Glycemic Control and Weight Outcomes for Exenatide Once Weekly Versus Liraglutide in Patients with Type 2 Diabetes: A 1-Year Retrospective Cohort Analysis

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ABSTRACT

Purpose: Data comparing real-world effectiveness of the glucagon-like peptide-1 receptor agonists (GLP-1RAs) exenatide once weekly (QW) and liraglutide in the treatment of type 2 diabetes (T2D) are limited. Furthermore, there is limited information on exenatide QW or liraglutide response by glycemic control and insulin use status. This study identifies 1-year glycated hemoglobin (HbA1c) and weight outcomes with exenatide QW and liraglutide in the real-world setting overall and in insulin-naive patients with uncontrolled T2D.

Methods: This retrospective cohort study using national electronic medical record data compared 1-year HbA1c and weight outcomes in patients with T2D prescribed exenatide QW or liraglutide. Included patients were adults (≥18 years old) with T2D who were GLP-1RA naive when newly prescribed exenatide QW or liraglutide between January 1, 2012, and March 31, 2013 (index date). Outcomes were reported descriptively overall and in subsets of insulin-naive patients with baseline HbA1c ≥7.0% or ≥9.0%. Multivariable linear regression analyses were performed to estimate adjusted change in HbA1c and weight.

Findings: The study included 808 exenatide QW and 4333 liraglutide patients. Mean (SD) age was 57 (11) years in both groups. Mean baseline HbA1c was 8.3% (1.5%) in exenatide QW patients and 8.4% (1.6%) in liraglutide patients (P = 0.66); 16 (2%) of the exenatide QW and 1099 (25.4%) of the liraglutide patients were newly prescribed insulin on the index date (P < 0.001). Adjusted mean HbA1c change at 1 year was −0.37% (95% CI, −0.53% to −0.21%) for exenatide QW and −0.37% (95% CI, −0.55% to −0.18%) for liraglutide. Adjusted HbA1c reduction was more pronounced in insulin-naive patients with baseline HbA1c ≥7.0% (−0.71% and −0.80% for the exenatide QW and liraglutide patients, respectively, P > 0.05) and ≥9.0% (−1.73% and −1.57% for exenatide QW and liraglutide patients, respectively, P > 0.05). Mean (adjusted) weight loss was −2.22 kg (95% CI, −3.06 to −1.37 kg) with exenatide QW and −2.21 kg (95% CI, −3.18 to −1.23 kg) with liraglutide.

Implications: Exenatide QW and liraglutide lead to similar HbA1c and weight reductions at 1 year in the real-world setting. Greater HbA1c reductions occurred in insulin-naive patients with baseline HbA1c ≥7.0%. Both agents are appropriate options for patients needing antidiabetes therapy to lower HbA1c while promoting weight loss. (Clin Ther. 2016;38:1133–1143) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: diabetes mellitus, exenatide, glycemic control, liraglutide, observational study, weight.

INTRODUCTION

Effective management of type 2 diabetes (T2D) can be a significant challenge for patients, practitioners, and
health care systems. T2D is a progressive disease associated with high comorbidity. Thus, even adherent patients eventually require multiple diabetes medications to manage hyperglycemia and reduce the risk of developing diabetes complications. Although consistent in recommending metformin as first-line therapy, guidelines are less specific with second-line treatment, recommending that practitioners select second-line therapy based on patient-specific treatment goals and product characteristics.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are beneficial as second-line T2D therapeutic alternatives because they are associated with significant reductions in glycosylated hemoglobin (HbA1c) and weight with low risk of hypoglycemia. Numerous GLP-1RAs are approved for treatment of T2D. Exenatide dosed BID was the first GLP-1RA, approved in 2005. Exenatide BID targets mealtime, or postprandial, glucose and is approved as add-on treatment to basal insulin based on complementary pharmacologic effects on prandial and fasting glycemia. Liraglutide dosed once daily was the second GLP-1RA approved (2010), followed by a once-weekly (QW) formulation of exenatide (2012). Albiglutide and dulaglutide were approved in late 2014; both are dosed once weekly.

