Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

Real-World Utilization and Effectiveness of Glucagon-Like Peptide-1 Receptor Agonists Dosed Weekly and Daily in Patients with Type 2 Diabetes Mellitus: Results from Retrospective Electronic Medical Records in China

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Aim: This study aimed to conduct a retrospective observational study in China to investigate the real-world utilization of glucagon-like peptide-1 receptor (GLP-1RA) in China.

Methods: Type 2 diabetes mellitus (T2DM) patients were retrieved from the electronic medical records of 18 hospitals from 2016 to 2020. A descriptive analysis detailed patient characteristics and clinical outcomes. Multivariate logistic regression analysed the factors associated with daily and weekly GLP-1RA.

Results: Fifteen thousand one hundred and seventy-six individuals were included. At the 6-month follow-up, the overall estimated mean change from baseline in HbA1c was −1.26±1.91% ($p < 0.001$), the "Weekly GLP-1RA" group was −1.58±2.03% ($p < 0.001$), and the "Daily GLP-1RA" group was −1.25±1.90% ($p < 0.001$). At the 12-month follow-up, the overall estimated mean change from baseline in HbA1c was −0.95±1.80% ($p < 0.001$), the "Weekly GLP-1RA" group was −1.05±1.93% ($p < 0.001$), and the "Daily GLP-1RA" group was −0.95±1.80% ($p < 0.001$). At 6 months following GLP-1RA initiation, there were statistically significant improvements in the mean TC, LDL-C, and TG at 6 months or 12 months separately following GLP-1RA initiation. Statistically significant improvements were observed in the mean HDL-C after 6 months. Compared with the baseline (11.92%), the proportion of patients who had an incidence of all hypoglycemia was lower at the 6-month follow-up (9.73%). Patients with dyslipidemia were more likely to use weekly GLP-1RA (OR =1.61, 95% CI: 1.27–2.06, $p < 0.001$).

Conclusion: In China, weekly GLP-1RA demonstrated better effectiveness compared to the daily GLP-1RA. The results confirmed the efficacy of GLP-1RA in clinical trials.

Keywords: type 2 diabetes mellitus, glucagon-like peptide-1 receptor agonist, GLP-1RA, retrospective, China, electronic medical record, real-world

Introduction

Type 2 diabetes mellitus (T2DM) is a cardio-renal metabolic illness characterized by chronically increased blood glucose levels.[1] T2DM accounted for 90% of 537 million adult diabetes cases globally in 2021.[2] A total of 127 million T2DM adult patients are in China.[2] Cardiovascular disease (CVD) is the leading cause of mortality among patients with T2DM,[3] accounting for nearly half the deaths of T2DM patients in China.[4,5] Furthermore, cardiovascular risk factors, including

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hyperglycaemia, hypertension, and dyslipidaemia, are prevalent among Chinese T2DM patients[6] and may continue to place a significant burden on public health.[7,8]

Glucagon-like peptide-1 receptor agonists (GLP-1RA), as a class of anti-diabetes drugs, have demonstrated effectiveness in reducing glycated haemoglobin A_{1c} (HbA_{1c}), weight loss, and the risk of hypoglycemia and cardiovascular diseases.[9] The mechanisms of GLP-RA include increasing hypoglycemia-induced insulin secretion, inhibiting glucagon secretion at hyper or euglycemia, slowing stomach emptying to avoid significant postmeal glycaemic increases, and decreasing caloric intake and body weight.[9,10] GLP-1RA were recommended for T2DM therapy by the American Diabetes Association, the Chinese Diabetes Society, the International Diabetes Federation, the American Association of Clinical Endocrinologists, and the National Institute of Health and Care Excellence.[11–15]

According to their different half-lives, GLP-1RA can be classified into weekly injections (once per week) and daily injections (once, twice, and three times per day). At present, eight GLP-1RA have been launched in China for the treatment of T2DM, of which semaglutide, dulaglutide, polyethylene glycol loxenatide, and exenatide extended-release are administered weekly, and injections of liraglutide, lixisenatide, benaglutide, and exenatide are given daily. Multiple clinical trials have demonstrated the significant effectiveness of GLP-1RA in patients with T2DM.[16–20] However, limited evidence from real-world clinical data exists to evaluate the use of different GLP-1RA,[21] especially in different dosing forms.

