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ORIGINAL RESEARCH

Clinical Effectiveness of Liraglutide Across Body Mass Index in Patients with Type 2 Diabetes in the United States: A Retrospective Cohort Study

Abhishek S. Chitnis · Michael L. Ganz · Nicole Benjamin · Jakob Langer · Mette Hammer

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ABSTRACT

Introduction: Clinical trials have shown that liraglutide effectively lowers glycated hemoglobin A1c (A1C) levels in adult patients with type 2 diabetes (T2D). However, no studies have evaluated the effectiveness of liraglutide by body mass index (BMI) in the United States (US) in clinical practice. This study examined liraglutide's clinical effectiveness to lower A1C and body weight after 6 months in T2D patients stratified by baseline BMI.

Methods: This was a retrospective cohort study using the General Electric Centricity electronic medical records database. Adult patients with T2D (≥18 years and BMI≥ 25 kg/m^2) and A1C >7% at baseline who started liraglutide between January 1, 2010 and January 31, 2013 and who did not use insulin or a glucagon-like peptide-1 analog 12 months before initiating liraglutide ($N = 3{,}005$) were selected. Changes from baseline, stratified by BMI, in A1C, body weight, A1C <7% goal attainment, and incidence of severe hypoglycemia at 6-month follow-up were examined.

Results: After 6 months, A1C levels decreased on average by 0.95%, 1.02%, 0.99%, and 0.84% for BMI categories 25.0–29.9 ($n = 333$), 30.0–34.9 ($n = 793$), 35.0–39.9 ($n = 821$), and ≥40.0 kg/m^2 ($n = 1{,}058$), respectively ($P = 0.30$). The proportions of patients achieving A1C <7% at 6 months were 38.2%, 37.0%, 40.9%, and 41.0% ($P = 0.54$). The absolute body weight decreased by 1.5 to 4.0 kg across BMI and the rate of severe hypoglycemia (0.2%) was low.

Conclusion: Patients with T2D experienced statistically significant decreases in A1C and body weight after initiating liraglutide regardless of their BMI. Liraglutide reduced A1C equally well across baseline BMI in clinical practice in the US.

Keywords: Body mass index; Clinical effectiveness; Glycated hemoglobin; Liraglutide; Type 2 diabetes

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INTRODUCTION

In recent years, diabetes mellitus has emerged as a global public health concern. Already the most common metabolic disorder, the global prevalence rates of diabetes have been increasing [1]. As of 2012, about 9.3% of the US population (29.1 million people of all ages) were affected by diabetes, which was the seventh leading cause of death in the United States (US) [2]. The American Diabetes Association (ADA) estimated the total costs of diagnosed diabetes to be $245 billion in 2012, which increased from $174 billion in 2007 [3]. Numerous complications are linked to diabetes including heart disease, stroke, hypertension, and kidney disease, which could potentially increase total costs incurred [2]. About 90–95% of all diabetes cases involve type 2 diabetes (T2D); therefore, the clinical and economic burdens incurred by T2D need to be investigated [2].

Liraglutide is a once-daily glucagon-like peptide-1 (GLP-1) receptor agonist used to improve glycemic control in adults with T2D. The liraglutide effect and action in diabetes (LEAD) pivotal clinical trials and the 1860 liraglutide dipeptidyl peptidase-4 inhibitor (LIRA-DPP-4) study have analyzed liraglutide against various active comparators across the treatment cascade [4–11]. These studies have demonstrated that liraglutide improves glycemic control with a low incidence of hypoglycemia, and has the additional benefit of clinically relevant weight loss.

High body mass index (BMI) is an independent risk factor for cardiovascular diseases and all-cause mortality for people with T2D [12, 13]. High BMI, also involved in the pathogenesis of T2D, can complicate the treatment of T2D by altering lipid levels, increasing insulin resistance, and raising blood glucose levels [13]. Several studies have examined changes in body weight, BMI, or body fat over a follow-up period for patients treated with liraglutide, given the effects of excess body weight in T2D patients. Substantial weight reduction [12–18] or BMI reduction [12, 17, 19] was found in several investigations. However, to date, no study has evaluated the relative clinical effectiveness of liraglutide to achieve glycemic control and weight loss in patients with T2D across baseline BMI levels in real-world clinical practice in the US. The objective of this study is to address this gap and examine liraglutide's effectiveness on glycated hemoglobin A1C (A1C) (a minor component of hemoglobin to which glucose is bound), body weight, cholesterol, and blood pressure across different BMI levels.

