ORIGINAL ARTICLE

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Aims

The p rpose of his s d as o e amine he effec i eness of beinagl ide on bod eigh , gl ca ed haemoglobin (HbA_{1c}), blood press re and lipid profiles in pa ien s i h pe 2 diabe es melli s (T2DM) in a real- orld se ing in China.

Materials and methods

This as a m l icen re, obser a ional, re rospec i e, open-label s d cond c ed in China. Da a ere collec ed from T2DM pa ien s ho s ar ed rea men i h beinagl ide be een 2017 and 2018.

Results

A o al of 314 pa ien s ere incl ded in he s d . Af er 3 mon hs of rea men i h beinagl ide, here ere significan red c ions 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 pos prandial plasma gl cose (−5.46 mmol L^{-1} [−4.96 o −

increasing a en ion o ing o heir comprehensi e effec s on bo h gl caemic con rol and eigh loss i h lo h pogl caemia incidence.

Beinagl ide (formerl kno n as benagl ide), a GLP-1RA, is recombinan h man gl cagon-like pep ide-1 and shares 100% homolog i h h man GLP-1(7-36) (5). The dr g as appro ed b he China Food and Dr g Adminis ra ion for he rea men of T2DM in December 2016. Beinagl ide is one of he GLP-1RAs recommended for he rea men of T2DM b he Chinese g ideline for he pre en ion and rea men of pe 2 diabe es (2017 edi ion) (6). The efficac and safe of beinagl ide ha e been assessed in randomi ed con rolled rials (RCTs) in China (7–9). Similar o o her GLP-1RAs, beinagl ide as effec- i e in lo ering gl ca ed haemoglobin (HbA_{1c}), fas ing plasma gl cose (FPG) and pos prandial plasma gl cose (PPG) in pa ien s i h T2DM (7,8). In addi ion, beinagl ide red ced bod eigh and bod mass inde (BMI) in T2DM pa ien s i h o er eigh and obesi (7,9). These RCTs pro ided e idence of he effec i eness of beinagl ide in a ell-defined pa ien pop la ion nder a s ric l con rolled en ironmen , e i is ncer ain o

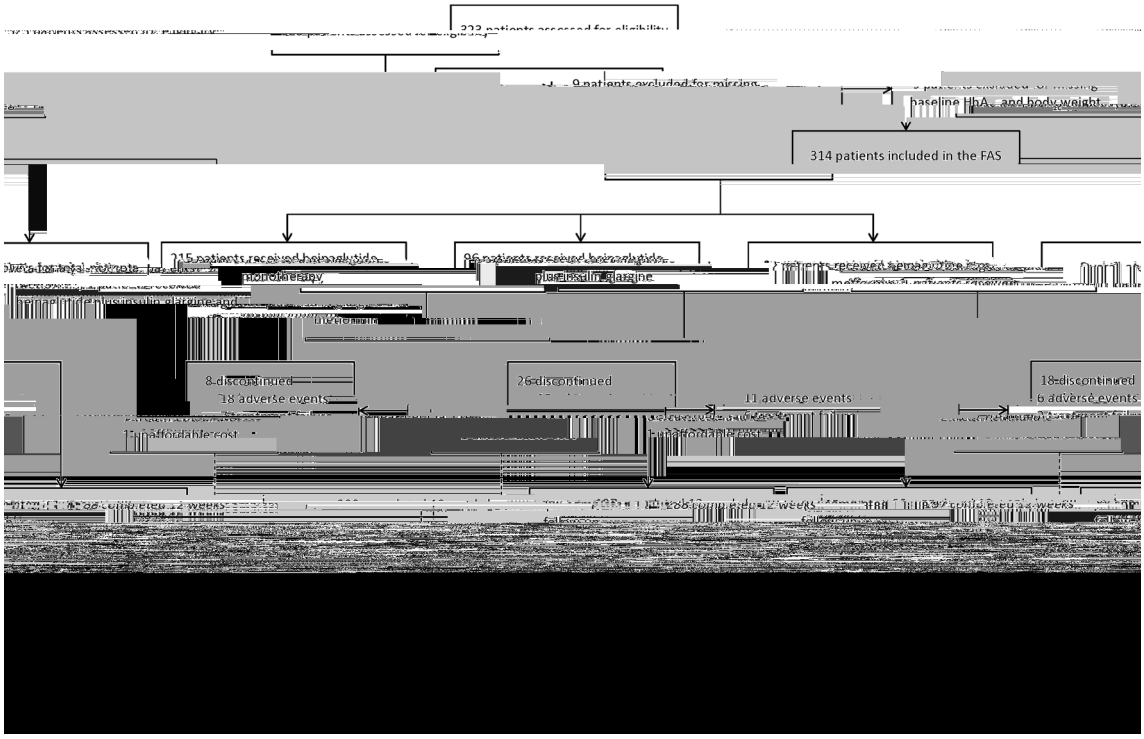
of HbA_{1c} red c ion and eigh loss. Independen ari-ables incl ded age, se , diabe es d ra ion, baseline HbA_{1c}, BMI, SBP, rigl cerides, LDL-C, HDL-C and he dose of beinagl ide. $p < 0.05$ as considered s a is i-call significan (o ailed). Da a ere anal sed sing SPSS 23 sof are (IBM SPSS, USA).

Based on he da a i ho imp a ion for missing al es (i.e. obser ed da a onl), a sensi i i anal sis as cond c ed o assess he her he LOCF me hod for handling missing da a migh ha e infl enced an cri ical concl sions.

