Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic?

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The novel coronavirus causing the COVID-19 pandemic, SARS-CoV-2, gains entry to pulmonary cells after binding to membrane ACE2 [1]. This enzyme is a homologue of ACE1, which converts angiotensin I to angiotensin II, is active in cardiovascular control, can be an element in cardiovascular disease, and is therapeutically targeted in hypertension and heart failure, using ACE1 inhibitors such as enalapril and lisinopril.

The biology and therapeutic potential of ACE2 is much less clear. Commonly, it is viewed in the cardiovascular sphere as somehow antagonistic to the adverse effects of ACE1, and beneficial. This remains not well worked out, and currently there are no specific cardiovascular therapies involving ACE2. One action of ACE2 is to enzymatically cleave angiotensin II to angiotensin (1–7).

Given the importance of ACE2 in SARS-CoV-2 entry to cells, cardiovascular illnesses or cardiovascular drugs, which increase ACE2 expression, and there are several important instances of this [2–6], may perhaps increase human SARS-CoV-2 infectivity and illness severity. We understand that hypertension increases the severity of COVID-19 illness. This is surprising, on two counts. First, ACE2 expression typically is reduced in hypertension models, and second, hypertension does not appear to impact other infections. One of us (M.E.), a cardiologist with more than four decades of hypertension tertiary care experience, cannot recall one of his patients ever dying from an infection. Infection predisposition in diabetes is evident, but not in hypertension.

Perhaps in the COVID-19 pandemic, a new infection risk is arising from special properties of some antihypertensive drugs? Angiotensin receptor-blocker (ARB) drugs, now becoming the most commonly used antihypertensive drug class, typically increase ACE2 expression, often very substantially (perhaps two-fold to five-fold) [3–6]. This is sufficiently clear to have sometimes been used in marketing for ARBs, with a claim by pharmaceutical companies that this provides specific benefit in cardiovascular diseases. Perhaps, although this is unproven. With SARS-CoV-2 infection increased ACE2 expression very definitely would not be beneficial, and could be adverse. Increased ACE2 expression with angiotensin receptor blockers has been demonstrated in the kidneys and heart [4–6] but has not been tested to our knowledge, and this is now necessary, in the lungs.

Reducing ACE2 expression as a therapeutic principle for COVID-19 control?

How might angiotensin receptor blockers increase ACE2 expression. Plasma levels of angiotensin II increase with ARB dosing [7–10]. Angiotensin II is the known substrate for ACE2. Perhaps this is a case of substrate availability increasing the expression of the linked enzyme. This is hypothetical, but could be used as a framework to consider alternative drugs to ARBs during the COVID-19 pandemic. Both ACE1 inhibitors and beta-adrenergic blockers reduce plasma concentrations of angiotensin II, the ACE2 substrate, for ACE1 inhibitors by reducing cleavage of angiotensin I to angiotensin II, and with beta-blockers by reducing release of renin from the kidneys. This might suggest they are potentially suitable replacements and preferred, because they potentially reduce ACE2 expression. Calcium channel blockers, another antihypertensive class mainstay, are neutral concerning angiotensin II availability, and potentially suitable. Diuretics and mineralocorticoid antagonists increase angiotensin II production, because of body sodium losses, which in the context of a COVID-19 pandemic might be adverse; sodium loading does reduce ACE2 expression. But in truth, inferences of ACE2 expression changes during antihypertensive dosing from known changes in angiotensin availability may possibly not be valid. The crucial point is that angiotensin receptor blocker drugs increase ACE2 expression remarkably, which is a significant demerit, emphasized by the fact that one favoured path of vaccine development is immunological antagonism of the ACE2 binding site for the SARS-CoV-2 virus spike protein.

We have presented the hypothesis that prescribing of angiotensin receptor-blocking drugs during the COVID-19 pandemic might possibly be harmful, and suggested that

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other antihypertensive drug classes are preferred. We hope that the clinical data base from the pandemic so far could provide sufficient detail on hypertension diagnosis and antihypertensive drug prescribing to test our hypothesis. If the hypothesis was confirmed, how might this be applied clinically? One application would be in those SARS-CoV-2-infected patients who have a blood pressure rise during their acute illness, which has been noted. Any current dosing of ARB drugs should not be escalated, or new ARB therapy initiated. Perhaps ARBs currently prescribed should be entirely replaced in the acute illness by other antihypertensives as needed. The caveat here is that the rate at which excess ACE2 protein would disappear from cell membranes after discontinuation of ARBs is not known. More contentious, perhaps, would be the advice to replace ARBs with other antihypertensive agents as the pandemic approaches and intensifies. Although this is an option which should be considered, our recommendation at present is to not discontinue angiotensin receptor blockers prior to confirmation of the hypothesis. Any resulting destabilizing of blood pressure control in hypertension, which might possibly occur with treatment changes, would carry risks which are not just hypothetical. Simply discontinuing antihypertensives is strongly discouraged and is not an option.

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Conflicts of interest

There are no conflicts of interest.

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