Adv Ther (2014) 31:202–216
DOI 10.1007/s12325-014-0098-8

ORIGINAL RESEARCH

Real-World Cost-Effectiveness: Lower Cost of Treating Patients to Glycemic Goal with Liraglutide versus Exenatide

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Received: December 2, 2013 / Published online: January 30, 2014

ABSTRACT

Introduction: While the liraglutide effect and action in diabetes (LEAD-6) clinical trial compared the efficacy and safety of liraglutide once daily (LIRA) to exenatide twice daily (EXEN) in adult patients with type 2 diabetes, few studies have explored the associated per-patient costs of glycemic goal achievement of their use in a real-world clinical setting.

Methods: This retrospective cohort study used integrated medical and pharmacy claims linked with glycated hemoglobin A1C (A1C) results from the IMS Patient-Centric Integrated Data Warehouse. Patients' ≥18 years and naïve to incretin therapies during a 6-month pre-index period, with ≥1 prescription for LIRA or EXEN between January 2010 and December 2010, were included. Patients with evidence of insulin use (pre- or post-index) were excluded. Only patients who were persistent on their index treatment during a 180-day post-index period were included. Follow-up A1C assessments were based on available laboratory data within 45 days before or after the 6-month post-index point in time. Diabetes-related pharmacy costs over the 6-month post-index period were captured and included costs for both the index drugs and concomitant diabetes medications.

Results: 234 LIRA and 182 EXEN patients were identified for the analysis. The adjusted predicted diabetes-related pharmacy costs per patient over the 6-month post-index period were higher for LIRA compared to EXEN ($2,002 [95% confidence interval (CI): $1,981, $2,023] vs. $1,799 [95% CI: $1,778, $1,820]; $P < 0.001$). However, a higher adjusted predicted percentage of patients on LIRA reached A1C < 7% goal (64.4% [95% CI: 63.5, 65.3] vs. 53.6% [95% CI: 52.6, 54.6]; $P < 0.05$),

The data related to the key study findings included in this manuscript were presented at the 16th European International Society for Pharmacoeconomics and Outcomes Research (ISPOR) conference in Dublin, Ireland, November 2013.

Electronic supplementary material The online version of this article (doi:10.1007/s12325-014-0098-8) contains supplementary material, which is available to authorized users.

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translating into lower average diabetes-related pharmacy costs per successfully treated patient for LIRA as compared to EXEN ($3,108 vs. $3,354; $P < 0.0001$).

Conclusions: Although predicted diabetes-related pharmacy costs were greater with LIRA vs. EXEN, a higher proportion of patients on LIRA achieved A1C < 7%, resulting in a lower per-patient cost of A1C goal achievement with LIRA compared to EXEN.

Keywords: Cost-effectiveness; Endocrinology; Exenatide; Glycated hemoglobin A1C goal attainment; Glycemic control; Liraglutide; Type 2 diabetes

INTRODUCTION

Current estimates of health care costs and recent increases in health care costs attributable to the management of diabetes and its complications in the United States (US) are staggering and continue to increase. Total estimated costs of diagnosed diabetes have increased 41%, to $245 billion in 2012 from $174 billion in 2007 [1]. Most of the costs are attributable to the care of individuals with type 2 diabetes mellitus (T2DM) and treating the complications of T2DM, while only 12% of total health care costs relate to antidiabetic medications and supplies.

To reduce the costs of diabetes, preventing the development of diabetes complications through glycemic control is imperative [1, 2]. Consequently, glycemic control is an essential component of the effective management of T2DM [3] and its associated health care costs [2].

The American Diabetes Association (ADA) recommends a glycated hemoglobin A1C (A1C) goal of <7.0% in most patients to reduce the incidence of microvascular complications [3]. Recent guidelines have highlighted the need to individualize treatment goals based on comorbidities, duration of diabetes, life expectancy, presence and severity of complications, and history of hypoglycemia.

Metformin—either alone or in combination with another glucose-lowering agent—is the first-line antidiabetic therapy for patients with T2DM [2, 3]. Several treatment options are recommended for patients who do not achieve their glycemic targets on metformin alone, including the most recent incretin-based therapies: dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists. Currently available GLP-1 receptor agonists include exenatide (EXEN) twice daily, EXEN once weekly, and liraglutide (LIRA) once daily.

