Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes[1]

FIDELIO-DKD Trial Summary

SUMMARY

- In **FIDELIO-DKD,** patients with **T2DM** and **CKD** with **moderately elevated albuminuria** (UACR ~ 3-30 mg/mmol, eGFR of 25-60 mL/min/1.73m^2, and diabetic retinopathy) **or severely elevated albuminuria** (UACR 30-500 mg/mmol, eGFR of 25-75 mL/min/1.73m^2) who were treated with finerenone experienced **lower risk of CKD progression** (HR 0.82, 95% CI; 0.73-0.93, **NNT ≈ 31/2.6yr**) and **CV events** (HR 0.86, 95% CI; 0.75-0.99, **NNT ≈ 56/2.6yr**) compared to placebo. (Subgroup with UACR **≥ 85mg/mmol** accounted for all kidney 1° outcome benefit)
- Treatment with finerenone also resulted in **an increased risk of hyperkalemia** (18.3% vs. 9.0%, **NNH ≈ 11/2.6 yr**); however, there were no fatal hyperkalemic adverse events reported and discontinuation due to hyperkalemia was low among patients treated with finerenone (2.3%). This was likely in-part due to the use of potassium binding agents, withholding finerenone when K^+ concentrations exceeded 5.5 mmol/L until K^+ concentrations were below 5 mmol/L, and excluding patients with a baseline $K^+ \geq 4.8$ mmol/L

Bottom Line: Finerenone improves cardiorenal outcomes in patients with T2DM & CKD and moderate-severely elevated albuminuria; however, one will need to manage the ↑ **risk of hyperkalemia** with short-term treatment pauses, use of K^+ binding agents, etc. Only 4.6% & 6.9% of participants were on an SGLT2i or GLP-1 at baseline, respectively, which is not reflective of the current practice for these patients. Whether similar efficacy & safety results would be seen in a population already on an SGLT2i and/or a GLP-1RA is somewhat uncertain.

BACKGROUND

- T2DM is the leading cause of CKD. While managing hypertension, hyperglycemia, RAAS inhibition, and treatment with an SGLT2i are currently the standard components of care for patients with T2DM and CKD, the risk of CKD progression remains despite optimization of these therapies
- Finerenone **KERENDIA** is a non-steroidal, selective MRA. The proposed advantage of finerenone over steroidal MRAs (spironolactone, eplerenone) is a lower risk of hyperkalemia[2] and endocrine adverse events (gynecomastia, sexual dysfunction).
- Finerenone was approved by Health Canada in 2022 as an adjunct to standard of care therapy in adults with CKD and T2DM to reduce the risk of ESRD/sustained decrease in eGFR, CV death, MI, and hospitalization for heart failure.
- A **meta-analysis** (2019)[3] theorizes that in combination with ACEi/ARB, finerenone has a lower risk of hyperkalemia than eplerenone and spironolactone, but the **MRAs were not compared in head-to-head trials** .
- As explained in the **FINEART-HF** RxFiles Trial Summary, there are no large phase 3 head-to-head trials comparing the MRAs. There are small (n=65 to 1066) phase 2 trials comparing finerenone to spironolactone and eplerenone (**ARTS**[4], **ARTS-HF**[5]). **ARTS**[4] suggested finerenone causes less hyperkalemia than spironolactone, but this is hypothesis generating only based on the trial design, small sample size, etc.
- **FINEART-HF**[6] (2024) found that finerenone may have benefit in heart failure using a relatively high dose of 20-40mg daily, however finerenone is not currently Health Canada approved for the treatment of heart failure.
- **FIDELIO-DKD** was designed to test the hypothesis that finerenone slows CKD progression and reduces CV morbidity and mortality among patients with advanced CKD (primarily s was a parallel study investigating the use of finerenone in patients at somewhat less risk of kidney failure but still at a high risk of CV events; the **primary outcome was a CKD composite**.

