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ORIGINAL RESEARCH

Real-world Effectiveness of Liraglutide vs. Sitagliptin Among Older Patients with Type 2 Diabetes Enrolled in a Medicare Advantage Prescription Drug Plan: A Retrospective Observational Study

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ABSTRACT

Introduction: Liraglutide and sitagliptin were compared on glycemic control and all-cause healthcare costs over a 1-year period among older adults with type 2 diabetes (65–89 years) enrolled in a national Medicare Advantage Prescription Drug health plan.

Methods: This was a retrospective study in which the index date was the first prescription fill for liraglutide or sitagliptin between 25 January 2010 and 31 December 2014. Post-index treatment persistence and glycosylated hemoglobin ($HbA1_c$) at baseline and 1 year (± 90 days) post-index date were required. Patients were excluded if their record included use of insulin during the baseline period. Inverse probability of treatment weighting using stabilized weights was employed with final covariate adjusted regression modeling to estimate the primary outcome (mean change in $HbA1_c$) and secondary outcomes (achieving glycemic goal and costs), each at 1-year post-index date.

Results: Overall, 3056 patients met the selection criteria, of whom 218 filled prescriptions for liraglutide and 2838 for sitagliptin. Adjusted mean change in $HbA1_c$ at 1 year post-index was − 0.42 with liraglutide versus − 0.12 with sitagliptin ($P = 0.0012$). Adjusted odds of achieving the treatment goals of $HbA1_c < 7\%$ and achieving an $HbA1_c$ reduction of $\geq 1\%$ were higher for those on liraglutide than for those on sitagliptin (1.68, 95% confidence interval [CI] 1.25–2.24 and 1.76, 95% CI 1.31–2.36), respectively. Total healthcare costs in those achieving an $HbA1_c$ of < 7% were not significantly different between treatment groups but were higher within the liraglutide group for those achieving an $HbA1_c < 8\%$.

Conclusions: When compared to sitagliptin, liraglutide was associated with greater achievement of an $HbA1_c < 7\%$ over a 1-year period in an older population. This finding was not associated with a statistically significant increase in all-cause total healthcare costs, although costs were slightly higher in the liraglutide group than in the sitagliptin group.

Keywords: Clinical outcomes; Liraglutide; Older adults; Sitagliptin; Type 2 diabetes

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Key Summary Points

Why carry out this study?

Type 2 diabetes (T2D) is a rising health concern in the USA, particularly within an aging population.

Despite the importance of effectively managing T2D in older adults, this patient population has often been excluded from randomized clinical trials, and limited data exist on this older population regarding real-world outcomes related to different glucose-lowering therapies.

What was learned from the study?

Liraglutide and sitagliptin were compared on glycemic control and all-cause healthcare costs over a 1-year period among older adults with T2D enrolled in a national Medicare Advantage Prescription Drug health plan.

When compared to sitagliptin use, liraglutide use was associated with greater achievement of an glycosylated hemoglobin level of < 7% over a 1-year period in an older population.

This finding was not associated with an increase in all-cause total healthcare costs.

INTRODUCTION

Type 2 diabetes (T2D) is a rising health concern in the USA, particularly within an aging population. In 2015, 9.4% of the total US population was estimated to have diabetes; this number increased to 17.0% when this analysis was restricted to adults aged 45–64 years only and to 25.2% among adults aged 65 years or older [1]. This number is expected to continue to rise due to the aging US population and increased life expectancy of people with diabetes. Older diabetic patients have a higher risk for diabetes-related complications, including microvascular and macrovascular damage and hypoglycemia, and therefore present significant challenges in achieving strict glycemic control and constitute a growing burden on the US healthcare system [2–4].

Despite the importance of effectively managing T2D in older adults, this patient population has often been excluded from randomized clinical trials, and limited data exist on this older population regarding real-world outcomes related to different glucose-lowering therapies [4]. The class of incretin-based therapies, including glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase 4 (DPP-4) inhibitors, may allow for improved control of hyperglycemia and offers important advantages to an older population (i.e., minimal risk for hypoglycemia, weight loss, and lower risk for cardiovascular disease associated with GLP-1 RAs) [5]. Previous studies have found that the GLP-1 analogue liraglutide provides sustained glycosylated hemoglobin ($HbA1_c$) reduction, achievement of specific $HbA1_c$ goals, and weight loss when compared to the DPP-4 inhibitor sitagliptin [6–12]. Additionally, retrospective observational studies have demonstrated the cost-effectiveness of liraglutide when compared within and between antidiabetic drug classes; however, cost-effectiveness has not been specifically explored in a T2D population aged 65 years and older [11, 13–16].

The aim of the current study was to compare liraglutide with sitagliptin in achieving glycemic control among older people with T2D enrolled in a Medicare Advantage Prescription Drug (MAPD) plan. This was accomplished by evaluating mean change in $HbA1_c$, mean reduction in $HbA1_c$ of $\geq 1\%$, and the percentage of patients achieving the treatment goals of $HbA1_c < 7\%$ and $HbA1_c < 8\%$ over a 1-year period. The analysis also compared all-cause healthcare costs (pharmacy and medical combined) in this population. This information may be important when considering real-world treatment in the growing older population with T2D in the USA.

