Title

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Implications of ACE-I and ARBs on COVID-19 Prognosis in Hypertensive Patients

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Introduction

SARS-CoV-2 is a positive sense, enveloped single stranded RNA virus belonging to the betacoronavirus genus and causes COVID-19 (Di Wu et al., 2020). In December 2019, the novel virus first broke out in a seafood market in Wuhan, Hubei Province, China. It is spread through human-to-human transmission, such as respiratory droplets and contaminated surfaces. The virus can be spread during asymptomatic, presymptomatic, and symptomatic stages of infection, making it highly contagious (Wiersinga et al., 2020). The pathogenesis of SARS-CoV-2 continues to be mostly unknown (Yu Shi et al., 2020). SARS, or severe acute respiratory syndrome, is caused by viral infection that presents with flu-like symptoms (Sims et al., 2008). SARS-CoV and SARS-CoV-2 have over 90% amino acid similarity with small variances in the spike protein domain (Pillay et al., 2020).

The virus can utilize two separate fusion pathways: plasma membrane or endosomal fusion (Hoffman et al., 2020). The plasma membrane fusion pathway is triggered by cell membrane-bound proteases, such as TMPRSS2 and trypsin, that cleave at the S2' site of the spike protein and prime the virus to release RNA into the cell (Hoffman et al., 2020). The endosomal pathway begins with the envelope embedded surface-located spike (S) glycoprotein on SARS-CoV-2 binding to the ACE2, causing the structural rearrangement of S1 and S2 subunits (Shang et al., 2020). Under acidic conditions, cathepsin-L protease is activated and interacts with the spike protein, which enables fusion into the target membrane (Tang et al., 2020). The specific domain of the S protein that is required for the binding to ACE2 is still unclear (Raghuvamsi et al., 2020). The SARS-CoV-2 spike glycoprotein contains a fusion receptor binding domain (RBD) and a transmembrane domain (Pillay et al., 2020). The receptor binding domain is present on the C-terminus of the S1 subunit on the spike protein and binds to the peptidase domain of ACE2. After ACE2 binding, Subunit 2 presents a cleavage site which is cleaved by the host membrane proteases that precede membrane fusion (Pillay et al., 2020).

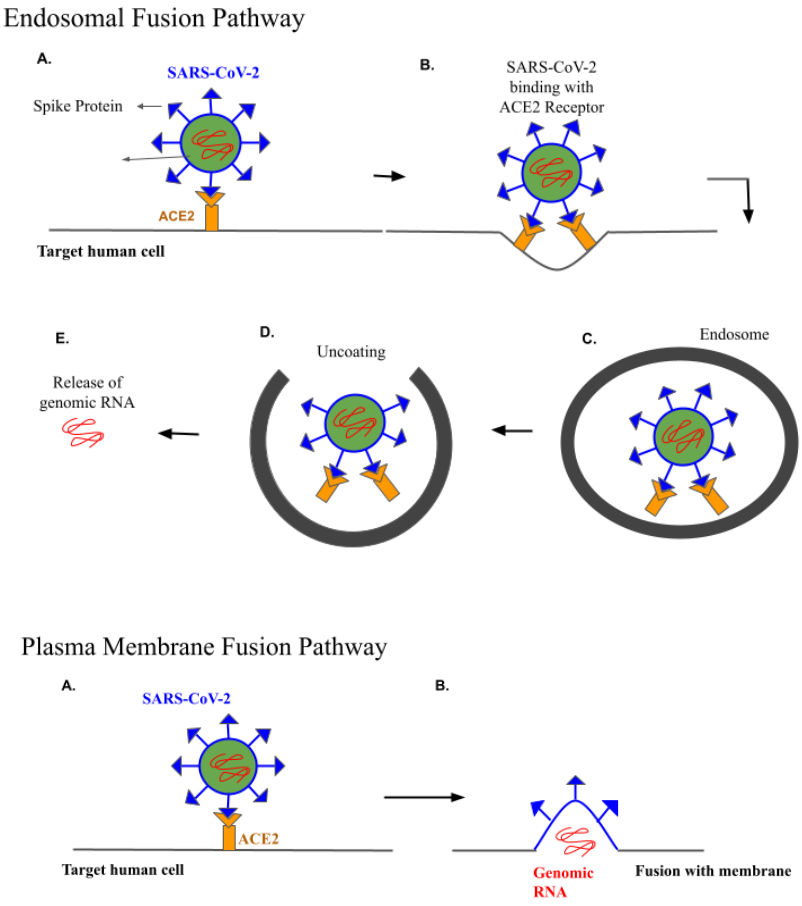

Figure 1: SARS-CoV-2 can utilize two entry

mechanisms to enter cells. Endosomal fusion pathway binds to ACE-2 receptors and enters the cell via pathway also binds to the ACE-2 receptors and then fuses its membrane with the host membrane and inserts it's genomic RNA.

SARS and MERS

Members of the *Coronaviridae* family commonly cause respiratory or enteric infections. In November 2002, the first case of SARS occurred, which caused an epidemic caused by SARS-CoV (de Wit et al., 2020). MERS-CoV first emerged in 2012 and was found to have originated from dromedary camels of Saudi Arabia (de Wit et al., 2020). In SARS-CoV, MERS-CoV, and SARS-CoV-2, they are all spread through respiratory droplets. SARS and MERS are illnesses that also see cardiovascular disease (CVD) as a comorbidity in the cycle of infection (Clerkin et al., 2020).

