

Article 4

Should ACE Inhibitors and Angiotensin Receptor Blockers Be Withdrawn in the Current Setting of COVID-19 Infection?

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At the end of February 2020 and early March 2020, the *British Medical Journal* and the *Lancet Respiratory Medicine Journal*, respectively, published reports which hypothesized that patients with cardiac diseases, hypertension or diabetes, who are treated with angiotensin converting enzyme ACE inhibitors or angiotensin receptor blockers (ARBs), were more susceptible to COVID-19 (SARS-CoV-2) infection.(1,2) In one of the largest published series in Wuhan, China, cardiovascular comorbidities such as hypertension, coronary artery disease and diabetes have reported to be common in patients admitted to hospital with COVID-19 infection.(3) In this study of 1099 patients with confirmed COVID-19 infection and of 173 who were classified as having severe diseases, hypertension was reported to be prevalent in 23.7%, diabetes mellitus in 16.2% and coronary artery disease in 5.8%.(3) Although these conditions are often treated in hospitals with ACE inhibitors and ARBs, the effects of these treatment strategies on mortality were not assessed in this study.

COVID-19 AND ACE 2

The reports urging caution in the use of ACE inhibitors and ARBs for hypertension, diabetes and cardiovascular disease are based on laboratory data which found that SARS-CoV and COVID-19 virus binds to ACE 2 receptor which is found in the epithelial cells of the lung, kidney, intestine and blood vessels.(4,5) The ACE 2 is an integral protein and contributes to a host of physiologic functions and is highly expressed in alveolar cells of the lungs, providing the main entry site for the virus into human hosts.(5) Once the COVID-19 virus binds to ACE 2 and gains entry, it subsequently downregulates ACE 2 expression. It is postulated that this may lead to unopposed angiotensin II activity and renin–angiotensin–aldosterone-system

(RAAS) activation, leading to neutrophil infiltration into the lungs and lung injury.(6)

However, ACE 2 also has potential protective effects in that it counters the effects of angiotensin II via angiotensin 1 receptor activation, by promoting the conversion of angiotensin II to angiotensin 1–7, which in turn modestly lowers blood pressure through vasodilatation and increases renal excretion of sodium and water. ACE 2 may also attenuate inflammation through the activation of nitric oxide pathways. In some experimental studies with animal models, it has been shown that there is increased expression and activity of ACE 2 in the heart and brain after treatment with ACE inhibitors and ARBs.(7) Furthermore, the upregulation of ACE 2 in humans is supported by recent evidence showing an increased secretion of ACE 2 in the urine of hypertensive patients treated with olmesartan, an ARB.(8)

Although ACE 2 receptor upregulation may be induced by ACE inhibitors and ARB treatment and hence a theoretical risk of increased susceptibility to COVID-19 infection, currently there is no data that has demonstrated a definitive causal relationship between ACE 2 activity and COVID-19 mortality. Interestingly, ACE 2 and angiotensin 1–7 may in fact have a salutatory role in the lungs since it has been found to be protective in a number of lung injury models. In a mouse model with acid lung injury, ACE 2 downregulation induced by SARS-CoV, the virus responsible for the SARS virus outbreak in 2003, worsened lung injury, but this lung injury was improved by therapy with an ARB.(9) These findings suggest that SARS-CoV may induce lung injury, but the injury can be ameliorated by ARB administration.(9) These preclinical findings suggest a possible protective role of ARB in SARS-CoV-associated lung injury and lend credence to the hypothesis that primary activation of the RAAS in cardiovascular

patients, rather than its inhibition, renders them more prone to a deleterious outcome. However, currently there is no clinical evidence that has proven that ACE inhibitors or ARB-induced ACE 2 activity is an effective therapy for COVID-19-induced lung injury. In addition, ACE 2 activity may not correlate with the degree of severity of infection with COVID-19 infection. Although ACE 2 is presumed to be an important mediator for SARS-CoV infection, the absence of SARS-CoV has been found in some cell types expressing ACE 2.(10) On the other hand, infection was present in cells apparently lacking ACE 2, suggesting that additional co-factors may be needed for adequate cellular infection.(10)

