Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists and SARS-CoV-2 infection

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ABSTRACT

Angiotensin converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs) and mineralocorticoid receptor antagonists (MRAs) reduce morbidity, mortality and hospitalisations from hypertension, chronic kidney disease and heart failure. Patients and clinicians will be aware of the recently publicised interaction between the renin-angiotensin-aldosterone system (RAAS) and SARS-CoV-2, the orthocoronavirus responsible for coronavirus disease 2019 (COVID-19). Consequently, concern has abounded in regard to whether prescribed blockers of the RAAS like ACE-Is, ARBs and MRAs may, in fact, increase or decrease susceptibility to SARS-CoV-2 infection. Limited scientific evidence has been contradictory. Scientists have postulated both potentially harmful and potentially beneficial effects of these drugs on the natural history of COVID-19. Membrane-bound angiotensin-converting enzyme 2 (ACE2) participates in the entry of SARS-CoV-2 into human cells, and animal studies show that ACE-Is and ARBs upregulate ACE2 expression, which would theoretically increase risk for or severity of COVID-19. Conversely, RAAS blockers could benefit patients with COVID-19 through various mechanisms: ACE2 converts angiotensin II to angiotensin, which has potentially beneficial vasodilatory and anti-inflammatory properties. Observational studies have failed to provide compelling data on whether COVID-19 patients on RAAS blockers fare better or worse than otherwise similar patients, though there is emerging evidence that RAAS inhibitors may be protective in COVID-19 and are associated with lower cardiovascular and all-cause mortality. Most professional societies, including the World Health Organization and the South African Heart Association and the South African National Department of Health have recommended that patients on RAAS blockers with COVID-19 should continue taking them. In this article, we review the existing evidence for the interplay between RAAS blockers and SARS-CoV-2 infection. SAHeart 2020;17:352-361

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is the clinical manifestation of the pandemic infection caused by a positive-sense RNA virus named the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), initially described in Wuhan, China (Table 1 for abbreviations).[1] SARS-CoV-2 forms a clade within the subgenus sarbecovirus, subfamily Orthocoronavirinae. Different from both MERS-CoV and SARS-CoV, 2019-nCoV (or SARS-CoV-2) is the seventh member of the family of coronaviruses that infect humans.[2] Common symptoms of COVID-19 are fever, breathlessness, fatigue and dry cough. In addition, patients may report headaches, myalgia, nasal congestion, rhinorrhoea, anosmia, sore throat or diarrhoea. Symptoms are usually mild, many are infected but remain asymptomatic, and over 80% recover from COVID-19 without special treatment. Those at risk of severe illness and hospitalisation include those with multimorbidity, obesity, hypertension, cardiovascular disease (CVD), lung disease, cancer, diabetes and the elderly.[2,3]

SARS-CoV-2 infects host cells through the angiotensin-converting enzyme type 2 (ACE2) receptors, leading to COVID-19.[4] COVID-19 is transmitted through small droplets and may be airborne from the nose or mouth during speech, exhalation, singing, laughing and coughing. Incubation period

for COVID-19 ranges from 1 - 14 days, commonly around 5 days; asymptomatic individuals may still transmit the virus.[5]

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM AND ITS INHIBITORS

The renin-angiotensin-aldosterone system (RAAS) plays a central role in regulating blood volume and systemic vascular resistance (SVR), which together influence cardiac output/stroke volume and blood pressure (BP) – Figure 1. Renin, which is released primarily by the kidneys, stimulates the formation of angiotensin in blood and tissues, which in turn stimulates the release of aldosterone from the adrenal cortex.[6] Renin is a proteolytic enzyme that is released into the circulation by the kidneys, as a consequence of: (i) sympathetic nerve activation, through β_1-adrenoceptors; (ii) renal artery hypotension from systemic hypotension or renal artery stenosis; and (iii) decreased sodium delivery to the distal tubules of the kidney. When renin is released into the blood, it acts upon a circulating substrate, angiotensinogen, that undergoes proteolytic cleavage to form the decapeptide angiotensin-(1-7). Vascular endothelium, particularly in the lungs, has an enzyme, angiotensin converting enzyme (ACE) that cleaves off two amino acids to form the octapeptide, angiotensin II (AII), although many other tissues in the body (heart, brain, vascular) also can form AII[7] – Table 2 summarises the important role of the RAAS in human physiology. RAAS is not only regulated by the mechanisms that stimulate renin release, but is also modulated by natriuretic peptides released by the heart,[8] which act as an important counter-regulatory system (Figure 1). Therapeutic manipulation of the RAAS is important for management of hypertension, kidney disease, heart failure and diabetes, through use of RAAS blockers, which decrease arterial BP, ventricular afterload, blood volume and hence ventricular preload, as well as inhibit and reverse cardiac and vascular hypertrophy (Figure 2).[9]

TABLE I: Abbreviations.

