Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease[1]

FIGARO-DKD Trial Summary

SUMMARY

- In **FIGARO-DKD**, patients with T2DM and stage 2-4 CKD with moderately elevated albuminuria (eGFR between **25-90mL/min** and ACR between **~3-30mg/mmol**) OR stage 1-2 CKD with severely elevated albuminuria (eGFR **≥60mL/min** and ACR between **~30-500mg/mmol**), **finerenone therapy improved cardiovascular (CV) outcomes compared to placebo** (**NNT ≈ 56/3.4yr**, HR 0.87, 95% CI: 0.76-0.98).
- The **FIGARO-DKD** trial was a parallel randomized controlled trial (RCT) to the **FIDELIO-DKD** trial, both evaluating the effects of finerenone in patients with T2DM and CKD. **FIDELIO-DKD** studied a higher-risk renal population with more advanced CKD compared to **FIGARO-DKD**.
- The improvement in CV composite outcome in **FIGARO-DKD** was primarily driven by a reduction in **heart failure (HF) hospitalizations (NNT ≈ 83/3.4yr)**, a result that was statistically significant despite excluding patients with HFrEF and persistent symptoms from the study population. **Only 7.8% of patients enrolled had a diagnosis of HF at baseline**.
- The secondary outcomes included a kidney composite that showed statistical significance for a reduction in progression to end-stage kidney disease (ARR ↓ **0.4%**) and an associated kidney composite including a sustained **≥57%** decrease in the eGFR (ARR ↓ **0.9%**).
- During this trial, the recommended treatment standard for patients with CKD/T2DM expanded with guidelines recommending the use of **SGLT2i and GLP1a medications**. CV benefits of finerenone were observed independently and in combination with both SGLT2i and GLP1a medications, with some suggestion of additive benefits with combination use (as assessed in the subgroup analysis). **Further data is required** to determine if greater cardiorenal protection results from the addition of finerenone with an SGLT2i/GLP1a.

Bottom Line:

- Finerenone therapy in addition to standard of care treatment **improved CV outcomes** (**NNT ≈ 56/3.4yr**, primarily reduced HF hospitalizations) compared to placebo in patients with T2DM over a broad spectrum of kidney disease (stage 2-4 CKD with moderately elevated albuminuria OR stage 1-2 CKD with severely elevated albuminuria). **Hyperkalemia** was a common AE of treatment (13.5% vs 6.4%, **NNH ≈ 14/3.4yr**), but was infrequently serious (**NNH ≈ 176/3.4yr**) and rarely led to treatment discontinuation (**NNH ≈ 125/3.4yr**) Screening at risk patients for albuminuria allows for identification of those who may receive CV benefit from treatment.

BACKGROUND[1,5,6,7,8,9,10]

- T2DM is the leading cause of CKD. **RAAS inhibition** (e.g., ACEi, ARB) and treatment with an **SGLT2i** are currently the standard components of care for patients with T2DM and CKD, however the risk of CKD progression remains a concern despite optimization of these therapies.
- Finerenone **KERENDIA** ☎ 𝒻 is a non-steroidal, selective MRA. The proposed advantage of finerenone over steroidal MRAs (spironolactone, eplerenone) is a lower risk of hyperkalemia[5] and endocrine AEs (gynecomastia, sexual dysfunction). Finerenone **KERENDIA** 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.[4]
- A **meta-analysis** (2019)[6] theorizes that in combination with ACEi/ARB, finerenone has a lower risk of hyperkalemia than eplerenone and spironolactone, but the MRAs were not compared head-to-head in the trials they base this conclusion on.
- As explained in the **FINEARTS-HF** RxFiles Trial Summary, there are no large phase III head-to-head trials comparing the MRAs. There are small (n=65 to 1066) phase II trials comparing finerenone to finerenone to spironolactone and eplerenone (**ARTS**[8], **ARTS-HF**[9]). **ARTS**[8] suggested finerenone causes less hyperkalemia than spironolactone, but this is hypothesis generating only based on the trial design, small sample size, etc.
- **FINEART-HF**[7] (2024) suggests that finerenone 20-40mg daily may have benefit in HF, however it is not currently approved for the HF treatment. Health Canada
- **FIDELIO-DKD**[10] demonstrated that in patients with CKD & T2DM, treatment with finerenone resulted in a lower risk of CKD progression and CV morbidity/mortality than placebo. In **FIDELIO-DKD**[10], patients were limited to those with ~stage 3 or 4 CKD. **FIGARO-DKD**[1] included patients with earlier (less severe) stages of CKD with intent to extend the findings of **FIDELIO-DKD**[10]. **FIGARO-DKD**[1] is the first trial examining the effect of finerenone on CV outcomes in less advanced stages of CKD.

