE2 mRNA, and higher plasma Ang 1-7 in response to lisinopril or enalapril, and the latter two effects also found with losartan.⁵ However, conflicting evidence can also be found, with ramipril failing to increase ACE2 despite a similar duration of ACE inhibition.⁶ Mechanistically, Ang II induces lysosomal internalization of ACE2, and thus reduces tissue expression; losartan prevents this through interaction and stabilization of ACE2 with AT1 receptors.⁷ This leads to the converse argument, that ARBs could reduce SARS-CoV-2 cell entry by reducing availability of binding sites and reducing internalization of ACE2. However, a virus only needs one receptor to infect a cell, and the effect of ARB on Ang II breakdown to Ang 1-7 was not studied.

There has not been any good evidence of ACE2 up-regulation associated with these drugs in humans^{2,3} and, despite 61% sequence similarity between ACE1 and ACE2, ACE inhibitors do not effect ACE2 receptors. It is notable that animal work is predominantly based on tissue expression, and human work on soluble/circulating ACE2, when the relationship between these remains unclear. Furthermore, mice and rats are not

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intermediate hosts of SARS-CoV, raising questions about the generalizability of the data to humans.

Loss of regulation of Ang II: Considering whether there is evidence of RAAS dysfunction in COVID-19, hypokalaemia has been a reported complication not clearly explained by gastrointestinal loss, and correlating with disease severity, though the study omitted to report medication use.⁸ Renal potassium losses (as seen in hyperaldosteronism) may be a consequence of elevated Ang II due to SARS-CoV S protein binding to and reducing ACE2 expression, thus removing the homeostatic mechanism limiting Ang II (Figure 1).¹ ACE2 knockout mice support the protective effect of regulating Ang II through ACE2 metabolism to Ang 1-7 as, in a viral influenza model, pathology and survival were inferior in knockout animals.⁹ Use of losartan to block the AT1 receptor improved lung injury in this mouse model.⁹

Clinical outcomes with ACE inhibitors/ARBs: A study of a cohort of 539 viral pneumonia patients found that ACE inhibitor use was associated with an increased risk of death or need for intubation [odds ratio (OR) 3; 95% CI 1.3–7.0], but continued use during the admission was possibly beneficial (OR 0.25; 95% CI 0.1–0.6).¹⁰ However, demographic and clinical features broken down by ACE inhibitor use/continuation were omitted, despite association of ACE inhibitor use with cardiovascular disease; and discontinuation of the drug was more likely to occur in deteriorating patients.

Long-term outcomes: Outcomes of the disease remain largely unknown. Following SARS, lipid metabolism may remain altered even at 12

years follow-up in comparison with both healthy controls (age and body mass index matched) and those with bacterial pneumonia; though the authors hypothesize that this may relate to use of methylprednisolone rather than the virus itself.¹⁵ Compared with healthy controls, higher rates of cardiovascular and glucose metabolism abnormalities were reported, as was further hospitalization.

Conclusion

In relation to the above evidence, the American College of Physicians, Canadian Cardiovascular Society, European Society of Cardiology Council on Hypertension, European Society of Hypertension, Hypertension Canada, International Society of Hypertension and The Renal Association (UK) have all supported continued ACE inhibitor/ARB use, unless there is an alternative clinical reason to suspend them in the face of COVID-19. The morbidity and mortality risk of stopping such drugs is significant, particularly given the myocardial damage that may occur in COVID-19.

Conflict of interest: none declared.

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