MATERIALS AND METHODS

Data Source

This was a retrospective and observational study. The Humana Research Database (Humana, Louisville, KY), which contains administrative claims data for individuals enrolled in Humana's fully insured commercial and medicare plans was used to compare clinical and cost outcomes between patients treated with liraglutide and those treated with sitagliptin. The database included medical, pharmacy, and laboratory claims of individuals with T2D enrolled in a MAPD plan for the period of 25 July 2009–30 March 2016. The research protocol associated with the manuscript was reviewed and approved as a minimal risk study by Schulman IRB, an independent institutional review board, which determined that the study met the criteria for a waiver of informed consent and waiver of authorization as set forth by the code of federal regulations.

Sample Selection

Analysis included patients (age 65–89 years at index date) who received their first prescription for liraglutide or sitagliptin between 25 January 2010, and 31 December 2014. Patients were also required to have continuous MAPD plan membership throughout the study period, including enrollment for at least 6 months pre-index date and 15 months post-index date (Fig. 1). Additional inclusion criteria were: evidence of T2D (ICD-9 [International Classification of Diseases, Ninth Revision, Clinical Modification] codes 250.x0 or 250.x2 in any position on ≥ 1 outpatient, acute inpatient, or emergency department [ED] claim in the study period); post-index persistence (defined as having no gaps in treatment of ≥ 60 days in the 365 day post -index treatment period), and available baseline and 1-year follow-up $HbA1_c$ values. Patients were excluded if their record contained evidence of type 1 diabetes mellitus, DPP-4 inhibitor use, or sodium glucose cotransporter 2 inhibitor use in the baseline period, and not meeting the requirement of persistence on medication for 1 year. To minimize possible biases and reduce baseline differences between the two groups, patients were also excluded if they had a record of insulin use in the baseline period.

Study Measures

Patient information included demographics, such as age, gender, and race/ethnicity, and baseline clinical characteristics, such as Deyo-Charleston Comorbidity Index, Diabetes Complications Severity Index (DCSI), $HbA1_c$ level, comorbidities, and the use of antidiabetic medications.

The primary outcome measure was mean change in $HbA1_c$ from baseline to the 1 year ($\pm$ 90 days) follow-up. If more than one HbA1c result was available, the test result closest to the index date was used for the baseline measure,

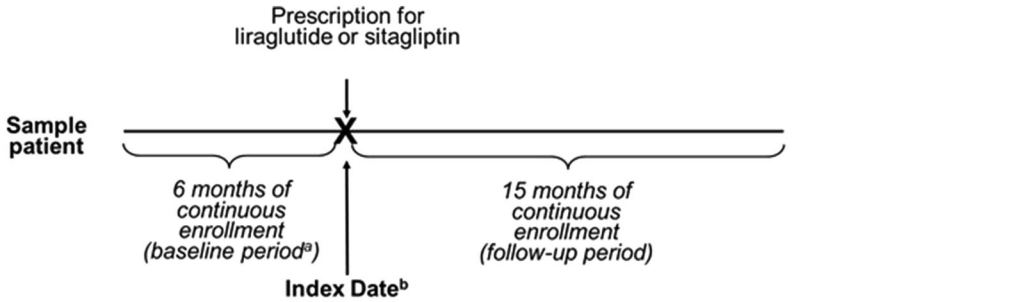

Fig. 1 Patient sample selection

and the test result closest to 1 year from the index date was used for the 1-year follow-up. Secondary outcome measures were percentage of patients achieving a mean reduction in $HbA1_c$ of $\geq 1\%$, percentage of patients achieving the treatment goals of $HbA1_c < 7\%$ and $HbA1_c < 8\%$, and percentage of patients achieving these treatment goals with no reported hypoglycemia. Total healthcare costs (all-cause pharmacy and medical) in patients achieving these goals with no reported hypoglycemia were also measured. Costs were calculated separately for inpatient hospital, ED, physician office visits, nursing facility, other outpatient encounters, and pharmacy services, and were based on the total amount allowed by the healthcare plan for a given procedure or healthcare encounter. To mitigate the potential for underestimating costs of services provided under capitated arrangements, costs for these services were imputed at the service-line level. Capitated costs were assigned the median value (allowed amount) from non-capitated fee-for-service claims matched by procedure and payment level. Payment level was derived from the source of billing (facility or professional) and the place of service (physician office or facility), similar to the Medicare prospective payment systems. Costs were adjusted to the 2015 value based on the Consumer Price Index Medical Component [17]. Due to a low number of post-index hypoglycemic events, 'no hypoglycemia' was not included in the composite outcome.

Statistical Analysis

Descriptive analyses included demographics, baseline characteristics, and primary and secondary outcomes and were reported as number with percentage, mean with standard deviation, or median with interquartile range. Changes in $HbA1_c$ were analyzed by the *t* test, the proportions of patients achieving treatment goals were analyzed using the Chi-square test, and costs of achieving treatment goals were analyzed using the Wilcoxon rank sum test. *P* values of < 0.05 were considered to be statistically significant.

