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An investigation into the durability of glycemic control in patients with type II diabetes initiated on canagliflozin or sitagliptin: A real-world analysis of electronic medical records

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ABSTRACT

Aims: The aims of this study were to assess glycemic control, weight loss, and durability of glycemic control in patients initiated on canagliflozin (CANA) versus sitagliptin (SITA).
Methods: Adults with type II diabetes mellitus initiated on CANA or SITA (index date) were identified from IQVIA™ Real-World Data Electronic Medical Records – US database (03/29/2012–04/30/2016). Inverse probability of treatment weighting accounted for baseline differences between cohorts. Outcomes were compared using weighted Cox regression and Kaplan-Meier curves and included time to reaching HbA1c thresholds (<7% [53 mmol/mol], <8%[64 mmol/mol], <9%[75 mmol/mol]), weight loss ≥5%, failure to maintain HbA1c below threshold, new antihyperglycemic (AHA) prescription, and failure to maintain HbA1c/new AHA prescription.
Results: Weighted cohorts were well balanced (N_{CANA} = 14,542; N_{SITA} = 15,151). CANA patients were 12–15% more likely to reach the HbA1c thresholds, 47% more likely to lose ≥5% of body weight, 31% less likely to have a new AHA prescription, 10–15% less likely to fail to maintain HbA1c, and 13–26% less likely to fail to maintain HbA1c or have a new AHA, versus SITA patients.
Conclusions: CANA patients were more likely to reach HbA1c and weight loss thresholds and maintain HbA1c below threshold versus SITA patients, while being less likely to have a prescription for a new AHA, suggesting more durable glycemic control with CANA.

1. Introduction

Type II diabetes mellitus (T2DM) is a chronic condition that is estimated to affect more than 29 million people in the United States (US), nearly 10% of the population.[1] T2DM is characterized by high levels of blood glucose and can lead to serious long-term complications such as retinopathy, glaucoma, peripheral vascular disease, and cardiovascular disease.[1,2]

Goals for glycemic control in adults with T2DM may vary based on the patient population and on clinical judgement, but having an HbA1c < 7% (53 mmol/mol) is suggested by the American Diabetes Association as a reasonable goal for most adults.[2,3] On the other hand, achieving HbA1c < 8% (64 mmol/mol) may be more appropriate for certain populations including older patients and patients with a high level of comorbidity or a history of hypoglycemia,[2] and having HbA1c > 9% (75 mmol/mol), considered poor control, is an indicator used to measure performance in managed care settings as part of the Healthcare Effectiveness Data and Information Set.[3] Modest weight loss of ≥5% is also recommended for patients with T2DM who are overweight or obese and can help to improve glycemic control.[2]

Canagliflozin (CANA) is a sodium-glucose co-transporter 2 (SGLT2) inhibitor that was approved in 2013 for T2DM treatment.[4] CANA acts independently of insulin to increase renal glucose excretion thereby

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lowering blood glucose while also inducing modest weight loss and lowering systolic blood pressure. Sitagliptin (SITA), a dipeptidyl peptidase-4 (DPP-4) inhibitor, is another antihyperglycemic agent (AHA) approved for T2DM.[5] Unlike CANA's mechanism of action, SITA is believed to work by inhibiting the inactivation of incretin hormones, leading to insulin-dependent reductions in blood glucose levels.[5] DPP-4s including SITA have not been associated with meaningful impacts on body weight,[6] and although they have been associated with reductions in systolic blood pressure, these reductions were relatively insignificant compared to other classes of AHAs including SGLT2s.[7]

Previous clinical trials[8–11] have demonstrated non-inferiority of HbA1c reduction for CANA 100 mg versus SITA 100 mg and significantly improved HbA1c reduction for CANA 300 mg versus SITA 100 mg. In a pooled analysis of two clinical trials, CANA 100 mg demonstrated similar or superior glycemic control as well as superior attainment of body weight-related quality measures compared to SITA 100 mg.[11] In the same analysis, CANA 300 mg was superior to SITA 100 mg in terms of attaining glycemic control and weight-related quality measures.[11]

In contrast to available clinical trial data, real-world data comparing CANA versus SITA are limited. One recent observational study evaluated glycemic control in patients initiated on CANA versus SITA.[12] Thayer et al. found that patients treated with CANA had greater HbA1c reductions (consistent with findings from the clinical trials) and longer persistence on medication compared to patients treated with SITA. However, to the best of our knowledge, there are no previously published real-world studies that directly compare the impact of CANA versus SITA on durability of glycemic control or weight loss. Indeed, while clinical trials and published real-world evidence have observed outcomes over 26–52 weeks,[8–10,12–14] there remains a need for data testing whether early comparative advantages of CANA over SITA on HbA1c decline are sustained long-term.

Given these current knowledge gaps, there is a need for real-world comparisons between these agents as well as a better understanding of the long-term durability of HbA1c reduction in patients treated with CANA or SITA. The aim of the present study is to compare glycemic control, weight loss, and durability of glycemic control in the real world, among patients initiated on CANA versus SITA.