TRIAL BACKGROUND (SEE ORIGINAL ARTICLE/SUPPLEMENT FOR FULL CRITERIA)

DESIGN: Phase 3, randomized, double-blinded, placebo-controlled, parallel-group, multicenter (~650 study centres in 48 countries) clinical trial

- Study involved a 4-16 week run-in period (to adjust ACEi/ARB to max tolerated labelled dose), screening, and a double-blind treatment phase
- Randomization was stratified by region, type of albuminuria at screening (high or very high), and eGFR at screening
- Funding was provided by Bayer; involved in multiple phases of the trial in collaboration with the executive committee (some potential for bias).

POPULATION

INCLUSIONS: Adults ≥ 18 (mean age 65.6 yr) with type 2 diabetes and a diagnosis of diabetic kidney disease taking a maximally tolerated label dose of an ACEi or ARB (but not both), with a serum potassium ≤ 4.8 mmol/L; CKD was defined according to one of two sets of criteria:

- **Persistent high albuminuria:** UACR 3 – 30 mg/mmol, eGFR 25-60 mL/min/1.73m^2, and diabetic retinopathy
- **Persistent very high albuminuria:** UACR 30 – 500 mg/mmol, eGFR 25-75 mL/min/1.73m^2

EXCLUSIONS: Non-diabetic renal disease (including renal artery stenosis), UACR > 500 mg/mmol, A1c > 12%, uncontrolled arterial hypertension (SBP ≥ 170 or DBP ≥ 110 mmHg at the run-in visit or SBP ≥ 160 mmHg or DBP ≥ 100 mmHg at the screening visit), SBP < 90 mmHg, HFrEF + persistent symptoms (NYHA class II-IV), stroke/TIA/cerebral attack/ACS/hospitalization for worsening HF 30 days prior to run-in, hepatic insufficiency (Child-Pugh C), dialysis for acute renal failure within 12 weeks prior, renal allograft in place or a scheduled kidney transplants within the next 12 months, Addison's disease, concomitant therapy with eplerenone, spironolactone, any renin inhibitor, or potassium-sparing diuretic that cannot be discontinued 4 weeks prior to screening, concomitant therapy with both an ACEi and ARB which could not be discontinued, concomitant therapy with potent CYP 3A4 inhibitors or inducers (to be stopped 7 days before randomization), patients pregnant/breastfeeding.

POPULATION at baseline: n=5734 randomized; mean age 65.6 yr, 70% male, 63% White, 25% Asian, 4.7% Black

- **Clinical presentation:** 16.6 yr x T2DM diagnosis, mean A1c 7.7%, mean SBP 138 mmHg, mean eGFR 44.3 mL/min/1.73m^2, median UACR 85 mg/mmol (87.5% of patients UACR was ≥ 30 mg/mmol), mean serum K+ 4.37 mmol/L
- **Baseline medications:** ACEi 34.2%, ARB 65.7% (> 98% of participants were being treated with the max tolerated labelled dose of an ACEi/ARB), diuretic 56.6%, statin 74.3%, K+ lowering agent (sodium polystyrene sulfonate, calcium polystyrene sulfonate, and potassium-binding agents) 2.4%, insulin 64.1%, GLP-1RA 6.9%, SGLT2i 4.6%
- ~98 of patients were on the max tolerated dose of an ACEi/ARB for > 4 weeks prior to the screening visit; however, the max *tolerated* dose was rarely the max *labelled* dose (21.4%/56.6% of patients were on the max *label* recommended dose of their ACEi/ARB, respectively)

INTERVENTION/COMPARISON: Finerenone 10mg or 20mg once daily vs placebo, in addition to usual therapy (max tolerated dose of ACEi or ARB)

Starting and maintenance dose was based on baseline eGFR (mean daily dose of finerenone = 15.1 mg)