METHODS

Data Source

The data for this retrospective cohort study were obtained from the General Electric (GE) Centricity electronic medical record (EMR) database from January 1, 2009 to January 31, 2013. The GE Centricity EMR database contains data on more than 15 million individuals receiving care from more than 10,000 general practitioners. Forty-seven US states are represented and the average length of follow-up for individuals in the dataset is approximately 3 years. The GE Centricity EMR database contains detailed information that typical medical claims databases do not, such as patient demographic characteristics (patient height, weight, BMI, and smoking status) and certain laboratory values (cholesterol, A1C, and vital signs [blood pressure]). This general

practitioner (ambulatory) EMR database provides complete information on all prescribed drugs for patients receiving care from that practice. Patient information from a variety of sources is routinely integrated into a common database and includes the number of patient encounters, insurance data, medication data that reflect not only prescription drug data, but also over-the-counter (OTC) medications prescribed by the physician, and historical drug use. However, the GE database is unable to provide specific dose information.

Compliance with Ethics Guidelines

This study was exempt from ethics approval from an institutional review board and informed consent since it involved assessment of existing data and the subjects could not be identified directly or through identifiers linked to the subjects [45 CFR 46.101(b)].

Sample Selection

Patients were included in the study sample if they had T2D and a prescription order for liraglutide between January 1, 2010, and January 31, 2013. The index date was defined as the date of the first prescription order for liraglutide. T2D was defined using the following criteria: (1) at least one diagnosis for T2D based on an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for 250.x0 or 250.x2; (2) one or more prescription orders for a non-insulin antidiabetic drug; or (3) two consecutive fasting blood glucose levels of $\geq$126 mg/dL [20]. These analyses focused on outcomes at 6 months after starting liraglutide (6-month post-index).

Patients were excluded if they (1) were not continuously enrolled during 12 months prior to the index date (pre-index period) and during 6-month follow-up, (2) had one or more prescription orders for any GLP-1 receptor agonist during baseline, (3) had one or more prescription orders for insulin use during baseline, (4) were less than 18 years of age, (5) had type 1 diabetes (ICD-9-CM codes: 250.x1 or 250.x3), polycystic ovarian syndrome (ICD-9-CM code 256.4) without the presence of T2D (ICD-9-CM codes 250.x0 or 250.x2), or were pregnant or had gestational diabetes (Supplemental Table 1) during any point in time during the pre-index period, (6) or their baseline A1C was $\leq$7% [21]. All patients were required to have at least one valid A1C measure at baseline (up to 45 days prior to the index date to up to 7 days after) and at least one valid A1C measure at their 6-month follow-up date ($\pm$45 days) for analyses of outcomes at 6 months follow-up. Due to very few ($N = 36$) patients in the baseline BMI category $<$25.0 kg/m^2, this category was excluded from the analysis.

Demographic and Clinical Characteristics

Demographic characteristics such as age, gender, race, geographic region (Midwest, Northeast, South, and West), and health plan type (Commercial, Medicare, Medicaid, Self-pay/Other, and Unknown) were captured at baseline. Baseline clinical characteristics included BMI and common diabetes-related complications identified using ICD-9-CM codes [22]. Clinical measures like A1C, weight, blood pressure (systolic blood pressure [SBP]; diastolic blood pressure [DBP]), lipid values (total cholesterol; high-density lipoprotein cholesterol [HDL]), and occurrence of severe hypoglycemia were reported at both baseline and follow-up. Severe hypoglycemia was defined according to type of service and ICD-9-CM codes (Supplemental Table 2) [23] and/or

a recorded glucose level of less than or equal to 40 mg/dL [24].

Patients may have had multiple measurements of the clinical outcomes during the baseline and follow-up periods. The baseline value was defined as the value closest to the index date (within 45 days prior to the index date to up to 7 days after). Values for outcomes at 6-month follow-up were defined as the measurements that were obtained on the day closest to 180-day post-index within a ±45-day window. All characteristics were stratified by baseline BMI categories, which were defined as 25.0–29.9, 30.0–34.9, 35.0–39.9, and ≥40.0 kg/m^2.

Clinical Outcomes

The authors assessed the following clinical outcomes at 6-month follow-up: absolute changes (follow-up minus baseline) in A1C, weight, blood pressure, and lipids; relative changes (absolute change divided by baseline) in body weight; and the proportion of patients treated with liraglutide reaching A1C targets. The American Association of Clinical Endocrinologists (AACE) target of A1C ≤6.5% and the American Diabetes Association (ADA) target of A1C <7% were used. Finally, the authors examined the occurrence of severe hypoglycemia at 6-month follow-up.