ACE 2	Angiotensin converting enzyme type 2
ACE-Is	Angiotensin converting enzyme inhibitors
ARBs	Angiotensin receptor blockers
BP	Blood pressure
COVID-19	Coronavirus disease 2019
CVD	Cardiovascular disease
MRAs	Mineralocorticoid receptor antagonists
RAAS	Renin-angiotensin-aldosterone system
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SVR	Systemic vascular resistance

TABLE II: Roles of RAAS in human physiology.

Constricts resistance vessels via AII and ATI receptors, thereby increasing SVR and BP.
Stimulates sodium reabsorption at multiple renal tubular sites, thereby increasing sodium and water retention.
Acts on adrenal cortex to release aldosterone, which acts on kidneys to promote sodium and water retention.
Stimulates release of vasopressin (antidiuretic hormone – ADH) from the posterior pituitary, thereby increasing fluid retention by the kidneys.
Stimulates thirst centres in the brain, thereby increasing fluid intake.
Facilitates noradrenaline release from sympathetic nerve endings and inhibits noradrenaline reuptake, thereby enhancing sympathetic adrenergic function.
Stimulates cardiac hypertrophy.
Stimulates vascular hypertrophy.
Release of ADH increases cardiac output.
Enhances potassium excretion in the urine.

COVID-19 AND HYPERTENSION

Increased mortality and morbidity of COVID-19 in patients with hypertension has been observed in several initial epidemiological studies outlining the characteristics of the COVID-19 epidemic in China. In a study of 201 patients confirmed to have SARS-CoV-2 infection, hypertension was reported to have a hazard ratio (HR) of 1.70 for death and 1.82 for acute respiratory distress syndrome.[10] In a separate study of 191 patients with COVID-19, hypertension reportedly had a HR of 3.05 for in-hospital mortality.[11] However, neither of these studies[10,11] adjusted for confounding variables, and the validity of the association of poor outcomes with hypertension remains unclear. In the largest case series from China, hypertension was the most frequent coexisting condition in 1 099 patients, with an estimated prevalence of 15%,[12] though this estimate is lower than the estimated prevalence of hypertension seen with other viral infections,[13] and in the general population in China,[14] or other parts of the world.[15]

Coexisting conditions, including hypertension, have consistently been reported to be more common among patients with COVID-19 who have had severe illness, been admitted to the intensive care unit, received mechanical ventilation, or died, compared to patients who have had mild illness. Concerns have been raised that medical management of coexisting conditions, including the use of RAAS blockers, may have contributed to the adverse health outcomes observed; however, these conditions track closely with advancing age, which is emerging as the strongest predictor of COVID-19 related

