Real-World Glycemic Control from GLP-1RA Therapy with and Without Concurrent Insulin in Patients with Type 2 Diabetes

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ABSTRACT

BACKGROUND: Glucagon-like peptide 1 receptor agonists (GLP-1RAs) are recommended as add-on therapy in patients with uncontrolled type 2 diabetes (T2D), with no specific guidance as to timing versus insulin. Furthermore, real-world data assessing GLP-1RA outcomes with or without concurrent insulin therapy are lacking.

OBJECTIVE: To identify glycemic response with GLP-1RAs by insulin use in patients with T2D at 1-year follow-up to inform decisions regarding GLP-1RA use with or without insulin.

METHODS: This uncontrolled retrospective cohort study included adults with T2D in the Quintiles Electronic Medical Records Database who were newly prescribed GLP-1RA therapy with exenatide once weekly or liraglutide once daily between February 1, 2012, and March 31, 2013 (index period). Primary outcomes were change in hemoglobin A1c (A1c) at 1 year and attainment of A1c < 7%, < 8%, and < 9%. Results were stratified by baseline insulin use, which was defined as no insulin use at baseline, insulin initiated with a GLP-1RA on index date, and insulin prescribed before starting GLP-1RA therapy. Secondary outcomes included 1-year weight, low-density lipoprotein cholesterol (LDL-C), and blood pressure outcomes for the study population. Adjusted mean (marginal) change in A1c at 1 year was estimated using multivariate linear regression, and multivariate logistic regression was used to estimate the likelihood of patients attaining A1c < 7% at follow-up, controlling for potential confounders.

RESULTS: This study included 5,141 patients with a mean (SD) age of 57.0 (10.9) years, 53.5% of whom were females, and with a mean baseline A1c of 8.4% (1.6). Overall, 35.4% had no baseline insulin use, 42.9% were prescribed insulin before starting GLP-1RA therapy, and 21.7% were started on insulin with a GLP-1RA. The adjusted mean A1c reduction at 1 year was 0.75% (95% CI = -0.86 to -0.63) for patients initiating insulin on index date, 0.61% (95% CI = -0.70 to -0.51) for patients with no baseline insulin use, and 0.23% (95% CI = -0.33 to -0.13) for patients prescribed insulin before GLP-1RA therapy. Patients with no baseline insulin or who coinitiated insulin and a GLP-1RA were more likely to attain A1c < 7% at follow-up versus patients prescribed insulin before initiating GLP-1RA therapy (OR = 1.50, 95% CI = 1.08 to 2.09 and OR = 1.85, 95% CI = 1.30 to 2.62, respectively). At 1-year follow-up, significant improvements in weight, LDL-C, and blood pressures were also observed.

CONCLUSIONS: GLP-1RA therapy was associated with significant improvements in glycemic control when used with or without insulin, as well as reductions in weight and LDL-C overall. However, greater A1c reductions and a higher likelihood of attaining A1c goal levels were observed when a GLP-1RA was initiated alone or with insulin than when a GLP-1RA was added to a regimen that included insulin. GLP-1RA therapy is an effective treatment option when used with or without insulin and may be considered in patients with uncontrolled glycemia.

J Manag Care Spec Pharm. 2017;23(3):267-75

What is already known about this subject

- Glucagon-like peptide 1 receptor agonists (GLP-1RAs) are effective in reducing hemoglobin A1c (A1c) and weight in the usual care setting.
- A GLP-1RA and insulin combination is more efficacious at lowering A1c in patients with poorly controlled type 2 diabetes (T2D) than either agent alone as observed in clinical trials.
- GLP-1RAs have been shown to improve some cardiovascular risk factors in patients with T2D.

What this study adds

- Patients with T2D started on a GLP-1RA alone or at the same time as insulin had greater A1c reduction and a higher likelihood of attaining A1c goal levels than patients who had a GLP-1RA added to a regimen that included insulin.
- A1c reduction with GLP-1RA therapy alone or with insulin was most pronounced in patients with an A1c ≥ 9% at baseline, enabling more than 50% of these patients to achieve A1c of < 9% at 1-year follow-up.
- Real-world evidence now exists that GLP-1RAs are associated with improvement in A1c, weight, low-density lipoprotein cholesterol, and blood pressure.

Type 2 diabetes (T2D) is a chronic disorder responsible for significant morbidity, mortality, and economic burden in the United States. The estimated total cost of diabetes in 2012 was more than $245 billion, including $176 billion in direct medical costs.[1] Diabetes-related complications are a significant driver of diabetes care costs and increase annual per-patient diabetes health care expenditures by approximately $10,000.[2] Fortunately, effective management of hyperglycemia, as measured by reduction in hemoglobin A1c (A1c), can reduce the risk of diabetes-related microvascular and macrovascular complications.[3]

Given the clear trial-based evidence, payer and provider organizations recognized and adopted glycemic control targets based on A1c as a measure of diabetes care performance. For instance, the Healthcare Effectiveness Data and Information Set (HEDIS) comprehensive diabetes care measures include the proportion of patients in a diabetes population with poor glycemic control (A1c > 9%).[4] Consistent with treatment

guidelines recommending individualized A1c targets, optimal A1c goal levels of <7% and <8% have also been incorporated into quality measures.

As a further incentive to improve diabetes outcomes and reduce costs, public and private payers are linking clinical performance vis-à-vis diabetes quality measures to provider reimbursement.[3] Since the passage of the Patient Protection and Affordable Care Act, there has been an expansion in the use of these pay-for-performance programs by private and public payers, particularly by Medicare and Medicaid. Specific to diabetes, the Centers for Medicare & Medicaid Services has established adequate glycemic control (A1c <9%) as a performance measure in the Quality Payment Program for Accountable Care Organizations and group practices, as well as in the Medicare Star Quality Rating System.[3,5,6] Thus, attaining outcomes-based quality measures is a high priority for payers and providers.

