FIDELITY Pooled Analysis[1]

Analysis of pooled results of FIDELIO-DKD and FIGARO-DKD trials

SUMMARY

- **FIDELIO-DKD** & **FIGARO-DKD** studied the effect of **10-20mg finerenone daily** on **CV** and **kidney** outcomes in patients with **T2DM and CKD**.
- **FIDELIO-DKD's** primary outcome was a **kidney composite** in pts with **more advanced CKD (**Stage ~3-4 CKD with moderately elevated albuminuria and diabetic retinopathy OR stage ~2-4 CKD with severely elevated albuminuria) whereas **FIGARO-DKD's** primary outcome was a **CV composite** in pts with **less advanced CKD** (stage 2-4 with moderately ↑ albuminuria or stage 1-2 with severely ↑ albuminuria)
- **FIDELITY** was a prespecified pooled efficacy and safety analysis designed to combine the findings from **FIDELIO-DKD** & **FIGARO-DKD** and analyze potential **cardiorenal** benefit across a spectrum of patients with DKD. Below are the main efficacy outcomes from **FIDELITY**:
  - **Composite kidney:** HR 0.77, 95% CI: 0.67 - 0.88, **NNT ≈ 63/3yr**
  - **Composite CV:** HR 0.86, 95% CI: 0.78 - 0.95, **NNT ≈ 59/3yr** (**only individual component statistically significant, HF Hosp**)
- **FIDELITY** highlighted that finerenone increases hyperkalemia rates relative to placebo (14% vs 6.9%, **NNH ≈ 14/3yr**); however, it did *not* lead to marked permanent treatment discontinuation (1.7% vs. 0.6%) *or* hospitalization (0.9% vs. 0.2%). Patient's dietary K^+ intake was not restricted but **management of hyperkalemia** involved dose reductions, temporary holds, and use of K^+ binders.

Bottom Line:

Finerenone therapy shows **cardiorenal benefit** over a broad spectrum of CKD stages compared to placebo. Use is limited by adverse events (specifically **hyperkalemia**) and **cost** (~$117/month, 10 or 20mg tablets).

FIDELIO & FIGARO TRIAL DESIGN AND POPULATION (SEE ORIGINAL ARTICLE/SUPPLEMENT FOR FULL CRITERIA)

Trial/Comparator	**FIDELIO-DKD** n=5734	**FIGARO-DKD** n=7437
Publication Year	2020	2021
Median Follow-Up	2.6 years	3.4 years
Trial Design Funding: Bayer	Randomized, double-blind, placebo-controlled, parallel-group, multicentre, event driven Phase III study. Patients from ~900 study centers worldwide. Patients were randomized 1:1 between groups.	
Intervention/Control	**Finerenone 10-20mg daily AM** vs identical **placebo** as control, in addition to guideline recommended drug therapy.	
Inclusion Criteria median baseline population	≥ 18yr, T2DM, serum K^+ < 4.8mmol/L, on max tolerated ACEi or ARB for ≥4 weeks {FIDELITY Pooled Analysis: Age ~65, A1C ~7.7%, SBP ~137/76, eGFR ~57.6, UACR ~58mg/mmol, serum K^+ ~4.35, RAASi ~99.8%, GLP1 ~7.2%, SGLT2i ~6/7%}	
CKD Stage See heat maps below	Stage **~3-4 CKD** with **moderately elevated albuminuria** and diabetic retinopathy OR stage **~2-4 CKD** with **severely elevated albuminuria**	Stage **~2-4 CKD** with **moderately elevated albuminuria** OR Stage **~1-2 CKD** with **severely elevated albuminuria**
Median eGFR	**44** mL/min/1.73m^2	**68** mL/min/1.73m^2
Mean UACR (SI Units)	**~85** mg/mmol (subgroup ≥85mg/mmol accounted for all kidney 1° outcome benefit)	**~30.9** mg/mmol
CV Outcome & Results	**CV** composite** (2° outcome) HR: 0.86; 95% CI: 0.75 - 0.99	**Cardiovascular** composite** (1° outcome) HR: 0.87; 95% CI: 0.76-0.98
Kidney Outcome & Results	**Kidney** composite (≥40% decrease in eGFR)* (1° outcome) HR: 0.82; 95% CI: 0.73 - 0.93	**Kidney** composite (≥40% decrease in eGFR)* (2° outcome) HR: 0.87; 95% CI: 0.76-1.01
Hyperkalemia (Investigator Reported)	18.3% finerenone vs. 9.0% placebo	10.8% finerenone vs. 5.3% placebo

