

Beinaglitide improves body weight, glycaemic control, blood pressure and lipid profiles in patients with type 2 diabetes mellitus in a real-world setting in China

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Abstract

Aims

The purpose of this study was to examine the effectiveness of beinaglitide 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 beinaglitide between 2017 and 2018.

Results

A total of 314 patients were included in the study. After 3 months of treatment with beinaglitide, 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 glycosylated 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 a well-defined patient population under a strictly controlled environment, but it is uncertain to

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 beaglitide. $p < 0.05$ was considered statistically significant (two-tailed). Data were analysed using SPSS 23 software (IBM SPSS, USA).

Based on the data 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 beaglitide were extracted from the electronic medical records system. Of those, 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 previous anti-diabetic medications before initiating beaglitide, 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 beaglitide 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

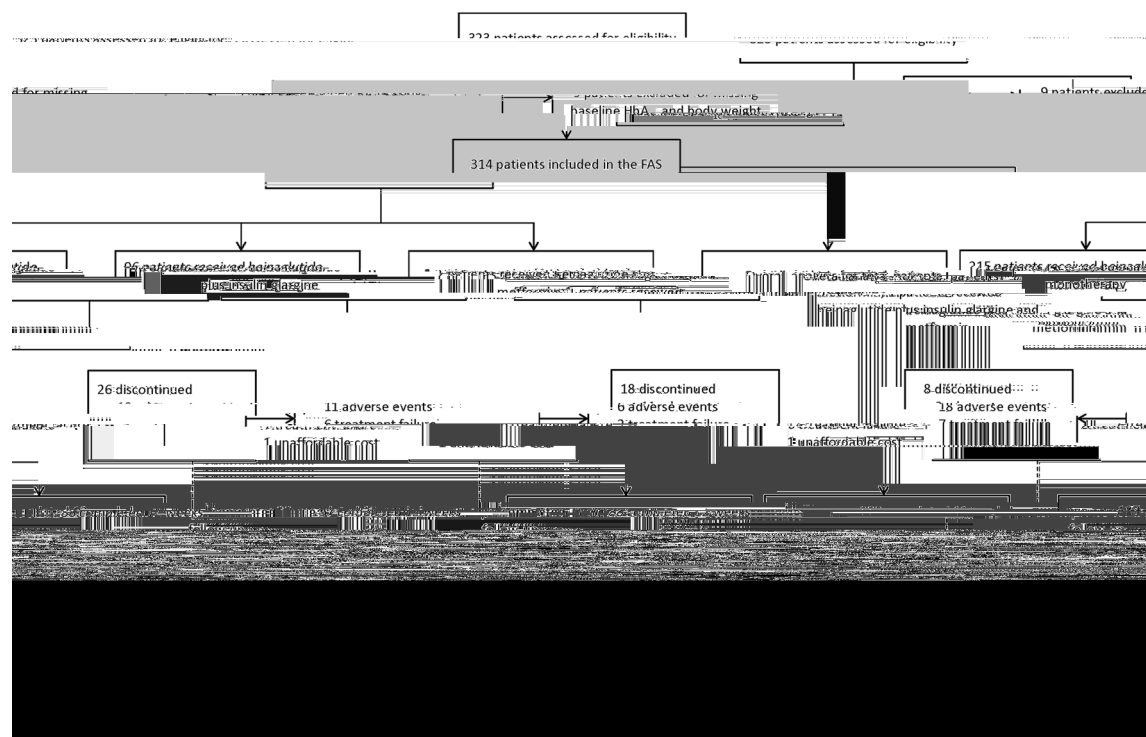


Figure 1 Study flow chart. FAS, full analysis set; HbA_{1c}, glycosylated haemoglobin.

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 beinaglide. 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 beinaglide 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 supplemental lifestyle interventions.