Glycemic control outcomes were modeled using linear regression (mean change in $HbA1_c$) and multiple logistic regression (proportions of patients achieving $HbA1_c$ treatment goals). Rigorous weighting methods (inverse probability of treatment weighting [IPTW] using stabilized weights) [18] were used in adjusted analyses to reduce bias and measured confounding attributed to the nature of the retrospective study design. For the primary outcome, the sample size requirement was estimated to be 140 older patients with T2D in the liraglutide group and 1258 in the sitagliptin group, based on group weights of 10 vs. 90%, respectively, and the detection of a mean change in $HbA1_c$ of 0.4 using a two-sided test with $\alpha = 0.05$ and power $1 - \beta = 0.80$. To ensure that these statistical methods had achieved adequate balance, baseline covariates were compared between treatment groups by calculating standardized differences. These baseline covariates were considered to be balanced across patient groups if standardized differences were < 0.10 (see Table 1). After weighting, balance was achieved for most variables, except for four covariates (gender, race, health plan type, and level of prior antidiabetic medication use). These four variables were included as independent variables in the final IPTW regression models, along with post-index antidiabetic treatment additions. The final model to detect the difference in change in mean $HbA1_c$ between the treatment groups was adequately powered. Estimated outcomes of glycemic control were reported as odds ratios with 95% confidence intervals (CIs).

Estimated all-cause total cost data (pharmacy and medical) were analyzed using generalized linear models based on a log link and gamma distribution, with and without covariate adjustment.

RESULTS

Overall, 3056 patients met the criteria of persistence on index treatment and had $HbA1_c$ results available within the baseline period and 1 year later (Fig. 2). Within this study population, 218 (7.1%) patients were treated with liraglutide and 2838 (92.9%) patients were treated with sitagliptin.

Table 1 Assessment of balance between treatment groups between observed and weighted

Characteristic	Observed			Weighted (stabilized IPTW)		
	Liraglutide cohort (*n* = 218)	Sitagliptin cohort (*n* = 2838)	Standardized difference	Liraglutide cohort (*n* = 218)	Sitagliptin cohort (*n* = 2838)	Standardized difference
Age, years, mean (SD)	70.5 (4.7)	73.2 (5.9)	0.5187	70.5 (4.7)	73.2 (5.9)	0.0829
Gender, *n* (%)						
Female	115 (52.8)	1451 (51.1)		115 (52.8)	1451 (51.1)	
Male	103 (47.3)	1387 (48.9)	0.0325	103 (47.3)	1387 (48.9)	0.137
Geographic region, *n* (%)						
Northeast	–[a]	28 (1.0)	0.0071	–[a]	28 (0.99)	0.0132
Midwest	49 (22.5)	443 (15.6)	0.1756	49 (22.5)	443 (15.6)	0.049
South	140 (64.2)	2079 (73.3)	0.1959	140 (64.2)	2079 (73.3)	0.0586
West	27 (12.4)	288 (10.2)	0.0708	27 (12.4)	288 (10.2)	0.023
Race/ethnicity, *n* (%)						
White	202 (92.7)	2189 (77.1)	0.4442	202 (92.7)	2189 (77.1)	0.0544
Black	–[a]	403 (14.2)	0.3545	–[a]	403 (14.2)	0.1014
Hispanic	–[a]	104 (3.7)	0.1121	–[a]	104 (3.7)	0.0385
Other	–[a]	142 (5.0)	0.2075	–[a]	142 (5.0)	0.0151
Healthcare plan type, *n* (%)						
HMO	125 (57.3)	1712 (60.3)	0.0607	125 (57.3)	1712 (60.3)	0.0031
PPO	75 (34.4)	794 (28.0)	0.139	75 (34.4)	794 (28.0)	0.0733
POS	–[a]	39 (1.4)	0.0367	–[a]	39 (1.4)	0.0464
FFS	11 (5.1)	166 (5.9)	0.0354	11 (5.1)	166 (5.9)	0.007
Other	–[a]	127 (4.5)	0.1847	–[a]	127 (4.5)	0.2387
Healthcare plan characteristics, *n* (%)						
LIS status only	17 (7.8)	174 (6.1)	0.0655	17 (7.8)	174 (6.1)	0.0765
Dual eligibility only	–[a]	–[a]	0.0703	–[a]	–[a]	0.0678
LIS status and dual eligibility	31 (14.2)	628 (22.1)	0.2062	31 (14.2)	628 (22.1)	0.0102
Deyo-CC Index, mean (SD)	1.7 (1.47)	2.31 (1.9)	0.3558	1.7 (1.5)	2.31 (1.9)	0.022
DCSI, mean (SD)	0.69 (1.3)	1.27 (1.6)	0.4028	0.69 (1.3)	1.27 (1.6)	0.0271
Presence of comorbidity: *n* (%)						
Cardiovascular disease	26 (11.9)	755 (26.6)	0.3788	26 (11.9)	755 (26.6)	0.0318

