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Treatment Outcomes and Tolerability Following Initiation of GLP-1 Receptor Agonists Among Type 2 Diabetes Patients in Primary Care Practices in Germany

Qing Qiao, MD, PhD[1], Kristina Johnsson, MD[1], Susan Grandy, MD[2], and Karel Kostev, DMSc, PhD, Pr[3]

Abstract

Background: The aim was to investigate real-world treatment outcomes and tolerability of GLP-1 receptor agonist (GLP-1RA) therapy in patients with type 2 diabetes in Germany.

Methods: Patients from 323 primary care practices who started any GLP-1RA therapy (89 Byetta, 108 Bydureon, 347 Victoza patients) between January 1, 2011, and December 31, 2013 (index date) were analyzed retrospectively (Disease Analyzer database, Germany). Changes from baseline in HbA1c, weight, and hypoglycemia were evaluated in 3 follow-up periods of 0-6, 7-12, and 13-18 months.

Results: A total of 544 diabetes patients (mean age: 57.9 years; men: 54%) were eligible for the study. Mean (SD) HbA1c (%) decreased from 8.3 (1.4) at baseline to 7.4 (1.2) in 6 months, 7.6 (1.3) in 7-12 months and 7.6 (1.4) in 13-18 months, respectively ($P < .001$ for all), while the proportion of patients with HbA1c <7% increased from 15% at baseline to 38%, 36% and 35% in the corresponding periods ($P < .0001$ for all). Multivariate-adjusted beta coefficients corresponding to changes in HbA1c (%) from baseline were –.52, –.44, and –.44, respectively, in the follow-up periods for baseline HbA1c (%) ($P < .0001$ for all). The prevalence of hypoglycemia at baseline was 0.7%; this did not change significantly after treatment.

Conclusions: In clinical practice, GLP-1RA treatment was associated with improved glycemic control without increased hypoglycemia for up to 18 months. The higher the baseline HbA1c, the greater the HbA1c reduction recorded.

Keywords
type 2 diabetes, GLP-1 receptor agonists, HbA1c, BMI

Introduction

Glucagon-like peptide 1 (GLP-1) is an incretin hormone secreted from gastrointestinal cells shortly after an ingested meal.[1,2] GLP-1 stimulates insulin secretion in a glucose-dependent manner, suppresses glucagon secretion, delays gastric emptying, and suppresses appetite.[1,2] Because of the decreased release of and response to incretins in patients with type 2 diabetes and the potential benefits of these mechanisms, the incretin axis is a target for pharmacologic therapy.[1,2] The clinical advantages of GLP-1 receptor agonists (GLP-1 RAs) compared to other diabetes drugs are significant improvements in glycemic control with a weight loss and a low risk of hypoglycemia.[3]

The glucose-lowering efficacy of GLP-1RAs has been shown by multiple randomized clinical trials, with HbA1c reductions up to 1.9% over time.[4-8] However, it has been known that GLP-1 RAs use is associated with the occurrence of transient gastrointestinal side effects, including nausea, vomiting or diarrhea.[9] Data on clinical outcomes and tolerability of GLP-1 RAs among type 2 diabetes patients treated in primary care practices in a real-world setting are rare.[10,11]

The aim of this study was to investigate real-world treatment outcomes and tolerability (HbA1c, BMI/weight, hypoglycemia) of available GLP-1 RA therapies in type 2 diabetes patients treated in primary care practices in Germany.