*Kidney Composite (time-to-event): time to onset kidney failure, a sustained ≥40% decrease in eGFR from baseline, or renal death; of **Cardiovascular Composite (time-to-event): non-fatal MI, non-fatal stroke, hospitalization for HF, CV death.

FIDELITY POOLED ANALYSIS RESULTS

COMPOSITE OUTCOMES

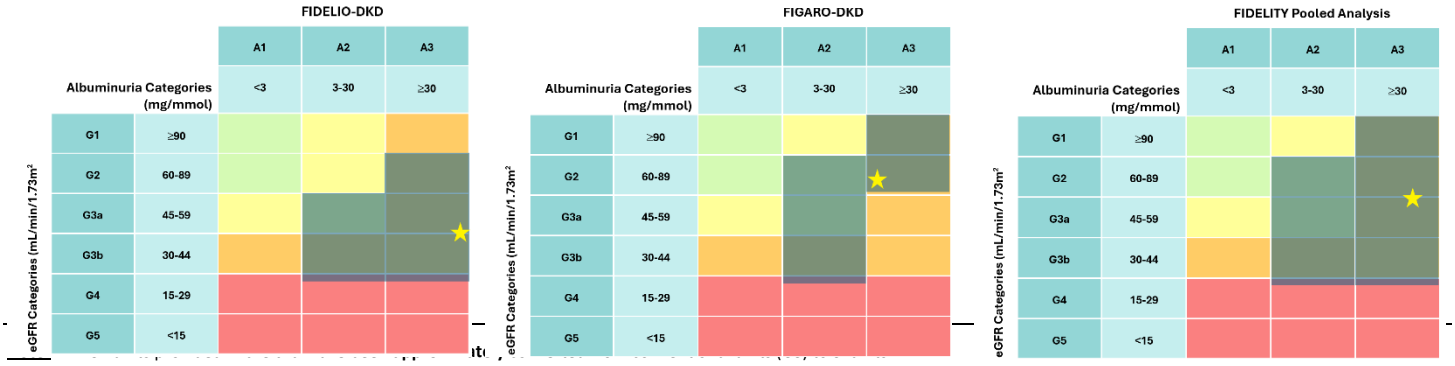
CLINICAL ENDPOINTS	FINERENONE N=6519	PLACEBO N=6507	HR (95% CI)	ARR/ARI (%)	NNT/NNH /3YR
Kidney Composite+ (≥57% ↓ in eGFR)	**5.5% (360)**	**7.1% (465)**	HR 0.77, 95% CI: 0.67 - 0.88	**1.6% ↓**	**63**§
CV Composite++	**12.7% (825)**	**14.4% (939)**	HR 0.86, 95% CI: 0.78 - 0.95	**1.7% ↓**	**59**§
Death from any cause	**8.5% (552)**	**9.4% (614)**	HR 0.89, 95% CI: 0.79 - 1.001	**0.9% ↓**	NS

Note: For the Kidney Composite: Kidney failure: 3.9% vs 4.6%, HR 0.84, 0.71-0.99; **NNT=77/3YR**; { a) ESRD: 2.3% vs 2.9%, HR=0.80, 0.64-0.99; + b) decrease in eGFR to <15}

SAFETY/OTHER OUTCOMES

CLINICAL ENDPOINTS	FINERENONE	PLACEBO	ARR/ARI (%)
Serious adverse events (SAE)	31.6%	33.7%	**↓ 2.1%**
Hyperkalemia	14%	6.9%	**↑ 6.9%**
Hyperkalemia related treatment discontinuation	1.7%	0.6%	**↑ 1.1%**
Hospitalization due to hyperkalemia	0.9%	0.2%	**↑ 0.7%**

+ Kidney Composite (time-to-event): Kidney failure, sustained ≥ 57% decrease in eGFR from baseline over ≥ 4 week, or renal death; ++ Cardiovascular Composite (time-to-event): Non-fatal MI, non-fatal stroke, hospitalization for HF, CV death; § Author reports NNT of 60/3yr for the kidney composite and 46/3yr for the CV composite; they calculate NNT in 6-month intervals from cumulative incidences based on Aalen-Johansen accounting for mortality as completing risk; we have calculated and reported NNT in the table based on event occurrence reported in Table 2 (Efficacy Outcomes) within the trial.