Analyses

Means and standard deviations (SD) were reported for continuous measures and percentages were reported for categorical measures. Statistical significance between baseline and follow-up values were assessed using the paired *t*-test for continuous measures and McNemar's test for categorical measures. Analysis of variance (ANOVA), for continuous variables, and the Chi-square test, for categorical variables, were used to assess the statistical significance across the BMI categories. Differences with a *P* value of less than 0.05 were considered statistically significant. Analyses were performed using SAS software version 9.2 (SAS Institute, Cary, North Carolina, USA).

RESULTS

A total of 3,005 patients with T2D sub-optimally controlled at baseline (A1C >7%) initiating liraglutide between January 1, 2010 and January 31, 2013 were identified (Fig. 1). Table 1 shows the demographics and clinical characteristics of the sample stratified by baseline BMI. The mean age (SD) of the study sample was 54.7 (10.9) years and ranged from 52.1 (10.7) to 57.8 (11.1) years across the BMI categories ($P < 0.01$). More than one-third of patients in all BMI categories were in the 50–59 year age group. About 53% of the sample was female and this proportion, too, varied by BMI category (46.5–59.3%, $P < 0.01$). There were no statistically significant differences across BMI category by race/ethnicity, region, plan type, smoking status, or the presence of comorbid conditions.

The mean baseline BMI (SD) of the study sample was 38.3 (7.7) kg/m^2 with group means of 28.1 (1.3), 32.6 (1.4), 37.3 (1.4), and 46.6 (6.1) kg/m^2 for BMI categories 25.0–29.9, 30.0–34.9, 35.0–39.9, and ≥40.0 kg/m^2, respectively. Average (SD) baseline A1C, which was 8.65% (1.4) for the entire sample, did not vary significantly by BMI category ($P = 0.358$). Total cholesterol and HDL measures at baseline also did not vary significantly by BMI category ($P = 0.62$ and $P = 0.19$, respectively). However, blood pressure did vary by BMI category, with blood pressure increasing as baseline BMI increased ($P < 0.01$). The proportion of patients

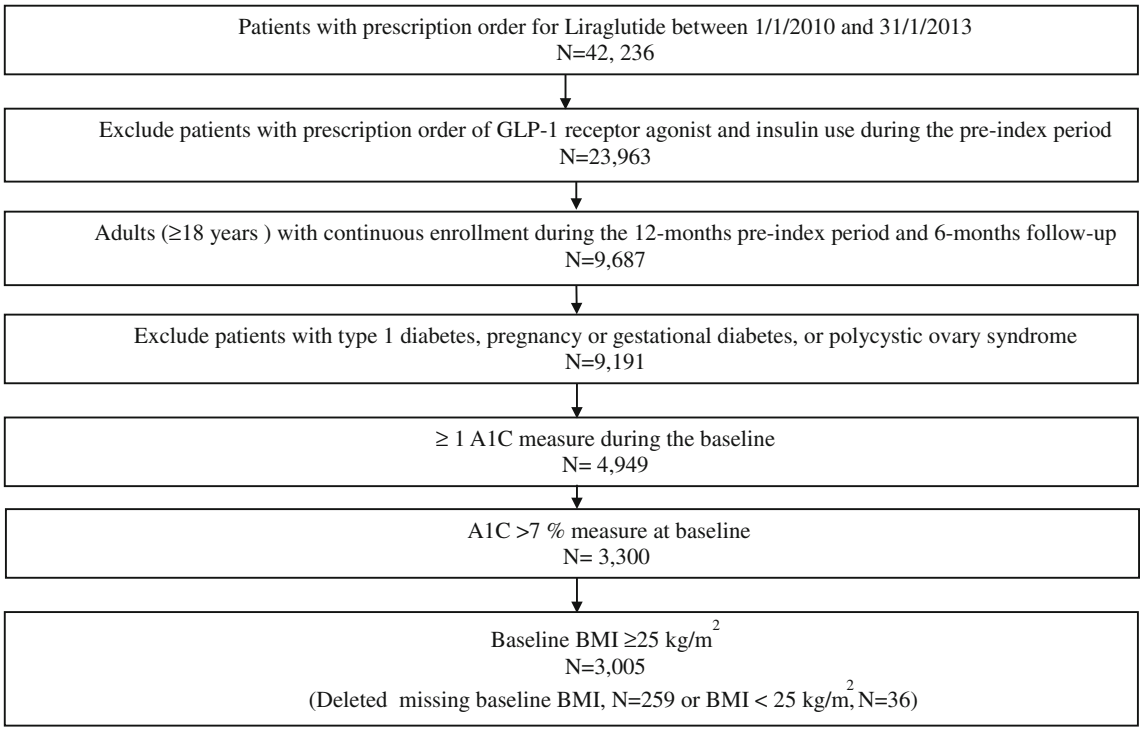

Fig. 1 Sample selection. *A1C* Glycated hemoglobin A1c, *BMI* body mass index, *GLP-1* glucagon-like peptide 1

who experienced severe hypoglycemia within the baseline period around the index date (45 days prior to 7 days after) was low (0.1%).

