Comparison of Characteristics Between Chinese Patients Taking Glucagon-like Peptide 1 Receptor Agonists and Insulin: A Cross-sectional Database Analysis

Ke Wang, PhD[1]; Yun Chen, PhD[1]; Alena Strizek, MS[2]; Kristina Boye, PhD[3]; Liqun Gu, MD[1]; Yanjun Liu, MS[4]; and Shuli Qu, MPH[4]

[1]Lilly Suzhou Pharmaceutical Company, Ltd., Shanghai, China; [2]Eli Lilly and Company, Sydney, Australia; [3]Eli Lilly and Company, Indianapolis, IN, USA; and [4]Real World Insights, IQVIA, Shanghai, China

ABSTRACT

Purpose: In China, although insulin has been prescribed for decades, glucagon-like peptide 1 receptor agonists (GLP-1-RAs) have been available as an injectable treatment for patients with type 2 diabetes mellitus (T2DM) since 2009. GLP-1 RAs are listed as second-line treatment in the 2017 Chinese Guideline for patients with T2DM in whom prior oral antidiabetic therapy has failed. This study compares the baseline characteristics of Chinese patients with T2DM taking different prescriptions of first injectable therapy (GLP-1-RA or insulin).

Methods: The IQVIA Patient Diary Study database, which captures data from a patient medical record–based physician online survey, was the data source used in this study. Cross-sectional patient data were collected from hospitals in 15 major Chinese cities from June 1, 2016, to June 30, 2018. Adults with T2DM commencing either GLP-1-RA or insulin use as their first injectable antidiabetic therapy were included. Baseline demographic and clinical characteristics were compared between the GLP-1-RA and insulin treatment groups, using *t* tests and χ^2 or Fisher exact tests.

Findings: Overall, 563 patients using GLP-1-RAs and 2387 using insulin were identified. In general, patients using GLP-1-RA were younger (mean [SD], 49.6 [10.8] years vs 59.3 [10.9] years), had lower mean (SD) glycosylated hemoglobin levels (8.5% [1.2%] vs 9.6 [1.7%]), had lower mean (SD) fasting plasma glucose levels (9.0 [1.9] mmol/L vs 10.8 [2.6] mmol/L), higher mean (SD) body mass indexes (29.4 [3.9] kg/m^2 vs 24.6 [3.1] kg/m^2), had higher comorbidity of obesity (75% vs 15%), had a higher occurrence of hyperlipidemia (63% vs 44%), and had lower occurrence of neuropathy (13% vs 34%) when compared with those using insulin ($P < 0.0001$ for all). The results of multivariate logistic regression model indicate that when controlling other variables in the multivariate logistic regression model, a higher fasting plasma glucose level and a longer diagnosis duration are associated with higher odds of insulin therapy commencement, but higher body mass index and some comorbidities, such as obesity and hyperlipidemia, are associated with higher odds of being a GLP-1-RA user.

Implications: Significant differences were identified between selected baseline characteristics of patients initiating GLP-1-RA and insulin therapy, suggesting that these medicines are more likely to be prescribed to different types of patients with T2DM in China. These findings may help to inform Chinese physicians regarding the characteristics of those patients with T2DM who are initiating treatment with a GLP-1-RA or insulin. Because the Patient Diary Study data were collected from hospitals in 15 major cities in China, one noteworthy limitation is that the results may not represent the overall treatment pattern in rural areas of China. (*Clin Ther*. 2019;41:2057–2065)

Keywords: cross-sectional study, GLP-1-RA, insulin, patient characteristics, type 2 diabetes mellitus.