- Starting dose: **10 mg once daily**: for patients with an eGFR of 25 to < 60 mL/min/1.73m^2; **20 mg once daily**: if eGFR of ≥ 60 mL/min/1.73m^2
- An increase in the dose from 10 to 20 mg once daily was encouraged after 1 month, provided the serum potassium was 4.8 mmol/L or less and the eGFR was stable (less than 30% below the value last measured); a reduction in the dose from 20 to 10 mg once daily was allowed any time after the initiation of finerenone or placebo (patients in the placebo group underwent sham dose adjustment)

Trial visits were conducted at month 1, month 4, and every 4 months until trial completion – finerenone or placebo was withheld if K+ concentrations exceeded 5.5 mmol/L and restarted when K^+ levels fell to 5.0 mmol/L or less

TABLE 1: EFFICACY RESULTS — MEAN FOLLOW-UP 2.6 YR

Clinical Endpoints	FINERENONE n=2833	PLACEBO n=2841	HR/RR (95% CI)	ARR	NNT/NNH /2.6 yr	Comments
PRIMARY OUTCOME (Composite, Time-to-Event Analysis)						**Primary and Secondary Outcomes** **1° Endpoint Kaplan-Meier Estimate NNT @ 3 yr = 29 (95% CI, 16-166)** **Key 2° Endpoint Kaplan-Meier Estimate NNT @ 3 yr = 42 (95% CI, 22-397)** -Separation of Kaplan-Meier curves for primary outcome ~12 months -Finerenone's effect on the primary outcome was consistent across subgroups with the exception of patients taking an SGLT2i or GLP1a at baseline (see limitations for further discussion) **Safety/AE/Other/Subgroups** -Finerenone was associated with a 31% greater ↓ in UACR from baseline to month 4 vs. placebo (HR 0.69, 95% CI, 0.66-0.71) -Patients receiving finerenone had a higher mean serum K^+ (max difference of 0.23 mmol/L @ month 4, stable thereafter) -Finerenone associated with ↓ GFR (6.3% compared to 4.7% with placebo) -Finerenone ↓pneumonia (4.5% vs. 6.4%) -Occurrence of AKI was balanced between groups (4.6% finerenone, 4.8% placebo) -Finerenone had modest effects on BP (-2.1 mmHg change from baseline to month 12) -Changes to A1c and body weight were similar between treatment groups -Gynecomastia AE occurred in 0.2% (n=6) of patients in both the finerenone and placebo groups
Kidney failure*, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes	17.8% (n=504)	21.1% (n=600)	0.82 (0.73-0.93)	3.3%	31	
PRIMARY OUTCOME – Components of the Composite (ITT)						
Kidney failure*	7.3% (n=208)	8.3% (n=235)	0.87 (0.72-1.05)	1%	NS	
Sustained decrease of ≥ 40% in eGFR from baseline	16.9% (n=479)	20.3% (n=577)	0.81 (0.72-0.92)	3.4%	30	
Death from renal causes	< 0.1% (n=2)	< 0.1% (n=2)	---	---	NS	
KEY SECONDARY OUTCOME (Composite, Time-to-Event Analysis)						
Key secondary (CV) composite outcome	13.0% (n=367)	14.8% (n=420)	0.86 (0.75-0.99)	1.8%	56	
Death from cardiovascular disease	4.5% (n=128)	5.3% (n=150)	0.86 (0.68-1.08)	0.8%	NS	
Nonfatal myocardial infarction	2.5% (n=70)	3.1% (n=87)	0.80 (0.58-1.09)	0.6%	NS	
Nonfatal stroke	3.2% (n=90)	3.1% (n=87)	1.03 (0.76-1.38)	↑ 0.1%	NS	
Hospitalization for heart failure	4.9% (n=139)	5.7% (n=162)	0.86 (0.68-1.08)	0.8%	NS	
SAFETY & OTHER SECONDARY OUTCOMES **						
Death from any cause §	7.7% (n=219)	8.6% (n=244)	0.90 (0.75-1.07)	0.9%	NS	
Any adverse events	87.3% (n=2468)	87.5% (n=2478)	0.99 (0.98-1.02)	0.2%	NS	
Serious adverse events ‡	31.9% (n=902)	34.3% (n=971)	0.93 (0.86-1.01)	2.4%	NS	
Hyperkalemia (investigator reported)	18.3% (n=516)	9.0% (n=255)	2.03 (1.76-2.33)	↑ 9.3%	11	
Serious hyperkalemia ‡	1.6% (n=44)	0.4% (n=12)	3.68 (1.95-6.94)	↑ 1.2%	84	
Discontinuation of trial regimen due to hyperkalemia	2.3% (n=65)	0.9% (n=25)	2.60 (1.65-4.12)	↑ 1.4%	72	