The efficacy of LIRA as monotherapy, in combination with other agents, and in comparison to other incretin therapies is well documented by randomized clinical trials, meta-analyses, and systematic reviews [4–11]. The LEAD-6 (liraglutide effect and action in diabetes) clinical trial (NCT00518882) compared the efficacy and safety of LIRA once daily to EXEN twice daily in adult patients with T2DM inadequately controlled on metformin, a sulfonylurea, or both [9]. LIRA provided significantly greater reductions in A1C and higher rates of A1C goal achievement compared to EXEN. A second study reported greater A1C reductions, higher rates of A1C goal achievement, and greater weight loss with LIRA once daily vs. EXEN once weekly [10].

An understanding of the true costs of helping patients achieve A1C goals, particularly based on real-world data, may facilitate clinical decision making in candidates for LIRA or EXEN. The objective of this study is to evaluate real-world costs of successful A1C < 7% goal attainment with LIRA

and EXEN in clinical practice, to provide health care providers and payers in the USA with transparent cost-effectiveness data to help inform decisions regarding treatment as well as coverage.

METHODS

Data Source

Data were accessed through the IMS Patient-Centric Data Warehouse, an extensive US database with linked laboratory, pharmacy and medical claims. The database contains de-identified longitudinal data, as well as clinical and demographic information (e.g., sex, age, comorbidities, insurance plan type), inpatient and outpatient claims (e.g., service charges, admission and discharge dates, procedure and diagnosis codes), laboratory tests and results, and pharmacy claims data (de-identified prescribing physician, drug dispensed based on national drug codes (NDCs), quantity and date dispensed, drug strength, days' supply, prescription cost). The warehouse is Health Insurance Portability and Accountability Act (HIPAA) compliant. The patients for this study were selected by linking the medical and pharmacy elements of the database to the laboratory data asset to augment the number of patients with A1C laboratory values, one of two key outcome variables associated with the study's objective.

Patient Selection

This was a retrospective cohort study, with all patients having at least one claim for LIRA or EXEN identified between January 1, 2010 and December 31, 2010. The date of the first drug identified during this time was considered the index date and the drug was designated as the index drug. To be included in the cohort, all patients had to be at least 18 years of age on the index date, be GLP-1 and DPP-4-naïve during a 6-month pre-index period, and have at least one claim for a physician visit within the 12-month study period (6-month pre-index and 6-month post-index). Only patients who were considered persistent to the index medication during the 6-month post-index period were included in the analysis to avoid introducing bias based on historic medication use. Persistent patients included those who remained on their index drug (LIRA or EXEN) until discontinuation, medication switch, or augmentation to another index medication. Patients with evidence of gestational diabetes and/or pregnancy, Type 1 diabetes, or dopamine receptor agonists in the pre-index period or the use of insulin at any point during the study period were excluded from the analysis. Please see Table 1 for details on patients' concomitant medications.

The A1C change from baseline and glycemic goal attainment of A1C $< 7\%$ over the 6-month post-index period for each cohort relied on available laboratory data. For the follow-up A1C measurement at the 6-month post-index point in time, the laboratory value was identified during the time period ± 45 days to the 6-month post-index point in time, utilizing the mean of the laboratory values available during that time interval if several measures were present. The costs that were captured included both index drug (LIRA or EXEN) pharmacy costs and the costs of other diabetes-related pharmacy costs for concomitant medications.

Statistical Analysis

All patient demographic and clinical characteristics as well as diabetes-related pharmacy costs were descriptively reported.

Table 1 Physician specialty, use of concomitant glucose-lowering agents, comorbidities, and pre-index healthcare costs