Accepted for publication August 1, 2019
https://doi.org/10.1016/j.clinthera.2019.08.003
0149-2918/$ - see front matter

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic and progressive disease characterized by a deterioration of blood glucose control over time, which is associated with 2 core dysfunctions, progressive β-cell dysfunction against a background of obesity-related insulin resistance, making it difficult for patients to maintain glycemic control.[1] Currently, 425 million people have diabetes mellitus worldwide, with T2DM representing approximately 90% of cases.[2] In 2017, an estimated 114.4 million people in China had T2DM, which accounted for approximately a quarter of the global diabetes population, and this number is expected to increase to 119.8 million by 2045.[2]

The goal of hypoglycemic therapy is to achieve and maintain glycemic control. Current American Diabetes Association and European Association for the Study of Diabetes treatment guidelines[3] advise a patient-centered management approach of lifestyle management, diet, weight control diabetes education, and, if target glycosylated hemoglobin (HbA_{1c}) levels are not reached, the introduction of metformin then other glucose-lowering agents, often followed by insulin treatment. Although many treatment options exist, achieving adequate glycemic control remains challenging,[4] and the introduction of newer agents that can effectively lower blood glucose and cause no weight gain or hypoglycemia have the potential to improve health outcomes of patients with T2DM.

Glucagon-like peptide 1 receptor agonists (GLP-1-RAs) mimic, at supraphysiologic levels, the action of endogenous GLP-1 in stimulating glucose-dependent insulin secretion and by suppressing glucagon secretion. Gastric emptying is delayed, especially in the early weeks of therapy. These actions and perhaps a direct or indirect hypothalamic action result in appetite or satiety changes and thus loss of weight.[5]

In China, although insulin has been prescribed for decades, GLP-1-RAs have been available as an injectable therapy for patients with T2DM since 2009 (including exenatide, liraglutide, lixisenatide, and benaglutide). In the latest Chinese T2DM guideline, GLP-1-RAs are recommended to be added to treatment for patients who did not achieve the HbA_{1c} target as a second-line therapy and can be considered as first injectable therapy option alongside insulin.[6] Some of the GLP-1-RAs are now reimbursed at the national or provincial level in China.

Several published studies[7–9] have investigated the current status and influence factors of oral antidiabetes drug (OAD) therapy in Chinese patients with T2DM. However, there are no known published data on the clinical and sociodemographic profile of patients initiating treatment with GLP-1 in China. A study by Yu et al[10] that used an electronic health record database to describe and identify clinical and demographic characteristics associated with the choice of first injectable therapy in United States suggested that GLP-1-RAs and basal insulin are prescribed to different types of patients with T2DM. Hence, this study aims to describe the characteristics of patients who commence GLP-1-RA therapy in China for the treatment of T2DM and explores whether these characteristics differ from patients prescribed basal insulin.

METHODS

Data Source

This observational, retrospective database study used data extracted from the Chinese IQVIA Patient Diary Study (PDS) database. The PDS database includes data on inpatients and outpatients with diabetes visiting the participating hospitals. The database has collected deidentified patient data directly from hospital physicians in the form of a monthly basis questionnaire since 2009. The questionnaire consists of 18 multiple-choice and gap-filling questions, including patient profile (demographic characteristics), physician characteristics, clinical profile (diagnosis and prescription data), physician preference data, and reasons for injectable initiation. Thus, the data can be used to understand the evolution of prescription behaviors to define the different treatment patterns and market trends. Representative samples of physicians from endocrinology departments are randomly recruited. Physicians are selected if they treated patients with diabetes and recorded prescriptions for each patient. Every month, the physicians reported their latest patient cases to the PDS database by filling out the questionnaire. The cross-sectional data set used in this study was collected from 300 hospitals in 15 major cities throughout different areas of China (Beijing, Shanghai, Guangzhou, Hangzhou, Nanjing, Chongqing, Shenyang, Tianjin, Chengdu, Wuhan, Xi'an, Jinan, Qingdao, Shenzhen, and Shijiazhuang) from June 1, 2016 to June 30, 2018.

