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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The authors reply:

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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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Thus, ACE2 expression in males could explain more renal injury in males in acute COVID-19. We hypothesize that decreased renal ACE2 expression in males could explain more severe acute COVID-19-induced AKI and perhaps enhanced responses to ARBs.

Patients who have had AKI who survive have an increased risk of ongoing renal dysfunction, decreased recovery during outpatient follow-up, and even progression to chronic kidney disease. The dialysis rates after discharge from hospital in patients who had AKI and acute COVID-19 are 1/6 at 60 days (9). ARBs and ACEis are used in chronic kidney disease for treatment of hypertension and mitigation of progression of renal dysfunction. It is unknown to date whether use of ARBs and ACEis in acute COVID-19 survivors modifies the prognosis of AKI recovery. Furthermore, the role of sex determinants in AKI recovery and response to ARBs and ACEis after discharge is also unknown.

Observational studies such as ours (2) are essentially hypothesis-generating. The strongest evidence will come from randomized controlled trials of ARBs in acute COVID-19 that we and others are doing that will determine safety and efficacy of ARBs for mortality and organ dysfunction including renal injury. To date, none of the few published RCTs (10–15) report differential sex effects of ARBs in acute COVID-19.

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