Clinical outcomes after 3 months of beinaglide

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

Beinaglide administration

At baseline, 215 patients (68.5%) used beinaglide monotherapy, 96 (30.6%) used beinaglide in combination with insulin glargine, two (0.6%) in combination with

T. 2 Clinical parameters compared with baseline after 3-month beinaglide treatment

Variables	S bgroup						Beinaglide + insulin glargine (N = 96)					
	Total (N = 314)			Beinaglide (N = 215)			Beinaglide + insulin glargine (N = 96)					
	N	Baseline	After treatment	p	N	Baseline	After treatment	p	N	Baseline	After treatment	p
Body weight, kg	266	77.84 (10.70)	67.80 (10.42)	<0.0001	187	77.63 (11.19)	67.65 (10.75)	<0.0001	76	77.49 (8.28)	67.19 (8.10)	<0.0001
HbA _{1c} , %	208	9.02 (1.53)	6.16 (0.87)	<0.0001	134	8.78 (1.36)	5.96 (0.93)	<0.0001	73	9.46 (1.72)	6.52 (0.63)	<0.0001
2-h PPG, mmol L ⁻¹	255	14.21 (3.29)	8.75 (1.99)	<0.0001	186	14.41 (3.11)	8.98 (2.21)	<0.0001	67	13.36 (3.31)	8.12 (0.95)	<0.0001
FPG, mmol L ⁻¹	256	9.24 (1.79)	6.20 (1.00)	<0.0001	187	9.11 (1.65)	6.13 (1.09)	<0.0001	67	9.42 (1.76)	6.33 (0.59)	<0.0001
C-peptide, nmol L ⁻¹	97	0.98 (0.45)	0.86 (0.20)	0.0016	35	1.13 (0.30)	0.94 (0.10)	<0.0001	62	0.89 (0.50)	0.82 (0.23)	0.4464
BMI, kg m ⁻²	262	27.93 (4.11)	24.05 (2.95)	<0.0001	187	27.96 (4.47)	24.03 (2.90)	<0.0001	76	27.64 (2.48)	23.85 (2.33)	<0.0001
WC, cm	244	95.84 (14.63)	86.01 (12.50)	<0.0001	177	100.20 (13.96)	89.04 (12.78)	<0.0001	67	84.37 (9.17)	78.01 (7.09)	<0.0001
Heart rate, bpm	105	76.55 (6.78)	73.86 (4.27)	<0.0001	39	76.56 (7.24)	73.87 (4.12)	0.0029	66	76.55 (6.54)	73.85 (4.39)	<0.0001
SBP, mmHg	178	143.60 (19.04)	128.50 (8.78)	<0.0001	108	147.70 (16.61)	129.60 (8.78)	0.0001	67	149.06 (19.04.7(bpm64))	(1617)	
<0.0001	6394640.0003	(0.637)	9(472)	<0.0001								