2. Subjects

2.1. Study design and patient selection

A retrospective cohort study was conducted to follow patients with T2DM initiated on CANA or SITA on or after 03/29/2013 until either loss of follow-up (i.e., end of clinical activity) or the end of available data (i.e., 04/30/2016). For inclusion into the study, patients were required to have ≥1 diagnosis for T2DM at any time (International Classification of Diseases, 9th revision [ICD-9-CM]: 250.x0, 250.x2; International Classification of Diseases, 10th revision [ICD-10-CM]: E11.xx), been initiated on CANA or SITA on or after 03/29/2013 with no prescription for that agent in the past 12 months (the first prescription was defined as the index date), ≥12 months of clinical activity (baseline period) before the index date, ≥18 years of age on the index date, and ≥1 HbA1c measurement available during the 12-month baseline period. Patients were excluded if they had a diagnosis for type 1 diabetes mellitus at any time (ICD-9-CM: 250.x1, 250.x3; ICD-10-CM: E10.xx) or if they had baseline chronic kidney disease stage IIIb or higher or diabetic kidney disease (i.e., an estimated glomerular filtration rate [eGFR] <45 ml/min/1.73 m^2 or ICD-9-CM: 585.4–585.6, 250.4 or ICD-10-CM: N18, E11.2). Patients were then grouped into two study cohorts (CANA and SITA) based on the first of these two agents prescribed on or after 03/29/2013 (i.e., index therapy). CANA and SITA patients on the same day were excluded.

Because of the non-experimental nature of this study, CANA patients may be different, in terms of observable demographic and clinical characteristics, from SITA patients. To address these differences, inverse probability of treatment weighting (IPTW)[15] was used to weight patients such that CANA and SITA cohorts were balanced with respect to baseline demographic and clinical characteristics. All analyses during the follow-up period were conducted using these weighted samples.

3. Material and methods

3.1. Data source

Electronic medical records (EMRs) between 03/29/2012 and 04/30/2016 were retrieved from IQVIA™ Real-World Data Electronic Medical Records – US database. As CANA was approved for the treatment of T2DM by the US Food and Drug Administration (FDA) on 03/29/2013,[4] the start of the study period was chosen to allow for ≥12 months of data prior to the use of CANA in patients initiated on CANA. This IQVIA™ database gives a physician-centric view of approximately 35 million patients, and contains information such as patient demographics (e.g., age, gender), laboratory test results, vital signs, medication orders (e.g., National Drug Codes [NDC]), and diagnoses (e.g., ICD-9-CM and ICD-10-CM).

3.2. Study outcomes

The primary outcomes of this study were HbA1c over time, time-to-reach HbA1c below specific thresholds, time-to-weight loss ≥5% of baseline body weight, time to a prescription for a new AHA, time-to-failure to maintain HbA1c below threshold, and the composite outcome of time-to-failure to maintain HbA1c below threshold or to a prescription for a new AHA. The composite endpoint served as an estimate of the durability of glycemic control. The hypothesis was that a new AHA initiation likely indicated that a patient was unable to maintain his/her HbA1c below the threshold over time. HbA1c thresholds of <7%, <8%, <9%, and reduction of >1% (10.9 mmol/mol) from baseline were tested for the HbA1c outcomes. Time-to-index treatment discontinuation (defined as a gap >90 days between days of supply of CANA or SITA), time-to-a prescription for a new glucagon-like peptide 1 agonist (GLP-1), time-to-insulin, time-to-a prescription for a new injectable (i.e., earliest of GLP-1 or insulin), time-to-a prescription for a new DPP-4, and time-to-a prescription for a new SGLT2 were also evaluated.

Demographic and clinical characteristics during the 12-month baseline period were also compared between study cohorts. Demographic characteristics included age, gender, year of index date, race/ethnicity, and US region. Baseline clinical characteristics included the Quan-Charlson comorbidity index (Quan-CCI); the Diabetes Complications Severity Index (DCSI), a score designed to quantify diabetes-related complications and a predictor of adverse outcomes (higher score indicates higher disease severity); the dose of CANA/SITA prescribed on the index date; the number and types of AHAs prescribed; types of antihyperlipidemic and antihypertensive agents prescribed; HbA1c; body mass index (BMI); eGFR; low-density lipoprotein cholesterol (LDL-C); high-density lipoprotein cholesterol (HDL-C); systolic and diastolic blood pressure; and prevalence of urinary tract infection (UTI) and genital mycotic infection (GMI).

HbA1c values over time were described both among patients with baseline HbA1c ≥ 7% and among patients with baseline HbA1c ≥ 9% at 3-month intervals from 12 months pre-index to 30 months post-index. To evaluate this outcome, available HbA1c measurements were grouped into mutually exclusive 3-month periods (i.e., the time point ±45 days) during the baseline period, at the index date, and post-index. If multiple measurements were available during one interval, the closest reading to the time point was used. If multiple readings were available on the same day for the same patient, the mean value was used. Examining HbA1c at 3-month time points allowed us to characterize the similarity between the weighted cohorts in terms of HbA1c values at multiple time points during the baseline period, and also to characterize the impact of CANA and SITA on HbA1c over the

30 months post-index. For this outcome, patient follow-up was censored at the first date of a prescription for a new AHA (i.e., an AHA not prescribed during the 12-month baseline period or on the index date) to specifically characterize the impact of CANA and SITA prior to other additions to the therapeutic regimen.

