Finerenone in Diabetic Kidney Disease

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About the Author

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Introduction

Diabetic kidney disease (DKD) affects 40% of individuals with diabetes mellitus (T2DM)[1] and is associated with an increased risk of cardiovascular events, hospitalization for heart failure, and premature death. Existing treatments focus on lifestyle measures, glycemic control, blood pressure and lipid management, inhibition of the renin-angiotensin-aldosterone system (RAAS), and the use of sodium glucose cotransporter 2 inhibitors (SGLT2-i).[2] However, substantial residual risk of progression to end-stage kidney disease (ESKD) or cardiovascular complications remain despite optimal therapy.[3] Finerenone, a non-steroidal mineralocorticoid antagonist (MRA), has been shown to reduce important outcomes when added to evidence-based therapies, and is approved by Health Canada as an adjunct to standard of care therapy in adults with chronic kidney disease (CKD) and T2DM to reduce the risk of ESKD and a sustained decrease in estimated glomerular filtration rate (eGFR), cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure.[4]

Mechanism of Action

Finerenone distinguishes itself from steroidal MRAs such as spironolactone and eplerenone through its "bulky" nonsteroidal structure, which confers high affinity and selectivity for the mineralocorticoid receptor.[5] By antagonizing aldosterone, finerenone mitigates its pro-inflammatory and pro-fibrotic effects on renal and cardiovascular tissues. In contrast to steroidal MRAs, the selective activity of finerenone causes fewer of the off-target, estrogen-related side effects such as gynecomastia.

Phase 2 Clinical Trials

The ARTS trial, a multicentre, randomized, parallel-group, Phase II study with double-blind placebo and open-label spironolactone comparator arms, enrolled patients with HFrEF and CKD (eGFR 30-90 mL/min/1.73 m^2).[6] The safety and tolerability of various doses of finerenone in patients with HFrEF and mild CKD were confirmed. The mean increases in serum potassium concentration were significantly smaller in the finerenone group than in the spironolactone group. GFR decreased significantly more in the spironolactone group than in the finerenone group. Systolic blood pressure (SBP) decreased significantly in the spironolactone group,

whereas in the finerenone group it remained similar to placebo. In another multicentre, randomized, double-blind, placebo-controlled, parallel-group trial of patients with T2DM with albuminuria who were receiving a RAS blocker, finerenone reduced the ratio of urine albumin-creatinine-ratio (UACR) at 90 days in a dose-dependent manner by up to 48%.[7] There was no significant change in eGFR or significant difference in adverse events between the groups. Twelve of 821 participants (who were all receiving finerenone) experienced serum potassium readings of at least 5.6 mmol/L, leading to discontinuation of study treatment.

Phase 3 Clinical Trials

FIDELIO-DKD[8] and FIGARO-DKD[9] were two large double-blind, randomized, placebo-controlled trials with complementary designs, aimed at investigating kidney-related and cardiovascular endpoints, respectively, in adult patients with T2DM and CKD (eGFR 25-90 mL/min/1.73 m^2 and uACR >30 mg/g) treated with maximum tolerated dose or RAAS inhibition. In the FIDELIO-DKD trial, 5734 patients with T2DM and CKD (mean eGFR: 44.3 ± 12.6 mL/min/1.73 m^2; median UACR: 852 mg/g) were randomized to finerenone or placebo. Patients randomized to finerenone experienced an 18% reduction in the primary endpoint (composite of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline over a period of at least 4 weeks, or death from renal causes). Cardiovascular outcomes also occurred less commonly in the finerenone group compared to placebo. In FIGARO-DKD, 7437 patients with T2DM and less advanced CKD (mean eGFR: 67.8 ± 21.7 mL/min/1.73 m^2; median UACR: 308 mg/g) were randomized to finerenone or placebo. Finerenone reduced composite cardiovascular outcomes by 13% compared to placebo. The composite kidney outcome was reduced by 23% in the finerenone group compared to placebo.

The incidence of adverse events was similar in both active and placebo arms of both studies. The incidence of hyperkalemia was higher in the finerenone arms of both studies (18.3% vs 9.0%, 10.8% vs 5.3% respectively). There were no deaths attributable to hyperkalemia. A total of 2.3% and 1.2% of FIDELIO-DKD and FIGARO-DKD finerenone-treated participants discontinued the drug permanently because of hyperkalemia, compared to 0.9% and 0.4% in the respective placebo arms.

In a pre-specified meta-analysis of these two trials, FIDELITY, the combined data from these two trials was analyzed.[10] In the combined analysis, finerenone reduced cardiovascular outcomes by 14%. There was a 22% relative risk reduction in the incidence of hospitalization for heart failure and a 23% reduction in the composite kidney outcome. This included a 30% reduction in decrease of eGFR by ≥57% and a 20% reduction in ESKD.