Clinical Outcomes

Table 2 shows the baseline and 6-month follow-up values for each clinical outcome for those patients who had available data at both time points; the fraction of the sample with data at both baseline and 6-month follow-up ranged from 23% for HDL to 55% for A1C. Liraglutide patients across all BMI categories experienced a statistically significant decrease in A1C ($P < 0.01$) at 6 months from baseline ranging from −0.84% to −1.02%. Similarly, liraglutide patients across all BMI categories experienced statistically significant decreases from baseline in absolute and relative body weight, total cholesterol, and SBP (all $P < 0.05$) at 6 months. The results were mixed for HDL and DBP—significant changes from baseline to 6 months were observed in only some BMI categories. The proportions of patients achieving the ADA target of A1C <7% were 38.2%, 37.0%, 40.9%, and 41.0% for BMI categories 25.0–29.9, 30.0–34.9, 35.0–39.9, and ≥40.0 kg/m^2, respectively. None of these changes were statistically significantly different *across* BMI categories, except for body weight, in which case patients in higher BMI categories tended to lose more absolute and relative weight. In other words, for all clinical outcomes examined, except for body weight, patients experienced similar decreases in A1C, total cholesterol, and SBP regardless of their baseline BMI. These results are displayed graphically in Figs. 2, 3, 4, and 5. The proportion of patients with severe hypoglycemia at 6-month follow-up was low (0.0%, 0.7%, 0.0%, 0.2% for BMI categories 25.0–29.9, 30.0–34.9, 35.0–39.9, and ≥40.0 kg/m^2, respectively).

Table 1 Baseline demographic and clinical characteristics stratified by baseline BMI

	Baseline BMI kg/m^2					
	All (N = 3,005)	**25.0–29.9 (N = 333)**	**30.0–34.9 (N = 793)**	**35.0–39.9 (N = 821)**	**≥40.0 (N = 1,058)**	***P* value***
Age, years	54.7 (10.9)	57.8 (11.1)	56.5 (10.7)	55.0 (10.7)	52.1 (10.7)	<0.01
Age, %						
18–39 years	8.9	6.0	5.4	7.8	13.2	<0.01
40– 49 years	21.8	16.2	19.7	21.6	25.3	
50–59 years	36.4	35.1	36.6	35.8	37.1	
60–69 years	24.1	28.2	26.6	25.9	19.6	
70–79 years	7.8	11.4	10.3	8.0	4.4	
80+ years	1.1	3.0	1.4	0.9	0.4	
Gender, %						
Female	52.6	50.2	46.5	50.9	59.3	<0.01
Male	47.4	49.8	53.5	49.1	40.7	
Race/ethnicity, %						
White	63.9	61.6	61.3	64.3	66.4	0.10
African American	7.7	8.1	7.9	7.8	7.4	
Hispanic	1.8	2.4	1.9	1.1	2.1	
Other	3	4.5	3.8	3.4	1.6	
Unknown	23.6	23.4	25.1	23.4	22.6	
Region, %						
Midwest	20.6	21.6	20.1	18.2	22.5	0.13
Northeast	19.2	18.6	17.8	19.0	20.7	
South	48.3	47.5	49.4	52.1	44.7	
West	11.9	12.3	12.7	10.7	12.1	
Plan type, %						
Commercial	33.2	29.1	33.3	35.0	33.1	0.27
Medicare	15.6	17.7	17.2	14.7	14.6	
Medicaid	0.6	0.6	0.4	0.4	0.9	
Self-pay/other	1.5	2.7	1.5	0.9	1.6	
Unknown	49.1	49.9	47.7	49.1	49.9	
Smoking status, %						
Never smoked	25.0	31.8	23.0	25.2	24.2	0.13