	LIRA ($n = 234$)	EXEN ($n = 182$)	*P* value
Prescriber physician specialty (*n*, %)			0.77
General practice/family practice	67 (28.6%)	50 (27.5%)	
Internal medicine	73 (31.2%)	63 (34.6%)	
Endocrinology	61 (26.1%)	38 (20.9%)	
Cardiology	3 (1.3%)	2 (1.1%)	
Other	26 (11.1%)	24 (13.2%)	
Unknown	4 (1.7%)	5 (2.7%)	
Concomitant oral antidiabetic medication use in the pre-index period (*n*, %)			
Any oral antidiabetic medication	196 (83.8%)	161 (88.5%)	0.17
Sulfonylureas (SUs)	84 (35.9%)	60 (33.0%)	0.53
Biguanides	132 (56.4%)	105 (57.7%)	0.79
Alpha-glucosidase inhibitors	0 (0.0%)	2 (1.1%)	0.19
Thiazolidinediones (TZDs)	48 (20.5%)	40 (22.0%)	0.72
Other oral antidiabetic medication	5 (2.1%)	8 (4.4%)	0.19
No drug use	38 (16.2%)	21 (11.5%)	0.17
Concomitant oral antidiabetic medication use in the post-index period (*n*, %)			
Any oral antidiabetic medication	189 (80.8%)	159 (87.4%)	0.07
Sulfonylureas (SUs)	63 (26.9%)	60 (33.0%)	0.18
Biguanides	142 (60.7%)	127 (69.8%)	0.05
Alpha-glucosidase inhibitors	0 (0.0%)	1 (0.5%)	0.44
Thiazolidinediones (TZDs)	31 (13.2%)	37 (20.3%)	0.05
Other oral antidiabetic medication	3 (1.3%)	5 (2.7%)	0.31
No drug use	45 (19.2%)	23 (12.6%)	0.07
Diabetes-related macrovascular complications in the pre-index period (*n*, %)			
Any diabetes-related macrovascular complication	25 (10.7%)	16 (8.8%)	0.52
Cerebrovascular disease	6 (2.6%)	2 (1.1%)	0.47
Ischemic heart disease	18 (7.7%)	10 (5.5%)	0.37
Myocardial infarction	0 (0.0%)	1 (0.5%)	0.44
Peripheral vascular disease	5 (2.1%)	6 (3.3%)	0.46
Diabetes-related microvascular complications in the pre-index period (*n*, %)			
Any diabetes-related microvascular complication	33 (14.1%)	22 (12.1%)	0.55
Chronic kidney disease	11 (4.7%)	6 (3.3%)	0.47
Diabetic neuropathy	17 (7.3%)	14 (7.7%)	0.87

Table 1 continued

	LIRA ($n = 234$)	EXEN ($n = 182$)	P value
Diabetic retinopathy	5 (2.1%)	4 (2.2%)	1.00
Diabetes-related comorbidities in the pre-index period (n, %)			
Any diabetes-related comorbidity	161 (68.8%)	120 (65.9%)	0.54
Amputation/ulceration	0 (0.0%)	3 (1.6%)	0.08
Depression	12 (5.1%)	12 (6.6%)	0.52
Diabetes with hypoglycemia	0 (0.0%)	4 (2.2%)	0.04
Dyslipidemia	124 (53.0%)	93 (51.1%)	0.70
Heart failure	7 (3.0%)	3 (1.6%)	0.52
Hypertension	120 (51.3%)	88 (48.4%)	0.55
Metabolic syndrome	3 (1.3%)	3 (1.6%)	1.00
Obesity	26 (11.1%)	21 (11.5%)	0.89
Other renal disease	4 (1.7%)	6 (3.3%)	0.34
Charlson Comorbidity Index (CCI) Score (n, %)			
0	51 (21.8%)	40 (22.0%)	0.96
1–2	167 (71.4%)	128 (70.3%)	
3–4	14 (6.0%)	13 (7.1%)	
5+	2 (0.9%)	1 (0.5%)	
Mean	1.1	1.1	0.92
SD	0.9	0.9	
Median	1.0	1.0	
Pre-index healthcare costs			
Mean	$3,844	$3,634	0.59
SD	$4,311	$3,662	
Median	$2,683	$2,436	
Pre-index total outpatient pharmacy costs			
Mean	$704	$567	0.02
SD	$782	$435	
Median	$524	$455	

EXEN exenatide, *LIRA* liraglutide

For continuous variables, findings were presented as the mean, standard deviation (SD), and median. For categorical measures, data included the frequency [number of cases (N)] and percentage (%) of patients observed in each category. *P* values using the Student's *t* test or Wilcoxon rank-sum test for continuous variables and the Pearson Chi square test for

categorical variables were produced. A P value of <0.05 was considered statistically significant.

For the outcome measures of glycemic goal attainment of A1C < 7% and total diabetes-related pharmacy costs, multivariate analyses were performed to account for baseline and post-index differences between the two treatments of interest. The likelihood of reaching A1C goal of <7% was estimated using a logistic regression model. A generalized linear model (GLM) was developed (controlling for the same independent variables as in the logistic regression model) to estimate the total diabetes-related pharmacy costs over the 6-month post-index period. Covariates in the models included gender, plan type, pre- and post-index concomitant medications, history of diabetes-related comorbidities, and patient copayment, among other explanatory variables.

Predicted values for both diabetes-related pharmacy cost per patient and A1C < 7% goal attainment over 6-month follow-up were estimated from the multivariate regression models based on the method of recycled predictions, along with constructing 95% confidence intervals from the bootstrap distribution. This method entails comparisons of two predictive margins where a particular attribute (in this case the index treatment) is assumed present or absent.

All statistical analyses were conducted using SAS® (version 9.2, Cary, NC, USA).

This article does not contain any new studies with human or animal subjects performed by any of the authors.

