The Highs and Lows of SGLT-2 Inhibitors

Abstract

Objective: The primary outcome is to measure the reduction in hemoglobin A1C after initiating SGLT-2 inhibitor therapy in adult patients at UnityPoint Health. The secondary outcome is to measure the weight reduction in our study population.

Hypothesis: The hemoglobin A1C reduction in clinical practice is comparable to the hemoglobin A1C reduction on the SGLT-2 inhibitor package insert.

Method: This is a retrospective observational study using EPIC electronic medical record. The study population includes UnityPoint Health male and female patients greater than 18 years old who were prescribed an SGLT-2 inhibitor for at least 90 days.

Results: After 90 to 149 days for all SGLT-2 inhibitor medications, the change from baseline hemoglobin A1C was a reduction of 0.85 and the average weight loss was 5.0 pounds. Both the reduction in hemoglobin A1C and weight is highly significant between days 90 to 149, but there is no significant reduction between days 150 to 360. There is no significant difference between the SGLT-2 inhibitors or their dose on hemoglobin A1C and weight reduction.

Conclusion: The hemoglobin A1C and weight reduction in clinical practice is comparable to the SGLT-2 inhibitor package insert from 90 to 149 days of use.

Introduction

In the United States, more than 29 million people are living with diabetes and 86 million people, more than 1 in 3, are living with prediabetes. Each year, there are more than 200 000 deaths in people with diabetes. It was the seventh leading cause of death in 2013. It is also the leading cause of kidney failure, lower-limb amputations, and adult-onset blindness. During the 32 year period from 1980 to 2012, the number of adults with diagnosed diabetes in the United States nearly quadrupled, from 5.5 million to 21.3 million. Approximately 1.7 million adults are diagnosed with diabetes each year. If this trend continues, up to 1 in 2 US adults could have diabetes by 2050. The health and economic costs are enormous. In 2012, diabetes cost the US an estimated 245 billion dollars[1].

Due to both the health statistics and economic burden of diabetes, novel therapy will be needed to combat this disease. The development of a new class of anti-diabetes agents called sodium glucose co-transporter type 2 (SGLT-2) inhibitors have provided a new treatment option for the management of type 2 diabetes mellitus. SGLT-2 inhibitors, which include canagliflozin, dapagliflozin, and empagliflozin, act by decreasing renal glucose reabsorption, which increases urinary glucose excretion, and subsequently,

reduces plasma glucose and hemoglobin A1C concentrations. Modest reduction in body weight and blood pressure have also been observed following treatment with SGLT-2 inhibitors. This class of medication is generally well tolerated and have been safely used as a monotherapy or in combination with other oral anti-diabetic medications and insulin. The most common adverse events include genital mycotic infections and lower urinary tract infections[2].

Canagliflozin (Invokana) has been studied as a monotherapy, in combination with metformin, sulfonylurea, metformin and sulfonylurea, metformin and thiazolidinedione, and in combination with insulin. Treatment with canagliflozin produced clinically and statistically significant improvements in hemoglobin A1C compared to placebo. The recommended starting dose is 100mg once daily, taken before the first meal of the day. The dose can be increased to 300mg once daily in patients tolerating 100mg, and who have a eGFR of 60mL/min. Renal function should be assessed prior to starting the drug and monitored during use[3].

The monotherapy clinical trial studies showed statistically significant improvement in hemoglobin A1C ($p < 0.001$) at a once daily dose of canagliflozin 100mg and 300mg compared to placebo. The greatest proportion of patients achieved a hemoglobin A1C less than 7%, a significant reduction in fasting plasma glucose, improved postprandial glucose, and percent body weight reduction compared to placebo[3].

Stenlof et al. (2013) studied the efficacy and safety of canagliflozin monotherapy in patients with type 2 diabetes mellitus. In their 26 week, randomized, double-blind, placebo-controlled study, 584 patients received a placebo, or 100mg or 300mg of canagliflozin. The hemoglobin A1C was significantly reduced from baseline with canagliflozin 100mg and 300mg at week 26, compared to placebo. Canagliflozin decreased fasting plasma glucose and body weight ($p <0.001$)[4].

The clinical trial studies involving add-on combination therapy with metformin showed statistically significant improvement in hemoglobin A1C with canagliflozin 100mg and 300mg when added to metformin compared to placebo. There was also a significant reduction in percent body weight reduction compared to placebo[3].

