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Aims

The purpose of this study was to examine the effectiveness of beinaglide on body weight, glycaemic haemoglobin (HbA_{1c}), blood pressure and lipid profiles in patients with type 2 diabetes mellitus (T2DM) in a real-world setting in China.

Materials and methods

This was a multicentre, observational, retrospective, open-label study conducted in China. Data were collected from T2DM patients who started treatment with beinaglide between 2017 and 2018.

Results

A total of 314 patients were included in the study. After 3 months of treatment with beinaglide, there were significant reductions in body weight (−10.05 kg [95% confidence interval −9.29 to −10.80]), HbA_{1c} (−2.87% [−2.62 to −3.11]), 2-h postprandial plasma glucose (−5.46 mmol L^{−1} [−4.96 to −

increasing attention owing to their comprehensive effects on both glycaemic control and weight loss with low hypoglycaemia incidence.

Beinaglutide (formerly known as benaglutide), a GLP-1RA, is recombinant human glucagon-like peptide-1 and shares 100% homology with human GLP-1(7-36) (5). The drug was approved by the China Food and Drug Administration for the treatment of T2DM in December 2016. Beinaglutide is one of the GLP-1RAs recommended for the treatment of T2DM by the Chinese guideline for the prevention and treatment of type 2 diabetes (2017 edition) (6). The efficacy and safety of beinaglutide have been assessed in randomised controlled trials (RCTs) in China (7–9). Similar to other GLP-1RAs, beinaglutide was effective in lowering glycaemic haemoglobin (HbA_{1c}), fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) in patients with T2DM (7,8). In addition, beinaglutide reduced body weight and body mass index (BMI) in T2DM patients with overweight and obesity (7,9). These RCTs provided evidence of the effectiveness of beinaglutide in well-defined patient populations under a strictly controlled environment, which is uncertain whether the results can be translated to real-world clinical practice where a more general patient population is treated with the new intervention in outpatient clinics.

Real-world studies are an important of further evaluate the performance of new drugs once they reach the market. Such studies can complement RCTs and assess their results in a more general patient population. The real-world effects of beinaglutide have not been reported to date. Thus, the purpose of this study was to evaluate the effectiveness of beinaglutide on HbA_{1c}, body weight, blood pressure, and lipid profiles in a real-world setting in China. The authors hypothesised that the efficacy of beinaglutide in RCTs will also be observed in the real-world study.

METHODS

This was a multicentre, observational, retrospective, open-label study conducted in 10 hospitals in Hebei Province (northern China). The GLP-1RA beinaglutide was launched in February 2017 in China. Since then, data from T2DM patients treated with beinaglutide under routine clinical practice conditions were consecutively collected until March 2018, i.e. over a time frame of 14 months. Data were extracted from the electronic medical records system and gathered in an Excel database by the researchers. Adult T2DM patients (≥18 years) were eligible for the study. The inclusion criteria were patients with type 2 diabetes mellitus and those who refused to provide informed consent. The following data were collected at baseline and/or three subsequent visits (after

1, 2 and 3 months of treatment): age, sex, diabetes duration, HbA_{1c}, 2-h PPG, FPG, body weight, BMI, waist circumference (WC), C-peptide, heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), antihyperglycaemic and lipid-lowering therapies and history of previous anti-diabetic medications. Moreover, the dosage of beinaglutide and concomitant anti-diabetic therapies was recorded. The values of HbA_{1c}, FPG, 2-h PPG, C-peptide, triglycerides, LDL-C and HDL-C were extracted from standardised laboratory test results. Body weight, WC, heart rate, SBP and DBP were measured by proficient nurses using standard equipment.

The primary study objectives were to assess the effectiveness of beinaglutide in controlling glycaemia after 3 months of treatment. Secondary objectives included assessing changes in body weight, the proportions of patients with weight loss ≥ 5% and ≥ 10% and other clinical parameters related to diabetes after 3 months of treatment. Adverse events, hypoglycaemic events and discontinuation of beinaglutide were also tracked.

This study was approved by the local ethical committees and performed in accordance with the Declaration of Helsinki (revised in 2013).