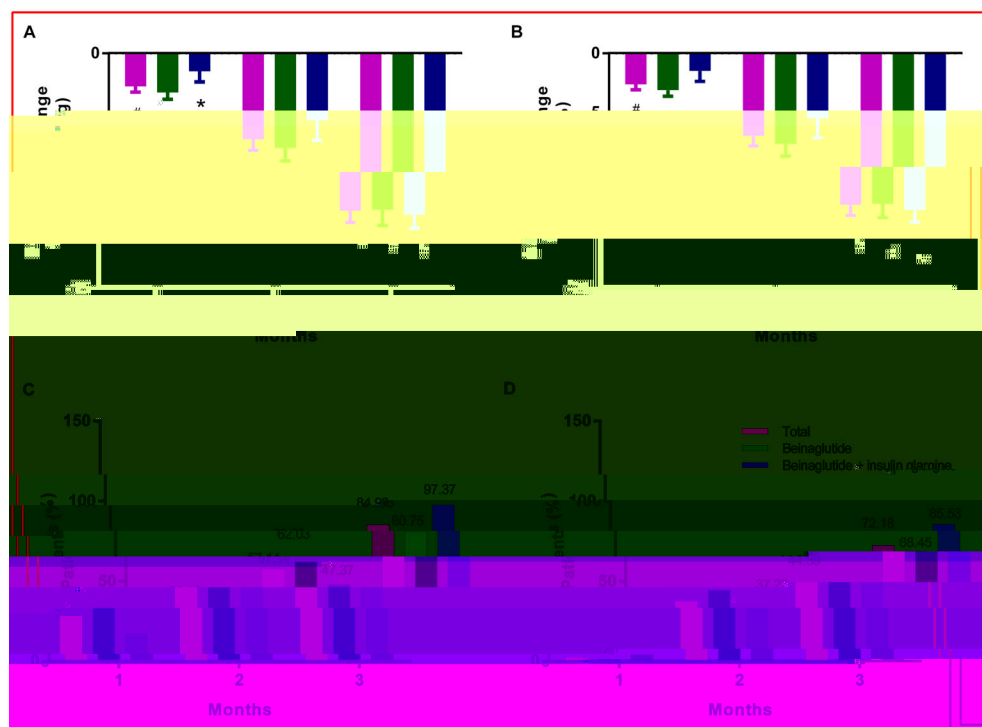


Figure 2 Temporal trends in body weight between baseline and 3 months. (A) Absolute change in body weight (kg). (B) Relative change in body weight (%). (C) The proportion of patients with weight loss of $\geq 5\%$. (D) The proportion of patients with weight loss of $\geq 10\%$. The bars show lower limits 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.]

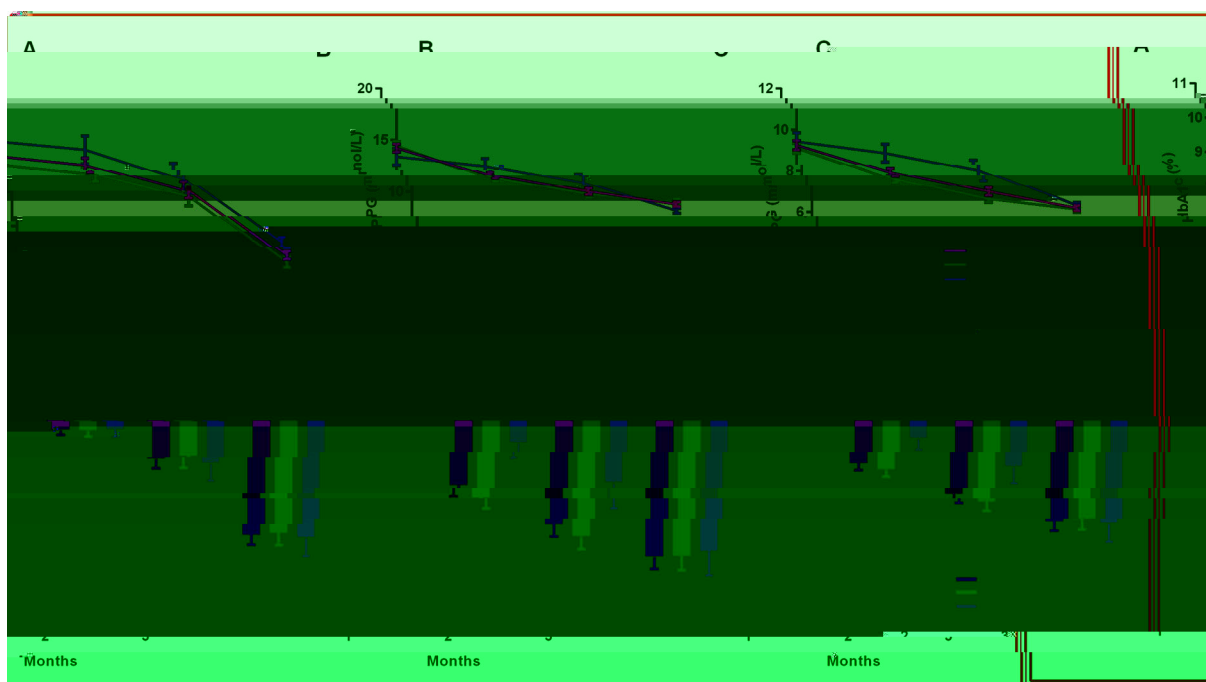


Figure 3 Temporal trends of glycaemic parameters between baseline and 3 months. (A) Mean values of HbA_{1c}. (B) Mean values of PPG. (C) Mean values of FPG. (D) Mean change in HbA_{1c}. (E) Mean change in PPG. (F) Mean change in FPG. The bars show lower limits of 95% CIs. Significant changes from baseline 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 beaglutide 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 beaglutide 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 beaglutide