Targeting patients with poorly controlled diabetes (A1c ≥9%) for more aggressive drug therapy management is a potential approach health plans and providers could use to focus efforts and resources toward improving patient outcomes and achieving quality performance goals. For patients with poorly controlled diabetes, the American Diabetes Association and American College of Endocrinology/American Association of Clinical Endocrinologists guidelines recommend combination therapy, including regimens with insulin and/or a glucagon-like peptide 1 receptor agonist (GLP-1RA).[3,7]

At the time of this study, the predominant agents in the GLP-1RA class were liraglutide once daily (QD) and exenatide once weekly (QW). These agents have been shown in clinical trials to lower elevated A1c and are generally well tolerated.[8] Unlike insulin, GLP-1RAs have relatively low rates of hypoglycemia and the added benefit of reducing weight.[8-10] However, uncertainty remains regarding when to initiate a GLP-1RA relative to other agents, including insulin. Further, the real-world effectiveness of GLP-1RA drugs in patients with poor diabetes control is not well established.

The goal of this study was to obtain real-world evidence to inform payers and providers on the effectiveness of GLP-1RA therapy overall and in combination with baseline insulin. The objective of this study was, therefore, to identify the effect of GLP-1RAs on glycemic control quality targets (A1c <7%, <8%, and <9%) at 1 year stratified by baseline glycemic control status and concurrent insulin use. We also determined the impact of GLP-1RAs on weight change and other diabetes-related quality measures.[4]

Methods

Study Design and Data Source

A retrospective cohort study was conducted to assess 1-year treatment outcomes with GLP-1RA according to baseline insulin use in patients with T2D who initiated exenatide QW or liraglutide QD. This study used the Quintiles Electronic Medical Records (Q-EMR) Database extending from January 1, 2011, through March 31, 2014. The Q-EMR is a large, centralized EMR-based data source containing data on 38 million patients provided by more than 725 member institutions and 33,000 providers from 49 U.S. states and the District of Columbia. The database includes patient-level demographic, diagnostic, laboratory, and vital sign data and is well suited to assess clinical outcomes in patients with T2D. The Investigational Review Board at the University of Utah approved the protocol for the study.

Study Population

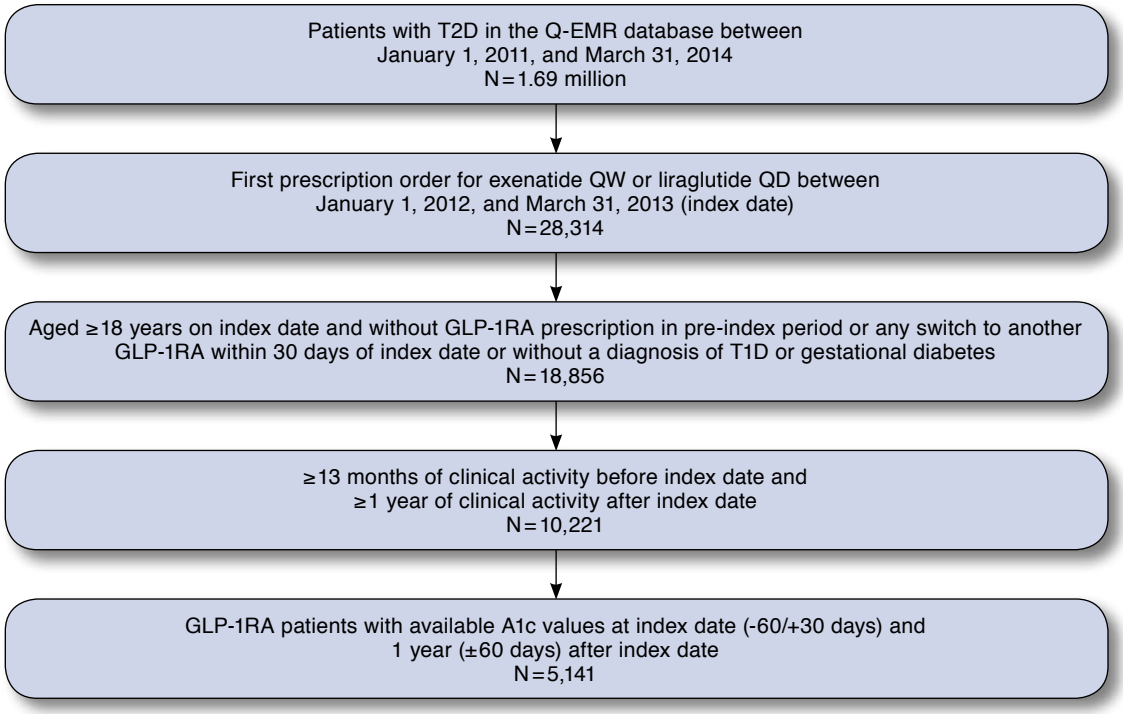
Patients with T2D were identified in the database if they met at least 1 of the following inclusion criteria: an *International Classification of Diseases, Ninth Revision, Clinical Modification* code of 250.x0 or 250.x2; at least 1 A1c value >6.5%; diabetes drug treatment; or 2 consecutive fasting blood glucose levels ≥126 mg/dL. Patients selected from this T2D population for study inclusion were adults (aged 18+ years) newly prescribed with exenatide QW or liraglutide QD between February 1, 2012, and March 31, 2013. The T2D medications were identified at the class level from the prescription order and medication history data based on Generic Product Identifier[11] therapeutic class designation. Index date was defined as the date of the first exenatide QW or liraglutide QD prescription order in the database.

Included patients had clinical activity in the EMR from at least 13 months before to 1 year after their index date, as well as A1c values on index date (-60 to +30 days) and at 1-year follow-up (±60 days). Patients were excluded if they had documented use of a GLP-1RA in their medication history before index date, a diagnosis for type 1 diabetes or gestational diabetes, pregnancy, prescriptions for 2 or more GLP-1RAs on index date, or a switch to another GLP-1RA within 30 days after index date.