Fulcher et al. (2015) examined the efficacy and safety of canaglifozin in patients who were inadequately controlled on sulfonylurea monotherapy. Their study showed that canagliflozin added to sulfonylurea monotherapy resulted in an improvement in hemoglobin A1C and body weight. They examined data in the CANVAS trial (canagliflozin cardiovascular assessment study), which was a double blind, placebo controlled study, where participants were given placebo, canagliflozin 100mg or 300mg once daily in addition to a sulfonylurea. After 18 weeks, the reduction in hemoglobin A1C was 0.74% ($p < 0.001$) and 0.83% ($p < 0.001$) with canagliflozin 100mg and 300 mg, respectively[5].

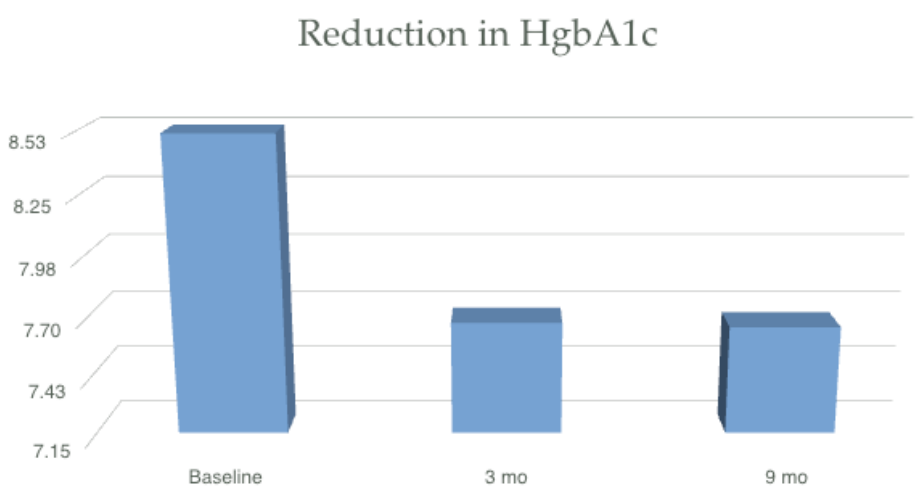
The clinical studies involving combination therapy with metformin and sulfonylurea also showed statistically improvement in hemoglobin A1C compared to placebo when added to metformin and sulfonylurea. Similarly, canagliflozin 100mg and 300mg daily resulted in a greater proportion of patient achieving a hemoglobin A1C less than 7%, significant reduction in fasting plasma glucose and percent body weight reduction[3].

Methods

This is a retrospective observational study. Patients were recruited using EPIC electronic medical records from UnityPoint Health. Patients with diabetes mellitus type 1 and 2 who were prescribed SGLT-2 inhibitor therapy for at least 90 days were used in the study. Data was collected from the spring of 2013 to the present. The study included 6417 patients, aged 18 and above. Specifically, the study included 3643 males with a median age of 58.6, and 2774 female patients with a median age of 58.3. A total of 3724 patients were prescribed canagliflozin, 1724 were prescribed dapagliflozin, and 939 were prescribed empagliflozin. Patients were excluded if they did not complete at least 90 days of therapy on the SGLT-2 inhibitor, or if the SGLT-2 inhibitor was initiated with another diabetic medication. Statistical analysis was done using paired and unpaired one-tail t-tests for measuring hemoglobin A1C and weight reduction.