Table 1 continued

	Baseline BMI kg/m^2					
	All (N = 3,005)	**25.0–29.9 (N = 333)**	**30.0–34.9 (N = 793)**	**35.0–39.9 (N = 821)**	**≥40.0 (N = 1,058)**	***P* value***
Former smoker	30.6	26.4	32.0	30.6	30.9	
Current smoker	7.5	8.1	7.9	8.0	6.6	
Other/ unknown	36.9	33.6	37.1	36.2	38.3	
Complications, %						
Retinopathy	0.3	0.9	0.5	0.2	0.0	0.04
Nephropathy	1.1	0.9	1.6	0.7	1.1	0.37
Neuropathy	1.9	0.9	2.0	2.3	1.9	0.47
Cerebrovascular	0.2	0.3	0.3	0.2	0.0	0.43
Cardiovascular	1.1	1.8	0.8	1.6	0.8	0.15
PVD	0.1	0.0	0.0	0.2	0.1	0.42
Diabetes medications, %						
Sulfonylureas	52.9	56.2	52.7	53.0	52.0	0.58
Metformin	79.8	82.3	80.3	78.7	79.4	0.54
Other OADs[a]	32.5	33.3	32.9	34.1	30.7	0.45
Clinical characteristics						
BMI, kg/m^2	38.3 (7.7)	28.1 (1.3)	32.6 (1.4)	37.3 (1.4)	46.6 (6.1)	<0.01
Weight, kg	110.4 (24.5)	82.4 (10.8)	95.2 (11.9)	108.0 (13.8)	132.6 (22.3)	<0.01
A1C, %	8.65 (1.4)	8.66 (1.42)	8.70 (1.47)	8.66 (1.35)	8.59 (1.37)	0.358
Lipids, mg/dL						
Total cholesterol	176.1 (43.0)	179.0 (46.1)	175.5 (44.7)	177.0 (45.0)	175.0 (38.8)	0.62
HDL	41.9 (11.4)	43.1(12.0)	42.2(11.5)	41.2(10.8)	41.7 (11.4)	0.19
Blood pressure, mmHg						
SBP	129.8 (15.3)	126.4 (14.3)	128.7 (16.0)	130.3(15.0)	131.2 (15.1)	<0.01
DBP	78.1 (9.6)	76.1 (9.3)	77.2 (9.7)	78.7 (9.4)	79.0 (9.8)	<0.01

For appropriate variables, results presented as mean (SD)

BMI body mass index, *PVD* peripheral vascular disease, *OADs* oral antidiabetic medications, *HDL* high-density lipoprotein cholesterol, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

* *P* values were determined using analysis of variance (ANOVA), for continuous variables, and the Chi-square test, for categorical variables, to assess statistical significance across BMI categories

[a] Other OADs include alpha-glucosidase inhibitors, dipeptidyl peptidase inhibitors, thiazolidinediones and meglitinides

Table 2 Liraglutide clinical outcomes by baseline BMI at baseline and 6-month follow-up

Clinical outcomes, mean (SD)	Baseline BMI, kg/m^2					
	All	25.0–29.9	30.0–34.9	35.0–39.9	≥40.0	*P* value$^{\Delta}$
A1C (*N*)	1,649	186	454	440	569	
Baseline A1C	8.59 (1.36)	8.58 (1.30)	8.71 (1.47)	8.58 (1.38)	8.51 (1.26)	0.12
6-month A1C	7.65 (1.43)*	7.63 (1.29)*	7.70 (1.40)*	7.59 (1.46)*	7.67 (1.48)*	0.71
Absolute change in A1C from baseline	−0.94 (1.57)*	−0.95 (1.56)*	−1.02 (1.61)*	−0.99 (1.55) *	−0.84 (1.55)*	0.30
A1C ≤6.5% at 6 months	20.6	18.3	20.9	21.1	20.6	0.87
A1C <7.0% at 6 months	39.5	38.2	37.0	40.9	41.0	0.54
Weight (*N*)	1,554	173	433	416	532	
Baseline weight, kg	109.6 (23.8)	82.5 (10.2)	95.0 (11.9)	108.8 (13.9)	131.0 (22.1)	<0.01
6-month weight, kg	106.7 (23.5)*	80.9 (10.8)*	93.1 (12.8)*	105.8 (14.5)*	126.9 (22.4)*	<0.01
Absolute change in weight from baseline, kg	−2.9 (5.7)*	−1.5 (4.8)*	−1.9 (4.2)*	−3.0 (4.8)*	−4.0 (7.3)*	<0.01
Relative change in weight from baseline, %	−2.5 (5.7)*	−1.8 (5.8)*	−2.1 (4.4)*	−2.7 (4.4)*	−3.0 (6.1)*	<0.01
TC (*N*)	700	84	206	188	222	
Baseline TC, mg/dL	175.7 (43.0)	176.7 (44.3)	175.6 (43.7)	177.9 (45.6)	173.5 (39.8)	0.75
6-month TC, mg/dL	165.2 (40.1)*	165.4 (39.5)*	162.1 (40.3)*	165.6 (42.4)*	167.7 (38.3)*	0.49
Absolute change in TC from baseline, mg/dL	−10.4 (36.5)*	−11.3 (40.1)*	−13.5 (38.6)*	−12.2 (34.6)*	−5.8 (34.3)*	0.14
HDL (*N*)	692	82	202	191	217	
Baseline HDL, mg/dl	41.8 (11.0)	43.4 (12.8)	42.1 (10.2)	40.7 (10.9)	41.9 (11.2)	0.34
6-month HDL, mg/dl	41.8 (11.3)	44.9 (14.3)*	42.2 (10.5)	40.2 (10.9)	41.7 (10.8)	<0.01
Absolute change in HDL from baseline, mg/dL	−0.02 (6.6)	1.5 (5.7)*	0.07 (6.6)	−0.6 (6.5)	−0.2 (6.5)	0.11
SBP (*N*)	1,549	172	430	411	536	
Baseline SBP, mmHg	129.9 (15.6)	126.4 (14.7)	128.9 (16.3)	130.8 (15.5)	131.2 (15.3)	<0.01
6-month SBP, mmHg	127.0 (14.5)*	123.8 (13.8)*	126.5 (15.1)*	127.0 (14.1)*	128.4 (14.2)*	<0.01
Absolute change in SBP from baseline, mmHg	−2.9 (16.5)*	−2.6 (15.6)*	−2.4 (16.8)*	−3.7 (15.8)*	−2.9(17.1)*	0.67

