Canagliflozin in Type 1 Diabetes: A Case Series of Patient Outcomes in a Diabetes Clinic

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Canagliflozin is a member of the sodium–glucose cotransporter 2 (SGLT2) inhibitor class and is approved by the U.S. Food and Drug Administration (FDA) for use in patients with type 2 diabetes as an adjunct to diet and exercise to improve glycemic control. Canagliflozin works by inhibiting SGLT2 in the proximal renal tubules, causing a reduction of filtered glucose reabsorption, lowering of the renal threshold for glucose, and increasing urinary glucose excretion (1).

The American Diabetes Association (ADA) *Standards of Medical Care in Diabetes—2017* (2) and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) (3) recommend SGLT2 inhibitors as add-on to metformin for patients with type 2 diabetes uncontrolled after 3 months of metformin use. The ADA lists the SGLT2 inhibitors as investigational agents for patients with type 1 diabetes because of the risk of diabetic ketoacidosis (DKA). Despite concerns for DKA in patients with type 2 diabetes treated with an SGLT2 inhibitor, a clinical review by an expert panel found that DKA occurred infrequently and recommended no change to their labeling (4). Although SGLT2 inhibitors are not FDA-approved for use in patients with type 1 diabetes, providers have prescribed these agents for off-label use in this patient population. Glycemic variability may be problematic in patients with type 1 diabetes; therefore, adding an SGLT2 inhibitor can assist in not only improving glycemic control but also reducing glycemic fluctuations. Although adding an SGLT2 inhibitor to insulin may increase the risk of hypoglycemia, the potential to reduce the need for increasing insulin doses may moderate this effect. Patients with type 1 diabetes uncontrolled with insulin therapy who are overweight/obese and have hypertension may benefit from the addition of an SGLT2 inhibitor because these medications help to lower A1C values and can reduce both weight and blood pressure.

Several studies have demonstrated reductions in A1C, weight, and blood pressure in patients with type 1 diabetes on either canagliflozin or empagliflozin, another SGLT2 inhibitor. These clinical trials showed A1C reductions in the range of 0.25–0.4% (5–9) and weight loss ranging from 2.1 to 4.2 kg (5,7,9). Systolic blood pressure (SBP) was found to be reduced by 7.9 mmHg in one study (9).

Although controlled studies have reported outcomes for patients with type 1 diabetes on canagliflozin, the present study is unique in examining real-world outcomes in an actual clinical practice in a small group of patients receiving care in a specialty diabetes clinic.

The purpose of this study was to determine clinical outcomes, mainly A1C, and characteristics of patients with type 1 diabetes prescribed canagliflozin in a specialty clinic, the

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Iowa Diabetes and Endocrinology Center (IDEC). There are currently few data available regarding the use of canagliflozin in this specific patient population, and the studies that exist are small clinical trials. This study examined actual use of canagliflozin in clinical practice because the authors wanted to see how outcomes compared to those in randomized controlled trials.

TABLE 1. Baseline Patient Characteristics (*n* = 11)

Age, years, mean (SD)	45.00 (9.84)
Male, %	63.64
Duration of diabetes, years, mean (SD)	25.45 (9.78)
A1C, %	8.06 (1.11)
BMI, kg/m^2, mean (SD)	35.36 (5.26)
Weight, kg, mean (SD)	103.78 (17.75)
SBP, mmHg, mean (SD)	117.27 (13.78)
DBP, mmHg, mean (SD)	72.36 (16.10)

Methods

This study was a retrospective electronic medical record (EMR) (Centricity; GE Healthcare, Barrington, IL) review of all patients with type 1 diabetes prescribed canagliflozin by IDEC providers from June 2013 to June 2015. The study was designed to report on canagliflozin because it was the only FDA-approved SGLT2 inhibitor available in the United States at the beginning of the study period. Patients were referred to this clinic by local or regional providers for management of advanced diabetes and complications. An inquiry of Centricity was conducted during July 2015 to search for all patients with type 1 diabetes within the clinic who were prescribed canagliflozin. All patients were de-identified through the assignment of unique study numbers to ensure that Health Insurance Portability and Accountability Act (HIPAA) of 1996 requirements were met.

