There is an unmet need for understanding the pathogenesis of progressive cardiac and kidney disease, calling for improved diagnostic, therapeutic, and preventive strategies in CKD. Clinical trials have demonstrated the cardiovascular and renal benefits of using renin-angiotensin system (RAS) blockers in the CKD population. The long-term beneficial effects of RAS blockers are variable, with their heterogeneity potentially linked to the causes for renal and cardiovascular disease. RAS blockers reduce plasma aldosterone levels in the initial treatment phase, but aldosterone levels may later reach or sometimes exceed pretreatment values. This phenomenon is known as aldosterone breakthrough and may limit the beneficial effects of RAS blockers and call for newer therapeutic targets.

In this issue of *CJASN*, Moranne et al. examined the incidence of aldosterone breakthrough and the factors associated with its development among patients with type II diabetes and overt nephropathy (urine albumin/creatinine ratio ≥700 mg/g) who were taking angiotensin receptor blockers (ARBs) (1). They conducted a secondary analysis of the AMADEO study, a 52-week, multicenter, randomized, double-blind clinical trial that compared the effects of losartan (ARB with short half-life) versus telmisartan (ARB with long half-life) on urinary albumin excretion (2). Results of the parent study showed that telmisartan was superior to losartan in reducing proteinuria in the study population despite a similar reduction in BP. For this post hoc analysis, serum aldosterone was measured from stored samples at baseline, 6 months, and 12 months using a RIA kit. The mean baseline serum aldosterone level was 8.4±2.1 ng/dl. Aldosterone breakthrough was defined as an increase of serum aldosterone levels >10% over baseline values (to account for assay variability) at follow-up after 6 and 12 months. The incidence of aldosterone breakthrough was 28% at 1 year, with 57% of participants taking losartan and 43% taking telmisartan. In the multivariate analysis, several factors were associated with aldosterone breakthrough at the 1 year follow-up. These include the following: (1) lower serum aldosterone and potassium levels (possibly due to the use of diuretics) at baseline, (2) greater decrease in systolic BP, sodium intake, and estimated GFR (eGFR) during treatment, (3) use of losartan versus telmisartan, and (4) an increase in serum potassium during the treatment period. In addition, the aldosterone breakthrough noted at 6 months did not predict the change in kidney function measures at 1 year (decline in eGFR or increase in albuminuria).

Why is it important to study the aldosterone breakthrough? Traditionally, aldosterone is known to have direct independent effects on sodium, potassium, and extracellular fluid volume regulation by binding to the mineralocorticoid receptor in the distal convoluted tubule (genomic effects) (3). However, in the past few decades, several experimental and human studies have suggested that aldosterone might contribute directly to initiation and progression of renal injury through multiple mechanisms (nongenomic effects) (4). High aldosterone levels activate proinflammatory and profibrotic pathways and induce endothelial dysfunction with resultant renal hypertension, glomerulosclerosis, tubulointerstitial fibrosis, and vascular remodeling (5,6). Local aldosterone levels increase after myocardial infarction, which contributes to cardiac fibrosis, ventricular hypertrophy, and eventual heart failure (7). Both animal and human studies have shown improved cardiac structure and function with the use of aldosterone antagonists (8). Subsequently, larger clinical trials in patients with congestive heart failure have demonstrated the survival benefit associated with the use of both selective (eplerenone) and nonselective aldosterone antagonists (spironolactone) despite the increased risk for hyperkalemia (9–11). Therefore, understanding the magnitude of the problem (aldosterone breakthrough) and the predictive factors would help us identify the target CKD population for further interventions.

What does this study add to the existing literature? Previous studies reported an aldosterone breakthrough incidence rate of 10%–53% using various definitions in patients with and without diabetes who were taking an angiotensin-converting enzyme inhibitor (ACEI) or an ARB (12). The aldosterone breakthrough rate was similar to that observed with the combined use of ACEIs and ARBs compared with either agent alone (13). Most of these single-center studies had a small sample size, had a shorter follow-up (often <6 months), and did not have sufficient power to explore the factors associated with the development of aldosterone breakthrough. Few studies have linked the aldosterone breakthrough to accelerated decline in eGFR compared with those...
who did not experience breakthrough (14). Because it is a multicenter randomized controlled trial, the study by Moranne et al. provides more generalizable data at 1-year follow-up. It also points out the population that should be monitored closely for aldosterone breakthrough because they might warrant additional treatment to enhance aldosterone suppression that might further reduce urinary protein excretion. In addition, they measured levels at follow-up at 6 months and 1 year, which informs us that an increase in aldosterone levels at 6 months might not be long lasting. The factors identified to predict higher plasma aldosterone levels at 1 year, particularly an increase in serum potassium levels due to the use of ARBs, lower sodium intake, and decline in eGFR, are known drivers of aldosterone secretion. These results confirm the known physiologic relationships and suggest that clinicians might monitor these parameters to assess who might develop aldosterone breakthrough while taking ARB therapy.

