ORIGINAL ARTICLE

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Aims

The p rpo e of hi d a o e amine he effec i ene of beinag ide on bod eigh , gl ca ed haemoglobin (HbA_{1c}), blood pre re and lipid profile in pa ien i h pe 2 diabe e melli (T2DM) in a real- orld e ing in China.

Materials and methods

Thi a a m l icen re, ob er a ional, re ro pec i e, open-label d cond c ed in China. Da a ere collec ed from T2DM pa ien ho ar ed rea men i h beinag ide be een 2017 and 2018.

Results

A o al of 314 pa ien ere incl ded in he d . Af er 3 mon h of rea men i h beinag ide, here ere ignifican red c ion in bod eigh (−10.05 kg [95% confidence in er al −9.29 o −10.80]), HbA_{1c} (−2.87% [−2.62 o −3.11]), 2-h po prandial pla ma gl co e (−5.46 mmol L^{-1} [−4.96 o −

increa ing a en ion o ing o heir comprehen i e effec on bo h gl caemic con rol and eigh lo i h lo h pogl caemia incidence.

Beinagl ide (formerl kno n a benagl ide), a GLP-1RA, i recombinan h man gl cagon-like pep ide-1 and hare 100% homolog i h h man GLP-1(7-36) (5). The dr g a appro ed b he China Food and Dr g Admini ra ion for he rea men of T2DM in December 2016. Beinagl ide i one of he GLP-1RA recommended for he rea men of T2DM b he Chine e g ideline for he pre en ion and rea men of pe 2 diabe e (2017 edi ion) (6). The efficac and afe of beinagl ide ha e been a e ed in randomi ed con rolled rial (RCT) in China (7–9). Similar o o her GLP-1RA , beinagl ide a effec- i e in lo ering gl ca ed haemoglobin (HbA_{1c}), fa ing pla ma gl co e (FPG) and po prandial pla ma gl co e (PPG) in pa ien i h T2DM (7,8). In addi ion, beinagl ide red ced bod eigh and bod ma inde (BMI) in T2DM pa ien i h o er eigh and obe i (7,9). The e RCT pro ided e idence of he effec i ene of beinagl ide in a ell-defined pa ien pop la ion nder a ric l con rolled en ironmen , e i i ncer ain o

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

Based on the data with imputation for missing values (i.e. observed data only), a sensitivity analysis was conducted to test the LOCF method for handling missing data might have influenced any critical conclusion.

Results

Baseline characteristics of patients

From January 2017 to March 2018, data from 323 patients treated with beinagliflozin were extracted from the electronic medical record system. Of those, nine patients lacked baseline data for HbA_{1c} and body weight (unknown reason) 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 summarized in Table 1. Approximately 27.7% of the FAS population were drug-naive patients who were newly diagnosed with T2DM. Regarding the history of previous anti-diabetic medications before initiating beinagliflozin, 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 thiazolidinedione, 7.0% with basal insulin, 1.9% with DPP4 inhibitor 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 beinagliflozin 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

