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EDITORIAL

COVID-19 and Angiotensin-Converting Enzyme Inhibitor/Angiotensin-Receptor Blocker Therapy

Coronavirus disease 2019 (COVID-19)–related concerns about angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) seem to have developed approximately as follows:

- The epidemic broke out widely in January and February.
- Early reports showed that common comorbid conditions, including hypertension, were statistically linked to worse illness severity.
- Many hypertensive persons take ACEIs or ARBs.
- Previous studies of a related coronavirus, the causal agent of the 2003–2004 severe acute respiratory syndrome epidemic, had shown that the ACE-2 membrane receptor is key to the ability of the virus to infect cells.
- Both ACEIs and ARBs may upregulate the ACE-2 receptor.

A cogent line of reasoning (1) therefore led to the following question (2): Could these drugs be magnifying the risk for COVID-19 or contributing to its severity?

We now have abundant data from Italy, China, the United Kingdom, and the United States to suggest otherwise. These reports are summarized in a systematic review by Mackey and colleagues (3). The authors present data from 3 studies that found, with moderate certainty of evidence, no relationship of ACEI or ARB use with testing positive for the virus or becoming ill from it. On the basis of further data from 14 observational studies encompassing more than 23 000 adults with COVID-19, they found high-certainty evidence that the drugs are not associated with greater illness severity.

In addition, common sense tells us that common comorbid conditions, such as hypertension and cardiovascular disease, are likely to be common in any population assessment. And it is a clinical truism that people with any chronic condition are more ill than those without. In the hallway vernacular, "What's common is common" and "The sicker you are, the sicker you are." Initial fears that hypertension or its therapy uniquely contribute to COVID-19 illness seem now to have been unfounded.

As a result of this progression from fear and theory through data and multiple analyses from different continents, we now have reasonable reassurance that drugs that alter the renin–angiotensin system (RAS) do not pose substantial threats as either COVID-19 risk factors or severity multipliers. And although there were reasons that RAS-related drugs might have been harmful, there are other reasons that they could be helpful (4). Furthermore, withdrawing these drugs if they are prescribed for evidence-based indications could harm patients, especially those with heart failure (5).

At this time, professional societies and expert editorialists agree: Until further data show otherwise, these drugs should continue to be used for their standard indications (6). One might also add that there are currently insufficient outcomes data to show that they provide specific benefit during COVID-19 illness.

Mackey and colleagues' review is one of a new class of "living systematic reviews." The conclusions reached on the basis of research available as of the publication date can of course change at any time. The analysis in their article will accordingly be updated whenever new data become available. Readers are referred to a recent *Annals* editorial explaining how these updates may be easily accessed (7).

The COVID-19 pandemic has placed the nation and the world under more stress than usual. Stress magnifies things; it can make fears loom larger and spawn hopes that may eventually prove illusory. Such has been the brief saga of COVID-19 and the RAS to this point. In any case, it comes as a welcome relief that we have clarification on at least 1 aspect of this pandemic.

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