The PDS database classifies prescription data into 3 types: naïve, change, and renewal. A naïve prescription refers to the first recorded prescription in the database. Prescriptions after patient treatment initiation are defined as change (where a prescription with drug change or dosage change occurred) or renewal (where the prescription remained unchanged). The PDS database collects historic and current prescription information for the patients with change and renewal prescriptions. For patients with naïve prescriptions, only current prescription information is available.

Collected baseline characteristics include age, sex, body mass index (BMI), diagnosis duration, most recent HbA_{1c} level, FPG, 2-hour postprandial glucose values, hospital tier, city tier, physician level, and current comorbidities.

Patient Selection

Study participants were adults with T2DM who had initiated GLP-1-RA or insulin therapy from June 1, 2016, to June 30, 2018. Patients were defined as GLP-1-RA users or insulin users. Among the users, patients were categorized into 2 cohorts according to the injectable treatment they initiated. Cohort 1 included Chinese, insulin-naive patients with T2DM who previously used OADs and initiated GLP-1 RA therapy within the study period. Cohort 2 included Chinese patients with T2DM who previously used OADs and initiated insulin therapy but did not receive GLP-1-RA therapy within the study period. To identify the drug therapy initiators, we excluded patients with a diagnosis of type 1 diabetes mellitus and those younger than 18 years. Then, we assumed that once patients start injectable hypoglycemic therapy, they would continue to use injectable drugs afterward and were not likely to switch back to OADs only in the later treatment. On the basis of this assumption, to include the patients who commenced GLP-1-RA or insulin use as their first injectable antidiabetic therapy within that period, we targeted the patients who used only OADs in their previous prescription and received GLP-1-RA or insulin therapy in current prescription. Hence, we excluded patient in the renewal and naïve groups. Next, we excluded patient who had previously received GLP-1-RA or insulin therapies. For the GLP-1-RA cohort, we also excluded patients currently using insulins.

Statistical Analysis

Baseline demographic and clinical characteristics were summarized by using numbers (percentages) for categorical variables and means (SDs) for continuous variables. The comparison between the GLP-1-RA and insulin treatment groups was performed using a 2-sample t test for continuous variables and the χ^2 test or Fisher exact test for categorical variables. A multivariate logistic regression was conducted to compare patient baseline and clinical characteristics before treatment initiation in patients beginning GLP-1-RA and insulin treatment. Odds ratios (ORs), 95% CIs, and P values are presented. An OR >1 indicates that the exposure is associated with higher odds of being GLP-1-RA user. A 2-sided significance level $P < 0.05$ was used. These analyses were conducted in R, version 3.4.3.[11]

RESULTS

From June 1, 2016, to June 30, 2018, there were 3689 GLP-1-RA users and 22,896 insulin users in the PDS database. Among the users, a total of 2950 patients met the study inclusion criteria, of whom 563 were GLP-1-RA users and 2387 were insulin users (Figure 1).

Baseline Characteristics and Univariate Comparisons

The analyses detected some differences between the 2 cohorts in terms of demographic characteristics, baseline characteristics, and comorbidities (Table I). In general, GLP-1-RA users were younger (mean [SD], 49.6 [10.8] years vs 59.3 [10.9] years) and reported lower mean (SD) HbA_{1c} values (8.5% [1.2%] vs 9.6% [1.7%]), lower fasting plasma mean (SD) glucose measurements (9.0 [1.9] mmol/L vs 10.8 [2.6] mmol/L), and higher BMIs (29.4 [3.9] kg/m^2 vs 24.6 [3.1] kg/m^2).

With regard to comorbidities, GLP-1-RA users reported higher rates of obesity (75% vs 15%) and hyperlipidemia (63% vs 44%) and lower rates of neuropathy (13% vs 34%), hypertension (49% vs 55%), retinopathy (6% vs 23%), peripheral arteriopathy disease (5% vs 11%), nephropathy (5% vs 19%), cerebral ischemia (2% vs 13%), coronary disease (2% vs 8%), and diabetic foot ulcers (0% vs 3%) than insulin users ($P < 0.05$ for all) (Table II).