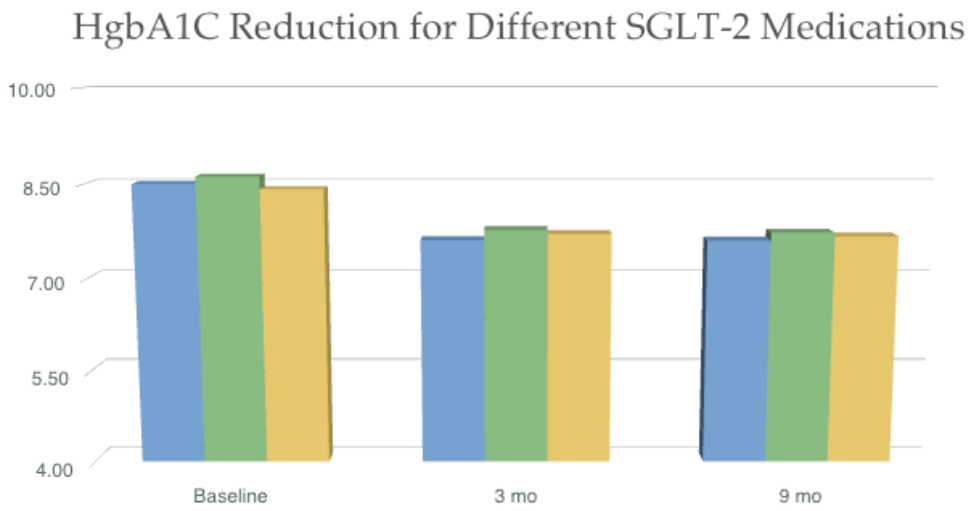
Results

The baseline hemoglobin A1C was 8.52%. After approximately 3 months of SGLT-2 inhibitor therapy, hemoglobin A1C improved to 7.67% ($p < 0.0001$). The change from baseline hemoglobin A1C was a reduction of 0.85. After approximately 9 months of SGLT-2 inhibitor therapy, hemoglobin A1C improved to 7.65% ($p < 0.33$). The change from baseline hemoglobin A1C was a reduction of 0.87. The reduction in hemoglobin A1C is highly significant between days 90 to 149, but there is no significant reduction between days 150 to 360.



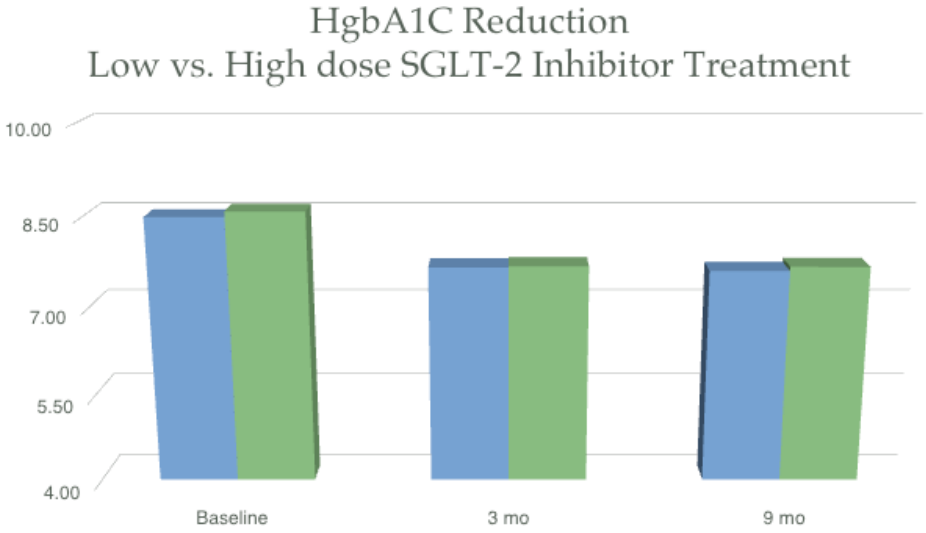
	Baseline (+/- 1 mo)	3mo (3-5 mo)	9mo (6-12 mo)
A1C	8.52%	7.67%	7.65%
Average Days from Baseline	-2.9	108	234
Change from baseline		-0.85	-0.87
n	1078	1078	1078
Significance (Paired T-Test)		<0.0001	<0.33 (NS)

There was no significant difference in hemoglobin A1C reduction between the approved SGLT-2 inhibitor medications.



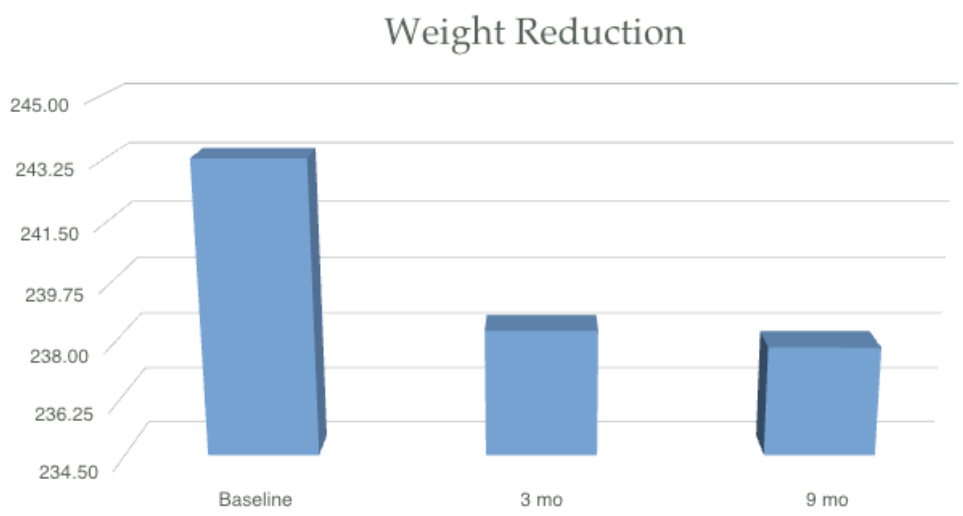
	Baseline (+/- 1 mo)	3mo (3-5 mo)	9mo (6-12 mo)
Canagliflozin	**8.50%**	**7.61%**	**7.60%**
Dapagliflozin	**8.62%**	**7.77%**	**7.73%**
Empagliflozin	**8.42%**	**7.71%**	**7.67%**
Significance (Unpaired T-Tests)	NS	NS	NS

There was also no significant difference in hemoglobin A1C reduction between high and lose dose SGLT-2 inhibitor medications.



