

Demographic and Clinical Profiles of Type 2 Diabetes Mellitus Patients Initiating Canagliflozin Versus DPP-4 Inhibitors in a Large U.S. Managed Care Population

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ABSTRACT

BACKGROUND: Canagliflozin is the first sodium-glucose co-transporter-2 (SGLT-2) inhibitor—a new class of oral antidiabetic (OAD) medication—approved for type 2 diabetes mellitus (T2DM) treatment in the United States. Approved less than 2 years ago, use of canagliflozin is largely uncharacterized.

OBJECTIVE: To investigate and compare baseline demographic, clinical, and economic characteristics of patients initiating canagliflozin and dipeptidyl peptidase-4 (DPP-4) inhibitors in the real-world setting.

METHODS: Using administrative claims data from a large, geographically diverse U.S. managed care organization, this retrospective study assessed adult T2DM patients (aged ≥ 18 years) initiating treatment with canagliflozin or DPP-4 agents. Eligible patients had ≥ 1 medical claim with a T2DM diagnosis and ≥ 1 outpatient pharmacy claim for canagliflozin or a DPP-4 agent between January 1, 2011, and September 30, 2013. Patients with ≥ 1 canagliflozin fill were selected first and assigned to the canagliflozin cohort following a hierarchical approach; the date of the earliest canagliflozin fill was defined as the index date. Remaining patients with DPP-4 fills were then assigned to the DPP-4 cohort, with the index date as the first DPP-4 fill. Only patients with at least 12 months of pre-index (baseline) enrollment were included. Patients with fills for their cohort-defining drug over 3 months before the index date were excluded in order to focus on new initiators. A subset of patients with ≥ 3 months of continuous enrollment following their index dates was used to examine medication patterns after initiation. Patients with hyperglycemia; type 1, gestational, or nonclinical diabetes; or diabetes with hyperosmolar coma were excluded. Demographic, clinical, and economic characteristics were assessed over baseline and compared using two-sample t-tests or chi-square/Fisher's exact tests. Multivariable logistic regression models were built to assess baseline factors associated with initiation of canagliflozin versus DPP-4.

RESULTS: Overall, 1,566 patients initiated canagliflozin, and 26,224 patients initiated DPP-4 treatment. Males constituted slightly more than 60% of each treatment group; mean age was approximately 55 years in each cohort. A significantly smaller proportion of canagliflozin patients (41.3%) initiated treatment with endocrinologists compared with DPP-4 patients (69.2%, $P < 0.001$), and canagliflozin patients were more likely (29.4%) to initiate treatment with a primary care physician compared with DPP-4 patients (9.9%, $P < 0.001$). Comorbidities were present more frequently in canagliflozin initiators: nephropathy (10.6% vs. 7.0%), retinopathy (10.4% vs. 7.5%), dyslipidemia (82.4% vs. 72.2%), and obesity (24.9% vs. 15.6%), respectively ($P < 0.001$ for all comparisons). The mean (SD) Quan-Charlson Comorbidity Index score was greater for canagliflozin, 1.05 (1.7), compared with DPP-4 initiators, 0.92 (1.6), $P = 0.002$. Among the subset of patients with available hemoglobin A1c (A1c) results, a significantly

smaller proportion of canagliflozin initiators (16.5%) versus DPP-4 initiators (26.7%) were at the A1c $< 7\%$ treatment goal at baseline ($P < 0.001$). Among patients with 3 months follow-up, 89.2% of canagliflozin and 75.1% of DPP-4 initiators had ≥ 1 fill for their index drugs over this time frame. Canagliflozin initiators had significantly greater baseline utilization of office visits, endocrinologist and outpatient services, and more prescription fills. Total diabetes-related medical costs at baseline (\$3,025 vs. \$3,477 for canagliflozin and DPP-4 initiators) were not significantly different, while mean diabetes-related pharmacy costs were higher in the canagliflozin group (\$4,037 vs. \$1,411, $P < 0.001$). Regression analysis indicated that baseline insulin and glucagon-like peptide-1 use, as well as comorbid dyslipidemia and obesity, were significantly associated with the initiation of canagliflozin versus DPP-4 agents.

CONCLUSIONS: In this sample of commercially insured patients within a large managed care plan, canagliflozin was often initiated as second- or third-line therapy, with a relatively high share of patients receiving concomitant antidiabetic injectables, compared with DPP-4 initiators. Canagliflozin initiators had highly elevated A1c levels and were frequently diagnosed with other metabolic conditions. Baseline pharmacy utilization and costs were higher among canagliflozin patients. Future research is needed to assess real-world clinical outcomes after canagliflozin initiation, while taking these baseline differences into account.

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What is already known about this subject

- Type 2 diabetes mellitus, the largest segment of diagnosed diabetes, increases hyperglycemia risks, microvascular complications, and macrovascular events including stroke, myocardial infarction, and death.
- Although numerous therapeutic options exist, the attainment of hemoglobin A1c (A1c) goals remains challenging—about half of all patients with diabetes attain the common A1c treatment goal of $< 7.0\%$.
- Canagliflozin, which received marketing approval in the United States in 2013, has been shown in clinical trials to improve glycemic control and weight loss relative to life style changes alone and to improve A1c and glycemic levels, while improving blood pressure management compared with a number of other glucose-lowering agents.

What this study adds

- In a real-world sample of patients, canagliflozin initiators tended to be sicker and have more comorbidities, concomitant medications, and greater use of health care resources, compared with dipeptidyl peptidase-4 initiators.
- Canagliflozin patients were more likely to have elevated A1c levels before initiation and to have fills for insulin and glucagon-like peptide-1 receptor agonist agents.
- The baseline differences found in this study need to be taken into account for comparisons of real-world outcomes and their use in health care decision making.

