ACP 2026 Early Career Physician Poster Competition

Projected Long-term Benefits of Combination Therapy with SGLT2 Inhibitors and Non-Steroidal MRA in Type 2 Diabetes and Chronic Kidney Disease based on the CONFIDENCE Trial

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Introduction

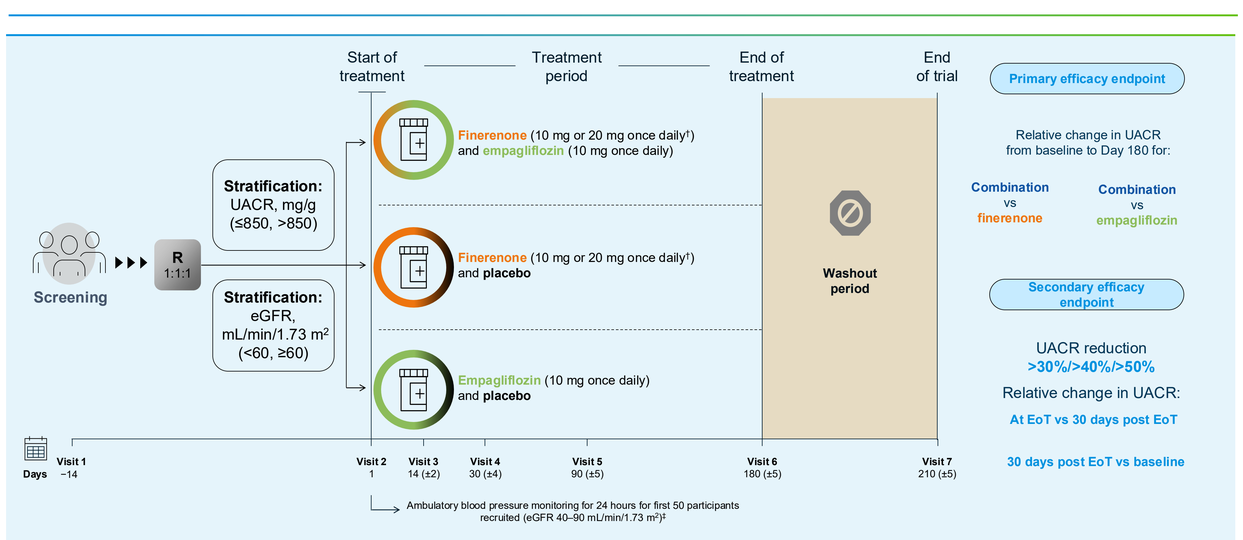
- Sodium-glucose co-transporter-2 inhibitors (SGLT2i) and the non-steroidal mineralocorticoid receptor antagonist finerenone (nsMRA) represent “pillars” of care for cardio-kidney-metabolic conditions.
- Traditionally, medical therapies for CKD are implemented sequentially in clinical practice. This “step-wise” approach may not be optimal and is subject to substantial clinical inertia and may expose patients to early cardiovascular and kidney risks.
- The CONFIDENCE trial (NCT05254002)[1] assessed the efficacy and safety of simultaneous initiation of the nsMRA finerenone and the SGLT2i empagliflozin to either agent alone in patients with CKD and T2D. The CONFIDENCE trial established their additive efficacy in reducing albuminuria levels by 180 days, but the longer-term benefits on kidney outcomes beyond this window are uncertain.
- We forecast the long-term *relative* and *absolute* clinical kidney benefits expected with combination therapy based on the observed early UACR reductions seen in the CONFIDENCE trial.

Methods

CONFIDENCE Trial

- The CONFIDENCE study was a phase 2, double-blind, randomized, active-controlled trial investigating the safety and efficacy of simultaneously initiated finerenone with an SGLT2i versus either therapy alone (**Figure 1**).
- Participants with an estimated glomerular filtration rate (eGFR) 30–90 mL/min/1.73 m^2, a urinary albumin-to-creatinine ratio (UACR) ≥100 to <5000 mg/g, T2D with HbA1c <11%, and on the clinically maximum tolerated dose of an ACEi/ARB for >1 month were enrolled.
- The study excluded participants with type 1 diabetes, serum potassium >4.8 mmol/L, chronic heart failure with reduced ejection fraction with New York Heart Association class II–IV, or use of another MRA or SGLT2i which cannot be discontinued at least 8 weeks prior to the screening visit.
- The primary hypothesis in CONFIDENCE was whether the combination of finerenone and an SGLT2i would decrease UACR more than either treatment alone at 180 days.