Statistical analysis

The Kolmogorov–Smirnov test was used to determine if all values were normally distributed. Data for continuous variables were expressed as the mean (standard deviation [SD]). Data for categorical variables were expressed as percentages (%). Baseline characteristics are reported on the basis of the full analysis set (FAS), which included all patients who met the eligibility criteria and had baseline measures for HbA_{1c} or weight. Efficacy analysis included all patients who received at least one dose of beinaglutide and had at least one post-baseline measurement for HbA_{1c} or body weight. Missing values were imputed using the last observation carried forward (LOCF) method. For paired samples, the paired *t*-test or Wilcoxon matched-pairs signed-rank test was used for time points, and repeated-measures analysis of variance or the Friedman test followed by Dunn's multiple-comparisons test was used for multiple time points. The mean (SD), mean difference, standard error (SE) and 95% confidence interval (CI) were calculated for each time point. Subgroup analyses for paired samples were performed with the same statistical methods. The changes in HbA_{1c} and weight were assessed by analysis of covariance, adjusting for baseline measures and the dose of beinaglutide as covariates. A multiple linear regression model was applied to identify determinants

of HbA_{1c} reduction and weight loss. Independent variables included age, sex, diabetes duration, baseline HbA_{1c}, BMI, SBP, triglycerides, LDL-C, HDL-C and the dose of beinagliptide. $p < 0.05$ was considered statistically significant (two-tailed). Data were analysed using SPSS 23 software (IBM SPSS, USA).

Based on the data which had an imputation for missing values (i.e. observed data only), a sensitivity analysis was conducted to assess whether the LOCF method for handling missing data might have influenced any critical conclusions.

Results

Baseline characteristics of patients

From January 2017 to March 2018, data from 323 patients treated with beinagliptide were extracted from the electronic medical records system. Of these, nine patients lacked baseline data for HbA_{1c} and body weight (unknown reasons) and were excluded from the analysis. The remaining 314 patients were included in the FAS (see flow chart in Figure 1). There were 163 (51.9%) men and 151 (48.1%) women, with an overall mean age of 47.6 (10.5) years. Most patients (60.3%) had a diabetes duration < 5 years. On average, baseline body weight

was 77.94 (10.91) kg, BMI was 27.95 (4.07) kg m⁻², HbA_{1c} was 9.05 (1.48)%, 2-h PPG was 14.23 (3.23) mmol L⁻¹ and FPG was 9.25 (1.77) mmol L⁻¹. Baseline characteristics of the FAS population are summarised in Table 1. Approximately 27.7% of the FAS population were drug-naïve patients who were newly diagnosed with T2DM. Regarding the history of pre-existing anti-diabetic medications before initiating beinagliptide, 30.3% of patients had been treated previously with metformin, 14.0% with repaglinide, 12.7% with acarbose, 10.8% with sulfonylurea, 8.6% with short-acting insulin, 7.0% with basal insulin, 1.9% with DPP4 inhibitors and 1.0% with liraglutide. In addition, 48.1% of patients had received one anti-diabetic agent, 21.0% received two anti-diabetic agents and a small proportion (3.2%) received three anti-diabetic agents prior to beinagliptide treatment. Regarding diabetic complications, 12.7% and 1.3% of patients presented with a personal history of coronary heart disease and brain infarction, respectively. Diabetic peripheral neuropathy, nephropathy and retinopathy were present in 40.4%, 13.7% and 2.2% of patients, respectively. A total of 10.5% of patients presented with both diabetic peripheral neuropathy and nephropathy, and a small proportion (0.1%) presented with diabetic peripheral neuropathy, nephropathy and retinopathy. Hypertension was present in 51.9% of patients, 84.0% of whom