[1]AstraZeneca, Gothenburg, Sweden
[2]AstraZeneca, Gaithersburg, USA
[3]IMS Health, Frankfurt am Main, Germany

Corresponding Author:
Karel Kostev, DMSc, PhD, Pr, IMS Health, Darmstädter Landstraße 108, 60598 Frankfurt am Main, Germany.
Email: kkostev@de.imshealth.com

Methods

The Disease Analyzer database (IMS Health) assembles drug prescriptions, diagnoses, and basic medical and demographic data directly from the computerized medical records of a representative sample of 323 general practitioners and internal medical practices throughout Germany (a coverage of about 3%).[12] Patients with type 2 diabetes, who initiated therapy with either exenatide (89 Byetta and 108 Bydureon) or Liraglutide (347 Victoza) between January 1, 2011, and December 31, 2013 (index date), were followed up until March 31, 2014, with up to 18 months of follow-up. Data on prescriptions and comorbidities were available for all patients included in the current study, but HbA1c and weight data were not available for everyone. The actual numbers of patients with data on HbA1c and weight are provided in notes under each of the tables in the result section. The practice visit records were used to determine baseline demographic characteristics 6 months before index date (July 1, 2010, to December 31, 2010). The changes in HbA1c and BMI, and the changes in episodes of hypoglycemia and gastrointestinal adverse events from baseline were assessed in 0-6 months, 7-12 months, and 13-18 months postindex. Hypoglycemia events were identified based on diagnostic codes.

Other clinical measures included changes in number of glucose lowering, cardiovascular and lipid-lowering drugs before and after index date and the Charlson index, a weighted index that accounts for number and severity of morbidities considered a general marker of comorbidity; the higher the values the more the comorbidities a patient has.[13] The Charlson index was calculated before and after GLP-1RA initiation.

The data were analyzed using multiple methods. Differences in characteristics of patients before and after index date were assessed using paired *t*-tests or McNemar's tests. Two-sided tests were used and a P value <.05 was considered as statistically significant. Multivariate linear regressions were fitted (dependent variable: absolute difference in HbA1c [%] between baseline and post GLP-1RA therapy) with baseline HbA1c, age, sex, health insurance (private/statutory), diabetologist care, and macro- and microvascular comorbidity. Multivariable adjusted beta-coefficients were generated from the linear regression analysis. In addition, multivariate logistic regression models were also fitted (dependent variable: HbA1c <7.0%) with the same baseline variables, and odds ratios were estimated based on the logistic regression analysis. All analyses were carried out following the German good practice recommendations of secondary data analysis[14] using SAS 9.3 (SAS Institute, Cary, NC, USA).

Results

A total of 544 type 2 diabetes patients who initiated GLP-1 RAs therapy (n = 89 for Byetta, n = 108 for Bydureon, and n = 347 for Liraglutide) in the index period were included in the data analysis. The age ranged from 20 to 84 years, with a mean age of 57.9 years; 54.4% of the patients were men (Table 1). Among patients who had baseline HbA1c or weight measured, 85.8% had a baseline HbA1c ≥7.0%, and 80.0% had a baseline BMI ≥30 kg/m^2. Prevalence of obesity diagnosis based on diagnostic codes was 15.8%. About a quarter of the type 2 diabetes patients with GLP-1 RA therapy were treated by a diabetologist; 14.0% were privately insured. Hypertension and dyslipidemia were the most common baseline comorbidities followed by coronary heart disease, peripheral neuropathy and microvascular complications, yielding a mean baseline Charlson comorbidity score of 1.8. Because of the short observation time, there were no differences in the comorbidity scores before and after index date.

Table 1. Baseline Characteristics of Type 2 Diabetes Patients With Newly Prescribed GLP-1 Receptor Agonists in Primary Care Practices in Germany (Disease Analyzer).

Variables	Patients with GLP-1 receptor agonists
N	544
Age (years)	57.9 (10.6)
Male (%)	54.4
Private health insurance (%)	14.5
Diabetologist care (%)	24.5
HbA1c %[a]	8.3 (1.4)
BMI ≥ 30 kg/m^2 (%)[a]	80.0
Diagnosis of obesity (yes/no) (%)	15.8
Peripheral neuropathy (%)	18.2
Retinopathy (%)	4.4
Nephropathy (%)	9.9
Hypertension (%)	79.8
Hyperlipidemia (%)	58.3
Myocardial infarction (%)	2.9
Coronary heart disease (%)	20.0
Peripheral vascular disease (%)	7.9
Charlson Comorbidity Score	1.8 (1.1)

Data are means (SD) or proportions (%).
[a]HbA1c: n = 310, BMI: n = 154.

