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Effectiveness, treatment durability, and treatment costs of canagliflozin and glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes in the USA

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ABSTRACT

Introduction This real-world study compared glycemic effectiveness, treatment durability, and treatment costs with canagliflozin 300 mg versus any dose of glucagon-like peptide-1 (GLP-1) receptor agonists in patients with type 2 diabetes mellitus (T2DM) in the USA.

Research design and methods A retrospective cohort study using administrative claims and laboratory data (1 April 2012 to 28 February 2017) from the HealthCore Integrated Research Database were used to assess mean HbA1c at 3-month intervals, achievement of HbA1c thresholds (<7.0%, <8.0%, <9.0%), and treatment durability (ie, adherence, discontinuation, switching, treatment failure (ie, exceeding threshold (7.0%, 8.0%, 9.0%), having a prescription for a new antihyperglycemic agent)) in adults with T2DM who initiated canagliflozin 300 mg or any dose of a GLP-1 receptor agonist. Medication costs were calculated for adherent patients.

Results There were no significant differences in the primary outcome of HbA1c levels at 3-month intervals (≤12 months) in the canagliflozin 300 mg versus any dose GLP-1 receptor agonist cohort. The likelihood of achieving HbA1c<8.0% was not different (p=0.666), the likelihood of achieving HbA1c<7.0% was lower (p=0.016), and the likelihood of achieving HbA1c<9.0% was higher (p=0.020) in the canagliflozin 300 mg versus any dose GLP-1 receptor agonist cohort. The likelihood of treatment failure after reaching any HbA1c target was not different between cohorts. A higher proportion of patients were adherent to treatment (p<0.0001) and a lower proportion discontinued (p<0.0001) or switched medication (p=0.023) in the canagliflozin 300 mg versus any dose GLP-1 receptor agonist cohort. Over 1 year, medication costs were $1421 (p<0.001) lower with canagliflozin 300 mg than any dose of GLP-1 receptor agonists.

Conclusions This real-world, US-based study found that initiation of canagliflozin 300 mg versus any dose of a GLP-1 receptor agonist in patients with T2DM was not associated with significant differences in the primary outcome of HbA1c levels at 3-month intervals for up to 12 months after index, but showed better adherence, less discontinuation, and lower drug acquisition costs compared with initiation of any dose of a GLP-1 receptor agonist.

Significance of this study

What is already known about this subject?
► The glycemic efficacy of sodium glucose co-transporter 2 (SGLT2) inhibitors versus glucagon-like peptide-1 (GLP-1) receptor agonists has not been compared in head-to-head clinical trials of patients with type 2 diabetes mellitus (T2DM); previous real-world studies based on electronic medical records data have shown similar HbA1c reductions with the SGLT2 inhibitor canagliflozin and GLP-1 receptor agonists in patients with T2DM.

What are the new findings?
► After initiating canagliflozin 300 mg versus any dose of a GLP-1 receptor agonist, there were no significant differences in mean HbA1c levels at 3-month intervals for up to 12 months (primary outcome), with similar or better achievement of HbA1c<8.0% and <9.0% and better adherence, less discontinuation, and lower drug acquisition costs when adherent.

How might these results change the focus of research or clinical practice?
► These findings provide comparative effectiveness data for canagliflozin 300 mg versus any dose of a GLP-1 receptor agonist in the absence of head-to-head clinical trial results and corroborate results from previous real-world studies.

INTRODUCTION

Managing hyperglycemia and cardiovascular risk are central to type 2 diabetes mellitus (T2DM) treatment and can help reduce the risk of diabetes-related morbidity and mortality.[1] The Healthcare Effectiveness Data and Information Set (HEDIS) uses HbA1c<8.0% as the cut-off for adequate glycemic control to measure quality metrics for many patients with T2DM and defines HbA1c>9.0% as poor glycemic control.[2] The American Diabetes Association (ADA)

recommends a target HbA1c of <7.0% for most adults and a less stringent target of <8.0% for some populations, including those with a history of severe hypoglycemia.[1]

Treatment guidelines emphasize lifestyle modifications for all patients along with pharmacologic intervention to achieve glycemic control.[1 3] Metformin is recommended in ADA and American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) guidelines as the first-line treatment for T2DM unless it is contraindicated. The AACE/ACE guidelines recommend using one of the newer antihyperglycemic agents (AHAs), like a glucagon-like peptide-1 (GLP-1) receptor agonist, a sodium glucose co-transporter 2 (SGLT2) inhibitor, a dipeptidyl peptidase-4 (DPP-4) inhibitor, or, with caution, an older agent like a thiazolidinedione or sulfonylurea, as monotherapy in patients who cannot tolerate metformin or as dual therapy in patients with inadequate glycemic control on metformin alone.[3] The ADA recommends the SGLT2 inhibitors canagliflozin and empagliflozin and the GLP-1 receptor agonist liraglutide as second-line therapy for patients with T2DM and cardiovascular disease,[1] as these agents have been shown to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke).[4–6]

No randomized controlled trial (RCT) has directly compared the efficacy of SGLT2 inhibitors versus GLP-1 receptor agonists in patients with T2DM, but meta-analyses and indirect treatment comparisons using RCT data suggest that reductions in HbA1c are similar with canagliflozin 300 mg versus specific GLP-1 receptor agonists when used in combination with a variety of other AHAs (ie, metformin, metformin plus sulfonylurea, insulin).[7–10] However, the effects of individual GLP-1 receptor agonists have not been differentiated in meta-analyses. Since the indirect comparisons of canagliflozin 300 mg and GLP-1 receptor agonists were based on RCT data, there remained a need to further validate these results in real-world practice settings.

The aim of the present study was to compare glycemic effectiveness, treatment durability, and treatment costs in patients with T2DM initiated on an SGLT2 inhibitor (canagliflozin 300 mg) or any dose of a GLP-1 receptor agonist in the USA using both claims and laboratory results from the HealthCore Integrated Research Database (HIRD). This study specifically focused on canagliflozin 300 mg and any dose of GLP-1 receptor agonists because selection of these agents may be influenced by treatment guidelines and because appropriate rigor could be applied for analysis of real-world outcomes using this comparison.