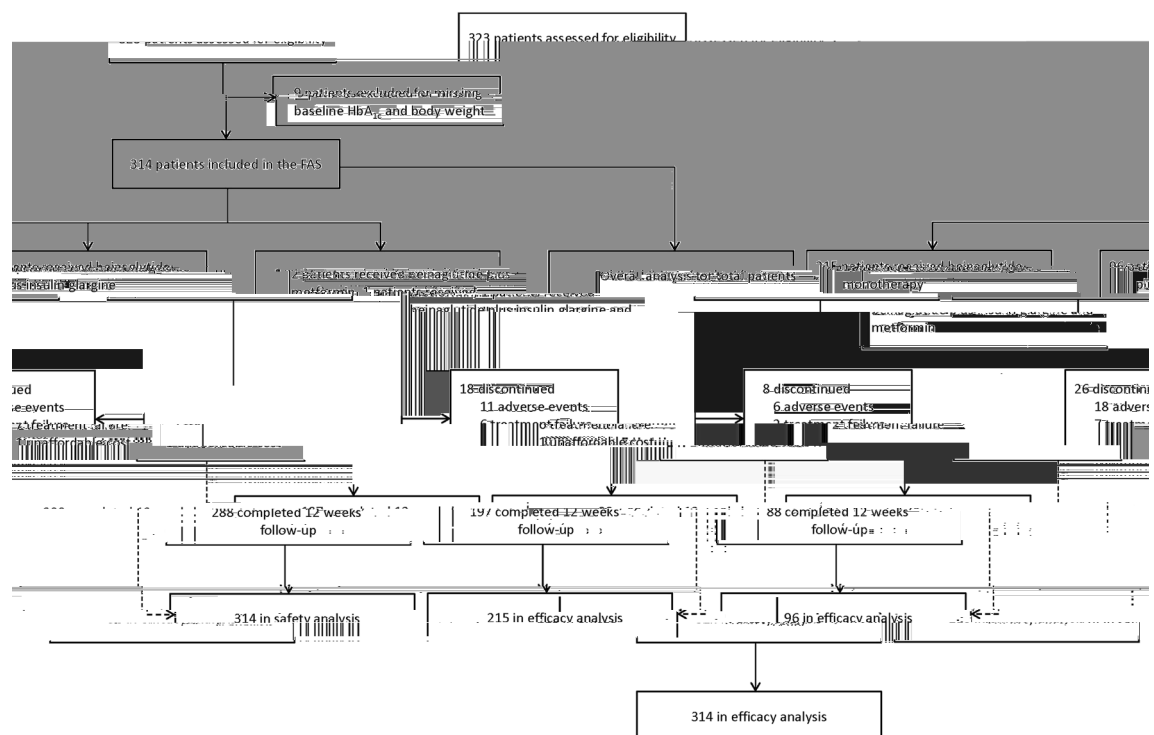


Figure 1 Study flow chart. FAS, full analysis set; HbA_{1c}, glycosylated haemoglobin.

metformin and one (0.3%) in combination with insulin glargine and metformin. At baseline, 37.6% of the patients were prescribed a daily dose of 0.2 mg, 52.3% received 0.3 mg, 5.5% received 0.4 mg, 0.5% received 0.45 mg and 4.1% received 0.6 mg of beinsulin. Following a period of dose escalation of 1–2 weeks, prescriptions of 0.2, 0.3, 0.4, 0.42, 0.48 and 0.6 mg of beinsulin were given to 31.2%, 5.7%, 2.1%, 11.3%, 22.7% and 27.1% of the patients, respectively. In addition, 96.0% of patients carried out complementary lifestyle interventions.

Clinical outcomes after 3 months of beinsulin treatment

Clinical parameters at baseline and the 3-month follow-up are presented in Table 2. Compared with baseline, after 3 months of treatment, the patients showed significant reductions in body weight, HbA_{1c}, 2-h PPG, FPG, BMI, WC, heart rate, SBP, DBP, triglycerides and LDL-C and a significant elevation in HDL-C (all $p < 0.0001$). In subgroups, patients receiving beinsulin monotherapy or beinsulin in combination with insulin glargine showed similar results ($p < 0.001$). C-peptide showed a significant reduction from baseline to 3 months in the total population of patients ($p = 0.0016$) and the patients who received monotherapy ($p < 0.0001$), but not in those receiving beinsulin in combination with insulin glargine ($p = 0.4464$).