With initiation of GLP-1RA therapy, mean (SD) HbA1c (%) was decreased while the proportion of patients having HbA1c value <7% increased significantly from baseline in each of the follow-up periods (Table 2). Of the patients, 27% had HbA1c <7.0% in all 3 postindex periods from 0-6 months up to 13-18 months.

A significant reduction in BMI was observed in the 7-12 months post the GLP-RAs treatment (Table 2). Mean body weight tended to decrease from 0-6 months up to 13-18 months with a relative reduction of >3.0% in all posttreatment periods, but the decrease was not statistically significant (Table 2).

Prevalence of hypoglycemia was 0.7% at baseline with no significant changes posttreatment with GLP-1RA (Table 2).

Table 2. Changes From Baseline in Treatment Effectiveness, Tolerability, and Comedications After Initiation of GLP-1 Receptor Agonist Therapy Among Type 2 Diabetes Patients (n = 544) of Primary Care in Germany.

Variables	≤6 months before treatment, N = 544	0-6 months after treatment, N = 544	7-12 months after treatment, N = 544	13-18 months after treatment, N = 544
HbA1c (%)[a], mean (SD)	8.3 (1.4)	7.4 (1.2)*	7.6 (1.3)*	7.6 (1.4)*
HbA1c (%)[a], percentage				
<7.0	15.4	38.2*	35.5*	34.5*
<9	74.9	90.5	83.9	86.7
≥9	25.1	9.5	16.1	13.3
Body mass index (kg/m^2)[b]	37.0 (7.1)	36.1 (7.2)	36.4 (7.5)*	36.5 (8.4)
Weight (kg)[b]	106.3 (20.3)	103.9 (21.2)	105.2 (22.1)	104.3 (21.9)
Weight reduction from baseline (%)	NA	- 3.2 (5.1)	- 3.1 (4.8)	- 3.4 (5.7)
Diagnosed hypoglycemia (%)	0.7	0.2	0.0	1.1
Antidiabetic treatment (%)				
Biguanides	50.2	70.4*	68.4*	68.4*
Sulfonylureas	19.3	16.9	16.7	17.3
Alpha-glucosidase inhibitors	0.4	0.4	0.2	0.2
Glinides	3.5	2.9	2.8	2.8
Thiazolidinediones	5.1	2.0*	1.7*	1.7*
DPP-4 inhibitors (monotherapy)	14.7	3.5*	3.5*	2.8*
DPP-4 inhibitors (fixed combinations)	26.3	9.4*	8.6*	8.5*
Insulin	23.5	15.1*	18.6*	23.0
Other drug treatment (%)				
Antihypertensive drugs	67.5	71.7	71.1	72.8
Lipid-lowering drugs	35.3	37.7	37.1	37.9
Antidepressants	6.1	8.1	7.2	7.2
Antiepileptic drugs	2.2	3.1	3.3	4.0

Data are means (SD) or proportions (%).
[a]HbA1c: n = 310, 254, 304, and 313, respectively, at baseline, 0-6 months, 7-12 months, and 13-18 months after treatment.
[b]BMI/weight: n = 107, 80, 111, and 111, respectively, at baseline, 0-6 months, 7-12 months, and 13-18 months after treatment.
*$P < .001$ for changes from baseline.

Changes in the use of other therapies were observed. Biguanides were prescribed most frequently, followed by DPP-4 inhibitors, insulin and sulfonylureas in the preindex period (Table 2). After initiation of therapy with GLP-1RAs, biguanide prescriptions increased but DPP-4 inhibitor prescriptions decreased in all 3 follow-up periods. Insulin use decreased in the first year following the initiation of GLP-1RAs therapy but increased to baseline level at 18 months. Thiazolidinediones were rarely used at baseline, and their use decreased further after initiation of GLP-1RAs therapy. No significant changes from baseline were observed for sulfonylurea prescription. There were also no changes in comedications for diseases other than diabetes (Table 2).

