Mediators of the effect of ertugliflozin on a composite kidney outcome in patients with type 2 diabetes and atherosclerotic cardiovascular disease: analyses from VERTIS CV

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Introduction: Sodium–glucose cotransporter 2 (SGLT2) inhibitors have been shown to slow the decline of kidney function in outcome trials, but the biological mediator(s) underlying the therapeutic benefit are not well established.

Purpose: We performed a post-hoc analysis exploring potential mediators of the effects of the SGLT2 inhibitor ertugliflozin on the VERTIS CV exploratory kidney composite outcome (sustained 40% decrease from baseline in estimated glomerular filtration rate [eGFR], chronic kidney replacement therapy or kidney death).

Methods: In VERTIS CV, 8246 participants with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease were randomised to placebo, ertugliflozin 5 mg or 15 mg (pooled for analyses, as prospectively planned), and were followed for a mean of 3.5 years. The hazard ratio (HR; 95% confidence interval) for the pre-specified exploratory kidney composite outcome was 0.66 (0.50, 0.88). Cox regression models were used to evaluate covariates that were significantly differentially changed from baseline with ertugliflozin treatment as candidate mediators, with a mediator identified as a covariate when added to an unadjusted model of randomised treatment assignment a) yielded a larger hazard ratio; and b) the mediator retained $P<0.05$ in the model (eGFR was excluded as a covariate). The percentage of mediation was determined by the proportional increase in the HR between the unadjusted and adjusted models for each post-randomisation period: early (first change from baseline measurement) and average (weighted average of change from baseline from all post-baseline measurements). Each potential mediator was tested individually, so across analyses, mediation % sums to >100%.

Results: Of 22 covariates significantly changed by ertugliflozin, nine were identified as potential mediators (Table). The covariates with a high percentage of mediation were those related to changes in blood erythrocytes (haemoglobin, haematocrit and red blood cell mass), with average changes in haemoglobin having the highest percentage of mediation (61.8%). Serum uric acid was associated with a mediation of 29.4% and 50.0% for the early and average post-randomisation effect periods, respectively. Early changes in glycated haemoglobin had a large mediation (50%), but the average change during the trial was not significant. Average change in serum albumin had a large mediation (29.4%). Average changes in body weight and systolic blood pressure had percentages of mediation of 41.2% and 14.7%, respectively.

Conclusion: Multiple factors may be involved in the reduction of the kidney composite outcome observed with ertugliflozin. In the short-term, changes in glycaemia had a high mediation effect. Over the long-term, changes suggestive of haemoconcentration and/or haematopoiesis (natriuresis-related effects), showed the highest percentage of mediation, followed by changes in serum uric acid and body weight (glucosuria-related effects).

Table. Percentage of mediation by biomarkers on a pre-specified exploratory kidney composite outcome

	Association with early change† in biomarker		Association with average change‡ in biomarker	
Potential mediators	HR (95% CI)	% Mediation	HR (95% CI)	% Mediation
Blood haematocrit	0.79 (0.58, 1.08)	38.2	0.86 (0.62, 1.18)	58.8
Blood haemoglobin	0.77 (0.57, 1.04)	32.4	0.87 (0.64, 1.18)	61.8
Red blood cell count	0.74 (0.54, 1.00)	23.5	NC	NC
Serum urate	0.76 (0.57, 1.02)	29.4	0.83 (0.62, 1.11)	50.0
Glycated haemoglobin	0.83 (0.61, 1.13)	50.0	NC	NC
Body weight	NC	NC	0.80 (0.59, 1.08)	41.2
Serum albumin	NC	NC	0.76 (0.56, 1.02)	29.4
Systolic blood pressure	NC	NC	0.71 (0.53, 0.95)	14.7
High-density lipoprotein cholesterol	NC	NC	0.67 (0.49, 0.92)	2.9

CI, confidence interval; HR, hazard ratio; NC, not calculated, as there was not a statistically significant association for the biomarker on the composite kidney outcome at the specified time period.
†First change from baseline measurement.
‡Weighted average of change from baseline from all post-baseline measurements.