Time-to-reaching HbA1c below threshold was evaluated among patients with a baseline HbA1c value above the respective threshold (e.g., time-to-reach HbA1c < 7% was evaluated among patients with baseline HbA1c ≥ 7%). Time-to-weight loss ≥5% was evaluated among patients with ≥1 baseline weight measurement. Time-to-a prescription for a new AHA was evaluated among all patients and was defined as the time to the first prescription for an AHA post-index, with no prescription for that agent on or during the 12 months pre-index. Time-to-failure to maintain HbA1c below threshold was evaluated among patients who either had a baseline HbA1c value below threshold (i.e., measured from index to the first date with HbA1c above the threshold) or among patients reaching below the threshold during follow-up (i.e., measured from the date of the first HbA1c measurement below threshold to the first date with HbA1c above threshold). The composite endpoint, time-to-failure to maintain HbA1c below threshold or to a prescription for a new AHA, was based on the hypothesis that having a new AHA prescription may represent a treatment failure (e.g., adding/switching to a new AHA due to inadequate glycemic control or intolerance to the medication).

AHA treatment patterns (i.e., adherence to the index therapy and proportion of patients with newly prescribed AHA by type of AHA) during follow-up were also compared between cohorts. Adherence measures included: medication possession ratio (MPR), defined as the sum of the days of supply of prescribed medication divided by the number of days from the index date up to the last day with available medication; and proportion of days covered (PDC) over the first 6 and 12 months post-index, defined as the sum of non-overlapping days covered by a prescription of medication divided by the number of days during each period of time (i.e., 6 or 12 months).

3.3. Statistical analysis

Weights for IPTW were based on the propensity score (PS) of being treated with CANA, estimated using multivariable logistic regression including the following baseline covariates: age, gender, US region, race/ethnicity, Quan-CCI, use of fixed-dose combination at index date, baseline number of medical visits, HbA1c value closest to index date, closest BMI value to index date, obesity diagnosis, and quarter of the index date. Each patient was assigned a weight calculated as 1/PS for the CANA cohort and 1/(1-PS) for the SITA cohort and then normalized by the mean weight. As a result of weighting, the effective sample sizes of each weighted cohort differed from those of the original cohorts although the same patients were contributing to the analysis. The results therefore represent a balanced comparison of the average treatment effect across patients initiating each treatment. For subgroup analyses based on age, weights were recalculated among the sub-populations.

Standardized difference was used to assess whether there were clinically and statistically meaningful differences between cohorts, defining balance as a standardized difference of <10% which is an accepted threshold in the literature.[16,17]

HbA1c over time was assessed post-index using a moving average (to smooth curves) and comparisons were made at each time point using weighted linear regression models containing a single indicator for treatment group, with generalized estimating equations to account for repeated measurements. Treatment patterns evaluated during follow-up were compared between weighted cohorts using chi-squared tests and Student's *t*-tests for categorical and continuous variables, respectively. Time-to-event outcomes were compared using hazard ratios (HRs; with 95% confidence intervals [CIs] and p-value) calculated using weighted Cox proportional hazards regression models containing a single indicator for treatment cohort. Median time-to-event was also examined using Kaplan-Meier analysis for the following outcomes: time-to-a prescription for a new AHA and time-to-a prescription for a new injectable AHA.

Since patients from the current study with moderate renal disease can be prescribed SITA at lower doses, a sensitivity analysis was performed to compare patients initiated on SITA 100 mg vs. patients initiated on CANA 100/300 mg.[18]

All analyses were performed using SAS software, Version 9.3 of the SAS System for Windows, SAS Institute Inc., Cary, NC, USA.

4. Results

4.1. Demographic and clinical characteristics

A total of 14,165 patients initiated on CANA and 15,528 patients initiated on SITA were identified and formed the study population (Fig. 1). Unweighted and weighted patient characteristics are included in supplementary material (Table S1). Prior to weighting, 62.3% and 34.0% of CANA patients were prescribed CANA 100 mg and 300 mg on the index date, respectively. Also prior to weighting, 37.9% and 59.5% of patients initiated on SITA were prescribed SITA 50 mg and 100 mg on the index date, respectively. Similar proportions of CANA and SITA patients (unweighted) were prescribed a biguanide or a sulfonylurea during the 12-month baseline period; however more CANA patients were prescribed insulin (32.5% vs. 14.1%; standardized difference: 44.8%) or a GLP-1 (23.7% vs. 10.2%; standardized difference: 36.8%) compared to SITA patients. Baseline use of antihypertensive agents (i.e., angiotensin-converting enzyme inhibitors, diuretics, beta blockers, and calcium channel blockers) was also similar between unweighted cohorts. In addition, patients initiated on CANA were more likely to have a BMI ≥35 kg/m^2 (50.7% vs. 41.6%; standardized difference: 18.4%) compared to patients initiated on SITA.

After applying IPTW, the effective sample sizes of the CANA and SITA cohorts were 14,542 and 15,151 respectively (the analytic population). Weighted cohorts were well-balanced with respect to all demographic and clinical characteristics examined.

4.2. HbA1c over time

After weighting and among patients with baseline HbA1c ≥ 7%, HbA1c values during the 12-month pre-index period (grouped in 3-month intervals) were similar between CANA and SITA patients (Fig. 2). Following index therapy initiation, mean HbA1c prior to a prescription for a new AHA declined steeply in both cohorts, with a larger decline in mean HbA1c observed in CANA patients (Fig. 2). The HbA1c reduction observed post-index therapy initiation, as well as the separation between CANA and SITA patients in terms of mean HbA1c, appeared to be maintained over 30 months of follow-up among those with available HbA1c data at those time points (Fig. 2). Specifically, mean HbA1c was significantly lower among CANA patients than SITA patients at all post-index date time points up to 30 months with the exception of 21 months post-index (Fig. 2).

