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Journal News and Commentary

Use of Renin-Angiotensin System Blockers During the COVID-19 Pandemic: Early Guidance and Evolving Evidence

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The COVID-19 pandemic invoked the need for prompt guidance and rapid research to address emerging clinical questions. In response to early theoretical concerns regarding the use of renin-angiotensin system (RAS) blockers, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and angiotensin receptor–neprilysin inhibitors (ARNIs) during the COVID-19 pandemic, the Canadian Cardiovascular Society (CCS) and Canadian Heart Failure Society (CHFS) issued guidance to continue these therapies among patients with heart failure and hypertension.[1] This advice was consistent with statements from other organisations, including the American Heart Association, American College of Cardiology, Heart Failure Society of America, and European Society of Cardiology.[2] The CCS COVID-19 Rapid Response Team subsequently updated and expanded these recommendations (https://www.ccs.ca/images/Images_2020/CCS_CHFS_Update_COVID__CV_medications_Mar20.pdf).

These preliminary consensus-based recommendations were developed by balancing the known benefits of RAS blockers on morbidity and mortality in patients with cardiovascular disease (and the potential harm of withdrawing therapy) against the absence of clinical evidence of harm at that time. In the present article, we provide an expanded discussion of the emerging evidence regarding RAS blocker use in the COVID-19 pandemic.

Competing Hypotheses: Are RAS Blockers Beneficial or Harmful?

Several competing mechanisms have been postulated based on preclinical studies that suggest the potential for either benefit or harm from RAS blockers in COVID-19.[2,3] The initial concerns that prompted the CCS/CHFS guidance stemmed from the hypothesis that these medications may up-regulate ACE2, which is used by SARS-CoV-2 as an entry portal into pneumocytes and other cells. Theoretically, RAS blockers could increase both vulnerability for COVID-19 infection and illness severity. Conversely, other mechanisms have been proposed by which RAS blockers may be beneficial, including reducing angiotensin II–mediated lung injury and cytokine release via ACE2 up-regulation, and even decreasing viral entry by formation of complexes between angiotensin II type 1 receptors and membrane-bound ACE2. Based on these

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hypotheses, RAS blockers could "restore the balance" and improve outcomes in patients with COVID-19. All of these hypotheses are plagued by the absence of any study data definitively demonstrating that RAS blockers meaningfully affect ACE2 activity in humans.

The Evidence We Have: Observational Studies

At least 18 observational studies addressing RAS blockers in COVID-19 have been reported as of May 23, 2020.[2-5] Most, but not all, analyses provide reassuring evidence in support of the CCS/CHFS guidance. Eight of these studies, including patients from various countries, used strategies to mitigate the potential confounding and bias inherent to observational studies, including multivariable-adjusted case-control studies and cohort studies implementing propensity score matching or overlap-weighting (see Supplemental Table S1 for citations and further details). Among the general population, 3 studies consistently found no association between previous use of RAS blockers and the risk of testing positive for COVID-19,[3] and 1 study did not find an association between RAS blocker use and COVID-19 hospitalisation.[4] Findings have been less consistent among studies evaluating the risk of complications in patients with confirmed COVID-19: RAS blockers were associated with lower or neutral risk of death or intensive care admission in all but 1 study, which found them to be associated with a higher risk of hospitalisation and intensive care admission.[5]

Although most of these studies provide reassuring results, the inconsistency in findings between them and important methodologic limitations decrease the certainty of evidence. The method for ascertaining medication exposure in most studies resulted in a high risk of misclassification bias, with exposure definitions ranging from outpatient pharmacy fills before the pandemic, previous documentation in the electronic medical record, and use recorded on admission or throughout hospitalisation for COVID-19. This bias risks distorting or even obscuring any association, whether beneficial or harmful, between RAS blockers and COVID-19 outcomes. However, 1 study minimised this bias by defining exposure based on outpatient prescription fills with sufficient supply, compared with non-RAS antihypertensives, and found no association between RAS blocker use and COVID-19 hospitalisation.[4]

Further sources of bias include potential selection bias relating to both RAS blocker use and COVID-19 testing, particularly in centres where testing capacity was limited during the study period and directed at vulnerable patients.[5] Finally, studies that defined RAS blocker exposure based on use in hospital suffer from immortal-time bias, because patients classified in the RAS blocker group, by definition, had to survive long enough to be prescribed a RAS blocker in hospital. It is notable that one study that suggested a beneficial association between RAS blocker use and COVID-19 outcomes had the highest risk of this bias (reference 3 in Supplemental Table S1). Finally, one high-profile study that had suggested benefit from ACE inhibitors has been retracted due to concerns of data fabrication (references 10-12 in Supplemental Table S1).

