REVIEW ARTICLE

Renin Angiotensin Aldosterone System Antagonism in 2019 Novel Coronavirus Acute Lung Injury

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It has been established that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) uses angiotensin-converting enzyme 2 (ACE2), a membrane-bound regulatory peptide, for host cell entry. Renin-angiotensin-aldosterone system (RAAS) inhibitors have been reported to increase ACE2 in type 2 pneumocyte pulmonary tissue. Controversy exists for the continuation of ACE inhibitors, angiotensin II receptor blockers, and mineralocorticoid receptor antagonists in the current pandemic. ACE2 serves as a regulatory enzyme in maintaining homeostasis between proinflammatory angiotensin II and anti-inflammatory angiotensin 1,7 peptides. Derangements in these peptides are associated with cardiovascular disease and are implicated in the progression of acute respiratory distress syndrome. Augmentation of the ACE2/Ang 1,7 axis represents a critical target in the supportive management of coronavirus disease 2019–associated lung disease. Observational data describing the use of RAAS inhibitors in the setting of SARS-CoV-2 have not borne signals of harm to date. However, equipoise persists, requiring an analysis of novel agents including recombinant human-ACE2 and existing RAAS inhibitors while balancing ongoing controversies associated with increased coronavirus infectivity and virulence.

Keywords. ALI; ARDS; ACE2; ACE inhibitor; angiotensin receptor blocker: COVID-19; SARS-CoV-2.

The therapeutic use of renin-angiotensin-aldosterone inhibitors remains a contentious question during the coronavirus disease 2019 (COVID-19) pandemic. In mid-March, major societies including the American Heart Association, American College of Cardiology, Heart Failure Society of America, European Society of Cardiology, and International Society of Hypertension had unanimously recommended continuation of therapy for existing indications. However, these organizations acknowledged the scant evidence supporting either approach in the setting of COVID-19. Since the publication of these consensus statements, important observational data have been published advancing the position on renin-angiotensin-aldosterone system (RAAS) inhibitors as they relate to cardiovascular care in infected patients [1]. Epidemiologic data suggest that hypertension, among other cardiometabolic disorders, is not only pervasive in up to 30% of patients but portends more severe illness

and is associated with a 3-fold increase in mortality [2–5]. Controversial associations with RAAS inhibitors and increased infection have upended consistency in cardiovascular management. The coexistence of RAAS and COVID-19, however, may traverse beyond chronic management and serve as a central target for acute respiratory distress syndrome (ARDS) itself.

CONTROVERSY

The natural history of COVID-19 can be separated into 3 overlapping stages including viral, pulmonary, and hyperinflammatory phases [6]. As an extensive neurohormonal network, RAAS plays an intrinsic role spanning all 3 phases of COVID-19 and may serve as an additional therapeutic focus. In contrast, antiviral and immunomodulatory therapies may be confined to a specific phase, namely the viral phase and hyperinflammatory phase, respectively.

COVID-19 exploits the RAAS system to gain access, proliferate, and inflict multisystem organ damage, notably respiratory in nature. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been reported to use angiotensin-converting enzyme 2 (ACE2) as a portal of tissue entry. This has generated a theoretical concern that RAAS blockers may upregulate ACE2 and increase infectivity, calling into question the continued or de novo use of this therapeutic class [7]. In order to evaluate the role of RAAS in COVID-19, we performed a balanced and thorough review.

RAAS PATHWAY

RAAS is divided into classical and alternative pathways. The classical pathway (Ang II/AT-1 axis) is dependent on 2 main enzymes including renin, which cleaves angiotensinogen into Ang I. This substrate is further reduced to Ang II via ACE. Ang II is an agonist at the AT-1 receptor, which is known to exhibit vasoconstrictive, fibroproliferative, pro-inflammatory, and fluid-retaining properties. In 2000, an ACE homolog was identified and designated as ACE2. Though this enzyme shares ~42% of its catalytic residues with ACE, its role in RAAS serves as a counterregulatory glycoprotein found in various tissues including the lungs, heart, vascular endothelium, kidneys, and intestinal tract [8]. This homolog is a vital component of the alternative pathway also known as the Ang 1–7,1–9/Mas axis.

Ang 1–7,1–9/Mas Axis

The primary purpose of the Ang 1–7,1–9/Mas axis is to counteract the classical Ang II/AT-1 axis. Upstream Ang I has 2 fates, either direct metabolism to Ang 1,7 via neprilysin or conversion to Ang 1,9 via ACE2. Ang 1,9 has activity on the AT-2 receptor

and offers reported protective benefits. Ang 1,9 can also be converted to Ang 1,7 through ACE, but catalytic output is low.

Though ACE2 has catalytic activity on Ang I, it has a 400-fold greater efficiency targeting Ang II as a substrate. By metabolizing and reducing plasma Ang II, less substrate is available to activate the deleterious effects of the Ang II/AT-1 axis. Ang 1,7 is the main byproduct of ACE2-Ang II metabolism. Ang 1,7 peptides have activity on both the MrgD and Mas receptors, providing anti-inflammatory, antifibrotic, vasodilatory, and natriuretic effects that directly oppose Ang II/AT-1 receptor activity (Figure 1) [7–9].