Findings were similar when HbA1c over time was examined among patients with baseline HbA1c ≥ 9% (Fig. 3) and HbA1c ≥ 8% (data not shown). After weighting, HbA1c in this population was balanced at each time point pre-index date (Fig. 3). Post-index date, HbA1c prior to having a new AHA prescription declined sharply in both treatment cohorts and was significantly lower for CANA patients compared to SITA patients at all post-index time points up to 15 months; HbA1c at 18, 21, 27, and 30 months post-index was not significantly different between treatment cohorts (Fig. 3).

4.3. Time-to-event outcomes

Patients initiated on CANA were 15% more likely to reach an HbA1c < 7% (HR [95% CI]: 1.15 [1.09, 1.22]; p < 0.001), 14% more likely

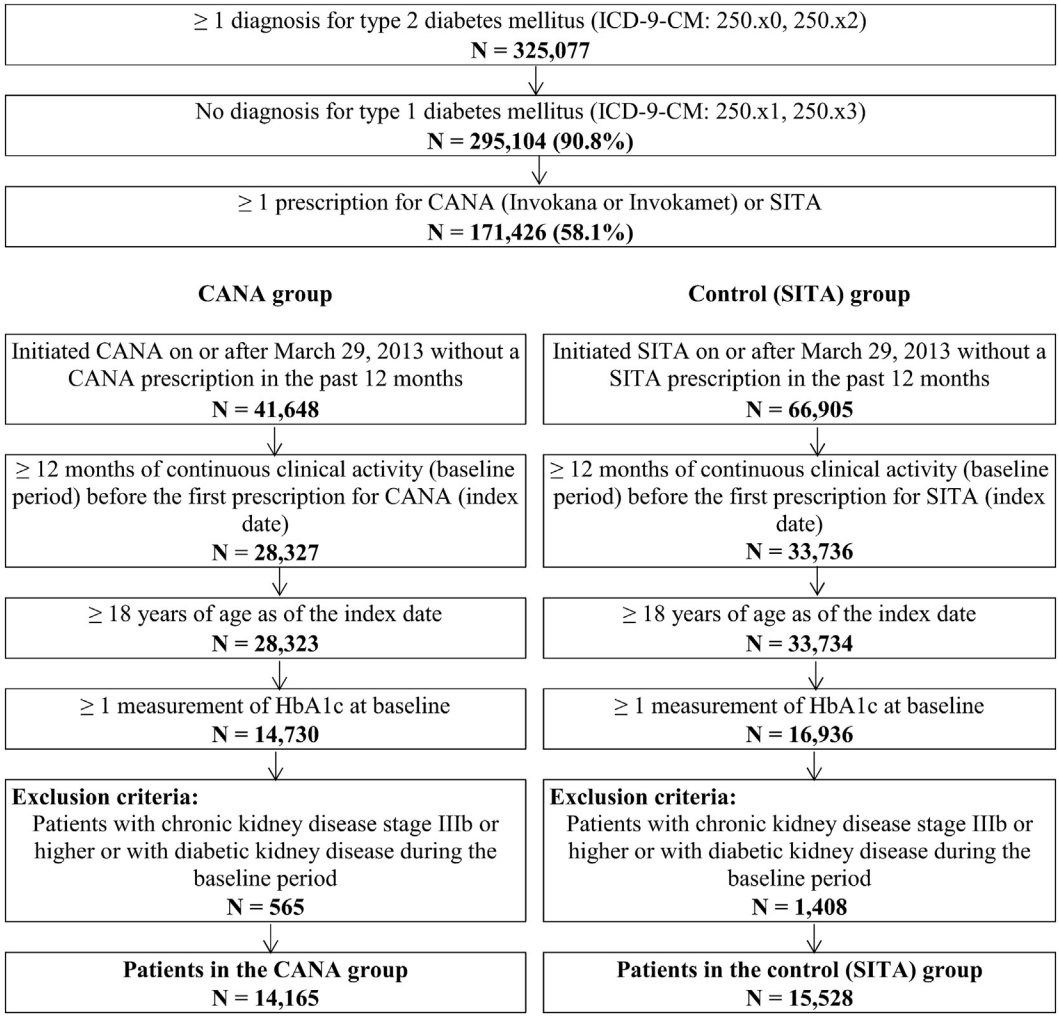


Fig. 1. Patient disposition. CANA = canagliflozin; ICD-9-CM = International Classification of Diseases, 9th revision; SITA = sitagliptin.

to reach an HbA1c < 8% (HR [95% CI]: 1.14 [1.07, 1.20]; p < 0.001), and 12% more likely to reach an HbA1c < 9% (HR [95% CI]: 1.12[1.04, 1.21]; p = 0.002) relative to patients initiated on SITA (Fig. 4). Similarly, among patients <65 years old with HbA1c ≥ 7%, patients initiated on CANA were 21% more likely to reach HbA1c < 7% relative to patients initiated on SITA (HR [95% CI]: 1.21 [1.13, 1.30]; p < 0.001; Fig. 4). Among patients ≥65 years old with HbA1c ≥ 7%, there was no significant difference in the hazard of reaching HbA1c < 7% between patients initiated on CANA or SITA (HR [95% CI]: 1.04 [0.94, 1.17]; p = 0.439; Fig. 4). Patients initiated on CANA were also significantly more likely to have an HbA1c reduction >1% (HR [95% CI]: 1.17 [1.11, 1.23]; p < 0.001; Fig. 4). The likelihood of achieving weight loss ≥5% was 47% higher in CANA patients relative to SITA patients (HR [95% CI]: 1.47 [1.40, 1.54]; p < 0.001; Fig. 4).