RAAS pathway and SARS CoV-2 effect on RAAS

The RAAS pathway (renin-angiotensin-aldosterone system) is important in maintaining blood pressure homeostasis within the body. This pathway is tightly regulated and ultimately strives to increase blood pressure when it's too low through vasoconstriction. The kidney can sense the renal perfusion rate as well as the sodium in blood. When blood pressure is low and sodium chloride levels are low, the sympathetic nervous system stimulates juxtaglomerular cells in the kidney to secrete renin into the blood (Fountain et al., 2021). Renin is created through the proteolytic activation of prorenin in the kidney and serves the purpose of cleaving the leucine valine bond of angiotensinogen secreted from the liver into angiotensin I (Patel et al., 2017). Angiotensin I by itself is biologically inactive but can be activated by Angiotensin Converting Enzyme (ACE), an endothelial bound carboxypeptidase to Angiotensin II. This occurs in the kidney epithelial cells and lung endothelial cells of the capillaries. Angiotensin II, when bound to Angiotensin II type 1 receptor (AT-1R), causes multiple effects in different organs. Blood vessels experience arteriolar vasoconstriction. The adrenal gland is stimulated to produce aldosterone, which can increase blood pressure through the increased retention of sodium and increased excretion of potassium by the kidney. In addition, binding of Angiotensin II to AT-1R can lead to inflammation, proliferation, and hypertrophy (Forrester et al., 2018). To counter this inflammation, Angiotensin II can also bind to Angiotensin II type 2 receptor (AT-2R). Angiotensin II can also be converted to Angiotensin 1,7, shorter peptide, with ACE2, which also happens to be the receptor in which the receptor binding domain of SARS CoV-2 binds to. When binded to Mas Receptor, Angiotensin 1-7 has antioxidant and anti-inflammatory effects much like Angiotensin II does when bound to AT-2R. ACE2 is a negative regulator of RAAS. When a person is infected with SARS CoV-2, their ACE2 receptors bound to the virus are endocytosed (Albini et al., 2020). This reduction in ACE2 leads to increased amounts of Angiotensin II in the blood and decreased amounts of Angiotensin 1,7 which can cause complications such as augmented vascular inflammation and adverse cardiac effects (Tikellis et al., 2012).

Function of ACE-I and ARBs in the body

RAAS inhibitors such as angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARBs) are often used as treatments for patients with hypertension, heart failure, diabetes, and chronic kidney disease. ACE-Is (such as lisinopril, ramipril, perindopril, and captopril) bind to the angiotensin-converting enzyme with high affinity and block the conversion of Angiotensin I into Angiotensin II (Bünning, 1987). When the production of Angiotensin II decreases, the adrenal cortex fails to release aldosterone which enables the kidney

to excrete sodium and water while retaining potassium. Through the decrease of blood volume and relaxation of blood vessels, blood flow increases and blood pressure is lowered. On the other hand, ARBs such as losartan, irbesartan, and candesartan are antagonists that selectively block the activation of the angiotensin II type 1 receptor (AT_1R) pathway (Patel, 2017). This prevents the binding of Angiotensin II to the receptor and protects against inflammation, vasoconstriction, cell proliferation, and vascular leaks. ARBs lower blood pressure due to vasodilation, reduced secretion of antidiuretic hormone (ADH), and reduced production of aldosterone. Unlike ACE inhibitors, ARBs do not inhibit the breakdown of bradykinin or other kinins (Rossi, 2020). However, both classes of RAAs inhibitors are expected to increase the expression of ACE-2, which leads to the concern of whether RAAS inhibitors affect the risk of infection or mortality of SARS-CoV-2.

SARS-CoV-2 interaction with ARBs and ACE-I

ACE2 is a membrane receptor that is found in the heart, kidney, small intestine, and lungs. The problem with using ARBs and ACEIs, is the consideration that it may cause an increase in ACE2 expression and inherently escalate the amount of viral load in the body. It has been shown in animal models that various types of ARBs, such as olmesartan, telmisartan, losartan, and azilsartan, have increased the levels of mRNA or ACE2 in heart diseases and chronic kidney disease in animal experiments, however it is still unclear whether this would result in increased susceptibility to SARS-CoV-2 (Kai, 2020). It is recommended that COVID-19 patients with cardiovascular comorbidities should be treated with ACEI and ARB medications. (Clerkin, 2020). Myocardial injury may occur due to the cytokine storm caused by increased levels of interleukin-6 (IL-6), ferritin, lactate dehydrogenase (LDH), and a D-dimer or due to direct ACE2 myocardial association with SARS-CoV- 2 (Clerkin, 2020).