FIGARO-DKD TRIAL DESIGN AND POPULATION (SEE ORIGINAL ARTICLE/SUPPLEMENT FOR FULL CRITERIA)

DESIGN: Randomized, double-blind, allocation concealed, placebo-controlled, parallel-group, multicentre, event driven Phase III study. Patients from ~900 study centers worldwide were randomized 1:1 between groups. Enrolment: September 2015 – October 2018. Funding: Bayer.

POPULATION:

- **INCLUSION:** ≥18yr, T2DM, serum K+ <4.8mmol/L, on max tolerated ACEi or ARB for ≥4 weeks, with:
  - Stage 2-4 CKD with moderately elevated albuminuria (eGFR between **25-90mL/min** and ACR between **3-30mg/mmo**l) OR
  - Stage 1-2 CKD with severely elevated albuminuria (eGFR **≥60mL/min** and ACR between **30-500mg/mmol**).
- **EXCLUSIONS included:** HFrEF with persistent symptoms (MRA indication), hospitalization for heart failure in preceding 30 days, recent CV event, uncontrolled HTN, SBP <90mmHg, significant non-diabetic renal disease, A1C >12%, UACR >500mg/mmol, pregnancy/breastfeeding.
  - Those with higher renal risk who were represented in **FIDELIO-DKD** were excluded (urinary ACR of 30-500mg/mmol, eGFR of 25-60mL/min).
- **POPULATION at baseline (n=7352)**
  - **Age**: mean age 64.1 (±9.8yr)
  - **Sex**: 69% male
  - **Race/ethnicity**: White ~72%, Asian ~20%, Black ~3.5%
  - **CV:** History of CV disease ~45%, diagnosed heart failure ~7.8%, mean SBP 135.8±14mmHg
  - **Diabetes:** mean duration of diagnosis 14.5yr (±8.5yr)
  - **Renal**: eGFR (mL/min): ≥60 ~62%, 45-60 ~21%.....25-45 ~17%.....<25 ~0.4%
    - Urinary ACR (mg/mmol): <3 ~2.8%.....3-<30 ~46%.....≥30 ~51%
  - **Potassium**: mean 4.33±0.43mmol/L
  - **Baseline medications**: RAAS ~100%, statin ~71%, insulin ~54%, diuretic ~48%, SGLT2i ~8%, GLP1 ~7.5%
  - Groups appear well balanced, patients were stratified for geographic region, eGFR, albuminuria, and CV history.
    - However, there were higher rates of GLP1 use in finerenone group (8.4%) compared to placebo group (6.6%).

INTERVENTION/COMPARISON:

- **Finerenone 10 or 20mg daily AM** vs **identical placebo** as control, in addition to guideline recommended drug therapy.
  - Patients were treated with a RAAS inhibitor (ACEi or ARB) that had been adjusted before randomization to the maximum dose on the manufacturer's label that did not cause unacceptable side effects (on max label recommended dose ~38%, between min and max dose ~30%, minimum label recommended dose ~26%, less than minimum label recommended dose ~5.1%).
  - **Starting dose:** 10mg if eGFR of 25-60 mL/min, 20mg if eGFR ≥60 mL/min. **Target dose:** 20mg daily, dose increase to 20mg encouraged **if K^+ <4.8mmol/L and eGFR stable.** Adjustment of the dose down from 20mg to 10mg once daily was allowed for any safety reason.
    - Finerenone/placebo was withheld if K+ was >5.5 mmol/L and was restarted when K+ levels < 5.0mmol/L.
    - Labs were performed on day 1, month 1, month 4, and then every 4 months until month 24, then every 12 months. Labs were also performed ~4 weeks after any dose adjustments or restarting treatment.
    - The mean daily dose of finerenone throughout the trial was **17.5mg**.

OUTCOMES:

- **Primary:** A composite of death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for heart failure.
- **Secondary**: All cause hospitalization, all-cause mortality, ACR change from baseline, and a kidney composite outcome.
  - The kidney composite outcome included first onset of kidney failure, sustained decrease from baseline of ≥40% OR ≥57% of the eGFR for ≥4 weeks, or death from renal causes.

