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The controversy of using angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in COVID-19 patients

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In December 2019, a respiratory illness was reported in the city of Wuhan, China and this was reported to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel strain of coronavirus and later named as coronavirus disease 2019 (COVID-19). Human to human transmission of the virus was confirmed by the World Health Organization (WHO) on the 21st January 2020.[1] By this point, the virus had already spread beyond China's borders, and a pandemic was subsequently declared by WHO on 11th March 2020.[1] At the time of writing, there have been 66,623,914 confirmed cases in 191 countries with 1,530,296 global deaths.[2]

As the reach of the disease extended, it became apparent that certain factors such as age,[3] sex,[4] and ethnicity[5] may leave certain populations more vulnerable to the virus. As with previous coronavirus outbreaks, such as SARS in 2002 and Middle East Respiratory Syndrome (MERS) over 2012–2014, it has been established that patients with underlying cardiovascular disease (CVD) and hypertension are particularly susceptible to COVID-19. Early in the pandemic, a cohort study of 191 patients in the city of Wuhan found that 48% of hospitalized patients had a comorbidity; this was reported in 67% in those who died of the virus. Of these patients, 30% had hypertension and 8% had underlying CVD (48% and 13%, respectively, in those who died).[6] Furthermore, findings of a large-scale analysis by the Chinese Centre for Disease Control and Prevention revealed that the case fatality rate of individuals with comorbid CVD was 10.5%, and those with comorbid hypertension was 6.0%. The fatality rate amongst patients with CVD was considerably greater than those with other comorbidities, including those with previous diagnoses of chronic respiratory disease (6.3%) or cancer (5.6%) and much higher than the overall fatality rate (2.3%).[7] Throughout the pandemic, numerous studies from various countries have echoed these early findings—CVD and hypertension are common comorbidities in patients with COVID-19, importantly in those who develop severe disease.

In addition to the concerning evidence surrounding hypertension and COVID-19, the possibility of adverse outcomes resulting from drug-disease interactions is another pertinent issue. The use of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) in patients with COVID-19 has become a highly researched topic. National Institute for Health and Care Excellence (NICE) guidelines recommend using ACEi/ARBs in the first-line management of hypertensive patients age <55 and not of Black African or African-Caribbean origin.[8] Given the widespread use of ACEi and ARBs in managing hypertension and other CVD, concerns arose due to conflicting evidence surrounding the potential for antihypertensive medication to progress the disease. This is due to the mechanism of viral entry into cells. The interaction between viral spike (S) protein on SARS-CoV-2 and angiotensin-converting enzyme 2 (ACE2) is crucial in initiating the entrance of the virus into host cells.[9] It has been theorized that ACEi and ARBs upregulate the expression of ACE2—this has been shown in animal models.[10,11]

The meta-analysis by Yang et al.[12] was performed investigating the effects of ACEi and ARB in hypertensive patients with confirmed COVID-19 infection. They performed a literature search for relevant terms including "ACEi," "ARB," "COVID-19," and their variants. After

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careful review, they selected six studies involving 1808 patients between December 2019 and April 2020 that met their criteria, allowing for a quantitative comparison of signs and symptoms in ACEi/ARB and non-ACEi/ARB groups in confirmed cases of COVID-19 infection. Namely, they compared the incidence of fever, dry cough, diarrhoea, and the levels of a range of laboratory tests (e.g. D-dimer, CRP, creatinine, calcitonin, white cell count, urea, PT, neutrophils, lymphocytes, ALT, AST, and LDH). They found that in the ACEi/ARB group, D-dimer levels are lower, fever is less common, and creatinine is higher.

While we commend the authors on this work and their efforts to help us understand the correlation between ACEi/ARB and COVID-19 outcomes, there are several limitations within this study. The number of studies involved in the meta-analysis is limited including the selected time range which is now far from timing of their paper selections or search studies. It is clear that certain comparators were only found in a few of those studies, for example procalcitonin (PCT) in four studies. Although the authors tried to employ the I-squared test to look for heterogeneity arising due to inclusion of particular studies, and Egger's regression test for small-study effects. However, the data plots for these tests could be presented for each comparator, instead of exclusively those found to involve an element of bias, such as in the case of PCT.

It is unclear how each selected clinical manifestation were chosen. One can presume that those were the data available to the authors considering these studies were performed early on in the pandemic (December 2019 to April 2020). However, including a range of signs, symptoms and laboratory tests would have been desirable since we do not yet have a complete explanation for their incidence/level in COVID-19 infection, such as loss of sensation of taste and smell, myalgia, headache, blood pressure, ferritin level, cytokine level, and more. In particular, considering they discuss the ability of ACEi/ARB to reduce morbidity and mortality in hypertensive patients, and the increased risk of COVID-19 in hypertensive patients, it would have been appropriate to compare data on morbidity and mortality in the two groups. This could include ICU admission and intubation, length of hospital stays, use of non-invasive ventilation, and more. This would allow for further and stronger conclusions to be made on the benefits of ACEi/ARB in hypertensive COVID-19 patients.