PATHOPHYSIOLOGY

SARS-CoV-2 is associated with a myriad of multisystem manifestations ranging from neurological deficits to renal dysfunction. Given that RAAS and its accompanying peptides are ubiquitously expressed throughout the human body, this may offer an important link in the pathophysiologic derangements associated with COVID-19. Liu and colleagues
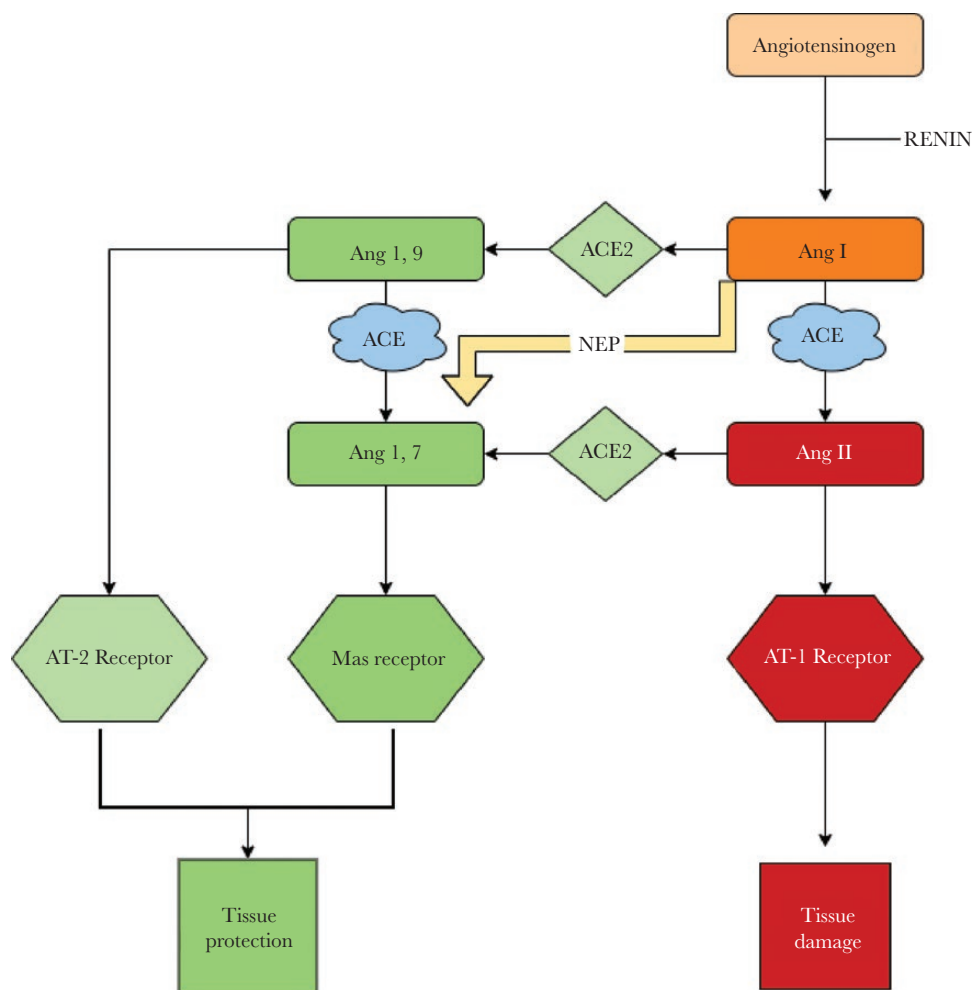

Figure 1. Renin angiotensinogen and Mas pathway.

reported epidemiologic and biomarker data associated with disease severity compared with healthy controls. Though only hypothesis-generating, results by Liu et al. indicated marked elevations in Ang II that were linearly associated with viral load and specifically lung injury. ARDS survivors have also been noted to have higher average Ang 1,7 and Ang 1,9 compared with ARDS nonsurvivors [10]. Anatomical ACE expression may offer a logical explanation for these findings. ACE expression in most organ systems including the heart is at most 20%. In contrast, pulmonary vasculature is exclusively dominated by ACE, making the lungs particularly sensitive to RAAS [11].

Excess ACE activation in pulmonary capillaries promotes vasoconstriction, vascular permeability, cytokine production, edema, hypoxemia, and extensive alveolar damage [11, 12]. Specifically located in type II alveolar epithelium, the counterregulatory mechanisms provided by ACE2 are compromised. Left unchecked, ACE accelerates apoptosis and drives fibroproliferation [11, 12].

The RAAS system is an intricate balance of regulatory and counterregulatory pathways. Disruption by SARS-CoV-2 may detrimentally impact pulmonary tissue and influence each stage of lung disease progression spanning from the viral phase to the hyperinflammatory phase [13].

Viral Phase
In the viral phase, viral spikes, or S-proteins, located on the surface of SARS-CoV-2 form hydrophobic and salt bridge interactions with transmembrane ACE2. Once docked, the S-proteins undergo a conformational change enhancing interactions with TMPRSS2, a principal serine protease. TMPRSS2 cleaves S-proteins and merges viral and pulmonary tissue membranes, which leads to cytoplasmic infiltration. Ultimately, the virus uses ACE2 to gain tissue entry, becomes endocytosed, envelopes itself in a protein vesicle resembling normal tissue phospholipid bilayers, and downregulates ACE2 activity post–tissue entry [7, 8, 14].

As the viral phase progresses, ACE2 continues to become downregulated. Though ACE2 is the primary port of entry for SARS-CoV-2, viral proliferation persists despite downregulation. This suggests that the virus uses concealed methods of spreading. Fehr and colleagues postulate that once the initial virion transcribes S-proteins, these migrate to the host cell membrane, creating a hybrid cell membrane with both host and viral fusion proteins, known as a syncytium. This initially allows the virus to evade detection by coronavirus-specific antibodies. Such a mode of viral transmission would explain how SARS-CoV-2 is able to propagate despite ACE2 downregulation. The plausibility of a syncytial mode of infectious spreading independent of ACE2 may invalidate concerns surrounding the continuation of angiotensin II receptor blocker (ARB)/ACE-I beyond the viral phase [15].