* Kidney Failure: End-stage kidney disease [initiate long-term dialysis (≥ 90 days) or kidney transplant] or an eGFR of < 15 mL per minute per 1.73m^2.
‡ Serious adverse events (SAE) resulted in death, were life-threatening, resulted in inpatient hospitalization (or prolonged existing hospitalization), caused persistent or clinically significant disability or incapacity, was a congenital abnormality or birth defect, or was judged by the investigator to be serious.
§ Other secondary outcomes (in order of hierarchical testing) included death from any cause, hospitalization for any cause, change in UACR from baseline to month 4, and a kidney composite; because there was no significant difference in the risk of death from any cause, analysis of other secondary outcomes was exploratory
** Risk ratios for safety outcomes were calculated manually as they were not provided in the trial; safety outcomes calculated using a more conservative denominator (n=2827 in the finerenone group, n=2831 in the placebo group)

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS

- Overall, trial was well designed and managed; allocation concealment, blinding, and intention-to-treat analysis to increase validity
- **FIDELIO-DKD** studied patients with relatively advanced CKD (almost 55% of participants had baseline eGFR < 45 mL/min/1.73m^2)
- Although finerenone caused ↑ hyperkalemia, discontinuation of the trial due to this was low (2.3%) and much lower than trials investigating ACEi or ARB + direct renin inhibitors (4.8%)[7] or ACEi + ARB (9.2%)[8]. Patients weren't asked to restrict dietary K^+ during **FIDELIO-DKD**
- Serum K^+ appears to stabilize around ~4 months – potentially most problematic early in treatment
- Benefits of finerenone on primary renal outcome were seen at ~12 mo *(may support theory that finerenone influences tissue remodelling)*
- Mean adherence to the trial regimen was high (92.1% in the finerenone group and 92.6% in the placebo group) despite being allowed to temporarily withhold finerenone when K^+ concentrations exceeded 5.5 mmol/L until K^+ concentrations were below 5 mmol/L

LIMITATIONS

- Surrogate endpoint (sustained ↓ in eGFR) drove the primary outcome (however, patient important outcomes like kidney failure still favouring finerenone, but trial likely not long enough to capture this)
- Trial run-in period to ensure treatment with maximally tolerated dose of ACEi or ARB may have contributed to the relatively moderate incidence of hyperkalemia[9] by specifying and analyzing a population more resistant to hyperkalemia at baseline (assuming a portion of the 8177 patients excluded after screening/dose optimization was due to hyperkalemia)
- Even with closely-monitored, protocolized hyperkalemia management, serious hyperkalemia did occur
- Potassium lowering agents were allowed to be stared during treatment with the study drug. At baseline, 2.5% of participants in the finerenone group were taking potassium-lowering agents and 2.3% of participants in the placebo group**. During the trial, 10.8% of participants taking finerenone started taking a K^+ lowering agent compared to 6.5% of participants taking placebo**. Use of K^+ lowering agents was at the investigator's discretion based on standard local guidelines, so **no standard approach to take away from this trial.**
- Lack of definitive data in adding finerenone to an **SGLT2i**, which is a component of the current standard of care – subgroup analysis suggests benefit of finerenone may not have extended to patients on SGLT2i (HR 1.38, 95% CI, 0.61-3.10) but small number of patients to consider $^{n=259}$. Subgroup analysis also shows benefit may not have extended to patients on a **GLP1a** (HR 1.17, 95% CI, 0.71-1.90) $^{n=394}$.
- 309 participants in the finerenone arm discontinued the trial regimen due to adverse events (although this is balanced as 294 participants in the placebo arm discontinued due to adverse events; patients who discontinued after randomization still included in full analysis set)