It is not mentioned at what point during the COVID-19 infection the laboratory biomarkers were measured. The values of biomarkers can vary wildly from day-to-day changes during the period of infection. A subgroup analysis on the positive effect ACEi/ARBs have on D-dimer levels could have been done to give us more information on the precise stage of the infection where this effect occurs. There may be little use of a drug that lowers D-dimer levels at a stage when patients are already too unwell for such benefits to have a meaningful effect. Additionally, the authors could have carried out a subgroup analysis comparing the effect of ACEi versus ARB as a class, or indeed different ACEi/ARB medications on the incidence of signs and symptoms, since one drug may be found to have a specific effect that may be masked by the other drug(s) having a weaker or even the opposite effect.

Furthermore, the authors concede certain limitations of the studies involved, specifically mentioning their retrospective nature. A randomized controlled trial (RCT) would allow tracking of ACEi/ARB use, rather than relying on testimony months later that medications were taken regularly. It would permit direct comparison between one specific drug or a set number of specific drugs versus no drug treatment, rather than what is likely to be a range of different antihypertensives grouped together in a class. There would also be established endpoints and minimization of bias. Finally, only COVID-19 patients were included in these studies—there is no mention of people with COVID-19 who were not hospitalized being investigated. An RCT could reveal differences in D-dimer, fever, creatinine, and other results between the two groups in patients who are not unwell enough to be hospitalized, thus exploring the ability of antihypertensives to produce their alleged beneficial effects early on in the infection.

ACE2 receptors are expressed on lung epithelial cells, kidney, heart, and testes where it catalyzes the conversion of angiotensin (Ang) II to Ang-(1–7) and also Ang I to Ang 1–9.[13–15] ACEi have been speculated to upregulate and increase the expression of ACE2 receptors which many fear will promote COVID-19 infection.[14] However, neither ACEi or ARBs interact with ACE2 directly, nor have further studies presented evidence of increased expression due to either class of drug. With regards to COVID-19 patients with renal insufficiency, administration of ACEi/ARBs should be guided by the patient's clinical status, cardiovascular stability, and renal function.[13]

A study by Hippisley-Cox et al.,[16] showed that the use of ACEi/ARBs are associated with decreased risk of COVID-19 disease and no increased risk of ICU care in those that had COVID-19. There have also been studies to show that ACEi in fact reduced ACE2 in the lungs expression, while ARBs had no effect on ACE2 gene expression.[17] However, studies regarding ACEi/ARB treatment and the RAAS system have also shown mixed results.[18–21] There is no substantial evidence that upregulated ACE2 increases vulnerability to viral infections. Hence, there is still uncertainty about ACEi and COVID-19 interactions which shows how complex the RAAS system is. More research needs to be done to understand the roles of enzymes involved and other possible variables that may influence substrate levels.

At the moment, ACEi/ARBs are still recommended to be continued in COVID-19 patients according to NICE.[22]

The benefits of ACEi/ARBs on hypertension, heart failure and many more conditions are known and certain. Recently, the first RCT looking into the role of ACEi/ARBs in COVID-19 patients, the BRACE CORONA trial, is the most hotly discussed in the ESC Congress 2020.[23] This phase 4 trial selected COVID-19 patients currently on ACEi/ARBs and randomly assigned them to either continue ACEi/ARBs or discontinue temporarily for 30 days.[24] The primary outcome was the number of days survived and out of hospital at 30 days. This was 21.9 days and 22.9 days in those who continued and those who discontinued respectively. The average ratio between discontinuing and continuing was 0.95 (CI 0.90–1.01, $p = 0.09$). The proportion of those who survived in the discontinuing group versus continuing group is 91.8% and 95% respectively; mortality rates were 2.7% and 2.8%, respectively, with hazard ratio of 0.97.[23] It concluded that there is no clinical benefit from halting ACEi/ARBs in COVID-19 patients.

When SARS-CoV-2 binds to ACE2 receptors it forms a ACE2–SARS-CoV-2 complex and endocytosis occurs, downregulating ACE2.[25,26] In the context of respiratory pathology and CVD, ACE2 is considered protective.[27] ACE2 is able to decrease Ang II levels which are found to cause lung injury and increase disease severity.[28] There has been research about the administration of recombinant human ACE2 (rhACE2) where it was shown to decrease Ang II levels[29] and resulted in better outcomes for patients with acute lung injuries and acute respiratory distress syndrome presumably due to vasodilatory effects.[28] Thus, more trials are currently in action to investigate the lowering of Ang II levels using rhACE2 and ARBs as potential treatment choices for COVID-19 patients.[29–31] In the meantime, the usage of ACEi/ARBs still holds a vital role in controlling hypertension in COVID-19 patients and should not be halted.

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