The Evidence We Need: Randomised Controlled Trials

As of May 21, 2020, 20 randomised controlled trials (RCTs) evaluating RAS blockers in COVID-19 (total target of ~24,666 patients) have been registered at ClinicalTrials.gov (Supplemental Table S2). Many of these trials are already underway and are expected to be completed in late 2020 to early 2021. The trials registered to date have key differences that may offer important insights on this clinical question.

First, 19 of them are evaluating whether RAS blockers modulate disease severity in patients with confirmed SARS-CoV-2 infection (mostly hospitalised in a noncritical care setting at baseline), with primary outcomes ranging from death, hospitalisation, and composite measures of organ dysfunction and severity. Conversely, the CORONACION trial (NCT04330300) is enrolling patients without COVID-19 infection at baseline to evaluate whether continuing RAS blockers for hypertension vs switching to an alternate antihypertensive agent for up to 12 months affects downstream risk of COVID-19 infection and related morbidity and mortality. In this respect, CORONACION will be the only trial testing whether RAS blockers predispose patients to a higher risk of COVID-19 infection.

Second, the trials differ subtly in terms of the tested intervention. Some trials are evaluating *de novo* ACEI or ARB initiation vs placebo in patients without heart failure or other indications for RAS blockers, thus directly testing whether short-term use of RAS blockers is beneficial in the management of COVID-19. Other studies aim to compare discontinuation vs continuation of established RAS blocker therapy among patients already receiving these medications for a chronic indication. These will provide definitive evidence regarding the net effect of continuing these therapies in patients with an indication for RAS blocker use and established COVID-19 infection. Notably, none of these trials is evaluating ARNI use.

Third, trials are testing a range of agents and doses (eg, 2.5 mg ramipril orally once daily, 160 mg valsartan orally twice daily, captopril administered by nebulizer) for durations of 5-30 days, which will allow for the exploration of class effects and dose-response relationships. Finally, although randomisation eliminates most biases present in the published observational studies, 6 trials blinding participants and outcome assessors and 2 open-label RCTs focusing on all-cause death will provide particularly robust evidence regarding the potential efficacy and safety of RAS blockers in patients with SARS-CoV-2 infection.

Conclusion

RAS blockers are pillars of the cardiovascular pharmacologic armamentarium based on substantial RCT evidence of cardiovascular benefit. Evidence addressing their use during the COVID-19 pandemic is rapidly evolving. As we await definitive RCT evidence in COVID-19, the CCS/CHFS guidance remains to continue RAS blockers regardless of SARS-CoV-2 infection, as supported by the majority of available observational studies.

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References

1. CCS COVID-19 Rapid Response Team. COVID-19 and use of ACEi/ARB/ARNi medications for heart failure or hypertension. March 15, 2020. Available at: http://www.ccs.ca/images/Images_2020/CCS_CHFS_statement_regarding_COVID_EN.pdf. Accessed May 20, 2020.

2. Sparks M, Hiremath S, et al. ACE2 and Hypertension. NephJC. Available at: http://www.nephjc.com/news/covidace2. Accessed May 20, 2020.

3. 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: a living systematic review [e-pub before print]. Ann Intern Med https://doi.org/10.7326/M20-1515.

4. de Abajo FJ, Rodríguez-Martín S, Lerma V, et al. Use of renin-angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. Lancet 2020;395:1705-14.

5. Mehta N, Kalra A, Nowacki AS, et al. Association of use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with testing positive for coronavirus disease 2019 (COVID-19) [e-pub before print]. JAMA Cardiol https://doi.org/10.1001/jamacardio.2020.1855.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2020.05.033.