Exenatide QW and liraglutide are GLP-1RAs commonly used in the United States. They are indicated as add-on therapy adjunct to diet and exercise to improve glycemic control in adults with T2D. Clinical trials have found both agents to be effective and generally well tolerated. Although they differ in injection frequency, differentiation in terms of efficacy and tolerability is complex but limited because of mixed evidence. A head-to-head comparison of liraglutide versus exenatide QW found a small but statistically greater HbA1c reduction of 0.21% (95% CI, 0.08–0.33) for liraglutide versus exenatide QW. Common adverse events were reported more often in the liraglutide group, including nausea, diarrhea, and vomiting. Furthermore, more patients taking liraglutide than exenatide QW discontinued the study because of adverse events. A recent medication adherence study found that patients receiving exenatide QW were more likely to be adherent than patients receiving liraglutide.

Given the differences in tolerability and adherence, we hypothesized the differences in HbA1c outcomes between exenatide QW and liraglutide seen in the head-to-head clinical trial may not be observed in a real-world setting. A prior study evaluated glycemic control and weight outcomes of exenatide QW versus liraglutide, but the study outcome period was limited to 6 months. Furthermore, there is limited information on response to exenatide QW or liraglutide according to glycemic control and insulin use status, which would be of use to prescribers considering the addition of GLP-1RA to therapy. Therefore, the purpose of this study was to compare real-world HbA1c and weight outcomes at 1 year in patients with T2D prescribed exenatide QW or liraglutide overall and in subsets of insulin-naive patients with uncontrolled T2D.

PATIENTS AND METHODS

Study Design and Timeline

A retrospective cohort study was conducted using a national electronic medical record database to assess 1-year HbA1c and weight outcomes in adult patients with T2D newly prescribed exenatide QW or liraglutide between January 1, 2012, and March 31, 2013.

Data Source

This study used the Quintiles electronic medical record (Q-EMR) database, a national ambulatory care dataset. At the time of this study, Q-EMR included patient-level data on >38 million individuals from 49 states and the District of Columbia. Q-EMR includes demographic data, vital signs, International Classification of Diseases, Ninth Revision (ICD-9)–based medical diagnoses, laboratory tests and results, procedures, insurance information, prescription medication orders, and medication history. Data were available through March 31, 2014.

Cohort Selection

The study cohort was drawn from adult patients with a diagnosis of T2D (ICD-9 codes 250.0 or 250.2, taking a diabetes drug, HbA1c ≥ 6.5%, or 2 consecutive fasting blood glucose values ≥ 126 mg/dL). Included patients were GLP-1RA naive when newly prescribed exenatide QW or liraglutide between January 1, 2012, and March 31, 2013 (index date), which allowed for identification of baseline characteristics before the index date and 1-year outcomes data using the available data. Included patients had HbA1c values on the index date (−60 to +30 days) and
at 1 year (±60 days) after the index date and had clinical activity in the database for at least 13 months before and 1 year after the index date. Patients with type 1 diabetes, women with gestational diabetes, those with prescription orders for 2 different GLP-1RAs on the index date, and those prescribed a different GLP-1RA within 30 days after index date were excluded.

**Outcome Variables**

Primary study outcomes were changes in HbA1c and weight from index date to 1-year follow-up. Secondary outcomes included proportion of patients with HbA1c <7.0% at 1-year follow-up in those with baseline HbA1c ≥7.0%. In addition, subgroup analyses were conducted to investigate outcomes in patients with poor glycemic control at baseline (HbA1c ≥7.0% and ≥9.0%) who were not treated with insulin on or up to 13 months before the index date (insulin naive).

**Independent Variables**

Additional baseline characteristics were captured in the 13 months before the index date to describe the study cohort and to control for confounding, including age, sex, race, baseline HbA1c, body mass index, weight, blood pressure, select comorbidities (by diagnosis codes), and the Charlson Comorbidity Index (CCI). The specialty of the patient’s practitioner was also captured and reported as primary care, endocrinology, or other.

