ZODIAC Clinical Study Report

1. Introduction

Endothelin Receptor Antagonists (ERA) and Sodium Glucose co Transporter 2 inhibitors (SGLT2i) have been shown to significantly reduce albuminuria and delay progressive kidney function loss in patients with chronic kidney disease through distinct yet possibly synergistic mechanisms. ERA cause sodium and fluid retention which may result in edema and heart failure. In contrast SGTL2i exerts natriuretic and diuretic effects. Since SGLT2 inhibitors exert natriuretic / diuretic effects while ERAs cause sodium and fluid retention, there may be complementary effects as the diuretic properties of an SGLT2i can abrogate the sodium/fluid retaining effects of an ERA while the antialbuminuric effects may be complimentary owing to the different mechanisms of action of the two drug classes. The aim of this study was to test the hypothesis that the effects on albuminuria of combination treatment with the ERA Zibotentan and SGLT2i Dapagliflozin are complimentary and additive (primary) while the fluid retaining effects of Zibotentan can be mitigated by Dapagliflozin (secondary).

2. Methods Summary

The ZODIAC trial was a randomized, double-blind, placebo-controlled, crossover study conducted at six sites across five countries. It evaluated the effect of zibotentan (1.5 mg/day), and dapagliflozin (10 mg/day), alone and in combination, on albuminuria in adults, aged 18–75 years, with chronic kidney disease (CKD) (eGFR ≥30 mL/min/1.73 m² and UACR 100–3500 mg/g), with or without type 2 diabetes. Key exclusions included type 1 diabetes, NYHA class III–IV heart failure, recent acute coronary syndrome, and severe peripheral edema.

Participants were randomized into one of two treatment sequences and underwent three treatment periods, each separated by a washout. The first two periods (4 weeks each) involved monotherapy or placebo; the third included 2 weeks of dapagliflozin or placebo, followed by 4 weeks of combination therapy (Figure 1). Study visits occurred at screening, the beginning and end of each treatment period, and post-washout, totaling at least nine

visits per participant. Assessments included blood and urine sampling, bioimpedance spectroscopy, mGFR by iohexol plasma clearance, and safety monitoring. Urine samples were collected using three consecutive first-morning voids further supplemented with at home-based collection kits.

The primary endpoint was the percent change in UACR after four weeks of combination therapy versus zibotentan alone. Secondary endpoints included changes in mGFR, systolic blood pressure, body weight, NT-proBNP, hemoglobin, total body water and extracellular fluid volume. Exploratory comparisons included zibotentan versus dapagliflozin and placebo, as well as sequential versus simultaneous initiatiation of combination therapy.

