Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in the time of COVID-19: what the evidence suggests

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Coronavirus disease 2019 (COVID-19) remains of global concern due to its devastating impact on human health. Several comorbidities have already been established as risk factors for poor outcome, with cardiovascular disorders among them. Given the mechanistic attributes of several drug classes, much contention has been raised about the benefit and/or risk of using some while COVID-19-positive. The antihypertensive angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin II receptor blocker (ARB) drug classes are among these that have received attention due to their overlapping biological properties with the angiotensin-converting enzyme-2 metallopeptidase; this enzyme facilitates viral entry of the severe acute respiratory syndrome coronavirus 2. Although there are theoretical risks, to date, no studies have shown an increased risk of using these drug classes during COVID-19, with some suggesting potential benefit of use. Given the evidence available, and without robust enough trials available to show otherwise, current recommendations are that starting or discontinuing ACE-I or ARB treatment during COVID-19 should only be guided by hypertension clinical practice guidelines and not the COVID-19 status of the patient.

Keywords: angiotensin-converting enzyme inhibitor, angiotensin II receptor blockers, coronavirus disease 2019, severe acute respiratory syndrome coronavirus-2

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Introduction

As of 14 April 2021, 53 498 individuals in South Africa have lost their lives due to the coronavirus disease 2019 (COVID-19), with 1 561 559 individuals positive for its viral pathogen: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Afflicted individuals may present with a myriad of symptoms, including fever, cough, dyspnoea,[2-4] sputum production, myalgia, neurological symptoms,[5] fatigue, headaches, rhinitis, pharyngeal symptoms, and the loss of taste and smell;[2,3] however, many asymptomatic instances are also observed.[6,7] Patients most at risk of severe COVID-19 outcomes include those older than 50 years of age, smokers, or patients suffering from comorbidities, such as cardiovascular disease, chronic respiratory disease, and diabetes.[8] Although associations between COVID-19 severity and hypertension have been reported,[8-10] there is some contention on whether it contributes to unfavourable disease outcomes.[2,9,11,12] Regardless of its impact on COVID-19 outcomes, concern has been raised about the antihypertensive angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin II receptor blocker (ARB) drug classes on COVID-19 outcomes. The fears associated with it arise from the potential biological impact on the angiotensin-converting enzyme 2 (ACE-2), the metallopeptidase that facilitates SARS-CoV-2 entry into the cell.[13,14]

How do ACE-Is and ARBs relate to COVID-19?

The ACE-Is (*-pril* drugs, such as captopril, enalapril, lisinopril, and ramipril) and ARBs *(-sartan* drugs; such as candesartan, irbesartan, losartan, and valsartan) are frequently used in hypertension and associated cardiovascular diseases.[7] Both drug classes reduce the activity of angiotensin II, a driver of increased blood pressure, by targeting two distinct parts of the renin-angiotensin system.[15] The ACE-Is prevent the angiotensin-converting enzyme-mediated conversion of angiotensin I to angiotensin II; the ARBs prevent the binding of angiotensin II to the angiotensin II receptor type 1.[15] In doing so, the renin-angiotensin-aldosterone system (RAAS) fails to increase blood pressure (thus preventing hypertension) due to lower aldosterone production, vasoconstriction, and sympathetic nervous system activation, among others.[15]

The concern of ACE-I and ARB use ties into the theoretical impact on ACE-2. As a consequence of reducing angiotensin II receptor type 1 activation,[16] ACE-2 up-regulation has been noted in experimental animal models.[17,18] This is debated though[19] as data is not available to support the effect in humans. Should ACE-2 be increased, the theoretical consequence may be an increased entry of SARS-CoV-2 into cells, thus worsening clinical symptoms due to further viral replication and disease burden.

What does the evidence say?