Diabetes medication use at baseline (up to 13 months before the index date) was reported at the class level and by the number of medication classes. Diabetes medications were categorized as metformin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, pramlintide, and other (α-glucosidase inhibitors, dopamine agonists, meglitinide analogues). Sodium glucose co-transporter 2 inhibitors were not available at the time of the study. Baseline insulin use was further categorized as pre-index use or insulin initiated on index date.

**Statistical Analysis**

Descriptive statistics were used to describe baseline characteristics by treatment groups. Independent t tests and χ² tests were used to detect differences in continuous and categorical variables, respectively. Independent t tests were used to determine if the change in HbA1c or weight differed by treatment. A χ² test was used to report the statistical significance between the proportions of patients not at goal at baseline who attained HbA1c <7.0% at follow-up by treatment group.

Multivariate linear regression was used to assess adjusted changes in HbA1c and weight with exenatide QW relative to liraglutide. Multivariate logistic regression was used to report the odds of attaining HbA1c <7.0% at follow-up for exenatide QW versus liraglutide in patients with baseline HbA1c ≥7.0. Initial regression models controlled for confounders, including baseline HbA1c and weight, demographic characteristics, and clinical and treatment characteristics. Parsimonious models were identified using stepwise backward selection. Final models controlled for age, sex, baseline HbA1c and weight, practitioner specialty, coronary heart disease, microvascular complications, CCI, and baseline use of insulin and oral diabetes medications. The final multivariate linear regression models were used to estimate the adjusted mean change in HbA1c and weight by treatment group.

All statistical tests were performed using SAS software, version 9.2 (SAS Institute, Cary, North Carolina), with P < 0.05 considered statistically significant. The protocol for this study was reviewed and approved by the University of Utah Institutional Review Board.

**RESULTS**

Of the 1.69 million patients with T2D in the Q-EMR database during the study period, 28,314 had a new prescription order for exenatide QW or liraglutide between January 1, 2012, and March 31, 2013. There were 5141 patients who met study inclusion criteria; 808 were newly prescribed exenatide QW, and 4333 were newly prescribed liraglutide (Figure 1). The larger number of patients in the liraglutide group reflects, in part, that liraglutide was approved for use in the United States in 2010 versus 2012 for exenatide QW.

The 2 cohorts were similar in most baseline characteristics, including age and sex (Table I). Mean (SD) baseline HbA1c was 8.3% (1.5%) and 8.4% (1.6%) (P = 0.66); mean (SD) baseline weight was 107.6 (25.0) kg and 108.4 (24.8) kg (P = 0.38) for exenatide QW and liraglutide patients, respectively. A higher proportion of liraglutide patients had hypertension (73.6%) than exenatide QW patients (70.0%) (P = 0.04); however, baseline systolic blood pressure and diastolic blood pressure did not differ (Table I).
Insulin was prescribed during the 13-month index date period for 41.3% of the exenatide QW patients and 43.2% of the liraglutide patients ($P = 0.34$). However, the proportion of patients initiating insulin treatment on the index date was significantly higher in the liraglutide group (25.4% versus 2.0%; $P < 0.001$). A greater proportion of exenatide QW patients were prescribed metformin up to 13 months before or on the index date (72.5%) compared with the liraglutide group (67.1%; $P = 0.002$).

There were slight differences in age between the overall cohort and the insulin-naive subpopulations. Mean (SD) age overall was 57.0 (10.9) years versus 56.8 (10.8) years in the insulin-naive subpopulation with baseline HbA$_{1c}$ ≥7.0%. Age was numerically lower in the insulin-naive subpopulation with baseline HbA$_{1c}$ ≥9.0% at 54.4 (10.8) years. There were more men in the insulin-naive population than in the overall cohort (46.5% in the overall cohort and 50.1% and 52.1% in the insulin-naive cohorts with baseline HbA$_{1c}$ ≥7.0% and ≥9.0%, respectively). Finally, more patients were treated by primary care practitioners in the insulin-naive cohort than in the overall cohort (48.9% in the overall cohort and 65.8% and 70.2% in the insulin-naive cohorts with baseline HbA$_{1c}$ ≥7.0% and ≥9.0%, respectively).