METHODS
Data source
Administrative claims data were retrieved from the HIRD, which contains fully adjudicated paid claims from the largest commercially insured population in the USA

(over 45 million patients) and includes data from health maintenance organizations (HMO), preferred provider organizations (PPO), consumer-directed health plans (CDHP), Medicare Advantage plans, and indemnity plans. The HIRD also contains diagnostic laboratory testing results for about 33% of members receiving outpatient laboratory services from two large national reference laboratories. This observational study was exempt from informed consent stipulations as researchers accessed a limited data set without individual enrollee identifiers, and only summary statistics were reported. Data were accessed and used in compliance with the Health Insurance Portability and Accountability Act. HealthCore has in place a Data Use Agreement with the covered entities from which the data were used for this study (45 CFR 164.514(e)(4)(ii)). Data were in a Limited Data Set format (45 CFR 154.514(e)(2)).

Study design and patient selection
This retrospective administrative claims study compared patients initiating canagliflozin 300 mg or any dose of a GLP-1 receptor agonist. Given the time frame for this study and relative launch dates for SGLT2 inhibitors, the decision to evaluate canagliflozin alone was based on the need to ensure sufficient sample size while clearly delineating individual SGLT2 inhibitor results; in addition, canagliflozin was suggested to be more effective than other SGLT2 inhibitors by a meta-analysis.[11] The 300 mg dose of canagliflozin was chosen for evaluation in this study based on its widespread real-world use as well as findings from prior real-world studies of canagliflozin versus GLP-1 receptor agonists. Sensitivity analysis of these prior studies has shown that patients initiated on canagliflozin 100 mg had similar HbA1c levels over time compared with those initiated on canagliflozin 300 mg[12 13]; hence, for simplicity and additional rigor, only the 300 mg dose of canagliflozin was used in this study. In addition, as individual GLP-1 receptor agonists have not been differentiated in meta-analyses, the comparison group included all GLP-1 receptor agonist use. The patient identification period ranged from 1 April 2013 through 28 February 2016. The study period (1 April 2012 through 28 February 2017) was chosen to allow 1 year of claims data before and after initiation of canagliflozin 300 mg or any dose of a GLP-1 receptor agonist. The index date was defined as the date of the first prescription filled for canagliflozin 300 mg or any dose of a GLP-1 receptor agonist (ie, liraglutide, dulaglutide, exenatide, lixisenatide, or albiglutide). Patients were followed for 12 months after the index date. Claims codes are listed in online supplementary table 1.

Study eligibility criteria included ≥1 medical claim with T2DM, identified by the *International Classification of Diseases, Ninth/Tenth Revision* (ICD-9/10) codes, during the entire study period; ≥1 claim for canagliflozin 300 mg or any dose of a GLP-1 receptor agonist; ≥1 HbA1c laboratory value before and after the index

date; ≥18 years of age on the index date; and ≥12 months of continuous health plan enrollment, including both medical and pharmacy coverage, both before and after the index date. Exclusion criteria included a diagnosis of type 1 diabetes, pregnancy or gestational diabetes, or steroid-induced diabetes; stage 3 or 4 chronic kidney disease, end-stage renal disease, renal transplant, or dialysis using ICD-9/10-Clinical Modification diagnosis/procedure codes and Current Procedural Terminology codes; and use of index or non-index medication in the baseline period (eg, SGLT2 inhibitor use in the GLP-1 receptor agonist cohort or canagliflozin 100 mg or another SGLT2 inhibitor in the canagliflozin 300 mg cohort). For patients who filled for both canagliflozin 300 mg and any dose of a GLP-1 receptor agonist as their very first fill during the patient identification period, the first fill date for canagliflozin 300 mg was defined as the index date, and canagliflozin 300 mg was defined as the index medication.

Baseline characteristics

Demographic characteristics, including age, sex, region of residence, health plan type (ie, HMO, PPO, CDHP), and Medicare Advantage versus commercially insured, were reported during the 12-month baseline period. Clinical characteristics reported during the 12-month baseline period included HbA1c level, AHAs used, comorbidities, Elixhauser Comorbidity Index,[14] Diabetes Complications Severity Index,[15] and specialty of prescribing physician.

Outcomes

The primary outcome was HbA1c level at 3-month intervals over 12 months for the overall population; HbA1c levels at 3-month intervals over 12 months were also reported for patients with baseline HbA1c between 7.0% and <8.0%, between 8.0% and <9.0%, and ≥9.0%. The secondary outcomes included achievement of HbA1c levels below prespecified thresholds (<8.0% (HEDIS quality measure), <7.0% (ADA target), and <9.0% (>9.0% is the HEDIS measure for poor glycemic control)) among patients with a baseline value above the threshold and were analyzed using an intent-to-treat approach.

Secondary outcomes included (1) adherence, measured by the proportion of days covered (calculated as the total number of days the index medication was available divided by the total number of days in the follow-up period; proportion of days covered ≥80% was defined as adherent)[16]; (2) switching, defined as starting a non-index AHA medication not filled in the baseline period, within 60 days of the run-out date of the last prescription of the index medication (the date of the first non-index AHA medication was referred to as the switch date); (3) need for add-on therapy, defined as starting a non-index AHA medication within 60 days of a refill of the index medication; (4) treatment discontinuation, defined as failure to refill index medication within 90 days after the depletion of the previous

days' supply (down-titration of canagliflozin 300 mg to canagliflozin 100 mg was not considered discontinuation); (5) treatment durability, including proportion of patients exceeding HbA1c≥7.0%, ≥8.0%, or ≥9.0% after reaching the HbA1c target; (6) treatment failure, a novel composite outcome defined as the composite endpoint of HbA1c exceeding the target threshold or having a prescription for a non-index AHA; and (7) medication costs for continuous therapy with canagliflozin only in the canagliflozin 300 mg cohort or with a GLP-1 receptor agonist only in the any dose GLP-1 receptor agonist cohort over 12 months.