Patients meeting inclusion criteria had a diagnosis of type 1 diabetes, were at least 18 years old, received regular care at the clinic, received their initial canagliflozin prescription (index date) from a clinic prescriber, returned for a minimum of two follow-up office visits after the canagliflozin index date, and had a baseline estimated glomerular filtration rate (eGFR) >45 mL/min for a starting dose of 100 mg or eGFR >60 mL/min for a starting dose of 300 mg (as recommended in the package insert). Patients were excluded if they were not receiving canagliflozin continuously from the index date to the second follow-up office visit for reasons such as presumed tolerability or efficacy issues, patient-volunteered nonadherence, or if the patient's dose was changed between the index date and second follow-up office visit.

Baseline characteristics extracted from the EMR on the index date included sex, age, duration of diabetes (years), type of insulin therapy, A1C, BMI, weight (kg), SBP, diastolic blood pressure (DBP), and dose of canagliflozin (either 100 or 300 mg throughout the entire study period). First and second follow-up office visits were defined as the first and second time the patient returned to the diabetes clinic after the index date. Values recorded for each follow-up office visit included A1C, BMI, weight, SBP, and DBP. Although it is a standard of practice to assess eGFR at baseline and at least annually, data were obtained after the second follow-up office visit, which was often before the annual eGFR would have been monitored. The Clinical Laboratory Improvement Amendments–waived Alere Afinion AS-100 Analyzer (Alere, WAltham, Mass.)was used by properly trained clinic staff to analyze and report whole blood A1C results during the entire study period. Quality control procedures were followed and documented routinely by clinic staff as specified by the manufacturer.

Sample population characteristics were analyzed using descriptive statistics. Paired *t* tests were performed on the primary (A1C) and secondary (BMI, weight, SBP, DBP) outcomes. *P* values less than $\alpha = 0.05$ were considered statistically significant. The Shapiro-Wilk test confirmed that all variables were normally distributed. Means and SDs for all variables were calculated. The study was approved by the Mercy Medical Center institutional review board and adhered to all HIPAA and human subjects protection standards.

Results

Of the 53 patients screened, 11 were included in the final analysis. Reasons for excluding patients from the final analysis were based on provider notes in the EMR that indicated either the patient did not adhere to prescribed use, the patient self-reported intolerance or lack of effectiveness, or the provider reported lack of effectiveness. Baseline population characteristics are listed in Table 1. Mean age was 45 years, weight was 103.78 kg, and A1C was 8.06%. The majority of the patients were male with a mean duration of diabetes of 25.45 years. The mean time interval from index date to first follow-up visit and from first to second follow-up visit was 105 and 99 days (about 6 months), respectively. Canagliflozin 100 mg was the dose at index date of canagliflozin prescribing for 63.64% of patients, and 300 mg was the dose at index date for 36.36% of patients.

Mean reductions in the primary outcome of A1C were 0.66% from baseline to first follow-up office visit and 0.71% from baseline to second follow-up office visit, both of which were statistically significant (P = 0.001 for both) (Table 2). Reductions in A1C for patients taking the 100-mg dose of canagliflozin were 0.59

TABLE 2. Primary and Secondary Outcomes With Canagliflozin 100 mg and 300 mg Combined (*n* = 11)

	Baseline Mean (SD)	First Follow-Up, Mean (SD)	Difference: Baseline to First Follow-Up	*P*	Second Follow-Up, Mean (SD)	Difference: Baseline to Second Follow-Up	*P*
A1C, %	8.06 (1.11)	7.40 (0.99)	–0.66	0.001***	7.35 (0.94)	–0.71	0.001***
BMI, kg/m^2	35.36 (5.26)	34.37 (5.48)	–0.98	0.013**	33.40 (4.62)	–1.95	0.056*
Weight, kg	103.78 (17.75)	101.05 (19.34)	–2.73	0.022**	98.65 (19.98)	–5.13	0.054*
SBP, mmHg	117.27 (13.78)	116.00 (6.93)	–1.27	0.758	118.00 (14.91)	0.73	0.789
DBP, mmHg	72.36 (16.10)	68.36 (8.80)	–4.00	0.330	67.64 (10.73)	–4.73	0.331