Type 2 diabetes mellitus (T2DM) results from progressive defects in the production of insulin as well as from the response, generally resistance, to insulin secreted in the pancreas.^{1,2} Other contributory factors include ethnicity, family history, a sedentary lifestyle and obesity.^{1,3,4} Given the relationship between obesity and diabetes, other comorbidities, including hypertension, dyslipidemia, and nonalcoholic fatty liver disease, are typically more prevalent among patients diagnosed with diabetes.^{1,3,4} T2DM, the overwhelming majority (95%) of all diagnosed diabetes, increases hyperglycemia risks as well as attendant microvascular complications and macrovascular events such as stroke, myocardial infarction, and death.^{1,2,5}

One of the principal goals of diabetes management is to attain hemoglobin A1c (A1c) treatment goals and prevent the onset or decrease the rate of occurrence of microvascular conditions.^{2,6} Numerous treatment options are available for the management of T2DM, although for most patients, lifestyle changes, including healthy eating, weight control, and increased physical activity, are typically the first step. Unless there are clear contraindications, metformin monotherapy is prescribed, and if A1c targets are not attained after 3 months, 1 (or more) of several classes of agents could be added, such as sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, or basal insulin.^{2,6} Despite the broad range of therapeutic options, the attainment of A1c goals among patients with diabetes remains challenging, with just slightly more than half (52%) of diabetes patients attaining the common A1c goal of <7.0%.⁷

In March 2013, the U.S. Food and Drug Administration (FDA) approved canagliflozin—the first sodium-glucose co-transporter-2 (SGLT-2) inhibitor—for use as an oral anti-diabetic (OAD) for the treatment of T2DM in the United States.⁸⁻¹² Canagliflozin is indicated as an add-on to lifestyle changes aimed at attaining glycemic control.^{8,13} In clinical trials, patients receiving canagliflozin have been shown to achieve improved glycemic control and weight management versus diet, exercise, and other lifestyle changes,^{13,14} greater

A1c reduction versus glimepiride,¹⁵ better glycemic control and weight reduction than patients receiving sitagliptin,¹⁶ and improved blood pressure, body weight, and glycemic control compared with a range of blood glucose-lowering medications.¹⁷ Two other SGLT-2 inhibitors have been approved subsequently by the FDA—dapagliflozin and empagliflozin—in January and August 2014, respectively.^{18,19}

SGLT-2 agents have a mechanism of action that is independent of insulin secretion and function by normalizing high blood glucose levels and maintaining the body's equilibrium. Acting as transporters that reabsorb glucose from the renal filtrate, SGLT-2 agents inhibit the loss of glucose in the urine as compared with other treatments that cause the renal excretion of glucose.^{8,18-22} This novel pathway may render SGLT-2 agents particularly useful for advanced patients for whom other OADs have started to show diminished effectiveness.²³

The purpose of this retrospective study was to examine the baseline demographic, clinical, and economic characteristics of commercially insured patients initiating canagliflozin using administrative claims. The real-world use of canagliflozin is not well characterized because of its relatively short time on the U.S. market. To assist in the interpretation of the findings on canagliflozin, a cohort of patients initiating DPP-4 inhibitors was also analyzed. DPP-4 agents are another relatively new and successful class of second/third-line OADs, first approved in the United States in 2006 and currently including 4 FDA-approved formulations (sitagliptin, saxagliptin, linagliptin, and alogliptin).^{24,25}

Methods

Data Source and Study Design

This was a retrospective cohort study that employed administrative claims and electronic laboratory results from the HealthCore Integrated Research Database (HIRD) for the period from January 1, 2011, to September 30, 2013. A repository of more than 40 million researchable lives, the HIRD contains medical and pharmacy claims data originating in 14 geographically dispersed commercial health plans across the continental United States. Outpatient laboratory test results are directly available for a subset of patients who get tested at 2 large national laboratory service providers. Hierarchical selection was used to derive the final sample for analysis. The index date for patients with 1 or more fills for canagliflozin between January 1, 2012, and September 30, 2013, was defined as the date of the earliest outpatient pharmacy claim for canagliflozin (Generic Product Identifier [GPI] beginning with 2770). Among remaining patients, the date of the first prescription claim for any DPP-4 agent (GPI beginning with 2755, plus fixed-dose combinations) between January 1, 2012, and September 30, 2013, was defined as the index date. This nonexperimental study, which was exempt from institutional review board review, was fully compliant with applicable provisions of the

Health Insurance Portability and Accountability Act. Patient confidentiality was maintained throughout, and all data remained anonymous; researchers had access to the relevant datasets after all individual patient identifiers were removed.

Inclusion/Exclusion Criteria

Patients were required to have ≥ 1 medical claim indicating presence of T2DM (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] diagnosis codes 250.x0 or 250.x2) any time during the study period. Included patients were aged 18 years or older on the index date, enrolled in a commercial health plan for the duration of the study, and had ≥ 12 months (365 days) pre-index continuous medical and pharmacy enrollment (baseline period). To evaluate short-term medication use after initiation, a subsample of patients with ≥ 3 months (92 days) of continuous medical and pharmacy enrollment was created (follow-up period). Patients with ≥ 1 claim at any point during the study period with ICD-9-CM diagnosis codes indicating type 1 diabetes, gestational/neonatal diabetes, hyperglycemia (not otherwise specified), nonclinical diabetes, and diabetes with hyperosmolar coma were excluded from the study (see Appendix A for codes, available in online article). Patients with fills for their cohort-defining drugs over 3 months before the index date were also excluded in order to focus on new initiators.