Statistical Analyses

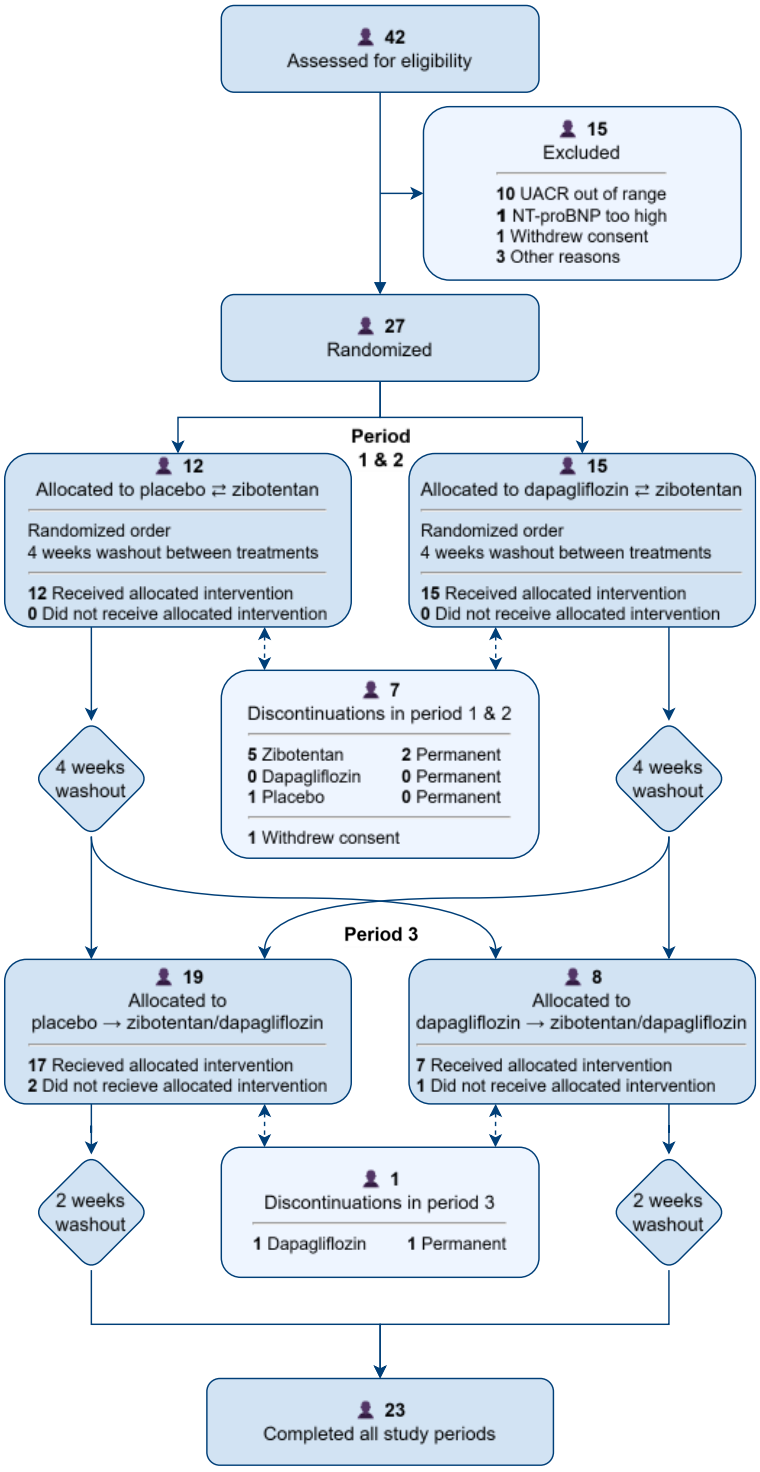
A sample size of 25 participants completing all treatment periods was estimated to provide >80% power to detect a 30% reduction in UACR with combination therapy (zibotentan + dapagliflozin) compared to zibotentan alone, assuming a within-subject standard deviation of 0.6 on the log-transformed scale and a two-sided alpha of 0.05. To account for an anticipated dropout rate of approximately 10%, the target enrollment was set at 28 participants.

The primary endpoint, percentage change from baseline in UACR following four weeks of combination therapy (zibotentan + dapagliflozin) versus zibotentan monotherapy, was assesed using a mixed model for repeated measures (MMRM) on log-transformed UACR. The model included fixed effects for treatment, treatment period, treatment sequence, and baseline log-transformed UACR. Results were back transformed for presentation with 95% confidence intervals and associated p-values.
Secondary and exploratory endpoints, including changes in mGFR, systolic blood pressure, NT-proBNP, hemoglobin, body weight, total body water and extracellular fluid volume, were analyzed using similar MMRM models. To assess the impact of sequential versus simultaneous initiation of combination therapy, period 3 data were further analyzed using ANCOVA, with baseline log-transformed UACR as a covariate and treatment as a fixed effect.

Role of the funder

The study was conducted with a grant from AstraZeneca. The funder had no influece in the study design, execution of the study, data analysis or interpretation.