Study Outcomes

The primary outcome was glycemic control at 1 year, defined as change in A1c from baseline (index date) and proportion of patients with A1c <7%, <8%, and <9%. Glycemic control outcomes were reported overall and stratified by baseline insulin use. Outcomes were defined as "no insulin prescribed during the baseline period," "insulin first prescribed with GLP-1RA on index date," or "insulin prescribed before index date." Glycemic outcomes were also reported in subsets of patients with baseline A1c ≥7%, ≥8%, and ≥9%. Secondary outcomes reported for the overall cohort included changes in weight and low-density lipoprotein cholesterol (LDL-C) from baseline to 1-year follow-up, patients with follow-up LDL-C <100 mg/dL and follow-up blood pressure <140/90 mmHg and <130/80 mmHg, per 2004 Seventh Joint National Committee and 2007 National Committee for Quality Assurance/HEDIS guidelines.[4]

FIGURE 1 Patient Cohort Identification Flowchart



A1c = hemoglobin A1c; GLP-1RA = glucagon-like peptide 1 receptor agonist; QD = once daily; Q-EMR = Quintiles Electronic Medical Records; QW = once weekly; T1D = type 1 diabetes; T2D = type 2 diabetes.

Independent Variables

Demographic and clinical variables were captured to describe the study cohort and control for confounding factors. Demographic variables included age, sex, race, region, provider specialty, and insurance status; clinical covariates included baseline body mass index (BMI), blood pressure, comorbidities (hypertension, acute myocardial infarction, cardiovascular diseases [CVDs], cerebrovascular diseases, kidney disease, hyperlipidemia, and microvascular complications). The Charlson Comorbidity Index (CCI) was also calculated using the 2008 version designed to predict resource use in the primary care setting. The CCI was assessed as a method of adjusting for comorbidity in the analyses versus individual diabetes-related comorbidities.[12,13] Non-GLP-1RA diabetes medication use during the 13-month baseline period and newly prescribed on index date was captured, as was the total number of diabetes medication classes used during the baseline period. Baseline antihypertensive use was also captured as a possible confounder.

Statistical Analysis

Descriptive statistics identified the baseline characteristics of the overall study population and by insulin use subgroups. Independent t-test for continuous variables and chi-square test for categorical variables compared differences in baseline characteristics across the 3 insulin subgroups. A paired t-test compared the differences in A1c and weight from baseline to 1-year follow-up overall and within insulin use groups; pairwise independent t-tests compared the change in A1c and weight between groups with insulin prescribed before index date considered as the reference group. Chi-square goodness-of-fit tests reported the change in the proportion of patients with A1c < 7%, < 8%, and < 9% at 1-year follow-up overall and for subsets of patients with baseline A1c ≥ 7%, ≥ 8%, and ≥ 9%.

Multivariate linear regression estimated the adjusted mean incremental change in A1c from baseline to follow-up by baseline insulin use. Multivariate logistic regression models identified the likelihood of patients attaining A1c < 7% at follow-up for those with baseline A1c ≥ 7% and separately for patients with baseline A1c ≥ 9%. The saturated multivariate models controlled for baseline A1c, age, sex, race, region, insurance status, BMI, blood pressure, provider specialty, comorbidities (hypertension, acute myocardial infarction, CVDs, cerebrovascular disease, kidney disease, hyperlipidemia), microvascular complications, the CCI, as well as diabetes medication and antihypertensive medication use. Regression models also

TABLE 1 Baseline Characteristics Overall and by Baseline Insulin Use

Variable	Overall (N = 5,141)	Baseline Insulin Use				
		Insulin Newly Prescribed on Index Date (n = 1,115)	No Baseline Insulin (n = 1,822)	Insulin Prescribed Pre-index (n = 2,204)	*P* Value[a]	*P* Value[b]
Mean (SD) age, years	57.0 (10.9)	56.2 (11.3)	56.9 (10.8)	57.5 (10.8)	0.001	0.079
Female (%)	53.5	56.1	52.6	53.1	0.105	0.749
Race (%)						
White	70.3	69.6	73.6	67.9	0.648	0.003
Black	7.3	6.7	6.9	7.9		
Hispanic	4.0	4.6	3.3	4.4		
Other	2.8	3.2	2.4	2.9		
Unknown	15.6	15.9	13.8	16.9		
Insurance status (%)						
Commercial	31.9	36.4	32.1	29.5	<0.001	0.003
Medicare	26.0	23.9	23.9	28.9		
Medicaid	0.9	0.5	0.9	1.1		
Self-pay	1.1	0.7	1.6	0.9		
Other/unknown	40.0	38.5	41.5	39.6		
Mean (SD) baseline A1c (%)	8.4 (1.6)	8.2 (1.6)	8.2 (1.5)	8.6 (1.6)	<0.001	<0.001
Mean (SD) baseline weight (kg)	108.0 (24.8)	107.7 (25.0)	106.9 (24.7)	109.3 (24.6)	0.078	0.002
Baseline blood pressure < 140/90 mmHg (%)	73.6	72.7	72.7	74.8	0.197	0.132
Baseline LDL-C < 100 mg/dL (%)[c]	66.2	65.9	65.3	67.1	0.639	0.423
Antihypertensive drugs (%)	83.6	81.7	84.5	83.8	0.136	0.540
Comorbidities (%)						
Hypertension	73.0	72.3	74.2	72.4	0.960	0.191
Hyperlipidemia	83.1	84.3	81.8	83.6	0.590	0.145
Kidney disease	10.3	10.2	8.3	11.9	0.143	<0.001
Cardiovascular disease	8.3	7.3	7.6	9.3	0.044	0.053
Microvascular complications	7.6	6.9	7.1	8.3	0.145	0.135
Cerebrovascular disease	2.3	1.7	2.7	2.4	0.218	0.505
Acute myocardial infarction	0.6	0.4	0.4	0.8	0.125	0.137

[a] *P value indicating significant difference between insulin prescribed before index date versus insulin newly prescribed on index date.*

[b] *P value indicating significant difference between insulin prescribed before index date versus insulin not prescribed on or before index date.*

[c] *LDL-C values were available in 1,734 out of 5,141 overall patients, 397 patients with insulin newly prescribed on index date, 680 patients with insulin not prescribed on or before index date, and 657 patients with insulin first prescribed on index date.*

A1c = hemoglobin A1c; LDL-C = low-density lipoprotein cholesterol; SD = standard deviation.

controlled for insulin use on or up to 13 months before index date. Final, reduced models included covariates that contributed significantly to the model ($P > 0.20$) or in which there was a strong clinical rational for inclusion as a possible confounder. Stata software package 13 (StataCorp, College Station, TX) and SAS software package 9.3 (SAS Institute, Cary, NC) were used to perform all statistical analysis with an a priori alpha of 0.05.

