

Angiotensin drugs and COVID-19: More reassuring data

By Sue Hughes

Internal Medicine News, May 2020, p8.

Initial data from one Chinese center on the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in patients hospitalized with COVID-19 appear to give some further reassurance about continued use of these drugs.

The report from one hospital in Wuhan found that, among patients with hypertension hospitalized with the COVID-19 virus, there was no difference in disease severity or death rate in patients taking ACE inhibitors or ARBs and those not taking such medications.

The data were published online April 23 in JAMA Cardiology (2020 Apr 23. doi: 10.1001/jamacardio.2020.1624).

The study adds to another recent report in a larger number of COVID-19 patients from nine Chinese hospitals that suggested a beneficial effect of ACE inhibitors or ARBs on mortality (Circ Res. 2020 Apr 17. doi: 10.1161/CIRCRESAHA.120.317134).

Additional studies

Two other similar studies have also been recently released. Another study from China, published online March 31 in Emerging Microbes & Infections, included a small sample of 42 hospitalized patients with COVID-19 on anti-hypertensive therapy (2020 Mar 31. doi: 10.1080/2222.1751.2020.1746200). Those on ACE inhibitor/ ARB therapy had a lower rate of severe disease and a trend toward a lower level of IL6 in peripheral blood. In addition, patients on ACE inhibitor/ARB therapy had increased CD3+ and CD8+ T-cell counts in peripheral blood and decreased peak viral load compared with other anti-hypertensive drugs.

And a preliminary study from the United Kingdom, which has not yet been peer reviewed, found that treatment with ACE inhibitors was associated with a reduced risk of rapidly deteriorating

severe COVID-19 disease. The study, available online on MedRxiv, a preprint server for health sciences, reports on 205 acute inpatients with COVID-19 at King's College Hospital and Princess Royal University Hospital, London (2020 Apr 11. doi: 10.1101 /Z020.04.07.20056788).

Of these, 51.2% had hypertension, 30.2% had diabetes, and 14.6% had ischemic heart disease or heart failure. Of the 37 patients on ACE inhibitors, five (14%) died or required critical care support compared with 29% (48/168) of patients not taking an ACE inhibitor.

New Wuhan study

The authors of the new article published in JAMA Cardiology, led by Juyi Li, MD, reported on a case series of 1,178 patients hospitalized with COVID-19 at the Central Hospital of Wuhan, Hubei, China, between Jan. 15 and March 15, 2020.

Patients were a median age of 55 years, and 46% were men. They had an overall in-hospital mortality rate of 11%.

Of the 1,178 patients, 362 (30.7%) had a diagnosis of hypertension. These patients were older (median age, 66 years) and had a greater prevalence of chronic diseases. Patients with hypertension also had more severe manifestations of COVID-19 compared to those without hypertension, including higher rates of acute respiratory distress syndrome and in-hospital mortality (21.3% vs. 6.5%).

Of the 362 patients with hypertension, 31.8% were taking ACE inhibitors or ARBs.

Apart from a greater prevalence of coronary artery disease, patients taking ACE inhibitors or ARBs had similar comorbidities to those not taking these medications, and also similar laboratory profile results including blood counts, inflammatory markers, renal and liver function tests, and cardiac biomarkers, although those taking ACE inhibitors/ARBs had higher levels of alkaline phosphatase.

The most commonly used anti-hypertensive drugs were calcium blockers. The percentage of patients with hypertension taking any drug or drug combination did not differ between those with severe and nonsevere infections and between those who survived and those who died.

Specifically regarding ACE inhibitors/ARBs, there was no difference between those with severe

versus nonsevere illness in the use of ACE inhibitors (9.2% vs. 10.1%; $p = 0.80$), ARBs (24.9% vs. 21.2%; $P = 0.40$), or the composite of ACE inhibitors or ARBs (32.9% vs. 30.7%; $P = .65$).

Similarly, there were no differences in nonsurvivors and survivors in the use of ACE inhibitors (9.1% vs. 9.8%; $P = .85$), ARBs (19.5% vs. 23.9%; $P = .47$), or the composite of ACE inhibitors or ARBs (27.3% vs. 33.0%; $P = .34$).

The frequency of severe illness and death also did not differ between those treated with and without ACE inhibitors/ ARBs in patients with hypertension and other various chronic conditions including coronary heart disease, cerebrovascular disease, diabetes, neurological disease, and chronic renal disease.

The authors noted that these data confirm previous reports showing that patients with hypertension have more severe illness and higher mortality rates associated with COVID-19 than those without hypertension.