KKS pathway and how it's affected by ACE-I

A lesser understood system called KKS (kinin-kallikrein system) is interconnected with the RAAS system through angiotensin-converting enzyme, ACE. The activation of KKS pathway results in activation of proenzymes leading to the upregulation of bioactive molecules or expression of genes involving molecular mechanisms of vasodilation, blood coagulation, and fibrinolysis (Bryant et al., 2009). Bradykinin (BK), a vasoactive, proinflammatory peptide in the KSS, binds to the Bradykinin B1 receptor which follows a downstream pathway ultimately resulting in vasodilation, contraction of non-vascular smooth muscles, increased vessel permeability, and edema (Krvavac et al., 2020). A function of ACE is to degrade bradykinin. The interaction between the KKS and RAAS pathways could explain some of the differences in clinical outcomes seen in research studying effects of ACE-I and ARB therapy. In the case of ACE-I treatment of patients, angiotensin converting enzyme is inhibited so its function of hydrolyzing bradykinin is impeded. This results in elevated BK levels in ACE-I treated patients leading to edema. Furthermore, the increase in BK levels increases contraction of non-vascular smooth muscles, leading to bronchoconstriction and dry cough. In addition to ACE-I playing a role in reducing blood pressure by inhibiting ACE from converting Angiotensin I to Angiotensin II in the RAAS pathway, it also regulates blood pressure in the KKS pathway as well. As mentioned before, ACE degrades BK so the inhibition of ACE by ACE-I will result in elevated BK levels which reduce blood pressure through vasodilation (Alkotaji et al., 2021).

Discussion:

Morbidity rates of people with hypertension, in ACE inhibitors and ARB users

One of the most prevalent comorbidities in COVID-19 affected patients is hypertension. ACE-2 is a negative regulator of the RAAS system that protects against hypertension, but endocytosis decreases the function of the enzyme with the binding of SARS-CoV-2 (Albini, 2020).

In many studies conducted on COVID-19 patients, a large number of individuals have underlying CVD, including hypertension. The association of hypertension with people infected has played a fatal role in the course of the SARS-CoV-2

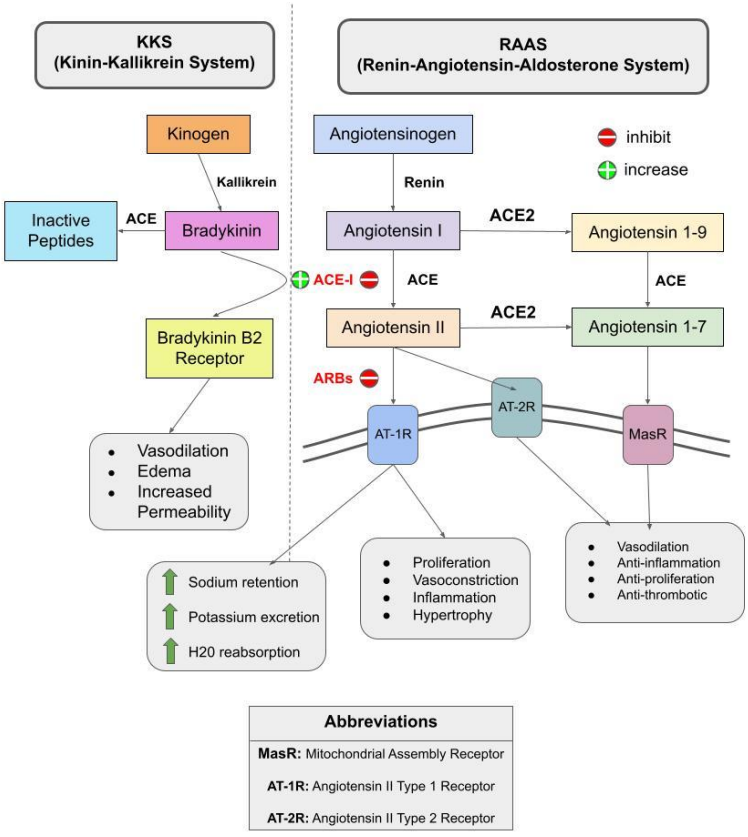

Figure. 2. Interactions between KKS and RAAS and their effects on blood pressure.

infection (Guo et al., 2020). One study from The Henry Ford Health System in metropolitan Detroit, Michigan, from March 2020 found that 94% of 463 patients had at least one comorbidity and 63.7% of all patients were inflicted with hypertension (Suleyman, 2020).

In a meta-analysis of 1527 patients, 8.0% of patients with COVID-19 suffered acute cardiac injury (Li, 2020). Cardiac injury has been seen in COVID-19 patients, making patients with preexisting conditions like CVD more vulnerable (Tajbakhsh, 2020). One cohort study conducted in Wuhan, saw 19.7% of 416 consecutive patients were noted to experience cardiac injury during hospitalization (Shi, 2020). Cardiac injury is usually measured in terms of specific biomarker levels found in the body. Acute myocardial injury can be caused by many ailments including acute coronary syndrome (ACS), myocarditis, heart failure, hypotension or shock, and sepsis (Tajbakhsh, 2020). In the event of acute myocardial injury, the COVID-19 patient could have an elevation of cardiac troponins, fulminant myocarditis, or shock. The relationship between COVID-19 and the cardiovascular system has not yet been determined but there has been inflammation, cytokine storms, and lung injury connected to the illness.