Multiple linear regression analysis was performed to examine the association of baseline variables with the linear changes in HbA1c levels from baseline. Results of the multiple linear regression analyses (Table 3) showed baseline HbA1c (%) was strongly but inversely associated with HbA1c (%) changes in all posttreatment periods after adjusting for age, sex, health insurance, diabetologist care and comorbidity. This means that patients with higher baseline HbA1c had larger HbA1c reduction after initiating therapy with a GLP-1RA. Obesity diagnosis appeared to be inversely associated with the HbA1c (%) changes in all 3 postindex periods but the association did not reach statistical significance. Nephropathy was positively and peripheral vascular disease was inversely associated with the change in HbA1c (%) in only 1 of the 3 postindex periods (Table 3). Age and gender were not associated with the HbA1c (%) changes from baseline. Changes in glucose-lowering medications were also not related to a change in HbA1c (data not shown).

Logistic regression analysis was also used to assess the association of baseline variables with having the treatment goal of HbA1c<7.0% (vs ≥7.0%). Baseline HbA1c (%) level was negatively associated with achieving a treatment goal of HbA1c <7.0% in the postindex periods of 0-6 months, 7-12 months, and 13-18 months, respectively (Table 4), and was the only baseline factor significantly associated with glycemic control during all periods studied over 18 months. Age (negatively) and peripheral vascular disease (positively) were associated with having HbA1c of <7.0% only in the first 6 months postindex. Sex, private health insurance, diabetologist care, diagnosis of obesity, and nephropathy were not independently associated with optimal glycemic control in any of the time periods (Table 4).

Table 3. Multivariate-Adjusted Linear Regression Models for Absolute Difference in HbA1c (%) Between Baseline and Post-GLP-1 Receptor Agonists Therapy in Type 2 Diabetes Patients.

Baseline variables	0-6 months, ß coefficients, N = 237	*P* value	7-12 months, ß coefficients, N = 278	*P* value	13-18 months, ß coefficients, N = 286	*P* value
Age (per year)	–.0028	.7033	.0002	.9800	–.0001	.9951
Sex (males)	.1292	.3717	.1749	.2779	.1889	.2929
Private health insurance (yes/no)	–.4178	.0770	–.3594	.1714	–.4123	.1593
Diabetologist care (yes/no)	–.0355	.8523	–.1087	.6093	–.1903	.4225
Baseline HbA1c (%)	–.5258	<.0001	–.4350	<.0001	–.4418	<.0001
Obesity diagnosis (yes/no)	–.0635	.6500	–.0844	.5884	–.1307	.4525
Nephropathy (yes/no)	.3896	.0713	.5112	.0340	.3009	.2607
Peripheral vascular disease (yes/no)	–.7053	.0063	–.3756	.1884	–.2383	.4534

All models further adjusted for Charlson comorbidity score, coronary heart disease, myocardial infarction, stroke, retinopathy, peripheral neuropathy, hypertension, and hyperlipidemia.

Table 4. Multivariate-Adjusted Odds Ratios (95% Confidence Intervals) for Having HbA1c <7% After Initiating GLP-1 Receptor Agonists Therapy in Type 2 Diabetes Patients.

Baseline variable	0-6 months, n = 237	*P* value	7-12 months, n = 278	*P* value	13-18 months, n = 286	*P* value
Age (per year)	0.96 (0.93-0.99)	.0332	0.97 (0.94-1.04)	.0862	0.98 (0.94-1.12)	.1900
Sex (males)	0.67 (0.35-1.31)	.2457	0.76 (0.37-1.54)	.4385	0.90 (0.43-1.89)	.7899
Private health insurance (yes/no)	1.00 (0.33-3.06)	.9947	1.08 (0.33-3.53)	.8944	1.25 (0.37-4.25)	.7163
Diabetologist care (yes/no)	0.76 (0.31-1.86)	.5492	0.99 (0.39-2.53)	.9901	0.88 (0.33-2.56)	.8060
Baseline HbA1c (%)	0.46 (0.34-0.62)	<.0001	0.40 (0.28-0.57)	<.0001	0.37 (0.26-0.55)	<.0001
Obesity diagnosis (yes/no)	1.47 (0.76-2.83)	.2541	1.68 (0.83-3.37)	.1472	1.89 (0.90-3.96)	.0915
Nephropathy (yes/no)	0.84 (0.31-2.31)	.7417	0.52 (0.16-1.68)	.2766	0.86 (0.26-2.88)	.8070
Peripheral vascular disease (yes/no)	3.60 (1.04-12.46)	.0430	0.99 (0.26-3.83)	.9975	1.03 (0.24-4.43)	.9651