Table 1 continued

Characteristic	Observed			Weighted (stabilized IPTW)		
	Liraglutide cohort (n = 218)	Sitagliptin cohort (n = 2838)	Standardized difference	Liraglutide cohort (n = 218)	Sitagliptin cohort (n = 2838)	Standardized difference
Nephropathy	29 (13.3)	754 (26.6)	0.3367	29 (13.3)	754 (26.6)	0.005
Retinopathy	–[a]	116 (4.1)	0.0216	–[a]	116 (4.09)	0.0545
Peripheral vascular disease	13 (6.0)	249 (8.8)	0.1077	13 (6.0)	249 (8.8)	0.0883
Cerebrovascular disease	–[a]	94 (3.3)	0.0934	–[a]	94 (3.3)	0.0299
Neuropathy	29 (13.3)	444 (15.6)	0.0666	29 (13.3)	444 (15.6)	0.092
Metabolic disease	–[a]	–[a]	0.0594	–[a]	–[a]	0.0573
Obesity	62 (28.4)	445 (15.7)	0.3114	62 (28.4)	445 (15.7)	0.0174
Hypoglycemia	–[a]	132 (4.7)	0.0255	–[a]	132 (4.7)	0.0529
Pre-index unique medication counts, mean (SD)	10.66 (3.9)	10.74 (4.2)	0.0199	10.66 (3.9)	10.74 (4.2)	0.0634
Pre-index prescription fill, counts, mean (SD)	13.58 (8.0)	14.65 (8.3)	0.1307	13.58 (8.0)	14.65 (8.3)	0.0059
Utilization of antidiabetic medications during pre-index period: n (%)						
Biguanides	166 (76.2)	2062 (72.7)	0.08	166 (76.2)	2062 (72.7)	0.0043
Sulfonylurea	130 (59.6)	1811 (63.8)	0.0861	130 (59.6)	1811 (63.8)	0.073
Thalidozlinide	39 (17.9)	489 (17.2)	0.0173	39 (17.9)	489 (17.2)	0.054
Other antidiabetic medication	–[a]	70 (2.5)	0.0179	–[a]	70 (2.5)	0.0591
Pre-index level of antidiabetic therapy, n (%)						
No medication use	12 (5.5)	217 (7.7)	0.0865	12 (5.5)	217 (7.7)	0.1229
1 non-insulin antidiabetic	100 (45.9)	1211 (42. 7)	0.0645	100 (45.9)	1211 (42.7)	0.0901
2 non-insulin antidiabetics	87 (39.9)	1221 (43.0)	0.0633	87 (39.9)	1221 (43.0)	0.0068
$\geq$ 3 non-insulin antidiabetics	19 (8.7)	189 (6.7)	0.0772	19 (8.7)	189 (6.7)	0.0508
Pre-index $HbA1_c$, mean (SD)	8.03 (1.4)	7.8 (1.4)	0.1714	8.03 (1.4)	7.8 (1.4)	0.0892

Table 1 continued

Characteristic	Observed			Weighted (stabilized IPTW)		
	Liraglutide cohort (n = 218)	Sitagliptin cohort (n = 2838)	Standardized difference	Liraglutide cohort (n = 218)	Sitagliptin cohort (n = 2838)	Standardized difference
Prescribing physician specialty, *n* (%)						
Primary care	91 (41.7)	1094 (38.6)	0.0652	91 (41.7)	1094 (38.6)	0.0067
Endocrinology	31 (14.2)	155 (5.5)	0.2973	31 (14.2)	155 (5.5)	0.0167
Internal and family medicine	65 (29.8)	1299 (45.8)	0.3336	65 (29.8)	1299 (45.8)	0.0036
Other	40 (18.4)	349 (12.3)	0.1686	40 (18.4)	349 (12.3)	0.0062

DCSI Diabetes Complications Severity Index, *Deyo-CC* Deyo-Charlson Comorbidity Index, *FFS* fee for service, *HbA1*$_c$ glycosylated hemoglobin, *HMO* health management organization, *IPTW* inverse probability of treatment weighting, *LIS* low income subsidy, *POS* point of service, *PPO* preferred provider organization, *SD* standard deviation