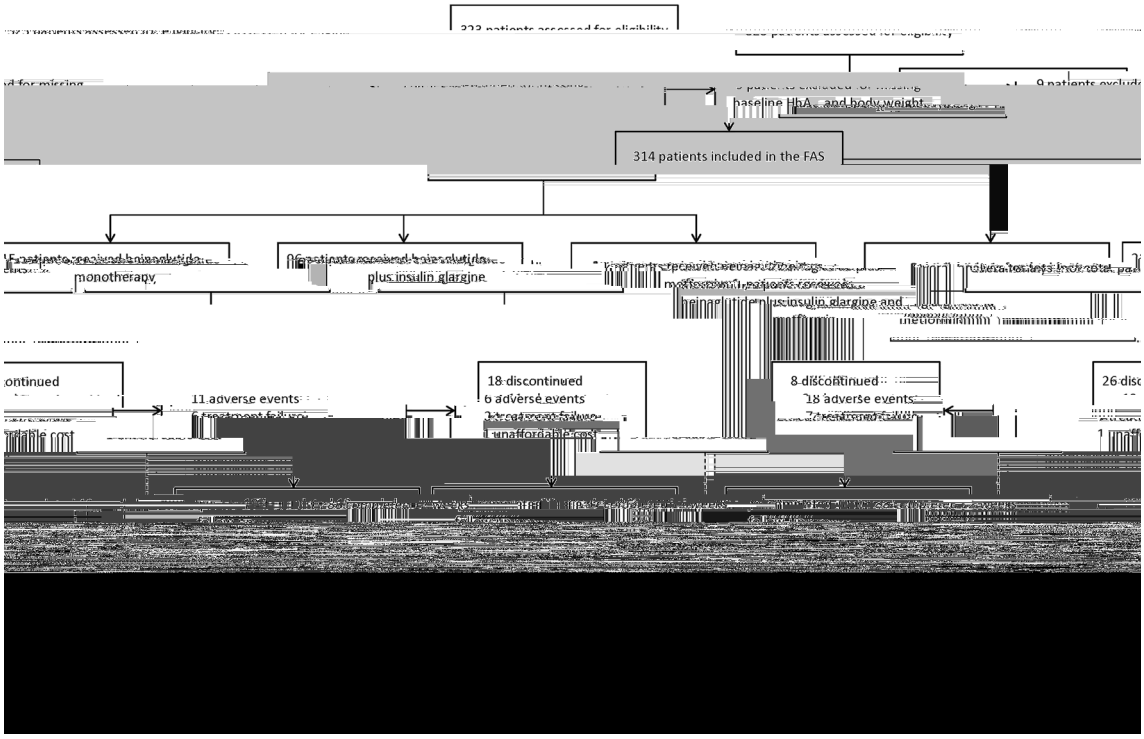


Figure 1 Study flow chart. FAS, full analysis set; HbA_{1c}, glycated haemoglobin.

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recei ed an i-h per en i e rea men . D lipidaemia a pre en in 33.4% of pa ien , 79.0% of hom recei ed lipid-lo ering rea men .

