What solid organ transplant healthcare providers should know about renin-angiotensin-aldosterone system inhibitors and COVID-19

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INTRODUCTION

The current coronavirus disease 2019 (COVID-19) pandemic is associated with unprecedented morbidity and mortality, and recent publications in the transplant literature report varying rates of mortality from 6% to 28%. Early reports from China and Italy have shown that co-existing conditions, including diabetes mellitus, hypertension, congestive heart failure, and coronary artery disease, are more common among patients who developed severe symptoms of COVID-19. Conventional medical management of these co-morbidities often includes the use of renin-angiotensin-aldosterone system (RAAS) inhibitors. Interestingly, coronaviruses interact with angiotensin-converting enzyme 2 (ACE2) to facilitate entry into target cells, raising concerns in several published commentaries that preexisting use of RAAS inhibitors may increase the risk of developing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Given the common use of RAAS inhibitors among solid organ transplant recipients, we sought to review the RAAS cascade, the mechanism of SARS-CoV-2 entry, and pertinent data related to the effect of RAAS inhibitors on ACE2 to guide management of solid organ transplant recipients during the COVID-19 pandemic. At present, there is no clear evidence to support the discontinuation of RAAS inhibitors in solid organ transplant recipients during the COVID-19 pandemic.

KEYWORDS
ACE2 receptor, COVID-19, renin-angiotensin-aldosterone inhibitors, solid organ transplant

Abstract
The data on the outcomes of solid organ transplant recipients who have contracted coronavirus disease 2019 (COVID-19) are still emerging. Kidney transplant recipients are commonly prescribed renin-angiotensin-aldosterone system (RAAS) inhibitors given the prevalence of hypertension, diabetes, and cardiovascular disease. As the angiotensin-converting enzyme 2 (ACE2) facilitates the entry of coronaviruses into target cells, there have been hypotheses that preexisting use of renin-angiotensin-aldosterone system (RAAS) inhibitors may increase the risk of developing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Given the common use of RAAS inhibitors among solid organ transplant recipients, we sought to review the RAAS cascade, the mechanism of SARS-CoV-2 entry, and pertinent data related to the effect of RAAS inhibitors on ACE2 to guide management of solid organ transplant recipients during the COVID-19 pandemic. At present, there is no clear evidence to support the discontinuation of RAAS inhibitors in solid organ transplant recipients during the COVID-19 pandemic.
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## 2 | RAAS, ACE2, AND SARS-CoV-2

The RAAS is a cascade of vasoactive peptides that orchestrate key physiological processes, including blood pressure regulation, fluid and electrolyte balance, and cardiac and renal function.15,16 In the classical view of the cascade, renin cleaves angiotensinogen and generates angiotensin (Ang) I, which is cleaved by angiotensin-converting enzyme (ACE), generating Ang II (Figure 1A). Ang II is the active form of angiotensin that binds to receptors in the adrenal cortex, releasing aldosterone. Ang II also induces arterial vasoconstriction and promotes fibrosis. A parallel pathway mediated by ACE2, a homolog of ACE, generates Ang (1-9) from Ang I and Ang (1-7) from Ang II (Figure 1B). Ang (1-7) has organ-protective properties which oppose the vasoconstrictive, inflammatory, sodium retaining, and remodeling properties of Ang II.

While ACE2 is predominantly a membrane-bound enzyme, its membrane anchor can be cleaved by a disintegrin and metalloprotease 17 (ADAM17), releasing ACE2 into blood, urine, and other body fluids. Membrane-bound ACE2 (found on pneumocytes) along with transmembrane protease serine 2 (TMPRSS2) is required to facilitate SARS-CoV-2 entry into target cells. On the other hand, soluble ACE2 has been shown to significantly block early stages of SARS-CoV-2 infections in vitro experiments and represents a potential therapeutic intervention (Figure 2).

### THE EFFECTS OF RAAS INHIBITORS ON ACE2

Although ACE2 shares significant homology with ACE (40% identity and 61% similarity), its substrate-binding pocket site is distinct from ACE; therefore, classical ACE inhibitors (ACEi) do not directly affect ACE2 enzymatic activity.19 In addition, ACEi use may be protective as it reduces Ang II which increases alveolar permeability and would potentiate acute lung injury. Several animal studies have reported mixed findings on the effect of ACEi on ACE2 mRNA expression or enzymatic activity in cardiac20-23 and renal tissues.24 In comparison, angiotensin II type I receptor blockers (ARBs) more consistently up-regulate ACE2 mRNA or protein level in cardiac tissue20,25-27 and renal vasculatures,28 though the effect varies across study models and requires high doses of ARBs. The upregulation of ACE2 by ARBs may be protective against lung injury via Ang-(1-7), a vasodilatory peptide.29

In contrast, there are very few studies in humans to assess the effect of RAAS inhibitors on ACE2 expression.30-35 It is important to note that all these studies reported the level of ACE2 activity in blood or urine, as quantifying membrane-bound ACE2 in vivo in human cardiac and kidney tissue would be technically challenging and invasive. There is no evidence to support that soluble ACE2 is a reliable surrogate for membrane-bound ACE2. Interestingly, membrane-bound ACE2 protein expression was found to be decreased in human autopsy hearts that were positive for SARS-CoV during the Toronto SARS outbreak in 2009.36 Hypothetically, if the animal data can be extrapolated to humans, increased membrane-bound ACE2 in human myocardium associated with preexisting use of RAAS inhibitors may be potentially protective against COVID-19-associated myocarditis.

