23 April 2020

BRIEF19

A daily review of covid-19 research and policy.

RESEARCH BRIEFING

Renin-Angiotensin System Inhibitors and COVID-19 Update. Previously on Brief19, we addressed how the SARS-CoV-2 virus enters the lungs and a debate as to whether medications known as renin-angiotensin system inhibitors (RAASi) worsen or improve clinical outcomes in patients with covid-19. Three new papers provide some insight. The two classes of RAASi assessed in these studies include ACE inhibitors (ACEi) and angiotensin II receptor blockers (ARBs). The first paper, published in *Circulation Research*, assesses mortality of patients with hypertension taking ACEi/ARBs and covid-19 across multiple institutions in China. In this study, 188 hospitalized patients were taking ACEi and ARBs for high blood pressure and compared to 940 not taking these medications. The authors found that 3.7 percent of hospitalized covid-19 patients taking ACEi/ARBs died versus 9.8% who were not. This apparent protective effect of ACEi/ARBs holds even after applying statistical methods that attempt to control for disease severity and other patient characteristics. However, this was a retrospective analysis, not a clinical trial. The statistical methods are useful but do not fully mitigate biases inherent in this type of research. The second paper, published in *JAMA*, describes presenting symptoms, patient characteristics, comorbidities, and early outcomes of 5,700 hospitalized persons with confirmed covid-19 in New York City. The outcomes of the study were related to severity of disease: invasive mechanical ventilation, kidney replacement therapy, and death. At the time of publication, 46 percent of patients (2,634) reached a clinical outcome; approximately 10 percent of patients remain hospitalized (553). Of the 2,634 patients, 14 percent required ICU level care and 21 percent died during the study. Mortality among patients on mechanical ventilation was astounding: 76% of patients aged 18 to 65 years old died and 97% over 65 years old passed away. What about those ACEi and ARBs? "Mortality rates for patients with hypertension not taking an ACEi or ARB, taking an ACEi, and taking an ARB were 26.7%, 32.7%, and 30.6%, respectively." In other words, patients taking these medications had *higher* mortality than those not taking these medications, contradicting the previous study discussed above. However, unlike the previous study, the authors of this retrospective study did not perform statistical adjustments for illness severity, comorbidities, and other characteristics. So many questions remain.
Finally, hot off the press today from *JAMA Cardiology*, another retrospective study from China assesses the association between ACEIs/ARBs and the severity of illness and mortality in 1,178 patients with hypertension hospitalized for covid-19. In this study, 11 percent of patients died. Of 362 patients with hypertension in this paper, 31.8 percent were taking ACEi/ARBs and 21.3 percent died. Neither severity of disease nor mortality was associated with using ACEi/ARBs.

Analysis: It now appears that we have enough knowledge and yet sufficient uncertainty that a clinical trial of prescribing ACEi/ARBs to patients with severe covid-19 is warranted, ethical, and likely safe (this is what clinical researchers call "equipoise"--a necessary condition for conducting a prospective randomized clinical trial). At the very minimum, these papers suggest that doctors need not, at least at this time, discontinue the use of these medications in patients already prescribed them. However, these data may be more "noise than signal." In a separate

paper in *Circulation Research*, experts describe the substantial limitations of studies, like the ones covered here, that are retrospective and observational.

–Joshua Niforatos, MD, Research Section Editor.

POLICY BRIEFING

UPDATE: Was the Bright light snuffed out? In an update to yesterday's news that the director of the federal government's Biomedical Advanced Research and Development Authority (BARDA) Rick Bright was pushed out of his job, the former official released a statement today stating that he believes he was removed from his post in response to his insistence that "science--not politics or cronyism-- [had] to lead the way" in combating the SARS-CoV-2. Bright, who is an expert in vaccine development, specifically called out his hesitation around the administration's push of hydroxychloroquine and chloroquine as a central reason for his ouster. Reportedly, Bright became aware of the change only when he was locked out of his agency email account and his name was removed from the official BARDA website. He has called for an investigation into the Department of Health and Human Services' politicization of the work for which the agency is responsible. This includes medical countermeasures to pandemics and other health threats. Alternate reports have stated that Bright's move was over a year in the making. *Axios, Politico.* *–Jordan Warchol, MD, MPH.*

Reopening drama continues. Last week, President Trump claimed that the decision to re-open our communities for business was a decision reserved for the federal government and his administration, not state governors. This came in contrast to the way shelter in place orders rolled out, which was state by state. A few days later, he backpedaled and acknowledged that the decision to re-open was in fact a state decision, and one that governors were empowered to make. Last week, more overt civil unrest over shelter in place orders began to materialize. First in Michigan, then in other states, citizens began to publicly demand that governments re-open communities for business. In response to these protests, President Trump issued a series of tweets advocating for governors to "Liberate Michigan" or "Liberate Minnesota." When Georgia Governor Brian Kemp announced earlier this week that Georgia would become one of the first states to re-open, many expected President Trump to be supportive. Afterall, Governor Kemp declared the decision came in response to Trump's Opening Up America Again plan, stating Georgia had met the Phase 1 criteria for reopening. However, yesterday in an apparent about-face, President Trump announced that he "totally disagrees" with Governor Kemp's decision, and that it may be wiser to wait until Phase 2 before re-opening.

–Kimi Chernoby, MD, JD, Policy Section Editor.

Jeremy Samuel Faust MD MS, Editor-in-Chief. *Kane Elfman PhD, Publishing and Design.*

http://www.brief19.com/ Twitter: *@brief_19* *submissions@brief19.com*

Brief19 is a daily executive summary of covid-19-related medical research, news, and public policy. It was founded and created by frontline emergency medicine physicians with expertise in medical research critique, health policy, and public policy.