UNCERTAINTIES

- What is the optimal dose of finerenone in this population? (Mean daily dose was 15.1mg in this trial; ~50% on 10mg, ~50% on 20mg)
- How generalizable are these results? Would finerenone be effective in non-diabetic CKD? ...non-albuminuric CKD? ...patients with less advanced CKD? (See **FIGARO-DKD,** which was designed to extend the findings of **FIDELIO-DKD** in a population of less advanced CKD)
- How do we choose between a steroidal and nonsteroidal MRA when patients are indicated for both (e.g., CKD and HF)?
- How was diabetic retinopathy defined?
- 64.1% of participants on insulin at baseline; is this reflective of the real-world population and did this perhaps help ↓ hyperkalemia?

Other notes of interest:

Note: All ACR units provided in the trial have been **approximately** converted from conventional units (US) to SI units (Canadian)

At the time of print, finerenone **KERENDIA** is approximately $117/month (20mg daily). EDS on the Saskatchewan Drug Plan[10] and NIHB Prior Approval[11] are limited to use as an adjunct to standard of care therapy (max tolerated dose ACEi/ARB + SGLT2i) in those with an eGFR ≥ 25mL/min, an UACR ≥ 3mg/mmol who are not receiving an MRA and do not have NHYA class II-IV HF, prescribed in consultation with a nephrologist or other provider with experience treating CKD and T2DM.

- The CDA (formerly CADTH) recommends that **KERENDIA** be reimbursed by public drug plans as an adjunct to standard-of-care therapy in adults with T2DM and CKD to reduce the risk of end-stage kidney disease, sustained decrease in eGFR, CV death, MI, and hospitalization for heart failure IF prescribed in consultation with a nephrologist for patients with an eGFR > 25mL/min AND albuminuria. **KERENDIA** should NOT be covered for patients with chronic heart failure or who are being treated with an MRA (e.g., spironolactone).[12]

Guideline recommendations: KDIGO: Suggests nonsteroidal MRA for those with T2DM, eGFR >25mL/min, normal serum potassium, and albuminuria >3mg/mmol despite max tolerated RAAS inhibitor. Nonsteroidal MRA are most appropriate for adults with T2DM who are at high risk of CKD progression and CV events, as demonstrated by persistent albuminuria despite other standard-of-care therapies. [13]

RxFILES RELATED LINKS

- **FIDELIO-DKD** Trial Summary link; **FIGARO-DKD** Trial Summary link; **FIDELITY Analysis** (combined FIDELIO-DKD + FIGARO=DKD) link.
- FINEARTS-HF: Finerenone versus Placebo in Patients with Mildly Reduced or Preserved Ejection Fraction

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Abbreviations

T2DM = type 2 diabetes mellitus, CKD = chronic kidney disease, UACR = urinary albumin-to-creatinine ratio, eGFR = estimated glomerular filtration rate, NNT = number needed to treat, NNG = number needed to harm, CV = cardiovascular, yr = years, MRA = mineralocorticoid receptor antagonist, RAAS = renin-angiotensin-aldosterone system, SGLT2i = sodium glucose co-transporter 2 inhibitor, HF = heart failure, K+ = potassium, RCT = randomized control trial, ACEi = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blocker, HbA1c = hemoglobin A1C, SBP = systolic blood pressure, DBP = diastolic blood pressure, HFrEF = heart failure with reduced ejection fraction, NYHA = New York Heart Association, TIA = transient ischemic attack, ACS = acute coronary syndrome, GLP-1RA = glucagon like peptide 1 receptor agonist, AKI = acute kidney injury, AE = adverse event, ARR = absolute risk reduction, CI = confidence interval, HR = hazard ratio, DRI = direct renin inhibitor