Temporal trends in body weight change are shown in Figure 2. Significant weight loss was observed at all time points. For the total population of patients, body weight was decreased by -10.05 kg (-9.29 to -10.80) and -12.90% (-12.02 to -13.78) after 3 months (all $p < 0.0001$). After 3 months, 84.96% and 72.18% of patients attained weight loss of $\geq 5\%$ and $\geq 10\%$, respectively. Subgroup analyses showed similar results. After 3 months, body weight was decreased by -9.98 kg (-8.97 to -10.99) and -12.81% (-11.64 to -13.97) in beinsulin monotherapy patients and by -10.30 kg (-9.43 to -11.16) and 13.33% (-12.28 to -14.38) when administered in combination with insulin glargine (all $p < 0.0001$). Furthermore, at 3 months, the proportions of patients with weight loss of $\geq 5\%$ and $\geq 10\%$ were 80.75% and 68.45% for monotherapy and 97.37% and 85.53% for the combination therapy with insulin glargine, respectively.

Temporal trends in HbA_{1c}, 2-h PPG and FPG are shown in Figure 3. For the total population of patients, the average change in HbA_{1c}

received an individualized treatment. Dyslipidaemia was present in 33.4% of patients, 79.0% of whom received lipid-lowering treatment.

Beinsulin administration

At baseline, 215 patients (68.5%) used beinsulin monotherapy, 96 (30.6%) used beinsulin in combination with insulin glargine, and 0 (0.6%) in combination with

T 2 Clinical parameters compared at baseline after 3-month beinagliptide treatment

Variables	Total (N = 314)				Subgroup				Beinagliptide + insulin glargine (N = 96)			
	Baseline		After treatment		Baseline		After treatment		Baseline		After treatment	
	N		N		N		N		N		N	
Body weight, kg	266	77.84 (10.70)	266	67.80 (10.42)	187	77.63 (11.19)	187	67.65 (10.75)	76	77.49 (8.28)	76	67.19 (8.10)
HbA _{1c} , %	208	9.02 (1.53)	208	6.16 (0.87)	134	8.78 (1.36)	134	5.96 (0.93)	73	9.46 (1.72)	73	6.52 (0.63)
2-h PPG, mmol L ⁻¹	255	14.21 (3.29)	255	8.75 (1.99)	186	14.41 (3.11)	186	8.98 (2.21)	67	13.36 (3.31)	67	8.12 (0.95)
FPG, mmol L ⁻¹	256	9.24 (1.79)	256	6.20 (1.00)	187	9.11 (1.65)	187	6.13 (1.09)	67	9.42 (1.76)	67	6.33 (0.59)
C-peptide, nmol L ⁻¹	97	0.98 (0.45)	97	0.86 (0.20)	35	1.13 (0.30)	35	0.94 (0.10)	62	0.89 (0.50)	62	0.82 (0.23)
BMI, kg m ⁻²	262	27.93 (4.11)	262	24.05 (2.95)	187	27.96 (4.47)	187	24.03 (2.90)	76	27.64 (2.48)	76	23.85 (2.33)
WC, cm	244	95.84 (14.63)	244	86.01 (12.50)	177	100.20 (13.96)	177	89.04 (12.78)	67	84.37 (9.17)	67	78.01 (7.09)
Heart rate, bpm	105	76.55 (6.78)	105	73.86 (4.27)	39	76.56 (7.24)	39	73.87 (4.12)	66	76.55 (6.54)	66	73.85 (4.39)
SBP, mmHg	178	143.60 (19.04)	178	128.50 (8.78)	108	147.70 (16.61)	108	129.60 (8.37)	69	136.60 (20.45)	69	126.80 (9.27)
DBP, mmHg	178	87.97 (8.29)	178	81.95 (5.02)	108	88.92 (7.84)	108	81.91 (5.05)	69	86.55 (8.86)	69	82.32 (4.34)
Triglyceride, mmol L ⁻¹	188	3.09 (1.78)	188	1.52 (0.65)	115	3.18 (1.87)	115	1.55 (0.66)	73	2.95 (1.63)	73	1.46 (0.65)
LDL-C, mmol L ⁻¹	148	3.38 (0.94)	148	1.84 (0.83)	79	3.44 (0.80)	79	2.03 (0.84)	69	3.31 (1.07)	69	1.62 (0.77)
HDL-C, mmol L ⁻¹	147	1.31 (0.54)	147	2.30 (1.02)	78	1.18 (0.47)	78	1.91 (0.97)	69	1.46 (0.59)	69	2.74 (0.88)

Data are expressed as mean (SD).