Statistical analysis

To reduce the potential for treatment selection and confounding bias and allow the use of all patients in this study, the propensity score method with inverse probability of treatment weighting was used. The analysis was conducted in two phases. First, the probability of receiving canagliflozin 300 mg or any dose of a GLP-1 receptor agonist was estimated using a logistic regression model. Next, absolute standardized differences were used to assess the balance of baseline covariates between the two cohorts. Inverse probability of treatment weights was calculated to normalize the inflated sample size.[17] A standardized difference of <10% after applying inverse probability of treatment weighting indicated well-balanced baseline covariates.[18 19]

Descriptive statistics (means and SDs for continuous variables, frequency and percentages for categorical variables) were provided for baseline demographic and clinical characteristics, and other study measures of interest. Student's (or unpaired) t-tests were used to compare mean HbA1c values between cohorts at 3-month intervals. Student's t-tests and χ^2 tests were used to compare adherence and AHA initiation patterns in the canagliflozin 300 mg and any dose GLP-1 receptor agonist cohorts. Cox proportional hazards models were used for multivariable regression analyses, and estimates were reported using HRs and 95% CIs for achievement of HbA1c targets and treatment durability outcomes. Patients were followed from the index date until the first event of interest or censoring, whichever occurred first. Censoring was defined as the end of the follow-up time of 12 months if no event of interest was observed. All analyses were conducted using SAS Enterprise Guide V.7.15.

Medication costs for each cohort were calculated by totaling only the cost of canagliflozin 300 mg or the GLP-1 receptor agonist at any dose that was paid by patients and the health plan for each cohort. The cost was reported only for patients who had HbA1c<8.0% (HEDIS quality measure) at any time from baseline through the follow-up period. Costs were discounted in 2017 dollar values according to data from the Bureau of Labor Statistics.

This manuscript was written in accord with the Reporting of Studies Conducted Using Observational Routinely Collected Health Data statement.[20]

RESULTS
Baseline demographic and clinical characteristics

Of the 76 603 patients with T2DM and a claim for canagliflozin 300 mg or any dose of a GLP-1 receptor agonist, a total of 3171 met all inclusion and exclusion criteria (755 initiated on canagliflozin 300 mg, and 2416 initiated on any dose of a GLP-1 receptor agonist; online supplementary figure 1). Prior to inverse probability of treatment weighting, patients initiated on canagliflozin 300 mg versus any dose of a GLP-1 receptor agonist were older (mean age 54.6 vs 53.1 years, standardized difference 17%) and less likely to be female (38.0% vs 52.9%, standardized difference 30%; table 1). Mean Elixhauser Comorbidity Index was lower for patients initiated on canagliflozin 300 mg compared with patients initiated on any dose of a GLP-1 receptor agonist (3.17 vs 3.35, standardized difference 11%). Patients initiated on canagliflozin 300 mg were more likely to be treated with

Table 1 Demographic and clinical characteristics

	Before inverse probability of treatment weighting			After inverse probability of treatment weighting		
	Canagliflozin 300 mg (n=755)	Any dose of GLP-1 receptor agonist (n=2416)	Absolute standardized difference*	Canagliflozin 300 mg (n=750)	Any dose of GLP-1 receptor agonist (n=2417)	Absolute standardized difference*
Age (years), mean (SD)	54.6 (8.7)	53.1 (9.1)	17%	53.4 (9.1)	53.5 (9.0)	1%
18–24, n (%)	≤10	≤10	18%	≤10	≤10	8%
25–34, n (%)	11 (1.5)	66 (2.7)		18 (2.4)	60 (2.5)	
35–44, n (%)	75 (9.9)	348 (14.4)		89 (11.9)	329 (13.6)	
45–54, n (%)	264 (35.0)	865 (35.8)		274 (36.5)	850 (35.2)	
55–64, n (%)	331 (43.8)	935 (38.7)		305 (40.6)	973 (40.3)	
65–74, n (%)	61 (8.1)	171 (7.1)		51 (6.8)	175 (7.2)	
≥75, n (%)	11 (1.5)	24 (1.0)		≤10	24 (1.0)	
Age breakdown (years)						
<65	683 (90.5)	2221 (91.9)	5%	690 (91.9)	2218 (91.8)	1%
≥65	72 (9.5)	195 (8.1)	5%	60 (8.1)	199 (8.2)	1%
Female, n (%)	287 (38.0)	1277 (52.9)	30%	369 (49.3)	1190 (49.2)	0%
Insurance plan type, n (%)						
HMO	288 (38.1)	890 (36.8)	9%	281 (37.5)	899 (37.2)	1%
PPO	393 (52.1)	1344 (55.6)		410 (54.6)	1323 (54.8)	
CDHP	74 (9.8)	182 (7.5)		59 (7.9)	195 (8.1)	
Geographic region, n (%)						
Northeast	76 (10.1)	345 (14.3)	16%	102 (13.6)	322 (13.3)	1%
Midwest	108 (14.3)	410 (17.0)		120 (16.1)	394 (16.3)	
South	418 (55.4)	1244 (51.5)		393 (52.5)	1266 (52.4)	
West	153 (20.3)	417 (17.3)		134 (17.9)	436 (18.0)	
Medicare Advantage, n (%)	19 (2.5)	106 (4.4)	10%	26 (3.4)	95 (3.9)	3%
Baseline HbA1c (%), mean (SD)	8.7 (1.7)	8.4 (1.7)	15%	8.5 (1.7)	8.5 (1.7)	4%
Elixhauser Comorbidity Index, mean (SD)	3.17 (1.58)	3.35 (1.65)	11%	3.33 (1.69)	3.31 (1.63)	1%
0, n (%)	≤10	20 (0.8)	14%	≤10	20 (0.8)	4%
1–2, n (%)	288 (38.1)	805 (33.3)		266 (35.5)	832 (34.4)	
3–4, n (%)	336 (44.5)	1082 (44.8)		327 (43.6)	1075 (44.5)	
5+, n (%)	128 (17.0)	509 (21.1)		153 (20.4)	491 (20.3)	
Diabetes Complications Severity Index, mean (SD)	0.63 (0.98)	0.67 (1.10)	4%	0.67 (0.99)	0.66 (1.10)	1%
0, n (%)	472 (62.5)	1522 (63.0)	14%	455 (60.6)	1532 (63.4)	4%
1–2, n (%)	244 (32.3)	735 (30.4)		254 (33.9)	728 (30.1)	
3–4, n (%)	35 (4.6)	123 (5.1)		36 (4.8)	121 (5.0)	
5+, n (%)	≤10	36 (1.5)		≤10	36 (1.5)	

*Absolute standardized difference >10% is considered significant.
CDHP, consumer-driven health plan (health reimbursement account, health savings account); GLP-1, glucagon-like peptide-1; HMO, health maintenance organization; PPO, preferred provider organization.

sulfonylureas (47.7% vs 37.3%, standardized difference 21%) or DPP-4 inhibitors (50.7% vs 33.7%, standardized difference 35%) during the baseline period than those initiated on GLP-1 receptor agonists at any dose (online supplementary table 2). After inverse probability of treatment weighting, baseline demographic and clinical characteristics were well balanced in the canagliflozin 300 mg and any dose GLP-1 receptor agonist cohorts (canagliflozin 300 mg cohort: n=750; any dose GLP-1 receptor agonist cohort: n=2417; all standardized differences <10%; table 1 and online supplementary table 2). The mean (SD) baseline HbA1c values were similar in the canagliflozin 300 mg (8.5% (1.67)) and any dose GLP-1 receptor agonist cohorts (8.5% (1.74); standardized difference 4%).