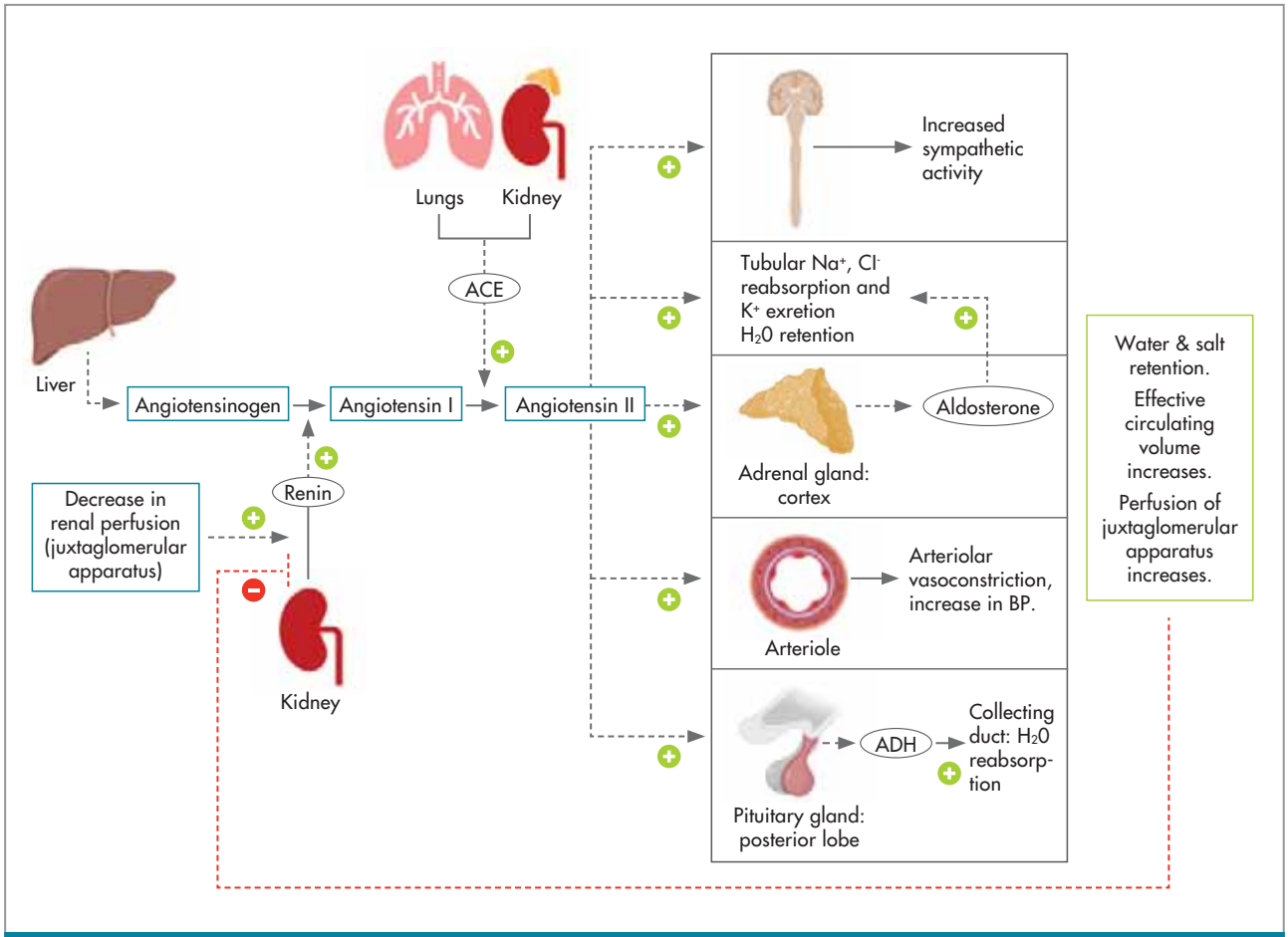

FIGURE 1: Renin-angiotensin-aldosterone system.

ACE = angiotensin converting enzyme, ADH = antidiuretic hormone.

death.[16] To date, most of the published reports have not rigorously accounted for age or other risk factors as potential confounders for risk prediction. Data showing patterns of use of RAAS blockers and associated health outcomes that rigorously account for treatment indication and illness severity among patients with COVID-19, are urgently needed.

The association between hypertension and COVID-19 morbidity and mortality has been linked to the ACE2 upregulation and RAAS blocker use, severe hypokalaemia associated with COVID-19 infection in one study,[17] and immune dysregulation in the setting of poorly controlled hypertension.[18] The understanding of these mechanisms and their effect on hypertension as a predictor of morbidity and mortality is still to be determined.

BIOLOGY OF ACE2

Given its centrality to viral entry (Figure 3) and mechanism of action of RAAS blockers, the biology of ACE2 warrants consideration. The putative link between angiotensin converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs) and mineralocorticoid receptor antagonists (MRAs) and SARS-CoV-2, is predicated on the understanding that ACE2 is the co-receptor for viral entry for SARS-CoV-2, and has a critical role in the pathogenesis of COVID-19. ACE2 has a broad expression pattern in the human body with strong expression noted in the heart, kidneys, lungs, and gastrointestinal system. These common areas of expression of ACE2 are extrapolated from ACE2 activity levels in mice, with the highest level of expression in the gastrointestinal tract and kidneys, followed by the heart and lungs. Recent studies in human models show discordance between mice models on the protein expression, activity and mRNA levels of ACE2 in various parts of the human body, proving that the delicate physiological balance of the components of RAAS is not yet fully understood.[12,13] Fears about RAAS blockers and poor outcomes in COVID-19 are due to a suggestion that ACE-Is directly inhibits ACE2; however, ACE2 functions as a carboxypeptidase and is not inhibited by clinically prescribed