	Baseline (+/- 1 mo)	3mo (3-5 mo)	9mo (6-12 mo)
Low dose	**8.49%**	**7.66%**	**7.60%**
High dose	**8.58%**	**7.68%**	**7.67%**
Significance by unpaired t-test	0.13 (NS)	0.69 (NS)	0.31(NS)

The baseline weight was 243.3 pounds. After approximately 3 months of SGLT-2 inhibitor therapy, weight decreased to 238.3 pounds ($p < 0.001$). After approximately 9 months of SGLT-2 inhibitor therapy, weight decreased to 237.8 pounds ($p < 0.37$). The average weight loss was 5.0 pounds after 90 to 149 days for all SGLT-2 inhibitor medications. The weight reduction between days 90 to 149 months is highly significant, but there was no significant weight reduction between days 150 to 360 for all SGLT-2 inhibitor medications.

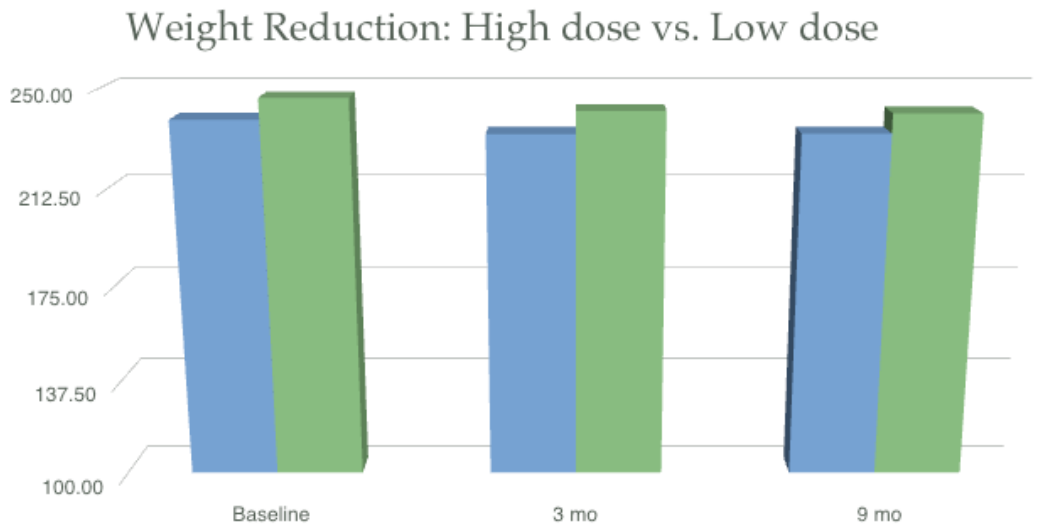


	Baseline (+/- 1 mo)	3mo (3-5 mo)	9mo (6-12 mo)
Weight (lbs)	243.3	238.3	237.8
Average Days from Baseline	-5.1	110	205
n	2355	2355	2355
Significance (Unpaired T-Test)		<0.001	<0.37 (NS)

There was no significant weight reduction between SGLT-2 inhibitor medications.