BMI, body mass index; bpm, beats min⁻¹; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA_{1c}, glycaemic haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PPG, postprandial glucose; SBP, systolic blood pressure; SD, standard deviation; WC, waist circumference.

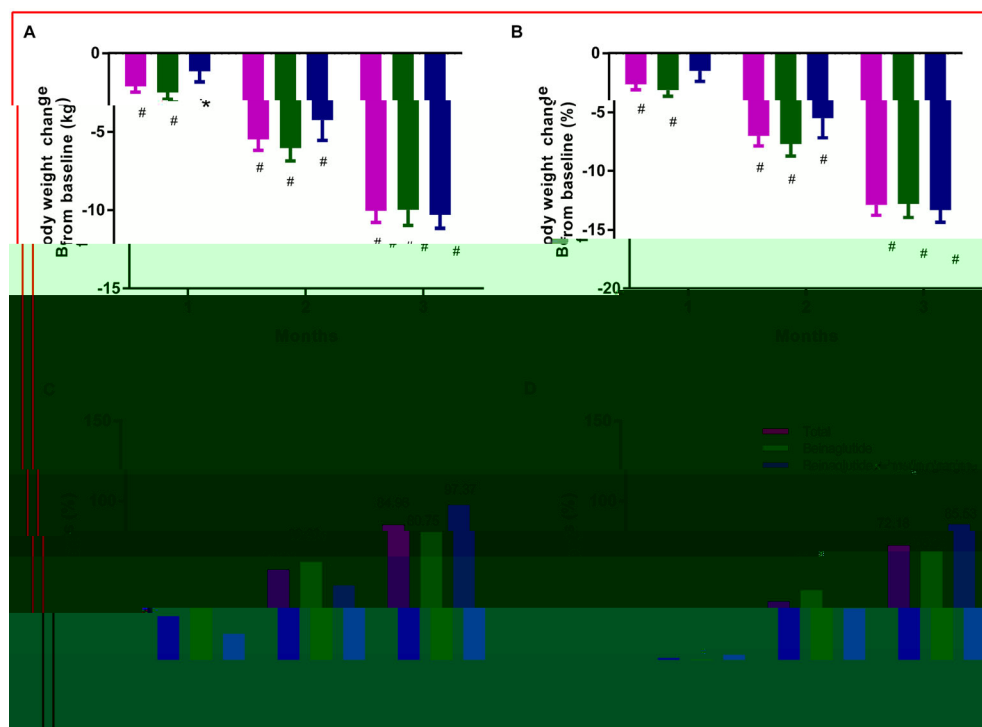


Figure 2 Temporal trends in body weight between baseline and 3 months. (A) Absolute change in body weight (kg). (B) Relative change in body weight (%). (C) The proportion of patients with weight loss of $\geq 5\%$. (D) The proportion of patients with weight loss of $\geq 10\%$. The bars show lower limits of 95% CIs. Significant changes from baseline are indicated (* $p < 0.01$, # $p < 0.0001$). [Correction added on 10 July 2019, after first online publication: Figure 2 has been replaced in this version.]