Pulmonary and Hyperinflammatory Phase
Once SARS-CoV-2 has infiltrated host cells and replicated, tissue dysfunction and a cytokine storm ensue. A dysregulated RAAS parallels hyperactivated innate immunity, contributing to damaging downstream effects. RAAS dysregulation is a culmination of ACE2 downregulation, Ang 1–7,1–9/Mas axis quiescence, and unopposed Ang II/AT-1 activity.

Initial ACE2 downregulation is caused by viral endocytosis (Figure 2). Subsequent downregulation is enhanced by proteolytic cleavage via A disintegrin and metalloprotease-17 (ADAM-17), a tumor necrosis factor (TNF) alpha–activating enzyme (TACE). The catalytic domain, or ectodomain, of ACE2 rests on the extracellular surface and is anchored by a transmembrane and intracellular tail. ADAM-17 cleaves the membrane-anchoring domains of ACE2, shedding the extracellular catalytic domain into soluble plasma ACE2. ADAM-17 is further amplified by extracellular cytokines including TNF-alpha and elevated levels of Ang II. Ang II incites reactive oxygen species formation, which activate kinases and upregulate ADAM-17-mediated ACE2 cleavage and shedding [7, 8, 14]. As ACE2 continues to become depleted, Ang II metabolism to Ang 1,7 is depressed. With no ACE2 to metabolize Ang II as substrate for the Ang 1–7/MAS axis, counterregulatory measures are crippled. Experimental models indicate that in the presence of ARDS, ACE2 deficiency magnifies interleukin (IL)-1B, IL-6, and TNF-alpha, contributing to a hyperactive immune system [16–18]. These inflammatory markers augment kinases (MAPK) and reactive oxygen species (ROS) to further upregulate ADAM17 and insidiously participate in ACE2 shedding and collectively produce a positive feedback loop (Figure 3).

Ectodomain shedding and elevated plasma concentrations of ACE2 are associated with the extent of tissue damage in acute lung injury data [19–21]. Though plasma ACE2 remains catalytically active, enzymatic efficiency in metabolizing Ang II may be diminished compared with membrane-bound ACE2.

ARB/ACE-I/MINERALOCORTICOID RECEPTOR ANTAGONISTS AND ACE2 ENHANCEMENT

Given the intrinsic connection between RAAS and ARDS pathophysiology, exploring RAAS inhibitors is warranted. Various pharmacologic and genetic techniques have been explored, including gene therapy, rhACE2 infusions, and direct ACE2 agonists in both the heart failure and ARDS arenas, though all experimental agents promising surrogate results have been noted, including decreases in IL-6 production, enhanced Ang 1–7,1–9/Mas axis, and overall improvement in acute lung injury caused by SARS-CoV [7, 8].

ACE2 Enhancement
Infusion of rhACE2 is designed to mimic soluble plasma ACE2. Animal models infected with various respiratory viruses including RSV, H5N1, and H7N9 mimic similar RAAS derangements noted in SARS-CoV-2, along with histopathological
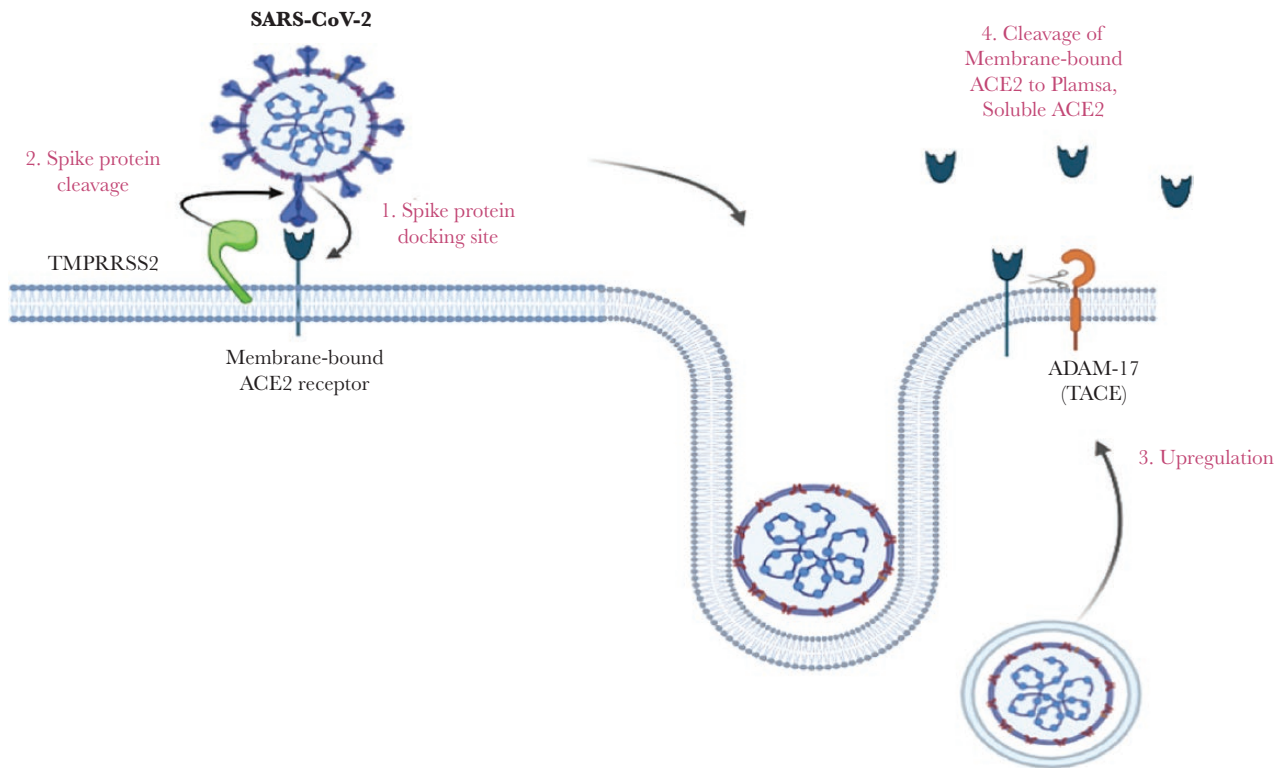
Figure 2. SARS-CoV-2 cellular entry. Abbreviations: ACE2, angiotensin-converting enzyme 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TACE, tumor necrosis factor alpha–activating enzyme.