Table 2 continued

Clinical outcomes, mean (SD)	Baseline BMI, kg/m^2					
	All	**25.0–29.9**	**30.0–34.9**	**35.0–39.9**	**≥40.0**	***P* value**$^{\Delta}$
DBP (*N*)	1,548	172	430	410	536	
Baseline DBP, mmHg	77.7 (9.8)	76.2 (9.5)	76.6 (9.9)	77.9 (9.7)	79.0 (9.7)	<0.01
6-month DBP, mmHg	76.5 (9.6)*	73.9 (8.7)*	75.9 (9.9)	77.0 (9.7)	77.4 (9.4)*	<0.01
Absolute change in DBP from baseline, mmHg	−1.26 (10.3)*	−2.3 (9.1)*	−0.7 (10.5)	−0.9 (9.9)	−1.6 (10.7)*	0.28

Includes adults with type 2 diabetes with valid data at baseline and follow-up

DBP diastolic blood pressure, *HDL* high-density lipoprotein, *SPB* systolic blood pressure, *TC* total cholesterol

* Differences between baseline and 6 month follow-up values statistically significant ($P < 0.05$). *P* values were determined using paired *t*-test for continuous measures and McNemar's test for categorical measures. $^{\Delta}$Statistical significance across BMI categories was determined through analysis of variance (ANOVA) for continuous variables and Chi-square test for categorical variables

DISCUSSION

This study found that liraglutide lowered A1C as well as other key T2D-related complications equally well across baseline BMI categories 6-month post-initiation. This study, to the authors' knowledge, is the first to evaluate liraglutide's real-world effectiveness for different levels of BMI in clinical practice in the US. The results of this study could provide valuable insights to clinicians when prescribing liraglutide to patients with T2D across different BMI groups. The findings may also be useful to patients and formulary decision makers when choosing between available T2D medications. The overall results from this study are consistent with those of the pivotal LEAD trials. Pooled analyses of seven Phase III liraglutide trials found that A1C dropped by 1.05–1.15% from baseline, for 1.2 and 1.8 mg dosages, respectively [25]. Although these reductions were marginally larger than the overall A1C reduction of 0.94% (AIC reduction ranged from 0.84% and 1.02% depending on BMI categories) found in this current study, the results are comparable given the differences between the tightly controlled setting of a clinical trial and real-world clinical practice. This same meta-analysis of clinical trials reported that the absolute reduction in body weight from baseline stratified by liraglutide dose ranged from 1.69 kg (1.2 mg) to 2.27 kg (1.8 mg) [25]. Similarly, this study reported an overall absolute body weight reduction of 2.9 kg, ranging from 1.5 kg to 4.0 kg across BMI groups.

The results of this study, by baseline BMI, are consistent with two recently published studies. No differences were found in A1C reductions across six BMI categories before and after adjustment for baseline factors, such as baseline A1C and ethnicity, using Association

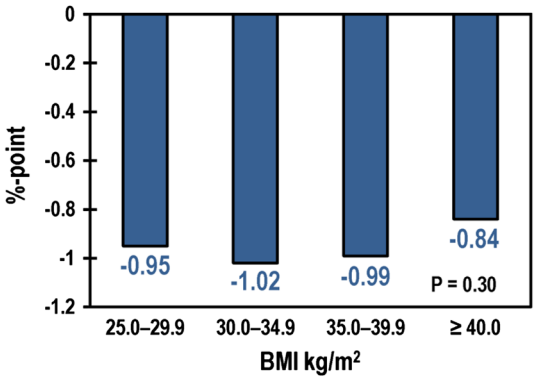

Fig. 2 Absolute change in A1C from baseline to 6-month follow-up: (%). Statistical significance across body mass index (BMI) categories was determined through analysis of variance (ANOVA)

