The Effect of Simultaneous Initiation of Finerenone with Empagliflozin on UACR in CKD and T2DM[1]

CONFIDENCE Trial Summary

Summary

- Simultaneous initiation and combination use of finerenone with empaglifozin (an SGLT2i) resulted in:
  - **greater reduction in UACR** than either drug alone (the benefit). **Interpretive caution is required as ↓in UACR is a surrogate endpoint, and may not correlate with desired clinical outcomes**. SGLT2i have previously demonstrated benefit in CKD RCTs. Finerenone was associated with somewhat improved CV but mostly limited to hospitalization for HF and CKD outcomes in previous RCTs.
  - a higher risk of potential harms: a) an initial 30% decline in eGFR and possibly b) (numerically) acute kidney injury (AKI)
- The risk of hyperkalemia seen with finerenone monotherapy seems to be mitigated somewhat by co-initiation/use of an SGLT2i.
- Overall this RCT was underpowered, and the duration too short, to assess for patient important clinical outcomes, and trends were not favourable. {However, for finerenone specifically, one would look to FIDELITY, FIDELEO and FIGARO for such outcome evidence, although few patients in these RCTs were already on an SGLT2i, raising uncertainties in applying the results to current practice.}
- Since SGLT2i plus maximally tolerated ACEi or ARB is already core of therapy in CKD, and one may look at this RCT specifically for clues regarding the role and/or timing of finerenone. This RCT suggests that it's early addition to the combination of ACEi or ARB + SGLT2i may be considered in CKD patients with T2DM. The SGLT2i on board reduces somewhat the risk of hyperkalemia seen with finerenone alone. The combination of finerenone and SGLT2i reduces UACR (especially in those whose baseline SBP >130mmHg, or who's age >65).
- Starting finerenone simultaneously with an SGLT2i is an option, but one would need to monitor for rapid ↓ in eGFR & AKI.

Background

- 4 medications/groups have evidence for improving outcomes and slowing the progression of CKD in patients at risk (ACEi or ARB, SGLT2i, GLP1a (ie. semaglutide), NS-MRA (ie. finerenone). Background therapy for the latter 3 med groups included ACEi or ARB at maximum tolerated dose.
- Finerenone, has demonstrated a degree of cardiovascular benefit in CKD patients (especially in reducing hospitalization for HF). It has also demonstrated a slowing of the progression of CKD.FIDELIO, FIGARO, FIDELITY Pooled Analysis
- There is uncertainty over the areas of combination therapy and sequential (ie. step-up) vs concomitant initiation of agents, specifically:
  - To what degree finerenone may offer benefit in those with CKD already on ACEi or ARB and an SGLT2i;
  - Whether finerenone initiated concomitantly with an SGLT2i would demonstrate a favourable efficacy/safety profile. A more rapid stacking of agents is desired by some to overcome "clinical inertia" (i.e. prolonged time to get to more effective therapy)

Trial Design and Population

- **Design:** Randomized, double-blind, allocation concealed, active comparator-controlled, multicentre, trial. Patients from Asia 46%, North America 45%, and Europe 27% were randomized 1:1:1. Enrolment: Jun 2022 – Aug 2024. Funding: Bayer (who had significant input into all aspects of the study). Analysis was by modified intention to treat (mITT); e.g. participants had to receive at least 1 dose, and "avoid good critical practice violations" to be included. Randomization stratified according to eGFR and UACR.
- **Inclusion criteria** abridged: T2DM, A1c<11%; CKD: eGFR 30-90ml/min per 1.73m² body surface area, AND albuminuria (UACR 11-565mg/mmol);
- **Exclusion criteria** abridged: HFrEF with persistent symptoms, K+ >4.8mmol/L, CV history (recent within previous 90days stroke, MI, hosp for HF), T1DM, kidney transplant; not on, and no use of, an SGLT2i or potassium-binding agent in previous 8 weeks.
- **Typical (mean/average) participant**: age 67, male 75%, White or Asian, A1c=7.3%, 82kg, eGFR=54, UACR=65mg/mmol, SBP=135mmHg, K+=4.5, atherosclerotic CVD history 28%, >98% on ACEi or ARB, 75% on a statin, 36% on a diuretic, 23% on a GLP1a
  - Groups were fairly well balanced at baseline with exception of: on a GLP1a (>25% in combo group vs 19% in finerenone group), favouring the combination group given GLP1a now also showing benefit in slowing progression of CKD FLOW
- **Primary efficacy outcome (NOTE, this is a SURROGATE OUTCOME RCT):** the relative change in the log-transformed mean UACR from baseline to 180 days. Various secondary efficacy and safety outcomes were included (e.g. see results table).