Patient Characteristics and Outcomes

At baseline, demographic characteristics including age, gender, and geographic region were evaluated. Among the clinical characteristics evaluated at baseline were concomitant medication use including OADs, number of patients with ≥ 1 hypoglycemic event (overall and stratified by inpatient and outpatient place setting),²⁶ and chronic comorbidities (using ICD-9-CM codes; see Appendix A). Quan-Charlson Comorbidity Index (QCI) scores were also calculated at baseline.²⁷ In the canagliflozin cohort, the average daily dose of the index medication was evaluated at first prescription and again at the 3-month follow-up. Concomitant medication use was also evaluated at follow-up. Laboratory results assessed at baseline included A1c, random blood glucose, serum creatinine, and estimated glomerular filtration rate (eGFR) using the chronic kidney disease epidemiology equation.²⁸ These tests were assessed in subgroups based on availability of laboratory results in the HIRD. Additionally, mean A1c change between baseline and the 3-month follow-up was evaluated for patients receiving canagliflozin. All-cause and diabetes-related (defined as claims with ICD-9-CM codes of 250.xx) health care resource utilization and costs were evaluated for all patients at baseline. Resource utilization and costs were stratified by place of service (inpatient, emergency room, physician office visits, and other outpatient visits). Costs were adjusted to 2013 U.S. dollars using medical care price index information provided by the Bureau of Labor Statistics.²⁹

Statistical Analysis

Descriptive statistics included means (standard deviation [SD]) and relative frequencies for continuous and categorical variables, respectively. Continuous variables were compared between canagliflozin and DPP-4 initiators with two-sample t-tests, while categorical variables were compared with chi-square tests or Fisher's exact tests, as appropriate. Multivariable logistic regression modeling was conducted with the dependent variable indicating canagliflozin versus DPP-4 initiation; covariates included key baseline demographic and clinical characteristics. The regression was applied to a subsample of patients with metformin use at baseline. Two models, one without and one with A1c at baseline (resulting in a smaller sample) were evaluated; the results for the larger sample without baseline A1c are presented as a Forest plot. Alpha was set a priori at 0.05 for statistical significance. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Patient Disposition

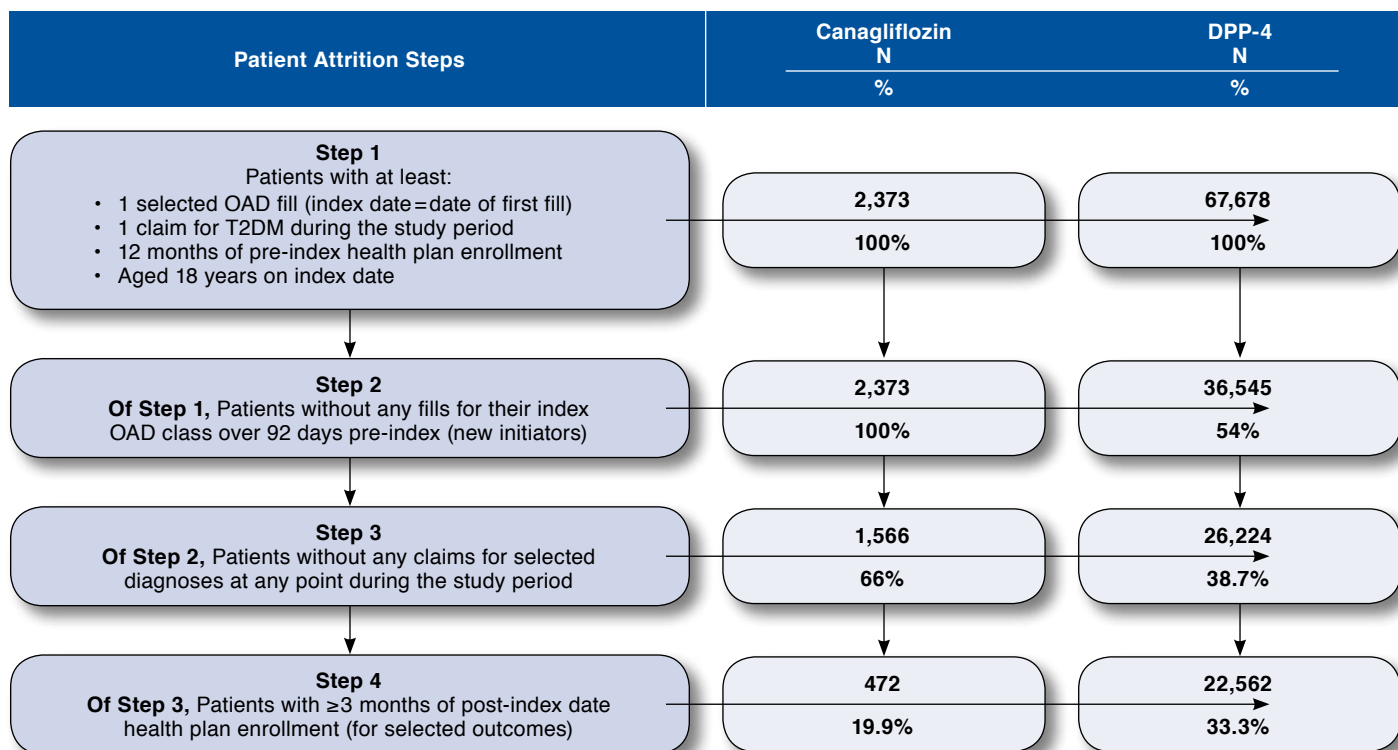
The database query identified 2,373 canagliflozin and 67,678 DPP-4 initiators who had ≥ 1 medical claim for T2DM and ≥ 1 index drug fill and satisfied the age and enrollment requirements. Removal of patients without the 3-month clean period and of those with claims for excluded diagnoses resulted in 1,566 canagliflozin and 26,224 DPP-4 initiators, as shown in Figure 1. A total of 472 canagliflozin and 22,562 DPP-4 initiators had at least 3 months of post-index health plan enrollment.