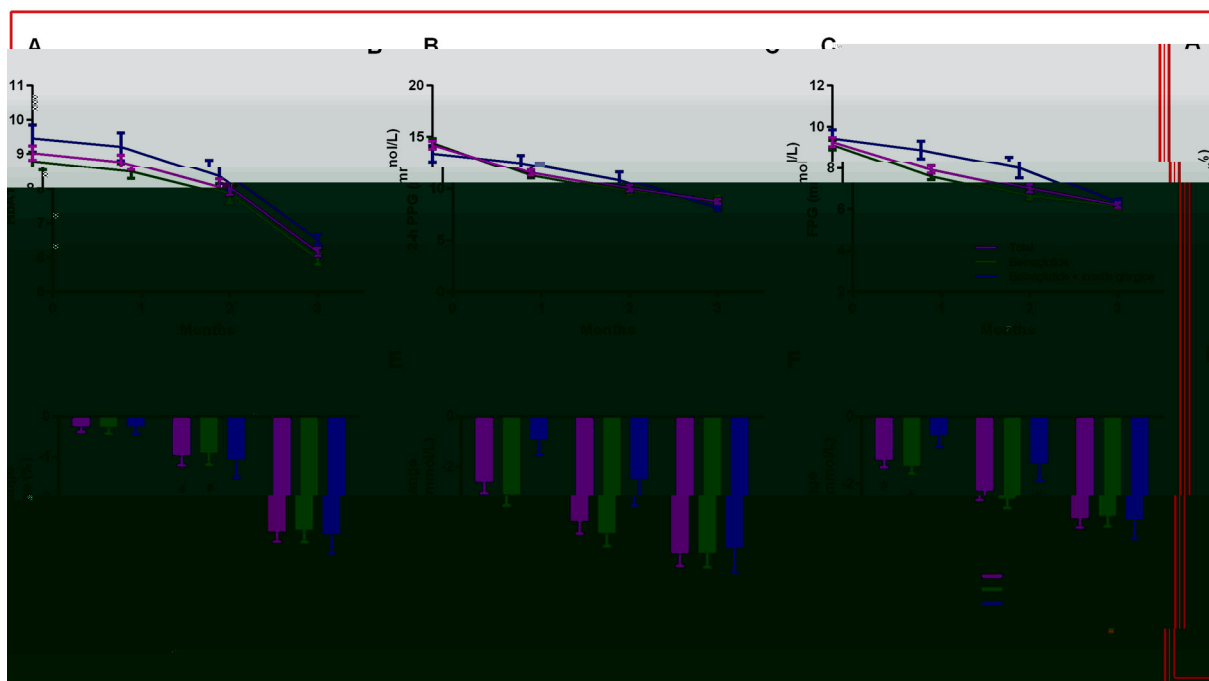


Figure 3 Temporal trends of glycaemic parameters between baseline and 3 months. (A) Mean values of HbA_{1c}. (B) Mean values of PPG. (C) Mean values of FPG. (D) Mean change in HbA_{1c}. (E) Mean change in PPG. (F) Mean change in FPG. The bars show lower limits of 95% CIs. Significant changes from baseline are indicated (* $p < 0.01$, # $p < 0.0001$). FPG, fasting plasma glucose; HbA_{1c}, glycosylated haemoglobin; PPG, postprandial glucose.

changes in 2-h PPG and FPG after 3 months reached $-5.46 \text{ mmol L}^{-1}$ (-4.96 to -5.95) and $-3.04 \text{ mmol L}^{-1}$ (-2.78 to -3.31) (all $p < 0.0001$), respectively. The statistical results of the subgroups showed a similar trend. For patients receiving beaglide monotherapy, the average change in HbA_{1c} , 2-h PPG and FPG gradually decreased over 3 months and reached -2.83% (-2.53 to -3.12), $-5.44 \text{ mmol L}^{-1}$ (-4.88 to -5.99) and $-2.97 \text{ mmol L}^{-1}$ (-2.67 to -3.27) (all $p < 0.0001$) after 3 months of treatment, respectively. For patients receiving combination therapy with beaglide and insulin glargine, the average change in HbA_{1c} , 2-h PPG and FPG after 3 months reached -2.94% (-2.49 to -3.39), $-5.24 \text{ mmol L}^{-1}$ (-4.27 to -6.21) and $-3.10 \text{ mmol L}^{-1}$ (-2.55 to -3.64) (all $p < 0.0001$), respectively.

Detailed results (mean differences, standard error and 95% CI) of the temporal trends in HbA_{1c} , 2-h PPG, FPG and body weight are reported in Tables S1–S3.