Change in HbA1c levels and target attainment

Mean HbA1c levels over 12 months of follow-up, measured at 3-month intervals, were similar between the canagliflozin 300 mg and any dose GLP-1 receptor agonist cohorts in the overall population (figure 1A) and regardless of baseline HbA1c (7.0% to <8.0%, 8.0% to <9.0%, and ≥9.0%; figure 1B). Cox proportional hazards model estimates showed no difference in the achievement of HbA1c<8.0% in the canagliflozin 300 mg and any dose GLP-1 receptor agonist cohorts (51.9% vs 49.7%; HR 1.04, 95% CI 0.89 to 1.21; p=0.666). Patients in the canagliflozin 300 mg cohort were less likely to achieve HbA1c<7.0% than those in the any dose GLP-1 receptor agonist cohort (27.1% vs 30.4%; HR 0.81, 95% CI 0.68 to 0.96; p=0.016) and more likely to achieve HbA1c<9.0% (69.4% vs 61.9%; HR 1.24, 95% CI 1.04 to 1.48; p=0.020; figure 2).

Adherence

During the 12-month follow-up period, a greater proportion of patients in the canagliflozin 300 mg cohort were adherent to the index medication (proportion of days covered ≥80%) compared with those in the any dose GLP-1 receptor agonist cohort (47.5% vs 37.5%; p<0.0001; table 2), with an average of 67% vs 59% days covered (p<0.0001) by the index medication.

Treatment patterns

A lower proportion of patients in the canagliflozin 300 mg cohort switched AHA medications compared with those in the any dose GLP-1 receptor agonist cohort (33.8% vs 38.4%; p=0.023). Among those who switched medications, the average time to switch was longer in the canagliflozin 300 mg cohort than the any dose GLP-1 receptor agonist cohort (198 vs 176 days; p=0.002). Patients in the canagliflozin 300 mg cohort most frequently switched to metformin (15.5%), DPP-4 inhibitors (8.9%), or sulfonylureas (8.2%). In the any dose GLP-1 receptor agonist cohort, patients most frequently switched to metformin (18.0%), insulin (7.8%), or sulfonylureas (7.5%).

In the 12 months after index, the proportion of patients in the canagliflozin 300 mg and any dose GLP-1

receptor agonist cohorts who added on a new AHA medication (32.6% and 33.1%; p=0.801) was not statistically different, as was mean time to initiation between cohorts (158 vs 160 days; p=0.751). A lower proportion of patients in the canagliflozin 300 mg cohort had a new prescription for insulin (add-on and switch) compared with patients in the any dose GLP-1 receptor agonist cohort (5.0% vs 8.1%; p=0.004).

The likelihood of discontinuation from the index medication was lower in the canagliflozin 300 mg cohort than in the any dose GLP-1 receptor agonist cohort (49.6% vs 57.4%; HR 0.78, 95% CI 0.70 to 0.88; p<0.0001; table 2). Among those who discontinued the index medication, the mean time to discontinuation was longer in the canagliflozin 300 mg cohort than the any dose GLP-1 receptor agonist cohort (187 vs 163 days; p=0.001).

Treatment durability

The likelihood of HbA1c going above thresholds after having achieved them was not statistically different for patients in the canagliflozin 300 mg and any dose GLP-1 receptor agonist cohorts for thresholds of HbA1c≥7.0% (HR 1.06, 95% CI 0.82 to 1.38; p=0.648), HbA1c≥8.0% (HR 0.96, 95% CI 0.77 to 1.19; p=0.716), and HbA1c≥9.0% (HR 0.79, 95% CI 0.60 to 1.03; p=0.086; figure 2).

The likelihood of treatment failure (defined as HbA1c going above threshold or having a prescription for a new AHA) was not statistically different for patients in the canagliflozin 300 mg and any dose GLP-1 receptor agonist cohorts after achieving HbA1c<7.0% (HR 1.05, 95% CI 0.87 to 1.28; p=0.60), HbA1c<8.0% (HR 1.00, 95% CI 0.87 to 1.16; p=0.96), and HbA1c<9.0% (HR 0.95, 95% CI 0.82 to 1.10; p=0.48).

Cost analyses

Medication costs for 1 year were $3218 for patients in the canagliflozin 300 mg cohort and $4639 for patients in the any dose GLP-1 receptor agonist cohort. Thus, the mean annual medication costs were $1421 less with canagliflozin 300 mg versus any dose of a GLP-1 receptor agonist (p<0.001).

DISCUSSION

The current study, which used both claims and laboratory results from the HIRD, adds to the existing literature on the real-world effectiveness and costs related to treatment with canagliflozin 300 mg versus GLP-1 receptor agonists at any dose in patients with T2DM. Our findings showed no significant differences in HbA1c levels over time (at 3-month intervals over 12 months) with canagliflozin 300 mg and any dose of GLP-1 receptor agonists, as well as no significant difference in achieving secondary outcome of HbA1c<8.0%, but a lower and higher likelihood of achieving HbA1c<7.0% and HbA1c<9.0%, respectively, greater adherence, less discontinuation, and lower medication costs.