Based on these studies, regulators and professional societies have recommended finerenone be used in addition to standard of care for reducing kidney and cardiovascular complications of DKD.

- **Kidney Disease:**
  Improving Global Outcomes (KDIGO) 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease: *Recommendation 1.4.1:* We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for patients with T2DM, an eGFR ‡25 mL/min per 1.73 m^2, normal serum potassium concentration, and albuminuria (>30 mg/g [>3 mg/mmol]]) despite maximum tolerated dose of RAS inhibitor (RASi) (2A).[11]

- **American Diabetes Association.**
  Chronic Kidney Disease and Risk Management:
  Standards of Care in Diabetes 2024:
  Recommendation 11.5d: As people with CKD and albuminuria are at increased risk for cardiovascular events and CKD progression, a nonsteroidal mineralocorticoid receptor antagonist that has been shown to be effective in clinical trials is recommended to reduce cardiovascular events and CKD progression (if eGFR is ≥ 25 mL/min/1.73 m^2). Potassium levels should be monitored. A.[12]

Practical Aspects and Implementation

Finerenone has been studied as an add-on therapy on top of a maximally tolerated ACEi or ARB dose. For individuals with eGFR >60 mL/min/1.73 m^2 and a serum potassium ≤4.8 mmol/L, a 20 mg once daily dose is used. Serum potassium should be rechecked after 1 month, and periodically thereafter. For those with an eGFR >25 to <60 mL/min/1.73 m^2, and serum potassium ≤4.8 mmol/L, a 10 mg dose of finerenone is initiated. If the serum potassium remains below 4.8 mmol/L at one month, the dose is raised to the target 20 mg daily dose with a further recheck of potassium after one month and periodically thereafter. If potassium rises above 5.5 mmol/L in a 20 mg treated patient, the dose is usually reduced to 10 mg daily. If the serum potassium returns to acceptable levels the lower

eGFR (mL/min)	Starting Dose of Finerenone
>60 mL/min	20 mg
>25 to <60	10 mg
<25 mL/min	Not recommended

Table 1. Starting patients on finerenone; *courtesy of Adam Cohn, MD, FRCPC.*

Serum Potassium (mmol/L)	Current dose of finerenone of 10 mg	Current dose of finerenone of 20 mg
<4.8	Increase to 20 mg if eGFR has not decreased >30% vs. prior measurement	Maintain 20 mg
>4.8 to 5.5	Maintain 10 mg	Maintain 20 mg
>5.5	Withold. Restart at 10 mg if serum potassium <5.0 mmol/L.	Withhold. Restart at 10 mg if serum potassium <5.0 mmol/L

Table 2. Adjusting the dose of finerenone; *courtesy of Adam Cohn, MD, FRCPC.*

dose can be continued. It is advised that patients be counselled on sick day advice for finerenone and ACEi/ARB therapy. Serum potassium is rechecked at 4 months and periodically thereafter (**Tables 1 and 2**).

In both FIDELIO-DKD and FIGARO-DKD, patients were eligible to receive a SGLT2i at the discretion of the treating physician. For example, in the FIDELIO-DKD study, 259/5674 patients were taking an SGLT2i at study enrollment, and a further 328 patients initiated SGLT2i during the trial.[13] In those patients, the benefits of finerenone compared to placebo were similar with and without SGLT2i use. There were fewer hyperkalemia-related events with finerenone in the SGLT2i treated group (**Figure 1**).

Finerenone is well tolerated with few systemic side effects. There is a much lower incidence of gynecomastia compared to agents such as spironolactone or eplerenone.[14]

The starting dose is based on the patient's eGFR (**Table 1**).

Do not initiate if serum potassium is >5.0 mmol/L. If serum potassium >4.8 to 5 mmol/L, initiation may be considered with additional monitoring in the first 4 weeks based on patient characteristics and serum potassium levels.

Dose adjustments are based on the patient's serum potassium and eGFR. Check serum potassium 4 weeks after initiation, restart or dose adjustment, and periodically thereafter. For patients with renal impairment, measure eGFR 4 weeks after initiation to determine up titration (**Table 2.**).

Conclusion

Finerenone, a novel non-steroidal MRA, has been demonstrated to reduce albuminuria and preserve eGFR. In patients with T2DM and a wide range of eGFR and albuminuria levels, finerenone has reduced progression of CKD and the incidence of ESKD and has reduced the incidence of heart failure and cardiovascular outcomes in general. This medication is now recommended by numerous global guidelines to prevent progression of CKD and heart disease in this population, in addition to standard of care with a RAASi agent. It is safe and effective when used concurrently with a SGLT2i. Patients will require periodic monitoring of serum potassium levels, and dose adjustment will usually mitigate hyperkalemia. Finerenone is now part of the growing list of medications that have been shown to help patients living with T2DM and CKD prevent development of devastating complications such as progressive loss of kidney function, ESKD and heart failure.

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