Results

Baseline Characteristics

Of the 1.69 million patients with diabetes in the Q-EMR database from January 1, 2011, to March 31, 2014, 5,141 patients met all inclusion criteria and were included in the final study cohort (Figure 1). Table 1 shows the demographic and clinical characteristics of the study cohort. Mean age (standard deviation [SD]) for the overall study cohort was 57.0 (10.9) years; 53.5% were female, and the majority (70.3%) were white. Mean baseline A1c for the overall study cohort was 8.4% (1.6). Overall, 35.4% of patients had no insulin prescriptions during the baseline period, 42.9% of patients were prescribed insulin before index date, and 21.7% of patients were first prescribed insulin on index date.

Table 1 also reports baseline characteristics stratified by baseline insulin use. Mean age was 57.5 (10.8) years for patients with an insulin prescribed before index date versus 56.9 (10.8) years for those with no insulin prescriptions during the baseline period ($P = 0.079$) and 56.2 (11.3) years for patients first prescribed insulin along with the GLP-1RA on index date ($P = 0.001$). Baseline A1c was higher in patients with previous insulin use at 8.6% (1.6) versus 8.2% (1.5) in those with

TABLE 2 A1c Outcomes at 1 Year by Baseline A1c and Baseline Insulin Use

	Baseline A1c, %				Baseline Insulin Use		
	Overall (n = 5,141)	A1c ≥ 7% (n = 4,268)	A1c ≥ 8% (n = 2,804)	A1c ≥ 9% (n = 1,535)	Newly Prescribed on Index Date (n = 1,115)	Not Prescribed on or Before Index Date (n = 1,822)	First Prescribed Before Index Date (n = 2,204)
Baseline mean (SD) A1c	8.4 (1.6)	8.8 (1.4)	9.4 (1.3)	10.3 (1.2)	8.2 (1.6)	8.2 (1.5)	8.6 (1.6)
Follow-up mean (SD) A1c	7.9 (1.6)	8.1 (1.6)	8.5 (1.7)	8.9 (1.8)	7.6 (1.5)	7.7 (1.5)	8.2 (1.6)
Mean difference (SD)	-0.5 (1.5) $P<0.001$	-0.6 (1.6) $P<0.001$	-0.9 (1.7) $P<0.001$	-1.4 (1.9) $P<0.001$	-0.6 (1.5) $P<0.001$	-0.5 (1.5) $P<0.001$	-0.4 (1.6) $P<0.001$
A1c goal attainment,[a] n (%)							
<7%	1,581 (30.7)	979 (22.9)	437 (15.6)	190 (12.4)	–	–	–
<8%	3,082 (59.9)	2,284 (53.5)	1,191 (42.5)	513 (33.4)	–	–	–
<9%	4,069 (79.1)	3,225 (75.6)	1,885 (67.2)	869 (56.6)	–	–	–

[a]P < 0.001 for change in population proportions from baseline using chi-square goodness-of-fit.
A1c = hemoglobin A1c; SD = standard deviation.

no baseline insulin use ($P<0.001$) and versus 8.2% (1.6) in patients first prescribed insulin on index date ($P<0.001$).

Glycemic Control Outcomes

The overall mean (SD) A1c reduction from baseline to 1-year follow-up was 0.5% (1.5). The proportion of patients with A1c below glycemic control quality targets of <7%, <8%, and <9% improved at 1 year for all target levels ($P<0.001$ for all; Table 2).

According to baseline insulin use, the mean A1c reduction from baseline to 1-year follow-up was 0.4% (1.6) in patients with insulin prescribed before index date, 0.5% (1.5) in those with no baseline insulin use, and 0.6% (1.5) in patients first prescribed insulin on index date ($P<0.001$ for A1c change, all groups; Table 2). The proportion of patients attaining A1c < 7% by baseline insulin use is presented in Figure 2. The proportion of patients attaining A1c goal was higher at follow-up than baseline ($P<0.001$ for all groups), with the proportions tending to be lower for patients prescribed insulin before index date (23.9% vs. 37.7% and 34.8%).

Among patients with baseline A1c ≥ 9%, there were 476 patients without insulin prescription on or before index date, 312 patients prescribed insulin on index date, and 747 patients prescribed insulin before index date. A higher proportion of patients on GLP-1RA who were not prescribed insulin on or before index date were able to reach goal versus the group of patients who were coprescribed insulin and GLP-1RA and patients who were prescribed insulin before index date, respectively (63.2% vs. 57.7% and 51.9%).