**Significant at α = 0.10. **Significant at α = 0.05. ***Significant at α = 0.01.*

and 0.67% from baseline to the first and second follow-up office visit, respectively, and were statistically significant (P = 0.002 and P = 0.016, respectively). Additionally, the reductions in A1C for patients taking the 300-mg dose of canagliflozin, when compared to patients on the 100-mg dose, showed greater mean A1C reductions of 0.80% from baseline to first follow-up office visit and 0.78% from baseline to second follow-up office visit. The mean A1C reduction was not statistically significant at the first follow-up office visit (P = 0.096) but was significant at the second follow-up office visit (P = 0.031) (Tables 3 and 4).

Of the secondary outcomes, BMI reduction for all patients combined showed mean changes (SD) of 0.98 (1.08) and 1.95 (2.99) from baseline to first and second follow-up office visits, respectively; BMI change was statistically significant from baseline to first follow-up office visit (P = 0.013), but was not significant from baseline to second follow-up office visit (P = 0.056). Mean weight reduction of the aggregated patients was 2.73 kg (3.34) from baseline to first follow-up office visit and 5.13 kg (7.80) from baseline to second follow-up office visit. These changes were statistically significant from baseline to the first follow-up office visit (P = 0.022) and not significant from baseline to the second follow-up office visit (P = 0.054). Reductions in both SBP and DBP were not statistically significant (Tables 2–4).

TABLE 3. Primary and Secondary Outcomes With Canagliflozin 100 mg (*n* = 7)

	Baseline Mean (SD)	First Follow-Up Mean (SD)	Difference: Baseline to First Follow-Up	*P*	Second Follow-Up Mean (SD)	Difference: Baseline to Second Follow-Up	*P*
A1C, %	7.70 (1.04)	7.11 (1.00)	–0.59	0.002*	7.03 (0.77)	–0.67	0.016**
BMI, kg/m^2	36.66 (5.13)	35.86 (4.93)	–0.80	0.132	34.36 (3.65)	–2.29	0.154
Weight, kg	103.71 (17.64)	101.76 (19.02)	–1.96	0.204	98.00 (19.57)	–5.71	0.171
SBP, mmHg	114.00 (14.51)	114.00 (6.63)	0.00	1.000	116.86 (15.66)	2.86	0.466
DBP, mmHg	66.29 (13.92)	67.14 (8.63)	0.86	0.824	64.86 (10.64)	–1.43	0.783

**Significant at α = 0.01. **Significant at α = 0.05.*

TABLE 4. Primary and Secondary Outcomes With Canagliflozin 300 mg (*n* = 4)

	Baseline Mean (SD)	First Follow-Up Mean (SD)	Difference: Baseline to First Follow-Up	*P*	Second Follow-Up Mean (SD)	Difference: Baseline to Second Follow-Up	*P*
A1C, %	8.70 (1.04)	7.90 (0.88)	–0.80	0.096*	7.93 (1.04)	–0.78	0.031**
BMI, kg/m^2	33.08 (5.37)	31.76 (6.11)	–1.31	0.056*	31.72 (6.21)	–1.36	0.103
Weight, kg	103.90 (20.68)	99.83 (22.80)	–4.08	0.054*	99.80 (23.70)	–4.10	0.094*
SBP, mmHg	123.00 (11.94)	119.50 (6.81)	–3.50	0.667	120.00 (15.58)	–3.00	0.406
DBP, mmHg	83.00 (15.45)	70.50 (9.98)	–12.50	0.188	72.50 (10.38)	–10.50	0.354

**Significant at α = 0.10. **Significant at α = 0.05.*

Discussion

The results of this real-world study performed in a diabetes clinic showed a statistically significant decrease in the primary outcome of A1C reduction when canagliflozin was added to insulin therapy in this small case series of patients with type 1 diabetes. Reductions in A1C exceeded those reported in published clinical trials; however, the small number of patients limits generalizability of the data. Patients prescribed 300 mg had greater reductions in A1C and had higher baseline A1C values. The reasons for a higher proportion of patients being prescribed 100 mg in this study are unclear but are perhaps related to the desire by the prescribers to minimize adverse effects in patients with type 1 diabetes by using a lower dose. Weight loss achieved statistical significance at the first follow-up office visit; however, changes in SBP and DBP did not achieve statistical significance.