Figure 1: Patient disposition and study design



3. Baseline Characteristics

Table 1: Baseline characteristics of the study participants

Characteristic	Study Sequence		Total
	Placebo-Zibotentan (n=12)	Zibotentan-Dapagliflozin (n=15)	(n=27)
Age, years	60.2 (12.6)	65.7 (5.8)	63.3 (9.6)
Gender, n (%)			
Female	1 (8.3)	2 (13.3)	3 (11.1)
Male	11 (91.7)	13 (86.7)	24 (88.9)
Race, n (%)			
White	9 (75)	12 (80)	21 (77.8)
Other	3 (25)	3 (20)	6 (22.2)
Weight, kg	77 (10.9)	84.9 (15.5)	81.4 (14)
Type 2 diabetes, n (%)	10 (83.3)	14 (93.3)	24 (88.9)
Cardiovascular disease, n (%)	1 (8.3)	5 (33.3)	6 (22.2)
Blood pressure, mmHg			
Systolic	144.7 (23.3)	143.4 (17.4)	144 (19.8)
Diastolic	78.9 (11.1)	80.5 (7.3)	79.8 (9)
eGFR, mL/min/1.73 m²	70.8 (30.4)	71.9 (27.7)	71.4 (28.3)
UACR, mg/g	281.1 [176.5-544.5]	430.9 [146.5-949.5]	304.3 [146.5-711.8]
NT-proBNP, pmol/L	18.3 (18.2)	40 (42.2)	30.4 (34.9)
Concomitant medication, n (%)			
RAS inhibition	12 (100)	14 (93.3)	26 (96.3)
GLP1-RA	6 (50)	10 (66.7)	16 (59.3)
MRA	1 (8.3)	6 (40)	7 (25.9)
Diuretics	7 (58.3)	8 (53.3)	15 (55.6)

Data are n (%), mean (SD), or median (IQR). eGFR=estimated glomerular filtration rate. UACR=urinary albumin-to-creatinine ratio. NT-proBNP=n-terminal pro b-type natriuretic peptide. RAS=renin-angiotensin system. GLP1-RA=glucagon-like peptide-1 receptor agonist. MRA=mineralocorticoid receptor antagonist.

4. Key Results

The ZODIAC trial screened 42 individuals, of whom 27 were randomized and received at least one dose of study medication. Twenty-three participants (85.2%) completed all treatment periods. Four discontinued early: three due to adverse events, one by withdrawal of consent (Figure 1). Participants had a mean (SD) age of 63.3 (9.6) years; 11% were female. Mean (SD) eGFR was 71.4 (28.3) mL/min/1.73 m², and median UACR was 304.3 mg/g (IQR: 145.5–711.8). Most participants (89%) had type 2 diabetes (Table 1).

Combination therapy with zibotentan and dapagliflozin reduced UACR by 48.9% (95% CI –65.5, –24.5) after four weeks, compared with reductions of 35.7% (95% CI –56.5, –5.0) with zibotentan monotherapy, 18.1% (95% CI –49.6, 33.2) with dapagliflozin monotherapy,

and 0.7% (95% CI –41.9, 70.6) with placebo (Figure 2A). The reduction was statistically significant versus placebo (p=0.044), but not versus zibotentan (p=0.39) or dapagliflozin (p=0.15). eGFR decreased by 5.6 mL/min/1.73 m² with combination therapy (Figure 2B), compared to a smaller decline with dapagliflozin and no change with zibotentan. Systolic blood pressure was reduced by 10.7 mmHg with combination therapy, compared to 5.5 mmHg with zibotentan, 9.7 mmHg with dapagliflozin, and an increase of 4.2 mmHg with placebo (Figure 2C).

Body weight increased by 1.9 kg with zibotentan, decreased by 1.7 kg with dapagliflozin, and remained stable with the combination. Similar patterns were observed for NT-proBNP or hemologlbin (Figure 3A-C).