Clinical and Demographic Characteristics at Baseline

Mean age (SD) was 54 (8.5) years for canagliflozin and 55 (9.9) years for DPP-4 initiators. Approximately 61% of patients in both cohorts were male. The majority of patients were enrolled in midwestern and southern-based preferred provider organization health plans. Overall, 3.6% of canagliflozin initiators, as opposed to 2.2% of DPP-4 initiators, had ≥ 1 hypoglycemic event at baseline ($P < 0.001$); the proportions were similar (0.5%) in the inpatient setting but significantly greater for canagliflozin patients (3.2%) versus DPP-4 initiators (1.8%) in the outpatient setting ($P < 0.001$). A significantly smaller proportion of patients initiating canagliflozin (41.3%) received their index scripts from a specialist (endocrinologist) as compared with DPP-4 initiators (69.2%, $P < 0.001$). Also, a significantly larger proportion of patients (29.4%) initiated canagliflozin therapy with a primary care physician (PCP) compared with DPP-4 initiators (9.9%, $P < 0.001$), as shown in Table 1. Major diabetes-related comorbidities were significantly more common among canagliflozin versus DPP-4 initiators: nephropathy (10.6% vs. 7.0%), retinopathy (10.4% vs. 7.5%), dyslipidemia (82.4% vs. 72.2%), and obesity (24.9% vs. 15.6%, $P < 0.001$). The mean (SD) QCI score was greater among canagliflozin, 1.05 (1.7), as compared with DPP-4 initiators, 0.92 (1.6), $P = 0.002$.

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FIGURE 1 Patient Sample Extraction



DPP-4 = dipeptidyl peptidase-4; OAD = oral antidiabetic; T2DM = type 2 diabetes mellitus.

A1c values were available for approximately 30% of patients in each cohort. Among this subset, mean (SD) A1c values at baseline were 8.5% (1.7) for canagliflozin and 8.3% (1.9) for DPP-4 initiators ($P=0.095$). A significantly lower proportion of canagliflozin initiators (16.5%) versus DPP-4 initiators (26.7%) were at the A1c <7% treatment goal at baseline ($P<0.001$). Progressively greater proportions of patients initiated canagliflozin relative to DPP-4 treatment at A1c levels $\geq 7\%$ as shown in Figure 2. Mean values and proportions of patients achieving targets for random blood glucose, serum creatinine, and eGFR were similar across the 2 cohorts. Among a subsample of canagliflozin patients with A1c levels available at baseline and follow-up ($n=31$), the mean (SD) change in A1c (post minus pre) was -0.93 (1.81), with a baseline mean (SD) of 8.6 (1.69) and a follow-up mean (SD) of 6.4 (1.81). The largest reductions were observed in patients with A1c $\geq 9\%$ at baseline ($n=10$).

Medication Treatment Patterns at Baseline and Follow-up

Approximately two thirds of patients in each initiating cohort received metformin, and a significantly larger proportion of canagliflozin initiators (45.6%) received sulfonylureas compared with DPP-4 initiators (37.2%) at baseline ($P<0.001$).

Significantly larger proportions of canagliflozin relative to DPP-4 initiators were treated with GLP-1 receptor agonists (31.0% vs. 4.3%) and insulin (24.7% vs. 9.1%), respectively ($P<0.001$). As indicated in Table 2, the proportions of patients who received 0, 1, or 2 classes of OADs at baseline were similar across cohorts, while slightly more canagliflozin patients had 3 or more classes. The proportions of patients using any dyslipidemic, cardiovascular disease, or antihypertensive medication were significantly greater among canagliflozin relative to DPP-4 initiators ($P<0.001$).

Among a subset of patients with 3 months of follow-up, the average daily dose for canagliflozin initiators was 166.1 milligrams (mg) at index, increasing to 187.3 mg at the 3-month follow-up (although 89% of patients did not experience any up-titration). As shown in Table 2, at the 3-month follow-up significantly larger proportions of canagliflozin initiators relative to DPP-4 initiators were receiving metformin (53.2% vs. 36.7%), any insulin (18.0% vs. 9.3%), and any GLP-1 receptor agonist (20.8% vs. 2.6%, $P<0.001$). Canagliflozin users also appeared more adherent than DPP-4 initiators based on the proportion of patients with ≥ 1 fill of the index drug (89.2% vs. 75.1%).

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TABLE 1 Baseline Demographics, Comorbidities, and Laboratory Values

