The Effects of Sotagliflozin in Type 1 Diabetes on Clinical Markers Associated With Cardiorenal Protection: An Exploratory Analysis of inTandem3

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The dual sodium–glucose cotransporter 1 (SGLT1) and SGLT2 inhibitor sotagliflozin improved glycemic control, weight, and blood pressure (BP) as an adjunct to insulin in patients with type 1 diabetes (T1D) (1). Cardiorenal benefits with other SGLT2 inhibitors are mediated by changes in uric acid, albuminuria, hematopoiesis, and plasma volume rather than glucose (2). These glucose-independent mechanisms are considered similarly relevant in patients with T1D.

To evaluate the effects of sotagliflozin on mediators of cardiorenal protection in patients with T1D, we conducted a post hoc analysis of data from the 24-week, randomized, double-blind inTandem3 trial (NCT02531035). InTandem3 assessed sotagliflozin 400 mg/day or placebo as an insulin adjunct in 1,402 adults with T1D and estimated glomerular filtration rate (eGFR) $\geq$45 mL/min/1.73 m^2 (1). Based on previous cardiorenal mediation analyses performed with SGLT2 inhibitors, variables related to kidney function measured during the trial, including A1C, weight, BP, urine albumin-to-creatinine ratio (UACR), eGFR, uric acid, hematocrit, hemoglobin, and estimated plasma volume (ePV), were analyzed and least squares mean changes (geometric means for UACR) were compared between treatment groups. Percent change from baseline in ePV was determined using the Strauss equation (3). Correlation analysis between changes from baseline in eGFR, systolic BP, UACR, and ePV were performed using the Spearman correlation coefficient. Qualified researchers may request access to patient-level data and related study documents. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants.

The mean age of inTandem3 participants was 43 years (1); 4.3% had a history of cardiovascular disease (previous myocardial infarction, coronary revascularization, stroke, or peripheral vascular disease), and 38% were taking a renin-angiotensin system inhibitor. Mean eGFR was 92 mL/min/1.73 m^2 (5.3% with eGFR $<$60 mL/min/1.73 m^2), with a geometric mean UACR of 1.33 mg/mmol (13.3% with UACR $>$3.4 mg/mmol). Compared with placebo, sotagliflozin significantly reduced uric acid, BP, weight, and ePV, with a corresponding increase in hematocrit and hemoglobin (Table 1). In the subset of patients with UACR $>$3.4 mg/mmol, change in UACR did not reach significance (P = 0.061). Significant, albeit modest, correlations were observed between the change in eGFR and change in UACR (r = 0.093, P = 0.0245), change in eGFR and change in ePV (r = 0.24, $P < 0.0001$), and change in systolic BP and change in ePV (r = 0.08, P = 0.04).

In this cohort of participants with T1D without significant kidney or cardiovascular disease, the effect of sotagliflozin on clinical markers associated with cardiorenal protection was consistent with changes in these variables anticipated from cardiovascular and kidney outcome trials involving individuals with and without type 2 diabetes (T2D) (2). Moreover, the direction and magnitude of changes were consistent with mediation analyses performed with other SGLT inhibitors. Although a statistically nonsignificant reduction in UACR was observed, the inTandem3 population was not enriched for proteinuric chronic kidney disease and was likely underpowered for this analysis. These effects on mediators of cardiorenal benefits support the hypothesis that physiologic mechanisms of cardiorenal protection may also be relevant in T1D treated with an SGLT inhibitor.

SGLT inhibition is associated with a modest 2–4% increase in hematocrit, possibly because of hemoconcentration with a decrease in plasma volume, a sustained effect that occurs with SGLT

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Table 1—Effect of sotagliflozin on clinical factors associated with cardiorenal benefits