damage consistent with ARDS [22]. Infusion of rhACE2 seems to attenuate vascular permeability, edema, and infiltrates and to improve oxygenation by ~40%. Limited human studies substantiate animal findings in ARDS and pulmonary hypertension. Observations have noted decreases in Ang II, ROS, TNF-alpha, and interleukins 1, 6, and 8. Conversely, an increase
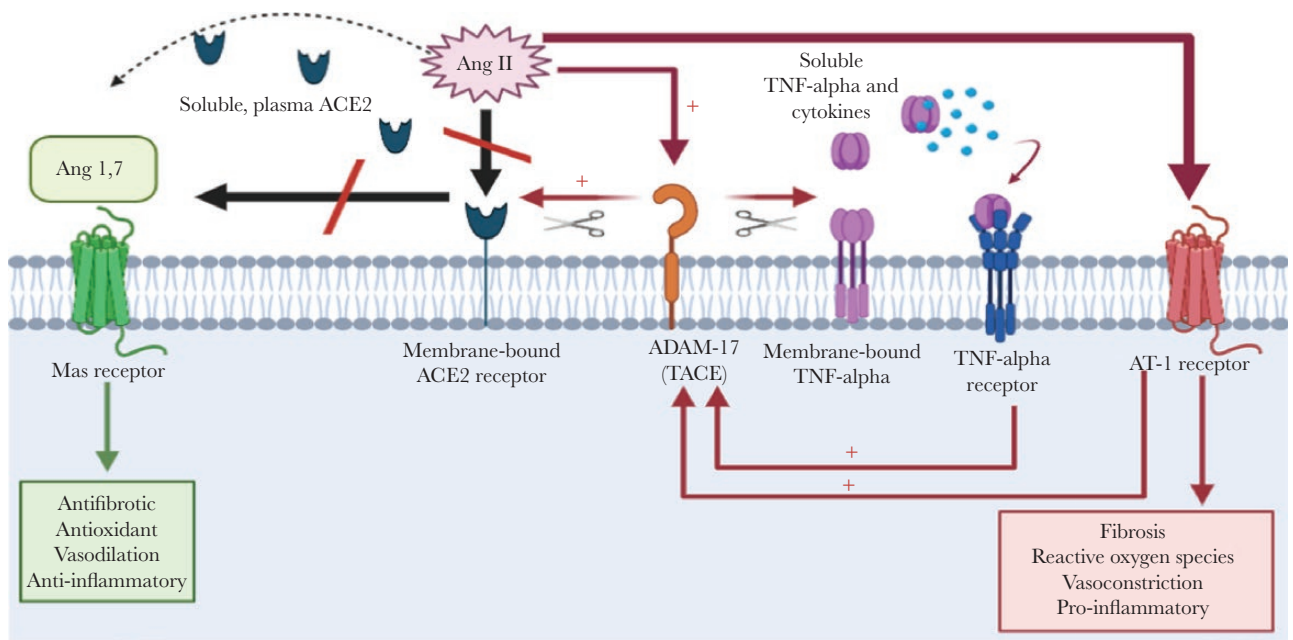
Figure 3. Dysregulated RAAS pathway hyperinflammatory sequelae. Abbreviations: ACE2, angiotensin-converting enzyme 2; TACE, tumor necrosis factor alpha–activating enzyme; TNF, tumor necrosis factor.

in Ang 1–7 improved pulmonary vascular resistance without systemic hemodynamic effects.

Despite promising preliminary data, theoretical limitations exist with rhACE2 treatment. Ectodomain shedding releases plasma soluble ACE2, which mirrors worsening tissue damage. Though catalytically active, the tissue-protective effects of soluble ACE2 seem limited. Recombinant human-ACE2 mimics soluble ACE2 and may share a similar fate. The large molecular size of rhACE2 dampens tissue penetration and diminishes Mas receptor activation. Thus, rhACE2 in SARS-CoV-2 is better served as a decoy docking site for viral particles and S-proteins [8] and moderate viral propagation rather than inflammatory modulation.

ARB/ACE-I/Mineralocorticoid Receptor Antagonists

Marking the limitations of soluble ACE2, directly manipulating membrane-bound ACE2 offers alternative mechanisms to enhance or preserve the Ang 1–7,1–9/Mas axis through conventional ACE-I, ARB, and mineralocorticoid receptor antagonist (MRA) therapies. Descriptions of ACE-I and ARB mechanisms are traditionally described within the context of blunting the classical ACE pathway. However, their interaction with alternative pathways within RAAS (Ang 1–7,1–9/Mas axis) are of equal importance and merit further discussion.