Although the recommended starting dose of canagliflozin is 100 mg,[21] approximately one-third of patients in
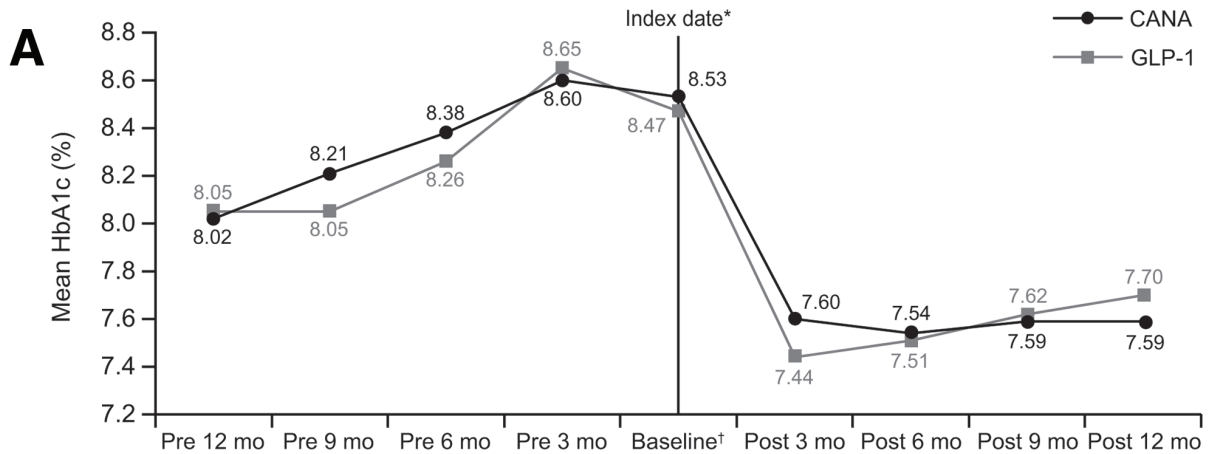
Number of patients with HbA1c measurements at each time point (A)

Sample size	Pre-index				Index date	Post-index			
	12 mo	9 mo	6 mo	3 mo		3 mo	6 mo	9 mo	12 mo
CANA (n=750)	303	312	355	555	750	362	387	373	375
GLP-1 (n=2417)	908	1002	1045	1862	2417	1027	1322	1198	1190
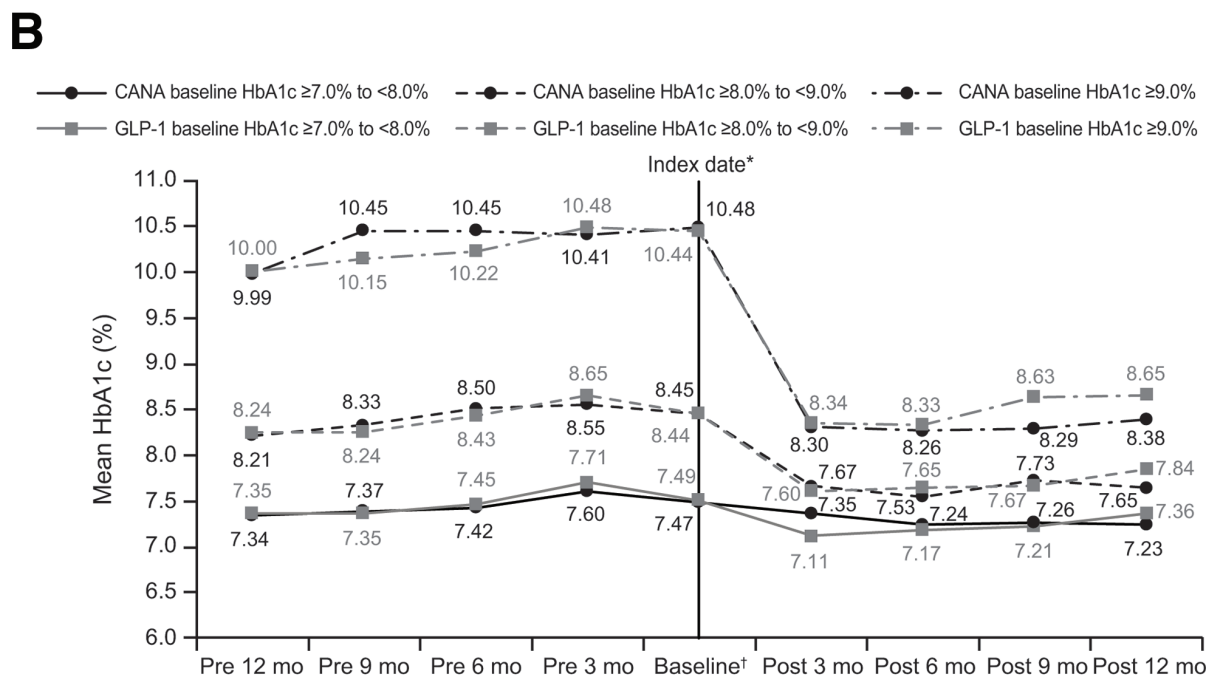
Number of patients with HbA1c measurements at each time point (B)

Sample size	Pre-index				Index date	Post-index			
	12 mo	9 mo	6 mo	3 mo		3 mo	6 mo	9 mo	12 mo
Baseline HbA1c ≥7.0% to <8.0%									
CANA (n=229)	111	120	125	169	229	106	119	123	114
GLP-1 (n=629)	285	331	298	485	629	260	365	334	322
Baseline HbA1c ≥8.0% to <9.0%									
CANA (n=171)	69	71	81	132	171	79	97	87	86
GLP-1 (n=501)	204	217	233	410	501	235	277	263	247
Baseline HbA1c ≥9.0%									
CANA (n=243)	71	76	99	180	243	120	119	114	116
GLP-1 (n=819)	239	253	307	638	819	334	434	390	391