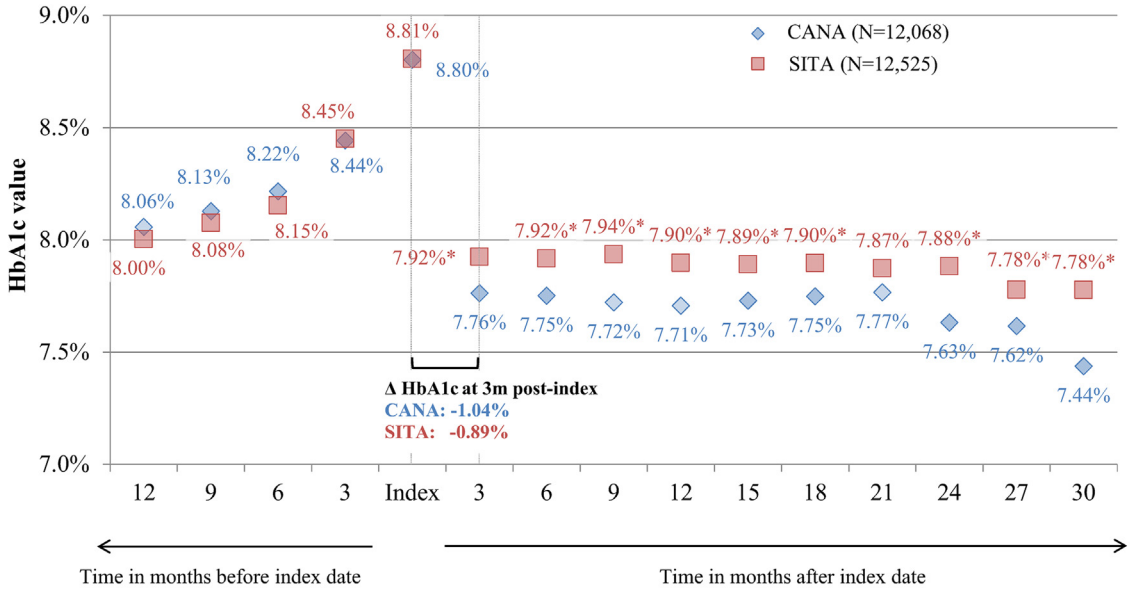
CANA and SITA patients discontinued their index medication (i.e., gap >90 days) at similar rates during follow-up (HR [95% CI]: 1.01 [0.97, 1.05]; p = 0.590; Fig. 4). However, CANA patients were 31% less likely to have a prescription for a new AHA (HR[95% CI]: 0.69 [0.66;0.72]; p < 0.001), 24% less likely to have a prescription for a new injectable AHA (i.e., insulin or a GLP-1 agent; HR [95% CI]: 0.76 [0.71, 0.82]; p < 0.001), and 64% less likely to have a prescription for a new SGLT2 agent (HR [95% CI]: 0.36 [0.33, 0.39]; p < 0.001; Fig. 4). Having a prescription for a new DPP-4 agent was more likely in CANA patients than in SITA patients (HR [95% CI]: 1.76 [1.61, 1.91]; p < 0.001; Fig. 4). Median time-to-a prescription for a new AHA was 7.2 months longer for CANA versus SITA patients (i.e., 20.3 vs. 13.1 months). Median time-to-a prescription for a new injectable AHA was not reached.

After reaching HbA1c below threshold, CANA patients were 10 to 15% less likely to fail to maintain their HbA1c below threshold (e.g., HbA1c ≥ 9% after reaching or having baseline HbA1c < 9%; HR [95% CI]: 0.85 [0.79, 0.92]; p < 0.001; Fig. 4). When failure to maintain HbA1c below threshold and having a prescription for a new AHA were considered together as a surrogate for durability of glycemic control, CANA patients were 13 to 26% less likely to fail to maintain HbA1c below threshold or to have a prescription for a new AHA (all p < 0.001; Fig. 4).

Similar results were found when comparing patients initiated on SITA 100 mg versus patients initiated on CANA 100/300 mg (Fig. S1).