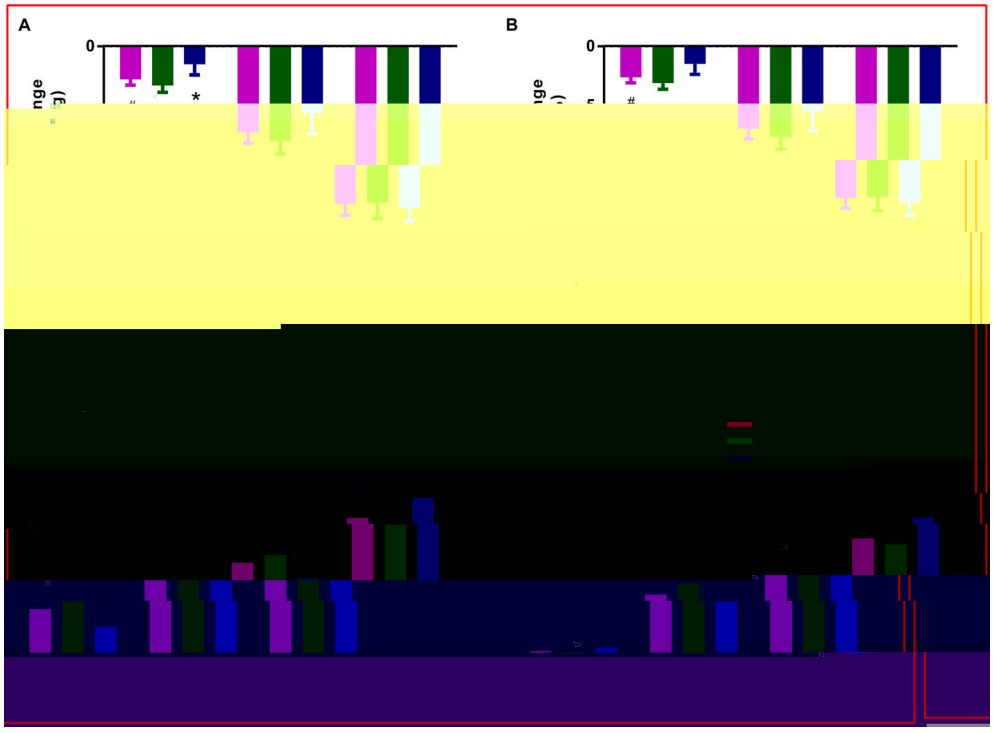
Beinagl ide admini ra ion

A ba eline, 215 pa ien (68.5%) ed beinagl ide mono herap , 96 (30.6%) ed beinagl ide in combina- ion i h in lin glargine, o (0.6%) in combina ion i h me formin and one (0.3%) in combina ion i h in lin glargine and me formin. A ba eline, 37.6% of he pa ien ere pre cribed a dail do e of 0.2 mg, 52.3% recei ed 0.3 mg, 5.5% recei ed 0.4 mg, 0.5% recei ed 0.45 mg and 4.1% recei ed 0.6 mg of beinagl ide. Follo ing a period of do e e cala ion of 1–2 eek , pre crip ion of 0.2, 0.3, 0.4, 0.42, 0.48 and 0.6 mg of beinagl ide ere gi en o 31.2%, 5.7%, 2.1%, 11.3%, 22.7% and 27.1% of he pa ien , re pec i el . In addi- ion, 96.0% of pa ien carried o pplemen al life le in er en ion .

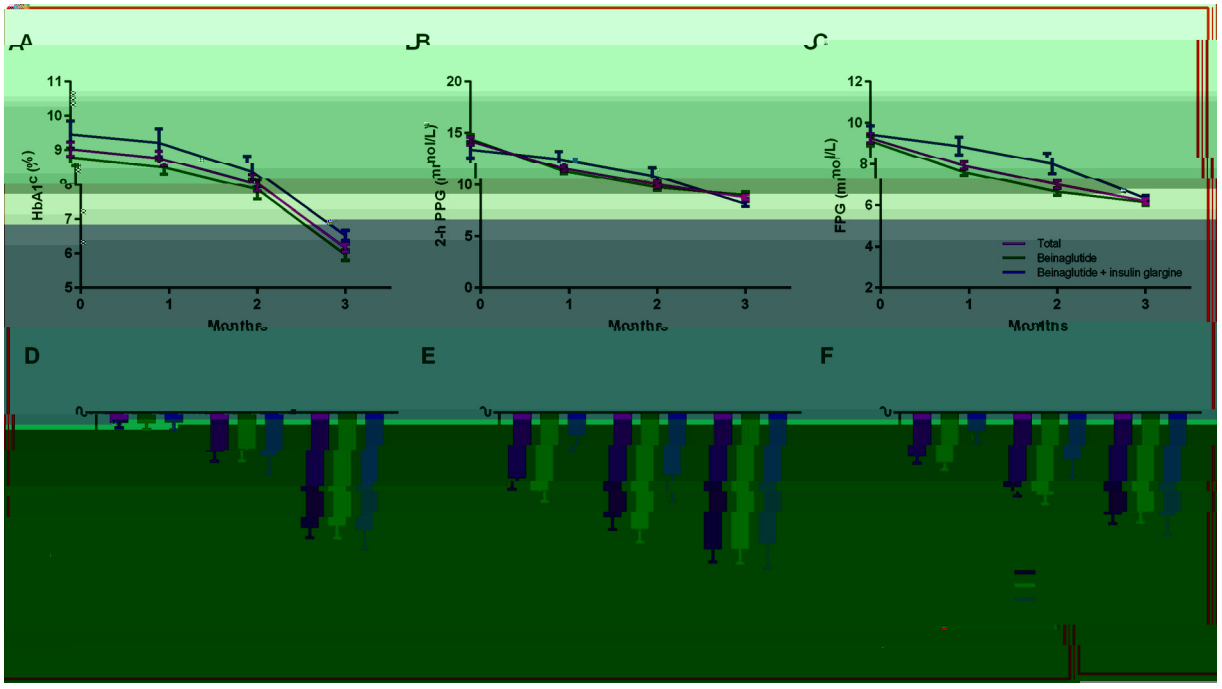
Clinical o come af er 3 mon h of beinagl ide

T ` 2 Clinical parame er compared i h ba eline af er 3-mon h beinagl ide rea men

					US bgro p							
	To al (*N* = 314)				Beinagl ide (*N* = 215)				Beinagl ide + in lin glargine (*N* = 96)			
Variable	*N*	Ba eline	Af er rea men	*p*	*N*	Ba eline	Af er rea men	*p*	*N*	Ba eline	Af er rea men	*p*
Bod eigh , 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-pep ide, 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
Hear ra e, 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	606)6803306((19.04.7(bpm64))		(1617)
<0.0001	b3944640.0013 (0.63		9(4672)	<0.0001								



