Brigham and Women's Hospital
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HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Simultaneous versus Sequential Initiation of CKM Therapies

An Indirect Comparison of CONFIDENCE and FIDELITY

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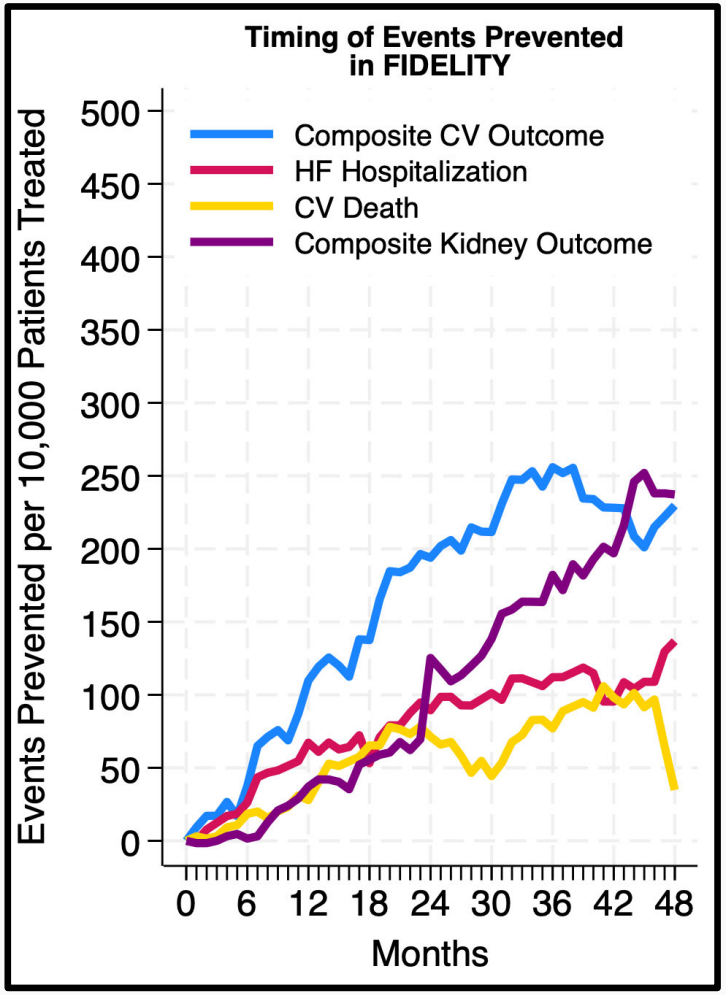
August 30th, 2026

CONFIDENCE and FIDELITY were sponsored by Bayer AG

Background

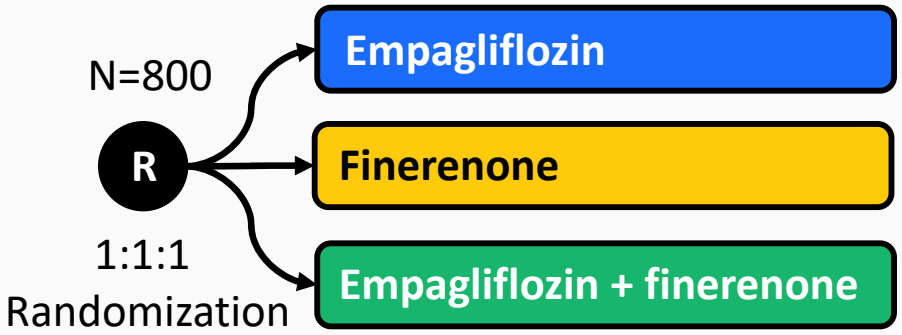
- Simultaneous initiation of CKD therapies offers the potential for more rapid reductions in high short-term cardiorenal risks
- However, patients and clinicians may prefer gradual sequential initiation strategies due to safety concerns
- *In this analysis of CONFIDENCE and FIDELITY*:
  - We indirectly compared the efficacy and safety of **sequential vs. simultaneous** initiation strategies with finerenone and SGLT2i