ARBs, ACE-Is, and MRAs encourage several direct and indirect beneficial modalities. The putative benefits of MRAs involve downregulation of ROS generation, kinase activity, and diminishing ADAM-17-induced ACE2 cleavage. ACE-Is and ARBs have been shown to increase ACE2 detection according to 4 parameters including protein activity, ACE2 mRNA expression, Ang II levels, and Ang 1–7 effects [8]. Measurements of ACE2 detection are confined to cardiac and kidney animal modeling [23]. ARBs demonstrate consistent ACE2 detection across all 4 parameters [21,24–29]. The purported beneficial effects of ARBs on RAAS biomarkers are independent of blood pressure control. Despite achieving comparable hemodynamics to atenolol or hydralazine, olmesartan demonstrated augmented ACE2 activity vs other antihypertensives [27]. Specifically, animal lung tissue samples are limited to losartan exposure. Rat models in the treatment arms showed upregulated ACE2 activity and blunted Ang II in bronchoalveolar fluid [30, 31].

ACE-I animal models are primarily limited to lisinopril, enalapril, and ramipril (Table 1). These agents, however, have shown variance in their capacity to increase ACE2 activity or mRNA expression [26, 28, 32]. The discrepant actions between ACE-Is and ARBs may very well lie in differences between experimental methodology and modeling. Mechanistically, however, it merits some hypothetical acknowledgment. ACE-Is offer less consistency perhaps because they operate too far upstream in RAAS. Specifically, blocking the conversion of Ang 1 to Ang II creates a dam effect, siphoning Ang 1 toward Ang 1–9 conversion via ACE2. Though Ang 1–9 elicits tissue-protective benefits on the AT-2 receptor, the effects may be less profound

than those provided by Ang 1–7. Additionally, Ang 1–9 can be converted to Ang 1–7; however, this requires functional, uninhibited ACE activity. Thus, ACE inhibitors may prevent conversion of Ang 1–9 to Ang 1–7 and significantly decrease Ang II substrate for ACE2. As mentioned earlier, ACE2 has a greater efficiency to convert Ang II to Ang 1–7 by 400-fold, which may stunt Mas axis optimization [8, 33, 34].

In contrast, ARBs by design will increase Ang II substrate and magnify Ang 1–7 activity to promote anti-inflammatory and antiproliferative tissue effects while blocking the damaging effects of the AT-1 receptor. The excess Ang II that is encouraged by ARBs promotes competition with SAR-CoV-2 for ACE2 attachment and catalysis. Finally, even if ARBs/ACE-Is only increase soluble plasma ACE2 with variable effects on tissue-bound ACE2 activity, this may still serve the benefit of acting as decoy mechanisms or amplification of plasma conversions to Ang 1–7.

Direct infusion of Ang 1–7 in ARDS rat models was noted to have an improvement in oxygenation and decrease in white blood cell migration along with a decrease in polymorphonuclear count with early Ang 1–7 administration. Additionally, late-stage ARDS modeling noted a decrease in collagen formation despite delayed Ang 1–7 administration, further substantiating Ang 1–7 as a pharmacologic prospect [35].

CLINICAL OUTCOMES

COVID-19-specific data have been generated to inform the safety of these agents in hypertension specifically. One of the initial signals of safety published by Meng et al. analyzed 42 hypertensive patients, 17 of whom were on ACE-I/ARB therapy. Patients on RAAS therapy were noted to have lower IL-6 levels, neutral C-reactive protein levels, higher CD-3+/CD-4+ counts, and lower peak viral loads compared with the non-RAAS antihypertensive group [36]. Clinical data from Wuhan, China, noted that of the 362 hypertensive patients in this cohort, 115 were on ACE-I/ARB therapy [37]. This subgroup demonstrated no increase in disease progression or mortality independent of disease severity or underlying comorbidities. Of note, this was a purely observational report with no multivariate analyses.

A more robust propensity-matched multicenter Chinese observational study using mixed-effects modeling, E-value score analysis, and sensitivity analyses further substantiated previous data. Zhang and colleagues proceeded further by suggesting that ACE-I/ARB demonstrated a decrease in 28-day all-cause mortality by at least 58% vs a non-ACE-I/ARB antihypertensive group along with lower rates of septic shock. ACE-I/ARB vs non-ACE-I/ARB cohorts showed no differences in effect on blood pressure or mean arterial pressure readings, demonstrating that any putative benefit of this class of medication may be independent of its antihypertensive properties and related to neurohormonal elements [38].

Table 1. RAAS Inhibitors Effect on Ang II and ACE2 Pathways

	Tissue	Plasma Ang II	Ang 1,7	ACE2 mRNA	ACE2 Activity
ACE inhibitors					
Lisinopril	Heart	↓	↑	↑	≠
Lisinopril	Heart			↑	↑
Lisinopril	Heart/kidney	↓	↑	↑	
Enalapril	Kidney			≠	↑
Ramipril	Heart				↑
ARB					
Losartan/olmesartan	Heart	↑	↑	↑	
Losartan	Heart	↑	↑	↑	↑
Irbesartan	Heart			↑	↑
Losartan	Heart/kidney	↑	↑	↑	
Telmisartan	Kidney			↑	↑
Irbesartan	Aorta			↑	↑
Olmesartan	Aorta	↑	↑	↑	↑
MRA					
Spironolactone	Human macrophage			↑	↑
Eplerenone	Heart/kidney			↑ ≠	↑ ≠
Eplerenone	Heart			↑	
Eplerenone	Heart			≠	≠

Adapted from Gheblawi et al. [8].

Abbreviations: ACE2, angiotensin-converting enzyme 2; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist; RAAS, renin-angiotensin-aldosterone system.