Therefore, this study aimed to conduct a retrospective observational study in China to investigate the real-world utilization of GLP-1RA, analyse their real-world effectiveness, and explore the factors affecting daily and weekly GLP-1RA in China.

Methods

Study Design and Data Source

This study utilized a retrospective research design. The data for this study was obtained from the Tianjin Healthcare Database Platform, which is maintained by Inspur (https://www.inspur.com/lcjtww/jkyldsj/index.html). This database includes clinical data from hospitals in Tianjin City, with sensitive and identifiable information removed to protect privacy. Known for its high data quality, this database is highly respected for researching diabetes in China. We obtained approval from the Tianjin Healthcare Database Platform to access and report anonymized data through a formal application.

Retrospective electronic medical records from 18 tier-II and tier-III hospitals in Tianjin were used to identify the study population during a 5-year selection window from 1 January 2016 to 31 December 2020. The "index date" was defined as the date when patients were first prescribed GLP-1RA during the selection window. For each patient, there was a 12-month baseline period before the index date to collect baseline characteristics and a follow-up period of at least 12 months after initiating GLP-1RA treatment to observe treatment patterns and clinical outcomes. Including the baseline period and the follow-up period, the whole study period was from 1 January 2015 to 31 December 2021. An overview of the study design is shown in Figure 1.

Study Population

The study population was adult patients with T2DM who initiated GLP-1RA treatment without any previous use of GLP-1RA and visited hospitals at least once a year after initiation of GLP-1RA.

The inclusion criteria were as follows: (1) patients diagnosed with type 2 diabetes (ICD-10 E11) and GLP-1RA naïve at baseline; (2) ≥18 years old on the index date; and (3) patients who had at least one hospital visit during the baseline period and the first year of follow-up.

The exclusion criteria included the following: (1) patients who used any GLP-1RA in the baseline period; (2) patients who had a diagnosis of type 1 diabetes or gestational diabetes; and (3) patients who lacked age and sex information.

Outcomes

Primary outcomes: the Chinese Diabetes Society integrated recommendations from various international organizations in diabetes management and suggested that most non-pregnant adults with T2DM should have an HbA1c control goal of