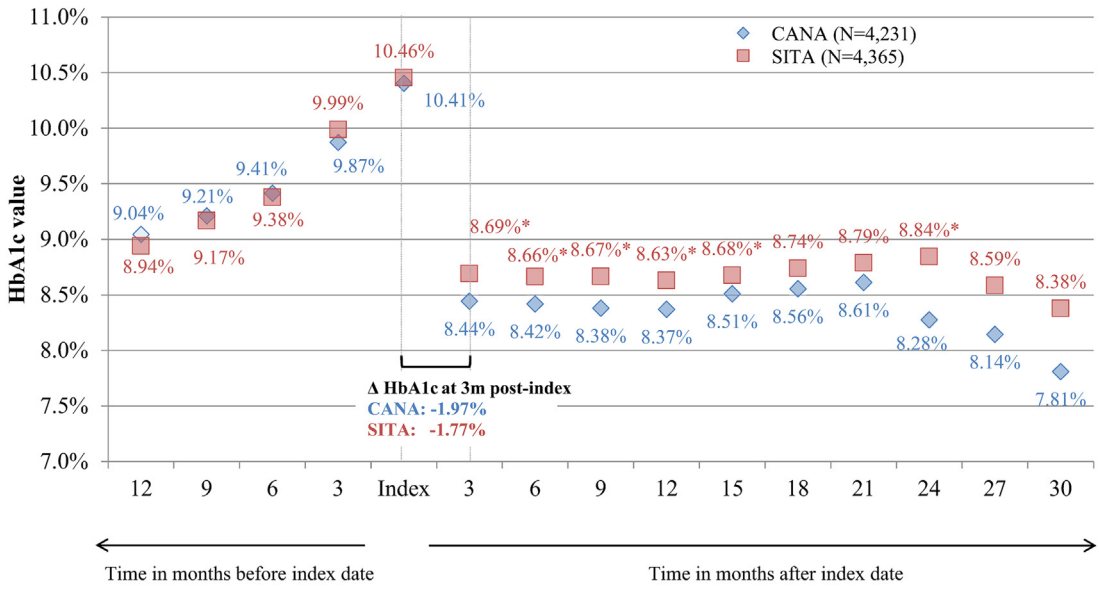
4.4. Treatment patterns

During follow-up, patients initiated on CANA had lower MPR and PDC for the index therapy on average, compared to patients initiated on SITA (e.g., mean PDC at 12 months: 72.6% vs. 73.7%; p = 0.020; Table 1). Fewer CANA patients were prescribed a new AHA (36.5% vs. 48.9%; p < 0.001) or insulin (6.9% vs. 9.2%; p < 0.001) during follow-up compared to SITA patients (Table 1). CANA patients were most commonly prescribed a new DPP-4 agent (11.5%), followed by an SGLT2 agent (9.6%; Table 1). SITA patients were most commonly prescribed a new SGLT2 agent (23.7%), followed by a GLP-1 agent (10.3%; Table 1).



Sample size	Before index date				Index	After index date									
	12m	9m	6m	3m		3m	6m	9m	12m	15m	18m	21m	24m	27m	30m
CANA (N=12,068)	5,107	4,988	5,104	4,921	7,858	4,502	2,958	2,222	1,680	1,165	858	524	404	261	125
SITA (N=12,525)	4,824	4,757	4,950	4,807	8,102	4,255	2,756	1,863	1,402	907	616	414	247	148	88

Fig. 2. Mean HbA1c values over time (prior to a prescription for a new AHA) in patients with baseline HbA1c ≥7%. AHA = antihyperglycemic agent; CANA = canagliflozin; SITA = sitagliptin. Note: * indicates p-value <0.05.



Sample size	Before index date				Index	After index date									
	12m	9m	6m	3m		3m	6m	9m	12m	15m	18m	21m	24m	27m	30m
CANA (N=4,231)	1,526	1,507	1,511	1,509	2,830	1,450	926	709	506	384	261	180	126	81	44
SITA (N=4,365)	1,409	1,416	1,350	1,437	2,885	1,406	880	561	425	287	161	109	61	42	18

Fig. 3. Mean HbA1c values over time (prior to a prescription for a new AHA) in patients with baseline HbA1c ≥9%. AHA = antihyperglycemic agent; CANA = canagliflozin; SITA = sitagliptin. Note: * indicates p-value <0.05.