For both cohorts, the most common reason for patients switching to injectable therapy was that

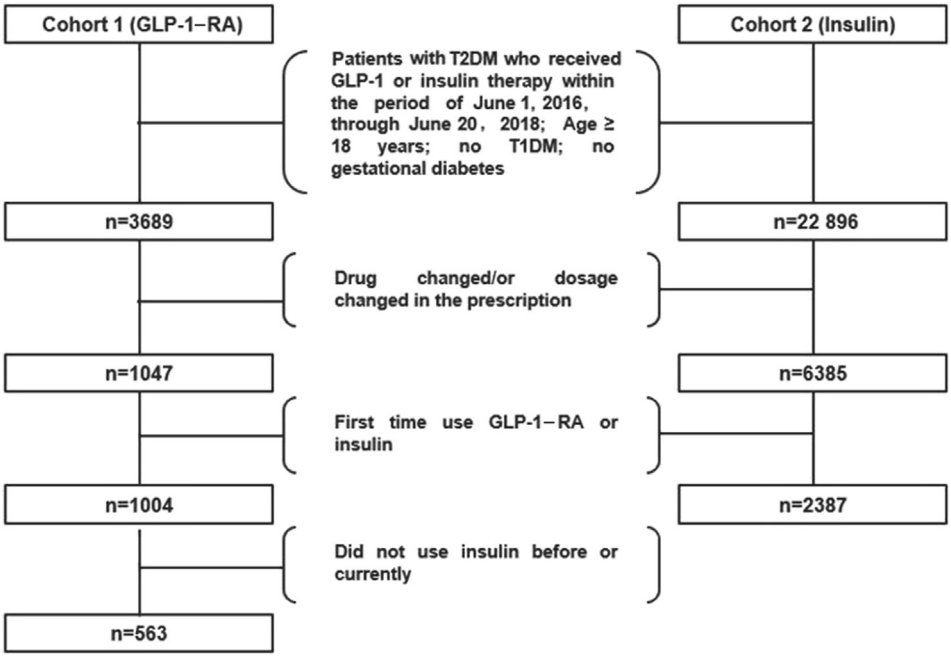

Figure 1. Patient selection flow chart. GLP-1-RA = glucagon-like peptide 1 receptor agonist; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

previous OAD therapy could not control the level of postprandial glucose. Forty-nine percent of GLP-1-RA users reported weight gain as a reason for treatment change compared with 5% of insulin users (Figure 2).

Multivariate Comparisons

Patients with complete records in demographic characteristics and comorbidity variables (131 GLP-1-RA users and 173 insulin users) were used to construct the multivariate logistic regression model. Results indicate that when controlling for other variables in the multivariate logistic regression model, patients reporting a higher fasting plasma glucose level (OR, 0.73; 95% CI, 0.61−0.87) and longer diagnosis duration (OR, 0.9; 95% CI, 0.84−0.95) were more likely to be prescribed insulin therapy, whereas those patients who reported higher BMI (OR, 1.40; 95% CI, 1.28−1.53), obesity (OR, 8.25; 95% CI, 5.06−13.45), and hyperlipidemia (OR, 1.65; 95% CI, 1.04−2.63) were more likely to be prescribed GLP-1-RA therapy (Figure 3).