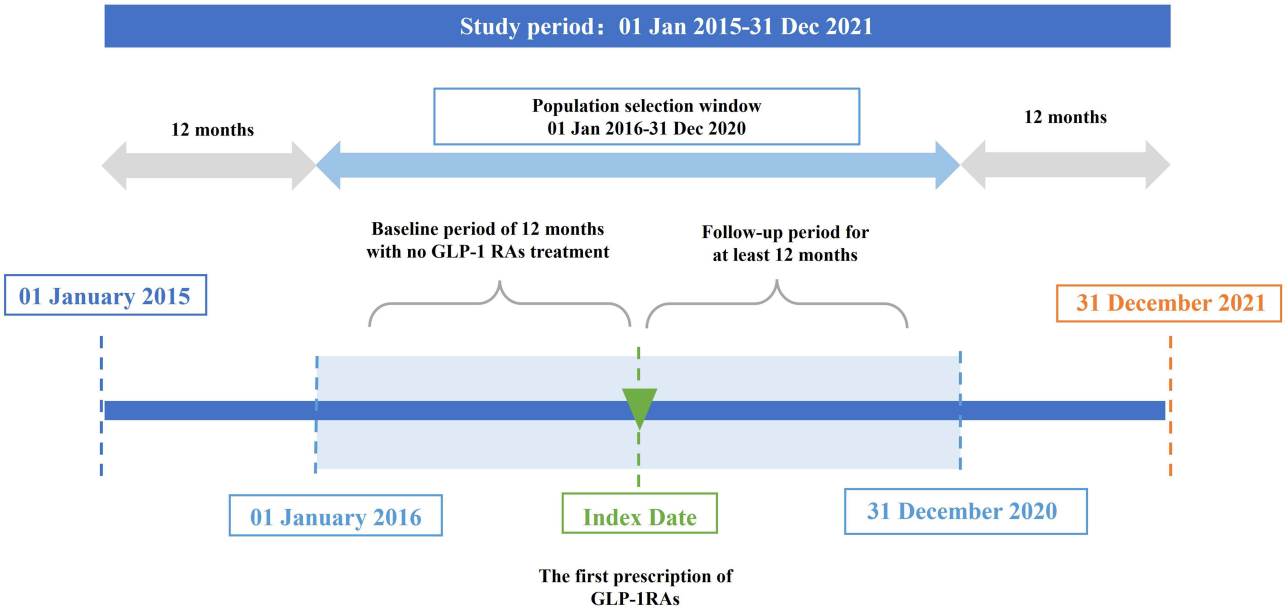

Figure 1 Overview of study design.

<7%.[22] So, the primary outcomes in this study were the change in HbA1c from baseline and the proportion of patients achieving the target of HbA_{1c}<7%.

Secondary outcomes: (1) changes in blood lipids, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG); (2) rate of hypoglycemic event: hypoglycemia was defined (according to Chinese standard) as a glycemic value of <3.9 mmol/L or diagnosed as "hypoglycemia", and severe hypoglycemia was defined as a glycemic value of <2.8 mmol/L or hospitalization administration due to hypoglycemia.

Statistical Analysis

Descriptive statistics were used to describe patients' baseline characteristics among all participants who met the inclusion criteria. Continuous variables are presented as the standard deviation (SD), while categorical variables are expressed as percentages.

The primary and secondary endpoints were assessed among patients with available lab test results at 6- or 12-month follow-ups. Differences between the two groups were assessed using the Wilcoxon rank sum test. All tests were 2-sided, with a statistical significance at $p < 0.05$.

Multivariate logistic regression was used to identify factors associated with initiating daily GLP-1RA and weekly GLP-1RA. Patients initiating daily GLP-1RA were set as a reference group. Age, sex, baseline HbA1c, Charlson Comorbidity Index (CCI),[23] comorbidities/complications at baseline (including hypertension, dyslipidemia, and CVD)[24,25] insulin use at baseline, number of oral antidiabetic drugs at baseline, and all-cause medical costs were included in the model. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported. All statistical analyses were performed using R4.1.

Results

Patient Population and Baseline Characteristics

A total of 19,831 patients with at least one prescription for GLP-1RA were identified in the database from January 2016 to December 2020. Of these, 15,176 individuals met the selection criteria. The flow chart of patient selection is shown in Figure 2.

Table 1 summarised the characteristics of the included patients with T2DM. The average age of the included patients was 54.17±12.99 years, and 55.36% were male. The mean baseline HbA_{1c} was 8.75±1.83. The mean CCI was 4.12±1.96, with 47.97% of the participants being comorbid with dyslipidemia and 55.36% comorbid with hypertension. Patients had