RESULTS

Demographic and Clinical Characteristics

There were few significant differences when comparing the clinical characteristics between LIRA and EXEN patients (Table 2). Mean A1C at baseline was 7.8% in both groups. A greater proportion of LIRA patients resided in the south compared to EXEN (67.5% vs. 52.7%; $P < 0.01$). In addition, a significantly greater proportion of LIRA patients had a third party health plan type compared to EXEN (94.4% vs. 73.6%; $P < 0.0001$) and more EXEN patients had claims for hypoglycemia in the pre-index period compared to LIRA patients (2.2% vs. 0.0%; $P = 0.04$). The total average outpatient pharmacy costs in the pre-index period were higher for patients initiating LIRA compared to EXEN ($704 vs. $567; $P = 0.02$) (Table 1).

Descriptive A1C and Cost Outcomes: Unadjusted Results

Prior to adjusting for confounding factors, a significantly greater proportion of LIRA patients achieved an A1C value of <7% as compared to EXEN patients (64.5% vs. 54.4%; $P = 0.04$) (Table 3). The difference in A1C from baseline to 6 months post-index was also significantly greater for LIRA patients compared to EXEN patients (−0.99% vs. −0.68%; $P = 0.02$). Over the 6-month post-index period, descriptive unadjusted total diabetes-related pharmacy costs per patient were similar between the two groups ($1,993 vs. $1,924; $P = 0.376$) (Table 4).

Adjusted A1C and Cost Outcomes: Multivariable Models

The factors associated with achieving A1C < 7% were estimated using a multivariable logistic regression model (Table 5). EXEN patients were 43.5% less likely to reach A1C < 7% compared to LIRA patients (OR = 0.565; $P = 0.015$). Plan type as well as certain pre- and post-index concomitant medications had a significant impact on the likelihood of reaching A1C < 7%.

Table 2 Demographic and baseline characteristics

	LIRA ($n = 234$)	EXEN ($n = 182$)	*P* value
Age, years			
Mean	54.3	54.6	0.73
SD	9.6	10.6	
Median	54	55	
Age group, *n* (%)			0.11
18–34 years	5 (2.1%)	9 (4.9%)	
35–44 years	34 (14.5%)	25 (13.7%)	
45–54 years	79 (33.8%)	50 (27.5%)	
55–64 years	87 (37.2%)	62 (34.1%)	
65+ years	29 (12.4%)	36 (19.8%)	
Female (%)	129 (55.1%)	106 (58.2%)	0.53
Mean A1C at baseline, % (SD)	7.8 (1.5)	7.8 (1.4)	0.89
Geographic region, *n* (%)			<0.01
Northeast	30 (12.8%)	25 (13.7%)	
Midwest	18 (7.7%)	17 (9.3%)	
South	158 (67.5%)	965 (52.7%)	
West	28 (12.0%)	44 (24.2%)	
Health plan type, *n* (%)			<0.0001
Cash	0 (0.0%)	0 (0.0%)	
Medicaid	5 (2.1%)	14 (7.7%)	
Medicare	8 (3.4%)	34 (18.7%)	
Third party	221 (94.4%)	134 (73.6%)	

A1C glycated hemoglobin A1C, *EXEN* exenatide, *LIRA* liraglutide, *SD* standard deviation

The factors associated with total diabetes-related pharmacy costs over the 6-month post-index period were identified via a GLM model. After controlling for covariates such as age, gender, baseline A1C level, comorbidity history and concomitant medication use, diabetes-related pharmacy costs per patient were lower for EXEN patients compared to LIRA patients (parameter estimate = −$203.1; $P = 0.0002$) (Table 6). As for the logistic regression model, plan type as well as certain pre- and post-index concomitant medications had a significant impact on the estimated total diabetes-related pharmacy costs in this GLM model.

Cost per Patient to Achieve A1C < 7%

The cost per patient to achieve A1C < 7% portrays a simplistic and transparent way of assessing the short-term cost-effectiveness of the treatment alternatives. The adjusted predicted diabetes-related pharmacy costs per patient were

Table 3 Unadjusted descriptive glycated hemoglobin A1C (A1C) outcomes at 6-month follow-up

	LIRA ($n = 234$)	EXEN ($n = 182$)	*P* value
6 months Post-index (*n*, %)			
% of patients achieving A1C value of <7.0%	151 (64.5%)	99 (54.4%)	0.04
Unadjusted difference between baseline and 6 months Post-index (%-point)			
Mean	0.99	0.68	0.02
SD	1.40	1.34	
Median	0.60	0.40	