**Glycemic Control**

At 1-year follow-up, mean observed HbA$_{1c}$ reduction was 0.5% for both groups (SDs of 1.5 and 1.6 for the exenatide QW and liraglutide cohorts, respectively; $P = 0.75$) (Figure 2). Furthermore, the proportion of patients attaining HbA$_{1c}$ <7.0% at 12 months did not differ between groups and was 31.4% for the exenatide QW patients versus 30.6% for the liraglutide patients ($P = 0.65$) (Figure 3).

In the subset of 376 exenatide QW and 1098 liraglutide insulin-naive patients with baseline HbA$_{1c}$ ≥7.0%, mean (SD) unadjusted HbA$_{1c}$ reduction at 1 year was also similar. A mean (SD) HbA$_{1c}$ reduction of 0.7% (1.5) from a baseline of 8.6% (1.3) was observed for exenatide QW patients, and a 0.7% (1.6) reduction from a baseline of 8.7% (1.4) was seen with liraglutide ($P = 0.81$) (Figure 2). However, the proportion of patients attaining HbA$_{1c}$ <7.0% was significantly higher for exenatide QW patients (30.6%) than for liraglutide patients (24.1%; $P = 0.01$) (Figure 3).

In 107 exenatide QW and 369 liraglutide patients with poorly controlled diabetes (baseline HbA$_{1c}$ ≥9.0%) who were insulin naive, mean (SD) unadjusted baseline HbA$_{1c}$ values were 10.3% (1.1) and 10.2% (1.2) for the exenatide QW and liraglutide cohorts, respectively, and HbA$_{1c}$ change was more pronounced, with reductions of 1.4% (1.8) and 1.5% (1.9), respectively ($P = 0.61$ for reduction between groups) (Figure 2). Of these, 14.0% of exenatide QW and 12.7% of liraglutide patients attained HbA$_{1c}$ <7.0% at 12 months ($P = 0.73$) (Figure 3), whereas 60.7% and 64.0% attained follow-up HbA$_{1c}$ <9.0%, respectively ($P = 0.54$) (data not shown).