But they added: "Our data provide some reassurance that ACE inhibitors/ARBS are not associated with the progression or outcome of COVID-19 hospitalizations in patients with hypertension."

They also noted that these results support the recommendations from almost all major cardiovascular societies that patients do not discontinue ACE inhibitors or ARBs because of worries about COVID-19.

However, the authors did point out some limitations of their study, which included a small number of patients with hypertension taking ACE inhibitors or ARBs and the fact that a nonsevere disease course was still severe enough to require hospitalization. In addition, it was not clear whether ACE inhibitor/ ARB treatment at baseline was maintained throughout hospitalization for all patients.

This was also an observational comparison and may be biased by differences in patients taking versus not taking ACE inhibitors or ARBs at the time of hospitalization, although the measured baseline characteristics were similar in both groups.

But the authors also highlighted the finding that, in this cohort, patients with hypertension had three times the mortality rate of all other patients hospitalized with COVID-19.

"Hypertension combined with cardiovascular and cerebrovascular disease, diabetes, and chronic kidney disease would predispose patients to an increased risk of severity and mortality of COVID-19. Therefore, patients with these underlying conditions who develop COVID-19 require particularly intensive surveillance and care," they wrote.

Experts' cautious optimism

Some cardiovascular experts were cautiously optimistic about these results.

Michael A. Weber, MD, professor of medicine at the State University of New York, Brooklyn, and editor in chief of the journal of Clinical Hypertension, said: "This new report from Wuhan, China, gives modest reassurance that the use of ACE inhibitors or ARBs in hypertensive patients with COVID-19 disease does not increase the risk of clinical deterioration or death.

"Ongoing, more definitive studies should help resolve competing hypotheses regarding the effects of these agents: whether the increased ACE2 enzyme levels they produce can worsen outcomes by increasing access of the COVID virus to lung tissue; or whether there is a benefit linked to a protective effect of increased ACE2 on alveolar cell function," Dr. Weber noted.

"Though the number of patients included in this new report is small, it is startling that hypertensive patients were three times as likely as nonhypertensives to have a fatal outcome, presumably reflecting vulnerability due to the cardiovascular and metabolic comorbidities associated with hypertension," he added.

"In any case, for now, clinicians should continue treating hypertensive patients with whichever drugs, including ACE inhibitors and ARBs, best provide protection from adverse outcomes," Dr. Weber concluded.

John McMurray, MD, professor of medical cardiology, University of Glasgow, commented: "This study from Wuhan provides some reassurance about one of the two questions about ACEI/ARBS: Do these drugs increase susceptibility to infection? And if [the patient is] infected, do they increase the severity of infection? This study addresses the latter question and appears to suggest no increased severity."

However, Dr. McMurray pointed out that the study had many imitations. There were only small patient numbers and the data were unadjusted, "although it looks like the ACE inhibitor/ARB treated patients were higher risk to start with." It was an observational study, and patients were not randomized and were predominantly treated with ARBS, and not ACE inhibitors, so "we don't know if the concerns apply equally to these two classes of drug.

"Other data published and unpublished supporting this (even showing better outcomes in patients treated with an ACE inhibitor/ARB), and, to date, any concerns about these drugs remain unsubstantiated and the guidance from medical societies to continue treatment with these agents in patients prescribed them seems wise," Dr. McMurray added.

Franz H. Messerli, MD, professor of medicine at the University of Bern (Switzerland), commented: "The study from Wuhan is not a great study. They didn't even do a multivariable analysis. They could have done a bit more with the data, but it still gives some reassurance."

Dr. Messerli said it was "interesting" that 30% of the patients hospitalized with COVID-19 in the sample had hypertension. "That corresponds to the general population, so does not suggest that having hypertension increases susceptibility to infection but it does seem to increase the risk of a bad outcome."

Dr. Messerli noted that there are two more similar studies due to be published soon, both said to suggest either a beneficial or neutral effect of ACE inhibitors/ARBS on COVID-19 outcomes in hospitalized patients.

"This does help with confidence in prescribing these agents and reinforces the recommendations for patients to stay on these drugs," he said.

"However, none of these studies address the infectivity issue-whether their use upregulates the ACE2 receptor, which the virus uses to gain entry to cells, thereby increasing susceptibility to the infection," Dr. Messerli cautioned. "But the similar or better outcomes on these drugs are encouraging," he added.

The Wuhan study was supported by the Health and Family Planning Commission of Wuhan City. The authors have reported no relevant financial relationships.

A version of this article originally appeared on Medscape.com.

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