Because of the connection of the ACE 2 pathway with COVID-19 infection, there has been widespread concern amongst physicians and patients, whether RAAS antagonists such as ACE inhibitors and ARBs confer an increased risk of COVID-19 infection. Many patients and their physicians, including those in South Africa, have contemplated a cessation of ACE inhibitors or ARB medications. In the Wuhan study,(2) there was no information of how many of the patients with severe COVID-19 infection were on ACE inhibitors or ARBs. Furthermore, there are no published studies to date showing that diabetes and hypertension are independent predictors of mortality with COVID-19 infection. Thus, a clear causal relationship between those with cardiovascular disease, hypertension, heart failure with reduced ejection fraction (HFrEF), and diabetes with chronic kidney disease (DCKD) on ACE inhibitors or ARB treatment and an increased risk of COVID-19 does not exist. There are alternative agents that can be used for the management of hypertension, but DCKD and HFrEF are compelling indications for these drugs. Patients, influenced by the media, may request an alternative anti-hypertensive agent, and that may be appropriate for them, but it is inappropriate to recommend discontinuation of ACE inhibitors or ARB treatment in patients with HFrEF and DCKD based on a hypothetical adverse outcome with COVID-19 infection. Importantly, the indication for which the drugs were originally prescribed may have changed since the drugs were initiated, and a patient with hypertension may not be aware of that they have developed LV systolic dysfunction or that a diabetic has developed proteinuria.

A recent report suggested a reverse causality relationship by the fact that patients who are receiving ACE inhibitors or ARB may be more susceptible to viral infections and more likely to have a higher risk of dying because they are older and hence would have a higher prevalence of hypertension, renal disease and diabetes.(11) It is important to recognize that pathophysiological mechanisms that lead to cardiovascular disease are known to overlap with pathways that regulate immunological functions. Thus, age is one of the strongest risk predictors for cardiovascular disease and the effect of ageing on immune function may be equally

important for COVID-19 susceptibility and severity.(12) A dysregulated immunologic state corresponds with an elevated risk of incident cardiovascular disease and thus other traditional cardiovascular disease risk factors such as diabetes and hyperlipidaemia impact immune function.(13) Thus, the presence of cardiovascular disease may be a marker of accelerated immunologic ageing/dysregulation and relate indirectly to COVID-19 prognosis.(12)

CONTINUATION OF ACE INHIBITORS AND ARBs WITH SUSPECTED OR KNOWN COVID-19 INFECTION

In South Africa, hypertension, HFrEF and diabetes are common non-communicable diseases, and a significant proportion of patients are being treated with generic versions of ACE inhibitors or ARBs. There is extremely strong scientific evidence for the benefit of RAAS inhibition in patients with cardiovascular disease. In patients with HFrEF, RAAS inhibition is a foundation of therapy for these patients. Discontinuation of RAAS inhibition in patients with heart failure can precipitate clinical deterioration and may be associated with increased mortality.(14) Furthermore, ACE inhibitors and ARBs are common therapies for hypertension and after myocardial infarction.(15,16) There is significant mortality benefit with all three classes of these agents' post myocardial infarction. Based on the solid scientific foundation of these three agents in cardiovascular disease, diabetes and renal disease, there is a potential for significant adverse outcomes in discontinuing these agents. COVID-19 appears to be particularly severe in patients with cardiovascular disease and may cause myocarditis, myocardial stress and cardiomyopathy.(12) Thus, discontinuing RAAS inhibition in these high-risk patients can potentially lead to higher mortality.

Change of therapy for patients with hypertension is less risky. However, they are associated with other risks such as medication errors, rebound increase in blood pressure, frequent monitoring to assess adequate blood pressure control and management of side effects of newly prescribed medications. It has been shown that even short periods of loss of control of blood pressure may be associated with increased cardiovascular risk.(17) In response to the reports of a hypothetical risk of ACE inhibitors and ARBs, many societies have issued statements strongly recommending the continuation of ACE inhibitors and ARB therapies.(18,19) Patients are strongly discouraged from making autonomous decisions about their cardiovascular therapy and must be guided by their informed treating physician.

Moving forward it is clear that more research is needed to clarify and understand the relationship between the ACE 2 protein, ACE inhibitors and ARB use in cardiovascular disease and COVID-19 prognosis. In this regard an ongoing randomized trial evaluating recombinant ACE 2 in the setting of COVID-19 may help one to provide

mechanistic information in patients infected with this virus (ClinicalTrials.gov Identifier: NCT04287686).(20) This therapy has the possible potential to both decrease viral load and ameliorate the harmful effects of angiotensin II.

Until more robust evidence is available, it is prudent to advise that ACE inhibitors or ARB therapy should be continued in patients who are at risk for COVID-19 infection or who have COVID-19 infection. Even in patients with current COVID-19 infection, ACE inhibitors or ARB should be initiated in guideline-indicated conditions such as in patients with heart failure or myocardial infarction. We must not draw inappropriate conclusions from observational studies.

In conclusion, in the current COVID-19 pandemic in South Africa, both practitioners and patients need to be advised that ACE inhibitors and ARB therapy should be continued in patients with cardiovascular disease and in associated conditions such as diabetes and renal disease. Ongoing research efforts need to concentrate on assessing the role of ACE 2 in COVID-19 infection and the effect on mortality of known therapies for cardiovascular disease such as ACE inhibitors and ARBs. It is hoped that with the large numbers of patients currently infected worldwide with COVID-19, this information will be elucidated in the near future.

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