On the basis of linear regression analysis of the overall cohort controlling for age, sex, baseline HbA$_{1c}$...
### Table I. Baseline characteristics of patients newly prescribed exenatide QW or liraglutide.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (N = 5141)</th>
<th>Exenatide QW (n = 808)</th>
<th>Liraglutide (n = 4333)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>57.0 (10.9)</td>
<td>57.1 (10.6)</td>
<td>57.0 (11.0)</td>
<td>0.73</td>
</tr>
<tr>
<td>Age ≥65 y</td>
<td>1353 (26.3)</td>
<td>203 (25.1)</td>
<td>1150 (26.5)</td>
<td>0.70</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>2388 (46.5)</td>
<td>394 (48.8)</td>
<td>1994 (46.0)</td>
<td>0.15</td>
</tr>
<tr>
<td>Race, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>3614 (70.3)</td>
<td>572 (70.8)</td>
<td>3042 (70.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>Black</td>
<td>375 (7.3)</td>
<td>44 (5.4)</td>
<td>331 (7.6)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>208 (4.0)</td>
<td>28 (3.5)</td>
<td>180 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>143 (2.8)</td>
<td>27 (3.3)</td>
<td>116 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>801 (15.6)</td>
<td>137 (17.0)</td>
<td>664 (15.3)</td>
<td></td>
</tr>
<tr>
<td>Baseline HbA1c, mean (SD), %</td>
<td>8.4 (1.6)</td>
<td>8.3 (1.5)</td>
<td>8.4 (1.6)</td>
<td>0.66</td>
</tr>
<tr>
<td>HbA1c &lt; 7.0%, no. (%)</td>
<td>873 (17.0)</td>
<td>122 (15.1)</td>
<td>751 (17.3)</td>
<td>0.19</td>
</tr>
<tr>
<td>HbA1c ≥7% to &lt;9, no. (%)</td>
<td>2733 (53.2)</td>
<td>450 (55.7)</td>
<td>2283 (52.7)</td>
<td></td>
</tr>
<tr>
<td>HbA1c ≥9.0%, no. (%)</td>
<td>1535 (29.9)</td>
<td>236 (29.2)</td>
<td>1299 (30.0)</td>
<td></td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>37.7 (7.7)</td>
<td>37.2 (7.6)</td>
<td>37.8 (7.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>108.3 (24.8)</td>
<td>107.6 (25.0)</td>
<td>108.4 (24.8)</td>
<td>0.38</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>128.7 (15.4)</td>
<td>128.2 (15.3)</td>
<td>128.8 (15.4)</td>
<td>0.32</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SD), mm Hg</td>
<td>76.3 (9.6)</td>
<td>76.0 (9.3)</td>
<td>76.4 (9.6)</td>
<td>0.30</td>
</tr>
<tr>
<td>Patients’ practitioner specialty</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary care</td>
<td>2516 (48.9)</td>
<td>351 (43.4)</td>
<td>2165 (49.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>1932 (37.6)</td>
<td>368 (45.5)</td>
<td>1564 (36.1)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>693 (13.5)</td>
<td>89 (11.0)</td>
<td>604 (14.0)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>3753 (73.0)</td>
<td>566 (70.0)</td>
<td>3187 (73.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>Acute MI</td>
<td>30 (0.6)</td>
<td>7 (0.9)</td>
<td>23 (0.5)</td>
<td>0.31</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>426 (8.3)</td>
<td>71 (8.8)</td>
<td>355 (8.2)</td>
<td>0.57</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>83 (1.6)</td>
<td>16 (2.0)</td>
<td>67 (1.5)</td>
<td>0.36</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>529 (10.3)</td>
<td>79 (9.8)</td>
<td>450 (10.4)</td>
<td>0.60</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>4273 (83.1)</td>
<td>668 (82.7)</td>
<td>3605 (83.2)</td>
<td>0.71</td>
</tr>
<tr>
<td>Stroke</td>
<td>44 (0.9)</td>
<td>11 (1.4)</td>
<td>33 (0.8)</td>
<td>0.10</td>
</tr>
<tr>
<td>Neuropathy or retinopathy</td>
<td>390 (7.6)</td>
<td>52 (6.4)</td>
<td>338 (7.8)</td>
<td>0.18</td>
</tr>
<tr>
<td>Charlson Comorbidity Index, mean (SD)</td>
<td>0.9 (1.3)</td>
<td>0.9 (1.3)</td>
<td>0.9 (1.3)</td>
<td>0.30</td>
</tr>
<tr>
<td>Charlson Comorbidity Index, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2742 (53.3)</td>
<td>449 (55.6)</td>
<td>2293 (52.9)</td>
<td>0.28</td>
</tr>
<tr>
<td>1</td>
<td>1097 (21.3)</td>
<td>158 (19.6)</td>
<td>939 (21.7)</td>
<td>0.75</td>
</tr>
<tr>
<td>2</td>
<td>701 (13.6)</td>
<td>116 (14.4)</td>
<td>585 (13.5)</td>
<td>0.21</td>
</tr>
<tr>
<td>≥3</td>
<td>601 (11.7)</td>
<td>85 (10.5)</td>
<td>516 (11.9)</td>
<td></td>
</tr>
<tr>
<td>Baseline insulin use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescribed before index date</td>
<td>2204 (42.9)</td>
<td>334 (41.3)</td>
<td>1870 (43.2)</td>
<td>0.34</td>
</tr>
<tr>
<td>Started on index date</td>
<td>1115 (21.7)</td>
<td>16 (2.0)</td>
<td>1099 (25.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No baseline insulin</td>
<td>1822 (35.4)</td>
<td>458 (56.7)</td>
<td>1364 (31.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other baseline diabetes medication use, no. (%)</td>
<td>3493 (67.9)</td>
<td>586 (72.5)</td>
<td>2907 (67.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>Metformin</td>
<td>2063 (40.1)</td>
<td>344 (42.6)</td>
<td>1719 (39.7)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

(continued)
and weight, practitioner specialty, coronary heart disease, microvascular complications, CCI, and baseline use of insulin and oral diabetes medications, the estimated adjusted mean HbA1c reduction at 1 year did not differ between exenatide QW and liraglutide (Table II). At 1-year follow-up, the adjusted mean HbA1c change was −0.37 (95% CI, −0.53 to −0.21) for exenatide QW and −0.37% (95% CI, −0.55 to −0.18) for liraglutide (Table II). Insulin-naive patients with baseline HbA1c ≥7.0% had adjusted mean HbA1c changes of −1.73% (95% CI, −2.39 to −1.06) for exenatide QW and −1.57% (95% CI, −2.29 to −0.86) for liraglutide (Table II).