Variable	Sotagliflozin (n = 699)	Placebo (n = 703)	Difference in LS mean change from baseline at week 24 (95% CI)	P
HbA_{1c}				
Baseline, %	8.3 (1.0)	8.2 (0.9)		
LS mean change (95% CI)	−0.79 (−0.85 to −0.73)	−0.33 (−0.39 to −0.27)	−0.46 (−0.54 to −0.38)	<0.001
Baseline, mmol/mol	66.2	66.7		
LS mean change (95% CI)	−3.7 (−4.3 to −3.0)	−8.7 (−9.3 to −8.0)	−5.0 (−5.9 to −4.1)	<0.001
Weight, kg				
Baseline	82.4 (17.1)	81.6 (17.0)		
LS mean change (95% CI)	−2.2 (−2.5 to −2.0)	0.8 (0.5 to 1.0)	−3.0 (−3.3 to −2.7)	<0.001
Serum uric acid, μmol/L				
Baseline	265.5 (73.3)	264.0 (76.0)		
LS mean change (95% CI)	−14.7 (−18.2 to −11.2)	−0.1 (−3.5 to 3.4)	−14.6 (−19.2 to −10.1)	<0.001
Vascular tone				
Systolic BP, mmHg				
Baseline	122.0 (15.3)	121.8 (14.8)		
LS mean change (95% CI)*	−2.6 (−3.4 to −1.7)	0.7 (−0.2 to 1.6)	−3.3 (−4.5 to −2.1)	<0.001*
Diastolic BP, mmHg				
Baseline	76.4 (8.8)	76.7 (9.1)		
LS mean change (95% CI)	−1.1 (−1.7 to −0.5)	0.5 (−0.1 to 1.1)	−1.6 (−2.3 to −0.8)	<0.001
Pulse rate, beats/min				
Baseline	75.0 (11.5)	75.2 (11.2)		
LS mean change (95% CI)	0.7 (0.1 to 1.4)	1.2 (0.6 to 1.9)	−0.5 (−1.4 to 0.4)	0.291
Renal				
UACR in all patients, mg/mmol				
Baseline	1.33 (0.37)	1.32 (0.35)		
LS geometric mean at week 24 (SE)	1.30 (0.0)	1.33 (0.0)	−2.0% (−8.9 to 5.3)	0.579†
UACR in patients with baseline UACR ≥3.4 mg/mmol, mg/mmol				
Baseline	14.33 (0.40)	14.35 (0.38)		
LS geometric mean at week 24 (SE)	12.08 (0.01)	15.16 (0.01)	−20.3% (−37.2 to 1.1)	0.061†
Serum creatinine, μmol/L				
Baseline	74.4 (13.9)	74.1 (16.2)		
LS mean change (95% CI)	1.8 (1.1 to 2.5)	1.2 (0.5 to 1.9)	0.5 (−0.4 to 1.5)	0.242
eGFR, mL/min/1.73 m^2				
Baseline	91.5 (19.8)	92.5 (21.9)		
LS mean change (SE)	−2.1 (0.5)	−1.9 (0.5)	−0.2 (−1.5 to 1.0)	0.713
Volume status and hematopoiesis				
Hematocrit, %				
Baseline	42.2 (3.9)	42.2 (4.0)		
LS mean change (95% CI)	1.5 (1.2 to 1.7)	−0.4 (−0.6 to −0.2)	1.9 (1.6 to 2.2)	<0.001
Hemoglobin, g/L				
Baseline	140.8 (14.0)	140.7 (13.8)		
LS mean change (95% CI)	5.3 (4.7 to 6.0)	0.0 (−0.6 to 0.7)	5.3 (4.5 to 6.1)	<0.001
Estimated plasma volume, %				
Baseline‡				
LS mean change (95% CI)	1.1 (0.3 to 1.9)	−5.6 (−6.4 to −4.8)	−6.7 (−7.7 to −5.7)	<0.001
Serum albumin, g/L				
Baseline	43.2 (2.7)	43.3 (2.7)		
LS mean change (95% CI)	0.6 (0.4 to 0.7)	0.0 (−0.2 to 0.2)	0.6 (0.3 to 0.8)	<0.001
Serum sodium, mmol/L				
Baseline	137.8 (2.9)	137.8 (2.7)		
LS mean change (95% CI)	0.4 (0.2 to 0.6)	−0.1 (−0.3 to 0.1)	0.4 (0.2 to 0.7)	<0.001

Baseline data are mean (SD) except for baseline UACR, urine albumin, and urine creatinine values, which are geometric means (SD). LS, least squares. *At week 12. †Difference values are percentage of treatment difference in LS geometric mean ratio (95% CI). ‡Strauss equation estimates change from baseline using hemoglobin and hematocrit values (3).

inhibitors and which is also associated with BP reduction (2,3). In the Canagliflozin Cardiovascular Assessment Study (CANVAS), increases in hematocrit mediated 40–50% of observed risk reductions in heart failure and kidney outcomes in participants with T2D (2). Reductions in uric acid in inTandem3 are consistent with intact renal tubular effects; uric acid reductions mediated 35–40% of cardiorenal outcomes in CANVAS (2). inTandem3 was not designed to

assess heart or kidney outcomes, thereby limiting our ability to determine the relationship between changes in mediators and clinical outcomes in this cohort. However, we demonstrated modest correlations between changes in ePV and short-term changes in eGFR and BP. Specifically, decreases in ePV with sotagliflozin were associated with lowering of eGFR and BP, potentially consistent with acute hemodynamic effects of SGLT2 inhibition, changes that may also be associated with long-term kidney protection (4).

Results of the present analysis are consistent with a similar analysis of the Empagliflozin as Adjunctive to Insulin Therapy (EASE) trials (5). The results of these kidney outcome trials strongly suggest a class effect of SGLT inhibition in T2D and nondiabetic chronic kidney disease. Secondary analyses of EASE and inTandem3 suggest that this class effect may extend to T1D.

Since patients with T1D were excluded from cardiovascular or kidney disease trials of SGLT inhibitors, it is unknown whether this class of medications affords end-organ protection in people with T1D. Our findings suggest that mechanisms associated with cardiorenal protection are intact in inTandem3 participants with T1D, supporting the need for further investigation with clinical trials and/or real-world evidence, especially in people at high risk of diabetic kidney disease and/or cardiovascular disease progression.

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