	Canagliflozin Initiators		DPP-4 Initiators		P Value ^a
	N = 1,566		N = 26,224		
	N	%	N	%	
Baseline demographics					
Female	602	38.4	10,356	39.5	0.409
Age, mean (SD)	54.0	8.5	55.1	9.9	<0.001
Prescribing/treating physician specialty^b					
Primary care physician	460	29.4	2,595	9.9	<0.001
Endocrinologist	647	41.3	18,147	69.2	<0.001
Other/unknown	459	29.3	5,482	20.9	<0.001
Baseline comorbidities					
Quan-Charlson Comorbidity Index score, mean (SD)	1.05	1.7	0.92	1.6	0.002
Neuropathy	69	4.4	810	3.1	0.004
Nephropathy	166	10.6	1,844	7.0	<0.001
Retinopathy	163	10.4	1,972	7.5	<0.001
Gastrointestinal disease	232	14.8	4,000	15.3	0.639
Dyslipidemia	1,291	82.4	18,921	72.2	<0.001
Hypertension	1,200	76.6	18,603	70.9	<0.001
Obesity	390	24.9	4,099	15.6	<0.001
Laboratory results at baseline					
A1c, with ≥ 1 test result	521	33.3	7,643	29.2	0.001
Most recent lab result (%), mean (SD)	8.45	1.65	8.31	1.93	0.095
Patients with A1c ≤ 7%	86	16.5	2,037	26.7	<0.001
Random blood glucose, with ≥ 1 test result	574	36.7	8,053	30.7	<0.001
Most recent lab result (mg/dL), mean (SD)	176.03	64.75	174.63	72.31	0.653
Patients with RBG < 180 mg/dL	352	61.3	5,103	63.4	0.327
Serum creatinine, with ≥ 1 test result	597	38.1	8,361	31.9	<0.001
Most recent lab result (mg/dL), mean (SD)	0.89	0.21	0.90	0.30	0.220
Patients with serum creatinine 0.6-1.3 mg/dL	532	89.1	7,336	87.7	0.085
eGFR, with ≥ 1 test result	597	38.1	8,361	31.9	<0.001
Most recent lab result (mL/min/1.73 m ²), mean (SD)	94.13	11.96	93.72	12.76	0.243
Patients with eGFR ≥ 60 mL/min/1.73 m ²	559	94.6	8,187	97.9	0.070

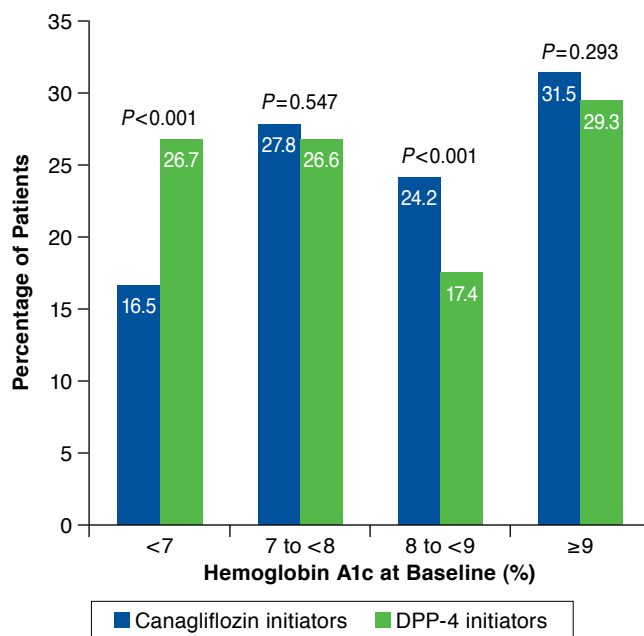
^aP values are from two-sample t-tests for continuous variables and from chi-square/Fisher's exact tests for categorical variables.

^bPrimary care physician includes family/general, internal medicine, and geriatrics. A1c = hemoglobin A1c; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; mg/dL = milligram per deciliter; mL/min = milliliter per minute; RBG = random blood glucose; SD = standard deviation.

Baseline Diabetes-Related Health Care Utilization and Costs

Significantly larger proportions of canagliflozin relative to DPP-4 initiators had ≥ 1 physician office visit (96.3% vs. 89.1%; mean 3.7 vs. 2.8), as well as ≥ 1 endocrinologist visit (28.0% vs. 8.1%; mean 0.7 vs. 0.2) at baseline, along with at least 1 other

FIGURE 2 Distribution of Hemoglobin A1c at Baseline



Note: P values are from chi-square tests. DPP-4 = dipeptidyl peptidase-4.

outpatient visit (88.2% compared with 79.6%; mean 2.6 vs. 2.1, $P < 0.001$). The use of emergency room and inpatient services was low in both cohorts, and differences were less pronounced. Canagliflozin initiators were significantly more likely to have ≥ 1 pharmacy fill and had a mean 12.4 fills, compared with 6.8 for DPP-4 patients ($P < 0.001$), as shown in Table 3. While the mean costs associated with physician office visits were significantly higher for canagliflozin initiators compared with DPP-4 patients (\$506 vs. \$359, $P < 0.001$), there was no significant difference in total medical costs (\$3,025 vs. \$3,477, $P = 0.197$). This may be due to the trend towards higher inpatient costs among DPP-4 patients, which, while not statistically significantly higher, appear to counterbalance the higher office visit costs in the canagliflozin cohort. The mean pharmacy costs were significantly greater for canagliflozin initiators (\$4,037 vs. \$1,411, $P < 0.001$). On average, canagliflozin initiators also had significantly greater combined medical and pharmacy costs (\$7,063 vs. \$4,888, $P < 0.001$). All-cause utilization and costs at baseline for the 2 cohorts show similar patterns and are provided in Appendix B (available in online article).

Multivariable Analysis

Regression analysis of a subgroup of patients with ≥ 1 metformin fill at baseline ($n = 1,005$ canagliflozin, $n = 16,431$

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TABLE 2 Baseline and Follow-up Medication Treatment Patterns