Multivariate logistic regression analysis of patients with baseline HbA1c ≥7.0% found no difference between exenatide QW and liraglutide in the likelihood of having a 1-year follow-up HbA1c <7.0% (odds ratio, 1.04; 95% CI, 0.85–1.28) (data not shown).

Weight

Mean weight loss at 1 year of follow-up was assessed in patients with documented weight values at baseline and follow-up. No significant difference was observed between groups with a mean (SD) weight loss of 2.3 (6.4) kg in the exenatide QW group versus 2.3 (7.1) kg in the liraglutide group (P = 0.98).

Figure 2. Percentages of patients attaining HbA1c <7.0% overall and for subsets of Insulin-naive patients with baseline HbA1c ≥7.0% and ≥9.0%. HbA1c, glycosylated hemoglobin; QW = once weekly.

Figure 3. HbA1c change from baseline to 12 months overall and for subsets of insulin-naive patients with baseline HbA1c ≥7.0% and ≥9.0%. HbA1c, glycosylated hemoglobin; QW = once weekly.
Table II. LS mean change in HbA1c and weight at 12 months for patients treated with exenatide QW or liraglutide.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exenatide QW</th>
<th>Liraglutide</th>
<th>Treatment Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LS Mean (SE)</td>
<td>95% CI</td>
<td>LS Mean (SE) 95% CI</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (N = 5141)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted*</td>
<td>-0.48 (0.02)</td>
<td>-0.53 to -0.43</td>
<td>-0.46 (0.05)</td>
</tr>
<tr>
<td>Adjusted†</td>
<td>-0.37 (0.08)</td>
<td>-0.53 to -0.21</td>
<td>-0.37 (0.09)</td>
</tr>
<tr>
<td>Insulin-naive baseline ≥7.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 1474)</td>
<td></td>
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</tr>
<tr>
<td>Unadjusted*</td>
<td>-0.67 (0.05)</td>
<td>-0.76 to -0.58</td>
<td>-0.69 (0.08)</td>
</tr>
<tr>
<td>Adjusted†</td>
<td>-0.71 (0.19)</td>
<td>-1.09 to -0.33</td>
<td>-0.80 (0.20)</td>
</tr>
<tr>
<td>Insulin-naive baseline ≥9.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 476)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted*</td>
<td>-1.54 (0.10)</td>
<td>-1.73 to -1.35</td>
<td>-1.43 (0.18)</td>
</tr>
<tr>
<td>Adjusted†</td>
<td>-1.73 (0.34)</td>
<td>-2.39 to -1.06</td>
<td>-1.57 (0.36)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (N = 5141)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted*</td>
<td>-2.25 (0.11)</td>
<td>-2.47 to -2.04</td>
<td>-2.26 (0.25)</td>
</tr>
<tr>
<td>Adjusted†</td>
<td>-2.22 (0.43)</td>
<td>-3.06 to -1.37</td>
<td>-2.21 (0.40)</td>
</tr>
</tbody>
</table>

HbA1c, glycosylated hemoglobin; LS, least squares; QW, once weekly.

*Univariate linear regression.
†Multiple linear regression adjusted for age, sex, baseline HbA1c, baseline weight, practitioner type, coronary heart disease neuropathy or retinopathy, Charlson Comorbidity Index, insulin prescription on and before index date, and number of noninsulin diabetes drug classes.
On the basis of a multivariate linear regression analysis controlling for age, sex, baseline HbA1c and weight, practitioner specialty, coronary heart disease, microvascular complications, CCI, and baseline use of insulin and oral diabetes medications, adjusted mean weight change at 1 year was –2.22 kg (95% CI, –3.06 to –1.37) for exenatide QW. Liraglutide patients experienced a similar reduction of –2.21 kg (95% CI, –3.18 to –1.23) (Table II).