5. Safety

Table 2: Adverse events occurring in >5% of participants

Adverse Event	DAPA, n (%)	ZIBO, n (%)	Placebo, n (%)	ZIBO+DAPA, n (%)	Total, n (%)
Fluid retention	0 (0%)	6 (23.08%)	1 (5%)	0 (0%)	6 (22.22%)
Weight increased	0 (0%)	4 (15.38%)	1 (5%)	0 (0%)	4 (14.81%)
Oedema	0 (0%)	2 (7.69%)	0 (0%)	0 (0%)	2 (7.41%)
Anemia	1 (5.88%)	1 (3.85%)	1 (5%)	1 (4.35%)	6 (22.22%)
Nasopharyngitis	0 (0%)	2 (7.69%)	3 (15%)	1 (4.35%)	5 (18.52%)
Diarrhea	1 (5.88%)	1 (3.85%)	1 (5%)	0 (0%)	3 (11.11%)
Dizziness	0 (0%)	1 (3.85%)	1 (5%)	0 (0%)	3 (11.11%)
Fatigue	1 (5.88%)	1 (3.85%)	1 (5%)	0 (0%)	3 (11.11%)
Cough	0 (0%)	0 (0%)	1 (5%)	0 (0%)	2 (7.41%)
Pruritus	0 (0%)	1 (3.85%)	1 (5%)	0 (0%)	2 (7.41%)
Nausea	0 (0%)	1 (3.85%)	0 (0%)	1 (4.35%)	2 (7.41%)
Headache	0 (0%)	2 (7.69%)	0 (0%)	0 (0%)	2 (7.41%)

Adverse events were most frequent with zibotentan monotherapy, particularly those related to fluid retention such as weight gain and edema. These events were absent when zibotentan was co-administered with dapagliflozin (table 2).