Figure 1: The CONFIDENCE Trial Design: Combination Therapy vs. Either Drug Alone



This figure is adapted from Green JB, et al.[8] under the terms of the Creative Commons Attribution-Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/). †Up/down titration based on eGFR, serum/plasma potassium, or safety and tolerability. ‡Participants with an eGFR of 40–90 mL/min/1.73 m^2 were recruited (Part A) prior to recruiting participants with an eGFR of 30–90 mL/min/1.73 m^2 (Part B). The number of participants will be capped in parts A and B as follows: 80% with an eGFR of ≤75 mL/min/1.73 m^2 and 20% with an eGFR of >75 mL/min/1.73 m^2.
eGFR, estimated glomerular filtration rate; EoT, end of trial; R, randomization; UACR, urinary albumin-to-creatinine ratio.

Step 1: Establishing Albuminuria as a “Mediator” of Long-term Kidney Benefits

- We first confirmed that nsMRA-induced early reductions in UACR strongly predict or “mediate” its subsequent effects on kidney outcomes in pivotal phase 3 trials of T2D and CKD (FIDELIO-DKD and FIGARO-DKD).
- We then leveraged this established association to estimate the expected *relative* reductions on kidney outcomes with combination use of SGLT2i and nsMRA based on the observed UACR lowering in the CONFIDENCE trial.

Figure 2: Schematic of Intermediate Biomarker as a “Mediator” of Long-term Clinical Benefit[2]

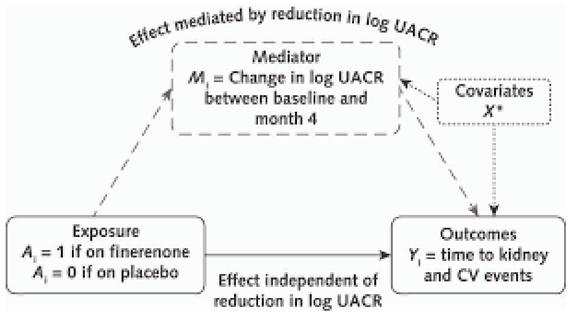
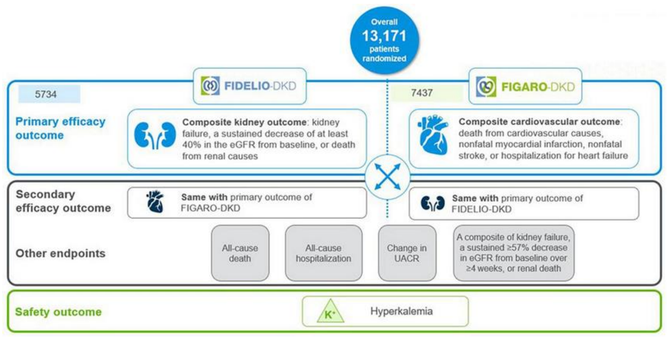


Figure 3: Pivotal Phase 3 Trials Establishing Long-term Efficacy of Finerenone[3,4]



- **The prespecified kidney composite endpoint of the FIDELIO-DKD and FIGARO-DKD pooled population was kidney failure (defined as ESKD or sustained eGFR <15 ml/min/1.73m2), a sustained ≥57% decrease in eGFR from baseline over ≥4 weeks, or renal death.**
- **In these pivotal trials, reduction in UACR (analyzed as a continuous variable) mediated 84% of the treatment effect on composite kidney outcome.[2]**

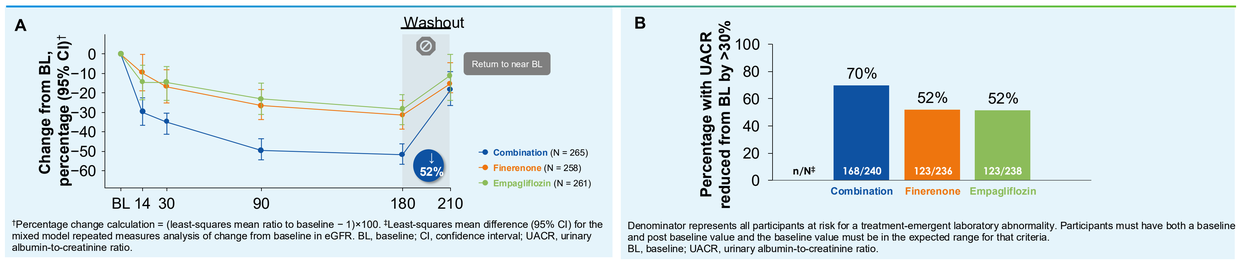
Results

Step 2: Evaluating the Early Effects on UACR Reduction with Combination Therapy Observed in the CONFIDENCE Trial

