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Discontinuation of renin–angiotensin system inhibitors brings no benefits in severe chronic kidney disease

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Comment on 'Renin–Angiotensin System Inhibition in Advanced Chronic Kidney Disease', which was published in the *New England Journal of Medicine*, https://doi.org/10.1056/NEJMoa2210639.

Key Points

- The STOP ACEi[1] is a multi-centre, open-label, randomized trial funded by the United Kingdom National Institute for Health Research and Medical Research Council, which assessed whether the discontinuation of renin–angiotensin system (RAS) inhibitors would increase or stabilize the estimated glomerular filtration rate (eGFR) in patients with progressive stage 4 or 5 chronic kidney disease (CKD) with eGFR < 30 mL/min/1.73 m^2 of body-surface area.
- Adults aged >18 years were eligible if they were not receiving dialysis and had not undergone kidney transplantation, if they had a decrease of >2 mL/min/1.73 m^2 per year in the eGFR during the previous 2 years and if they were receiving treatment with an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin receptor blocker (ARB), or both for more than 6 months. Exclusion criteria included uncontrolled hypertension or a history of myocardial infarction or stroke within the previous 3 months. Patients were randomly assigned in a 1:1 ratio either to discontinue or to continue RAS inhibitors.
- The primary outcome was the eGFR at 3 years calculated according to the Modification of Diet in Renal Disease (MDRD) study, as updated in 2005 (MDRD175).
- Secondary outcomes included the time until the development of end-stage kidney disease (ESKD); a composite of a decrease of >50% in the eGFR, the development of ESKD, or the initiation of renal replacement therapy; hospitalization for any cause; measures of cystatin C and blood pressure (BP); quality of life; and exercise capacity assessed by the 6-min walk test; cardiovascular events and death.
- The study randomized a total of 411 patients (206 in the discontinuation group and 205 in the continuation group) with a median age of 63 years and a greater proportion of male (68%) and white (85%) subjects. The median eGFR at baseline was 18 mL/min/1.73 m^2 and ~30% of patients had eGFR < 15 mL/min/1.73 m^2.
- At 3-year follow-up, eGFR was 12.6 mL/min/1.73 m^2 in the discontinuation group and 13.3 mL/min/1.73 m^2 in the continuation group with a non-significant difference of .7 mL/min/1.73 m^2 [95% confidence interval (CI), −2.5 to 1.0; $P = .42$). ESKD or renal replacement therapy occurred in 128 patients (62%) in the discontinuation group and in 115 (56%) in the continuation group (adjusted hazard ratio, 1.28; 95% CI, .99–1.65). The proportion of patients who underwent renal replacement therapy or had a decrease of >50% in the eGFR was 68% in the discontinuation group and 63% in the continuation group (adjusted relative risk RR, 1.07; 95% CI, .94–1.22). There were no significant differences between the discontinuation and continuation groups in the numbers of hospitalizations for any reason (414 vs. 413), cardiovascular events (108 vs. 88), and death (20 vs. 22). The numbers of serious adverse cardiovascular, vascular, and heart failure events were also similar in the two groups.

Comment

A large body of evidence has demonstrated that RAS inhibitors have beneficial effects in patients at risk of developing CKD, such as those with hypertension and diabetes, slowing the progression of renal disease and the reduction of eGFR.[2] Consistently, guidelines from the Kidney Disease: Improving Global Outcomes Work Group recommend the prescription of ACE inhibitors and ARBs in hypertensive patients with and without diabetes and urine protein excretion > 300 mg/day and suggest these pharmacological classes as the first-line strategy in patients

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with non-dialysis-dependent diabetic CKD and urine albumin excretion of 30–300 mg/day, even in the absence of high BP.[3]

However, most clinical trials excluded participants with eGFR < 30 mL/min/1.73 m^2, generating a lack of evidence-based recommendations about the initiation and continuation of these drugs in an important subset of advanced renal disease, with no indication of eGFR threshold(s) below which the discontinuation of RAS inhibitors is required or treatment initiation is contraindicated. Controversial findings, mostly from observational studies, have been produced in the last decades raising a warning on RAS inhibitors potentially compromising the residual kidney function and accelerating eGFR reduction in patients with CKD. A small observational study demonstrated that in subjects with advanced CKD who were treated with RAS inhibitors, the withdrawal of this treatment was associated with a slowing of eGFR decline.[4] In another observational study, patients with advanced CKD treated with ACE inhibitors or ARBs had a 25% increase in serum creatinine levels whereas those who discontinued RAS inhibitors experienced an improvement in kidney function.[5] The analysis of a large observational registry also suggested that the discontinuation of RAS inhibitors may reduce the risk of progression to ESKD.[6] As a result of these reports, physicians are often reluctant about the use of RAS inhibitors in patients with advanced chronic CKD, even when these compounds would be recommended for other concomitant indications, such as resistant hypertension, diabetes, heart failure, or post-myocardial infarction left ventricular dysfunction.

The STOP ACEi study has addressed these uncertainties with a randomized design but failed to show any advantage of discontinuing RAS inhibitors. In fact, the incidence of ESKD or renal replacement therapy and cardiovascular events trended in favour of the continuation of RAS inhibitors. However, several limitations of the study deserve to be outlined. First, the role of concomitant antihypertensive medications at baseline and during the follow-up period was not investigated, even though most patients (58%) were taking three or more antihypertensive drugs. The observation that at 1-year BP and proteinuria were higher in the discontinuation group, and thereafter, these differences faded, suggests that other antihypertensive agents were initiated in the discontinuation group. Second, in both groups, a small proportion of participants had previous major cardiovascular events, such as heart failure (1.5%), myocardial infarction (9%) and stroke (6%), or concomitant atrial fibrillation (4%) and peripheral vascular disease (5%). These percentages are not only lower than expected in a high-risk population, such as that with severe renal disease, but also preclude any extension of the current findings to patients with cardiovascular disease who might benefit from the use of RAS inhibitors. Third, the study population was composed by a large proportion of White male subjects; thus, the results cannot be extrapolated to other ethnic groups. Fourth, the trial had an open-label design, and this might have influenced the antihypertensive management and the evaluation of quality-of-life and functional endpoints. Fifth, the follow-up duration was relatively short, and the study was not powered to assess the potential benefits of the continuation of RAS inhibitors on cardiovascular events and death. Finally, the results cannot be generalized to patients with higher levels of proteinuria (e.g. urinary protein/creatinine ratio > 2655 mg/g), a key marker of CKD progression.[7]

Within the limitations outlined above, the STOP ACEi trial clearly showed that stopping RAS inhibitors brings no detectable benefits in severe CKD and may actually be associated with adverse effects that outweigh the risks of continuing the medication in many patients. This aspect may deserve further investigation especially in view of the clinical importance of RAS inhibitors in patients with concomitant cardiovascular diseases, such as ischaemic heart disease and heart failure.

Declarations

Disclosure of Interest

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