6. Discussion

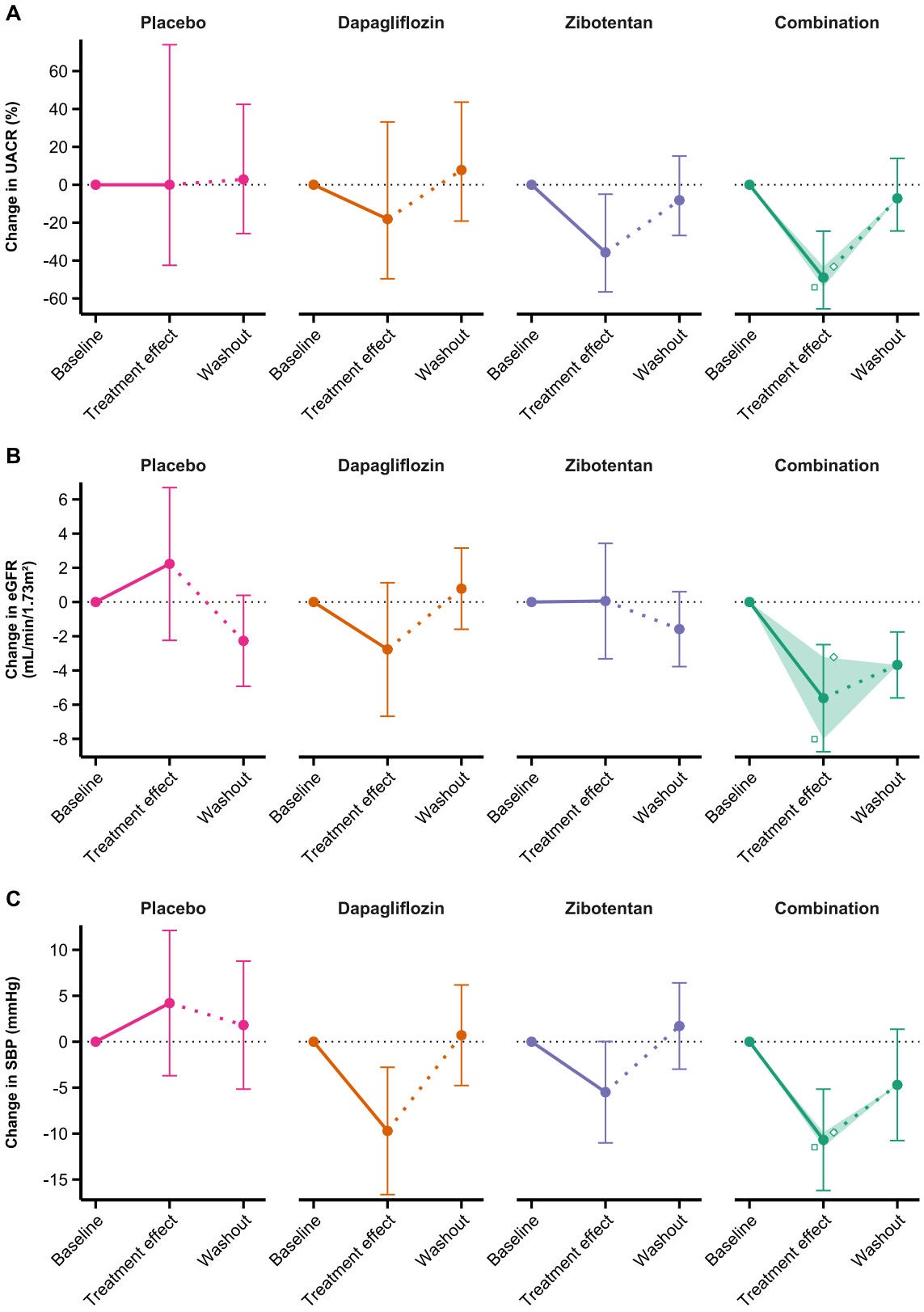
The ZODIAC trial offers compelling evidence that the combination of zibotentan and dapagliflozin achieves additive reductions in albuminuria, greater than either agent alone, while mitigating the adverse fluid retention effects associated with ERA therapy. Importantly, the combination mitigated NT-proBNP and body weight increases observed with zibotentan, and preserved hemoglobin more effectively; findings that align with the known diuretic and fluid volume-modulating effects of dapagliflozin.

Building on prior findings from ZENITH-CKD, ZODIAC adds a mechanistic layer by including both zibotentan low dose and dapagliflozin monotherapy arms, enabling direct attribution of effects and confirmation of additivity. Indeed the observed reduction of the combination treatment (49.8%) was fully additive (Multiplying the geometric mean ratios of the monotherapy arms: 0.643 [zibotentan] and 0.819 [dapagliflozin] provides a geometric mean ratio of 0.527, equivalent to 47.3% UACR reduction). Moreover, ZODIAC uniquely incorporates a crossover design and randomized sequencing, allowing for within-subject comparisons and the first evaluation of simultaneous versus rapid sequential combination treatment initiation.

Of clinical relevance, the safety profile of combination therapy resembled that of dapagliflozin alone, supporting that ERA-associated risks can be effectively managed through concurrent SGLT2 inhibition. We also demonstrated that simultaneous and sequential initiation strategies yielded similar results which simplifies clinical application, supporting fixed-dose combination approaches.