Although this study advances our understanding of aldosterone breakthrough, it has limitations and leaves questions unanswered that might temper our enthusiasm. Because serum aldosterone levels might increase in the setting of declining kidney function, availability of 24-hour urinary aldosterone excretion data would have helped us clarify whether the observed increase in serum aldosterone levels is related to decreased degradation versus increased production in the setting of ARB use. The authors also noted that the aldosterone breakthrough at 6 months was not associated with decline in renal function and albuminuria at 1-year follow-up. These results are not surprising and should be interpreted with caution because the follow-up may have been too short to see any clinically meaningful results. Furthermore, the baseline aldosterone level (geometric mean) was 8 ng/dl and the increase among those who had a >10% increase in aldosterone level was 6 ng/dl. It is important to highlight that no standard definition exists for aldosterone breakthrough and whether there is a graded increase in the risk for adverse outcomes with increasing aldosterone levels is unknown. Because only 9% of study participants were African American, these results might not be applicable to this subset, which is at higher risk for kidney disease progression. The serum aldosterone level was used from stored samples in this analysis and the influence of storage on serum aldosterone levels is unclear. More importantly, the fundamental question relating to whether the aldosterone breakthrough noted at 1-year follow-up had long-term implications remains unanswered. This is worth studying given recent data showing that fluctuations within the normal range of aldosterone levels might be associated with increased risk for adverse cardiac events in those without kidney disease (15).

Should we add aldosterone antagonists to the treatment of those patients who are taking RAS blockers? Few clinical trials have evaluated the effects of selective and nonselective aldosterone antagonists on albuminuria in patients with CKD (16–18). Predominantly, most studies included patients with diabetic nephropathy and used urinary albumin excretion as their primary end point. A recent systematic review evaluated the benefits and harms of treating CKD patients with selective and nonselective aldosterone antagonists who were already receiving RAS blockers (19). An ACEI and/or ARB plus spironolactone significantly reduced 24-hour proteinuria compared with an ACEI and/or ARB plus placebo (mean difference −0.80 g; 95% confidence interval [95% CI], −1.23 to −0.38). Both systolic and diastolic BP significantly decreased in patients treated with an ACEI and/or ARB plus spironolactone suggesting that the benefit noted with a reduction in proteinuria might be related to the improvement in BP. Subsequently, Mehdi et al. evaluated the BP-independent effects of spironolactone on urinary albumin excretion (20). This study confirmed the antiproteinuric effects of spironolactone on those patients taking an ACEI, with both groups exhibiting similar BP. None of the published studies was powered to detect a significant improvement in eGFR or creatinine clearance and as such, both the summary estimate from the meta-analysis and the trial by Mehdi et al. did not report improvement in kidney function with the addition of spironolactone. In the pooled analysis, there was a 3-fold increased risk of hyperkalemia (relative risk, 3.06; 95% CI, 1.26 to 7.41) with the addition of aldosterone antagonists to RAS blockers (19). Similarly, Mehdi et al. reported occurrence of hyperkalemic events (serum potassium ≥6.0 mEq/L) in 14 of 27 participants who were taking spironolactone (versus 2 of 27 in placebo group) and remind us “Primum non nocere” (20).

In summary, this commendable effort by Moranne et al. suggests that aldosterone breakthrough is a common occurrence among patients with type II diabetes who are taking both short- and long-acting ARBs. Certain clinical and laboratory parameters could be monitored to predict an increase in aldosterone levels of patients who are taking ARB therapy. However, the long-term data relating this breakthrough to adverse outcomes such as cardiac and kidney disease progression in the CKD population have not been demonstrated. Although some preliminary data suggest that aldosterone blockade might offer cardiac benefits in early stage CKD, clinical trials examining the long-term effects of aldosterone antagonists on cardiac and renal end points are lacking (21). With several questions remaining unanswered, this topic serves as a fertile source for future clinical research.

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