A1C glycated hemoglobin A1C, *EXEN* exenatide, *LIRA* liraglutide, *SD* standard deviation

Table 4 Unadjusted descriptive pharmacy costs at 6-month follow-up

	LIRA ($n = 234$)	EXEN ($n = 182$)	*P* value
Total diabetes-related pharmacy costs in 6 months			
Mean (SD)	$1,993 ($810)	$1,924 ($740)	0.376
Median	$1,873	$1,788	
Total index drug pharmacy costs in 6 months			
Mean (SD)	$1,641 ($584)	$1,423 ($372)	<0.0001
Median	$1,615	$1,432	
Total other diabetes-related pharmacy costs in 6 months			
Mean (SD)	$351 ($52)	$501 ($596)	0.007
Median	$98	$259	

EXEN exenatide, *LIRA* liraglutide, *SD* standard deviation

higher for LIRA compared to EXEN (all values are mean ± standard deviation) ($2,002 ± $502 vs. $1,799 ± $502, $P < 0.001$); however, significantly more LIRA patients reached A1C < 7% as compared to EXEN (64.4% ± 22.4% vs. 53.6% ± 23.1%; $P < 0.05$) (Fig. 1). In terms of cost per patient successfully achieving A1C < 7%, this translates into a lower cost of control for LIRA compared to EXEN ($3,108 ± $779 vs. $3,354 ± $936; $P < 0.0001$) (Fig. 2).

DISCUSSION

This study is among the first to evaluate the real-world cost-effectiveness of treating patients to A1C < 7% with LIRA once daily and EXEN twice daily using a real-world administrative claims dataset. In this analysis, the adjusted predicted diabetes-related pharmacy costs per patient were higher with LIRA than with EXEN ($2,002 vs. $1,799, $P < 0.001$). However, as a greater proportion of patients on LIRA reached A1C < 7% compared to patients on EXEN (64.4% vs. 53.6%, $P < 0.05$), total diabetes-related pharmacy costs per successfully treated patient were lower with LIRA than with EXEN ($3,108 vs. $3,354; $P < 0.0001$). In fact, the A1C reductions observed in this study are consistent with the findings reported in LEAD-6 [9].

Still, this retrospective study differs from clinical trials in that randomized clinical trials contain strict inclusion and exclusion criteria and pre-defined concomitant antidiabetic medication use. For example, this study included patients with baseline A1C < 7.0%, patients who would have been excluded from clinical trials of LIRA. Consequently, the mean A1C in this study was slightly lower (7.8%) than in LEAD-6 (8.2% with LIRA and 8.1% with EXEN). This difference likely explains, at least in part, the difference in the proportion of patients achieving A1C < 7.0% between this study and those reported in LEAD-6 [9]. In this study, 65% of patients on LIRA and 54% on EXEN achieved A1C < 7.0% ($P < 0.05$) (Fig. 1). In LEAD-6, 54% on LIRA and 43% on EXEN achieved A1C < 7.0% ($P = 0.0015$).

Table 5 Factors associated with reaching glycated hemoglobin A1C (A1C) < 7% over 6-month post-index period: logistic regression

Independent variables	95% Confidence limits			
	Odds ratio	Lower limit	Upper limit	*P* value
EXEN vs. LIRA	0.565	0.357	0.894	0.015
Age (years)	0.999	0.989	1.009	0.874
Gender (male/female)	0.957	0.785	1.167	0.666
Cash vs. third party	1.440	0.393	5.283	0.582
Medicaid vs. third party	0.591	0.381	0.917	0.019
Medicare vs. third party	1.282	0.987	1.667	0.063
Baseline A1C %	0.512	0.469	0.558	<.0001
Prior use of SUs (yes/no)	0.486	0.367	0.643	<.0001
Prior use of biguanides (yes/no)	0.936	0.735	1.193	0.595
Prior use of TZDs (yes/no)	0.463	0.348	0.617	<.0001
Prior use of other oral antidiabetic medication (yes/no)[a]	0.346	0.144	0.832	0.018
History of myocardial infarction (yes/no)	0.773	0.283	2.112	0.616
History of ischemic heart disease (yes/no)	1.227	0.885	1.701	0.220
History of congestive heart failure (yes/no)	1.020	0.568	1.831	0.947
History of peripheral vascular disease (yes/no)	0.913	0.545	1.527	0.728
History of cerebrovascular disease (yes/no)	1.333	0.780	2.281	0.293
History of diabetic retinopathy (yes/no)	1.038	0.631	1.708	0.884
History of macular edema (yes/no)	0.641	0.198	2.076	0.459
History of diabetic neuropathy (yes/no)	1.008	0.688	1.476	0.969
History of amputation and ulceration (yes/no)	0.678	0.175	2.628	0.574
History of renal disease (yes/no)	0.700	0.429	1.141	0.153
History of hypertension (yes/no)	1.075	0.862	1.342	0.519
History of dyslipidemia (yes/no)	1.026	0.824	1.278	0.819
History of depression (yes/no)	0.693	0.417	1.151	0.157
History of obesity (yes/no)	1.213	0.808	1.821	0.352
History of hypoglycemia (yes/no)	0.598	0.204	1.752	0.349
Post use of SUs (yes/no)	0.705	0.536	0.927	0.012
Post use of biguanides (yes/no)	1.240	0.951	1.616	0.112
Post use of TZDs (yes/no)	1.972	1.436	2.708	<.0001
Post use of other oral antidiabetic medication (yes/no)[a]	2.754	0.989	7.670	0.053
Post use of metformin combo (yes/no)	1.388	1.042	1.848	0.025
Index out of pocket per 30 days' supply (in $10)	0.991	0.965	1.018	0.521