Numerous studies have been conducted in several population groups with differing treatment regimens,[3-5,7,9,12,20-33] primarily as retrospective studies including hospitalised patients.[5,7,24,31,33-35] Additionally, most studies are constrained due to the small number of patients using ACE-Is and/or ARBs in their cohorts,[3-7,12,20,23,30,31,33,35,36] and as such, some results may appear noteworthy but lack statistical significance.[24,32,33,35] Many studies were able to control for certain patient factors using statistical models;[2,3,7,9,12,20,24,33,37] however, generally, the drug, dose, frequency, adherence, and division of ACE-I or ARB was not done and thus can interfere with the outcomes. Robust, prospective, placebo-controlled trials are needed, such as the RAMIC trial focusing on ramipril,[38] which has not been completed yet.

Although there has been much concern on the theoretical possibility of increased SARS-CoV-2 infection, neither the ACE-Is nor ARBs have been observed to increase infection risk.[6,27,32] Measures of disease severity included, among others, symptomatic profiles, mortality, intensive care admissions, need for mechanical ventilation, length of stay, and intubation.[5,20] There were no significant worsening of disease severity or outcomes when using ACE-Is or ARBs,[3-5,7,9,12,20,22,24-33] even when focusing on diabetic[2] and hypertensive[20] patients. Cardiac injury in hypertensive patients,[23] propensity for coughing, phlegm production, fever[36] or developing severe pneumonia[33] was also not different.

Interestingly enough, and what necessitates controlled studies, are several observations of potential benefits when using ACE-Is or ARBs. Some studies have shown that ACE-Is or ARBs may reduce mortality,[32,35,39-41] severity,[34,41] or mental confusion associated with COVID-19.[33]

What do we do now?

Current findings do not suggest any particular risk or benefit associated with ACE-I or ARB use while afflicted by COVID-19. Conclusions have been drawn from mostly retrospective studies with relatively small sample sizes, patients suffering from various comorbidities, instances of polypharmacy, and/or incomplete differentiation of antihypertensive drug class, dose, or frequency of use, weakening their scientific strength. More robust trials are thus needed to ensure the biological risks and benefits are described in full. At the time of writing, 20 studies are active, inviting participants or recruiting on the United States National Library of Medicine's ClinicalTrials.gov,[42] with six additional completed trials.[43] One such trial, entitled RAMIC, is a randomised, double-blind, placebo-controlled trial to determine whether ramipril may alter COVID-19 disease outcomes.[38]

Given evidence (or rather, the lack thereof), treatment with ACE-Is and ARBs should thus not be dictated by the COVID-19 status of a patient but rather by standard clinical practice and alterations to clinical indices.[15] The American College of Cardiology, American Heart Association, and Heart Failure Society of America, in a joint statement, posited that no alterations should be made to renin-angiotensin-system inhibitor treatment beyond standard clinical practice given the lack of data suggesting altered risk or benefit.[44] Similarly, the Clinical Pharmacology section of the Italian Society of Pharmacology warns against unjustified changes to antihypertensive treatments in patients lest it precipitates further cardiovascular complications, or the unwarranted use as protection without supporting evidence.[45] Alterations to hypertensive treatment may incur inadequate blood pressure control, thus worsening clinical outcomes and need for hospitalisation,[46] and placing patients at a greater risk of SARS-CoV-2 exposure and/or COVID-19 disease progression.

Conclusion

Regardless of concerns of ACE-Is or ARBs upregulating ACE-2 and worsening COVID-19 outcomes, this remains theoretical with no clinical evidence to suggest otherwise. Use of ACE-Is or ARBs during COVID-19, given the evidence at hand, does not lead to any significant alteration to SARS-CoV-2 infectivity and/or COVID-19 disease outcomes. Although some observations suggest benefits while using, no clear evidence is available to suggest clinical practice guidelines should be altered. Only time, and the availability of controlled, prospective trials, will tell whether any true risk or benefit is present. Till then, treatment with ACE-Is or ARBs should not be altered unless standard healthcare practice dictates it for another medical reason.

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Conflict of interest

The author has no conflict of interest to disclose.

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