Comparison between primary drugs

There have been concerns during the COVID-19 pandemic regarding whether hypertensive patients should continue their use of RAAS interfering drugs, such as ARBs or ACE-I. Some previous *in vivo* studies, for example, have shown these drugs to increase ACE2 expression, which may increase risk of SARS-COV-2 infection (Albini et al., 2020). There are various antihypertensive drugs with different mechanisms of action including ACE-I, ARBs, and CCBs (Calcium Channel Blockers) (Semenzato et al., 2021). Given these differences in blood pressure medications, we

wanted to research differences between RAAS interfering drugs with other antihypertensive medications such as CCBs, that don't interfere with RAAS, on disease prognosis of SARS-COV-2 infected patients. Calcium Channel blockers work to lower blood pressure through inhibiting L-type calcium channels in vascular smooth muscle to reduce muscle contraction, resulting in vaso relaxation and arterial vasodilation (McInnes, 2008). A retrospective cohort study conducted on 2 million hypertensive patients in France seeked to examine differing COVID-19 risks in patients based on the type of antihypertensive medication they used. Results from this study showed that patients on RAAS interfering drugs, either ACE-I or ARBs, were associated with lower risk of hospitalization, intubation, and death compared to those on CCBs. This study showed a possible protective effect in using RAAS inhibiting drugs to lower blood pressure in hypertensive patients compared to using CCBs (Semenzato et al., 2021). Further studies seek to elucidate the differences in SARS-COV-2 disease prognosis between the two RAAS inhibition drugs, ARBs and ACE-I. Drawing back to the cohort study conducted on the French population, data also showed a slightly lower risk of hospitalization, intubation, and death in hypertensive patients treated with ACE Inhibitors compared to patients treated with Angiotensin Receptor Blockers. In another retrospective cohort study on hypertensive patients diagnosed with SARS-COV-2 infection, ARB treatment was shown to significantly lower the risk of hospitalization. ACE inhibitors also had similar effects but the decrease in risk was not deemed to be significant (Golpe et al., 2020). The general consensus of many studies shows the RAAS interfering drugs (ACE-I and ARBs) aren't associated with worse clinical outcomes in hypertensive patients infected with SARS-COV-2, but there is differing evidence as to whether one confers more benefits over the other.

Effect of Inpatient Omission of ACE inhibitors and ARB

The use of ACE inhibitors and ARBs have been the main topic of interest in COVID-patients because of the similar affinity to the human angiotensin-converting ACE2 receptor (Oddy et al., 2021). A retrospective cohort analysis, out of St. Helier Hospital in the UK, was conducted that looked at the effects of inpatient omission of ACE-Is and ARBs and found that with omission, it became very likely that a patient would have a worse course with the virus. When examining the differences between ACE-I/ARB users and nonusers, they draw the conclusion that long term users were more notably likely to have increased mortality rate, admittance to an ICU, needing an flow rate of oxygen, and CPR. When comparing mortality rates between users and non-users, they found a slightly higher chance of fatality in ACE-I/ ARB users. 55.6% of ACE inhibitor/ARB users had the chance of mortality, while the ACE inhibitor/ARB non-users had a 42.7% chance of mortality (Oddy et al., 2021). The most common comorbidity in these patients is hypertension and diabetes, among others. When adjusting the study for factors such as age, sex, and comorbidites, morbidity indicators were less meaningful but remained important. They concluded that the proportions of omitted ACE inhibitor/ARB doses was associated with the negative outcome during acute COVID-19 illness. Suggesting that when patients who use antihypertensive medications regularly, are admitted to the ICU for COVID-19 and that it would be more favorable to not omit these medications.

Controversy surrounding ACE-inhibitors and ARBs treatment

The use of ACE inhibitors and ARBs as treatment for COVID-19 patients with

hypertension has recently been a controversial topic for physicians and researchers. Some argue that ACE-I and ARBs would facilitate SARS-CoV-2 infection by increasing circulating ACE2 levels, which is involved in the entry of SARS-CoV-2 into cells and would lead to increased viral load or more serious lung injury (Soria Arcos, 2020). A retrospective study conducted by Selçuk et al. determined that the use of ACE inhibitors and ARBs were associated with an increased in-hospital mortality in patients diagnosed with COVID-19 and pneumonia. Of 113 hypertensive patients admitted to the Ümraniye Training and Research Hospital in Turkey, 24 patients who were using RAAS inhibitors as anti-hypertensive treatment had coronary artery disease compared to 4 people who did not use RAAS inhibitors (p=0.009). Laboratory tests indicated that ACEi and ARB patients had significantly higher neutrophil counts, which can be associated with infection and inflammation (Selçuk, 2020). In addition, the frequency of ICU admission, endotracheal intubation and death were significantly higher in patients who were treated with RAAS inhibitors.