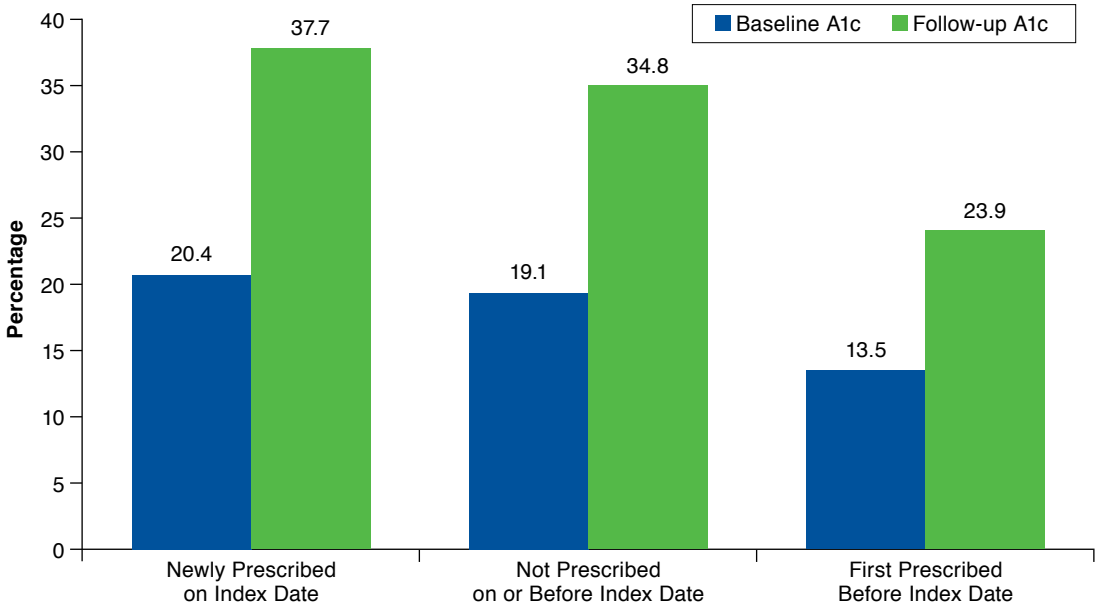
Glycemic control outcomes were also evaluated in subsets of patients with baseline A1c ≥ 7%, ≥ 8%, and ≥ 9%, regardless of baseline insulin use (Table 2). In patients with a baseline A1c ≥ 7%, mean A1c reduction was 0.6% (1.6) from a baseline of 8.8% (1.4). In those with baseline A1c ≥ 8%, mean A1c reduction was 0.9% (1.7) from a baseline of 9.4% (1.3), and mean A1c reduction was 1.4% (1.9) from a baseline of 10.3% (1.2) in those with a baseline A1c ≥ 9% ($P<0.001$ for all groups).

Multivariate regression analyses were conducted to identify the association between baseline insulin use and glycemic control with GLP-1RA therapy, with the final, reduced models controlling for age, sex, race, region, provider specialty, baseline A1c, diabetes-related comorbidities, and diabetes medication use before index date. The linear regression model (Table 3) indicated that patients with no baseline insulin use had a greater A1c reduction than patients prescribed insulin before index date (coefficient -0.38; 95% confidence interval [CI] = -0.55 to -0.21; $P=0.001$), as did patients who were newly initiated on insulin on index date (coefficient -0.52; 95% CI = -0.70 to -0.34; $P<0.001$). Furthermore, each 1% increase in baseline A1c was associated with a 0.5% greater reduction in A1c from baseline to 1-year follow-up (coefficient -0.51; 95% CI = -0.48 to -0.52; $P<0.001$).

Patients aged ≥ 65 years, females, or having a GLP-1RA prescribed by an endocrinologist had a higher A1c reduction relative to patients aged < 40 years, males, and having a GLP-1RA prescribed by a primary care provider. Further, patients with baseline CVD or with a sulfonylurea prescribed before index date had an increase in A1c relative to those without CVD or who had no use of a sulfonylurea in the baseline period ($P<0.05$ for all; Table 3). When setting the model covariates to the population mean or most common categorical value, the adjusted (marginal) mean A1c reduction at follow-up was 0.75% (95% CI = -0.86 to -0.63) for patients with insulin first prescribed on index date with a GLP-1RA, 0.61% (95% CI = -0.70 to -0.51) for patients with no baseline insulin use, and 0.23% (95% CI = -0.33 to -0.13) for patients prescribed insulin before index date (data not shown).

In multivariate logistic regression analyses controlling for potential confounders as listed above (Table 3 and Appendix A, available in online article), patients with no baseline insulin use were more likely to attain A1c < 7% at follow-up compared with patients prescribed insulin before index date (odds

FIGURE 2 Proportion of Patients with A1c Goal Attainment (A1c < 7%) at 1-Year Follow-Up by Insulin Use at Baseline



Note: P < 0.001 for percentage of patients with A1c < 7% at 1-year follow-up versus baseline for all 3 groups.
A1c = hemoglobin A1c.

ratio [OR] = 1.50, 95% CI = 1.08 to 2.09, *P* = 0.015), as were patients first prescribed insulin on index date with a GLP-1RA (OR = 1.85, 95% CI = 1.30 to 2.62, *P* = 0.001). In addition, each 1% increase in baseline A1c reduced the likelihood of achieving follow-up A1c < 7% by 50% (OR = 0.50, 95% CI = 0.47 to 0.54, *P* < 0.001), A1c < 8% by 53% (OR = 0.53, 95% CI = 0.50 to 0.56, *P* < 0.001), and A1c < 9% by 52% (OR = 0.52, 95% CI = 0.49 to 0.55, *P* < 0.001).

Patients with a history of CVD were less likely to attain A1c < 7%, whereas patients with baseline cerebrovascular disease were more likely to attain A1c < 7% (*P* < 0.05 for both). Additionally, sulfonylurea use in the past 13 months was associated with decreased likelihood of achieving A1c < 7% in patients with baseline A1c ≥ 7% (OR = 0.71, 95% CI = 0.51 to 0.97, *P* = 0.034) and likewise, in patients with baseline A1c ≥ 9% (OR = 0.69, 95% CI = 0.50 to 0.95, *P* = 0.021; Table 3).

Weight, LDL-C, and Blood Pressure Outcomes

A significant mean (SD) weight reduction of 2.2 (7.0) kg (*P* < 0.001) from baseline to 1-year follow-up was observed for the overall patient cohort. A small but statistically significant reduction in LDL-C was also observed (2.1 [30.5] mg/dL, *P* = 0.003), while the percentage of patients with LDL-C < 100 mg/dL did not differ from baseline (67.1%) to follow-up (69.2%; *P* = 0.722). The percentage of patients with blood pressure < 140/90 mmHg was greater at follow-up (76.5%) than at baseline (73.2%; *P* < 0.001) as was the percentage of patients with blood pressure < 130/80 mmHg (42.2% vs. 39.0%; *P* < 0.001; Appendix B, available in online article).

