Coronavirus disease 2019 (COVID-19): angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and cardiovascular disease

During the COVID-19 pandemic, people with heart disease are likely abandoning usual medical advice

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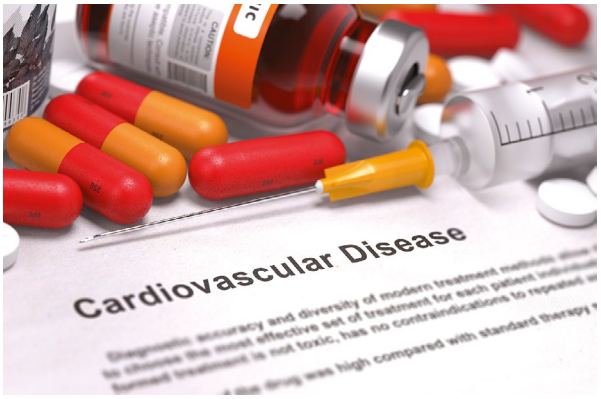
As the world watches the spread of the coronavirus disease 2019 (COVID-19) pandemic, affecting the health of millions of people and the lives of everyone, common health conditions including heart disease, stroke, cancer and other chronic diseases continue. While there is no doubt that there are direct consequences for morbidity and mortality of COVID-19, including its direct cardiovascular effects, it will be important to ensure that these are not matched by the indirect consequences. Countries are at different stages in the natural history of the pandemic, but there is a clear pattern. Overloaded health systems necessitate the hasty development of new protocols and pathways for common conditions that deviate from established guidelines and that may be caused by changes in community behaviour, either imposed or arising from fear. Unproven therapies are being tested in the field and, in the absence of evidence, there is the potential for theory to drive practice to an extent that is generally not seen in conditions with an established evidence base.

During the COVID-19 pandemic, emergency department (ED) attendances fell dramatically in England, with 89 584 attendances in the week after the lockdown (23–29 March 2020), down 25% compared with the 120 356 attendances during the previous week and almost 50% down on attendances in February 2020.[1] This decrease in ED attendances has also been reported in Europe, Canada and Australia.[2] ST elevated myocardial infarction (STEMI) rates fell by about 40% in reports from Austria[3] and the United States.[4] It is possible that COVID-19 is associated with plaque stabilisation and lower rates of STEMI, but it seems more likely that people with heart disease are abandoning usual medical advice at a time when they may need it the most.

In New York, US, a 50% decrease in ED visits for acute coronary syndromes has been reported at the same time as an eightfold increase in out-of-hospital cardiac arrest calls in the first week of April 2020.[5] It is not clear how many of these calls are COVID-19-related, but there seems to be no doubt that people have a reluctance to attend hospital during the peak of the epidemic, which is having a significant cost in mortality.

The angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers controversy

In the midst of all this, a controversy has emerged about the safety and value of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) — commonly used for the treatment of hypertension and heart failure — in the context of the COVID-19 pandemic. In ordinary times, these are considered to be among the safest, best tolerated and most effective drugs for the management of both hypertension and heart failure, with a strong evidence base showing a reduction in morbidity and mortality from these conditions.[6,7]



To date, there is insufficient clinical evidence that ACEIs, ARBs or other inhibitors of the renin angiotensin system are either harmful or beneficial in the acquisition of COVID-19 or its subsequent clinical course in individual patients. A number of clinical trials of losartan and recombinant angiotensin-converting enzyme 2 (ACE2) are underway, such as the Losartan for Patients with COVID-19 Requiring Hospitalization trial (ClinicalTrials.gov, NCT04312009). The debate has arisen because of circumstantial arguments based on COVID-19 pathophysiology and renin angiotensin system physiology.[8,9]

It is argued that ACEIs and ARBs may be harmful because:

- hypertension is overrepresented among people who develop the most severe complications of COVID-19;[10]
- severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) gains entry to a cell using ACE2 and type II transmembrane serine proteases;[11]
- ACE2 is highly expressed in the cardiovascular system, gut, kidneys and lungs (in the cardiovascular system, ACE2 is expressed in cardiomyocytes, epicardial adipose tissue, cardiac fibroblasts, vascular smooth muscle and endothelial cells);[11]

- ACEIs or ARBs upregulate ACE2 in heart cells in some experimental models;[12]
- these factors in theory may lead to a greater viral load and more serious infection.