In certain studies, ARBs were suggested as a better treatment option than ACE-Is for COVID-19 patients at higher risk for severe forms of disease. Due to accumulation of bradykinin, 11.4% of patients treated with ACE-Is for hypertension experience dry, irritating cough and angioedema as common side effects (Messerli, 2018). In comparison, patients who had taken ARBs experienced less adverse outcomes, thus leading to lower withdrawal rates. ARBs such as losartan function as an AT1R antagonist, which blocks the internalization, proteolytic degradation, and ubiquitination of ACE2 (Deshotels, 2014). In other words, ARBs stabilize the interaction between ACE2 and AT1R. Gurwitz suggests that ARBs could be a tentative therapy for COVID-19 patients before the development of acute respiratory failure, especially if the viral protein interaction with ACE2 is reduced in the presence of stabilized ACE2-AT1R complexes (Sanchis-Gomar, 2020). In a retrospective cohort study conducted by Krvavac et.al, the rate of invasive mechanical ventilation and 90-day mortality was higher in HCoV-NL63 patients who were on ACE-I therapy. Of 88 patients who were positive for HCoV-NL63, 28.1% of patients on ACE-Is received invasive mechanical ventilation compared to 7.1% in the non-ACE inhibitor group (p= 0.007). There was a 21.9% mortality rate in HCoV-NL63 patients of the ACE-I group, compared to 7.1% who did not receive ACE-I treatment (p=0.045). On the other hand, there were no statistically significant differences in mortality rates and ICU admission for HCoV-NL63 patients in the ARBs group and patients who did not receive ARBs treatment. No patients in the ARBs treatment group received invasive mechanical ventilation nor died within 90 days, which suggests that ACE-I therapy might be detrimental while ARB therapy could be beneficial (Krvavac, 2020).

Current clinical recommendations to continue ACE-I and ARBs treatment

Although studies using animal models have suggested that ACEI/ARBs would increase ACE2 expression, viral entry also requires transmembrane protease serine 2 (TMPRSS2) which is not affected by ACEI/ARB use (Hoffman, 2020).When the SARS-Co-V-2 spike protein binds to ACE2, ACE2 is downregulated and angiotensin II is overactivated which could lead to vasoconstriction and proinflammatory effects (Armstrong, 2020). Hence, higher levels of ACE2 could be helpful because it increases the conversion of angiotensin II into angiotensin 1–7 and reduces lung injury from angiotensin II.
Numerous studies have determined that ACE inhibitors and ARBs were both effective in lowering mortality rates and reducing the

severity of prognosis in COVID-19 patients with hypertension. Patients treated with RAAS inhibitors had a significantly higher median CD4+ cell count, 420.0 μL, compared to those who did not have RAAS inhibitor treatment, 311.5/μL (Pan, 2020). The mortality rate of patients in the RAAS inhibitor group was 9.8%, which was significantly lower than that 26.1% of patients who died in the non-RAAS inhibitor group (Pan, 2020). Hypertensive patients who used ACE inhibitors/ARBs had a better COVID-19 prognosis than patients who used other antihypertensive treatments, which supports the continuation of ACEi/ARB drug use. Although RAAS inhibitors did not directly inhibit viral replication, these drugs regulated immune function and inhibited the inflammatory response, taking on an indirect antiviral role. Withdrawing treatment of RAAS inhibitors may result in more complications in COVID-19 patients due to factors such as uncontrolled hypertension and renal function impairment. However, patients who are unable to drink sufficiently and have diarrhoea or vomiting or a persistently low blood pressure should stop using ACE inhibitors or ARBs medications to reduce the risk of acute kidney injury.

Confounding factors

In many COVID-19 patients, worse prognosis can be associated with comorbidities such as hypertension, but age could be a confounding factor as well. In a cohort study conducted by Armstrong et al., 46.2% of patients who used ACE-Is and ARBs to treat hypertension and other comorbidities were over the age of 65, compared to 1.3% of patients who were under the age of 30. The mean age of hypertensive patients with COVID-19 who did not use ACE-I/ARBs was 58 ± 10, which is significantly lower than the mean age of hypertensive patients who were treated with ACE-I/ARBs, which was 67 ± 11 (Selçuk, 2020). In analyses that were not adjusted for age and other confounding factors, the probability of COVID-19 diagnosis was significantly higher in ACE-I/ARB users (p=0.00). After adjustment for these demographic parameters, there was no association between ACE/ARB use and COVID-19 infection in patients between the ages of 65 to 74 (p=0.14). In patients of other age groups, the use of ACE-I/ARBs was associated with a significantly decreased risk of infection. However, no other classes of medications were associated with a reduced risk of COVID-19, including beta-blockers and calcium channel blockers (Armstrong, 2020). These results support the current clinical recommendations, which advise that ACE-Is or ARBs treatment should not be discontinued because of concern about COVID-19.

Alternative explanations for worse prognosis

Hypertension has been shown in studies to increase risks of adverse outcomes in people infected with SARS-COV-2 as well as is the most common comorbidity. 30% of COVID-19 patients that had a comorbidity in Jinyintan and Wuhan Pulmonary Hospitals had hypertension (Zhou et al., 2020). A retrospective multi-centre study determined that hypertensive patients had a significantly increased risk of either experiencing mechanical ventilation ($p<0.001$) or ICU admission ($p < .001$) as well as elevated chance of experiencing death ($p= 0.012$) (Xiong et al., 2020). Given the data in these studies, we seek to elucidate the observations made about the adverse effects of hypertension on COVID-19 positive patients. A study seeked to measure 57 different plasma inflammatory analytes in both COVID-19 positive and COVID-19 negative patients in the ICU. The six inflammatory analytes, tumor necrosis factor, interleukin-18, heat shock protein 70, elastase 2 , granzyme B, interferon-gamma-inducible protein 10, were significantly elevated in COVID-19 positive patients. In addition, heat shock protein 70 was associated with mortality