A1C glycated hemoglobin A1C, *EXEN* exenatide, *LIRA* liraglutide, *SD* standard deviation, *SU* sulfonylureas, *TZDS* thiazolidinediones

[a] Includes alpha-glucosidase inhibitors and antidiabetic amylin analog

A1C reductions were higher in DURATION-6, a randomized clinical trial (NCT01029886) that compared EXEN once weekly with LIRA once daily [10]. In this 26-week trial, A1C reductions were −1.48% with LIRA and −1.28% with EXEN once weekly ($P = 0.02$)

Table 6 Factors associated with total diabetes-related pharmacy costs over 6-month post-index period: generalized linear model

Independent variables	Wald 95% confidence limits				
	Parameter estimate	Standard error	Lower limit	Upper limit	*P* value
EXEN vs. Lira	−203.2	53.7	−308.5	−97.8	0.0002
Age (years)	−0.4	1.2	−2.8	1.9	0.709
Gender (male/female)	38.8	24.0	−8.2	85.9	0.106
Health plan type					
Cash vs. third party	71.0	146.4	−215.8	357.9	0.627
Medicaid vs. third party	146.4	50.0	48.3	244.5	0.003
Medicare vs. third party	69.1	31.5	7.3	130.9	0.029
Baseline A1C %	−2.1	8.4	−18.6	14.5	0.806
Prior use of oral antidiabetic agents (yes/no)					
Sulfonylureas	29.1	34.4	−38.3	96.4	0.398
Biguanides	26.0	28.9	−30.7	82.8	0.368
Thiazolidinediones	138.2	34.7	70.2	206.1	<0.0001
Other oral antidiabetic medication[a]	281.2	97.7	89.7	472.7	0.004
Medical history (yes/no)					
Myocardial infarction	182.4	114.9	−42.8	407.6	0.112
Ischemic heart disease	−6.9	39.7	−84.8	70.9	0.861
Heart failure	7.7	69.6	−128.7	144.1	0.911
Peripheral vascular disease	−16.3	62.6	−139.1	106.5	0.794
Cerebrovascular disease	33.9	65.2	−93.9	161.7	0.603
Diabetic retinopathy	−110.1	60.9	−229.5	9.3	0.071
Macular edema	320.8	146.7	33.2	608.3	0.029
Diabetic neuropathy	3.8	45.6	−85.6	93.2	0.934
Amputation and ulceration	114.5	156.3	−191.9	420.9	0.464
Renal disease	105.4	58.4	−9.1	219.8	0.071
Hypertension	3.3	26.8	−49.2	55.7	0.903
Dyslipidemia	−21.2	26.6	−73.3	30.9	0.425
Depression	−42.4	60.4	−160.8	76.0	0.482
Obesity	46.2	48.6	−49.0	141.4	0.342
Hypoglycemia	−206.2	129.0	−459.0	46.5	0.110
Post use of oral antidiabetic agents (yes/no)					
Sulfonylureas	101.6	33.8	35.3	167.9	0.003

Table 6 continued

Independent variables	Wald 95% confidence limits				
	Parameter estimate	Standard error	Lower limit	Upper limit	*P* value
Biguanides	213.5	31.7	151.5	275.6	<0.0001
Thiazolidinediones	1025.3	37.7	951.4	1099.2	<0.0001
Other oral antidiabetic medication[a]	828.0	114.5	603.5	1052.4	<0.0001
Metformin combination	−154.2	34.7	−222.2	−86.2	<0.0001