Changes in body weight and HbA_{1c} according to baseline characteristics and the dose of beaglide

The changes in body weight did not vary significantly by sex ($p = 0.097$), age ($p = 0.157$), diabetes duration ($p = 0.157$) or baseline HbA_{1c} categories ($p = 0.949$). The changes in HbA_{1c} also did not vary significantly by sex ($p = 0.471$), age ($p = 0.249$), diabetes duration ($p = 0.169$) or baseline BMI categories ($p = 0.964$). However, the changes in body weight were significantly greater in patients with $\geq 28 \text{ kg m}^{-2}$ of baseline BMI and in patients receiving beaglide 0.60 mg ($p = 0.007$ and $p < 0.0001$, respectively); and the changes in HbA_{1c} were significantly greater in patients with $\geq 9.0\%$ baseline HbA_{1c} and in patients receiving beaglide of 0.40 – 0.48 mg (all $p < 0.0001$) (Figure S1).

Determinants of weight loss and HbA_{1c} reduction

The results of multiple linear regression models showed that weight loss from baseline to 3 months positively correlated with baseline BMI levels and the dose of beaglide, and the HbA_{1c} reduction from baseline to 3 months positively correlated with baseline HbA_{1c} levels and the dose of beaglide (Table S4 and S5).

Adverse events, hypoglycaemic events and discontinuation

Among patients in the FAS, the most common adverse events were gastrointestinal symptoms, including nausea (51.0%) and vomiting (18.2%). Other reported adverse events were dizziness (17.2%) and headache (8.3%).

These adverse events mainly occurred in the first month after initiation of treatment, and most were mild to moderate. A total of 14 symptomatic hypoglycaemic events were recorded within the 3 months prior to beaglide treatment, but no such events were reported after beaglide treatment. A total of 26 patients (8.3%) discontinued beaglide therapy within 3 months owing to gastrointestinal side effects (5.7%), treatment failure (2.2%) or unaffordable costs (0.3%).

Sensitivity analysis performed on the completer's data with the LOCF imputation was generally consistent with the conclusions of the aforementioned study results (data not shown).

Discussion

The present study is the first multicentre, observational, retrospective, open-label analysis of beaglide effectiveness in T2DM patients, mostly with overweight and obesity, in China. These data demonstrated a mean weight loss of 10.05 kg and a mean reduction of 2.87% in HbA_{1c} after 3 months of treatment. These observations confirmed the effectiveness of beaglide in a real-world setting.

The patients included in the present study represented a general T2DM population in a real-world setting in China. Baseline data indicated that beaglide therapy was commonly prescribed for patients with overweight and obesity who had a relatively short disease duration. Notably, 27.7% of the patients were newly diagnosed with T2DM, indicating that beaglide was generally accepted as a second-line treatment.

For the Chinese people, a BMI between 24.0 and 27.9 kg m^{-2} is defined as overweight, and a BMI $\geq 28.0 \text{ kg m}^{-2}$ is categorised as obese (10). In the present study, 56.5% of patients were overweight, 41.2% were obese and only 2.3% were normal weight. When analysing the weight-loss effect of beaglide on the basis of baseline BMI, patients with overweight and obesity experienced greater weight-loss effects. This BMI-dependent effect was similar to that in a previous study of liraglide (11,12). Data for normal weight Chinese patients were not available for subanalyses, making estimates for this subgroup unreliable. Similar to other studies of GLP-1RAs (13,14), the weight-loss effect of beaglide was dose dependent, with the highest dose (0.6 mg) providing the greatest weight loss. In addition, based on our results, sex, age and disease duration had no impact on drug efficacy with regard to either glycaemic control or weight loss, which was consistent with previous studies of GLP-1RAs (11,15).

The mean reduction in HbA_{1c} in this study was higher than mean reductions reported in the previous RCTs of

beinaglipide, in which mean reductions from baseline were 0.7% and 1.2% have been reported (7,9). This result was also interesting because HbA_{1c} reductions in real-world groups have so far all been smaller than those in RCTs according to Edelman and Polonsky's study (16). Previous studies have reported that baseline HbA_{1c} levels might predict an early response to GLP-1RAs in terms of HbA_{1c} reductions (15,17). In the present study, HbA_{1c} reduction was positively correlated with baseline HbA_{1c} levels; that is, i.e. patients with higher baseline HbA_{1c} levels had a greater HbA_{1c} reduction after 3 months of treatment. Compared with previous RCTs of beinaglipide (mean baseline HbA_{1c} between 7.97% and 8.05%) (7,9), the higher baseline HbA_{1c} levels (9.02%) in this study may be an important reason for the increased efficacy observed with beinaglipide treatment.