Ostrominski JW, et al. *JACC* 2025

The CONFIDENCE Trial and FIDELITY Program

CONFIDENCE



Population
CKD with T2D, albuminuria, and taking maximally tolerated ACEi/ARB

Primary endpoint
Relative change in UACR at 180 days

FIDELITY

Prespecified pooled analysis (n=12,990)

Finerenone vs. placebo (1:1)

FIDELIO-DKD

FIGARO-DKD

Recruitment: 2015-2018

Population: CKD with T2D, albuminuria, and taking maximally tolerated ACEi/ARB

Primary endpoint
Composite kidney outcome

Primary endpoint
Composite CV outcome

Methods

- **Exposures**
  - **"Simultaneous Strategy" (CONFIDENCE)**
    - Concurrent initiation of empagliflozin and finerenone
  - **"Sequential Strategy" (FIDELITY)**
    - Finerenone initiation atop stable background SGLT2i therapy
- **Outcomes**
  - Descriptive comparisons of relative change in UACR, eGFR, systolic blood pressure, and serum potassium
  - Selected safety events, including laboratory-defined hyperkalemia, were additionally examined

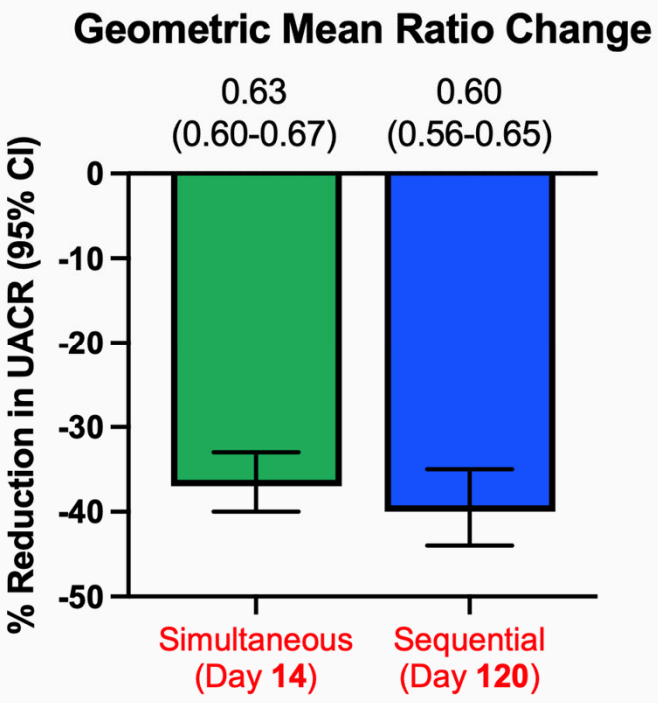
Baseline Characteristics

Characteristic	Simultaneous Strategy (CONFIDENCE) n=591	Sequential Strategy (FIDELITY) n=873
Randomized to finerenone	268 (50%)	436 (50%)
Age, years	67 ± 10	62 ± 10
Female sex	26%	24%
eGFR, mL/min/1.73 m^2	53 ± 17	66 ± 21
UACR, mg/g	591 [305, 1163]	448 [186, 946]
Systolic BP, mm Hg	135 ± 13	133 ± 14
Serum potassium, mmol/L	4.5 ± 0.4	4.3 ± 0.4

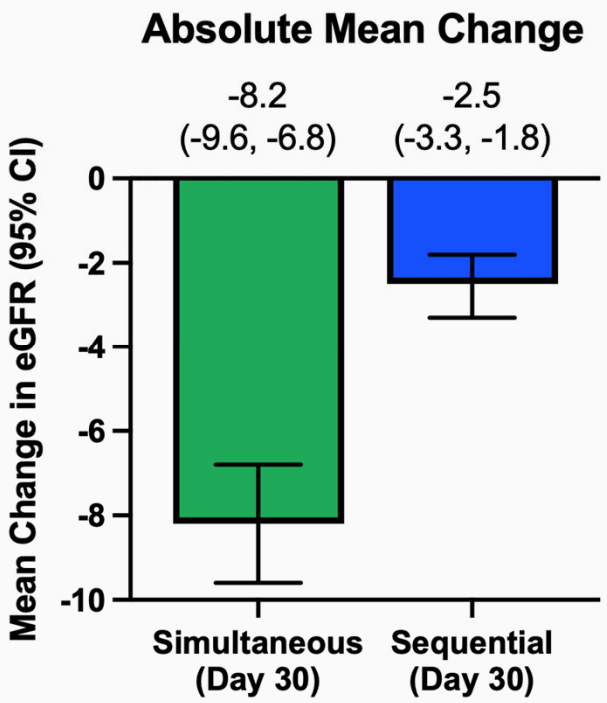
Characteristics reported as n (%), mean ± SD, or median [IQR].

