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COMMENTARY

Renin–angiotensin–aldosterone system inhibitors and COVID-19

Kieran L. Quinn MD MSc, Michael Fralick MD PhD, Jonathan S. Zipursky MD, Nathan M. Stall MD

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Emerging data suggest that people with hypertension or diabetes who are infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and diagnosed with coronavirus disease 2019 (COVID-19) are at an increased risk of respiratory failure and death. These patients are often prescribed renin–angiotensin–aldosterone system (RAAS) inhibitors, including angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). This has led to important questions about whether these medications are contributing to worse outcomes in patients with COVID-19. It is unclear if the theoretical harms of RAAS inhibitors are related to their potential to facilitate infection through modified expression of angiotensin-converting enzyme 2 (ACE2; which is used by SARS-CoV-2 to enter human cells), to underlying comorbid disease, or to other sources of confounding. Although high-quality studies are urgently needed to inform prescribing decisions for RAAS inhibitors in patients with, or those at risk of, COVID-19, guidance from international societies unanimously recommends not altering treatment at this time. We discuss the existing evidence, clinical and physiologic theory, and expert guidance on RAAS inhibitors and COVID-19.

Recent cohort studies report that patients with COVID-19 and hypertension or diabetes have an increased risk of respiratory failure (unadjusted hazard ratio [HR] 1.82–2.34) and death (unadjusted odds ratio [OR] 2.85–3.05).[1,2] The largest cohort study to date, which included 4103 patients with COVID-19 in New York City, reported an adjusted odds ratio for hospital admission and critical illness of 1.23 (95% confidence interval [CI] 0.97–1.57) and 0.95 (95% CI 0.68–1.33) for hypertension, and 2.81 (95% CI 2.14–3.72) and 1.14 (95% CI 0.83–1.58) for diabetes, respectively.[3] Multiple international professional societies recommend ACE inhibitors (or ARBs) as first-line therapy in the management of hypertension and diabetes in adults.[4] These initial observations have raised 2 critical questions: Are RAAS inhibitors causing harm in patients with COVID-19? And if so, what is the proposed mechanism?

Three key physiologic concepts are central to the hypothesis that use of ACE inhibitors or ARBs might be associated with worse outcomes in patients with COVID-19. First, SARS-CoV-2 gains entry to the cell by using the membrane-bound ACE2 protein as a receptor.[5] Second, ACE2 is expressed in human lung pneumocytes (along with epithelial cells of the intestine, kidney and blood vessels). Third, the expression of ACE2 might be increased in patients with diabetes who are treated with ACE inhibitors and ARBs.[6] Taken together, differential expression of ACE2 in patients under specific disease states (i.e., diabetes or hypertension) or medication exposure (i.e., ACE inhibitors, ARBs) may lead to worse clinical outcomes in select groups of patients.

Several justifiable concerns have been raised regarding the quality of current evidence linking RAAS inhibitors with harm in patients with COVID-19. First, older age is one of the strongest risk factors for death in COVID-19.[3] The presence of multiple chronic conditions, such as hypertension, diabetes and heart failure (which are often managed with RAAS inhibitors), is also higher among older patients with severe illness and among those who died from COVID-19.[3] It is therefore unclear if the potential

KEY POINTS

- Recent cohort studies report that patients with coronavirus disease 2019 (COVID-19) and hypertension or diabetes have an increased risk of respiratory failure and death; such patients are often prescribed renin–angiotensin–aldosterone system (RAAS) inhibitors.
- Because severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) gains entry to human cells by using the membrane-bound angiotensin-converting enzyme 2 (ACE2) protein as a receptor and cell expression of ACE2 may be increased in patients with diabetes who are treated with ACE inhibitors and angiotensin II receptor blockers, some have wondered if RAAS inhibitors may be causing increased harm in patients with COVID-19.
- However, existing studies are likely to have been subject to selection bias, unmeasured confounding and immortal time bias, which makes it impossible to establish causation.
- Abrupt withdrawal or substitution of RAAS inhibitors may lead to worse outcomes in patients with established indications for these highly beneficial drugs.
- International cardiovascular, nephrology and diabetes societies have published concordant guidance recommending or strongly encouraging continuation of RAAS inhibitors, pending the release of high-quality evidence to better inform decisions about withdrawal or substitution of these medications during the COVID-19 pandemic.

harm with RAAS inhibitors is a result of confounding related to a failure of previous studies to account for the prevalence of comorbid conditions by age, by indication or by other unmeasured factors.[5–7] A recent retrospective cohort study of 1128 patients in hospital with COVID-19 suggests that patients who received an ACE inhibitor or ARB while in hospital had improved outcomes over those who received neither medication.[8] However, these findings are unlikely to be causal, and instead reflect selection bias, unmeasured confounding and immortal time bias.[9]

Second, there are conflicting data on the effects of RAAS inhibition on ACE2 expression and how it relates to clinical outcomes in COVID-19, including the potential for ACE inhibitors and ARBs to increase the incidence of SARS-CoV-2 infection.[6] Angiotensin-converting enzyme 2 is a counterregulatory enzyme primarily responsible for cleaving angiotensin II to angiotensin-(1–7), thereby decreasing its effects on vasoconstriction and sodium retention. However, ACE inhibitors and ARBs exert opposite effects on angiotensin II, and thus could lead to differential expression and activity of ACE2. Experimental animal data suggest that RAAS inhibition increases expression of ACE2, but there are limited data to support this in humans.[6] The physiologic relevance of ACE2 may also be tissue specific, and data on the effects of RAAS inhibition on lung ACE2 are lacking. To complicate matters further, some data suggest that ACE2 may be protective in COVID-19. After SARS-CoV-2 infection, ACE2 decreases, and unregulated angiotensin II is hypothesized to lead to tissue damage.[6] Ongoing clinical trials assessing both recombinant ACE2 and losartan as potential treatments for COVID-19 hold promise for answering these important questions.

Third, abrupt withdrawal or substitution of RAAS inhibitors may lead to worse outcomes in patients with established indications for them. High-quality evidence from multiple randomized clinical trials show clear mortality benefit for RAAS inhibitors in patients with cardiovascular disease. Evidence has also shown that interruption of therapy after myocardial infarction or withdrawal of therapy in heart failure results in clinical decompensation.[6]

It is unclear how physicians and patients are currently altering the use of RAAS inhibitors during the COVID-19 pandemic. International cardiovascular, nephrology and diabetes societies have published concordant guidance recommending or strongly encouraging continuation of RAAS inhibitors, pending the release of high-quality evidence to better inform decisions about withdrawal or substitution of these medications (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.200619/-/DC1).[10] Renin–angiotensin–aldosterone system inhibitors are widely used and have established survival benefit in select groups of patients.[6] On balance, the totality of current clinical and experimental evidence for RAAS inhibitors to facilitate infection by SARS-CoV-2 or increase the risk of harm in patients with COVID-19 is insufficient to suggest altering current use.

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Affiliations: Department of Medicine (Quinn, Fralick, Zipursky, Stall), University of Toronto; Division of General Internal Medicine and Geriatrics (Quinn, Fralick, Stall), Sinai Health System; Institute of Health Policy, Management and Evaluation (Quinn, Zipursky, Stall), University of Toronto; Division of Clinical Pharmacology and Toxicology (Zipursky), Sunnybrook Health Sciences Centre, Toronto, Ont.

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Correspondence to: Kieran Quinn, kieran.quinn@sinaihealth.ca