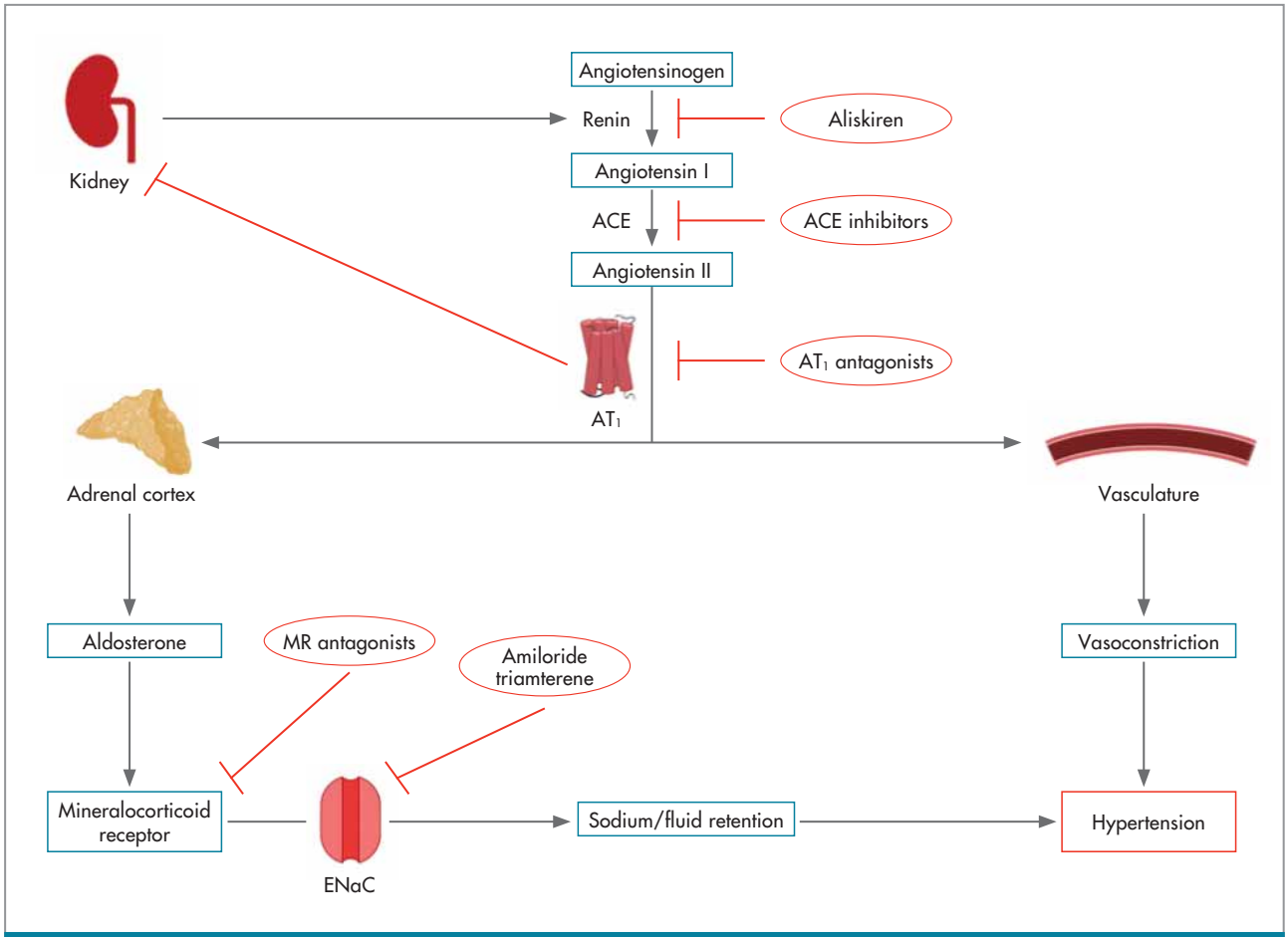

FIGURE 2: Mechanisms of action of RAAS blockers.

ACE = angiotensin converting enzyme, AT1 = Angiotensin I, ENac = Epithelial sodium channel.

ACE-Is;[5] there is also a concern that the use of RAAS blockers increases expression of ACE2 and may increase patient susceptibility to viral host cell entry and propagation; however, there is limited evidence showing changes in serum or pulmonary ACE2 levels. Importantly, the significance of ACE2 expression on COVID-19 pathogenesis and mortality is unknown.[19,20]

ACE2 primarily acts to counterbalance the effect of ACE. As ACE generates AII from angiotensin I, ACE2 generates angiotensin-(1-7) from AII, which shifts the balance from vasoconstriction with AII to vasodilation with Mas receptor activation in the effected vascular bed. The role this vasodilatory effect has in the pathogenesis of COVID-19 is unclear, but some animal data suggests a link.[21]

INTERACTIONS OF RAAS BLOCKERS AND ACE2

AII activates type I angiotensin receptors (AT1) and type II angiotensin receptors (AT2) resulting in a series of events that either promote inflammation, vasoconstriction or atherogenesis through AT1 receptor pathway or the opposite: vasodilation, decreased platelet aggregation and promotion of insulin action through the AT2 pathway.[22,23] AII is converted into angiotensin-(1-7) indirectly by ACE2, producing similar effects to the AT2 pathway due to normal expression of AT2 in adults being low. Conceptualising the intricate balance of the Ang II/AT1receptor and its opposing pathway ACE2/Ang-(1-7) and its effects (Figure 4) helps with understanding the consequences of imbalance and how the use of RAAS blockers may play a role in this intricate system.[24] Angiotensin converting enzyme inhibitors (ACE-Is) have a partial effect by decreasing the conversion of angiotensin I (Ang-1) to angiotensin II (Ang-2) and ACE levels are decreased through negative feedback in the presence of high AII levels. Angiotensin receptor blockers (ARBs) increase AII levels available for redirection through the anti-inflammatory AT2 pathway.[24] Circulating levels of soluble ACE2 are low and the functional role of ACE2 in the lungs and heart appears to be minimal under normal conditions,[25,26] but