Relative Change in UACR, eGFR, and Serum Potassium, by Strategy

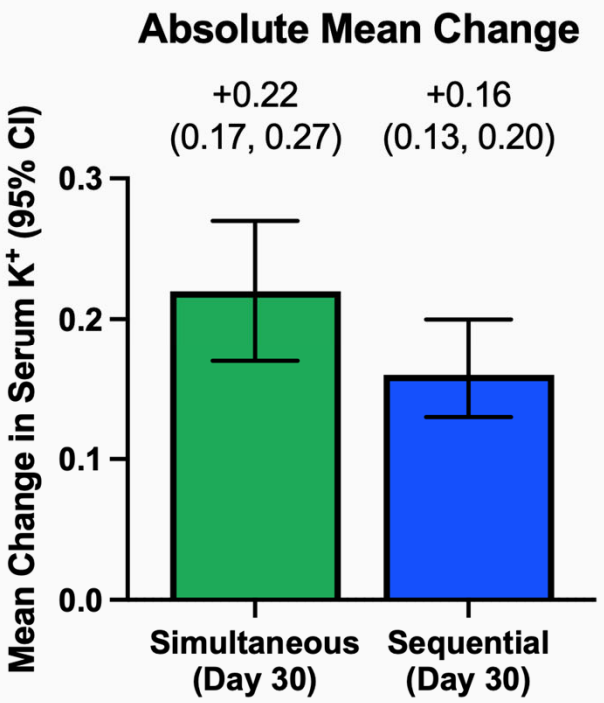
UACR (mg/g)



eGFR (mL/min/1.73 m²)



Serum K⁺ (mmol/L)



Mean changes (with 95% CI) estimated through linear regression with adjustment for baseline parameter values and the protocol-specified stratification factors.

Selected Safety Events at 180 Days, by Strategy

	Simultaneous Strategy (CONFIDENCE)		Sequential Strategy (FIDELITY)	
	Finerenone + Empagliflozin	Empagliflozin	Finerenone (+ SGLT2i)	Placebo (+ SGLT2i)
Any SAE, n (%)	19 (7.1%)	17 (6.4%)	28 (6.4%)	27 (6.2%)
SAE leading to treatment discontinuation, n (%)	3 (1.1%)	2 (0.8%)	1 (0.2%)	2 (0.5%)
Treatment-emergent AE leading to death, n (%)	1 (0.4%)	2 (0.8%)	1 (0.2%)	3 (0.7%)
Serum potassium >5.5 mmol/L, n (%)	40 (15.3%)	25 (9.7%)	8 (1.8%)	4 (0.9%)
Serum potassium >6.0 mmol/L, n (%)	12 (4.6%)	7 (2.7%)	1 (0.2%)	1 (0.2%)

Key Findings and Conclusions

- In this analysis of CONFIDENCE and FIDELITY:
  - Simultaneous finerenone + SGLT2i initiation achieved a comparable level of UACR reduction at least 3.5 months earlier than a sequential strategy
  - Serious adverse events were comparable between the strategies, although hyperkalemia events appeared more common with simultaneous initiation
- **Key limitation**: indirect trial comparison - these findings should be interpreted as exploratory and in the context of differences in trial design and population

This cross-trial analysis suggests that, with appropriate monitoring, simultaneous initiation of finerenone and a SGLT2i may be preferred to expedite cardiorenal risk reduction in CKD and T2D