(Fraser et al., 2020). Increased plasma levels of heat shock protein 70 in hypertensive patients have been shown to be positively correlated with development of atherosclerosis. Arterial hypertension can lead to disruption of protein chaperone balance during protein synthesis and endoplasmic reticulum stress (ER stress). In hypertensive patients, excessive ER stress is not able to be resolved and leads to the unfolded protein response (UPR) due to increase in unfolded proteins. The UPR tries to resolve this by trying to increase pro-inflammatory protein chaperons like HSP70 while putting a pause on protein synthesis. This can activate pathways leading to inflammation such as activation of NLRP3 inflammasomes and NF-κB leading to increased production of inflammatory cytokines and possibly cytokine storms (Heck et al., 2020). This inability to resolve inflammation as well as dysregulation of the heat shock response in hypertensive patients could possibly explain the adverse outcomes seen in COVID-19 positive, hypertensive patients in previous studies.

Conclusion:

The overall recommendation remains that patients should stay on their prescribed medication and should not be apprehensive of their medication. Data suggests that ARBs users have better outcomes than their counterparts who are on other antihypertensives. That being said, however, there is much more research that needs to be done on the topic. With CVD being one of the highest comorbidities, it is essential to find a method to mitigate those effects.

Further experiments include creating a mouse model with humanized mice. Testing the interaction between different antihypertensive drugs to see which would interact the least with a SARS-CoV-2 infection could be a possible experiment. Further, characterizing the HSP70 effects within the body would be best to understand the causes of cytokine storms in patients with comorbidities.

References:

Albini, A., Di Guardo, G., Noonan, D. M., & Lombardo, M. (2020). The SARS-CoV-2 receptor, ACE-2, is expressed on many different cell types: implications for ACE-inhibitor- and angiotensin II receptor blocker-based cardiovascular therapies. *Internal and emergency medicine*, *15*(5), 759–766. https://doi.org/10.1007/s11739-020-02364-6

Alkotaji, M., Al-Zidan, R.N. (2021)Indomethacin: Can It Counteract Bradykinin Effects in COVID-19 Patients?. *Curr Pharmacol Rep* 7, 102–106 . https://doi.org/10.1007/s40495-021-00257-6

Armstrong, K., Soltoff, A., Rieu-Werden, M., Metlay. J., Haas, J. (2021). Use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers associated with lower risk of COVID-19 in household contacts. *PLOS ONE 16*(3): e0247548. https://doi.org/10.1371/journal.pone.0247548

Azevedo, R.B., Botelho, B.G., Hollanda, J.V.G.d. *et al.* (2021). Covid-19 and the cardiovascular system: a comprehensive review. *J Hum Hypertens 35*, 4–11. https://doi.org/10.1038/s41371-020-0387-4

Bates, Paul. COVID-19 Symposium: Entry of Coronavirus into Cells. (2020) Youtube video uploaded by PennMedicine https://www.youtube.com/watch?v=6DxlkxA82FM

Brojakowska, A., Narula, J., Shimony, R., & Bander, J. (2020). Clinical Implications of SARS-CoV-2 Interaction With Renin Angiotensin System: JACC Review Topic of the Week. *Journal of the American College of Cardiology*, *75*(24), 3085–3095. https://doi.org/10.1016/j.jacc.2020.04.028

Bryant, J. W., Shariat-Madar,Z. (2009). " Human Plasma Kallikrein-Kinin System: Physiological and Biochemical Parameters", *Cardiovascular & Hematological Agents in Medicinal Chemistry, 7*(3). https://doi.org/10.2174/1871525097891054 4

Bünning P. (1987). Kinetic properties of the angiotensin converting enzyme inhibitor ramiprilat. *Journal of cardiovascular pharmacology*, *10*, 31–35. https://doi.org/10.1097/00005344-198706107-00005

Clerkin, K. J., Fried, J. A., Raikhelkar, J., Sayer, G., Griffin, J. M., Masoumi, A., Jain, S. S., Burkhoff, D., Kumaraiah, D., Rabbani, L., Schwartz, A., & Uriel, N. (2020). COVID-19 and Cardiovascular Disease. *Circulation*, *141*(20), 1648–1655. https://doi-org.libproxy.berkeley.edu/10.1161/CIRCULATIONAHA.120.046941

Deshotels, M. R., Xia, H., Sriramula, S., Lazartigues, E., & Filipeanu, C. M. (2014). Angiotensin II Mediates Angiotensin Converting Enzyme Type 2 Internalization and Degradation Through an Angiotensin II Type I Receptor–Dependent Mechanism. *Hypertension*, *64*(6), 1368–1375. https://doi.org/10.1161/hypertensionaha.114.03743

de Wit, E., van Doremalen, N., Falzarano, D., & Munster, V. J. (2016). SARS and MERS: recent insights into emerging coronaviruses. *Nature reviews. Microbiology*, *14*(8), 523–534. https://doi-org.libproxy.berkeley.edu/10.1038/nrmicro.2016.81

Forrester, S. J., Booz, G. W., Sigmund, C. D., Coffman, T. M., Kawai, T., Rizzo, V., Scalia, R., & Eguchi, S. (2018). Angiotensin II Signal Transduction: An Update on Mechanisms of Physiology and Pathophysiology. *Physiological reviews*, *98*(3), 1627–1738. https://doi.org/10.1152/physrev.00038.201

Fountain, J. H., & Lappin, S. L. (2020). Physiology, Renin Angiotensin System. In *StatPearls*..