- **UACR Reduction Observed with Monotherapy:** Among 12,149 participants in FIDELIO-DKD and FIGARO-DKD not treated with either an SGLT2i or nsMRA at baseline, finerenone reduced UACR by **31%** by day 120
- **UACR Reduction Observed with Combination Therapy:** Combination therapy with an SGLT2i and a nsMRA robustly reduced UACR by **52%** in the CONFIDENCE trial (**Figure 4**). Based on the established mediating role of UACR reduction, the key question is what might be expected with long-term treatment in preventing downstream kidney clinical events?
- **Kidney Clinical Events Prevented with Monotherapy:** In the FIDELIO-DKD and FIGARO-DKD trials, finerenone treatment resulted in a **20%** reduction in the primary kidney composite outcome.
- **Kidney Clinical Events Prevented with Combination Therapy:** Based on the established mediating role of UACR reduction, the key question is what might be expected with long-term treatment of combination therapy in preventing downstream kidney clinical events?

Figure 4. Early Albuminuria Reduction Observed in the CONFIDENCE Trial[1] with Combination Therapy with an SGLT2i and a nsMRA

Continuous Changes in Albuminuria from Baseline | **Proportion Achieving Guideline-Recommended Thresholds of UACR Reduction**



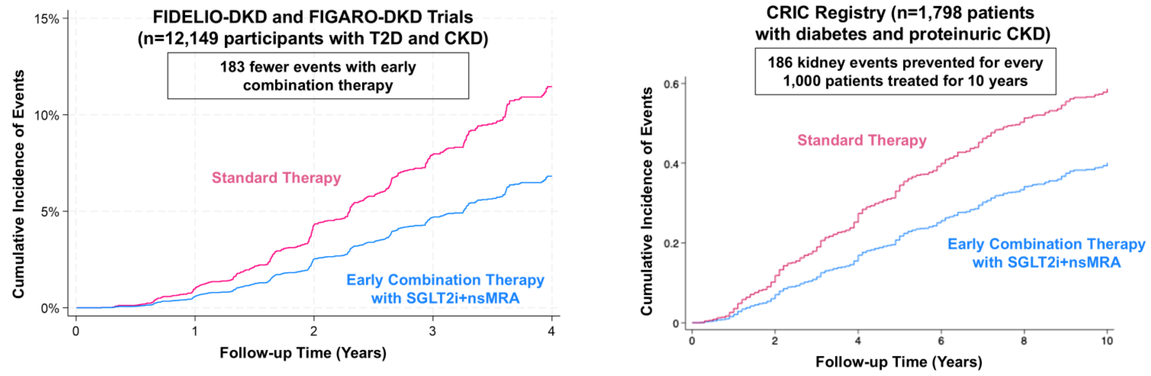
†Percentage change calculation = (least-squares mean ratio to baseline − 1)×100. ‡Least-squares mean difference (95% CI) for the mixed model repeated measures analysis of change from baseline in eGFR. BL, baseline; CI, confidence interval; UACR, urinary albumin-to-creatinine ratio.

Denominator represents all participants at risk for a treatment-emergent laboratory abnormality. Participants must have both a baseline and post baseline value and the baseline value must be in the expected range for that criteria.
BL, baseline; UACR, urinary albumin-to-creatinine ratio.

Step 3: Forecasting the Long-term Expected Benefits of Combination Therapy based on the Observed Early Effects Observed in the CONFIDENCE Trial

- In the FIDELIO-DKD and FIGARO-DKD trials, a 52% reduction in UACR (by 120 days) with upfront combination finerenone and empagliflozin (as expected based on CONFIDENCE) was forecasted to lead to a subsequent reduction in kidney outcomes by **42%** (HR 0.58; 95% CI 0.53-0.64).
- Over a median follow-up of 3.0 years (interquartile range 2.3–3.8 years), 448 kidney composite outcomes were observed in the placebo arm and 265 events (95% CI 242-292) would be projected with SGLT2i and nsMRA leading to 183 fewer events with early combination therapy.
- In the external validation cohort, among 1,798 individuals in the CRIC registry with diabetes and proteinuric CKD, 186 composite kidney events would be expected to be prevented for every 1,000 patients treated with early combination therapy over 10 years.

Figure 5. Forecasting Models in the Pivotal Trial Populations and an External Observational Cohort of Patients in Routine Clinical Care



Summary

The CONFIDENCE study provides supporting evidence on the combined benefits of multiple pillars of therapy and that early and intensive intervention can potentially provide greater UACR-lowering.

Early combination SGLT2i and nsMRA is projected to reduce clinically relevant kidney outcomes by over 40%, potentially preventing nearly 200 kidney events per 1,000 patients treated over 10 years in individuals with T2D and CKD.

References

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