Several important links in this logic chain are contested. Early reports of high rates of hypertension in people dying of COVID-19 or presenting with severe COVID-19 were not adjusted for age. However, it is clear that most of these patients have comorbidities, including hypertension, heart failure and diabetes, all of which are more common in an older population. The mortality rate in the intensive care unit in 72 regional hospitals in Lombardy, Italy, was 26%. Most patients were male (82%) and had extensive comorbidities, especially hypertension (49% overall and 62% of deaths).[10]

ACE2 and COVID-19 pathophysiology

The relationship between COVID-19 and the renin angiotensin system has been reviewed extensively.[11] Although there is no doubt that ACE2 is a receptor for COVID-19 and that the gene is widely expressed in the body, there is mixed evidence on whether it is upregulated by ACEIs or ARBs in animal models, and there is no evidence that it is increased de novo in tissues that have low expression.[13] COVID-19 suppresses ACE2.[11] If ACE2 expression is increased by ACEIs or ARBs, it does not necessarily imply that this enhances the ability of SARS-CoV-2 to infect cells. The affinity of the virus for ACE2 is very high, and it is not clear that a small increase in expression due to renin angiotensin inhibition would increase intracellular viral load.

Another counterargument to this hypothesis is that an increase in ACE2 expression would provide a counter to the suppression due to SARS-CoV-2 and allow the beneficial effects of ACE2, including anti-inflammatory activity, to manifest; that is, ACEIs or ARBs may be beneficial.

Trial design to resolve the matter

In considering the possibility of interactions between COVID-19 and medications, it is important to take into account the different stages in the evolution of the disease in an individual. The earliest stages are characterised by mild or absent upper respiratory symptoms and lymphopenia. A minority of people infected with SARS-CoV-2 subsequently develop pneumonitis and pulmonary complications. Even fewer people develop the most severe complications with hyperinflammation — also called "cytokine storm" — often with myocarditis and other major organ failures. It is quite likely that the renin angiotensin system and, by implication, drugs that interact with it, such as ACEIs or ARBs, have different actions at various stages of the condition according to the tissues affected. For example, ACE2 is protective in acute lung injury, suggesting that, although it facilitates viral entry through the epithelium, the ACE2 and its product, the angiotensin (1-7) axis, could be used to reduce tissue injury caused by SARS-Cov-2, a potential target for therapy.[11] This will be an important consideration in the design and setting of clinical trials.

What clinicians can do in the meantime

There are highly circumstantial arguments for and against the use of ACEIs and ARBs in patients with COVID-19 and there are many more in the literature — as preprints and on social media. In the absence of good epidemiological and clinical trial data, there is no immediate and definitive resolution to the debate. What is clear is that people with hypertension and heart failure benefit from ACEIs and ARBs where indicated, and withdrawing treatment is likely to have serious consequences in some people. We are thus left with a situation where stopping ACEIs or ARBs in some people has known and potentially serious sequelae, whereas continuing them in people with or vulnerable to COVID-19 has unknown consequences that, depending on how the experimental evidence is interpreted, may be negative, neutral or even positive. International and national authorities on cardiovascular disease, including the High Blood Pressure Research Council of Australia, the World Health Organization, the American Heart Association and the European Society of Cardiology, have been united in their recommendation that treatments with ACEIs or ARBs should be continued during the present pandemic pending evidence from clinical studies to the contrary.[14,15]

In a number of patient groups, ACEIs or ARBs are first line choices; for example, in patients with hypertension and proteinuria or in people with heart failure. Given the clear benefits they have provided over several decades, a decision to withdraw first line therapies should only be based on reasons supported by a strong evidence base. In other groups, such as in patients with uncomplicated essential hypertension, there are alternatives, including calcium channel blockers or diuretics. However, changing medications in patients with well controlled blood pressure requires careful monitoring and there is a risk in the short term that blood pressure will fall outside the optimal range. This may prove challenging during a period when telemedicine is the norm and given that not all households have home blood pressure monitoring equipment and training.

As the ACEIs and ARBs controversy has been wisely canvassed in the media, health professionals will need to have a conversation with patients about the benefits or otherwise of continuing their present therapies. It is important that people understand that no concerns have been raised about other medications they may be taking, such as statins, antithrombotic agents, or treatment for diabetes. In recommending continuation of ACEIs or ARBs, physicians can draw comfort that they are backed by almost every cardiovascular health authority in the world. Nevertheless, the clinical trial results of both administration or withdrawal of ACEIs or ARBs cannot come quickly enough, and in the best case, they will allow us to turn practice into the right theory.

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