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EDITORIALS

Drugs and the renin-angiotensin system in covid-19

Clinical effects are unpredictable, so treatment decisions must be tailored and pragmatic

Jeffrey K Aronson *clinical pharmacologist*[1], Robin E Ferner *honorary professor of clinical pharmacology*[2]

[1]Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK; [2]Institute of Clinical Sciences, University of Birmingham, Birmingham, UK

Covid-19, which is caused by the single stranded RNA coronavirus SARS-CoV-2, poses therapeutic dilemmas. Some suggestions for drug treatment seem problematic.[1] They include various antiviral drugs, some of which have primary targets that are DNA viruses not RNA; immunomodulatory drugs, which may suppress potentially protective acute inflammatory responses and do not specifically target the virus; the antimalarial drugs chloroquine and hydroxychloroquine, which have some antiviral activity in vitro but no evidence of clinical benefit in human viral infections and also have many adverse effects; and corticosteroids, which may be harmful when used to treat infection with the related virus SARS-CoV-1.[2]

Important questions have also been raised about the use of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). Do they have a role in treating covid-19? Should people currently taking them continue doing so, and should they stop if they become infected?

No trial evidence is yet available on the effects of ACE inhibitors or ARBs in treating covid-19. But for people already taking these drugs the European Society of Cardiology recommends "that physicians and patients should continue treatment … because there is no clinical or scientific evidence to suggest that treatment with ACEi or ARBs should be discontinued because of the covid-19 infection."[3] The American College of Cardiology advises that patients should continue taking them for conditions such as heart failure, hypertension, or ischaemic heart disease, and that if covid-19 occurs "individualized treatment decisions should be made according to each patient's hemodynamic status and clinical presentation."[4]

Little attention has been paid to the balance of benefits and harms associated with using these drugs, and whether this balance differs among individuals. However, their pharmacology and the biology of the virus offer important insights.

Key enzymes and receptors

The renin-angiotensin system includes two key enzymes, ACE-1 and ACE-2, which control the balance of peptides in the angiotensin family, including angiotensin I, angiotensin II, angiotensin-(1-9), and angiotensin-(1-7). The balance of these vasoactive peptides has profound effects on several organ systems and is altered by both ACE inhibitors (which block the action of ACE-1) and ARBs (which block the action of angiotensin II at AT1 receptors).

Both ACE inhibitors and ARBs substantially increase ACE-2 activity in cardiac myocytes over one to two weeks.[5] ACE-2 is also found on epithelial cells in the respiratory and gastrointestinal tracts. The Oxford Covid-19 Evidence Centre gives more details.[6]

Action on SARS-CoV-2

SARS-CoV-2 has a viral envelope studded with spikes—glycoproteins composed of two subunits. Subunit S1 binds to ACE-2 on the cell surface; subunit S2 fuses with the cell membrane. Another host enzyme, the serine protease TMPRSS2, then promotes cellular entry of SARS-CoV-2.[7,8] ACE-2 and TMPRSS2 are thus both essential for viral infectivity.

Theoretically, ACE-1 inhibitors and ARBs could be harmful in covid-19 since increased ACE-2 activity might increase viral entry into cells. Alternatively, increased ACE-2 activity could increase conversion of angiotensin II to angiotensin-(1-7), a peptide with potentially protective anti-inflammatory properties.[9] However, that effect would probably be small, and it is unclear whether increasing anti-inflammatory activity is harmful or beneficial in covid-19.[10]

Although understanding underlying mechanisms can inform drug treatment in many ways, it is unwise to base any treatment on an untested mechanistic hypothesis.[11] ACE inhibitors and ARBs should not be used to treat covid-19 without convincing evidence of clinical efficacy from randomized clinical trials or data mining studies.[1]

Decisions about continuing treatment

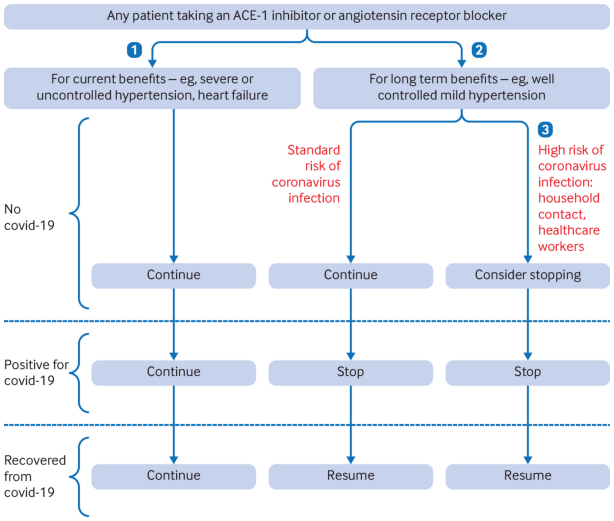
The balance of potential benefits and harms from continuing ACE inhibitor or ARB therapy during an acute infection depends

Correspondence to: jeffrey.aronson@phc.ox.ac.uk

on the reason for prescribing. Many people taking these drugs long term—for example, those with mild hypertension—will gain benefit over years, rather than weeks or months. During the covid-19 epidemic, the people most likely to be infected—household contacts of infected people and healthcare workers—might choose to adopt the precautionary principle, deferring long term cardiovascular benefit to reduce a theoretical short term risk from continuing treatment while they are infected.

Patients who may deteriorate rapidly if treatment with ACE inhibitors or ARBs is stopped, including those with heart failure or poorly controlled hypertension, should probably continue to take them, even during active infection.

Most patients, however, will be able to take their medications as usual during the pandemic, only considering withholding treatment if they get an infection. While we wait for better clinical evidence, these pragmatic recommendations, summarized in fig 1, are intended to help doctors advise patients with covid-19 on appropriate treatment.



Advice on continued use of ACE inhibitors and angiotensin receptor antagonists in people at risk of covid-19 or who develop it. The majority of patients will fall in column 2

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Competing interests: JKA is a member of the Centre for Evidence-Based Medicine in Oxford, which jointly runs the EvidenceLive Conference with the BMJ and the Overdiagnosis Conference with some international partners, which are based on a non-profit model. He is an associate editor of *BMJ Evidence Based Medicine* and was until recently vice-president publications for the British Pharmacological Society. REF was until recently a member of the Birmingham, Sandwell and Solihull Area prescribing committee, is a series editor of *The BMJ*'s Therapeutic Series, and has an honorary position in University College London.

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