	Canagliflozin Initiators		DPP-4 Initiators		P Value ^a
	N = 1,566		N = 26,224		
	N	%	N	%	
Baseline medication use, with ≥ 1 fill					
Metformin	1,005	64.2	16,431	62.7	0.227
Thiazolidinediones	287	18.3	5,053	19.3	0.358
Sulfonylureas	714	45.6	9,745	37.2	<0.001
DPP-4 inhibitors	394	25.2	4,180	15.9	<0.001
Meglitinides	54	3.5	417	1.6	<0.001
GLP-1 receptor agonists	485	31.0	1,115	4.3	<0.001
Liraglutide	337	21.5	654	2.5	<0.001
Exenatide	58	3.7	459	1.8	<0.001
Bydureon	132	8.4	64	0.2	<0.001
Insulin	387	24.7	2,381	9.1	<0.001
Basal only	237	15.1	1,737	6.6	<0.001
Basal-bolus	133	8.5	547	2.1	<0.001
Any dyslipidemic medication	1,154	73.7	16,941	64.6	<0.001
Any CVD medication ^b	1,064	67.9	15,829	60.4	<0.001
Any antihypertensive medication	1,140	72.8	17,144	65.4	<0.001
Number of OAD classes during baseline					
0 classes	463	29.6	8,168	31.2	0.189
1 class	863	55.1	14,209	54.2	0.475
2 classes	224	14.3	3,731	14.2	0.933
3+ classes	16	1.0	116	0.4	0.001
Follow-up medication use, with ≥ 1 fill^c					
	Subgroup n = 472		Subgroup n = 22,562		
Study (index) drug	421	89.2	16,934	75.1	<0.001
Metformin	251	53.2	8,272	36.7	<0.001
Thiazolidinediones	54	11.4	1,623	7.2	<0.001
Sulfonylureas	165	35.0	6,619	29.3	0.008
DPP-4 inhibitors	157	33.3	16,934	75.1	<0.001
Meglitinides	12	2.5	268	1.2	0.008
GLP-1 receptor agonists	98	20.8	586	2.6	<0.001
Insulin	85	18.0	2,102	9.3	<0.001
Any dyslipidemic medication	293	62.1	12,648	56.1	0.009
Any CVD medication ^b	270	57.2	11,678	51.8	0.019
Any antihypertensive medication	302	64.0	12,738	56.5	0.001

^aP values are from two-sample t-tests for continuous variables and from chi-square tests for categorical variables.

^bCVD medications include thrombolytics, nitroglycerines, clot preventing drugs, and antiplatelets.

^cAssessed over a 3-month time frame from index date in a subsample of patients with ≥ 3 months continuous enrollment after index date.

CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; OAD = oral antidiabetic.

DPP-4) identified factors that were significantly associated with the initiation of canagliflozin versus DPP-4 treatment as shown in Figure 3 (model c-statistic=0.77). Key baseline characteristics included the use of insulin (odds ratio [OR]=2.06; 95% confidence interval [CI]=1.72-2.45; P<0.001) and GLP-1 receptor agonists (OR=8.90; 95% CI=7.60-10.41;

TABLE 3 Diabetes-Related Health Care Utilization and Costs at Baseline

	Canagliflozin Initiators		DPP-4 Initiators		P Value ^a
	N = 1,566		N = 26,224		
	N	%	N	%	
Annual health care utilization					
Office visits, with ≥ 1 visit	1,508	96.3	23,377	89.1	<0.001
Office visits, mean (SD)	3.7	2.5	2.8	2.2	<0.001
Endocrinologist visits, with ≥ 1 visit ^b	438	28.0	2,128	8.1	<0.001
Endocrinologist visits, mean (SD) ^b	0.7	1.3	0.2	0.7	<0.001
Other outpatient visits, with ≥ 1 visit ^c	1,381	88.2	20,866	79.6	<0.001
Other outpatient visits, mean (SD) ^c	2.6	2.3	2.1	2.2	<0.001
Emergency room visits, with ≥ 1 visit	164	10.5	2,264	8.6	0.012
Emergency room visits, mean (SD)	0.1	0.4	0.1	0.4	0.075
Inpatient visits, with ≥ 1 visit	108	6.9	2,207	8.4	0.035
Inpatient visits, mean (SD)	0.1	0.4	0.1	0.4	0.127
Annual pharmacy utilization					
Pharmacy dispensing, with ≥ 1 fill	1,497	95.6	22,415	85.5	<0.001
Pharmacy dispensing, mean (SD)	12.4	8.0	6.8	5.9	<0.001
Annual health care costs per patient, 2013 USD					
Office visits, mean (SD)	506	1,340	359	470	<0.001
Other outpatient visits, mean (SD) ^c	780	3,226	719	3,098	0.445
Emergency room visits, mean (SD)	248	1,057	194	1,009	0.040
Inpatient visits, mean (SD)	1,491	10,539	2,206	12,785	0.030
Total medical costs, mean (SD)	3,025	11,729	3,477	13,556	0.197
Total medical costs, median	704	—	528	—	—
Pharmacy costs, mean (SD)	4,037	4,701	1,411	2,390	<0.001
Pharmacy costs, median	3,210	—	267	—	—
Total medical + pharmacy costs, mean (SD)	7,063	12,514	4,888	13,791	<0.001
Total medical + pharmacy costs, median	4,752	—	1,587	—	—

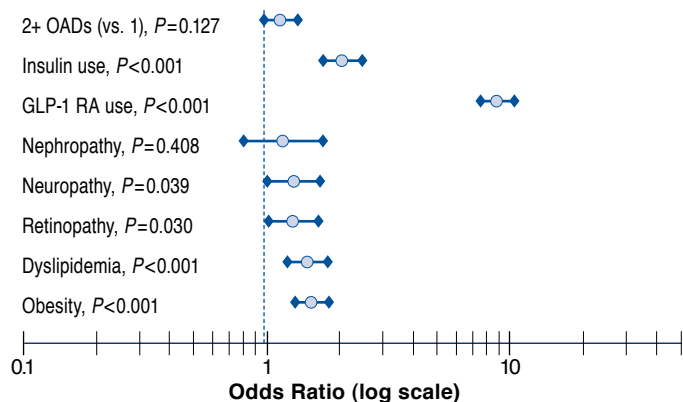
^aP values are from two-sample t-tests for continuous variables and from chi-square tests for categorical variables.