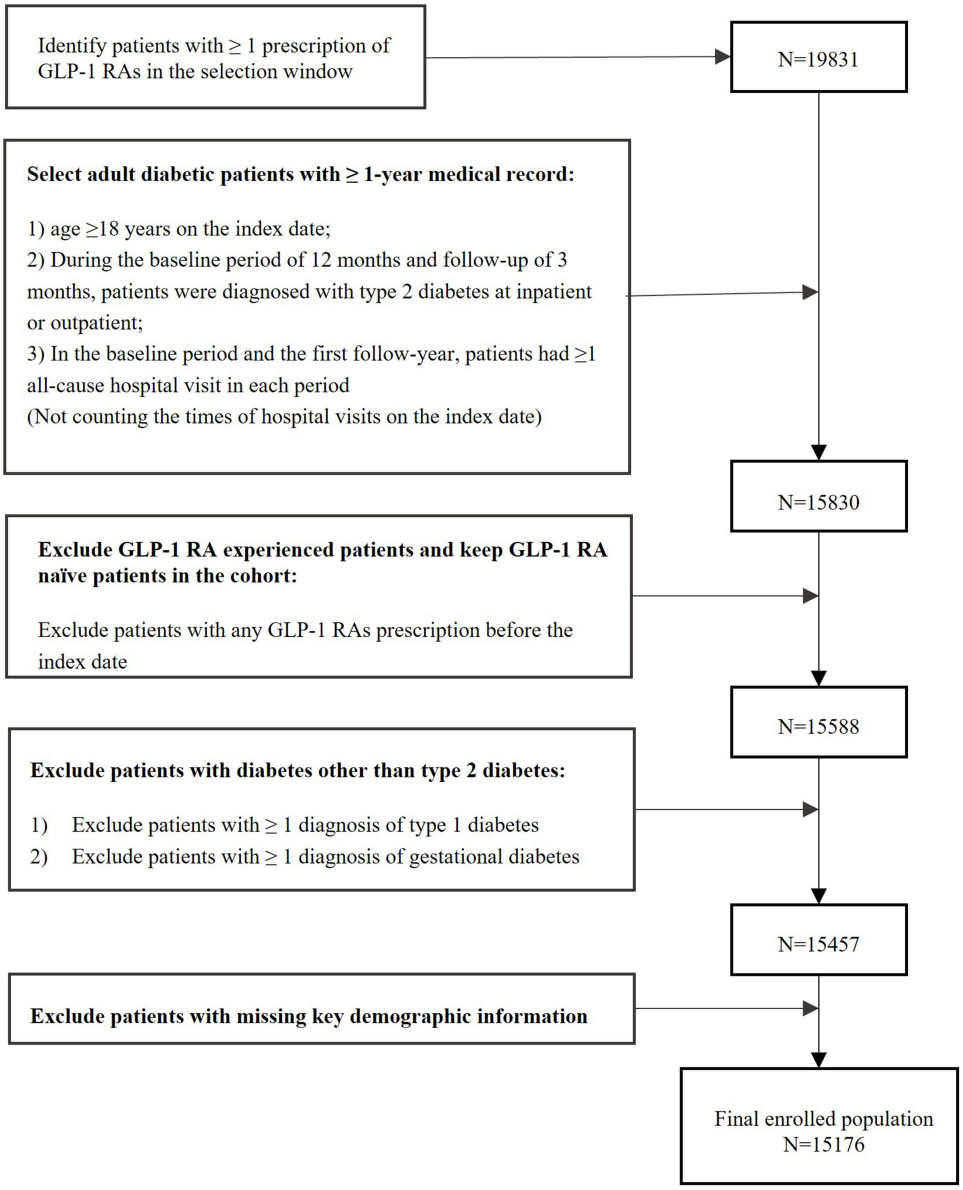

Figure 2 Flow diagram of inclusion–exclusion criteria and sample size.

a high prevalence of micro- and macrovascular complications, and 76.75% of them received cardiovascular medications. Patients were using a mean of 3.30±1.82 antidiabetic drugs at baseline, with most of them (63.50%) concurrently using oral antidiabetic drugs and insulin.

Clinical Outcomes

Primary Outcomes: Glycemic Control

As shown in Table 2, the number of people with HbA_{1c} results is constantly changing at each data collection time point. At the 6-month follow-up, 48.8% of patients achieved the target HbA_{1c} <7.0%. Therefore, we demonstrated the effect of GLP-1RA in terms of the proportion of patients with HbA_{1c} change values meeting the requirements at each time point. The proportion was higher in the "Weekly GLP-1RA" subgroup (71.2%) than in the "Daily GLP-1RA" subgroup (47.7%). The proportions of included patients who achieved an HbA_{1c} reduction ≥1% were 74.9% after 6 months and 70.1% after 12 months. Similar results were noted at the 12-month follow-up.