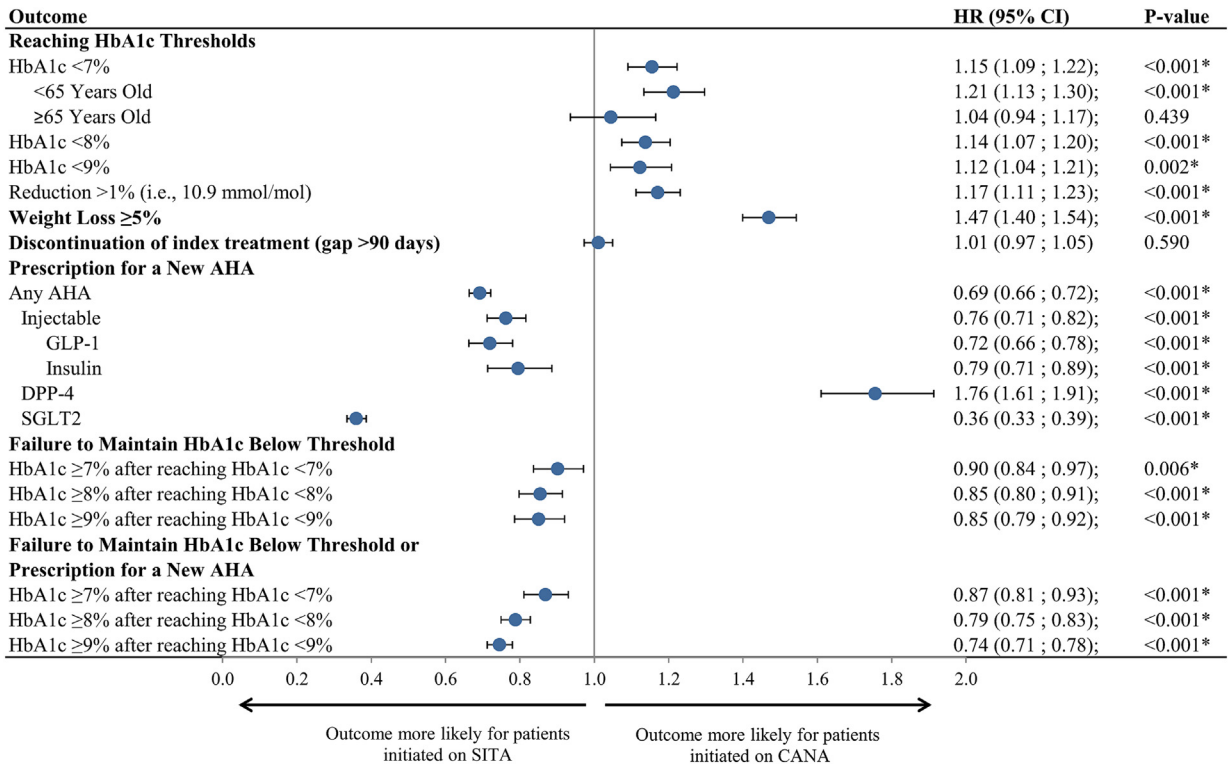


Fig. 4. Time to reaching HbA1c and weight loss thresholds, treatment discontinuation, and failing to maintain HbA1c below Threshold for patients initiated on CANA versus SITA. AHA = antihyperglycemic agent; CANA = canagliflozin; HR = hazard ratio; SITA = sitagliptin. Note: * indicates p-value <0.05.

5. Discussion

Patients initiated on CANA not meeting baseline HbA1c thresholds of <7% or <9% had lower mean HbA1c values post-index date when measured prior to a prescription for a new AHA. The lower mean HbA1c observed for those CANA patients also appeared to be maintained for >1 year following initiation. Furthermore, patients initiated on CANA were more likely to reach and maintain HbA1c thresholds of <7%, <8%, and <9% over a long-term follow-up, while requiring fewer additions of or switches to new AHA agents (based on newly prescribed medications) as compared to patients initiated on SITA. Given that SITA patients were less likely to attain HbA1c thresholds even though they had more new AHA prescriptions during follow-up and were more likely to have initiated on the highest daily dose, our comparisons of reaching HbA1c thresholds and maintaining HbA1c below threshold likely underestimate the improvements in HbA1c associated with CANA.

We also hypothesized that having a prescription for a new AHA was informative, possibly indicating that the patient was not achieving adequate glycemic control on the index therapy. To examine the durability of glycemic control while accounting for whether patients had a prescription for a new AHA, we incorporated having a prescription for a new AHA in a composite endpoint (i.e., failure to maintain HbA1c below threshold or a prescription for a new AHA). If indeed having a new prescription represents a type of treatment failure, our findings suggest that there may be an even greater impact for CANA versus SITA on durability of glycemic control than was observed for failure to maintain HbA1c below the threshold alone.

HbA1c over time was observed prior to a prescription for a new AHA to isolate the effects of the index medications and avoid capturing changes in HbA1c that may have resulted from other medications added/switched to during the follow-up period. Furthermore, we also considered the possible impact of adherence or discontinuation of the index treatment on attaining HbA1c and weight loss thresholds. To that point, we did not observe any substantial differences in adherence or discontinuation (based on prescription data) between groups, suggesting that differences in these treatment patterns likely did not account for the impact of CANA on HbA1c and weight loss.

Our use of the IPTW is important as it provides a caution related to making simple comparisons between these two medications in observational studies. We observed that CANA patients were more likely to have received insulin prior to initiating therapy as compared to SITA

Table 1
Treatment patterns during follow-up.

	CANA		SITA		P-value
	N(Eff) = 14,542		N(Eff) = 15,151		
MPR, mean ± SD	94.7	±16.2	95.1	±15.3	0.037*
PDC, n (%), mean ± SD					
≥6 months follow-up	10,725	(73.8%)	11,364	(75.0%)	0.013*
6-month PDC	83.2	±26.7	84.9	±25.0	<0.001*
≥12 months follow-up	7542	(51.9%)	8207	(54.2%)	<0.001*
12-month PDC	72.6	±29.5	73.7	±28.3	0.020*
Newly prescribed AHAs[a], n (%)	5309	(36.5%)	7415	(48.9%)	<0.001*
DPP-4 inhibitors	1676	(11.5%)	1181	(7.8%)	<0.001*
Sulfonylurea derivatives	740	(5.1%)	1458	(9.6%)	<0.001*
Insulins	1010	(6.9%)	1390	(9.2%)	<0.001*
GLP-1 agonists	1033	(7.1%)	1556	(10.3%)	<0.001*
SGLT2 inhibitors	1390	(9.6%)	3588	(23.7%)	<0.001*
Other[b]	1087	(7.5%)	1375	(9.1%)	<0.001*

AHA = antihyperglycemic agent; CANA = canagliflozin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide 1; MPR = medication possession ratio; N(Eff) = effective number of patients; PDC = proportion of days covered; SD = standard deviation; SGLT2 = sodium-glucose co-transporter 2; SITA = sitagliptin.
Notes:
* Indicates p-value<0.05.
[a] Newly prescribed agents were defined as agents prescribed on or after the index date, with no baseline prescription for any agent of the same class.
[b] Include alpha-glucosidase inhibitors, amylin analog, biguanides, dopamine receptor agonists, meglitinide analogs, and thiazolidinediones.

patients, which may be an indicator of an imbalance of these real-world populations with respect to disease state/progression (i.e. a marker of severity). By using IPTW, we have more appropriately balanced the cohorts to remove as much potential selection bias as possible and to more closely approximate randomization.