All models further adjusted for Charlson comorbidity score, coronary heart disease, myocardial infarction, stroke, retinopathy, peripheral neuropathy, hypertension, and hyperlipidemia.

Discussion

Few studies have focused on real-world characteristics associated with optimal HbA1c control in patients with GLP-1RA therapy in primary care. The present study indicates that initiation of GLP-1 RA therapy substantially improves glycemic control from baseline within 6 months after therapy initiation and the treatment effects remained for up to 18 months among patients with type 2 diabetes in primary care settings in Germany. There were no significant changes from baseline in occurrence of hypoglycemia and gastrointestinal adverse events among GLP-1 RA treated patients.

Efficacy of GLP-1RAs has been shown by randomized clinical trials,[5-8,15] with HbA1c reductions ranging from −0.5% to −1.9% within 16 to 52 weeks. But these randomized clinical studies may not reflect actual results in primary care practice, because the patient characteristics and care may be different. As an example, about 15% of the patients included in this study had a baseline HbA1c within 7.0%, these patients are usually not included in the clinical trials. They were prescribed with GLP-1RA probably due to their obesity status or other reasons not known. There is limited information on effectiveness and tolerability of patients treated with GLP-1RAs in a real-world primary care setting. A retrospective database study based on data collected in computerized primary care practices throughout the United Kingdom (The Health Information Network, THIN) showed that type 2 diabetes patients who initiated GLP-1 RA therapy had an HbA1c decrease of −0.6% at 12 months.[10] Another retrospective cohort study in the United Kingdom including 7133 primary care patients with a first prescription for GLP-1 RA (age: 58 years, HbA1c 9.2%, BMI 38.4 kg/m^2) revealed that 18% of the patients having dual-therapy with a GLP-1 RA achieved a −1% reduction in HbA1c at 6 months.[16] An Italian study consisting of 481 type 2 diabetes patients (baseline: mean age: 57 years, HbA1c 8.7%, BMI: 37 kg/m^2) from 6 outpatient units observed that a 35.9% of the patients had reached an HbA1c <7.0% after 12 months treatment with liraglutide.[11] Findings from these studies of primary care patients were consistent with the present investigation that GLP-1RA as add-on therapy could improve glycemic control among type 2 diabetes patients who had poor glycemic

control at baseline. Since antidiabetic medication has also changed significantly, the effects in the HbA1c are not only attributable to the GLP-1 RA but also to the comedications received.

In addition, a strong but inverse association between baseline HbA1c (%) and changes in HbA1c posttreatment observed in the current study indicates patients with severe hyperglycemia at baseline had greater HbA1c (%) reduction, which is consistent with previous work.[17] It was noted that most of the co-antidiabetic medications except for biguanide prescriptions have been reduced or remained unchanged after the initiation of GLP-1RA. Insulin prescriptions were significantly decreased in the first year of the follow-up.

