Can Renin-Angiotensin System Inhibitors Protect Against Acute Kidney Injury in Patients With COVID-19?

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We compliment Rocheleau et al (1) for reporting their meticulously planned prospective observational study, which investigated the sex-based differences in the clinical outcomes with the preadmission use of renin-angiotensin system (RAS) inhibitors (angiotensin II receptor blockers [ARBs] or angiotensin-converting enzyme (ACE) inhibitors) in hospitalized patients with coronavirus disease 2019 (COVID-19). We believe the findings of the prospective study are novel, which to the best of our knowledge is the first study in the existing literature that reported the differential effect of sex on clinical outcomes with the use of RAS inhibitors in patients with COVID-19. Indeed, the findings highlighted by the authors are interesting: preadmission use of ARBs in male patients was significantly associated with decreased odds for the requirement of ventilation (adjusted odds ratio, 0.52; 95% CI, 0.32–0.83) as well as decreased odds for the requirement of vasopressors (adjusted odds ratio, 0.55; 95% CI, 0.34–0.87), relative to their counterparts with nonuse of RAS inhibitors before admission (1).

Nevertheless, another interesting finding in the study caught our attention, where preadmission use of RAS inhibitors (ARBs or ACE inhibitors) in male patients was significantly associated with decreased odds for the requirement of renal replacement therapy (adjusted odds ratio, 0.52; 95% CI, 0.28–0.97), relative to their counterparts with nonuse of RAS inhibitors before admission; the finding was not discussed by the authors (1). We opine that such a finding also deserves attention since it suggests the protective effects of RAS inhibitors against the development of acute kidney injury and the subsequent requirement of renal replacement therapy, particularly in male patients with COVID-19.

The occurrence of acute kidney injury in patients with COVID-19, especially with the requirement of renal replacement therapy, was associated with a high mortality rate (2). However, other than the use of interleukin (IL)-6 inhibitors, which have previously been reported in a meta-analysis (3) performed by The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group to significantly reduce the odds of progression to kidney replacement therapy or death (pooled odds ratio, 0.79; 95% CI, 0.71–0.88) in patients with COVID-19, no treatment has been associated with kidney-related benefits in patients with COVID-19 in the randomized trials. Therefore, pharmacological therapy to prevent the development of acute kidney injury and its associated complications is still an unmet need, but the finding by Rocheleau et al (1) has provided a rationale to trial the use of RAS inhibitors in patients with COVID-19 to prevent kidney-related complications.

Potential explanations for the kidney-related benefits of RAS inhibitors include the ability of ARBs to compete with SARS-CoV-2 for the binding to the ACE2 receptors found in proximal tubular cells (4). In addition, the

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increased production of angiotensin II seems to drive the occurrence of kidney injury, and RAS inhibitors could block the physiologic effect of angiotensin II (5). Therefore, we urge the performance of clinical trials to investigate the potential protective effects of RAS inhibitors against the development of acute kidney injury in patients with COVID-19.

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We thank Kow et al (1) for their suggestion of the value of our finding that use of angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEis) was associated with significantly improved renal outcomes in males with acute COVID-19 in our observational cohort study (2). Our renal-related findings were only marginally significant and were part of multiple tests of significance so must be interpreted cautiously.

The overall effect of ARBs on risk of acute kidney injury (AKI) in acute COVID-19 is uncertain, and meta-analysis suggests ARBs could "increase" the risk of AKI in acute COVID-19 (3).

It is well recognized that males have increased risk of severe COVID-19—including AKI in COVID-19—but the therapeutic implications were unknown. Accordingly, our overarching aim was to examine sex determinants of responses to ARBs and ACEis in acute COVID-19. Mechanisms of preferential ARBs' efficacy for AKI in males in acute COVID-19 could include greater renal injury in males due to direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced renal injury, lymphocyte infiltration, diffuse proximal tubule injury, and acute tubular necrosis (4, 5). Postmortem renal tissue of COVID-19 patients with AKI shows viral particles in the kidney and SARS-CoV-2 nucleoprotein antigen accumulation in renal tubules (4, 5). There is a potential causal role for shock (cardiogenic, obstructive due to pulmonary emboli, or distributive shock) in acute COVID-19-induced AKI; consequent use of vasopressors could also contribute to AKI.

To link this with males, we note that males have higher risks of complications of acute COVID-19 such as shock and that may have contributed to their increased risk of AKI and better renal responses to ARBs. Angiotensin-converting enzyme 2 (ACE2) is on the X chromosome, expressed differentially (lower in males) in renal vasculature (6), rising plasma levels predict shock (7), and ACE2 genetic variants portend worse COVID-19 severity on males (8).

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