COMMENTARY

THE AMERICAN JOURNAL of MEDICINE®

Stopping RAS Inhibitors in Advanced Chronic Kidney Disease and Cardiorenal Outcomes—Several Unanswered Questions Remain

We read with fascination the recent Swedish study of cardiorenal outcomes after stopping renin-angiotensin system inhibitors (RASi) in 10,524 prevalent RASi users with advanced chronic kidney disease.[1] Compared with continuing RASi, stopping RASi was associated with a higher absolute 5-year risk of death and major adverse cardiovascular events, but with a lower risk of kidney replacement therapy.[1]

We were the first to report a large prospective nonrandomized study of RASi withdrawal in progressive chronic kidney disease at the Mayo Clinic Health System in Northwestern Wisconsin.[2,3] This single-center experience of discontinuing RASi in chronic kidney disease patients with recent >25% increase in baseline serum creatinine demonstrated clearly improved renal outcomes without increased cardiovascular mortality.[2,3] Coincidentally, another recent *Journal of the American Society of Nephrology* report on 2738 patients with moderate to severe chronic kidney disease, participants in the CRIC Study, demonstrated that slower estimated glomerular filtration rate declines, or indeed, improved estimated glomerular filtration rate over time, were associated with lower risks of death and cardiovascular events.[4] Furthermore, in a just-published Canadian population-based retrospective cohort study of RASi discontinuation in 49,571 older adults who developed hyperkalemia, RASi discontinuation was not associated with a higher risk of 1-year cardiovascular events (hazard ratio 0.96; 95% confidence interval, 0.91-1.02) or all-cause mortality (hazard ratio 1.05; 95% confidence interval, 0.96-1.15), compared with no intervention.[5]

The Swedish authors rightly acknowledged that, despite their sophisticated analytical design and very large population studied, residual confounding cannot be excluded.[1] Most importantly, and again acknowledged by the authors, the precise reasons for stopping RASi remain unknown and may have impacted study outcomes.[1] The unknown interplay of residual confounding remains the Achilles' heel of the Swedish report. Besides, the likely very huge impacts of ecological fallacy on the findings of this study remain unresolved.

We remain optimistic that the ongoing European STOP-ACEi Trial (trial registration: current controlled trials, ISRCTN62869767), an investigator-led, multicenter, open-label randomized controlled trial of 410 participants with advanced (Stage 4 or 5) progressive chronic kidney disease receiving angiotensin-converting enzyme inhibitor, angiotensin receptor blockers, or both, due to be completed in 2022, would shed further light on these vexing questions.

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Funding: None.
Conflicts of Interest: None.
Authorship: The author had access to all the data and completed the design, production, and approval of the manuscript.

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https://doi.org/10.1016/j.amjmed.2021.03.031