**DISCUSSION**

This retrospective analysis of >5000 patients with T2D newly prescribed exenatide QW or liraglutide found that both GLP-1RAs resulted in statistically significant and equal reduction in HbA1c at 1 year of 0.37%. They were both also associated with significant weight reduction of 2.2 kg. In the subset of insulin-naive patients with poorly controlled diabetes (HbA1c ≥9.0%), HbA1c reduction was notably greater with adjusted HbA1c mean reductions of 1.73% for exenatide QW and 1.57% for liraglutide. Although not an unexpected finding, these data add to the literature because glycemic outcomes associated with these GLP-1RAs in patients with poorly controlled diabetes are limited overall and for insulin-naive patients.

These real-world outcomes differed from those observed in a head-to-head randomized clinical trial (RCT).9 First, HbA1c reductions were not as pronounced in this real-world study, possibly because of less than optimal medication adherence and treatment inertia. In addition, many patients in this study had used multiple diabetes medications, including insulin. These observations suggest that patients in this real-world study had progressed to diabetes and were possibly more difficult to treat than patients in the RCT.

In a head-to-head RCT, a modest but significantly greater reduction in HbA1c for liraglutide compared with exenatide QW was also identified (difference, 0.21%; 95% CI, 0.08%–0.33%). This difference was not observed in the present study or in other observational studies. A recent study by Saunders et al11 also observed a significant reduction in HbA1c with exenatide QW or liraglutide at 6 months but with no difference in adjusted HbA1c change (~0.64% [1.32%] versus –0.65% [1.31%]). A network meta-analysis of RCTs and observational studies also failed to identify a difference in glycemic control in effectiveness.13 This lack of agreement may reflect differences in real-world medication adherence as driven by dosing schedules. Although adherence data are limited, an observational cohort study by Johnston et al16 found that patients taking liraglutide, which is dosed daily, were 20% less likely to be adherent to therapy than exenatide QW patients (odds ratio, 0.80; P < 0.001).

A notable study finding was that the proportion of patients who initiated insulin treatment on the index date was higher with liraglutide (25.4%) than with exenatide QW (20.0%). Insulin treatment initiation on the index date could have resulted in a greater proportion of patients attaining HbA1c <7.0% and greater mean HbA1c reduction in the liraglutide group, assuming insulin was titrated to facilitate HbA1c reduction. However, this was not observed.

This study assessed HbA1c change in all patients using exenatide QW or liraglutide, including patients with HbA1c <7.0%, who may have started therapy primarily for weight reduction versus improvement in glycemic control. A post hoc descriptive analysis conducted in this group found a modest mean increase in HbA1c at 12-month follow-up of 0.3% (SDs, 1.1% with exenatide QW and 1.0% with liraglutide) from a mean (SD) baseline HbA1c of 6.3% (0.5%) and 6.4% (0.4%), respectively. Thus, including patients with HbA1c <7.0% may have slightly attenuated HbA1c outcome results.

There are several practice implications from the findings of this study. In patients with T2D treated in usual care settings, treatment with exenatide QW or liraglutide leads to meaningful reductions in HbA1c and weight, but the real-world effectiveness of these products does not differ. Thus, it may be appropriate to base treatment selection on other factors, such as dosing preference, adherence concerns, tolerability, and patient out-of-pocket costs. Furthermore, the pronounced response to either GLP-1RA in insulin-naive patients with HbA1c ≥9.0% suggests that exenatide QW or liraglutide may be a reasonable alternative to insulin. This approach may be appropriate when avoidance of hypoglycemia and/or weight gain is a therapeutic priority and is consistent with American Association of Clinical Endocrinologists’ guidelines.3

A strength of this study is in the use of a large population of patients with T2D from a national EMR database. Although not nationally representative, the study has good generalizability for patients with T2D predominantly treated in the primary care setting.
setting. In addition, our prespecified subgroup analyses enhance the application of findings to a usual care setting where clinicians may treat a variety of patients, including those who are insulin naive with inadequately controlled T2D.