There are few published trials to compare to the current study. In the largest randomized trial published to date, Henry et al. (5) conducted a double-blind, placebo-controlled phase 2 study of 351 patients with type 1 diabetes treated with either multiple-dose insulin injections (37.6%) or continuous subcutaneous insulin infusion pump therapy (62.4%). Patients were randomized to either canagliflozin 100 mg, canagliflozin 300 mg, or placebo and followed for 18 weeks. Mean age was 42 years and 56% were male, with a baseline A1C of 7.9% and mean diabetes duration of 22.4 years. Patients followed a protocol-specified treat-to-target self-adjustment approach for changing insulin doses. Placebo-subtracted A1C reductions of 0.29 and 0.25% were reported in the 100- and 300-mg study arms, respectively, in patients achieving ≥0.4% reduction in A1C from baseline. Mean weight loss reported was 2.6 kg (3.1%) and 4.2 kg (5.1%) in the 100- and 300-mg study arms, respectively. Blood pressure changes were not reported. Rodbard et al. (6) conducted a substudy of the original study by Henry et al. (5) and examined 89 patients managed with continuous glucose monitoring. Canagliflozin-treated patients experienced a higher proportion of time spent in the glycemic target range, lower mean glucose, and greater improvement in patient satisfaction.

Argento and Nakamura (9) conducted a small retrospective study of 27 patients with type 1 diabetes who were using the Dexcom G4 for at least 1 year and had been prescribed canagliflozin 100 mg. A1C was reduced 0.4%, weight reduction was 2.1 kg, and SBP was reduced by 7.9 mmHg during the 3.7-month study.

An open-label proof-of-concept study of another SGLT2 inhibitor, empagliflozin, was published by Perkins et al. (7) and examined changes in A1C and weight in 40 patients with type 1 diabetes treated with empagliflozin 25 mg daily over 8 weeks. A1C was reduced 0.4% and weight reduced 2.6 kg (3.6%). Blood pressure changes were not reported. A separate analysis of this study by Perkins et al. (8) showed reduced glycemic exposure and variability in both the insulin pump and multiple daily injection patients.

A review of the website ClinicalTrials.gov indicates that a few more randomized trials are currently in progress. The results will add clarity to the efficacy and safety of the SGLT2 inhibitors when used for patients with type 1 diabetes.

This retrospective study could not control for confounders such as medication or lifestyle changes. It is unknown whether diabetes education was provided to the patients in the clinic before the index date, at index date, or subsequently because it was not possible to track education reliably. Either patients or non-diabetes clinic providers could have initiated changes that may have contributed to changes in A1C, weight, and blood pressure. Medication adherence could not be substantiated because refill histories and pill counts were not available. Adverse reactions to canagliflozin could not be reliably verified without access to medical claims data and thus were not reported. Concerns have been raised regarding a risk for DKA in patients treated with SGLT2 inhibitors (10); however, our study was unable to reliably verify ketosis in our sample. The small sample size of this study and results observed in a specialized diabetes clinic may not be generalizable to other clinic settings.

Conclusion

In the setting of actual clinical practice in a diabetes clinic, patients with type 1 diabetes who remained on canagliflozin through two follow-up office visits experienced a clinically and statistically significant reduction in A1C when canagliflozin was added to their current insulin regimen. Patients also experienced reductions in BMI, weight, and blood pressure; however, these results were not always statistically significant. Although canagliflozin poses potential risks, including DKA, for patients with type 1 diabetes, this medication may be an appropriate treatment for carefully selected, monitored, and educated patients. The results of ongoing clinical trials are anxiously awaited to determine whether efficacy and safety data will support broader use of this class of agents.

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Duality of Interest

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Author Contributions

T.M.R. and J.F.J. performed protocol development, collected data, and wrote and edited the manuscript. A.G.V. provided statistical analyses and wrote and edited the manuscript. T.M.R., J.F.J., and A.G.V. are the guarantors of this work and, as such, had full access to the data in the study and take full responsibility for the integrity and accuracy of the data analysis.

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