[a] Data suppressed to protect privacy

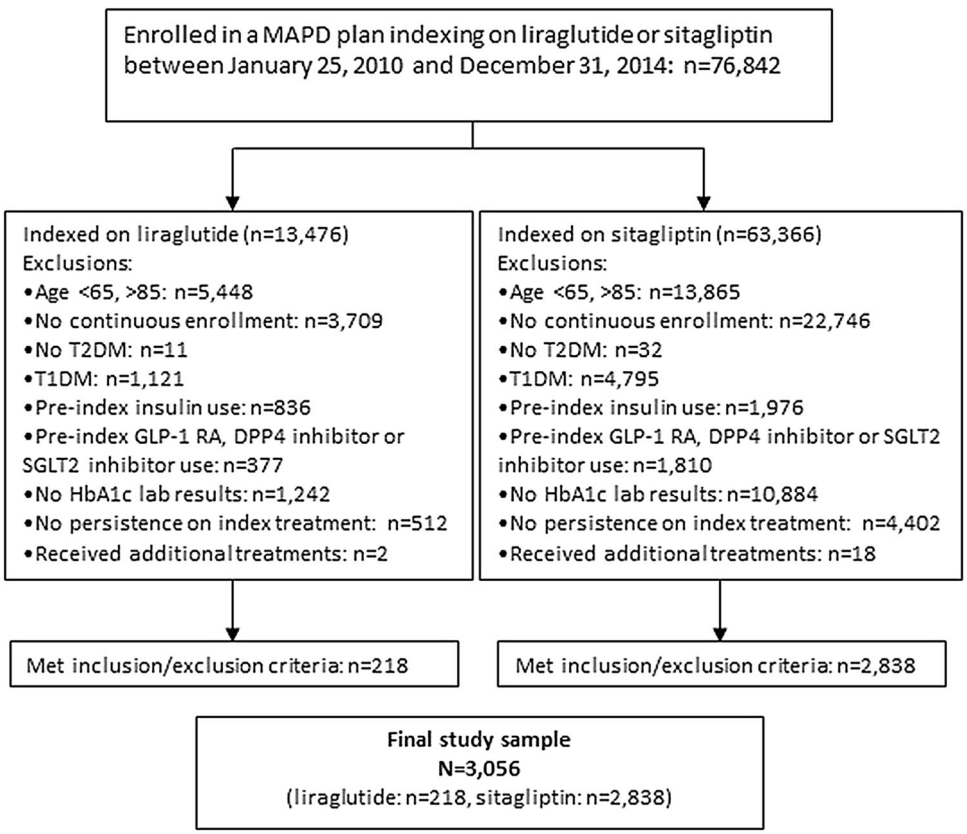

Fig. 2 Patient attrition. *DDP-4* Dipeptidyl peptidase 4, *HbA1*$_c$ glycosylated hemoglobin, *MAPD* Medicare Advantage Prescription Drug, *GLP-1* RA glucagon-like peptide-1 receptor agonist, *SGLT2* sodium glucose cotransporter 2 inhibitor, *T1DM*, *T2DM* type 1, type 2 diabetes mellitus, respectively

Table 2 Baseline characteristics of the liraglutide and sitagliptin cohorts

Characteristic	Liraglutide cohort (n = 218)	Sitagliptin cohort (n = 2838)	Total (N = 3056)
Age, years, mean (SD)	70 (4.7)	73 (5.9)	73 (5.8)
Gender, *n* (%)			
Female	115 (52.8)	1451 (51.1)	1566 (51.2)
Male	103 (47.3)	1387 (48.9)	1490 (48.8)
Race/ethnicity, *n* (%)			
White	202 (92.7)	2189 (77.1)	2391 (78.2)
Black	–[a]	403 (14.2)	412 (13.5)
Hispanic	–[a]	104 (3.7)	108 (3.5)
Other	–[a]	142 (5.0)	145 (4.7)
Deyo-CC Index, *n* (%)	1.7 (1.5)	2.3 (1.9)	2.3 (1.9)
DCSI, mean (SD)	0.7 (1.3)	1.3 (1.6)	1.2 (1.6)
Comorbidities, *n* (%)			
Cardiovascular disease	26 (11.9)	755 (26.6)	781 (25.6)
Nephropathy	29 (13.3)	754 (26.6)	783 (26.6)
Retinopathy	–[a]	116 (4.1)	124 (4.1)
Peripheral vascular disease	13 (6.0)	249 (8.8)	262 (8.6)
Cerebrovascular disease	–[a]	94 (3.3)	98 (3.2)
Neuropathy	29 (13.3)	444 (15.6)	473 (15.5)
Metabolic disease	–[a]	–[a]	–[a]
Obesity	62 (28.4)	445 (15.7)	507 (16.6)
Hypoglycemia	–[a]	132 (4.65)	141 (4.6)
Pre-index prescription fill, counts, mean (SD)	13.6 (8.0)	14.7 (8.3)	14.6 (8.3)
Pre-index antidiabetic medications, *n* (%)			
Biguanides	166 (76.2)	2062 (72.7)	2228 (72.9)
Sulfonylureas	130 (59.6)	1811 (63.8)	1941 (63.5)
Thiazolidinediones	39 (17.9)	489 (17.2)	528 (17.3)
Other antidiabetic medication	–[a]	70 (2.5)	76 (2.5)
Pre-index level of antidiabetic therapy, *n* (%)			
No medication use	12 (5.5)	217 (7.7)	229 (7.5)
1 non-insulin antidiabetic	100 (45.9)	1211 (42.7)	1311 (42.9)
2 non-insulin antidiabetics	87 (39.9)	1221 (43.0)	1308 (42.8)
$\geq$ 3 non-insulin antidiabetics	19 (8.7)	189 (6.7)	208 (6.8)

Table 2 continued

Characteristic	Liraglutide cohort (n = 218)	Sitagliptin cohort (n = 2838)	Total (N = 3056)
Pre-index $HbA1_c$, mean (SD)	8.0 (1.4)	7.8 (1.4)	7.8 (1.4)
Baseline glycemic control, n (%)			
Controlled: $HbA1_c < 7.0\%$	44 (20.2)	770 (27.1)	814 (26.6)
Less strictly controlled: $HbA1_c \geq 7.0\%$ but $< 8.0\%$	73 (33.5)	1038 (36.6)	1111 (36.4)
Uncontrolled: $HbA1_c \geq 8.0\%$ but $< 9.0\%$	55 (25.2)	597 (21.0)	652 (21.3)
Severely uncontrolled: $HbA1_c \geq 9.0\%$	46 (21.1)	433 (15.3)	479 (15.7)
Prescribing physician specialty, n (%)			
Primary care	91 (41.7)	1094 (38.6)	1185 (38.8)
Endocrinology	65 (29.8)	1299 (45.8)	1364 (44.6)
Internal and family medicine	31 (14.2)	155 (5.5)	186 (6.1)
Other	40 (18.4)	349 (12.3)	389 (12.7)

DCSI Diabetes Complications Severity Index, *Deyo-CC* Index Deyo-Charlson Comorbidity Index, *$HbA1_c$* glycosylated hemoglobin, *SD* standard deviation