A1C glycated hemoglobin A1C, *EXEN* exenatide, *LIRA* liraglutide
[a] Includes alpha-glucosidase inhibitors and antidiabetic amylin analog

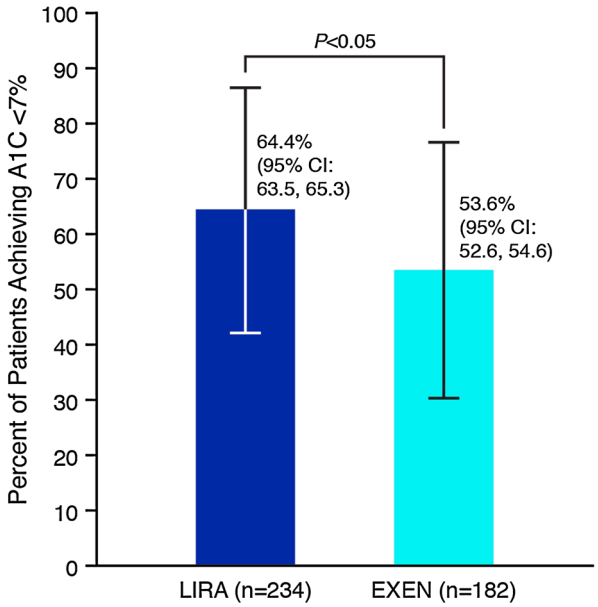

Fig. 1 Glycated hemoglobin A1C (A1C) < 7% goal attainment at 6-month follow-up. *CI* confidence interval, *LIRA* liraglutide, *EXEN* exenatide

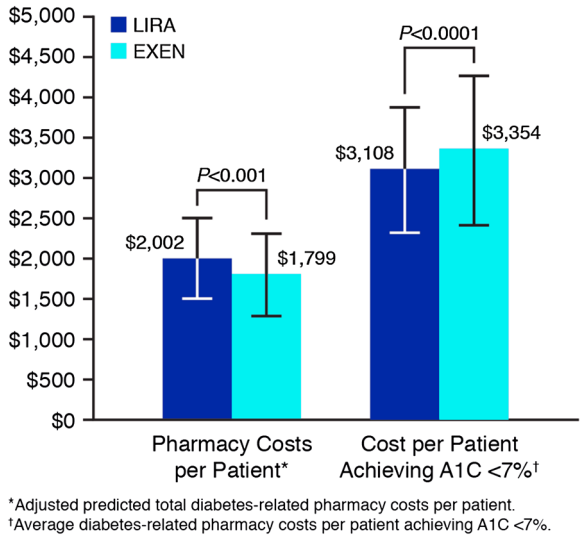

Fig. 2 Cost per successfully treated patient to glycated hemoglobin A1C (A1C) < 7% at 6-month follow-up

with 60% and 53% achieving A1C < 7% with LIRA and EXEN once weekly, respectively ($P = 0.0011$). However, direct comparisons should be warranted due to the higher baseline A1C values in DURATION-6 (8.4% and 8.5% for LIRA and EXEN once weekly, respectively) compared to those in our study (7.8% for both LIRA and EXEN). Furthermore, the patients who were randomized to LIRA in DURATION-6 had a forced titration to LIRA 1.8 mg, whereas the drug dose was not ascertained for this analysis.

While the clinical superiority of LIRA compared to EXEN has been well documented in a clinical trial setting, our findings contextualize the relative efficacy of these agents with the per-patient costs associated with A1C goal achievement in clinical practice. Real-world evidence has become increasingly important as a decision-making tool for policymakers and health care providers as they struggle to control increasing

health care costs and use cost-effective treatment options.

In the US, there is a shift towards more accountable patient care through the creation of voluntary accountable care organizations (ACOs) under the Affordable Care Act of 2010. These ACOs extend financial incentives to providers, including an advanced payment model, if they can reduce Medicare cost growth in particular service areas [12, 13]. Presumably, a metric such as cost per patient to A1C goal in diabetes care could be considered when evaluating provider performance under an ACO, making the findings of our study particularly relevant.

Studies that have examined the cost implications of improving glucose management have reported that the glycemic control costs are modest compared to total diabetes-related health expenditures [1, 14].

Other studies have evaluated the comparative costs and cost-effectiveness of glucose-lowering agents in T2DM, including the use of incretin therapies, both in the USA [15, 16] and in Europe [17, 18]. In the US retrospective cohort study by Pelletier and colleagues, patients receiving exenatide twice daily and liraglutide once daily had similar total 6-month follow-up (inpatient and outpatient) costs ($6,688 vs. $7,346) [15]. However, patients receiving exenatide had significantly lower mean pharmacy costs ($2,925 vs. $3,272, $P < 0.001$). Importantly, the study did not evaluate or relate these findings to outcomes in A1C or other indicators of glycemic control, such as microvascular complications or other outcomes associated with reductions in A1C.