Figure 1 Mean HbA1c values at 3-month intervals in (A) the overall population and (B) patients with baseline HbA1c between 7.0% and <8.0%, 8.0% and <9.0%, and ≥9.0%. (Student's t-test was used to analyze between-cohort differences at each time point.) *Date of initiation of CANA or GLP-1. †Last HbA1c value during 12 months before index date. CANA, canagliflozin 300 mg; GLP-1, any dose of a glucagon-like peptide-1 receptor agonist.
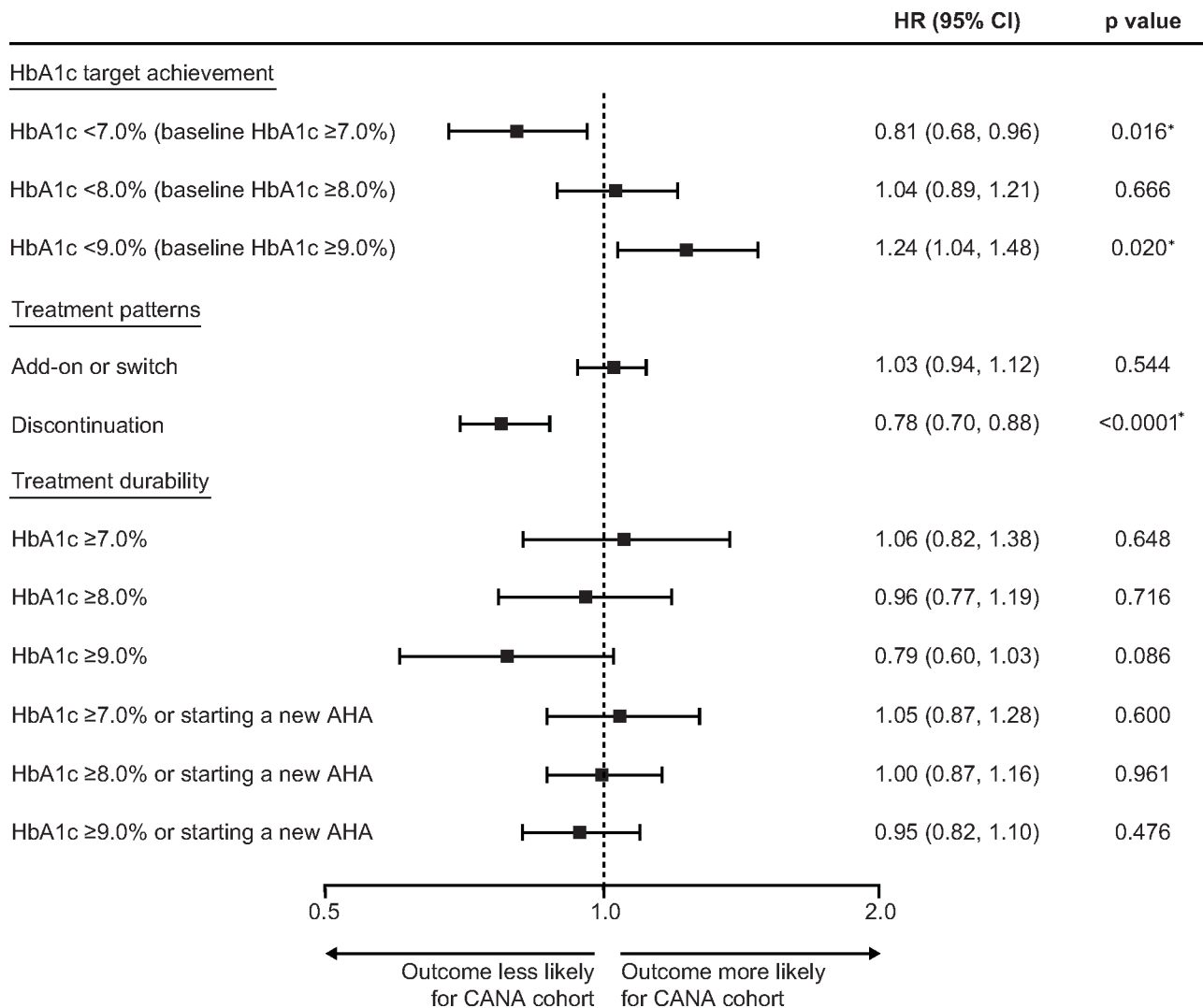
Figure 2 Achievement of HbA1c targets after initiation of canagliflozin 300 mg or any dose of a GLP-1 receptor agonist and treatment failure and treatment patterns over 12 months of follow-up. *Statistically significant. AHA, antihyperglycemic agent; CANA, canagliflozin 300 mg; GLP-1, any dose of a glucagon-like peptide-1 receptor agonist.

the real world are initiated on canagliflozin 300 mg and approximately two-thirds of patients are on canagliflozin 300 mg within 9 to 12 months, reflecting widespread real-world use of canagliflozin 300 mg.[22 23] Findings from our study of claims and laboratory data showed similar patterns of HbA1c over time with canagliflozin 300 mg and any dose of GLP-1 receptor agonists regardless of baseline HbA1c, which is consistent with previous real-world studies.[13 24–26] We found that at any time during follow-up, there was no difference in the likelihood of achieving HbA1c<8.0% (HEDIS quality measure) with canagliflozin 300 mg versus any dose of a GLP-1 receptor agonist. Patients were less likely to achieve HbA1c<7.0% and more likely to achieve HbA1c<9.0% with canagliflozin 300 mg. Some differences in HbA1c target attainment with canagliflozin 300 mg and GLP-1 receptor agonists have been observed in a prior study. In that study, an analysis of the IQVIA Real-World Data EMR—US database found that patients initiated on canagliflozin 300 mg versus a GLP-1 receptor agonist were less

likely to achieve HbA1c<7.0%, but no differentiation was observed in achievement of HbA1c<8.0% and <9.0%.[25 26] Differences in patient characteristics and sample size, the use of additional AHAs in intent-to-treat analyses and follow-up time across studies may explain some of the variation in the achievement of HbA1c<9.0%.

A greater proportion of patients were adherent to treatment with canagliflozin 300 mg versus any dose of a GLP-1 receptor agonist, as measured by the proportion of days covered, and, on average, patients in the canagliflozin 300 mg cohort had more days covered by the index medication than those in the any dose GLP-1 receptor agonist cohort. The rate of discontinuation of index medication was lower with canagliflozin 300 mg versus any dose of GLP-1 receptor agonists, and patients who discontinued index medication were treated longer with canagliflozin 300 mg versus a GLP-1 receptor agonist at any dose before discontinuation. The greater adherence and lower rate of discontinuation seen with canagliflozin 300 mg versus any dose of GLP-1 receptor agonists in this study are