[a] Data suppressed to protect privacy

Descriptive Analysis

Patient demographics and baseline characteristics of each cohort are shown in Table 2. The liraglutide treatment group had a lower mean age (70 vs. 73 years), a lower mean DCSI score (0.7 vs. 1.3), a higher prevalence of obesity (28.4 vs. 15.7%), and a lower prevalence of cardiovascular disease (11.9 vs. 26.6%) and nephropathy (13.3 vs. 26.6%) than did the sitagliptin treatment group. In addition, the liraglutide treatment cohort had a greater prevalence of uncontrolled ($HbA1_c \geq 8$ but < 9) or severely uncontrolled ($HbA1_c \geq 9$) $HbA1_c$ compared to the sitagliptin treatment group (46.3 vs. 36.3%, respectively). The former were also more likely than the sitagliptin treatment group to have received their prescription from an internal medicine or family medicine physician (14.2 vs. 5.5%) and less likely to have received their prescription from an endocrinologist (29.8 vs. 45.8%). Overall, a majority (72.6%) of patients were from the southern USA, and 60.1% were enrolled in a health maintenance organization-type insurance plan. Post-index date, insulin was added to the therapy of 5.1% of patients in the liraglutide group and 8.0% of those in the sitagliptin group.

The descriptive analysis included all primary and secondary outcome measures. Patients who received liraglutide compared with those who received sitagliptin exhibited a significantly greater decrease in mean $HbA1_c$ after 1 year of follow-up (-0.82 vs. -0.42; $P < 0.0001$) (Table 3). The proportion of patients achieving the treatment goal of $HbA1_c < 7\%$ was also significantly higher in the liraglutide group than in the sitagliptin group (51.8 vs. 42.1%; $P = 0.0052$). Similarly, the proportion of patients achieving the treatment goal of a reduction in $HbA1_c \geq 1\%$ was significantly higher in the liraglutide group than in the sitagliptin group (40.4 vs. 27.3%; $P < 0.0001$). Large proportions of both treatment groups achieved the endpoint treatment goal of $HbA1_c < 8\%$ (liraglutide group 78.4%; sitagliptin group 76.2%). No significant total cost difference was observed between liraglutide and

Table 3 Descriptive analysis of glycemic control and total healthcare costs at 1 year in the inverse probability of treatment weighting sample

Glycemic control and total healthcare costs	Liraglutide cohort (n = 218)	Sitagliptin cohort (n = 2838)	P value
Change in $HbA1_c$, mean (SD)	− 0.82 (1.46)	− 0.42 (1.34)	< 0.0001*
Patients reaching treatment goals, n (%)			
$HbA1_c < 7\%$	113 (51.8)	1195 (42.1)	0.0052*
$HbA1_c < 8\%$	171 (78.4)	2163 (76.2)	0.4562
Reduction in $HbA1_c \geq 1\%$	88 (40.4)	774 (27.3)	< 0.0001*
Total costs (medical and pharmacy combined costs) of reaching treatment goals, USD, median (IQR)			
$HbA1_c < 7\%$	10,248 (7560–14,715)	9014 (6452–14,531)	0.0936
$HbA1_c < 8\%$	10,514 (7350–15,307)	8774 (6171–13,863)	0.001*

Change in $HbA1_c$ was analyzed using the t test; proportions of patients achieving treatment goals were analyzed using the Chi-square test; costs were analyzed using the Wilcoxon rank sum test
IQR Interquartile range, *USD* US dollars
*Statistically significant difference at $P < 0.05$

Table 4 Estimated outcomes of glycemic control among patients achieving treatment goal at 1 year in the inverse probability of treatment weighting sample

Glycemic control outcomes	Treatment	Unadjusted estimates	P value	Adjusted estimates[a]	P value
Mean change in $HbA1_c$ (95% CI)	Sitagliptin	− 0.42 (− 0.47 to − 0.37)	< 0.0001*	− 0.12 (− 0.28 to − 0.04)	0.0012*
	Liraglutide	− 0.82 (− 1.00 to − 0.64)		− 0.42 (− 0.66 to − 0.19)	
Patients reaching treatment goals, odds ratio (95% CI)					
$HbA1_c < 7\%$	Sitagliptin	1.00	0.0054*	1.00	0.0005*
	Liraglutide	1.48 (1.12–1.95)		1.68 (1.25–2.24)	
$HbA1_c < 8\%$	Sitagliptin	1.00	0.4564	1.00	0.2153
	Liraglutide	1.14 (0.81–1.59)		1.26 (0.88–1.80)	
Mean reduction in $HbA1_c \geq 1\%$	Sitagliptin	1.00	< 0.0001*	1.00	0.0002*
	Liraglutide	1.81 (1.36–2.40)		1.76 (1.31–2.36)	

Change in $HbA1_c$ was analyzed by linear regression; patients achieving treatment goals were analyzed by logistic regression and odds ratios with 95% confidence interval (CI) is reported
*Statistically significant difference at $P < 0.05$
[a] Models were adjusted for gender, race, health plan type, pre-index level of antidiabetic medication use, post-index oral antidiabetic medication use, and post-index insulin use

sitagliptin groups achieving an $HbA1_c$ of < 7% prior to IPTW; although the cost of achieving an $HbA1_c$ of < 8% was significantly higher (P = 0.001) with liraglutide.