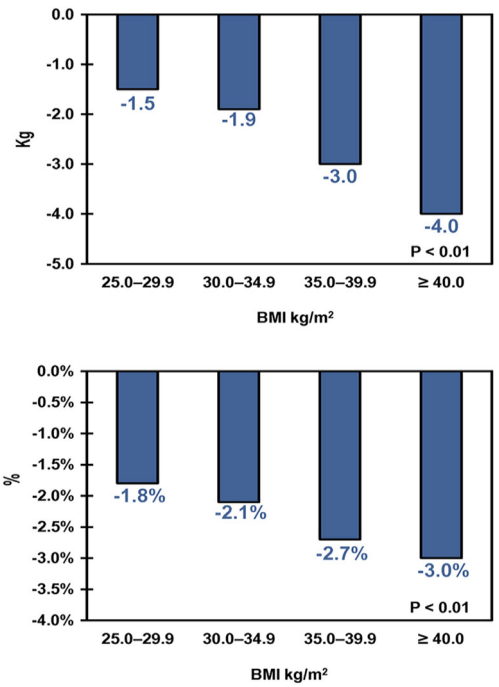

Fig. 3 Changes in body weight from baseline to 6-month follow-up. Statistical significance across body mass index (BMI) categories was determined through analysis of variance (ANOVA). *Upper panel* absolute change in body weight (kg), *lower panel* relative change in body weight (%)

of British Clinical Diabetologists (ABCD) nationwide data from the UK [26]. In addition, in a prospective follow-up study, Fadini et al. [15] found that liraglutide was equally effective

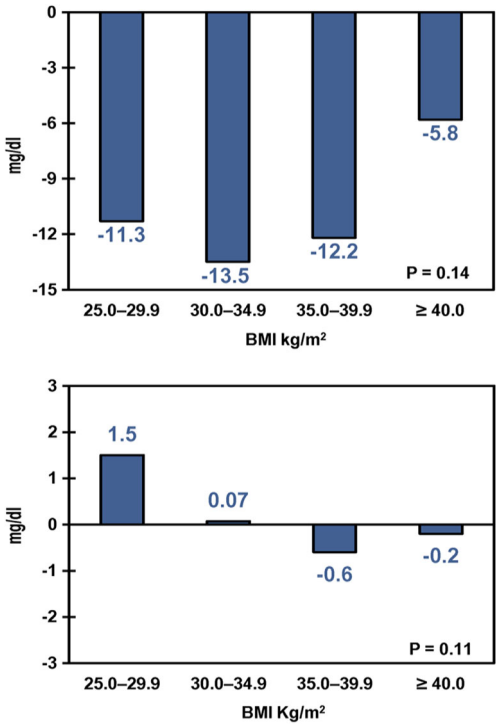

Fig. 4 Changes in lipids from baseline to 6-month follow-up. Statistical significance across body mass index (BMI) categories was determined through analysis of variance (ANOVA). *Upper panel* absolute change in total cholesterol (mg/dL), *lower panel* absolute change in high-density lipoprotein cholesterol (mg/dL)

in reducing A1C across baseline BMI tertiles measured at 4-month intervals, i.e., the A1C reductions across the BMI tertiles were not statistically significantly different from each other ($P = 0.94$).

Although the authors did not find evidence that A1C reductions were related to baseline BMI, the study did find that absolute and relative reductions in body weight were dependent on baseline BMI, which is consistent with the findings of Fadini et al. [15] of a statistically significant association between reductions in body weight (kg) at 4-month intervals and baseline BMI tertiles ($P < 0.01$), and with the findings of the UK study conducted by Ryder et al. [26] reporting an association between absolute weight