Discussion

This study demonstrated that patients with T2D treated in a real-world setting who initiated GLP-1RA therapy with exenatide QW or liraglutide QD had significantly improved glycemic control regardless of baseline insulin use. Further, for the subgroup of patients with poorly controlled diabetes (A1c ≥ 9%), the reduction in A1c was relatively higher compared with patients with A1c ≥ 7%. In addition to A1c reduction, clinical risk factors also improved as measured by weight reduction and achievement of comprehensive diabetes quality metrics for A1c, blood pressure, and LDL-C.

A key study finding showed the observed reduction in A1c was significant regardless of baseline insulin use. Patients with no prior insulin use were more likely to achieve glycemic goal with a GLP-1RA compared with patients who started insulin before initiating GLP-1RA treatment. This finding is likely due in part to higher baseline A1c in these patients, suggesting that prior insulin users may have had more disease progression and/or poorer adherence to medications and lifestyle recommendations. Patients who had the highest response to

TABLE 3 Multivariate Linear Regression for Change in A1c from Baseline to 1-Year Follow-up, and Logistic Regression for Patients Reaching A1c Goal < 7% at 1 Year for Patients with Baseline A1c ≥ 7% and ≥ 9%

	Linear Regression (N = 4,321)			Logistic Regression					
				Baseline A1c ≥ 7% (n = 4,319)			Baseline A1c ≥ 9% (n = 1,285)		
Variable	Coef	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value
Baseline A1c (%)	-0.51	-0.48 to -0.53	< 0.001	0.50	0.47 to 0.54	< 0.001	0.87	0.75 to 1.02	0.080
Baseline insulin use (ref: insulin prescribed before index date)									
Not prescribed on or before index date	-0.38	-0.55 to -0.21	0.001	1.50	1.08 to 2.09	0.015	2.21	0.89 to 5.49	0.088
Newly prescribed on index date	-0.52	-0.70 to -0.34	< 0.001	1.85	1.30 to 2.62	0.001	2.36	0.95 to 5.85	0.065
Age, years (reference: < 40)									
40-64	-0.09	-0.26 to 0.08	0.294	0.96	0.70 to 1.32	0.809	1.33	0.97 to 1.83	0.076
≥ 65	-0.23	-0.42 to -0.04	0.019	1.04	0.73 to 1.48	0.841	1.77	1.21 to 2.59	0.003
Female	-0.10	-0.19 to -0.02	0.017	1.17	1.00 to 1.36	0.045	1.18	0.99 to 1.40	0.059
Race (reference: white)									
African-American				0.68	0.50 to 0.92	0.013	1.10	0.80 to 1.51	0.560
Hispanic				0.93	0.63 to 1.37	0.725	0.69	0.46 to 1.05	0.081
Other				0.70	0.44 to 1.13	0.149	0.88	0.53 to 1.44	0.605
Region (reference: East)									
South	-0.22	-0.33 to -0.12	<0.001	1.48	1.22 to 1.79	<0.001	1.16	0.94 to 1.43	0.176
Midwest	-0.23	-0.35 to -0.10	<0.001	1.31	1.04 to 1.65	0.024	1.26	0.97 to 1.63	0.079
West	-0.25	-0.40 to -0.10	<0.001	1.46	1.12 to 1.92	0.006	1.49	1.09 to 2.05	0.013
Provider specialty (reference: primary care)									
Endocrinology	-0.10	-0.19 to -0.01	0.030	1.02	0.87 to 1.21	0.776	1.26	1.04 to 1.53	0.019
Other	-0.30	-1.01 to 0.41	0.410	1.24	0.33 to 4.58	0.749	2.01	0.41 to 9.90	0.390
Comorbidities									
Hypertension	0.00	-0.10 to 0.10	0.999	1.00	0.83 to 1.20	0.994	0.97	0.79 to 1.21	0.808
Acute MI	0.02	-0.49 to 0.52	0.953	1.05	0.42 to 2.60	0.922	0.80	0.29 to 2.16	0.657
Cardiovascular disease	0.15	0.00 to 0.31	0.046	0.71	0.54 to 0.95	0.020	0.74	0.55 to 1.01	0.054
Cerebrovascular disease	-0.28	-0.60 to 0.05	0.096	1.78	1.01 to 3.12	0.045	1.60	0.76 to 3.34	0.214
Kidney disease	-0.01	-0.15 to 0.13	0.895	1.02	0.78 to 1.33	0.897	0.99	0.73 to 1.32	0.922
Hyperlipidemia	0.02	-0.09 to 0.13	0.720	0.95	0.78 to 1.15	0.581	1.03	0.81 to 1.30	0.805
Microvascular complications	0.08	-0.08 to 0.24	0.315	0.74	0.55 to 1.00	0.050	0.83	0.61 to 1.13	0.231
Other diabetes medication classes prescribed prescribed before index date									
Metformin	-0.02	-0.20 to 0.16	0.814	1.19	0.84 to 1.67	0.329	0.95	0.68 to 1.34	0.773
Sulfonylurea	0.29	0.12 to 0.45	0.001	0.71	0.51 to 0.97	0.034	0.69	0.50 to 0.95	0.021
TZDs	0.13	-0.04 to 0.30	0.143	0.95	0.68 to 1.33	0.769	0.78	0.56 to 1.07	0.127
DPP-4	0.08	-0.08 to 0.24	0.337	0.89	0.64 to 1.22	0.465	0.96	0.71 to 1.31	0.818
Pramlintide	0.16	-0.24 to 0.57	0.429	1.32	0.63 to 2.80	0.463	0.69	0.33 to 1.46	0.333
Other OADs	0.20	-0.04 to 0.43	0.102	0.94	0.60 to 1.47	0.794	0.48	0.31 to 0.73	0.001

A1c = hemoglobin A1c; CI = confidence interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; MI = myocardial infarction; OADs = oral diabetes drugs; TZDs = thiazolidinediones.