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 beaglutide 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 beaglutide 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 beaglutide, and the HbA_{1c} reduction from baseline to 3 months positively correlated with baseline HbA_{1c} levels and the dose of beaglutide (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 beaglutide treatment, but no such events were reported after beaglutide treatment. A total of 26 patients (8.3%) discontinued beaglutide therapy within 3 months owing to gastrointestinal side effects (5.7%), treatment failure (2.2%) or unaffordable cost (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 beaglutide 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 beaglutide 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 beaglutide 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 beaglutide 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 categorized 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 beaglutide 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 liraglutide (11,12). Data for normal weight Chinese patients were only available for six individuals, making estimates for this subgroup unreliable. Similar to other studies of GLP-1RAs (13,14), the weight-loss effect of beaglutide 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

being a guide, in which mean reductions from baseline be-

Supporting Information

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Conflicts of Interest

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

References

1. Zhao X, Guo L, Yuan M, et al. Growing trend of China's contribution to global diabetes research: a systematic literature review. *Medicine (Baltimore)*. 2016; **5**: e3517.
2. Shen X, Vaidya A, Weiss S, Gao X. The diabetes epidemic in China: an integrated review of national surveys. *Endocr Pract*. 2016; **22**: 1119–1129.
3. Brackenborg M. The uneven seepage of science: diabetes and biosociality in China. *Health Place*. 2016; **3**: 212–218.
4. Xu Y, Wang L, He J, et al. Prevalence and control of diabetes in Chinese adults. *JAMA*. 2013; **310**: 948–959.
5. Tao L, Wang L, Yang X, Jiang X, Han F. Recombinant human glucagon-like peptide-1 protects against chronic intermittent hypoxia by improving myocardial energy metabolism and mitochondrial biogenesis. *Mol Cell Endocrinol*. 2019; **481**: 95–103.
6. Society CD. Chinese guideline for the prevention and treatment of type 2 diabetes mellitus (2017 edition). *Chin J Diabetes Mellitus*. 2018; **10**: 4–67.
7. Xin-guo H, Ke-hua Z, Xiao-hui Z, et al. Efficacy and safety of recombinant human glucagon-like peptide-1 in combination with metformin in patients with type 2 diabetes mellitus. *Journal of Shandong University (Health Science)*. 2011; **4**: 1–4.
8. Chen Z, Yi F, Shan J, Qian W, Wan F. Pharmacodynamics of recombinant human glucagon-like peptide-1 in Chinese type 2 diabetic patients. *Chinese Pharmaceutical Journal*. 2013; **48**: 2146–2149.
9. Yang H, Ting X, Gaopin Y, Jie G, Zhenmei A. Clinical study on treatment of type 2 diabetes with injection of recombinant human glucagon polypeptide-1(7–36) combined with metformin. *J Sichuan Univ (Med Sci Ed)*. 2011; **42**: 576–579.
10. Wang H, Zhai F. Programme and policy options for preventing obesity in China. *Obes Rev*. 2013; **14**: 134–140.
11. Meqia-Raia P, Reyes-Garcia R, Moreno-Pere O, Escalada-San MJ, Angel RHM, Lopez DLTC. Clinical effects of liraglutide in a real-world setting in Spain: eDiabetes-Monitor SEEN Diabetes Mellitus Working Group Study. *Diabetes Ther*. 2015; **6**: 173–185.
12. Chiunis AS, Gan ML, Benjamin N, Langer J, Hammer M. Clinical effectiveness of liraglutide across body mass index in patients with type 2 diabetes in the United States: a retrospective cohort study. *Adv Ther*. 2014; **31**: 986–999.

28. W sham C, Ble ins T, Arakaki R, et al. Efficac and safet of