DISCUSSION

GLP-1-RA and insulin therapies are recommended as the second-line medication after OAD failure in the current 2017 Chinese T2DM treatment guideline.[6] Despite its effectiveness in lowering glycemic levels, insulin may cause weight gain and hypoglycemia. However, GLP-1-RA–based therapies stimulate insulin secretion in a glucose-dependent manner and reduce glucagon secretion only during hyperglycemia. GLP-1-RAs also slow gastric emptying and reduce appetite.[12] Several randomized clinical trials have found that GLP-1-RAs and insulin can achieve similar improvements in overall glycemic control in patients with T2DM, and GLP-1 RA can significantly reduce weight, accompanied by less risk of hypoglycemia.[13–16]

This study found that significant differences were identified between the selected baseline characteristics of Chinese patients with T2DM initiating GLP-1-RA and insulin injectable therapy contained within the PDS database. Overall, results indicate that patients who were older, had a longer diagnosis duration, had

Table I. Demographic and baseline characteristics of the GLP-1-RA versus insulin cohorts.*

Characteristic	GLP-1-RA Cohort (n = 563)	Insulin Cohort (n = 2387)	OR (95% CI)	*P*
Age, mean (SD), y	49.6 (10.8)	59.3 (10.9)	—	<0.0001†
Age group, y				
18-49	259 (46)	399 (17)	—	
50-59	191 (34)	774 (32)	0.38 (0.3—0.47)	<0.0001
≥60	113 (20)	1212 (51)	0.14 (0.11—0.18)	<0.0001
Sex				
Female	230 (41)	1100 (46)	—	
Male	333 (59)	1287 (54)	1.24 (1.03—1.49)	0.0249
BMI, mean (SD), kg/m^2	29.4 (3.9)	24.6 (3.1)	—	<0.0001†
BMI group				
Underweight and normal (BMI ≤24.9 kg/m^2)	38 (8)	903 (53)	—	
Overweight (BMI 25.0—29.9 kg/m^2)	247 (53)	754 (44)	7.78 (5.46—11.1)	<0.0001
Obesity (BMI ≥30.0 kg/m^2)	178 (38)	47 (3)	90 (57—142.1)	<0.0001
Inpatients or outpatient				
Outpatient	346 (61)	840 (35)	—	
Inpatient	217 (39)	1547 (65)	0.34 (0.28—0.41)	<0.0001
Diagnosis duration, y	<0.0001†			
<1	115 (25)	175 (10)	—	
1-≤3	149 (32)	305 (17)	0.74 (0.55—1.01)	0.0575
<3-≤5	89 (19)	241 (14)	0.56 (0.4—0.79)	0.000804
<5-≤10	87 (19)	691 (39)	0.19 (0.14—0.26)	<0.0001
>10	27 (6)	355 (20)	0.12 (0.07—0.18)	<0.0001
Last HbA_{1c} value, mean (SD), %	8.5 (1.2)	9.6 (1.7)		<0.0001†
Last HbA_{1c} value				
<7%	22 (5)	14 (1)	—	
7%-<9%	311 (70)	332 (35)	0.6 (0.3—1.19)	0.137
≥9%	111 (25)	592 (63)	0.12 (0.06—0.24)	<0.0001
Last FPG value, mean (SD), mmol/L	9 (1.9)	10.8 (2.6)		<0.0001†
Last FPG value, mmol/L				
<6.1	18 (4)	26 (2)	—	
6.1-<7.0	29 (6)	31 (2)	1.35 (0.62—2.96)	0.455
≥7.0	450 (91)	1388 (96)	0.47 (0.25—0.86)	0.0128
Last 2-hour PPG value, mean (SD), mmol/L	13.5 (3.2)	15.9 (4.2)		<0.0001†
Last 2-hour PPG value, mmol/L				
<7.8	11 (2)	13 (1)	—	
7.8-<11.1	92 (19)	139 (10)	0.78 (0.34—1.82)	0.569
≥11.1	384 (79)	1242 (89)	0.37 (0.16—0.82)	0.0114
Hospital class‡				
Tier 2	80 (15)	530 (23)	—	

(*continued on next page*)

Table I. (*Continued*)

Characteristic	GLP-1-RA Cohort (n = 563)	Insulin Cohort (n = 2387)	OR (95% CI)	*P*
Tier 3	467 (85)	1778 (77)	1.74 (1.35–2.25)	<0.0001
Physician's position[§]				
Not chief	315 (56)	1375 (58)	–	
Chief	247 (44)	994 (42)	1.08 (0.9–1.31)	0.390
City class[‖]				
Not tier 1	386 (69)	1764 (74)	–	
Tier 1	173 (31)	608 (26)	1.3 (1.06–1.59)	0.011