![Figure 1](image-url)
4 | ROLE OF RAAS INHIBITORS IN KIDNEY TRANSPLANT RECIPIENTS

Kidney transplant recipients with cardiovascular disease and post-transplant erythrocytosis are commonly prescribed ACEi and ARB.37,38 Studies on RAAS blockade in kidney transplant patients have been mixed with regard to patient and graft survival.39-45 Interestingly, a rare condition that calls for the use of ARB post-transplant is antibody-mediated rejection related to angiotensin II type I receptor (AT1R), a G protein-coupled receptor expressed at the endothelial cell surface.46 In a prospective cohort of 1,845 kidney transplant recipients, circulating anti-AT1R antibodies have been associated with increased antibody-mediated rejection at 1-year post-transplant and overall reduced allograft survival.47 Anti-AT1R antibodies are thought to develop post-transplant in response to ischemia-reperfusion injury, which in turn triggers an alloantigen immune response and activates an inflammatory cascade, leading to increased antigen expression and cytokine production.48 The use of ARB may improve allograft survival in kidney transplant recipients with elevated anti-AT1R antibodies.49 Although there is a growing interest in the contribution of anti-AT1R antibodies to allograft rejection, its overall prevalence and exact role in the pathogenesis of allograft rejection requires further investigation.

5 | COVID-19, RAAS, AND KIDNEY TRANSPLANT

In recent weeks, emerging data are allowing insight into provider experiences with COVID-19 infection in transplant recipients. Early reports from Europe and China suggest that immunosuppressed patients are not at increased risk of severe complications in comparison with the general population.2,50-53 However, one study in the United States reported high early mortality of up to 28% among kidney transplant recipients with COVID-19. Almost 80% of patients required inpatient admission, with nearly 40% of those admitted requiring intubation. Mortality was very high, 64%, in patients requiring intubation.4 Similarly, a study of 20 kidney transplant recipients with COVID-19 from Italy found a 25% mortality rate.5 Contrary to these higher mortality rates, a single center cohort study out of Spain found a 6% mortality rate among 33 kidney transplant recipients infected with COVID-19 from the onset of the pandemic to mid-April of 2020.3 Similar to the study by Akalin et al, 80% of the identified renal transplant recipients required hospital admission with greater than 50% of those requiring ICU admission. No data on RAAS inhibitors were available in any of the above studies.

Currently, there are very limited numbers of SARS-CoV-2 infections documented in transplant recipients who were on ACEi or ARB therapy. A small cohort study of renal transplants afflicted with COVID-19 in the UK found that five out of seven patients required inpatient management, with one death in their cohort.2 Two patients were on RAAS inhibitors, which were continued through their course. A 67-year-old kidney transplant recipient who was on ACEi for hypertension developed acute kidney injury, ARDS, and passed away on hospital day 12. Guillen et al described the clinical course of a middle-aged kidney transplant recipient who was on Losartan therapy due to hypertension. The patient developed acute respiratory distress syndrome (ARDS), requiring ventilator support 10 days after onset of symptoms.54 At our transplant center, we observed the successful recovery of an elderly kidney transplant recipient from SARS-CoV-2 14 days after onset of symptoms while being continued on Losartan with no development of ARDS.
Currently, there is limited evidence that ARBs may upregulate membrane-bound ACE2 in renal and cardiac tissues of animal models. Unfortunately, the animals were not challenged by coronaviruses in these studies. To date, no comprehensive studies demonstrate the effect of RAAS inhibitors on the lung-specific expression of ACE2 in experimental animal models or humans though studies are continuing to emerge.\(^5\) Informative data can be potentially obtained by examining human epithelial cells from oral mucosa\(^5\) or endobronchial lining,\(^5\) which not only highly express membrane-bound ACE2 but are also more relevant to COVID-19’s route of transmission. Autopsy studies on the hearts of COVID-19 positive patients would be informative to elucidate the relationship between cardiac membrane-bound ACE2, ACE/ARB therapy, and predisposition to COVID-19-associated myocarditis. Mechanistic data on whether modulating the level of membrane-bound ACE2 in target tissue would affect the entry of SAR-CoV-2 would aid in our understanding. In short, the hypothetical concerns regarding the causal relationship between RAAS inhibitors, membrane-bound ACE2, and severity of COVID-19 are not supported by the available data.

Overall, there is no clear evidence to support discontinuation of ACEi and ARB in solid organ transplant recipients with COVID infection. Thus, we cautiously support the continuation of ACEi and ARB in solid organ transplant recipients with COVID infection without any direct survival benefit of continued use.

**CONFLICT OF INTEREST**

We have no conflict of interest.

**AUTHORS’ CONTRIBUTIONS**

All authors wrote, reviewed, and revised the manuscript.

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