Fraser, D. D., Cepinskas, G., Slessarev, M., Martin, C., Daley, M., Miller, M. R., O'Gorman, D. B., Gill, S. E., Patterson, E. K., & dos Santos, C. C. (2020). Inflammation Profiling of Critically Ill Coronavirus Disease 2019 Patients. *Critical Care Explorations, 2*(6), e0144. https://doi.org/10.1097/cce.0000000000000144

Golpe, R., Pérez-de-Llano, L. A., Dacal, D., Guerrero-Sande, H., Pombo-Vide, B., & Ventura-Valcárcel, P. (2020). Risk of severe COVID-19 in hypertensive patients treated with renin-angiotensin-aldosterone system inhibitors. *Medicina Clínica (English Edition), 155*(11), 488–490. https://doi.org/10.1016/j.medcle.2020.06.028

Guo, T., Fan, Y., Chen, M., Wu, X., Zhang, L., He, T., Wang, H., Wan, J., Wang, X., & Lu, Z. (2020). Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiology, 5*(7), 811. https://doi.org/10.1001/jamacardio.2020.1017

Heck, T., Ludwig, M., Frizzo, M., Rasia-Filho, A., & Homem de Bittencourt, P. I. (2020). Suppressed anti-inflammatory heat shock response in high-risk COVID-19 patients: lessons from basic research (inclusive bats), light on conceivable therapies. *Clinical Science, 134*(15), 1991–2017. https://doi.org/10.1042/cs20200596

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T. S., Herrler, G., Wu, N. H., Nitsche, A., Müller, M. A., Drosten, C., & Pöhlmann, S. (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*, *181*(2), 271–280.e8. https://doi-org.libproxy.berkeley.edu/10.1016/j.cell.2020.02.052

Kai, H., & Kai, M. (2020). Interactions of coronaviruses with ACE2, angiotensin II, and RAS inhibitors-lessons from available evidence and insights into COVID-19. *Hypertension Research, 43*(7), 648–654. https://doi.org/10.1038/s41440-020-0455-8

Krvavac, A., Patel, T. P., Karle, E. M., Epstein, N. B., Reznikov, E. A., Gates, L. G., & Holliday, Z. M. (2020). Increased Incidence, Morbidity, and Mortality in Human Coronavirus NL63 Associated with ACE Inhibitor Therapy and Implication in SARS-CoV-2 (COVID-19). *Missouri Medicine, 117*(4), 346–354.

McInnes, G. T. (2008). Clinical Pharmacology and Therapeutics of Hypertension. Netherlands: *Elsevier.*

Messerli, F. H., Bangalore, S., Bavishi, C., & Rimoldi, S. F. (2018). Angiotensin-Converting Enzyme Inhibitors in Hypertension. *Journal of the American College of Cardiology, 71*(13), 1474–1482. https://doi.org/10.1016/j.jacc.2018.01.058

Oddy, C., Allington, J., McCaul, J., Keeling, P., Senn, D., Soni, N., Morrison, H., Mawella, R., Samuel, T., & Dixon, J. (2021). Inpatient Omission of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers Is Associated With Morbidity and Mortality in Coronavirus Disease 2019. *Clinical Therapeutics*. https://doi.org/10.1016/j.clinthera.2021.02.004

Pan, W., Zhang, J., Wang, M., et al. (2020). Clinical Features of COVID-19 in Patients With Essential Hypertension and the Impacts of Renin-angiotensin-aldosterone System Inhibitors on the Prognosis of COVID-19 Patients. *Hypertension, 76*:732–741. https://www.ahajournals.org/doi/full/10.1161/HYPERTENSIONAHA.120.15289.

Patel, S., Rauf, A., Khan, H., & Abu-Izneid, T. (2017). Renin-angiotensin-aldosterone (RAAS): The ubiquitous system for homeostasis and pathologies. *Biomedicine & pharmacotherapy*, *94*, 317–325. https://doi.org/10.1016/j.biopha.2017.07.091

Pillay, T. S. (2020). Gene of the month: the 2019-nCoV/SARS-CoV-2 novel coronavirus spike protein. *Journal of clinical pathology*, *73*(7), 366–369. https://doi-org.libproxy.berkeley.edu/10.1136/jclinpath-2020-206658

Raghuvamsi, P. V., Tulsian, N. K., Samsudin, F., Qian, X., Purushotorman, K., Yue, G., Kozma, M. M., Hwa, W. Y., Lescar, J., Bond, P. J., MacAry, P. A., & Anand, G. S. (2021). SARS-CoV-2 S protein:ACE2 interaction reveals novel allosteric targets. *eLife*, *10*, e63646. https://doi-org.libproxy.berkeley.edu/10.7554/eLife.63646