BMI = body mass index; FPG = fasting plasma glucose; GLP-1-RA = glucagon-like peptide 1 receptor agonist; HbA_{1c} = glycosylated hemoglobin; PPG = postprandial plasma glucose; OR = odds ratio.
* Data are presented as number (percentage) of patients unless otherwise indicated.
† *t* test.
‡ Tier 3 hospital: the top tier general hospital in China, with >500 beds; tier 2 hospital: the second tier general hospital in China, with >100 beds.
§ Chief physician: physicians at associate director level and above; nonchief physician: physicians at levels lower than associate director.
‖ Tier 1 city: Beijing, Shanghai, Guangzhou, Shenzhen, Chengdu, Hangzhou, Ningbo, Qingdao, Shenyang, Tianjin, Wuhan, Xi'an, Chongqing, and Nanjing; not tier 1: Ji'nan and Shijiazhuang.

Table II. Current comorbidities, complications, and risk factors.

Variable	GLP-1-RA Cohort (n = 563)	Insulin Cohort (n = 2387)	OR (95% CI)	*P*
Obesity	422 (75)	365 (15)	16.58 (13.29–20.68)	<0.0001
Hyperlipidemia	355 (63)	1050 (44)	2.17 (1.8–2.63)	<0.0001
Hypertension	277 (49)	1309 (55)	0.80 (0.66–0.96)	0.0158
Family history of diabetes	156 (28)	687 (29)	0.95 (0.77–1.16)	0.612
Neuropathy	73 (13)	812 (34)	0.29 (0.22–0.37)	<0.0001
Gout	48 (9)	200 (8)	1.02 (0.73–1.42)	0.910
Retinopathy	36 (6)	548 (23)	0.23 (0.16–0.33)	<0.0001
Peripheral arteriopathy (peripheral artery disease)	26 (5)	264 (11)	0.39 (0.26–0.59)	<0.0001
Nephropathy	28 (5)	456 (19)	0.22 (0.15–0.33)	<0.0001
Cerebral ischemia (transient ischemic attack)	13 (2)	319 (13)	0.15 (0.09–0.27)	<0.0001
Proven coronary disease	11 (2)	186 (8)	0.24 (0.13–0.44)	<0.0001
Pancreatic disorder	1 (0)	7 (0)	0.61 (0.01–4.72)	>0.99*
Diabetic foot ulcers	0 (0)	66 (3)	0.00 (0.00–0.24)	<0.0001*
Other	3 (1)	118 (5)	0.1 (0.02–0.31)	<0.0001*
No risk factor[†]	24 (4)	129 (5)	0.78 (0.5–1.22)	0.272

GLP-1-RA = glucagon-like peptide 1 receptor agonist; OR = odds ratio.
* Fisher exact test.
† No risk factor was found for the patients.