Table 1 Baseline Patient Characteristics

	Daily GLP-1RA (N=14716)	Weekly GLP-1RA (N=460)	Total (N=15176)
Demographics			
Age, years	54.44±12.90	45.65±13.08	54.17±12.99
Male, n (%)	8121(55.18%)	280(60.87%)	8401(55.36%)
Female, n (%)	6055(44.82%)	180(39.13%)	6775(44.64%)
Lab and test results			
Baseline HbA1c, %	8.77±1.82	8.38±1.93	8.75±1.83
TC, mmol/L	5.02±1.30	5.26±1.34	5.03±1.30
LDL-C, mmol/L	3.15±1.01	3.57±1.00	3.17±1.01
HDL-C, mmol/L	1.14±0.29	1.12±0.24	1.14±0.29
TG, mmol/L	2.50±2.20	2.75±2.68	2.51±2.22
eGFR, mL/min/1.73 m^2	123.64±40.15	133.14±33.77	124.04±39.94
WBC,10^9/l	8.02±18.68	7.02±1.90	7.98±18.30
CCI	4.15(1.96)	3.27(1.72)	4.12(1.96)
Comorbidity/complications			
Hypertension	8244(56.02%)	158(34.35%)	8402(55.36%)
Dyslipidemia	7028(47.76%)	252(54.78%)	7280(47.97%)
Eye disease	**4351(29.57%)**	**76(16.52%)**	**4427(29.17%)**
Diabetic Retinopathy	3304(22.45%)	62(13.48%)	3366(22.18%)
Macular Edema	43(0.29%)	2(0.43%)	45(0.30%)
Proliferative Retinopathy & Macular Edema	2(0.01%)	0(0.00%)	2(0.01%)
Severe Visual Loss	8(0.05%)	1(0.22%)	9(0.06%)
Lower extremity disease	**9677(65.76%)**	**160(34.78%)**	**9837(64.82%)**
Peripheral neuropathy	6649(45.18%)	95(20.65%)	6744(44.44%)
Peripheral vascular disease	6685(45.43%)	127(27.61%)	6812(44.89%)
Lower Extremity Amputation	16(0.11%)	1(0.22%)	17(0.11%)
Diabetic foot	399(2.71%)	8(1.74%)	407(2.68%)
Kidney disease	**4951(33.64%)**	**77(16.74%)**	**5028(33.13%)**
Diabetic nephropathy	3234(21.98%)	39(8.48%)	3273(21.57%)
Microalbuminuria	669(4.55%)	16(3.48%)	685(4.51%)
Macroalbuminuria	234(1.59%)	1(0.22%)	235(1.55%)
End Stage Renal Disease	66(0.45%)	1(0.22%)	67(0.44%)
Macrovascular Complications	**8593(58.39%)**	**127(27.61%)**	**8720(57.46%)**
Ischemic Heart Disease	7250(49.27%)	96(20.87%)	7346(48.41%)
Myocardial Infarction	1510(10.26%)	16(3.48%)	1526(10.06%)
First Myocardial Infarction	509(3.46%)	9(1.96%)	518(3.41%)
Subsequent Myocardial Infarction	1001(6.80%)	7(1.52%)	1008(6.64%)
Stroke	2290(15.56%)	27(5.87%)	2317(15.27%)
First Stroke	1007(6.84%)	13(2.83%)	1020(6.72%)
Subsequent Stroke	1283(8.72%)	14(3.04%)	1297(8.55%)
Heart Failure	338(2.30%)	5(1.09%)	343(2.26%)
Number of antidiabetic drug class	3.31±1.82	2.95±1.85	3.30±1.82
Baseline antidiabetic medications			
Only oral antidiabetic drugs	3005(20.40%)	158(34.35%)	3163(20.8%)
Only insulin	754(5.10%)	28(6.09%)	782(5.20%)
Combination of oral antidiabetic and insulin	9438(64.10%)	197(42.83%)	9635(63.50%)
Not use any antidiabetic medications	1519(10.30%)	77(16.74%)	1596(10.50%)
Baseline cardiovascular medications	11380(77.33%)	268(58.26%)	11,648(76.75%)

Abbreviations: HbA1c glycated hemoglobin A1c, TC total cholesterol, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, TG triglyceride, CCI Charlson comorbidity index, eGFR estimated glomerular filtration rate, WBC white blood cell.