Body weight reduction with GLP-1RAs has been confirmed in randomized clinical trials in overweight patients with or without diabetes (weighted mean difference, –2.9 kg; 95%CI: –3.6 to −2.2).[18] The mean weight reduction in patients with diabetes was −2.8 kg based on a meta-analysis of 18 published clinical trials of all GLP-RA products.[18] Reductions in weight and BMI from baseline were also observed in the present real-world study from 6 months up to 18 months posttreatment, but the results did not reach statistical significance except for the 7- to 12-month time period for BMI, when a significant reduction from baseline in BMI was observed. This might be partly due to the low statistical power of the study since only around 100 patients had weight or BMI measured at both baseline and follow-up. A diagnosis of obesity based on the diagnostic codes was available for all patients, but the prevalence of obesity (15.8%) defined by the codes has markedly been underestimated compared with the high prevalence of obesity (80%) defined based on the BMI measurement in the same patient population.

The mechanisms behind the associations of several of the studied characteristics with HbA1c reduction is not clear, particularly, where the variable reached statistical significance in only 1 time period. In the current study, age was a determinant of the HbA1c changes in the first 6 months after index date but not up to 18 months, which has also been found in a previous study.[11] The reason is not clear. The association of the changes in HbA1c after GLP-1RA treatment with nephropathy or peripheral vascular disease was observed in only 1 of the 3 postindex periods which might be a chance finding and needs to be further examined.

The frequency of hypoglycemia is also an important aspect to consider when determining risk to benefit profiles of diabetes therapies.[19] Preventing hypoglycemic events through medication choice and the early detection of patients at high risk for hypoglycemia are important aspects of clinical care.[19] The glucose-dependent action of GLP-1 RA entails a lower risk of hypoglycemia compared with basal insulin and sulfonylureas.[20] In the present study, a low prevalence of recorded hypoglycemia was found at baseline without significant change post index while on GLP-1 RA therapy. The low prevalence at baseline was most likely attributed to the fact that only severe hypoglycemic events were recorded.[21] It has been estimated that only 15% of hypoglycemic episodes in patients with type 2 diabetes are reported to a doctor.[19]

The present study is based on data of primary care records made by physicians for administration use. It thus has both strength and weakness. It is a real-world, representative database of primary care in Germany. Information on prescription is unbiased. But valid information regarding onset of diabetes was not provided; frequency of obesity diagnosis based on ICD codes by primary care physicians has been underestimated; measurements of HbA1c values were not standardized and were missing in some patients, and only a small proportion of patients had weight measured, limiting statistical power of the study. Moreover, documentation of hypoglycemia is most likely incomplete and gastrointestinal symptoms have also not been recorded systematically and could not be investigated. The present study includes patients with 18 months of follow-up. Treatment dropouts were excluded but no information is available about the therapy discontinuation in these cases. Dropouts due to lack of efficacy or due to side effects could impact the positive selection for efficacy. Due to the lack of data, economic analyses of the effect of GLP-1 analogues on diabetes outcomes were not included. Future studies should model the long-term cost-effectiveness of GLP-1 receptor agonists with respect to change in HbA1c and other outcomes and its effects on life expectancy. Modeling the long-term cost-effectiveness of GLP-1 RA on life expectancy is important because several trials have demonstrated the cardiovascular benefits of various glucose lowering agents. As an example, in the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) study, cardiovascular death and all-cause mortality were decreased significantly when empagliflozin was added to therapy instead of a placebo.[22] Renal endpoints were also reduced to a significant extent. Furthermore, the cardiovascular outcome study with liraglutide (LEADER) also demonstrated a significant reduction in the composite endpoint (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke).[22]

In conclusion, initiation of GLP-1 RA therapy in mostly obese type 2 diabetes patients with inadequate glycemic control was associated with a substantial long-term improvement in HbA1c in the primary care setting in Germany. Greater improvement was observed in patients with severe hyperglycemia. This improvement was not accompanied by an increase in hypoglycemia and gastrointestinal side effects.

Abbreviations

ATC, Anatomical Therapeutic Chemical Classification System; BMI, body mass index; GLP-1, glucagon-like peptide 1; GP, general practitioner; HbA1c, hemoglobin A1c; ICD, International Classification of Diseases; SD, standard deviation; T2DM, type 2 diabetes mellitus.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: QQ, KJ, and SG are employees of AstraZeneca. KK is an employee of IMS Health with no conflict of interest.

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