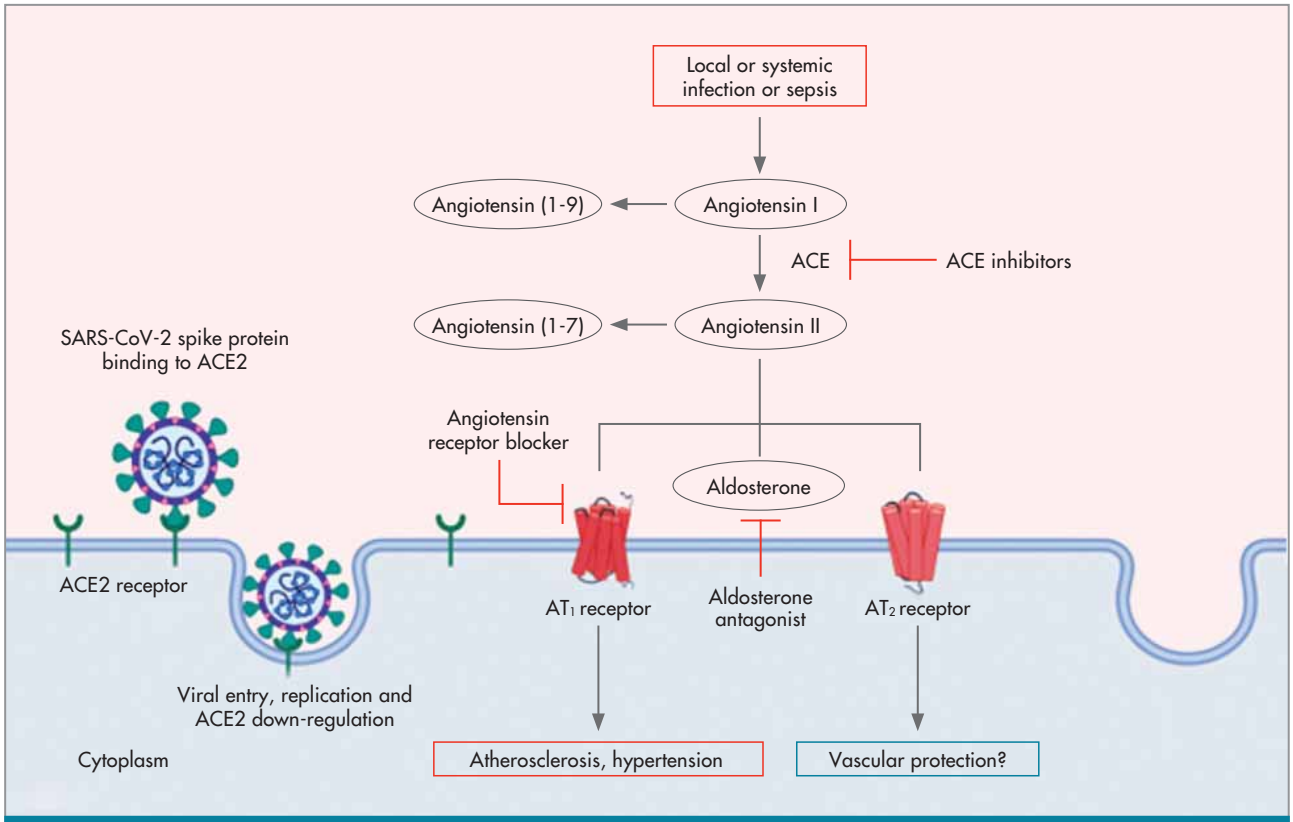

FIGURE 3: Interaction of SARS-CoV-2 and RAAS blockers.

ACE = angiotensin converting enzyme, ACE2 = angiotensin converting enzyme 2, AT_1R = type 1 angiotensin II receptor, AT_2R = type 2 angiotensin II receptor.