RESULTS — Follow up over 3.4yr

CLINICAL ENDPOINTS	FINERENONE n= 3686	PLACEBO n= 3666	HR/RR (95% CI)	ARR/ARI (%)	NNT/NNH /3.4YR
PRIMARY ENDPOINT (Cardiovascular composite)					
Cardiovascular Composite	12.4% (n=458)	14.2% (n=519)	0.87 (0.76 to 0.98) P=0.03	↓ 1.8%	56 (NNT by author = 47/3.5yr (Kaplan-Meier estimate)
PRIMARY ENDPOINT – Components of the Composite (ITT)					
Death from CV causes	5.3% (n=194)	5.8% (n=214)	0.90 (0.274-1.09)	↓ 0.5%	NS
Nonfatal MI	2.8% (n=103)	2.8% (n=102)	0.99 (0.76-1.31)	≈	NS
Nonfatal stroke	2.9% (n=108)	3% (n=111)	0.97 (0.74-1.26)	↓ 0.1%	NS
Hospitalization for heart failure	3.2% (n=117)	4.4% (n=163)	0.71 (0.56 to 0.90)	↓1.2%	83
SECONDARY/OTHER OUTCOMES					
Kidney composite: **≥57%** decrease in eGFR	2.9% (n=108)	3.8% (n=139)	0.77 (0.60-0.99)	↓ 0.9%	111
Kidney composite: **≥40%** decrease in eGFR	9.5% (n=350)	10.8% (n=395)	0.87 (0.76-1.01)	↓ 1.3%	NS
End-stage kidney disease	0.9% (n=32)	1.3% (n=49)	0.64 (0.41-0.995)	↓ 0.4%	250
All-cause mortality	9.0% (n=333)	10.1% (n=370)	0.89 (0.77-1.04)	↓ 1%	NS
Change in urinary ACR between baseline & month 4	0.62 (0.61-0.64)	0.92 (0.90-0.95)	The reduction in the urinary ACR ratio from baseline to month 4 was 32% greater with finerenone than with placebo (ratio least-squares mean change from baseline, 0.68; 95% CI, 0.65-0.70), RRR ≈ ↓32%		
SAFETY/OTHER OUTCOMES*					
Any adverse event	85.1% (n=3134)	85.5% (n=3129)	0.99 (0.98-1.02)	↓ 0.4%	NS
Any serious AE (SAE)	31.4% (n=1158)	33.2% (n=1215)	0.95 (0.89-1.01)	↓ 1.8%	NS
Hyperkalemia (K^+>5.5mmol/L) – Results from Central lab assessment	13.5% (n=495)	6.4% (n=233)	2.11 (1.82-2.45)	↑ 7.1%	14
Serious hyperkalemia	0.7% (n=25)	0.1% (n=4)	6.22 (2.17-17.84)	↑ 0.6%	167
Permanent discontinuation due to hyperkalemia	1.2% (n=46)	0.4% (n=13)	3.52 (1.90-6.50)	↑ 0.8%	125

COMMENTS

Primary, Secondary, and Other Outcomes:
Kidney composites: There were no statistically significant between-group differences for the composite including sustained decrease from baseline of ≥40% of the eGFR, but there were statistically significant differences for the composite with a sustained decrease from baseline of **≥57%** of the eGFR (a more sensitive surrogate outcome for kidney failure).
Other components of the kidney composites include kidney failure, end-stage kidney disease, and sustained decrease in eGFR of <15mL/min).
Blood pressure: Month 4; -3.5mmHg finerenone vs -2.6mmHg placebo

Safety/AEs:
Renal-related AEs: Similar between groups (e.g., balanced AKI incidence)
Hypokalemia: Lower in finerenone group vs placebo (1.1% vs 2.2%)
Gynecomastia: Rare (0.1% in both groups)
Pneumonia: Less common in finerenone vs placebo group (3.9% vs 5.6%)
Hyperkalemia: Hyperkalemia was reported with two methods, as an investigator-reported AE and as a central lab assessment. As an investigator-reported AE, finerenone group reported hyperkalemia at 10.8% vs 5.3% with placebo, compared to central lab results shown in table.
Note: SAE less in finereone group (potential range from small benefit to negligible difference)

*Risk ratios for safety/other outcomes were calculated manually as they were not provided in the trial