Table 2 Adherence and AHA initiation during 12 months of follow-up

	Canagliflozin 300 mg(n=750)	Any dose of GLP-1 receptor agonist (n=2417)	p value
Proportion of days covered by index medication, n (%)	750 (100.0)	2417 (100.0)	
Proportion of days covered among all patients, mean (SD)	0.67 (0.29)	0.59 (0.31)	<0.0001*
Proportion of days covered among all patients, median	0.79	0.66	
Proportion of days covered <80% (non-adherent), n (%)	394 (52.5)	1511 (62.5)	<0.0001*
Proportion of days covered ≥80% (adherent), n (%)	356 (47.5)	906 (37.5)	
Any new AHA, n (%)	244 (32.6)	800 (33.1)	0.801
Time to new AHA from index date (days), mean (SD)	158 (110)	160 (109)	0.751
Time to new AHA from index date (days), median	146	148	
Discontinuation of the index medication, n (%)	372 (49.6)	1388 (57.4)	<0.0001*
Time to discontinuation (days), mean (SD)	187 (120)	163 (120)	0.001*
Time to discontinuation (days), median	182	127	
Any switching of the index medication, n (%)	253 (33.8)	928 (38.4)	0.023*
Time to the first switching (days), mean (SD)	198 (103)	176 (96)	0.002*
Time to the first switching (days), median	224	166	
Newly started AHAs after switching, n (%)†			
SGLT2 inhibitors	20 (2.7)	68 (2.8)	0.835
GLP-1 receptor agonists	27 (3.6)	85 (3.5)	0.950
Sulfonylureas	62 (8.2)	181 (7.5)	0.523
Biguanides (metformin HCl)	116 (15.5)	435 (18.0)	0.115
DPP-4 inhibitors	67 (8.9)	104 (4.3)	<0.0001*
Thiazolidinediones	12 (1.6)	43 (1.8)	0.754
Insulin	31 (4.1)	188 (7.8)	0.001*
Amylin analogs (pramlintide acetate)	0 (0.0)	0 (0.0)	–
Alpha-glucosidase inhibitors	0 (0.0)	0 (0.0)	–
Meglitinide analogs	≤10	≤10	0.940
Others‡	0.5 (0.1)	≤10	0.875

*Statistically significant.
†The medication classes may not be mutually exclusive because patients may have filled prescriptions in more than one class on the same day.
‡Dextrose, bromocriptine, diazoxide, glucagon, glucagon (rDNA), glucagon HCl (rDNA), glucose-vitamin C, mifepristone (hyperglycemia), metformin HCl—dietary management product, aldose reductase inhibitors.
AHA, antihyperglycemic agent; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium glucose co-transporter 2.

consistent with observations from prior real-world studies which showed greater adherence with canagliflozin 100 and 300 mg versus a GLP-1 receptor agonist (medication possession ratio: 0.72–0.92 vs 0.33–0.67; proportion of days covered: 0.71–0.81 vs 0.33–0.58, respectively) and a 30% lower rate of discontinuation with canagliflozin 300 mg versus a GLP-1 receptor agonist.[26–28] A possible explanation for the better adherence to treatment with canagliflozin 300 mg versus any dose of a GLP-1 receptor agonist may be its mode of administration (ie, oral vs injection). Medication acquisition costs could also play a role in adherence to treatment.

In the current study, we found that the proportion of patients adding a new AHA was not different between cohorts; however, more patients in the any dose GLP-1 receptor agonist cohort initiated insulin compared with the canagliflozin 300 mg cohort. Furthermore, once patients achieved the glycemic target, those initiating canagliflozin 300 mg versus any dose of a GLP-1 receptor

agonist had a similar likelihood of treatment failure, defined as the composite outcome of the prescription of a new non-index AHA or having HbA1c above target. This is in contrast to a previous real-world analysis showing that a lower proportion of patients treated with canagliflozin 300 mg versus a GLP-1 receptor agonist initiated a new AHA or failed treatment.[26]

Our real-world data suggest that treatment with canagliflozin 300 mg versus any dose of a GLP-1 receptor agonist may be a suitable choice for achieving the triple aim of diabetes care (improving the patient experience of care, improving the health of populations, and reducing the cost of healthcare[29]). The results of this study highlight the potential impact of the lower adherence and persistence to GLP-1 receptor agonists as used in actual practice, as those on canagliflozin 300 mg remained on treatment longer, with fewer add-on medications, and no differences in HbA1c reductions at 3-month intervals. Furthermore, the real-world glycemic effectiveness of

canagliflozin 300 mg versus any dose of a GLP-1 receptor agonist is potentially achieved with lower overall medication costs. This may be helpful to inform clinical decisions regarding the choice of AHA medications.

Our study was strengthened by the use of the HIRD, which contains fully adjudicated claims information on filled prescriptions and laboratory data for about one-third of patients with claims data. The current findings support those of a similar real-world study that showed no difference in HbA1c reductions and lower medication costs with canagliflozin 300 mg versus GLP-1 receptor agonists (IQVIA Real-World Data Electronic Medical Records—US database), but with more accurate adherence and persistence data as adjudicated prescription information was used instead of electronic medical records data, which may overestimate adherence and persistence.[13] Our study was also strengthened by the use of the propensity score method, which reduced the potential bias due to dissimilar patient populations by controlling for differences in baseline characteristics.

Limitations

Due to approval dates and sample sizes, this analysis focused on canagliflozin only and did not include other SGLT2 inhibitors. Another limitation is that patients were required to initiate canagliflozin 300 mg rather than canagliflozin 100 mg, which is not consistent with the prescribing information.[21] However, it is known that approximately one-third of patients in the real world are initiated on canagliflozin 300 mg.[23] Furthermore, this study compared patients who initiated the highest dose of canagliflozin (300 mg) with those who initiated any dose of a GLP-1 receptor agonist, as the patients may be comparable in terms of disease severity and prior line of therapy. Data from a previous real-world study comparing canagliflozin versus GLP-1 receptor agonists found that most outcomes were generally similar for patients initiated on canagliflozin 100 mg (vs 300 mg).[26] Additionally, a prescription claim does not ensure that the medication was taken as prescribed and does not reflect the potential for use of medication samples (ie, the use of canagliflozin 100 mg samples prior to a prescription for canagliflozin 300 mg). Another limitation is that only ~33% of the population in the HIRD had laboratory data, and these patients may not be representative of the overall database. Furthermore, because all patients were commercially insured or had Medicare Advantage insurance, these results may not be generalizable beyond the US managed care population. In addition, interpretation of the novel composite endpoint based on exceeding HbA1c targets and initiation of a new AHA may not fully capture all possible aspects that could be used to define treatment failure. Similar to other retrospective analyses, this study is subject to possible measurement (ie, diagnosis coding) errors and residual confounding for variables that may differentially impact outcomes but are not available for use in the inverse probability of treatment weighting balancing methods. Additionally, this study was designed to assess effectiveness and treatment durability; therefore, safety data, including hypoglycemia, were not available. Lastly, the cost-effectiveness analysis used non-rebate prices, and may not reflect the amount actually paid by patients and health systems.