^bEndocrinologist visits that take place in an office setting.

^cOther outpatient facility visits such as clinics, ordered lab tests, and imaging. DPP-4 = dipeptidyl peptidase-4; SD = standard deviation; USD = U.S. dollars.

P<0.001) and the presence of comorbid conditions such as neuropathy (OR=1.30; 95% CI=1.01-1.66, P=0.039), retinopathy (OR=1.30; 95% CI=1.03-1.64; P=0.030), dyslipidemia (OR=1.48; 95% CI=1.23-1.79; P<0.001), and obesity (OR=1.54; 95% CI=1.31-1.81, P<0.001). In a subgroup of patients with A1c available at baseline (n=310 canagliflozin, n=4,874 DPP-4), a second logistic regression model (model c-statistic=0.81) suggested that baseline A1c ≥ 7% is associated with an increase in the likelihood of initiating canagliflozin (OR=1.80; 95% CI=1.26-2.55; P=0.001) after adjusting for other patient demographic and clinical characteristics.

FIGURE 3 Baseline Characteristics Associated with Initiation of Canagliflozin Versus DPP-4 Inhibitors



DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; OAD = oral anti-diabetic; RA = receptor agonist.

Discussion

This is one of the first studies in the United States to present real-world information on the clinical and demographic characteristics as well as associated health care utilization and cost patterns of T2DM patients initiating canagliflozin versus DPP-4 inhibitors. One previously published study also examined baseline clinical and demographic characteristics of patients with T2DM who initiated canagliflozin in a different U.S. managed care setting.³⁰ While this recent study did not present results for a comparison cohort, its findings regarding the characteristics of canagliflozin initiators are consistent with our findings.

In the time period investigated in this study, roughly 17 times the number of patients in the study sample initiated treatment with DPP-4 agents relative to canagliflozin. The overwhelming difference may be attributed foremost to the comparatively recent approval of canagliflozin (March 2013) compared with DPP-4 agents, which were marketed in the United States since 2006 beginning with the approval of sitagliptin.²⁴ Furthermore, unlike canagliflozin—the first agent in the SGLT-2 inhibitor class to be approved—DPP-4 agents have a long and familiar track record, as well as more efficacy and safety data. The approval of 3 new DPP-4 agents in the United States since sitagliptin became available demonstrates how well the DPP-4 class is established in the marketplace.²⁵

The health plans in this study cover pharmacy costs for canagliflozin and DPP-4 drugs but require prior authorization, including step therapy and quantity limits; canagliflozin also requires higher patient copay compared with preferred

DPP-4 agents. Approval for the use of canagliflozin requires that patients have not achieved glycemic control with titrated metformin and a DPP-4 agent; approval for the use of a DPP-4 agent itself requires that patients have not achieved glycemic control with titrated metformin (unless contraindicated). There are several inexpensive existing OADs that have known and acceptable safety records; therefore, at this time it does not seem likely that patients, payers, or providers would consider using canagliflozin as first-line therapy but more likely would consider it as second or third tier or as combination treatment.²³

In this study, a wider range of concomitant medications was used by canagliflozin initiators compared with DPP-4 initiators. In particular, insulin and GLP-1 receptor agonists were much more prevalent in canagliflozin initiators. Use of other concomitant medications, including metformin, sulfonylureas, dyslipidemic agents, antihypertensives, and cardiovascular disease medications, was also notably high. This could be a result of patient difficulties in reaching treatment goals, patient willingness to switch to other agents for better control of diabetes, and/or the attractiveness of a new class of agents with an entirely different mechanism of action.

Relative to patients initiating DPP-4 therapy, a significantly smaller proportion of study patients initiating canagliflozin were treated by endocrinologists, while a larger share initiated treatment with a PCP. The canagliflozin initiators used a broad range of OADs during the baseline period and seemed willing to change agents in hopes of improving their A1c levels. This could also be an indication that they were reluctant to start or continue treatment with injectables, which are more often prescribed by endocrinologists.^{31,32}

Patients initiating canagliflozin appeared to have more advanced T2DM and generally lower health status than patients initiating DPP-4 agents. Patients initiating canagliflozin had a higher mean QCI score and proportionately more microvascular comorbidities, as well as dyslipidemia and obesity, which signal more cardiovascular complications. A treatment regimen that acts differently from therapies tried in the past could have some appeal to patients interested in finding new, more effective ways to control A1c, blood pressure, and especially weight, which canagliflozin is associated with.¹³⁻¹⁷

That canagliflozin initiators were less healthy than the DPP-4 initiators is also indicated by the significantly smaller proportion of canagliflozin patients who were at A1c treatment goals at baseline. In fact, patients initiated canagliflozin in progressively greater proportions than DPP-4 patients at higher A1c levels. Multivariable modeling suggested that signs of more severe illness (such as prior insulin and GLP-1 treatments and microvascular complications) were linked significantly to initiation of canagliflozin in comparison with DPP-4 agents.

Overall, canagliflozin initiators had greater baseline use of office visits and endocrinologist and outpatient services and more prescription fills, which is consistent with more progressed disease. While mean total medical costs for the 2 patient groups were not significantly different, prescription costs and total expenditures on medical plus pharmacy services were greater for patients who initiated canagliflozin. These clinical and economic differences will need to be taken into account in future estimates of effectiveness, cost-effectiveness, and budget impact of canagliflozin using real-world data.