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- Evaluates finerenone's cardiorenal outcomes in **earlier-stage CKD**, extending findings of **FIDELIO-DKD**.
- Significant CV benefit, particularly in reducing heart failure events—a major source of morbidity and cost in T2DM with CKD.
- CV risk reduction in less advanced CKD supports early albuminuria screening alongside eGFR in patients with T2DM.
- Fewer AE and SAE in the finerenone group vs placebo, suggesting a favorable safety profile, except in those prone to hyperkalemia.
- The lower incidence of hyperkalemia and greater selectivity of finerenone compared to other MRAs could improve compliance by reducing potassium, hormonal AEs, and discontinuation. Total discontinuation rates were comparable between the finerenone 27.4% (n=1009) and placebo 27.7% (n=1014) groups.
- Discontinuation due to hyperkalemia was low (1.2%) despite ↑ rates of hyperkalemia in the finerenone group, indicating that this AE was manageable for most.
- K^+ increase appears greatest in the first ~month on therapy, then stabilizes based on the time-to-event analyses. No dietary K+ restrictions were applied.
- Randomized, double-blind design reduces bias, the trial demonstrated well-balanced groups and met power to detect significance of the primary outcome.
- Patient-important outcomes (e.g., CV death, MI, stroke, hospitalizations for HF) chosen for primary endpoints rather than surrogate markers.

LIMITATIONS

- Limited use of SGLT2i/GLP1a at baseline limits generalizability, especially as treatment standards evolve. While it's unlikely that addition of these therapies would reverse the benefit of finerenone, they may mute the extent of benefit. Serious harms seem unlikely but remain a possibility.
- Relatively high rates of insulin use at baseline were observed in both groups (~54%), use of insulin may contribute to lower rates of hyperkalemia.
- The use of **potassium-lowering agents**, permitted at the investigator's discretion, may have influenced AE results. The higher use of these agents in the finerenone group vs placebo group post-initiation (4.5% vs. 2.8%) despite similar use at baseline (0.7% vs 0.6%) should be considered. Even with closely-monitored protocols for hyperkalemia management, serious hyperkalemia did occur.
- Of 19,381 patients screened, 10,946 were excluded for not meeting eligibility criteria, which will affect generalizability of the findings.
- Kidney composite with >40% eGFR decline was not significant; significance was observed only at the composite for **>57% decline** (a more sensitive surrogate outcome of kidney failure).
- The cost of treatment and the need for ongoing potassium monitoring will be barriers for use.

UNCERTAINTIES

- With SGLT2i (and GLP1 antagonists) having a more prominent role in CKD, would further addition of finerenone achieve clinically significant benefit vs harm?
- What is the optimal dose of finerenone? **FIGARO-DKD** used a dose of 10-20mg daily, while other trials such as **FINEARTS-HF** used a dose of 20-40mg daily for those with an eGFR >60mL/min. Both trials showed benefit for CV outcomes, as such the target dose for CV event prevention is uncertain.

Other notes of interest:

Costs: At the time of print, finerenone **KERENDIA** ☎ ✆ is approximately $117/month (10 or 20mg daily). EDS on the Saskatchewan Drug Plan[2] and NIHB Prior Approval[3] are limited to use as an adjunct to standard of care therapy (max tolerated dose ACEi/ARB + SGLT2i) in those with an eGFR ³25mL/min, an UACR ³3mg/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).[9]

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.[10]

Abbreviations:

ACEi=angiotensin converting enzyme inhibitor(s) **ACR**=albumin-to-creatinine ratio **AE**=adverse event **ARB**=angiotensin receptor blocker(s) **ARI**=absolute risk increase **ARR**=absolute risk reduction **CADTH**=Canadian Agency for Drugs in Technology & Health **CDA**=Canada's Drug Agency **CKD**=chronic kidney disease **CV**=cardiovascular disease **DM**=diabetes mellitus **EDS**=Exception Drug Status **eGFR**=estimated glomerular filtration rate **ESRD**=end-stage renal disease **GLP1**=glucagon-like-peptide-1 **g**=gram **HF**=heart failure **HFrEF**=heart failure with reduced ejection fraction **K⁺**=potassium **L**=liter(s) **mg**=milligrams **MI**=myocardial infarction**min**=minute(s) **mL**=milliliters **mmol**=millimole **mmol/L**=millimole per liter **MRA**=mineralocorticoid receptor antagonist **n**=number **NIHB**=non-insured health benefits **NNH**=number needed to harm **NNT**=number needed to treat **NYHA**=New York Heart Association **RAAS**=renin angiotensin aldosterone system **SBP**=systolic blood pressure **SGLT2i**=sodium/glucose cotransporter 2 inhibitor(s) **T2DM=** type 2 diabetes mellitus **yr**=year

RxFILES RELATED LINKS

- **FIDELIO-DKD** Trial Summary link; **FIGARO-DKD** Trial Summary link; **FIDELITY Analysis** (combined FIDELIO-DKD + FIGARO=DKD) link.
- FINEARTS-HF RxFiles Trial Summary

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