In a retrospective chart audit of patients in the United Kingdom who received LIRA, EXEN, or a DPP-4 inhibitor (sitagliptin, saxagliptin, or vildagliptin), for a median of 48 weeks, significantly greater reductions in A1C (all $P < 0.05$) were seen with LIRA (−1.22%) than both EXEN (−0.71%), and the DPP-4 inhibitors (–0.66%) [17]. Estimated life-years gained per patient were 0.12 with LIRA, 0.08 with EXEN, and 0.07 with DPP-4 inhibitors, yielding a cost per quality-adjusted life year of £16,505, £16,648, and £20,661, respectively [17].

One recent report evaluated the short-term cost-effectiveness of LIRA vs. sitagliptin based on data from a randomized controlled trial of patients who failed to achieve A1C goals on metformin therapy [19, 20]. The simplistic and transparent short-term cost-effectiveness methodology applied in our real-world study of the *cost of control* follows the approach taken by Langer and colleagues in relating cost to treatment success [19].

Limitations

These results must be viewed with the typical limitations associated with studies based on administrative claims data. The correspondence between pharmacy submission of claims and patients' receipt and consumption of the medication was assumed and not directly measured. However, prior work suggests that medication exposure can be accurately derived from pharmacy claims [21, 22]. The study also assumed that all information needed for cohort stratification was present and similar across the cohorts of interest.

Of note, this study excluded any patients that had evidence of insulin use in either the pre- or post-index periods and cohorts were limited to consist of patients being persistent on their index therapy for a 6-month post-index period. Insulin users were excluded to remove any of the potentially additive or synergistic glucose-lowering effects of such a combination regimen, thereby focusing exclusively on the ability of LIRA and EXEN to improve glycemic control.

Although the treatment effects of LIRA 1.2 mg vs. LIRA 1.8 mg were ascertained in clinical trials, delineating LIRA 1.2 mg from LIRA 1.8 mg is a challenge in a claims database study. Exclusively relying on the NDC codes or derived dosing calculations would not completely capture patient practice realities (i.e., dosing, titration), and assigning those who titrated at some point in the 6-month follow-up period made it difficult to assign them to one category or another, though it did reflect actual clinical practice. Additionally, we did not differentiate or stratify EXEN 5 or 10 μg and patients on either dose were included in our analysis.

Despite these limitations, this study has provided valuable information regarding the real-world cost-effectiveness of LIRA compared to EXEN in the US.

CONCLUSION

Because this study paired A1C outcomes in clinical practice with an examination of real-world costs, it offers a useful point of reference for future assessments of the true health care costs of helping patients with T2DM achieve their glycemic goals.

In this analysis, adjusted predicted diabetes-related pharmacy costs per patient were higher with LIRA than with EXEN over 6-month follow-up. However, because a significantly greater proportion of patients on LIRA achieved A1C goal <7% compared with patients on EXEN, diabetes-related pharmacy costs per successfully treated patient were ultimately lower with LIRA than with EXEN. These findings can assist clinicians and formulary staff in choosing the most cost-effective GLP-1 and incretin formulations in an effort to reduce health care costs and improve patient outcomes.

ACKNOWLEDGMENTS

The authors wish to thank Nicole Cooper of MedVal Scientific Information Services, LLC, for providing professional writing and editorial assistance. Funding to support the preparation of this manuscript was provided to MedVal by Novo Nordisk Inc. This manuscript was prepared according to the International Society for Medical Publication Professionals' "Good Publication Practice for Communicating Company-Sponsored Medical Research: the GPP2 Guidelines" and the International Committee of Medical Journal Editors' "Uniform Requirements for Manuscripts Submitted to Biomedical Journals". Sponsorship and article processing charges for this study were funded by Novo Nordisk Inc. (NJ, USA).

Conflict of interest. Jon Bouchard is an employee and shareholder of Novo Nordisk with no further declarations of interest. Marjan Massoudi is an employee and shareholder of Novo Nordisk with no further declarations of interest. Jakob Langer is an employee and shareholder of Novo Nordisk with no further declarations of interest. Mitch DeKoven is an employee of IMS Health with no further declarations of interest. Won Chan Lee is an employee of IMS Health with no further declarations of interest. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. All named authors meet the ICMJE criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Compliance with ethics guidelines. This article does not contain any studies with human or animal subjects performed by any of the authors.

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