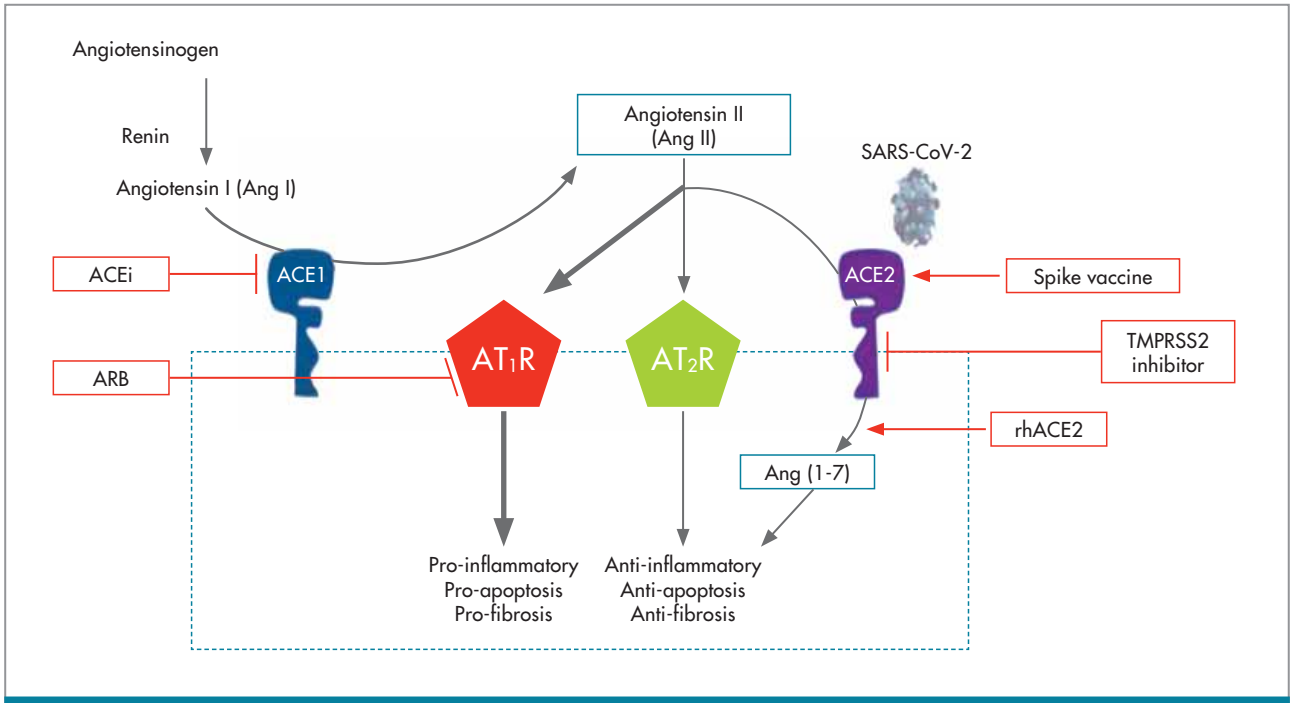

FIGURE 4: Counter-regulatory effects of angiotensin II receptor type 1 and angiotensin II receptor type II pathways.

Renin-angiotensin-aldosterone system in patients with COVID-19.
ACEi = angiotensin converting enzyme inhibitor, ACE1 = angiotensin converting enzyme, ACE2 = angiotensin converting enzyme 2, ARB = angiotensin receptor blocker, AT_1R = type 1 angiotensin II receptor, AT_2R = type 2 angiotensin II receptor, rhACE2 = recombinant human angiotensin converting enzyme 2.

may be up-regulated in certain clinical states. Because different RAAS blockers have variable effects on AII, the primary substrate of ACE2, the effects of these agents on ACE2 levels and activity may be anticipated to differ. Despite substantial structural homology between ACE and ACE2, their enzyme active sites are distinct; therefore ACE-Is in clinical use do not directly affect ACE2 activity.[27] Animal models have shown conflicting evidence of the impact of ACE-Is and ARBs on ACE2 levels.[13,28-30] In human studies, RAAS blockers did not influence angiotensin production (1-7), a finding that calls into question whether ACE-Is have any direct effects on ACE2-directed AII metabolism.[31,32] Furthermore, in studies of heart failure,[28] atrial fibrillation,[33] aortic stenosis[34] and coronary artery disease,[35] plasma ACE2 activity was not higher among patients who were taking ACE-Is or ARBs compared to untreated patients. However, in one study of patients with hypertension, urinary ACE2 levels were higher in patients who received long-term treatment with the ARB, olmesartan, than in untreated control patients, but that association was not observed with the ACE-I, enalapril, or with other ARBs (losartan, candesartan, valsartan, and telmisartan).[36]