Intervention/Comparison

- **Combination of finerenone 10 or 20mg po daily + empaglifozin 10mg po daily** vs **either alone**. (ie. 3 arms; 1:1:1 allocation)
  - Finerenone initiated at 20mg/day if eGFR ≥ 60mL/min

Results – primary follow-up over 180 days

Variable/Outcome		Combination Finer+Empa (n=269)	Finerenone (n=264)	Empaglifozin (n=267)	Comments
1° UACR change from baseline to day 180		**0.48** (0.44-0.54)*	**0.68** (0.1-0.76)* Vs combo: 0.68 0.61-0.76	**0.71** (0.64-0.79)* Vs combo: 0.71 0.64-0.79	↓UACR: most over 14, & 90 days **Subgroups** most likely to benefit: SBP baseline ≥130; age ≥65; Europe > N. America.
Reduction in UACR	>30%	70.0%	52.1% NNT ~5.6 **combo** vs finer	51.7% NNT ~5.5 vs **combo** vs empa	
	>50%	54.6%	35.6% NNT ~5.2 **combo** vs finer	31.9% NNT ~4.4 vs **combo** vs empa	
Safety/Other Endpoints	CV events**	2.6% assuming max 1 event/patient	0%	0.8%	**Combo best for**: ↓SBP (~7mmHg) **Combo worst for:** >30% decline in eGFR @30 days; numerically more AKI **Empa alone best for**: avoidance of hyperkalemia; insignificant A1c advantage, 0.2% **Empa alone, or Combo worst for**: genital mycotic infection **Note**: ↑K⁺ with finerenone partly mitigated by co-admin of SGLT2i
	All-cause Death**	1.1%	0%	1.1%	
	SAE serious adverse events	**7.1%**	6.1%	6.4%	
	Hyperkalemia	9.3% NNH ~18 combo vs empa	**11.4%**	3.8%	
	K+ >5.5 mmol/L	15.3%	**18.6%**	9.7%	
	K+ >6.0 mmol/L	4.6% NNH ~52 combo vs empa	4.6%	2.7%	
	>30% ↓in eGFR@30d	**6.3%** NNH ~19 combo vs empa	3.8%	1.1%	
	AKI	**1.9%**	1.1%	0.4%	

*Least-Squares Mean Ratio (95% CI); **For CV events, All-cause Death, and SAE: all were numerically ↑ in Combo group; but underpowered too short; too small

Strengths, Limitations, Uncertainties

- **Strengths**:
  - Appears to be well designed, reasonable generalizability
  - Few patients lost to follow-up, (although not so few relative to patient important safety endpoints)
- **Limitations**:
  - Significant assumptions: a) validity of surrogate endpoint to predict clinical outcomes; assume missing data missing at random
  - Very short duration makes predicting long-term benefits and harms uncertain
  - Limited to CKD in patients with T2DM
- **Uncertainties**:
  - Was the benefit of finerenone due to lowering of BP, and if so, would other antihypertensive treatment have done the same?
  - **Would the surrogate benefit seen with reduction in the UACR translate into meaningful clinical outcome benefit?**
    - Surrogate UACR endpoint strongly favourable; but most important endpoints of CV events, all-death, SAE unfavourable.
    - Surrogate targets are mostly derived from observational associations (including observational analysis of RCTs) and may or may not equate to causality. A **change in proteinuria or albuminuria results in inconsistent and overestimation of CV and all-cause mortality benefit**.[2,3,4,5] **A correlation with progression of CKD and specifically end stage kidney disease (ESRD) may be somewhat stronger.**[5]
      - Systematic Review/Meta-analysis (Can J Cardiology, 2019); N=36 trials
        - Proteinuria and CV events (N=20 $_{n=109,200}$): **inconsistent** treatment effects on CV morbidity & mortality
        - Proteinuria or albuminuria (N=21 $_{n=109,215}$): **inconsistent** treatment effects on all-cause mortality
        - Proteinuria or albuminuria (N=23 $_{n=99,889}$): **overall consistent** treatment effects on ESRD
    - Overall, one needs a high degree of uncertainty in linking a surrogate outcome to a subsequent hypothesized clinical benefit.
  - Would results be similar if using other agents in the SGLT2i class of medications?
  - Now that semaglutide (a GLP1a) is also indicated for CKD in T2DM, how would finerenone or combo (finer+empa) compare?

Other Notes of Interest

- CONFIDENCE = COmbinatioN effect of FInerenone anD EmpaglifoziN using a uaCr Endpoint study

RxFILES RELATED LINKS

- **Finerenone CKD and HF RCTs:**
  - **FIDELIO-DKD** Trial Summary link
  - **FIGARO-DKD** Trial Summary link
  - **FIDELITY Analysis** (combined FIDELIO-DKD + FIGARO=DKD) link.
  - **FINEARTS-HF** RxFiles Trial Summary
- **Outcome Comparison of Agents Used for Glycemic Control in Diabetes:**
  - GLP1 Agonists & **SGLT2 Inhibitors** - SUBSET of DIABETES AGENTS in T2DM: **Outcomes** Comparison Summary Table – Page 2

Abbreviations:

ACEi=angiotensin converting enzyme inhibitor(s) **ACR**=albumin-to-creatinine ratio **AE**=adverse event AKI=acute kidney injury **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 **UACR**=urinary albumin to creatinine ratio

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