Estimated Outcomes of Glycemic Control

Glycemic control outcomes, estimated using regression models, are presented in Table 4. The weighted estimated mean decrease in $HbA1_c$ was greater for patients who received liraglutide than for those who received sitagliptin (estimated difference − 0.40, 95% CI − 0.59 to − 0.22; P < 0.0001), and this difference remained statistically significant clinically when adjusted for covariates (estimated difference − 0.31, 95% CI − 0.49 to − 0.12; P = 0.0012). The weighted odds of achieving the treatment goal of $HbA1_c$ < 7% were 1.48-fold (95% CI 1.12–1.95) higher for patients on liraglutide compared with those on sitagliptin (P = 0.0054) in the unadjusted analysis, and 1.68-fold (95% CI 1.25–2.24) higher (P = 0.0005) in the adjusted analysis. Additionally, the weighted odds of achieving an $HbA1_c$ reduction of ≥ 1% were 1.81-fold (95% CI 1.36–2.40) higher (P < 0.0001) and 1.76-fold (95% CI 1.31–2.36) higher (P = 0.0002) for patients on liraglutide in the unadjusted and adjusted analyses, respectively. Regarding the treatment goal of $HbA1_c$ < 8%, no statistical difference was found between the liraglutide and sitagliptin groups in either the weighted unadjusted or adjusted analyses.

Estimated Total Healthcare Costs

Total all-cause healthcare costs (medical, pharmacy, outpatient, ED visits, and hospitalization) associated with achievement of the $HbA1_c$ < 7% target were estimated for both the liraglutide and sitagliptin treatment groups. Neither the weighted unadjusted nor adjusted analyses demonstrated statistically significant differences between treatment groups in total healthcare costs for patients achieving a treatment goal of $HbA1_c$ < 7% (Fig. 3), although total healthcare costs were slightly higher in the liraglutide treatment group. No difference in total healthcare costs between treatment groups was found among individuals achieving the treatment goal of $HbA1_c$ < 8% in the unadjusted analysis; however, when adjusted for post-index antidiabetic treatment, the total healthcare cost was 1.25-fold higher in the liraglutide group (US$23,088 vs. US$18,445; P < 0.0001).

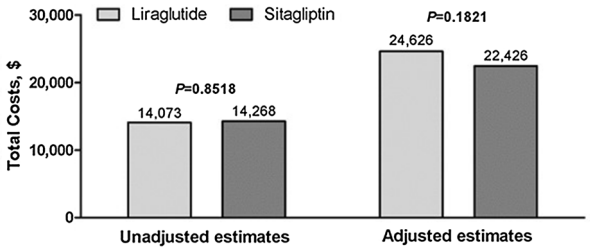

Fig. 3 Estimated unadjusted and inverse probability of treatment weighting adjusted total costs (medical and pharmacy combined) of achieving a $HbA1_c$ level of < 7%. Numbers above the bars represent the total costs in US dollars

DISCUSSION

After adjusting for baseline characteristics, the results of this study suggest that in an older population, improved glycemic control (greater mean decrease in $HbA1_c$ and increased likelihood of achieving glycemic treatment goals [$HbA1_c$ < 7%, $HbA1_c$ reduction of ≥ 1%]) was associated more with the use of liraglutide than with the use of sitagliptin. All-cause healthcare costs related to achieving an $HbA1_c$ < 7% were slightly higher in the liraglutide group compared to the sitagliptin group, but this difference did not reach statistical significance. This lack of significant difference could be the result of the small sample size.

Although no significant difference was detected between the liraglutide and sitagliptin treatment groups in rates of achieving an $HbA1_c$ level of < 8%, most patients in both groups (i.e., > 75%) achieved this less stringent endpoint. Additionally, the majority of patients in each treatment group had a baseline $HbA1_c$ level of < 8.0%, suggesting that a lower treatment goal (e.g., 7.0%) may have been considered the most appropriate for many of the study

participants. According to T2D treatment guidelines established by the American Diabetes Association, a reasonable $HbA1_c$ goal for many adults without an increased risk for hypoglycemia or other adverse effects of treatment is < 7%, even in an older T2D patient population who are otherwise healthy and should have low glycemic goals [19]. The relatively small prevalence of comorbidities observed in the liraglutide patient population therefore supports the relevance of a lower $HbA1_c$ goal and our focus on outcomes associated with achievement of an $HbA1_c < 7.0\%$ treatment goal.

GLP-1 RAs and DPP-4 inhibitors are recommended as components of diabetes therapy [20], with GLP-1 RAs reported to have superior glycemic efficacy, pharmacokinetics, and physiologic activity [21]. Compared to the DDP-4 sitagliptin, the GLP1-RA liraglutide may also provide improved cardiovascular safety risk and a reduction in body weight in an older population [2, 22]. In a clinical trial, compared to a placebo, liraglutide significantly reduced cardiovascular risk factors, including weight, blood pressure, and heart rate. In addition, patients taking liraglutide had a lower risk of nonfatal myocardial infarction, nonfatal stroke, and first occurrence of cardiovascular death compared to the placebo group [22]. In our analysis, the proportion of patients with cardiovascular disease was higher in the sitagliptin group than in the liraglutide group. Consideration of these factors may therefore be of key importance to clinicians, patients, and decision-makers interested in improving outcomes and managing costs associated with T2D.