GLP-1RA therapy were those who were prescribed both insulin and a GLP-1RA for the first time on index date, although the baseline A1c in this insulin group was the same (8.2%) as for those with no baseline insulin use. Thus, these data support a hypothesis that initiation of GLP-1RA therapy with or before insulin is an effective real-world treatment strategy.

The significant glycemic control and weight response with GLP-1RA therapy are consistent with clinical trial data.[8] In a pivotal head-to-head trial,[8] patients on exenatide QW or liraglutide QD for 6 months had a least square mean (SE) A1c reduction of 1.28% (0.05) and 1.48% (-0.05), respectively, and 60% of liraglutide QD patients and 53% of exenatide QW patients achieved A1c < 7% during the follow-up. The least square mean weight reduction in patients with exenatide QW and liraglutide QD in these clinical trials ranged from 2.68 (0.18) kg to 3.57 (0.18) kg, with no severe hypoglycemic events reported.

In observing reductions in A1c overall, the present study contributes to the real-world evidence regarding the effectiveness of GLP-1RAs. While the effect is consistent, the magnitude of A1c reduction in this study was less than observed in clinical trials. This study followed patients initiated on GLP-1RA therapy for 1 year and identified a mean A1c reduction of 50% (1.5), and 30.7% of patients achieved A1c < 7% at follow-up. The smaller A1c reduction observed in this study relative to clinical trials likely reflects the real-world setting where monitoring and treatment are not as regimented and consistent, and adherence to medication therapy and lifestyle recommendations may be lower. Additionally, the clinical trial included slightly more male patients than our study, was predominantly white, and was restricted to patients with active cardiac diseases and other comorbidities, whereas our real-world study did not exclude patients based on comorbidities.

This study also provides real-world evidence that patients with poorly controlled diabetes can have significant A1c reduction with GLP-1RA therapy. In a clinical trial with a subgroup of patients with A1c ≥ 9% and a follow-up of 6 months, Buse et al. (2013)[8] found a least square mean A1c reduction of 1.75% (0.09) and 2.04% (0.09) in exenatide and liraglutide groups, respectively. In our study, patients with A1c ≥ 9% prescribed exenatide QW or liraglutide QD had a mean A1c reduction of 1.4% (1.9) at 1-year follow-up, and 56.6% of patients had A1c < 9%. While this improvement in glycemic control was significant and clinically meaningful, the proportion of these patients who were able to attain A1c < 7% was 12.4%, which likely reflects their high starting A1c (10.3%) and the challenges in achieving such dramatic reduction in A1c.

Given the high cardiovascular (CV) comorbidities with T2D, the ideal diabetes therapy should improve glycemic control and other CV risk factor markers. Data from this study suggest that GLP-1RAs used with or without concomitant insulin have benefits on CV risk factors, including weight, blood pressure, and LDL-C, which is consistent with previous findings.[14-16] However, as secondary outcomes, weight, LDL-C, and blood pressure results were not adjusted for confounders, including concomitant therapy for hypertension and hyperlipidemia. Thus, these findings should be interpreted with caution, and future research assessing CV risk factor outcomes with GLP-1RA therapy in the real-world setting is warranted. Further, we only assessed these CV-related outcomes in the overall study population and did not identify if these outcomes were also observed in subsets of patients by baseline glycemic control or insulin use.

Sulfonylurea use during the 13 months before index date was associated with a decreased likelihood of attaining A1c goals in patients with A1c ≥ 7% and ≥ 9%, respectively (Table 3). This interesting finding could possibly be due to these patients being older with higher disease progression and with a less stringent A1c goal. These findings were observed in a subgroup analysis where sulfonylurea use was higher in patients ≥ 65 years (30% vs. 26% in patients < 65 years) as well as in patients with ≥ 3 antidiabetes drugs, where 75% of these patients were on a sulfonylurea (data not shown).

Limitations

While this study is the first to our knowledge to assess real-world GLP-1RA treatment outcomes according to patterns of insulin use, a number of limitations should be highlighted. First, this study was limited to assessing the outcomes associated with liraglutide QD and exenatide QW, as they were the predominant GLP-1RAs at the time of the study. Thus, the result may not be generalizable to newer GLP-1RAs, including albiglutide, dulaglutide, and lixisenatide. Also, the study did not control for patients who may have switched between the GLP-1RA medications after 30 days or had a change in index insulin prescription status.

Further, requirements that patients have a minimum duration of activity in the dataset and A1c data to assess outcomes may have introduced additional selection bias. Namely, included patients may have better continuity of care, follow-up, and monitoring than patients not meeting study inclusion criteria. We used prescription orders to capture the medication use, which may have introduced misclassification bias. Prescription orders indicate that a physician prescribed a medication, but orders do not provide information on whether the patient obtained the medication and then took it as prescribed.

In addition, this study used a pre-post design for assessing patient outcomes and did not include a non-GLP-1RA control group. Further, outcomes were only assessed at 1 year and not at interim periods, such as 3 and 6 months. Finally, research using administrative datasets is limited by the lack of data to control for other factors and patient behaviors that can affect outcomes, such as adherence to diet and exercise.

Conclusions

GLP-1RA therapy, alone or in combination with insulin, is effective in improving A1c and weight in patients with T2D in the real-world setting, which translates to improvement in quality measures. Patients treated with a GLP-1RA who were not prescribed insulin during the baseline period or on index date and patients who initiated insulin on index date had greater A1c reductions than patients who were prescribed insulin during the baseline period and before initiating GLP-1RA therapy. Further, patients with A1c ≥ 9% responded notably well to GLP-1RA therapy, supporting GLP-1RAs as another option for patients with A1c ≥ 9%, particularly if weight loss and hypoglycemia avoidance are treatment goals. Given these outcomes, use of GLP-1RAs is also effective in helping provider and payer organizations improve diabetes-related outcomes and performance measures.