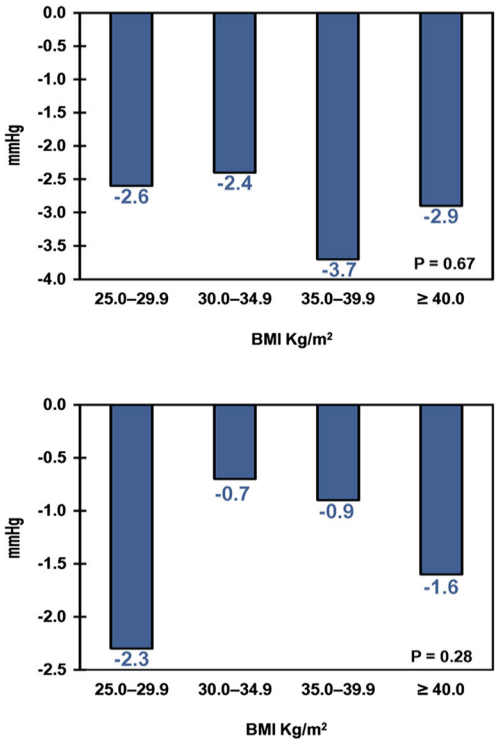

Fig. 5 Changes in blood pressure from baseline to 6-month follow-up. Statistical significance across body mass index (BMI) categories was determined through analysis of variance (ANOVA). *Upper panel* absolute change in systolic blood pressure (mmHg), *lower panel* absolute change in diastolic blood pressure (mmHg)

reductions and greater baseline BMI resulting from liraglutide treatment. The results of this study for relative weight loss are also consistent with the meta-analysis of the LEAD pivotal trials conducted by Niswender et al. [13], namely, those patients with higher baseline BMI lost more relative body weight than patients with lower baseline BMI.

Other outcomes evaluated in this study included severe hypoglycemia, lipids, and blood pressure. The low rate of severe hypoglycemia that the authors found is consistent with liraglutide's glucose-dependent mechanism of action and the results from the Bode et al. [27] meta-analysis. The authors' findings, that changes in total cholesterol and HDL were independent of baseline BMI, are also, if not indirectly, consistent with the findings that total and HDL cholesterol were not related to changes in body weight reported by Fadini et al. [15]. The overall reductions in SBP and DBP, respectively, were also consistent with those reported by Bode et al. [27] of 2.87 and 1.40 mmHg (liraglutide 1.2 mg) and reductions of 2.99 and 1.47 mmHg (liraglutide 1.8 mg).

Study Limitations

There were several limitations of this study. First, although the authors identified over 3,000 eligible patients with baseline data, relevant laboratory and clinical measures at 6-month follow-up were unavailable for many of them, as expected in a real-world study setting. The impact of this limitation is unclear but the authors do note that the average baseline laboratory and clinical values for the subset of patients with follow-up data were similar to those of the baseline values for the entire sample. Second, it is not possible to determine if patients actually filled or refilled their prescriptions using the GE Centricity EMR database, so the authors could not examine adherence to therapy as an outcome nor were they able to adjust for adherence. Therefore, this study used an intent-to-treat approach. Third, because dose information is often missing from drug records in the GE Centricity EMR database, the authors could not stratify the analyses by liraglutide dose. Fourth, the analyses did not adjust for potential confounding by measured (e.g., age, gender, race) and unmeasured factors (e.g., diet, exercise). Fifth, a post hoc power calculation showed that the statistical power ranged from 40% to 50% for all clinical outcomes except body weight, for which the power was about 90%. The low statistical power may affect the ability to detect changes in clinical outcomes

across BMI levels. However, as for other retrospective database studies, the authors had no control over the sample size after enforcing inclusion/exclusion criteria. Lastly, the authors may have misclassified baseline and 6-month follow-up measurements because the start and end dates of liraglutide that were recorded by physicians may have differed from actual start and end dates. However, it is unlikely that the possible discrepancy between actual and recorded dates would vary in any systematic way.

CONCLUSION

The authors found that liraglutide was equally effective in reducing A1C across baseline BMI categories suggesting that liraglutide may be effectively used for adult patients with T2D regardless of their BMI level. This study provides valuable insights for providers and formulary decision makers as it represents the first real-world evaluation of liraglutide's effectiveness to lower A1C, body weight, cholesterol, and blood pressure across BMI groups in clinical practice in the US.

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Conflict of interest. A. S. Chitnis is an employee of Evidera (Bethesda, Massachusetts, USA). M. L. Ganz is an employee of Evidera. N. Benjamin is an employee of Evidera. Evidera provides consulting and other research services to pharmaceutical, device, government, and non-government organizations. In this salaried position, A. S. Chitnis, M. L. Ganz and N. Benjamin work with a variety of companies and organizations and are precluded from receiving payment or honoraria directly from these organizations for services rendered. J. Langer is an employee of Novo Nordisk Inc. and is a shareholder of Novo Nordisk A/S (Bagsvaerd, Denmark). M. Hammer is an employee of Novo Nordisk Inc. and is a shareholder of Novo Nordisk A/S.

Compliance with ethics guidelines. This study was exempt from ethics approval from an institutional review board and informed consent since it involved assessment of existing data and the subjects could not be identified directly or through identifiers linked to the subjects [45 CFR 46.101(b)].

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