Data from other geographic epicenters including Lombardy, Italy, and New York, New York, have validated the findings of Zhang and colleagues. Mancia et al. performed a population-based case–control study between COVID-19-positive patients and noninfected patients according to age, sex, and residence [39]. Several antihypertensive classes were recorded, including ACE-Is/ARBs, calcium channel blockers, beta-blockers, MRAs, thiazides, and loop diuretics. A total of 6272 cases were matched to 30 759 controls. Antihypertensives were more frequently prescribed in the COVID-19 group, which correlated to a more pronounced presence of various chronic comorbidities. After adjustments, ACE-Is/ARBs were not associated with increased risk of COVID-19 independent of age, gender, or COVID-19 disease severity. Interestingly, loop diuretics did show an associated increased risk of COVID-19 after multivariate adjustments (OR, 1.46; 95% CI, 1.23–1.76). However, this may be an artifact of increased heart failure or renal disease, which portend worse outcomes.

Reynolds and colleagues from New York University performed a single-center observational report assessing RAAS inhibitors and the risk of developing a positive COVID-19 result in conjunction with degree of illness [40]. The Reynolds group reported 5894 positive patients, of whom 17% had severe disease, defined as ICU admission, need for mechanical ventilation, or death. Of the 12 594 patients with test results, 4357 patients (34.6%) had hypertension, of whom 2573 patients (59.1%) tested positive, and of those, 24.6% had severe illness. Propensity-matched results after

adjusting for confounders across multiple antihypertensives yielded no association with testing positive. ACE-Is, ARBs, and a composite of these classes represented >50% of the antihypertensives administered. With respect to severity of illness among hypertensive patients, no association was found with a 97.5% certainty across all medication classes except for calcium channel blockers. Irrespective of hypertension, lack of association was confirmed both for likelihood of testing positive and severity of illness. Of note, those taking beta-blockers had a lower likelihood of testing positive, which was likely due to unmeasured confounders.

Reinforcing the single-center data by Reynolds et al., Khera and colleagues [41] expanded their analysis to include American commercial insurance and Medicare databases. Hypertensive COVID-19 patients were identified and separated into inpatient and outpatient cohorts. In both cohorts, ACE-Is and ARBs were analyzed separately and propensity-matched against alternative antihypertensives. In the outpatient cohort, ACE-I was associated with decreased hospitalizations, with a hazard ratio (HR) of 0.61 (95% CI, 0.41–0.93) specifically in the Medicare subgroup. Further analyses did not detect any signal of harm or increased mortality with ACE-Is or ARBs. These data should be interpreted with caution as they are preliminary.

Clinical benefit with ACE-Is/ARBs may extend beyond SARS-CoV-2 and be observed with influenza as well.

Chung and colleagues investigated the incidence of influenza in adults who received ACE-Is from 1998 through 2016 [42]. Using the United Kingdom Clinical Practice Research Datalink (CPRD), 700 994 patients were prescribed ACE-Is and 230 028 patients received ARBs. Analyses were adjusted for influenza vaccination, demographics, and cardiopulmonary comorbidities. With a median of 8.7 years of follow-up, those prescribed ACE-Is had a lower risk of influenza, with an HR of 0.66 (95% CI, 0.62–0.7). Stratification of ACE-I/ARB prescription according to duration in years revealed decreasing incidence rates of influenza with increasing duration of medication.

The medical community has produced several important data sets describing use of RAAS inhibitors in COVID-19. The results, however, are restricted to observational findings and are inherently limited by design. Lack of prespecified primary hypothesis, selection bias, variability in COVID-19 testing, inability to definitively capture actual drug exposure beyond health records, and analysis of medication dose effects preclude drawing definitive conclusions. The totality of evidence, however, suggests lack of association with harm and further corroborates the neutral utilization of RAAS inhibitors in these patients. An ongoing, living systematic review by Mackey and colleagues performs literature surveillance at regular intervals and issues periodic updates. Thus far, the meta-analysis published by Mackey et al. using 14 observational trials confirms our assertions [43].

GAPS AND CALL TO ACTION

The influence of RAAS on pulmonary physiology and COVID-19 illustrates a complex link between SARS-CoV-2 and development of ARDS. Though histopathology and animal modeling offer viable pharmacologic targets, the capacity for RAAS inhibitors to modulate lung injury remains unknown. Animal models and tissue samples are mostly confined to nonpulmonary experiments. Further, a paucity of data exists for de novo treatment with RAAS inhibitors in those without an established chronic condition. Expanded investigation into the implications of RAAS inhibition using readily available agents and novel compounds in the setting of ARDS must be further explored (Table 2). Finally, we suggest that the burden of proof has been met to pursue randomized controlled trials of RAAS inhibitors for viral pneumonitis and that these trials would likely deliver important insights in the management of inflammatory conditions that manifest in ARDS.

In the interim, acknowledging the increased mortality among those with cardiovascular comorbidities and COVID-19 should dissuade RAAS therapy interruption. Discontinuing neurohormonal treatment leads to re-establishment of Ang II to pretreatment levels and an increase in end diastolic volumes in 4 and 15 days, respectively, and highlights the critical role of RAAS inhibition in maintaining cardiovascular homeostasis [44–47].

CONCLUSIONS

The purported mechanisms of concern associated with ACE-Is/ARBs during the COVID-19 pandemic should be balanced by the therapeutic benefits that RAAS pathway manipulation has in treating cardiovascular diseases. The most recent observational data do not offer substantial scientific rigor to support superiority of these drug classes over alternative antihypertensives, nor do they merit the widespread initiation of ACE-Is/ARBs across COVID-19 patients. There is an absolute void in data regarding whether ACE-Is/ARBs increase vulnerability to infection. However, once infected, current data suggest that ACE-Is/ARBs do not contribute to increased disease severity or progression. Furthermore, the importance of addressing uncontrolled hypertension indicates that initiation of ACE-Is/ARBs can be carefully considered and should not be immediately dismissed.