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DISCLOSURES

The study was funded by a collaborative research grant from AstraZeneca. Employees of AstraZeneca participated in most aspects of the study and in manuscript preparation. Nguyen and Hurd are employed by, and hold stock in, AstraZeneca. McAdam-Marx reports participation in the AMCP Diabetes Partnership and has stock ownership in GlaxoSmithKline.

Study concept and design were contributed by Nguyen, McAdam-Marx, and Singhal, along with Unni and Schauerhamer. Singhal, Unni, Nguyen, and McAdam-Marx collected the data, with assistance from Schauerhamer and Hurd, and data interpretation was performed by Unni, Hurd, McAdam-Marx, Singhal, Nguyen, and Schauerhamer. The manuscript was written by Singhal, Schauerhamer, Unni, and McAdam-Marx, along with Nguyen and Hurd, and revised by McAdam-Marx, Singhal, Unni, and Nguyen, along with Schauerhamer and Hurd.

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APPENDIX A Multivariate Logistic Regression for Patients Reaching A1c Goal <8% and <9% at 1 Year for Patients with Baseline A1c ≥7%

	Likelihood of Achieving <8% (n=4,321)			Likelihood of Achieving <9% (n=4,321)		
Variable	**Odds Ratio**	**95% CI**	***P* Value**	**Odds Ratio**	**95% CI**	***P* Value**
Baseline A1c	0.53	0.50 to 0.56	<0.001	0.52	0.49 to 0.55	<0.001
Baseline insulin use (ref: insulin prescribed before index date)						
No insulin prescribed on or before index date	1.92	1.44 to 2.55	0.000	1.72	1.25 to 2.39	0.001
Insulin newly prescribed on index date	2.72	2.00 to 3.70	<0.001	1.84	1.29 to 2.61	0.001
Age, years (reference: <40)						
40-64	1.19	0.90 to 1.59	0.227	1.33	0.97 to 1.83	0.076
≥65	1.65	1.18 to 2.29	0.003	1.77	1.21 to 2.59	0.003
Female	1.15	1.00 to 1.33	0.047	1.18	0.99 to 1.40	0.059
Race (reference: white)						
Black	0.76	0.58 to 1.00	0.050	1.10	0.80 to 1.51	0.560
Hispanic	0.81	0.56 to 1.16	0.249	0.69	0.46 to 1.05	0.081
Other	0.83	0.55 to 1.27	0.393	0.88	0.53 to 1.44	0.605
Unknown	0.88	0.72 to 1.07	0.189	1.04	0.83 to 1.32	0.718
Region (reference: East)						
South	1.30	1.09 to 1.55	0.004	1.16	0.94 to 1.43	0.176
Midwest	1.38	1.11 to 1.71	0.004	1.26	0.97 to 1.63	0.079
West	1.45	1.12 to 1.87	0.005	1.49	1.09 to 2.05	0.013
Provider specialty (reference: primary care)						
Endocrinology	1.19	1.02 to 1.40	0.031	1.26	1.04 to 1.53	0.019
Other	2.39	0.67 to 8.49	0.179	2.01	0.41 to 9.90	0.390
Comorbidities						
Hypertension	0.97	0.81 to 1.16	0.736	0.97	0.79 to 1.21	0.808
Acute MI	1.10	0.47 to 2.57	0.835	0.80	0.29 to 2.16	0.657
Cardiovascular disease	0.97	0.75 to 1.26	0.818	0.74	0.55 to 1.01	0.054
Cerebrovascular disease	1.25	0.71 to 2.20	0.434	1.60	0.76 to 3.34	0.214
Kidney disease	0.88	0.69 to 1.13	0.324	0.99	0.73 to 1.32	0.922
Hyperlipidemia	0.94	0.78 to 1.14	0.546	1.03	0.81 to 1.30	0.805
Microvascular complications	1.02	0.79 to 1.33	0.858	0.83	0.61 to 1.13	0.231
Other diabetes medication(s) classes prescribed before index date						
Metformin	0.88	0.65 to 1.19	0.407	0.95	0.68 to 1.34	0.773
Sulfonylurea	0.54	0.40 to 0.71	<0.001	0.69	0.50 to 0.95	0.021
TZDs	0.90	0.68 to 1.20	0.482	0.78	0.56 to 1.07	0.127
DPP-4	0.82	0.63 to 1.08	0.162	0.96	0.71 to 1.31	0.818
Pramlintide	0.79	0.40 to 1.54	0.485	0.69	0.33 to 1.46	0.333
Other OADs	0.69	0.47 to 1.02	0.066	0.48	0.31 to 0.73	0.001

A1c = hemoglobin A1c; DPP-4 = dipeptidyl peptidase-4 inhibitor; MI = myocardial infarction; OADs = oral antidiabetic drugs; TZDs = thiazolidinediones.

APPENDIX B Weight, LDL-C, and Blood Pressure Outcomes Overall at 1 Year

1-Year Follow-up Goal Attainment	Overall (n = 5,141)
Weight (kg)	n = 4,804
Baseline mean (SD)	108.0 (24.8)
Follow-up mean (SD)	105.7 (24.7)
Mean difference (SD)	-2.2 (7.0), $P < 0.001$
LDL-C (mg/dL)	n = 1,734
Baseline mean (SD)	90.1 (33.8)
Follow-up mean (SD)	87.9 (33.3)
Mean difference (SD)	-2.1 (30.5), $P = 0.003$
LDL-C goal attainment (%)	n = 1,734
Baseline < 100 mg/dL	67.1
Follow-up < 100 mg/dL	69.2, $P = 0.722$
Blood pressure goal attainment (%)	n = 4,826
Baseline < 140/90 mmHg	73.2
Follow-up < 140/90 mmHg	76.5, $P < 0.001$
Baseline < 130/80 mmHg	39.0
Follow-up < 130/80 mmHg	42.2, $P < 0.001$

LDL-C = low-density lipoprotein cholesterol; SD = standard deviation.