How to Cite this article: Jasleen Ghuman and Katherine Tuttle, A perspective on nonsteroidal mineralocorticoid receptor antagonism in diabetic kidney disease, Kidney360, Publish Ahead of Print, 10.34067/KID.0007072021

Article Type: Perspective

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DOI: 10.34067/KID.0007072021

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Key Points:

Abstract:

Disclosures: J. Ghuman has nothing to disclose. K. Tuttle reports the following: Current Employer: Providence Health Care, University of Washington; Consultancy Agreements: Eli Lilly; Boehringer Ingelheim; Gilead; Astra Zeneca; Goldfinch Bio, Novo Nordisk, Bayer; Research Funding: Goldfinch Bio; Bayer; Honoraria: Gilead, Goldfinch Bio, Bayer; and Scientific Advisor or Membership: CJASN, Lancet Diabetes Endocrinology, Nature Reviews Nephrology, NIDDK, Kidney Health Initiative.

Funding:

Author Contributions: Jasleen Ghuman: Conceptualization; Writing - original draft; Writing - review and editing Katherine Tuttle: Conceptualization; Supervision; Writing - review and editing

Data Sharing Statement:

Clinical Trials Registration:

Registration Number:

Registration Date:

The information on this cover page is based on the most recent submission data from the authors. It may vary from the final published article. Any fields remaining blank are not applicable for this manuscript.

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A perspective on nonsteroidal mineralocorticoid receptor antagonism in diabetic kidney disease

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Background:

Diabetes is the leading cause of end-stage kidney disease (ESKD) in the world. It is estimated that 30% of individuals with type 1 diabetes mellitus and 40% of individuals with type 2 diabetes mellitus (T2DM) develop kidney disease.1 Deaths related to diabetic kidney disease (DKD) are higher compared to any other type of chronic kidney disease (CKD).2 This excess mortality is mostly attributable to cardiovascular disease (CVD) and most patients with DKD will die without progression to ESKD.1 Thus, the unmet need for therapies that decrease risks of DKD is enormous.

Mechanisms of action of mineralocorticoid antagonism in the diabetic kidney:

The mechanisms by which diabetes causes kidney disease are myriad. Hemodynamic changes, metabolic disturbances, pro-inflammatory, and profibrotic processes culminate in structural changes within the kidney. Hallmarks of DKD include glomerular hypertrophy, glomerular basement membrane thickening and mesangial expansion, glomerulosclerosis, tubulo-interstitial fibrosis and inflammation, and arteriosclerosis.1 In recent years, our armamentarium to treat DKD has increased with the addition of sodium-glucose co-transporter-2 (SGLT2) inhibitors and most recently, with nonsteroidal mineralocorticoid receptor antagonist (MRA), finerenone. MRs are physiological binding sites for aldosterone, cortisol and to a lesser extent, progesterone. They are expressed in various cells of the kidney including epithelial cells of the collecting duct, podocytes, mesangial cells, tubulointerstitial fibroblasts, and macrophages (Figure). In the collecting duct, MR activation promotes sodium reuptake, potassium secretion, and fluid retention. In non-epithelial cells, the MR controls expression of many pro-inflammatory and profibrotic genes associated with DKD progression. The MR can be
inappropriately overactivated in DKD causing increased NADPH oxidase activity and upregulation of pro-inflammatory cytokines (e.g. tumor necrosis factor-α, interleukin-1β) and profibrotic proteins (e.g. connective tissue growth factor, transforming growth factor-β1, plasminogen activator inhibitor-1, matrix metalloproteinase-2). The resulting damage culminates in glomerulosclerosis and progressive tubulointerstitial injury.³

Finerenone’s binding to the MR changes its configuration such that ligands (e.g. aldosterone) are unable to bind, which prevents downstream transcription of pro-inflammatory and profibrotic factors (Figure).³ Finerenone has differential pharmacokinetics and physiological effects compared to steroidal mineralocorticoid antagonists that influence therapeutic actions for DKD as well as serum potassium. Unlike the steroidal MRAs (spironolactone and eplerenone), the nonsteroidal MRA finerenone, has higher selectivity for the MR and acts as an inverse agonist, whereas steroidal MRAs act as partial agonists. Thus, finerenone blocks activation of the receptor in the absence of a ligand with more complete disruption of recruitment of transcriptional co-factors.⁴ At comparable natriuretic doses, finerenone provides more potent inhibition of pro-inflammatory and profibrotic genes in the kidney than spironolactone or eplerenone. It also has less hyperkalemia risk. Effects that favor less hyperkalemia with finerenone include its shorter half-life, absence of active metabolites, a balanced distribution of MR selectivity between kidney and heart, and less epithelial sodium channel (ENaC) upregulation.⁵ Furthermore, unlike steroidal MRAs, finerenone also binds to mutant MR S180L, a receptor that is paradoxically activated by progesterone, which is usually an MR antagonist, leading to either gestational hypertension or worsening hypertension during pregnancy. This unique property, suggests its potential use in this condition.⁵
Clinical Evidence:

To-date, there are two notable trials for nonsteroidal MRAs. The Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial evaluated finerenone’s role in slowing CKD progression and reducing cardiovascular mortality in patients with T2DM and CKD (n = 5674) on the background of treatment with an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB). The participants had a mean (SD) estimated glomerular filtration rate (eGFR) of 44.3 (12.6) mL/min/1.73m$^2$ and median (IQR) urine albumin creatine ratio (UACR) of 852 (446-1634) mg/g. There was an 18% reduction in the primary kidney disease outcome (≥40% decrease in eGFR, kidney failure, or death from kidney causes). Additionally, there was a 14% reduction in the secondary CV outcome (death from CV causes, nonfatal myocardial infarction (MI), nonfatal stroke or hospitalization for heart failure (HF)).

The Efficacy and Safety of Finerenone in Subjects with Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease (FIGARO-DKD) trial (n = 7352) evaluated the same CV outcome as in FIDELIO-DKD as the primary outcome and the kidney disease outcome as a main secondary outcome in patients with T2DM and less severe CKD with mean (SD) eGFR 67.8 (21.7) mL/min/1.73m$^2$ and median UACR 308 (108-740) mg/g. There was a 13% reduction in the primary CV outcome in the finerenone group compared to placebo. Although there was reduction in the secondary kidney disease outcome in the finerenone group, it did not reach statistical significance.

To examine the safety and efficacy of finerenone in individuals with T2DM across a wide range of CKD, a prespecified analysis of combined FIDELIO-FIGARO trials called FIDELITY was conducted. For this pooled analysis population (n = 13,026) with median follow up of 3
years, there was a 14\% decrease in the CV outcome and a 23\% decrease in a composite kidney disease outcome (time to kidney failure, $\geq$57\% sustained decline in eGFR or kidney related death). As a result of these clinical trials, finerenone received United States Food and Drug Administration (US FDA) approval for reducing CKD progression, CV events, and HF hospitalizations in those with CKD due to T2DM.

The current standard-of-care for DKD is an ACE inhibitor or an ARB and an SGLT2 inhibitor. Based on the available evidence, finerenone can be considered an excellent choice for patients with DKD who cannot take an SGLT2 inhibitor or for those with persistently increased albuminuria despite treatment with the standard-of-care. The dose and titration of finerenone depend on both eGFR and serum potassium. The full dose of finerenone is 20 mg daily. Those with an eGFR 25-60 mL/min/1.73 m$^2$ or serum potassium 4.8-5 mEq/L, are recommended to take the lower dose of 10 mg daily per the US FDA label (Table).

Hyperkalemia risk:

A major risk of MRAs is hyperkalemia, and increased risk of hyperkalemia was observed in the finerenone group in FIDELIO-FIGARO. Overall the risk of hyperkalemia seems to be lower with a nonsteroidal MRA compared to steroidal MRAs. In a rat model of CKD, the risk of hyperkalemia was significantly lower with the nonsteroidal MRA PF-03882845 versus eplerenone. The Mineralocorticoid Receptor Antagonist Tolerability Study (ARTS) was a phase II trial of assessing safety of finerenone (BAY 94-8862) compared to spironolactone in patients with heart failure with reduced ejection fraction and mild or moderate CKD. Finerenone was associated with lower mean increase in serum potassium level compared to spironolactone. Although the maximum daily dose of finerenone in ARTS was 10 mg compared to 20 mg in
FIDELIO-FIGARO, the preclinical model of CKD and data from ARTS are supportive of lower risk of hyperkalemia with finerenone compared to steroidal MRAs. Moreover, the risk of hyperkalemia from MRA may be mitigated by SGLT2 inhibition. By increasing urine flow in the cortical connecting tubule, SGLT2 inhibitors could promote potassium excretion. Interestingly, big potassium (BK) channels that secrete potassium are activated via mechanosensing of urine flow by intercalated cells without directly requiring exchange for sodium, although long term increases in urine flow may activate ENaC and promote sodium reuptake in neighboring principal cells, and thereby, help to maintain electrochemical balance in the filtrate. Indeed, a recent post hoc analysis from CREDENCE found that canagliflozin compared to placebo reduced the risk for hyperkalemia by approximately 20% in study participants with DKD. Another post hoc analysis from FIDELIO-DKD showed that risk of hyperkalemia was reduced by more than half among SGLT2 inhibitor users. However, careful monitoring of serum potassium, with dose adjustment or treatment interruption as needed, is required in patients with CKD treated with finerenone (Table).