Table 2. RAAS Inhibitor Research in Progress

Study	Design	Relevance	Endpoints
Hypertension in Patients Hospitalized With COVID-19 (HT-COVID19)—NCT04318301	Single-center	ACEI/ARB vs non-ACEI/ARB in patients with hypertension	Primary: mortality Secondary: pneumonia severity, length of hospital stay
ACE Inhibitors, Angiotensin II Type-I Receptor Blockers and Severity of COVID-19 (CODIV-ACE)—NCT04318418	Retrospective case–control	ACEI/ARB exposure between nonsevere vs severe infection	Primary: severity of disease Secondary: mortality
Losartan for Patients With COVID-19 Requiring Hospitalization—NCT04312009	Prospective multicenter, randomized, double-blind study	Effect of losartan on lung function in hospitalized patients randomized to losartan 50 mg daily vs placebo for 7 d or discharge	Primary: difference in estimated (PEEP-adjusted) P/F ratio Secondary: hypotension, AKI, SOFA, 28/90-d mortality, ICU admission, vasopressor-free days, therapeutic oxygen-free days, ventilator-free days, LOS, incidence of respiratory failure, disease severity, viral load in blood and nasopharyngeal swab
Losartan for Patients With COVID-19 Not Requiring Hospitalization—NCT04311177	Prospective multicenter, randomized, double-blind study	Effect of losartan nonhospitalized patients randomized to losartan 25 mg daily vs placebo for 10 d or hospital admission	Primary: hospital admission Secondary: change in dyspnea limitations and severity, maximum temperature, emergency department/clinic presentation, disease severity, viral load via oropharyngeal swab, ventilator-free days, therapeutic oxygen-free days, need for hospital admission, need for oxygen therapy
Coronavirus (COVID-19) ACE-I/ARB Investigation (CORONACION)—NCT04330300	Randomized controlled trial	Switching patients already on ACE/ARB to alternative antihypertensive vs continuation of ACEI/ARB in essential hypertension	Primary: composite of mortality, ICU intubation, noninvasive ventilation Secondary: maximum troponin T value, mean systolic blood pressure, all-cause mortality, mortality, ICU intubation, noninvasive ventilation
ACE Inhibitors or ARBs Discontinuation in Context of SARS-CoV-2 Pandemic (ACORES-2)—NCT04329195	Randomized controlled trial	Patients with a history of cardiovascular disease comparing continued treatment with ACEI/ARB vs discontinuation	Primary: time to clinical improvement from day 0 to day 28 Secondary: composite of cardiovascular death, myocardial infarction, stroke or acute heart failure, therapeutic oxygen-free days, days alive outside of hospital, ICU and ventilation-free days, all-cause mortality, cardiovascular death, AKI-free days

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; COVID-19, coronavirus disease 2019; ICU, intensive care unit; LOS, length of stay; PEEP, positive end expiratory pressure; RAAS, renin-angiotensin-aldosterone system; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOFA, sequential organ failure assessment score.

References

1. Bavishi C, Maddox TM, Messerli FH. Coronavirus disease 2019 (COVID-19) infection and renin angiotensin system blockers. JAMA Cardiol **2020**; 5:745–7.
2. Guan WJ, Ni ZY, Hu Y, et al; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med **2020**; 382:1708–20.

3. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet **2020;** 395:1054–62.

4. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA **2020**; 323:1061–9.

5. Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. **In press**.

6. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. J Heart Lung Transplant **2020**; 39:405–7.

7. Brojakowska A, Narula J, Shimony R, Bander J. Clinical implications of SARS-CoV-2 interaction with renin angiotensin system: JACC review topic of the week. J Am Coll Cardiol **2020**; 75:3085–95.

8. Gheblawi M, Wang K, Viveiros A, et al. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. Circ Res **2020**; 126:1456–74.

9. Guignabert C, de Man F, Lombès M. ACE2 as therapy for pulmonary arterial hypertension: the good outweighs the bad. Eur Respir J **2018**; 51:1800848.

10. Reddy R, Asante I, Liu S, et al. Circulating angiotensin peptides levels in acute respiratory distress syndrome correlate with clinical outcomes: a pilot study. PLoS One **2019**; 14:e0213096.

11. Zhang H, Baker A. Recombinant human ACE2: acing out angiotensin II in ARDS therapy. Crit Care **2017**; 21:305.

12. Jia H. Pulmonary angiotensin-converting enzyme 2 (ACE2) and inflammatory lung disease. Shock **2016**; 46:239–48.

13. Akhmerov A, Marban E. COVID-19 and the heart. Circ Res **2020**; 126:1443–55.

14. Patel VB, Zhong JC, Grant MB, Oudit GY. Role of the ACE2/angiotensin 1-7 axis of the renin-angiotensin system in heart failure. Circ Res **2016**; 118:1313–26.

15. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol **2015**; 1282:1–23.

16. Zhong J, Basu R, Guo D, et al. Angiotensin-converting enzyme 2 suppresses pathological hypertrophy, myocardial fibrosis, and cardiac dysfunction. Circulation **2010**; 122:717–28.

17. Zhong J, Guo D, Chen CB, et al. Prevention of angiotensin II-mediated renal oxidative stress, inflammation, and fibrosis by angiotensin-converting enzyme 2. Hypertension **2011**; 57:314–22.

18. Hemnes AR, Rathinasabapathy A, Austin EA, et al. A potential therapeutic role for angiotensin-converting enzyme 2 in human pulmonary arterial hypertension. Eur Respir J **2018**; 51:1702638.