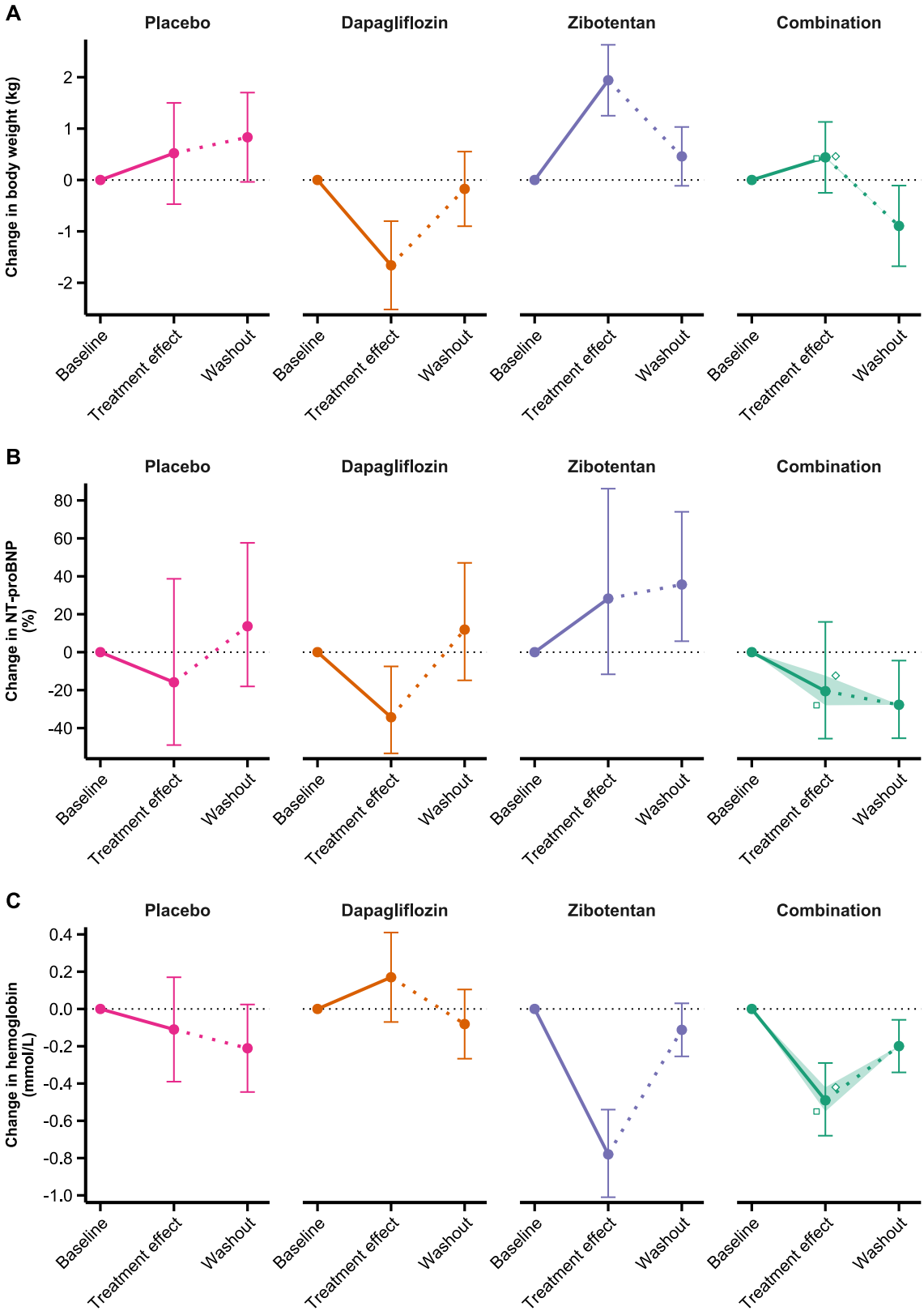
ZODIAC reinforces the potential of combined ERA/SGLT2 inhibition as a rational and practical strategy to address residual kidney risk in albuminuric CKD. These findings support ongoing and future trials to confirm long-term kidney and cardiovascular benefits.

Figure 2: Change in UACR, eGFR, and SBP



Combination therapy: Diamonds represent point estimates for participants who received placebo during the two-week lead-in to combination therapy; Squares represent those who received dapagliflozin during the same period. The shaded area denotes the range between the two estimates.

Figure 3: Change in body weight, NT-proBNP, and hemoglobin



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