Limitations

This observational study relied exclusively on secondary data, which were repurposed for research from the original transactional functions. As a result, these findings must be approached with caution and confined to the parameters explored by the study. The sample was selected from a large managed care repository, and while the study population was reflective of working-age diabetes patients in commercial health plans across much of the continental United States, the results may not be generalizable to patients enrolled in different types of health plans or outside the United States, where health care delivery follows different rules. Claims databases, such as the HIRD used in this study, do not typically provide information on race and ethnicity nor do they include risk factors such as family history, smoking status, body mass index, diet, exercise regimen, or socioeconomic status—all of which could substantively influence outcomes. Administrative data are subject to miscoding or missing entries, and it is possible that the disease codes in the database used to identify conditions may not correspond entirely to the true presence of disease, since codes are entered by health care providers for the purpose of insurance billing. Furthermore, presence of a claim for a filled prescription does not indicate that the medication was consumed or that it was taken as prescribed. Laboratory results were available only for a subset of patients who completed testing at 2 large national reference laboratories, which provide between 20%-50% of outpatient diagnostic testing on a state-by-state basis. The recent approval of SGLT-2 inhibitors precluded the use of in-class comparators and only allowed for a 3-month follow-up period for canagliflozin. This limited the ability to identify any emerging trends or changes in treatment patterns, as well as conducting a more comprehensive assessment of postinitiation outcomes. It is possible that the early initiators of canagliflozin examined in the current study may differ in their characteristics from patients who started treatment more recently; canagliflozin is also currently subject to stricter prior authorization requirements and higher copays compared with DPP-4 agents. It would be interesting to revisit this population in future research to investigate potential changes over time as the market evolves.

Conclusions

In this sample of commercially insured patients associated with a large managed care plan, canagliflozin was often initiated as a second- or third-line therapy, with a relatively high share of patients receiving concomitant antidiabetic injectables, compared with patients initiating DPP-4 agents. Canagliflozin initiators also had highly elevated A1c levels prior to initiation and were frequently diagnosed with other metabolic syndrome conditions. Future research is needed to examine changes in treatment patterns and real-world clinical outcomes after canagliflozin initiation, especially in comparison with other treatment alternatives, while taking the observed baseline differences into account.

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All authors contributed equally to the study design, interpretation of data, and writing and revision of the manuscript. Grabner and Geremakis collected the data.

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APPENDIX A ICD-9-CM Codes Used for Exclusion Criteria and Comorbidities

Condition	ICD-9-CM Code
Type 1 diabetes	250.x1, 250.x3
Gestational diabetes	648.8x
Hyperglycemia not other specified	790.6x
Neonatal diabetes mellitus	775.1x
Nonclinical diabetes	790.29
Diabetes with hyperosmolar coma	250.2x
Neuropathy	250.6x, 707.1x, 892.1, 785.4, 040.0
Nephropathy	250.4x
Retinopathy	250.5x, 362.0x, 366.41
Gastrointestinal disease	536.8, 536.3, 536.4x, 787.01, 780.02, 787.03, 787.3, 789.0x, 564.0, 564.01, 564.02, 564.03, 564.09, 787.91
Dyslipidemia	272.xx
Hypertension	401.x, 402.xx, 403.xx, 404.xx, 405.xx, 437.2
Obesity	278.0x, V85.3, V85.4

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

APPENDIX B All-Cause Utilization and Costs at Baseline

	Canagliflozin Initiators		DPP-4 Initiators		p Value ^a
	N = 1,566		N = 26,224		
	N	%	N	%	
Annual health care utilization					
Office visits, with ≥ 1 visit	1,548	98.9	25,574	97.5	<0.001
Office visits, mean (SD)	7.1	6.1	6.4	5.6	<0.001
Endocrinologist visits, with ≥ 1 visit ^b	444	28.4	2,260	8.6	<0.001
Endocrinologist visits, mean (SD) ^b	0.7	1.3	0.2	0.8	<0.001
Other outpatient visits, with ≥ 1 visit ^c	1,509	96.4	24,792	94.5	0.002
Other outpatient visits, mean (SD) ^c	7.7	8.4	7.3	9.4	0.129
Emergency room visits, with ≥ 1 visit	252	16.1	3,845	14.7	0.121
Emergency room visits, mean (SD)	0.2	0.6	0.2	0.6	0.391
Inpatient visits, with ≥ 1 visit	123	7.9	2,626	10.0	0.005
Inpatient visits, mean (SD)	0.1	0.4	0.1	0.5	0.010
Annual pharmacy utilization					
Pharmacy dispensing, with ≥ 1 fill	1,557	99.4	25,727	98.1	<0.001
Pharmacy dispensing, mean (SD)	29.6	17.0	20.9	15.2	<0.001
Annual health care costs per patient, 2013 USD					
Office visits, mean (SD)	1,025	2,841	930	1,750	0.045
Other outpatient visits, mean (SD) ^c	2,809	7,749	3,033	10,038	0.386
Emergency room visits, mean (SD)	355	1,266	317	1,275	0.255
Inpatient visits, mean (SD)	1,943	14,916	2,681	15,143	0.057
Total medical costs, mean (SD)	6,131	18,991	6,961	20,269	0.114
Total medical costs, median	1,970	—	1,757	—	—
Pharmacy costs, mean (SD)	6,457	13,538	3,445	5,138	<0.001
Pharmacy costs, median	4,791	—	2,221	—	—
Total medical + pharmacy costs, mean (SD)	12,588	23,957	10,406	21,602	<0.001
Total medical + pharmacy costs, median	7,812	—	5,009	—	—

^aP values are from two-sample t-tests for continuous variables and from chi-square tests for categorical variables.

^bEndocrinologist visits that take place in an office setting.

^cOther outpatient facility visits such as clinic, ordered lab tests, etc.

DPP-4 = dipeptidyl peptidase-4; SD = standard deviation; USD = U.S. dollars.