CONCLUSION

This real-world, US-based study demonstrated that initiation of canagliflozin 300 mg versus initiation of any dose of a GLP-1 receptor agonist resulted in no difference in HbA1c values up to 12 months after index at 3-month intervals, with no difference in achievement of HbA1c<8.0%, better achievement of HbA1c<9.0%, and worse achievement of HbA1c<7.0%, but with better adherence, less discontinuation, and lower drug acquisition costs when fully adherent in patients with T2DM.

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REFERENCES
1 American Diabetes Association. Standards of medical care in diabetes - 2018. *Diabetes Care* 2018;41:S1–159.
2 Fallon Health. Healthcare effectiveness data and information set (HEDIS®) measures, 2018. Available: http://www.fchp.org/providers/resources/hedis-measures.aspx [Accessed 5/1/18].
3 Garber AJ, Abrahamson MJ, Barzilay JI, *et al*. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2018 Executive Summary. *Endocr Pract* 2018;24:91–120.
4 Neal B, Perkovic V, Mahaffey KW, *et al*. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377:644–57.

5 Zinman B, Wanner C, Lachin JM, *et al*. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117–28.

6 Marso SP, Daniels GH, Brown-Frandsen K, *et al*. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;375:311–22.

7 Mearns ES, Sobieraj DM, White CM, *et al*. Comparative efficacy and safety of antidiabetic drug regimens added to metformin monotherapy in patients with type 2 diabetes: a network meta-analysis. *PLoS One* 2015;10:e0125879.

8. Taieb V, Pacou M, Schroeder M, *et al*. A network meta-analysis (NMa) to assess the longer-term relative efficacy of canagliflozin in patients with type 2 diabetes inadequately controlled on metformin. *Value in Health* 2015;18.

9. Taieb V, Pacou M, Schroeder M, *et al*. Bayesian network meta-analysis (NMa) to assess the relative efficacy of canagliflozin in patients with type 2 diabetes mellitus (T2DM) inadequately controlled with insulin. *Value in Health* 2015;18.

10. Van Sanden S, Diels J, Guillon P, *et al*. Bayesian network meta-analysis (NMa) to assess relative efficacy of canagliflozin (CANA) versus glucagon-like peptide-1 (GLP-1) agonists in dual and triple therapy in patients with type 2 diabetes mellitus (T2DM). *Value in Health* 2015;18.

11 Zaccardi F, Webb DR, Htike ZZ, *et al*. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. *Diabetes Obes Metab* 2016;18:783–94.

12 Rosenthal N, Meininger G, Ways K, *et al*. Canagliflozin: a sodium glucose co-transporter 2 inhibitor for the treatment of type 2 diabetes mellitus. *Ann N Y Acad Sci* 2015;1358:28–43.

13 Wysham CH, Pilon D, Ingham M, *et al*. HbA1c control and cost-effectiveness in patients with type 2 diabetes mellitus initiated on canagliflozin or a glucagon-like peptide 1 receptor agonist in a real-world setting. *Endocr Pract* 2018;24:273–87.

14 Elixhauser A, Steiner C, Harris DR, *et al*. Comorbidity measures for use with administrative data. *Med Care* 1998;36:8–27.

15 Young BA, Lin E, Von Korff M, *et al*. Diabetes complications severity index and risk of mortality, hospitalization, and healthcare utilization. *Am J Manag Care* 2008;14:15–23.

16 Peterson AM, Nau DP, Cramer JA, *et al*. A checklist for medication compliance and persistence studies using retrospective databases. *Value in Health* 2007;10:3–12.

17 Xu S, Ross C, Raebel MA, *et al*. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. *Value in Health* 2010;13:273–7.

18 Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011;46:399–424.

19 Normand ST, Landrum MB, Guadagnoli E, *et al*. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. *J Clin Epidemiol* 2001;54:387–98.

20 Benchimol EI, Smeeth L, Guttmann A, *et al*. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement *PLoS Med* 2015;12:e1001885.

21 *INVOKANA® (canagliflozin) tablets, for oral use [package insert]*. Titusville, NJ: Janssen Pharmaceuticals, 2018.

22 Buysman EK, Chow W, Henk HJ, *et al*. Characteristics and short-term outcomes of patients with type 2 diabetes mellitus treated with canagliflozin in a real-world setting. *Curr Med Res Opin* 2015;31:137–43.

23 Buysman EK, Anderson A, Bacchus S, *et al*. Retrospective study on the impact of adherence in achieving glycemic goals in type 2 diabetes mellitus patients receiving canagliflozin. *Adv Ther* 2017;34:937–53.

24 Wysham C, Pilon D, Ingham M, *et al*. Glycemic control and treatment costs in patients with type 2 diabetes mellitus initiated on canagliflozin 300 mg or a glucagon-like peptide-1 receptor agonist in a real-world setting. *Poster presented at the 77th Scientific Sessions of the American Diabetes Assosciation (ADA); June 9-13, 2017*. San Diego, CA.

25 Wysham C, Pilon D, Ingham M, *et al*. Real-World HbA1c levels in the context of persistence, treatment progression, and durability of HbA1c control in patients with type 2 diabetes mellitus initiated on canagliflozin or a glucagon-like peptide-1 receptor agonist. *Poster presented at the 26th Annual Scientific and Clinical Congress of the American Association of Clinical Endocrinologists (AACE); May 3-7, 2017. Austin, TX*.

26 Wysham CH, Pilon D, Ingham M, *et al*. Quality goal attainment and maintenance in patients with type II diabetes mellitus initiated on canagliflozin or a glucagon-like peptide-1 receptor agonist in an actual practice setting. *Curr Med Res Opin* 2018;34:1125–33.

27 Cai J, Divino V, Burudpakdee C. Adherence and persistence in patients with type 2 diabetes mellitus newly initiating canagliflozin, dapagliflozin, DPP-4s, or GLP-1s in the United States. *Curr Med Res Opin* 2017;33:1317–28.

28 Cai J, Wang Y, Baser O, *et al*. Comparative persistence and adherence with newer anti-hyperglycemic agents to treat patients with type 2 diabetes in the United States. *J Med Econ* 2016;19:1175–86.

29 Berwick DM, Nolan TW, Whittington J. The triple aim: care, health, and cost. *Health Aff (Millwood)* 2008;27:759–69.