This comparative effectiveness study provides valuable information to payers, clinicians, and patients to compare outcomes between commonly used GLP-1RAs in clinically and demographically diverse patients. This study also considers outcomes during a 1-year follow-up period versus 6-month outcomes, which is also a consideration in the usual care setting.

This study’s observational study design using EMR data is also associated with a number of limitations. First, data on key factors that influence diabetes outcomes are not systematically captured in EMR databases, including adherence to diet and exercise recommendations. Furthermore, the database used for this study includes information on medications prescribed but not on medications dispensed. Thus, it was not possible to control for medication adherence.

In addition, this study was not designed to assess outcomes of concomitant GLP-1RA and other diabetes medications; thus, we did not assess the effects of starting new classes of medications after the index data, which could bias results. In a post hoc analysis, we assessed outcomes in 457 patients who initiated insulin treatment at any time during the follow-up period because insulin was the class most commonly initiated after index date and generally associated with the greatest improvement in glycemic control. In this subgroup, the mean (SD) HbA1c change was −0.25% (1.7%); thus, we do not believe that postindex treatment initiation had an appreciable effect on outcomes.

Channeling bias is also possible because of the differences in approval dates of exenatide QW and liraglutide. More patients may have been prescribed liraglutide because of the longer time it has been available, resulting in more prescriber experience. In the present study, primary care practitioners prescribed liraglutide more frequently than endocrinologists, whereas the opposite was true for exenatide QW. It is likely that the endocrinology population had more difficult to control diabetes and/or received different levels of treatment and support with endocrinologist versus primary care physicians, which could also influence outcomes. However, baseline HbA1c and CCI were not different between the treatment groups despite the differences in practitioner specialty, and we used multivariate analysis to help control for this and other confounding bias.

A risk of measurement bias may have been introduced by allowing HbA1c values documented up to 30 days after the index date to be used as the baseline HbA1c, which could underestimate the true treatment effect. We therefore assessed HbA1c change in a post hoc analysis using a shortened post–index date HbA1c window of 7 days. In these analyses, results did not differ, suggesting that using the extended post–index date baseline HbA1c window did not affect outcomes.

Key reasons that exenatide QW and liraglutide patients were not included in the final cohort was inadequate duration of follow-up and missing HbA1c data to assess outcomes. This could introduce selection bias because included patients may differ from the larger population from which it was drawn. Although a full assessment of clinical differences is not possible because patients with limited duration of follow-up would likely have less complete records, we were able to compare basic demographic data between the population of newly treated exenatide QW and liraglutide patients with T2D (n = 19,637). We found that the study cohort is reasonably similar to the sampled group of patients. The mean (SD) age of the study cohort was slightly higher at 57.0 (10.9) years versus 55.4 (11.4) years in the sampled population, and the mean (SD) CCI in the study cohort was slightly lower at 0.9 (1.3) versus 1.2 (1.4) in the sampled population. Sex and race mix were fairly similar, with the study cohort being 46.9% male, 70.8% white, and 5.5% black versus 45.9% male, 68.8% white, and 9.0% black in the sampled population. Finally, since the initiation of this study, 2 additional GLP-1RAs were introduced to the US market: albiglutide and dulaglutide. Patients treated with these newer agents were not included because of a lack of follow-up data, and results from this study do not apply to the newer agents.

This real-world analysis of patients with T2D newly treated with exenatide QW or liraglutide identified no difference in glycemic control or weight outcomes at 1 year between these agents, although insulin was prescribed more frequently with liraglutide. Furthermore, more pronounced glycemic response was seen in insulin-naive patients with poorly controlled T2D. Although factors such as tolerability and dosing frequency differentiate these agents, either agent may be a reasonable alternative for the treatment of T2D.
particularly when improved glycemic response with
weight loss and low risk of hypoglycemia is desired.

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data acquisition, XY conducted data analysis with
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contributed to manuscript review and revision. The
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Mr Nguyen and Dr Cobden are employees of AstraZe-
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