Table 2 Proportion of Patients Achieving HbA1c<7% at the 6- and 12-Month Follow-Ups

	6-Month Follow Up		12-Month Follow Up	
	HbA1c<7% (n, %)	HbA1c≥1% (n, %)	HbA1c<7% (n, %)	HbA1c≥1% (n, %)
Total	3354, 48.8%	2571, 74.9%	2547, 42.4%	1947, 70.1%
Daily	3201, 47.7%	2436, 74.8%	2465, 41.9%	1872, 70.2%
Weekly	153, 71.2%	135, 76.3%	82, 58.5%	75, 68.0%

Note: n, the number of patients.

A total of 2571 and 1947 patients were included in the analyses of HbA_{1c} change from baseline at the 6-month and 12-month follow-ups (as shown in Table 3), respectively. At the 6-month follow-up, the estimated mean change from baseline in HbA_{1c} was −1.26±1.91% ($p < 0.001$). For subgroups, the "Weekly GLP-1RA" group experienced a reduction of HbA1c level by 1.58±2.03% from baseline HbA1c at 8.05% ($p < 0.001$), while the "Daily GLP-1RA" group experienced a reduction of HbA1c level by 1.25±1.90% from baseline HbA1c at 8.53% ($p < 0.001$). At the 12-month follow-up, the estimated mean change from baseline in HbA1c was −0.95±1.80% ($p < 0.001$). The estimated mean change was slightly higher in the "Weekly GLP-1RA" subgroup (−1.05±1.93%, $p < 0.001$) than in the "Daily GLP-1RA" subgroup (−0.95±1.80%, $p < 0.001$).

Secondary Outcomes

Blood Lipid Control

Changes in blood lipids using daily and weekly GLP-1RA are summarized in Table 3. At 6 months following GLP-1RA initiation, there were statistically significant improvements in the mean TC, low LDL-C, HDL-C, and TG levels. After 12 months, there were statistically significant improvements in the mean TC, LDL-C and TG, with the exception of HDL-C.

Table 3 Changes in HbA1c and Blood Lipids from Baseline at the 6- and 12-Month Follow-Ups

	6-Month Follow Up			12-Month Follow Up		
	n	Baseline, mean±SD	Change From Baseline, mean±SD	n	Baseline, mean±SD	Change From Baseline, mean±SD
HbA1c						
Total	2571	8.51±1.77%	−1.26±1.91%***	1947	8.48±1.70%	−0.95±1.80%***
Daily	2436	8.53±1.76%	−1.25±1.90%***	1872	8.51±1.69%	−0.95±1.80%***
Weekly	135	8.05±1.95%	−1.58±2.03%***	75	7.97±1.97%	−1.05±1.93%***
TC						
Total	2859	5.01±1.32	−0.26±1.22***	2190	5.02±1.26	−0.22±1.15***
Daily	2730	5.00±1.31	−0.26±1.23***	2114	5.02±1.26	−0.23±1.15***
Weekly	129	5.23±1.41	−0.23±1.17	76	5.20±1.34	0.15±0.89
LDL-C						
Total	2903	3.15±1.04	−0.19±0.95***	2209	3.16±1.02	−0.14±0.92***
Daily	2773	3.13±1.04	−0.19±0.95***	2133	3.15±1.01	−0.15±0.92***
Weekly	130	3.59±1.01	−0.21±0.87	76	3.58±1.14	0.07±0.74
HDL-C						
Total	2927	1.14±0.29	0.01±0.25***	2191	1.14±0.3	−0.01±0.26
Daily	2797	1.14±0.29	0.01±0.25***	2123	1.15±0.3	−0.01±0.26
Weekly	130	1.13±0.26	0.02±0.19	68	1.13±0.24	0±0.2
TG						
Total	2930	2.50±2.14	−0.26±1.91***	2197	2.46±1.89	−0.16±1.89***
Daily	2800	2.49±2.1	−0.26±1.9***	2129	2.46±1.9	−0.16±1.91***
Weekly	130	2.53±2.88	−0.46±2.12***	68	2.36±1.61	−0.08±1.1