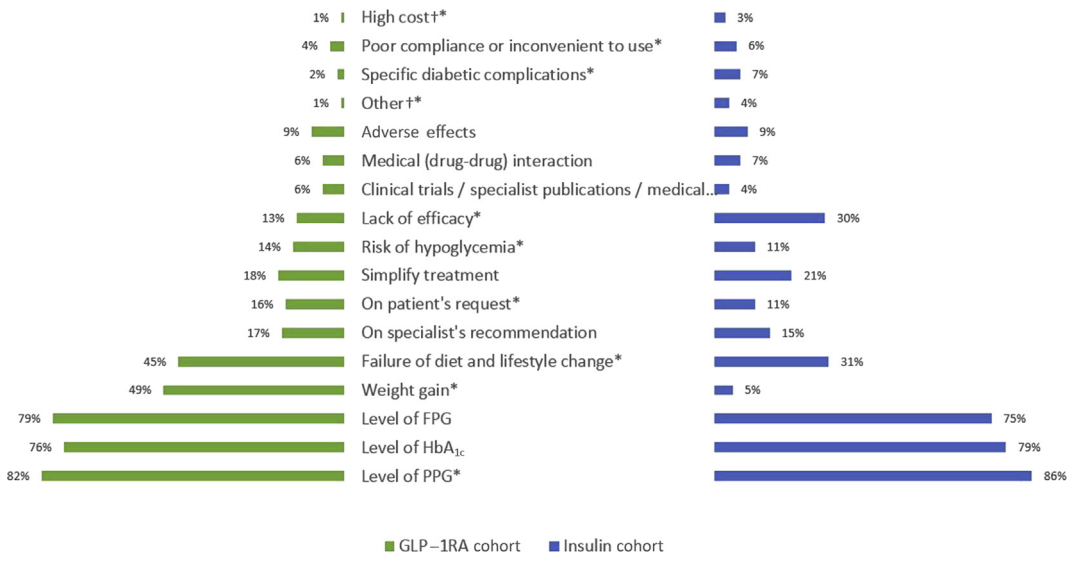

Figure 2. Reasons for change to current treatment. FPG = fasting plasma glucose; GLP-1-RA = glucagon-like peptide 1 receptor agonist; HbA_{1c} = glycosylated hemoglobin; PPG = postprandial plasma glucose. *Significant at the $P < 0.05$ level. †Fisher exact test.

higher HbA_{1c} values, and had comorbidities were more likely to be prescribed insulin therapy. These findings are consistent with results reported in previous US and European retrospective real-world studies.

Obesity and weight control are important considerations in the treatment of T2DM. Besides high glucose-lowering efficacy, evidence suggests that all GLP-1-RAs reduce weight. The reduction ranges from approximately 1.5 to 6.0 kg during approximately 30 weeks of therapy.[3] In our study, patients with a higher BMI were more likely to use GLP-1-RAs, with nearly half reporting that they commenced GLP-1-RA therapy because of the poor weight control of the previous treatment. Results suggest that there is increasing consideration of GLP-1-RA treatment for individuals with obesity and T2DM.

During the PDS data collection, the guidelines for management of T2DM in China were updated from the 2013 version to the 2017 version. Although the old and latest versions recommended GLP-1 or insulin for the first injectable therapy, we found that GLP-1-RA users are in a less severe disease state and higher BMI category compared with insulin users. In addition, other factors may influence the prescription of first injectable agents, such as drug cost, formulary restrictions, ease of use, and reimbursement. A previous study[17] suggested that the insurance coverage and formulary restrictions often factor into which GLP-1-RA is initially prescribed to patients. In a patient and physician survey, >80% of patients and physicians agreed on the importance of cost and copayment for adherence.[18] In addition, frequency of administration is another hurdle for patients to choose injectable therapy. Simpler dosing regimens appear to result in a higher adherence rate,[19] which may affect the choice of injectable therapy. With the recent broadened access and reimbursement of GLP-1-RAs in China, the characteristics and treatment patterns of Chinese patients with T2DM may change accordingly.

In this study, several limitations are acknowledged. The PDS data were collected from hospitals in 15 major cities in China, which may not represent the overall treatment pattern for patients in rural areas of China. Thus, results may not be generalizable to the overall Chinese population. In addition, data analyzed in this study were derived from a cross-sectional data set. Therefore, it was not possible to determine whether patients using GLP-1-RAs or insulin were using the medications for the first time or recommencing therapy. To address this, we assumed