These data are also supported by similar studies demonstrating superior efficacy and cost-effectiveness of liraglutide versus sitagliptin in the general adult population with T2D [6, 7, 12]. Specifically, the NN2211-1860 (-LIRA-DPP-4) trial comparing the efficacy and safety of liraglutide versus sitagliptin demonstrated a greater lowering of $HbA1_c$ after 26 weeks and 52 weeks of treatment with liraglutide [6, 7]. Additionally, multiple observational studies have confirmed greater reductions in $HbA1_c$ and a higher likelihood of achieving glycemic endpoints with liraglutide versus sitagliptin during a 6-month assessment [8–11]. A recent real-world study has also highlighted the long-term effectiveness of liraglutide in this population [12]. A meta-analysis also demonstrated the efficacy and safety of liraglutide compared with sitagliptin when combined with metformin [23]. Furthermore, various studies sourcing data from clinical trials and claims data demonstrated better cost-effectiveness of liraglutide compared with sitagliptin, with any increases in pharmacy costs associated with liraglutide being offset by decreases in other diabetes-related medical expenses [13–16].

LIMITATIONS

This analysis may be limited by the inconsistency in data collection processes inherent in claims data, including the absence of available disease severity information, an important prognostic factor in determining treatment outcomes. However, IPTW methodology was incorporated as a strategy of mitigating unmeasured confounding. The IPTW methodology may have increased standardized bias; additional sensitivity analysis could quantify any potential residual confounding. Results may also have been influenced by the exclusion of patients with baseline use of insulin, which may have resulted in the selection of individuals with less severe disease and may not be reflective of what is experienced in the real-world clinical setting. The analysis cohort sample size was also limited by the requirement of $HbA1_c$ results and persistence on index therapy; however, these data were considered essential in comparing the effects of liraglutide and sitagliptin treatments. Excluding patients that did not have HbA1c values at 1-year post-baseline could have introduced selection bias. Of note, previous clinical studies comparing the efficacy of liraglutide versus sitagliptin included stratification of liraglutide doses, with a higher dose demonstrating greater efficacy [6, 7]; however, assigning the liraglutide dose using claims data would be subject to a lack of patient information, and dosing information was therefore not included in the current analysis. The detection of hypoglycemic events using claims data was

also limited and potentially restricted to severe events requiring medical intervention, despite the importance of hypoglycemic risk in treating older people with diabetes. This lack of hypoglycemic event data precluded our ability to include 'no hypoglycemia' in composite outcomes. Finally, whereas the study was sufficiently powered for the main outcome, any inference on secondary outcomes (i.e., cost) may not have sufficient sample size and may be subject to type II error. Results reported on secondary outcomes should be used to inform additional research.

CONCLUSIONS

These real-world data add to a body of evidence that suggests liraglutide is associated with a greater $HbA1_c$ reduction compared to sitagliptin, and this association is maintained in an older population. Older people with T2D who initiate liraglutide treatment may be more likely to achieve treatment goals of $HbA1_c < 7\%$ and an $HbA1_c$ reduction of $\geq 1\%$ after 1 year of therapy compared with those who initiate treatment with sitagliptin. Additionally, cost data offer preliminary evidence that glycemic benefits of liraglutide are not associated with a significant increase in all-cause health care costs compared to sitagliptin, although further longer-term evaluation is warranted.

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Compliance with Ethics Guidelines. The research protocol associated with the manuscript was reviewed and approved as a minimal risk study by Schulman IRB, an independent institutional review board, which determined that the study met the criteria for a waiver of informed consent and waiver of authorization as set forth by the code of federal regulations.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

APPENDIX 1

See Table 5.

Table 5 Deyo-Charlson comorbidity index, related ICD-9-CM codes, and weighting

Comorbidity	ICD-9-CM codes	Weight
Myocardial infarction	410.xx, 412.xx	1
Congestive heart failure	428.xx	1
Peripheral vascular disease	441.xx, 443.9, 785.4, V43.4, 38.48*	1
Cerebrovascular disease	430.xx-437.xx, 438.xx	1
Dementia	290.xx	1
Chronic pulmonary disease	490.xx-496.xx, 500.xx-505.xx, 506.4	1
Connective tissue disease	710.xx, 714.xx, 725.xx	1
Peptic ulcer disease	531.4x-531.7x, 532.4x-532.7x, 533.4x-533.7x, 534.4x-534.7x, 531.0x-531.3x, 532.0x-532.3x, 533.0x-533.3x, 534.0x-534.3x, 531.9x, 532.9x, 533.9x, 534.9x	1
Mild liver disease	571.2, 571.4, 571.5, 571.6	1
Diabetes without complications	250.0x-250.3x, 250.7x	1
Diabetes with complications	250.4x-250.6x	2
Paraplegia and hemiplegia	342.x, 344.1	2
Renal disease	582.x, 583.0-583.7, 585.xx, 586.xx, 588.xx	2
Cancer (including leukemia and lymphoma)	140.xx-172.xx, 174.xx-195.xx, 200.xx-208.xx	2
Moderate or severe liver disease	572.2-572.8	3
Metastatic carcinoma	196.x-199.x	6
Acquired immunodeficiency syndrome (AIDS)	042.xx-044.x	6

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

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