19. Wang K, Gheblawi M, Oudit GY. Angiotensin converting enzyme 2: a double-edged sword. Circulation. **In press**.

20. Epelman S, Tang WH, Chen SY, et al. Detection of soluble angiotensin-converting enzyme 2 in heart failure: insights into the endogenous counter-regulatory pathway of the renin-angiotensin-aldosterone system. J Am Coll Cardiol **2008**; 52:750–4.

21. Patel VB, Clarke N, Wang Z, et al. Angiotensin II induced proteolytic cleavage of myocardial ACE2 is mediated by TACE/ADAM-17: a positive feedback mechanism in the RAS. J Mol Cell Cardiol **2014**; 66:167–76.

22. Gu H, Xie Z, Li T, et al. Angiotensin-converting enzyme 2 inhibits lung injury induced by respiratory syncytial virus. Sci Rep **2016**; 6:19840.

23. Ferrario CM, Jessup J, Gallagher PE, et al. Effects of renin-angiotensin system blockade on renal angiotensin-(1-7) forming enzymes and receptors. Kidney Int **2005**; 68:2189–96.

24. Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. Cardiovasc Res **2020**; 116:1096–100.

25. Ishiyama Y, Gallagher PE, Averill DB, et al. Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors. Hypertension **2004**; 43:970–6.

26. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation **2005**; 111:2605–10.

27. Igase M, Strawn WB, Gallagher PE, et al. Angiotensin II AT1 receptors regulate ACE2 and angiotensin-(1-7) expression in the aorta of spontaneously hypertensive rats. Am J Physiol Heart Circ Physiol **2005**; 289:H1013–9.

28. Jessup JA, Gallagher PE, Averill DB, et al. Effect of angiotensin II blockade on a new congenic model of hypertension derived from transgenic Ren-2 rats. Am J Physiol Heart Circ Physiol **2006**; 291:H2166–72.

29. Jin HY, Song B, Oudit GY, et al. ACE2 deficiency enhances angiotensin II-mediated aortic profilin-1 expression, inflammation and peroxynitrite production. PLoS One **2012**; 7:e38502.

30. Yuan YM, Luo L, Guo Z, et al. Activation of renin-angiotensin-aldosterone system (RAAS) in the lung of smoking-induced pulmonary arterial hypertension (PAH) rats. J Renin Angiotensin Aldosterone Syst **2015**; 16:249–53.

31. Wösten-van Asperen RM, Lutter R, Specht PA, et al. Acute respiratory distress syndrome leads to reduced ratio of ACE/ACE2 activities and is prevented by angiotensin-(1-7) or an angiotensin II receptor antagonist. J Pathol **2011**; 225:618–27.

32. Ocaranza MP, Godoy I, Jalil JE, et al. Enalapril attenuates downregulation of angiotensin-converting enzyme 2 in the late phase of ventricular dysfunction in myocardial infarcted rat. Hypertension **2006**; 48:572–8.

33. Vickers C, Hales P, Kaushik V, et al. Hydrolysis of biological peptides by human angiotensin-converting enzyme-related carboxypeptidase. J Biol Chem **2002**; 277:14838–43.

34. Guy JL, Jackson RM, Acharya KR, et al. Angiotensin-converting enzyme-2 (ACE2): comparative modeling of the active site, specificity requirements, and chloride dependence. Biochemistry **2003**; 42:13185–92.

35. Zambelli V, Bellani G, Borsa R, et al. Angiotensin-(1-7) improves oxygenation, while reducing cellular infiltrate and fibrosis in experimental acute respiratory distress syndrome. Intensive Care Med Exp **2015**; 3:44.

36. Meng J, Xiao G, Zhang J, et al. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. Emerg Microbes Infect **2020**; 9:757–60.

37. Li J, Wang X, Chen J, et al. Association of renin-angiotensin system inhibitors with severity or risk of death in patients with hypertension hospitalized for coronavirus disease 2019 (COVID-19) infection in Wuhan, China. JAMA Cardiol. **In press**.

38. Zhang P, Zhu L, Cai J, et al. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res **2020**; 126:1671–81.

39. Mancia G, Rea F, Ludergnani M, et al. Renin–angiotensin–aldosterone system blockers and the risk of Covid-19. N Engl J Med **2020;** 382:2431–40.

40. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin-angiotensin-aldosterone system inhibitors and risk of Covid-19. N Engl J Med. **In press**.

41. Khera R, Clark C, Lu Y, et al. Association of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers with the risk of hospitalization and death in hypertensive patients with coronavirus disease-19. J Am Heart Assoc. **In press**.

42. Chung SC, Providencia R, Sofat R. Association between angiotensin blockade and incidence of influenza in the United Kingdom. N Engl J Med **2020**; 383:397–400.

43. Mackey K, King VJ, Gurley S, et al. Risks and impact of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers on SARS-CoV-2 infection in adults. Ann Intern Med **2020**; 173:195–203.

44. Buckley LF, Cheng JWM, Desai A. Cardiovascular pharmacology in the time of COVID-19: a focus on angiotensin-converting enzyme 2. J Cardiovasc Pharmacol **2020**; 75:526–9.

45. Nicholls MG, Ikram H, Espiner EA, et al. Hemodynamic and hormonal responses during captopril therapy for heart failure: acute, chronic and withdrawal studies. Am J Cardiol **1982**; 49:1497–501.

46. Konstam MA, Rousseau MF, Kronenberg MW, et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. SOLVD Investigators. Circulation **1992**; 86:431–8.

47. Halliday BP, Wassall R, Lota AS, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. Lancet **2019**; 393:61–73.