**Effects on blood pressure:**

It is important to note that the anti-inflammatory and antifibrotic effects of nonsteroidal MRA are largely independent of blood pressure lowering. In FIDELIO-FIGARO, the effects of finerenone on blood pressure were nominal. In ARTS, spironolactone reduced systolic blood pressure, while blood pressure did not vary between the placebo and finerenone. Lesser blood pressure lowering with finerenone has been attributed to its shorter half-life and reduced effect on natriuresis. Therefore the steroidal mineralocorticoid antagonists have a more potent blood pressure lowering effects that make these agents preferred for treatment of hypertension.
**Future directions:**

With SGLT2 inhibitors and finerenone gaining regulatory approval for treatment of DKD, we now have new therapies to actualize kidney health. ACE inhibitors and ARBs, SGLT2 inhibitors, and finerenone work by complementary mechanisms to protect the kidneys and heart. Future research will further elucidate how these therapies can be used in combination and personalized to individual patients. We foresee a future of kidney care shifting from treating advanced kidney disease and kidney failure to promoting kidney health and prevention. Now that we have a growing armamentarium of safe and effective therapies, it is imperative to focus on dissemination and implementation for millions of people worldwide with DKD who can benefit.
Disclosures:

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Funding:

None

Acknowledgments:

The content of this article reflects the personal experience and views of the author(s) and should not be considered medical advice or recommendation. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or Kidney360. Responsibility for the information and views expressed herein lies entirely with the author(s).

Author Contributions:

Jasleen Ghuman: Conceptualization; Writing - original draft; Writing - review and editing.

Katherine Tuttle: Conceptualization; Supervision; Writing - review and editing.
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Table: Dose considerations for finerenone in patients with type 2 diabetes and chronic kidney disease.

| Finerenone | eGFR > 60 ml/min/1.73m² | eGFR > 25-60 ml/min/1.73m² | eGFR < 25 ml/min/1.73m² | Serum K ≤ 4.8 mEq/L | Serum K > 4.8 - < 5 mEq/L | Serum K > 5.5 mEq/L |
|------------|-------------------------|-----------------------------|------------------------|----------------------|--------------------------|---------------------|
| **Initial daily dose** | 20 mg | 10 mg | Not recommended | 10 or 20 mg | 10 mg | Withhold |

**Dose adjustments**
- Monitor K and eGFR at baseline and 4 weeks after initiation or dose adjustment
- FDA Label: [labeling.bayerhealthcare.com/html/products/pi/Kerendia_PI.pdf](labeling.bayerhealthcare.com/html/products/pi/Kerendia_PI.pdf)

- Maintain if eGFR does not decline > 30%
- Reduce to 10 mg or withhold if eGFR declines ≥ 30%

- Maintain if eGFR does not decline > 30%
- Withhold if eGFR declines ≥ 30%

- Not applicable

- Maintain if serum K ≤ 5.5 mEq/L
- Withhold if serum K > 5.5 mEq/L
- May start 10 mg if serum K declines to ≤ 5.0 mEq/L

- Increase to 20 mg if serum K ≤ 4.8 mEq/L
- Maintain if serum K > 4.8-5.5 mEq/L
- Withhold if serum K > 5.5 mEq/L
- May start 10 mg if serum K declines to ≤ 5.0 mEq/L

eGFR: estimated glomerular filtration rate; K: potassium
**Figure:** Schematic of a diseased nephron with structural changes associated with diabetes. Binding of finerenone to the mineralocorticoid receptor disrupts transcription of pro-inflammatory and profibrotic factors

ROS: reactive oxygen species; TNF-α: tumor necrosis factor-α; IL-1 β: interleukin-1β; TGF-β: transforming growth factor-β1; CTGF: connective tissue growth factor; PAI-1: plasminogen activator inhibitor-1; MMP-2: matrix metalloproteinase-2