The conflicting data above reinforces the concept that findings from preclinical models may not readily translate to human physiology. Therefore, effects on ACE2 should not be assumed to be uniform across RAAS inhibitors or even in response to therapies within a given drug class.[36] Importantly, plasma ACE2 levels may not be a reliable indicator of the activity of the full-length membrane-bound form, in part because ACE2 is shed from the membrane, a process that appears to be separately regulated by an endogenous inhibitor, and biologic relevance of ACE2 may vary according to tissue and clinical state.[37] There is an urgent and critical need for further human mechanistic studies to better define the unique interplay between SARS-CoV-2 and the RAAS network. The use of short and long-term use of RAAS blockers should be investigated as the effects on ACE2 levels appear to be variable, with low to normal levels with short-term use and mildly elevated levels with longer term use.[12]

EVIDENCE FOR BENEFIT OF RAAS BLOCKERS IN COVID-19

In an animal model, ACE2 downregulation by SARS-CoV worsened lung injury that was improved by treatment with an ARB.[38] However, there is no direct clinical evidence that has proven ACE2 to be an effective treatment for viral-induced lung injury. A preliminary trial of ACE2 infusion in 10 patients with acute respiratory distress syndrome (ARDS) was completed in humans, but was not powered to show efficacy on pulmonary function.[39] Downregulation of ACE2 activity in the lungs facilitates the initial neutrophil infiltration in response to bacterial endotoxin,[40] and may result in unopposed AII accumulation and local RAAS activation. Indeed, in experimental mouse models, exposure to SARS-CoV-1 spike protein induced acute lung injury, which is limited by RAAS blockade.[40] COVID-19 patients had elevated levels of plasma AII, which were in turn correlated with total viral load and degree of lung injury,[41] and restoration of ACE2 through the administration of recombinant ACE2 reversed this devastating lung-injury process in preclinical models of other viral infections,[42,43] and safely reduced AII levels in a phase 2 trial evaluating ARDS in humans.[39]

Recently, inpatient use of ACE-Is and ARBs in patients with COVID-19 was associated with lower mortality in hospitalised patients with known CVD, with an adjusted HR of 0.42.[44] In a study of 1 139 COVID-19 patients receiving ACE-Is and ARBs, there was no signal for harm from the use of RAAS inhibitors.[45] Of 19 486 patients with COVID-19, 1 286 were admitted to the intensive care unit. ACE-Is and ARBs were associated with reduced risk of COVID-19, but had no impact on admission to intensive care after adjusting for a wide range of confounders.[16] Finally, with a retrospective cohort of 4 480 patients with COVID-19, with 20% of these receiving either an ACE-I or an ARB, RAAS blocker use was not associated with increased risk of contracting COVID-19, COVID-19 disease severity, or COVID-19 mortality.[46]

POTENTIAL HARM FROM USE OF RAAS BLOCKERS IN COVID-19

Abnormal regulation of ACE2 may theoretically attenuate cardioprotection in the context of myocardial involvement and abnormal pulmonary haemodynamics in COVID-19.[47,48] Markers of myocardial injury are demonstrably elevated during the course of COVID-19,[49] and increase rapidly with clinical deterioration and preceding death.[11] As many viruses are cardiotropic, subclinical viral myocarditis is commonly seen in viraemia associated with a wide range of infectious agents. ACE2 plays an important role in myocardial recovery and injury response. For instance, ACE2 knockout animal models resulted in adverse left ventricular remodelling in response to acute injury driven by A II.[50] Autopsies of patients who died from SARS showed that 35% of heart samples had presence of viral RNA and reduced ACE2 protein expression.[51] Furthermore, administration of recombinant ACE2 normalises AII levels in human explanted hearts in dilated cardiomyopathy.[52]

Additionally, despite these theoretical uncertainties regarding whether pharmacologic regulation of ACE2 may influence the infectivity of SARS-CoV-2, there is clear potential for harm related to the withdrawal of RAAS blockers in patients with heart failure and chronic kidney disease, in an otherwise stable condition. COVID-19 is particularly severe in patients with underlying CVD,[1] and in many patients, active myocardial injury,[11,53-55] myocardial stress,[54] and cardiomyopathy[54] develop during the course of illness. RAAS inhibitors have established benefits in protecting the kidney and myocardium, and their withdrawal may risk clinical decompensation in high-risk patients.

GUIDANCE FOR CLINICIANS ON USE OF RAAS INHIBITORS IN PATIENTS WITH COVID-19

Despite the lack of evidence, there have been advocates for both the use and cessation of ACE-Is, ARBs, and/or MRAs during the treatment of COVID-19 in patients with hypertension, heart failure and coronary artery disease, prompting some patients to solicit changes in their CVD medications and growing the uncertainty from physicians on what should be done. Changes in CVD medications require patients to visit their physician/cardiologist, pharmacy and possibly obtain blood work, which would increase their exposure and risk of infection from SARS-CoV-2 during the pandemic. Antihypertensive medication changes between classes additionally requires frequent dose adjustment and management of adverse effects and increases the risk of medical errors. Consequently, the World Health Organization,[56] the European Medicines Agency,[57] and the South African National Department of Health[58] statements on RAAS blocker used in COVID-19, all advise against stopping ACE-Is or ARBs unless there is a compelling reason, other than COVID-19, to do so.