Rossi, G. P., Sanga, V., & Barton, M. (2020). Potential harmful effects of discontinuing ACE-inhibitors and ARBs in COVID-19 patients. *ELife*, *9*. https://doi.org/10.7554/elife.57278

Sanchis-Gomar, F., Lavie, C.J., Perez-Quilis, C., Henry, B.M., Lippi, G. (2020). Angiotensin-Converting Enzyme 2 and Antihypertensives (Angiotensin Receptor Blockers and Angiotensin-Converting Enzyme Inhibitors) in Coronavirus Disease 2019. *Mayo Clin Proc, 95*(6):1222-1230. doi:10.1016/j.mayocp.2020.03.026

Selçuk, M., Çınar, T., Keskin, M., Çiçek, V., Kılıç, A., Kenan, B., Doğan, S., Asal, S., Günay, N., Yıldırım, E., Keskin, M., & Orhan, A. L. (2020). Is the use of ACE inb/ARBs associated with higher in-hospital mortality in Covid-19 pneumonia patients? *Clinical and Experimental Hypertension*, *42*(8), 738–742. https://doi.org/10.1080/10641963.2020.1783549

Semenzato, L., Botton, J., Drouin, J., Baricault, B., Vabre, C., Cuenot, F., Penso, L., Herlemont, P., Sbidian, E., Weill, A., Dray-Spira, R., & Zureik, M. (2021). Antihypertensive Drugs and COVID-19 Risk. *Hypertension*, *77*(3), 833–842. https://doi.org/10.1161/hypertensionaha.120.16314

Shang, J., Wan, Y., Luo, C., Ye, G., Geng, Q., Auerbach, A., & Li, F. (2020). Cell entry mechanisms of SARS-CoV-2. *Proceedings of the National Academy of Sciences of the United States of America*, *117*(21), 11727–11734. https://doi-org.libproxy.berkeley.edu/10.1073/pnas.2003138117

Shi, Y., Wang, G., Cai, X. P., Deng, J. W., Zheng, L., Zhu, H. H., Zheng, M., Yang, B., & Chen, Z. (2020). An overview of COVID-19. *Journal of Zhejiang University. Science. B*, *21*(5), 343–360. https://doi-org.libproxy.berkeley.edu/10.1631/jzus.B2000083

Sims, A. C., Burkett, S. E., Yount, B., & Pickles, R. J. (2008). SARS-CoV replication and pathogenesis in an in vitro model of the human conducting airway epithelium. *Virus research*, *133*(1), 33–44. https://doi-org.libproxy.berkeley.edu/10.1016/j.virusres.2007.03.013

Soria Arcos, F., Romero Puche, A., & Vicente Vera, T. (2020). Controversy regarding ACE inhibitors / ARBs in COVID-19. *Revista Española de Cardiología (English Edition)*, *73*(6), 516. https://doi.org/10.1016/j.rec.2020.04.004

Suleyman, G., Fadel, R. A., Malette, K. M., Hammond, C., Abdulla, H., Entz, A., Demertzis, Z., Hanna, Z., Failla, A., Dagher, C., Chaudhry, Z., Vahia, A., Abreu Lanfranco, O., Ramesh, M., Zervos, M. J., Alangaden, G., Miller, J., & Brar, I. (2020). Clinical Characteristics and Morbidity Associated With Coronavirus Disease 2019 in a Series of Patients in Metropolitan Detroit. *JAMA Network Open, 3*(6), e2012270. https://doi.org/10.1001/jamanetworkopen.2020.12270

Tang, T., Bidon, M., Jaimes, J. A., Whittaker, G. R., & Daniel, S. (2020). Coronavirus membrane fusion mechanism offers a potential target for antiviral development. *Antiviral research*, *178*, 104792. https://doi-org.libproxy.berkeley.edu/10.1016/j.antiviral.2020.104792

Tikellis, C., & Thomas, M. C. (2012). Angiotensin-Converting Enzyme 2 (ACE2) Is a Key Modulator of the Renin Angiotensin System in Health and Disease.

International journal of peptides, *2012*, 256294. https://doi.org/10.1155/2012/256294

Wiersinga, W. J., Rhodes, A., Cheng, A. C., Peacock, S. J., & Prescott, H. C. (2020). Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA*, *324*(8), 782–793. https://doi-org.libproxy.berkeley.edu/10.1001/jama.2020.12839

Wu, D., Wu, T., Liu, Q., & Yang, Z. (2020). The SARS-CoV-2 outbreak: What we know. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases*, *94*, 44–48. https://doi-org.libproxy.berkeley.edu/10.1016/j.ijid.2020.03.004

Xiong, T. Y., Huang, F. Y., Liu, Q., Peng, Y., Xu, Y. N., Wei, J. F., Li, N., Bai, B., Li, J. H., Prendergast, B., Li, W. M., & Chen, M. (2020). Hypertension is a risk factor for adverse outcomes in patients with coronavirus disease 2019: a cohort study. *Annals of Medicine, 52*(7), 361–366. https://doi.org/10.1080/07853890.2020.1802059

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., Guan, L., Wei, Y., Li, H., Wu, X., Xu, J., Tu, S., Zhang, Y., Chen, H., & Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet, 395*(10229), 1054–1062. https://doi.org/10.1016/s0140-6736(20)30566-3