Note: Grey shading on above graphs indicates the CKD staging of each of the study's respective population

Trial notes:

- **FIDELIO-DKD** had a mean follow up duration of 2.6yr, while **FIGARO-DKD** had a mean follow up duration of 3.4yr. The differences in duration of follow-up may be attributed to **FIGARO-DKD's** lower renal risk population requiring a longer duration to see a statistically significant result compared to **FIDELIO-DKD'S** higher risk population.
- **Why did the trials use both a Kidney Composite endpoint of both a sustained ≥40% decrease in eGFR from baseline, and a sustained ≥57% decrease in eGFR from baseline?** In **FIDELIO-DKD**, statistical significance was reached for a ≥40% decrease in eGFR, whereas in **FIGARO-DKD** and **FIDELITY** Pooled Analysis, statistical significance was only reached for ≥57% decrease and not met for ≥40% decrease. The ≥57% decrease in eGFR marker is a more sensitive surrogate outcome for kidney failure than ≥40% decrease. A ≥57% decrease in eGFR has been used as an end point in clinical trials of real disease progression and is approximately equal to a doubling of serum creatinine.
    - It is reasonable that significance for the less sensitive outcome would be met by the **FIDELIO-DKD** study and not by **FIGARO-DKD**, as **FIDELIO-DKD's** study population had more advanced CKD and were at a higher risk for progression to kidney failure.
- Based on the mean doses of finerenone in the trials (15.1mg/day in **FIDELIO-DKD** and 17.5mg/day in **FIGARO-DKD**), those with less advanced CKD may better tolerate higher doses.

Practice points (based on trial use of medication):

- A reduction in dose to 10mg is both permissible and anticipated due to hyperkalemia.
- Potassium binders may be required, particularly for patients with more advanced chronic kidney disease (CKD).
- A notable number of patients discontinued treatment in the trials, with n=2023 in **FIGARO-DKD**, and n=1623 in **FIDELIO-DKD** stopping their assigned regimen. Discontinuation rates were similar between groups—with the pooled discontinuation rates of 28.1% for finerenone and 27.9% for placebo. It is reasonable to expect that not all patients will remain on treatment.

RxFILES RELATED LINKS

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

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References:

1) Agarwal R, Filippatos G, Pitt B, Anker SD, Rossing P, Joseph A, Kolkhof P, Nowack C, Gebel M, Ruilope LM, Bakris GL; FIDELIO-DKD and FIGARO-DKD investigators. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the **FIDELITY** pooled analysis. Eur Heart J. 2022 Feb 10;43(6):474-484.

2) Pitt B, Filippatos G, Agarwal R, Anker G, Bakris P, Rossing AJ, et al, for the **FIGARO-DKD** Investigators. Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes. *New England Journal of Medicine*. 2021;385(24):2252-2263 Online access.

3) Bakris GL, Agarwal R, Anker S, Pitt B, Ruilope LM, Rossing P, Kolkhof P, Nowack C, Schloemer P, Joseph A, Filippatos G; for the **FIDELIO-DKD** Investigators. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes; *The New England Journal of Medicine*. 2020 October 23; 10.1056/NEJMoa2025845. Online Access

Abbreviations: CV=cardiovascular, T2DM=type 2 diabetes mellitus, CKD=chronic kidney disease, DKD=diabetic kidney disease **eGFR**=estimated glomerular filtration rate**, K+**=potassium**, pts**=patients**, NNT**=number needed to treat**, NNH = number needed to harm, SAE**=serious adverse events**, yr**=years

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