This discrepancy might also be explained by a change in the formulation of beinaglipide. In previous RCTs, beinaglipide lophyllated powder was used for injection; that is, i.e. the powder had to be dissolved and then subcutaneously injected with a disposable sterile syringe (7–9). This formulation increased the difficulty for patients to self-administer, and the accuracy of the dose and patient compliance were affected. However, a new formulation (beinaglipide injection) was developed before entering the market. In clinical practice, patients can easily use an injection pen for subcutaneous administration, providing greater convenience for patients prescribed beinaglipide. Thus, the change in the formulation may be another reason for the increased efficacy of beinaglipide treatment in the real-world setting. In addition, the HbA_{1c} reductions were more significant in the relatively high-dose groups (0.40–0.48 and 0.60 mg), and this finding was consistent with that of previous studies of GLP-1RAs (18,19).

Decreased fasting C-peptide levels after beinaglipide monotherapy suggested potential efficacy for improving hyperinsulinaemia and β -cell reserve. As a short-acting meal-time GLP-1RA, beinaglipide has a short half-life (15 min) and duration of action (2 h) (6). Beinaglipide stimulates postprandial insulin secretion in a glucose-dependent manner (20), but the insulinotropic effect is not maintained in the fasting state owing to rapid degradation of the drug. This outcome is beneficial because β -cell reserve is protected against overstimulation and improved function (21,22). This phenomenon of β -cell reserve was also observed in previous studies of GLP-1 (7–36) and exendin-4 in the postprandial state (23–25). For patients receiving beinaglipide plus insulin glargine, there was a decrease in C-peptide levels, but there was no significant difference, which might be due to lower baseline C-peptide levels (i.e. poor β -cell function) in this group.

The present study also provides new information about the benefits of beinaglipide on other health indicators in a real-world setting. After 3 months of treatment, significant reductions in heart rate, SBP, DBP, total cholesterol and LDL-C were observed, whereas HDL-C increased significantly. These improvements in cardiovascular and lipid profiles were related to beinaglipide treatment and not partially contributed by concomitant antihypertensive or lipid-lowering treatments. These benefits together with weight loss implied a positive impact of beinaglipide on overall cardiovascular outcomes. However, this comprehensive beneficial efficacy was not unexpected, as indicated by previous studies of GLP-1RAs (13,26).

The safety characteristics of beinaglipide were also consistent with previous findings of GLP-1RAs (27–29). Gastrointestinal adverse events were common but mostly transient. No symptomatic hypoglycaemic events were reported during the 3-month treatment, which may be explained by the glucose-dependent insulinotropic effect and short half-life of beinaglipide. The main cause of beinaglipide discontinuation was adverse events (5.7%), which was similar to previous studies of GLP-1RAs (30,31).

The present study has significant strengths, such as extensive clinical information and minimal exclusion criteria, resulting in more fruitful data gained from a wide range of T2DM patients. As an observational and retrospective study, the lack of randomization and a control group are the main limitations of this study. In addition, the follow-up period was limited to the first 3 months from the start of beinaglipide. Additional RCTs and real-world studies are needed to evaluate the effectiveness and safety of long-term beinaglipide treatment.

In summary, this study confirmed the effectiveness of beinaglipide on Chinese T2DM patients in a real-world setting. Significant improvements were observed in body weight, HbA_{1c}, blood pressure and lipid profiles after 3 months of treatment with beinaglipide. A trend of improvement in hyperinsulinaemia and β -cell reserve also emerged. Such benefits were observed despite a wide range of patient baseline characteristics. These observational results suggest that beinaglipide may be an effective treatment for T2DM, especially for patients with overweight and obesity, in clinical practice.

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The authors have declared that they have no conflicts of interest associated with this study.

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