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Finerenone — Halting Relative Hyperaldosteronism in Chronic Kidney Disease

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Type 2 diabetes is the most common cause of chronic kidney disease (CKD) and end-stage renal disease. Cardiovascular risk and the risk of progression of kidney disease are very high among patients with diabetes mellitus, particularly among those with CKD. Clinical strategies to prevent cardiovascular disease and the development of new diabetic kidney disease or to slow the progression of CKD that is already present have been incorporated into clinical practice for the past three decades and include angiotensin-converting–enzyme inhibitors, angiotensin-receptor blockers and, more recently, sodium–glucose cotransporter 2 (SGLT2) inhibitors (gliflozins), such as dapagliflozin and empagliflozin. However, few of the other drug classes studied have ultimately proved renoprotective — witness, for example, the ultimately disappointing clinical trial experience with bardoxolone,[1] aliskiren,[2] and the erythrocyte stimulatory agent darbepoetin.[3]

Aldosterone, a mineralocorticoid hormone, is a downstream target of activation of the renin–angiotensin system (RAS) (reviewed in Barrera-Chimal et al.[4] with respect to CKD). Angiotensin II, corticotropin, and potassium are considered the main drivers of aldosterone release from the adrenal zona glomerulosa. However, other factors such as nitric oxide, endothelin, and a variety of pituitary and adipose-tissue factors can stimulate aldosterone synthesis. Once released, aldosterone binds to the mineralocorticoid receptor, leading to sodium retention and potassium loss, thereby controlling fluid and electrolyte status as well as blood pressure. Furthermore, the mineralocorticoid receptor also functions as a transcription factor that can increase the levels of inflammatory cytokines as well as genes targeting water resorption.[4] The mineralocorticoid receptor is present in the distal tubule of the kidney and also within glomeruli on podocytes and mesangial cells. Mild hyperaldosteronism, which occurs in patients with CKD, can also mediate inflammation through the mineralocorticoid receptor, increasing local levels of reactive oxygen species and profibrotic factors. Thus, high levels of aldosterone and its receptor may affect multiple kidney compartments.

Strategies to decrease aldosterone activation make sense, and drugs that interfere with the binding of aldosterone to its receptor have been used in a number of clinical conditions, particularly cardiovascular disease, for several decades. Spironolactone, first synthesized in 1957, is a steroidal, nonselective inhibitor of the mineralocorticoid receptor that is still widely used. The steroidal, selective inhibitor eplerenone has been available since the 1980s. Both of these steroidal mineralocorticoid receptor antagonists may lead to hyperkalemia in a high proportion of patients and have other unwelcome side effects, such as

gynecomastia, erectile dysfunction, and dysmenorrhea. Furthermore, steroidal mineralocorticoid receptor antagonists may decrease the glomerular filtration rate (GFR). In contrast, the dihydropyridine finerenone is a selective inhibitor, as are apararenone and esaxerenone, and less often cause hyperkalemia.

The use of mineralocorticoid receptor antagonists to affect CKD is a relatively recent concept.[4] In CKD, aldosterone levels are inversely proportional to the GFR and are also associated with inflammation. Although the evidence that antagonizing the mineralocorticoid receptor is beneficial in patients with cardiovascular disease has been known, evidence that such therapy helps in patients with CKD is less robust. In a 2008 meta-analysis, Bomback et al. observed that the use of mineralocorticoid blockers decreased proteinuria without resulting in hyperkalemia or decreasing the GFR.[5] A recent small, randomized, controlled trial by Minakuchi et al. compared eplerenone with placebo in patients with CKD and observed a benefit in terms of progression.[6] The phase 2b Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy, which compared finerenone with placebo in patients with type 2 diabetes and CKD, showed an improved urinary albumin-to-creatinine ratio (primary outcome).[7] Phase 3 trials have been widely anticipated.

Bakris et al. now report in the *Journal* the results of the phase 3 Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial.[8] They found a benefit of finerenone as compared with placebo with respect to CKD progression among patients with relatively advanced CKD and type 2 diabetes and thus for persons at high risk for kidney-related (and heart-related) events. A cardiovascular benefit was evident early (as soon as a month) and continued; the kidney-related benefit was seen after 1 year. However, the apparent benefit with respect to CKD progression was less than that reported with canagliflozin in the recent Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial.[9] One explanation for the different findings in the two trials, as noted by Bakris et al., is the fact that SGLT2 inhibitors were allowed in the present trial, whereas patients treated with mineralocorticoid receptor antagonists were excluded from the CREDENCE trial.

Data from laboratory models indicate that finerenone decreases inflammation and fibrosis, probably by reducing the activity of the mineralocorticoid receptor.[10] Although the present trial does not add mechanistic data, the concept seems apt, and the authors speculate that tissue remodeling may explain the results. Phase 3 trials of the other dihydropyridine mineralocorticoid receptor antagonists are awaited. In addition, trials that are longer term than the FIDELIO-DKD trial will be important. That being said, a way to decrease the relative hyperaldosteronism in patients with CKD seems a promising strategy.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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