Notes: n, the number of patients; ***p <0.001.
Abbreviations: TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride.

Hypoglycemia

Compared with the baseline (11.92%), the proportion of patients who had an incidence of all hypoglycemia was lower at the 6-month follow-up (9.73%) and similar at the 12-month follow-up (11.35%). The rate of severe hypoglycemia slightly decreased after 6 months (1.50%) compared with baseline (1.68%) but slightly increased after 12 months (1.88%). Overall, patients in the "Weekly GLP-1RA" subgroup experienced less hypoglycemia. No severe hypoglycemia was observed in the "Weekly GLP-1RA" subgroup during the follow-up period (see Table 4).

Factors Associated with the Type of Initiated GLP-1RA

As shown in Table 5, the regression results demonstrated that T2DM patients with older age (OR = 0.96, 95% CI: 0.95–0.97, $p < 0.001$), hypertension (OR = 0.45, 95% CI: 0.35–0.58, $p < 0.001$), and receiving insulin treatment at baseline (OR = 0.41, 95% CI: 0.31–0.53, $p < 0.001$) were more likely to use daily injection GLP-1RA, while patients with dyslipidemia were more likely to use weekly injection GLP-1RA (OR =1.61, 95% CI: 1.27–2.06, $p < 0.001$).

Discussion

To our knowledge, this is the first study to investigate the real-world utilization of weekly and daily dosing GLP-1RA in China. From real-world data of 15,176 patients, weekly GLP-1RA were associated with greater HbA1c reductions, greater lipid reductions, and a lower incidence of severe hypoglycaemic events. Overall, weekly dosing GLP-1RA provide better glycemic control than daily dosing.

GLP-1RA has proven efficacy in glycemic control in T2DM patients.[26] In this study, weekly dosing of GLP-1RA had a mean reduction in HbA1c of −1.58±2.03% and −1.05±1.93% (observations at 6 and 12 months), which was better than the daily dosing of GLP-1RA. Overall, GLP-1RA were associated with better glycemic control, as evidenced by larger HbA1c reduction and a greater percentage of patients reaching HbA1c. The results were in line with the findings in

Table 4 Rate of Hypoglycemia

	Baseline		6-Month Follow Up		12-Month Follow Up	
	All Hypoglycemia	Severe Hypoglycemia	All Hypoglycemia	Severe Hypoglycemia	All Hypoglycemia	Severe Hypoglycemia
Total	11.92%	1.68%	9.73%	1.50%	11.35%	1.83%
Daily	12.24%	1.73%	10.00%	1.54%	11.64%	1.88%
Weekly	1.74%	0.22%	1.09%	0.00%	2.17%	0.00%

Table 5 Impact Factors Influencing the Use of Daily GLP-1RA and Weekly GLP-1RA

Impact Factors	OR (95% CI)	*P* value
Demographic characteristics		
Increased Age by 1 year	0.96(0.95, 0.97)	**<0.001**
Male	1.16(0.91, 1.48)	0.221
Increased baseline HbA1c by 1%	0.90(0.84, 0.97)	**0.003**
Comorbidity		
Hypertension	0.45(0.35, 0.58)	**<0.001**
Dyslipidemia	1.61(1.27, 2.06)	**<0.001**
Cardiovascular disease	0.6(0.37, 0.93)	**0.021**
Antidiabetic medications at baseline		
With insulin treatment	0.41(0.31, 0.53)	**<0.001**