The Council on Hypertension of the European Society of Cardiology made the following statement: "The Council on Hypertension strongly recommends that physicians and patients should continue treatment with their usual anti-hypertensive therapy because there is no clinical or scientific evidence to suggest that treatment with ACE-Is or ARBs should be discontinued because of the COVID-19 infection."[59] This statement has been followed by similar statements from a number of different societies suggesting patients continue their current hypertensive medication regimen. The American Heart Association, the Heart Failure Society of America, and the American College of Cardiology announced a joint statement advocating for patients to continue ACE-Is and ARBs as prescribed and that changes in medications in the setting of COVID-19 should be completed only after careful assessment.[60]

TABLE III: Key take-home messages.

Hypertension and other CVD are over-represented among people who develop the most severe complications of COVID-19.
SARS-CoV-2 enters cells by utilising ACE2 and type II transmembrane serine proteases (TMPRSS2).
ACE2 is most expressed in the cardiovascular system, gastrointestinal tract, kidneys and lungs; in the cardiovascular system, ACE2 is expressed in the cardiomyocytes, epicardial adipose tissue, cardiac fibroblasts, vascular smooth muscle and endothelial cells.
ACE2 is an enzyme that physiologically counters RAAS activation.
Select preclinical studies have suggested that RAAS blockers may increase ACE2 expression, raising concerns regarding their safety in patients with COVID-19. Insufficient data are available to determine whether these observations readily translate to humans. Existing data suggests a lack of harm. Clinical trials are under way to test the safety and efficacy of RAAS modulators, including recombinant human ACE2 and the ARB losartan in COVID-19.
Abrupt withdrawal of RAAS inhibitors in high-risk patients, including those who have heart failure or have had myocardial infarction, may result in clinical instability and adverse health outcomes.
Until further data are available, we recommend that RAAS inhibitors should be continued in patients in otherwise stable condition, who are at risk for, being evaluated for, or known with COVID-19.

On the basis of available evidence, we think that, despite the theoretical concerns regarding the effect of RAAS inhibitors on ACE2 and the way in which these drugs may affect the propensity for severe COVID-19 disease, RAAS blockers should be continued in patients in otherwise stable condition who are at risk for, are being evaluated for, or have confirmed COVID-19. Furthermore, there is now compelling evidence of lack of harm and some evidence for benefit of use of RAAS blockers in COVID-19 (Table 3).

CONCLUSIONS

ACE-Is, ARBs and MRAs reduce morbidity, mortality and hospitalisations from hypertension, chronic kidney disease, heart failure and coronary artery disease. In recent months, there has been increased concern about the use of RAAS blockers in patients with COVID-19. Existing limited animal and human evidence has been contradictory, but overall, largely showing lack of harm and some evidence of protection from RAAS blockers in hospitalised COVID-19 patients. Membrane-bound angiotensin-converting enzyme 2 (ACE2) participates in the entry of SARS-CoV-2 into human cells, and animal studies show that ACE-Is and ARBs upregulate ACE2 expression, which would theoretically increase risk for or severity of COVID-19. Conversely, RAAS blockers could benefit patients with COVID-19 through various mechanisms: ACE2 con-

verts All to angiotensin-(1-7), which has potentially beneficial vasodilatory and anti-inflammatory properties. Observational studies have failed to provide compelling data on whether COVID-19 patients on RAAS blockers fare worse than otherwise similar patients.

The lack of definitive evidence on the use of RAAS blockers in COVID-19 provides an opportunity for the research community to better outline the RAAS and specifically the role of ACE2 in the pathogenesis of COVID-19, while clinical data are accumulated to determine if there is a link between the use of RAAS blockers and COVID-19 mortality and morbidity. Until more substantial data is available to guide decision-making, physicians should be available to listen to patients' concerns and provide reassuring advice about RAAS blocker medications in the era of the COVID-19 pandemic. Most professional societies have recommended that patients on RAAS blockers with COVID-19 should continue taking these drugs for their benefits in treating the underlying disease.

ACKNOWLEDGEMENTS

The figures have been created using Biorender® software.

FUNDING

This article is not funded. Ntobeko Ntusi gratefully acknowledges funding from the National Research Foundation, Medical Research Council of South Africa and the Lily and Ernst Hausmann Trust.

Conflict of interest: none declared.

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