F , **2** Temporal rend in bod eigh be een ba eline and 3 mon h . (A) Ab l e change in bod eigh (kg). (B) Rela i e change in bod eigh (%). (C) The propor ion of pa ien i h eigh lo of ≥5%. (D) The propor ion of pa ien i h eigh lo of ≥10%. The bar ho lo er limi of 95% CI . Significan change from ba eline are indica ed (*$p < 0.01$, $p < 0.0001$). [Correc ion added on 10 l 2019, af er fir online p blica ion: Fig re 2 ha been replaced in hi er ion.]



F , **3** Temporal rend of gl caemic parame er be een ba eline and 3 mon h . (A) Mean al e of HbA_{1c}. (B) Mean al e of PPG. (C) Mean al e of FPG. (D) Mean change in HbA_{1c}. (E) Mean change in PPG. (F) Mean change in FPG. The bar ho lo er limi of 95% CI . Significan change from ba eline are indica ed (*$p < 0.01$, $p < 0.0001$). FPG, fa ing pla ma gl co e; HbA_{1c}, gl ca ed haemoglobin; PPG, po - prandial gl co e.

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change in 2-h PPG and FPG after 3 months reached −5.46 mmol L^{-1} (−4.96 to −5.95) and −3.04 mmol L^{-1} (−2.78 to −3.31) (all $p < 0.0001$), respectively. The statistical results of the subgroup showed a similar trend. For patients receiving beinaglutide 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 mmol L^{-1} (−4.88 to −5.99) and −2.97 mmol L^{-1} (−2.67 to −3.27) (all $p < 0.0001$) after 3 months of treatment, respectively. For patients receiving combination therapy with beinaglutide 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 mmol L^{-1} (−4.27 to −6.21) and −3.10 mmol L^{-1} (−2.55 to −3.64) (all $p < 0.0001$), respectively.

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

Change in body weight and HbA_{1c} according to baseline characteristic and the dose of beinaglutide

The change in body weight did not significantly vary by age ($p = 0.097$), age ($p = 0.157$), diabetes duration ($p = 0.157$) or baseline HbA_{1c} categories ($p = 0.949$). The change in HbA_{1c} also did not significantly vary by age ($p = 0.471$), age ($p = 0.249$), diabetes duration ($p = 0.169$) or baseline BMI categories ($p = 0.964$). However, the change in body weight were significantly greater in patients with ≥28 kg m^{-2} of baseline BMI and in patients receiving beinaglutide 0.60 mg ($p = 0.007$ and $p < 0.0001$, respectively); and the change in HbA_{1c} were significantly greater in patients with ≥9.0% baseline HbA_{1c} and in patients receiving beinaglutide 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 level and the dose of beinaglutide, and the HbA_{1c} reduction from baseline to 3 months positively correlated with baseline HbA_{1c} level and the dose of beinaglutide (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%). The 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 beinaglutide treatment, but no such events were reported after beinaglutide treatment. A total of 26 patients (8.3%) discontinued beinaglutide 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 without LOCF imputation generally consistent with the conclusion of the aforementioned results (data not shown).

Discussion

The present study is the first multicentre, observational, retrospective, open-label analysis of beinaglutide effectiveness in T2DM patients, most of whom were overweight and obese, in China. The 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 beinaglutide 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 beinaglutide therapy was commonly prescribed for patients with overweight and obese who had a relatively short duration. Notably, 27.7% of the patients were newly diagnosed with T2DM, indicating that beinaglutide 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 ≥ 28.0 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 beinaglutide on the basis of baseline BMI, patients with overweight and obese 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 individual, making estimates for this subgroup unreliable. Similar to other studies of GLP-1RA (13,14), the weight-loss effect of beinaglutide was dose dependent, with the highest dose (0.6 mg) providing the greatest weight loss. In addition, based on other results, sex, age and diabetes duration had no impact on drug efficacy with regard to either glycaemic control or weight loss, which was consistent with previous studies of GLP-1RA (11,15).

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

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beinag ide, in hich mean red c ion from ba eline be-

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