Variable	Odds Ratio	(95% CI)
Baseline Characteristics		
Age	0.99	(0.97– 1.01)
Sex	0.95	(0.61– 1.47)
HbA_{1c}	0.91	(0.75–1.1)
FPG	0.73*	(0.61– 0.87)
2-Hour PPG	0.92	(0.84– 1.02)
Hospital class (level 3 vs level 2)	1.11	(0.6– 2.06)
Physician position (chief vs nonchief)	0.87	(0.55– 1.37)
BMI	1.40*	(1.28– 1.53)
City tier (tier 1 vs non–tier 1)	0.60	(0.35– 1.03)
Diagnosis duration	0.90*	(0.84– 0.95)
Comorbidities, complications, and risk factors		
Obesity	8.25*	(5.06– 13.45)
Hyperlipidemia	1.65*	(1.04– 2.63)
Neuropathy	0.86	(0.48– 1.54)
Retinopathy	0.65	(0.33– 1.27)
Peripheral ateriopathy (PAD)	1.44	(0.59– 3.49)
Nephropathy	0.56	(0.27– 1.16)
Cerebral ischemia (TIA)	0.55	(0.23– 1.32)
Proven coronary disease	1.19	(0.43– 3.28)
Hypertension	0.66	(0.4– 1.07)

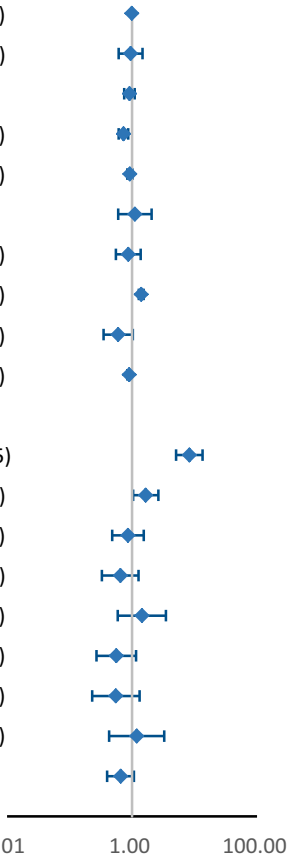

Figure 3. Multivariate regression for predictors of being glucagon-like peptide 1 receptor agonist (GLP-1-RA) users. BMI = body mass index; FPG = fasting plasma glucose; GLP-1-RA = glucagon-like peptide 1 receptor agonist; HbA_{1c} = glycosylated hemoglobin; PPG = postprandial plasma glucose; OR = odds ratio. *Significant at the $P < 0.05$ level.

that patients would not reuse OAD therapy alone once they had initiated injectable treatment, and the study population was restricted to patients whose prescription type had changed and whose prior prescription was for OADs.

CONCLUSION

This study identified differences between the baseline characteristics of patients initiating GLP-1-RA and insulin therapy who were included in the PDS database, suggesting that these medicines are prescribed to different types of patients with T2DM in China. In general, patients who had higher BMIs and rates of hyperlipidemia commenced use of GLP-1-RAs as their first injectable therapy. Conversely, patients with higher glycemic levels, longer disease duration, and comorbidities received insulin. These findings may help to inform physicians regarding the characteristics of those patients with T2DM who are beginning GLP-1-RA or insulin therapy.

FUNDING SOURCES

Funding for this study was provided to IQVIA by Lilly Suzhou Pharmaceutical Company Ltd, China.

ACKNOWLEDGMENTS

K. Wang, Y. Liu, and S. Qu participated in the study design. Y. Liu and S. Qu analyzed the data. K. Wang, Y. Liu, and S. Qu interpreted the results. All authors critically reviewed the manuscript. The authors were fully responsible for all content and editorial decisions.

DISCLOSURES

Lilly and IQVIA collaborated on study design, interpretation of results, and critical review of the manuscript. K. Wang, Y. Chen, A. Strizek, K. Boye, and L. Gu are all employees of Lilly. Y. Liu and S. Qu are employees of IQVIA. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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Address correspondence to: Shuli Qu, MPH, Real World Insights, IQVIA, Shanghai, China. E-mail: shuli.qu1@iqvia.com