University of Colorado Anschutz Medical Campus

colorado school of public health | UNIVERSITY OF COLORADO · COLORADO STATE UNIVERSITY · UNIVERSITY OF NORTHERN COLORADO

Effects of Zibotentan, Dapagliflozin, and Their Combination on Albuminuria and Fluid Parameters in Individuals With Chronic Kidney Disease: A Randomized Double-Blind Placebo-Controlled Crossover Trial

Victor Wasehuus, J. David Smeijer, Niels Jongs, Matthew Sayer, Neeraj Dhaun, Petter Bjornstad, Daniel Casillas, David Z. I. Cherney, Jessica Kendrick, Peter J. Greasley, Daniel van Raalte, Peter Rossing, Hiddo J.L. Heerspink

Presented by: Daniel Casillas

Background

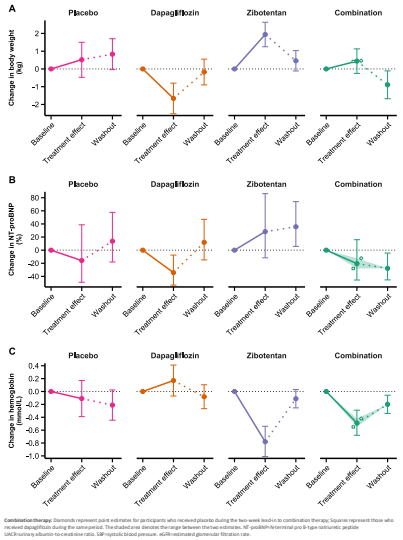
Albuminuria (UACR) is a strong, modifiable predictor of CKD progression and cardiovascular events. Despite guideline-directed therapy with ACEi/ARB and SGLT2 inhibitors, many patients have residual albuminuria and ongoing risk. Endothelin receptor antagonists (ERAs) lower albuminuria but can trigger fluid-retention signals, whereas SGLT2 inhibitors promote natriuresis and protect kidney function—complementary biology. We therefore tested whether combining the selective ERA zibotentan with dapagliflozin would maximize UACR reduction while attenuating fluid-retention signals versus ERA alone, SGLT2i alone, and placebo. Clarifying how hemodynamics and volume status relate to albuminuria could translate into fewer CKD progressions and events.

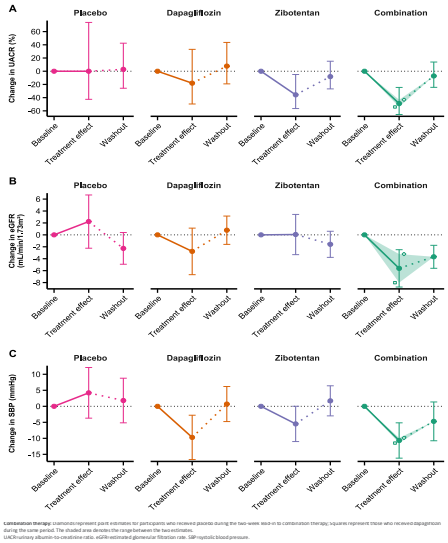
Objectives

- **Primary endpoint:** Percent change in UACR — combination (zibotentan + dapagliflozin) vs zibotentan alone.
- **Key secondary endpoints:** UACR vs placebo for each active arm; effects on eGFR, SBP, body weight, NT-proBNP; adverse events.

Results

- Participants: 27 randomized, 23 completed all periods.
- UACR vs placebo: −48.9% [95% CI −73.5, −1.8], p=0.044.
- Primary (combo vs ERA alone): −20.6% [95% CI −53.4, 35.3], p=0.39.
- eGFR (4-wk change): combo −5.62 mL/min/1.73 m² [95% CI −8.75, −2.49], between-group difference −5.68 mL/min/1.73 m², p=0.0087.
- SBP: decreased across active arms (combo ≈ −10.7 mmHg).
- Fluid signals: lower body weight vs ERA (−1.50 kg; p=0.0031) and trend toward lower NT-proBNP (−38.1%; p=0.051).





Methods

Design: Multicenter, randomized, double-blind, placebo-controlled, 4-period crossover (4 treatments in prespecified sequences with washout); 4 weeks/period.

Participants: Adults with CKD (UACR 100–3500 mg/g, eGFR ≥30 mL/min/1.73 m²).

Interventions: Zibotentan 1.5 mg, dapagliflozin 10 mg, combination, and placebo.

Analysis: Mixed-effects models for repeated measures (MMRM) on log-transformed outcomes with treatment and period effects; estimates back-transformed to % change; safety summarized by treatment period.

Conclusion

The combination of zibotentan + dapagliflozin lowered UACR vs placebo and attenuated ERA-associated fluid signals (↓weight, NT-proBNP trend). The primary comparison vs ERA alone was not statistically significant. A short-term eGFR dip was observed, consistent with expected hemodynamic effects, with acceptable short-term safety.

Implication: ERA–SGLT2i co-therapy is biologically plausible and merits larger, longer trials to test durability of UACR lowering, eGFR slope, and renal/cardiovascular endpoints, with monitoring of volume status and kidney function.

Colorado School of Public Health | 13001 East 17th Place, 3rd Floor, Mail Stop B119 | Aurora, CO 80045
coloradosph.cuanschutz.edu