Notes: The daily GLP-1RA group was set as the control group. *P* values in bold indicate *P* values < 0.05.

previous randomized controlled studies[27] and meta-analyses.[28,29] The better control of HbA1c with weekly dosing compared to daily dosing may be due to the long-acting pharmacokinetic characteristics, allowing for more stable blood concentrations over time.[30–32] Additionally, more patients achieved HbA1c levels of 7% or lower with the weekly dosing, likely due to its consistent ability to reduce postprandial glucose levels compared to the daily dosing.[33,34]

GLP-1RA can also reduce blood lipid levels.[35] In previous research, the results reported that GLP-1RA significantly reduced the levels of TC[36] and LDL-C.[37] Surprisingly, we found that GLP-1RA significantly decreased TC, LDL-C, HDL-C, and TG levels. The weekly dosing GLP-1RA resulted in greater lipid reductions than the daily dosing at the 6-month follow-up. However, one retrospective study in KAUH, Jeddah, Saudi Arabia, reported that the results did not demonstrate an association between GLP-1RA treatment and lipid profiles.[38] Thus, further research is needed to investigate the relationship between GLP-1RA and blood lipids.

The occurrence of hypoglycemia by using GLP-1RA in patients with T2DM is an important consideration for safety.[39,40] In this study, we found that the weekly dosing of GLP-1RA had a lower incidence of hypoglycemia events than the daily dosing, and there were no serious hypoglycemia events at the 6- and 12-month follow-ups in the weekly dosing group. This finding may be related to significantly lower insulin doses when using long-acting GLP-1RA.[29]

Different variables may impact the options of using GLP-1RA weekly or daily.[41,42] According to our study, individuals with dyslipidemia may prefer weekly dosing over daily dosing. In contrast, patients with advanced age, abnormal blood pressure, and concurrent insulin therapy may prefer daily dosing. Research in patients' preferences showed that dosing frequency was an important factor in addition to efficacy.[43–45] In addition, it was also pointed out that the patients who used weekly preparations had better compliance.[11]

This study has certain limitations that are worth noting. Firstly, we had insufficient weight or waist circumference data to evaluate the effectiveness of weight loss. Secondly, we lacked blood pressure or heart rate data to demonstrate cardiovascular benefits. Thirdly, the scope of the data was limited to analyzing significant differences in outcomes between weekly and daily groups. It is recommended that future studies address these limitations by collecting data on a larger scale.

Conclusion

This study found differences in the real-world application of GLP-1RA' weekly and daily dosing in the Chinese population. Weekly dosing showed better glycemic control, with significant reductions in HbA1c levels and a higher achievement of HbA1c targets. Additionally, it led to more noticeable improvements in lipid levels and a lower risk of severe hypoglycemia compared to daily dosing. These findings align with previous research, highlighting the effectiveness of long-acting weekly GLP-1RA. While the relationship between GLP-1RA and lipids is still under investigation, patient preferences and comorbidities have been identified as factors in determining dosing frequency. This study establishes a basis for further research on the clinical effects and long-term advantages of GLP-1RA dosing strategies for managing type 2 diabetes.

Abbreviations

CVD, cardiovascular disease; CCI, Charlson Comorbidity Index; CI, confidence intervals; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonists; HbA1c, glycated haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; SD, standard deviation; TC, total cholesterol; TG, triglyceride; T2DM, type 2 diabetes mellitus; WBC, white blood cell.

Ethics Declarations

This retrospective study obtained approval from the Tianjin Healthcare Database Platform to access and report anonymized data. It was also approved by the Panel on Research Ethics of the University of Macau (Approval No. BSERE23-APP008-ICMS). The Panel on Research Ethics of the University of Macau waived informed consent because no individually identifiable information was used in this study.

Data Sharing Statement

Data may be available from the corresponding author with a reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests in this work.

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