Previous clinical trial data have demonstrated that glycemic control is at least similar if not superior for CANA 100 mg compared to SITA 100 mg, while being superior for CANA 300 mg. Superiority of CANA 100 mg and CANA 300 mg compared to SITA 100 mg have also been shown for attainment of weight loss-related quality measures.[8–11] For instance, a post-hoc analysis of a 52-week trial found that more patients treated with CANA 300 mg achieved HbA1c goals of <7% (48% vs. 35%) and <8% (85% vs. 66%) and had weight loss of >10 lbs from baseline (among patients with BMI ≥25 kg/m^2; 16% vs. 7%), while fewer had an HbA1c ≥ 9% (2% vs. 9%) compared to patients treated with SITA 100 mg.[11] These appear consistent with the present findings given that our study included a large real-world case mix of patients initiated on CANA 100 mg and CANA 300 mg and of patients initiated on SITA 100 mg, 50 mg, or 25 mg. Notably, clinical trials of SITA have focused predominantly on patients randomized to receive SITA 100 mg.

Clinical trials often represent a selected study population and can operate differently from typical clinical settings. Importantly, our study demonstrates that even in real-world clinical practice CANA is associated with greater HbA1c reduction and weight loss compared to SITA, and that HbA1c reductions appear to be sustained over the long term. To our knowledge this is the first real-world study demonstrating that patients initiated on CANA are more likely to attain and sustain their HbA1c below goal over the long-term than patients initiated on SITA. Given the potential long-term benefits associated with improved glycemic control (such as lower risks of complications[19] and reduced healthcare costs[20,21]), future research is warranted to examine whether the impacts of CANA on glycemic control and durability may affect subsequent clinical and economic outcomes.

Previous observational studies without a comparator have demonstrated that T2DM patients treated with CANA experience improvements in HbA1c control[14,22–25] and other quality measures,[24] and that HbA1c reduction and goal attainment may be durable up to 12 months.[14] Similar to the current study, one prior study also compared matched cohorts of patients initiated on CANA or SITA and found that CANA use was associated with greater reductions in HbA1c (−0.93% vs. -0.57%; p = 0.004).[12]

5.1. Limitations

The present study was subject to limitations. First, the EMR data used were physician-centric and unlinked to healthcare claims meaning that secondary care information (e.g., institutional visits) are missing, thus making assessment of any adverse events impossible in the current study. Second, these EMR contained records of prescribed medications, but did not contain information about prescription claims (i.e., to indicate that these prescriptions were dispensed) or information about whether prescriptions were taken as prescribed. Accordingly, absolute rates of adherence within each cohort should be interpreted with caution as they are likely to be overestimated. Future work is needed to assess the validity of prescription-based measures of adherence and treatment patterns in this population. Third, in our analyses, we considered having a prescription for a new AHA during the follow-up period as a possible failure of durability of glycemic control. Without further information from the prescribing physician, it is not possible for us to ascertain the specific reason for the change in regimen nor is it possible to differentiate, with confidence, between adding versus switching to a new AHA. Therefore, we acknowledge that our definition of durability may not be widely-used in the literature, but it may be an interesting surrogate in retrospective studies using EMRs where HbA1c readings are scarcer. Moreover, although dose increase was also possible within each cohort, we did not consider dose increase or dose change when assessing quality measure attainment or treatment failure. Further work to examine dose change patterns in patients treated with CANA and SITA in real-world settings may be warranted, as dose change is likely to have different clinical significance for each of the two medications. For instance, in contrast with CANA, we expected that dose increases for SITA would be unlikely because, as per label, the recommended starting dose is the highest dose (100 mg), except for patients with moderate renal disease in whom it would be unlikely that the dose would be increased.[5] To that effect, we did observe that CANA patients were more likely to increase dose while SITA patients were more likely to have a prescription for a new AHA. There were no changes in the conclusions when considering the sensitivity analysis of CANA 100 mg/300 mg versus SITA 100 mg. Fourth, although cohorts were well balanced after weighting, findings may have been impacted by small differences in characteristics (i.e., residual confounding) between cohorts. Additional adjustments could have also been performed to account for the difference in the initial HbA1c drop and for the medication switches or add-ons following the initiation of CANA or SITA (e.g., when evaluating the failure to maintain HbA1c below threshold). However, such adjustments would have required the use of models such as marginal structural models that were not applied to remain coherent with the statistical techniques used for the evaluation of the other outcomes. Finally, HbA1c over time was assessed among patients with an HbA1c measurement for each specific time-point, meaning that the populations compared were not identical across all time points. To understand whether characteristics remained comparable among the subset of patients with HbA1c data at later time points, the population used in Fig. 2 was restricted to patients with an HbA1c measurement at 12 months post-index date. We observed that even among the subset of patients with a measurement at 12 months, HbA1c values at each pre-index time point remained not statistically different between cohorts and baseline characteristics continued to be generally well balanced. Due to this limitation in addition to the small sample sizes observed at later time points for this outcome, results for average HbA1c over time at later time points should be interpreted with some caution; future studies with longer follow-up and longitudinal analyses will be required to confirm these findings. Despite these limitations, well-designed retrospective studies, with relatively large populations and rich EMR information, can provide valuable information on real-world clinical practice.

6. Conclusions

This analysis of real-world data found that patients initiated on CANA were significantly more likely to reach HbA1c thresholds of <7%, <8%, and <9%, and were more likely to lose ≥5% of body weight compared to patients initiated on SITA. Patients initiated on CANA were also more likely to remain below HbA1c thresholds during the long-term follow-up than patients initiated on SITA, while SITA patients were more likely to have a prescription for a new AHA, suggesting more durable glycemic control with CANA.

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