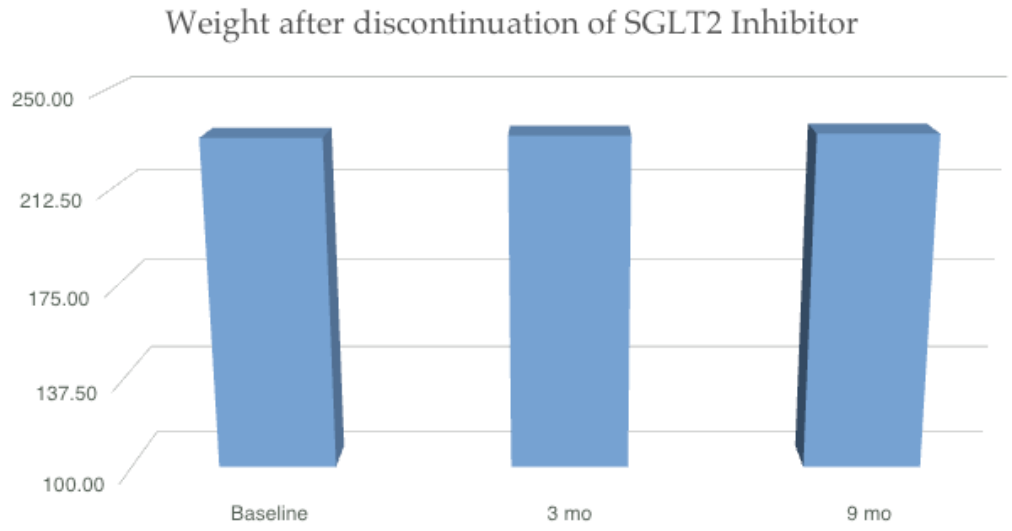
	Baseline (+/- 1 mo)	3mo (3-5 mo)	9mo (6-12 mo)
Wt on Canagliflozin (lbs)	**243.8**	**239.1**	**238.4**
Wt on Dapagliflozin (lbs)	**244.2**	**238.5**	**238.7**
Wt on Empagliflozin (lbs)	**239.7**	**235.1**	**233.9**
Significance (Unpaired T-Tests)		NS	NS

There was no significant weight reduction between high and low dose SGLT-2 inhibitor medication.



	Baseline (+/- 1 mo)	3mo (3-5 mo)	9mo (6-12 mo)
Low Dose SGLT-2 (lbs)	**238.5**	**233.2**	**233.3**
High Dose SGLT-2 (lbs)	**246.6**	**241.8**	**240.9**
Significance (unpaired t-test)		NS	NS*

There was no significant weight regain after cessation of SGLT-2 inhibitor medication at 3 and 9 months.



	Baseline (+/- 1 mo)	3mo (3-5 mo)	9mo (6-12 mo)
Weight (lbs)	232.3	233.2	233.9
Average Days from Baseline	7.2	109	194
n	738	738	738
Significance (paired T-Test)		0.76 (NS)	<0.8 (NS)

Conclusion

The purpose of this study was to compare the hemoglobin A1C after initiation of SGLT-2 inhibitor therapy in clinical practice versus the package insert. After 90 to 149 days for all SGLT-2 inhibitor medications, the change from baseline hemoglobin A1C was a reduction of 0.85 and the average weight loss was 5.0 pounds. Both the reduction in hemoglobin A1C and weight is highly significant between days 90 to 149, but there is no significant reduction between days 150 to 360. There is no significant difference between the SGLT-2 inhibitors or high versus low dose on hemoglobin A1C and weight reduction. We conclude that the hemoglobin A1C and weight reduction in clinical practice is comparable to the SGLT-2 inhibitor package insert from 90 to 149 days of use.

There are several limitations with the study. Some considerations for differences in the clinical setting include poor patient compliance versus a more controlled environment in the research setting. Our patient population may include a different patient selection versus the clinical trial studies. In some instances, the SGLT-2 inhibitor was prescribed, however, the patient may not have taken the medication. Also, we used the medication start and stop dates documented in EPIC, which may not correspond to the actual start and stop dates of the patient. The majority of patients were also taking another diabetic medication. The study does not factor in if patients made lifestyle modifications,

including exercise and dietary changes. The study does not factor in if there is a different response based on ethnicity.

Future direction would include an observational prospective study design and examine reasons for medication discontinuation. It could also determine the efficacy and side effects of SGLT-2 inhibitors in different ethnicities.

References

1. Diabetes. (2017, July 25). Retrieved from https://www.cdc.gov/chronicdisease/resources/publications/aag/diabetes.htm

2. Nuack, M. Update on developments with SGLT2 inhibitors in the management of type 2 diabetes. *Drug Design, Development and Therapy.* 2014:8 1335-1380. doi: 10.2147/DDDT.S50773.

3. Janssen Pharmaceuticals, Inc. Invokana (Canagliflozin) tablets. https://www.invokana.com/prescribing-information.pdf.2/2017. Last accessed May 16, 2017.

4. Stenlöf K, Cefalu WT, Kim K-, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab*. 2013;15(4):372-382. doi: 10.1111/dom.12054.

5. Fulcher G, Matthews DR, Perkovic V, et al. Efficacy and safety of canagliflozin used in conjunction with sulfonylurea in patients with type 2 diabetes mellitus: A randomized, controlled trial. *Diabetes Ther*. 2015;6(3):289-302. doi: 10.1007/s13300-015-0117-z.