R s

Baseline charac eris ics of pa ien s

From Jan ar 2017 o March 2018, da a from 323 pa ien s rea ed i h beinagl ide ere e rac ed from he elec ronic medical record s s em. Of hose, nine pa-ien s lacked baseline da a for HbA_{1c} and bod eigh (nkno n reasons) and ere e cl ded from he anal sis. The remaining 314 pa ien s ere incl ded in he FAS (see flo char in Fig re 1). There ere 163 (51.9%) men and 151 (48.1%) omen, i h an o erall mean age of 47.6 (10.5) ears. Mos pa ien s (60.3%) had a diabe es d ra ion < 5 ears. On a erage, baseline bod eigh as 77.94 (10.91) kg, BMI as 27.95 (4.07) kg m^{-2}, HbA_{1c} as 9.05 (1.48)%, 2-h PPG as 14.23 (3.23) mmol L^{-1} and FPG as 9.25 (1.77) mmol L^{-1}. Baseline charac eris-ics of he FAS pop la ion are s mmari ed in Table 1. Appro ima el 27.7% of he FAS pop la ion ere dr g-na è pa ien s ho ere ne l diagnosed i h T2DM. Regarding he his or of pre io s an i-diabe ic medica ions before ini ia ing beinagl ide, 30.3% of pa ien s had been rea ed pre io sl i h me formin, 14.0% i h repaglinide, 12.7% i h acarbose, 10.8% i h s lfon l rea, 8.6% i h shor -ac ing ins lin, 7.0% i h basal ins lin, 1.9% i h DPP4 inhibi ors and 1.0% i h liragl ide. In addi ion, 48.1% of pa ien s had recei ed one an i-diabe ic agen , 21.0% recei ed o an i-diabe ic agen s and a small propor ion (3.2%) recei ed hree an i-diabe ic agen s prior o beinagl ide rea men . Regarding diabe ic complica ions, 12.7% and 1.3% of pa ien s presen ed i h a personal his or of coronar hear disease and brain infarc ion, respec i el . Diabe ic peripheral ne ropa h , nephropa h and re inop-a h ere presen in 40.4%, 13.7% and 2.2% of pa ien s, respec i el . A o al of 10.5% of pa ien s presen ed i h bo h diabe ic peripheral ne ropa h and nephropa h , and a small propor ion (0.1%) presen ed i h diabe ic pe-ripheral ne ropa h , nephropa h and re inopa h . H per-ension as presen in 51.9% of pa ien s, 84.0% of hom



F · e 1 S d flo char . FAS, f ll anal sis se ; HbA_{1c}, gl ca ed haemoglobin.

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recei ed an i-h per ensi e rea men . D slipidaemia as presen in 33.4% of pa ien s, 79.0% of hom recei ed lipid-lo ering rea men .

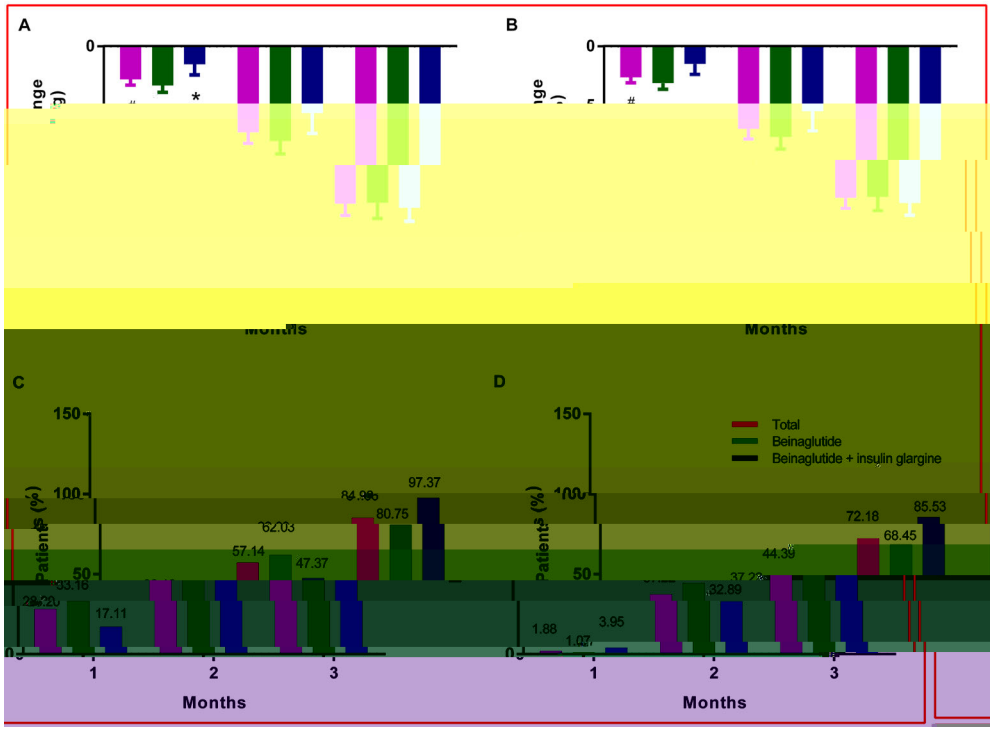
Beinagl ide adminis ra ion

A baseline, 215 pa ien s (68.5%) sed beinagl ide mono herap , 96 (30.6%) sed beinagl ide in combina- ion i h ins lin glargine, o (0.6%) in combina ion i h me formin and one (0.3%) in combina ion i h ins lin glargine and me formin. A baseline, 37.6% of he pa ien s ere prescribed a dail dose 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 dose escala ion of 1–2 eeks, prescrip ions 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 s, respec i el . In addi- ion, 96.0% of pa ien s carried o s pplemen al lifes le in er en ions.

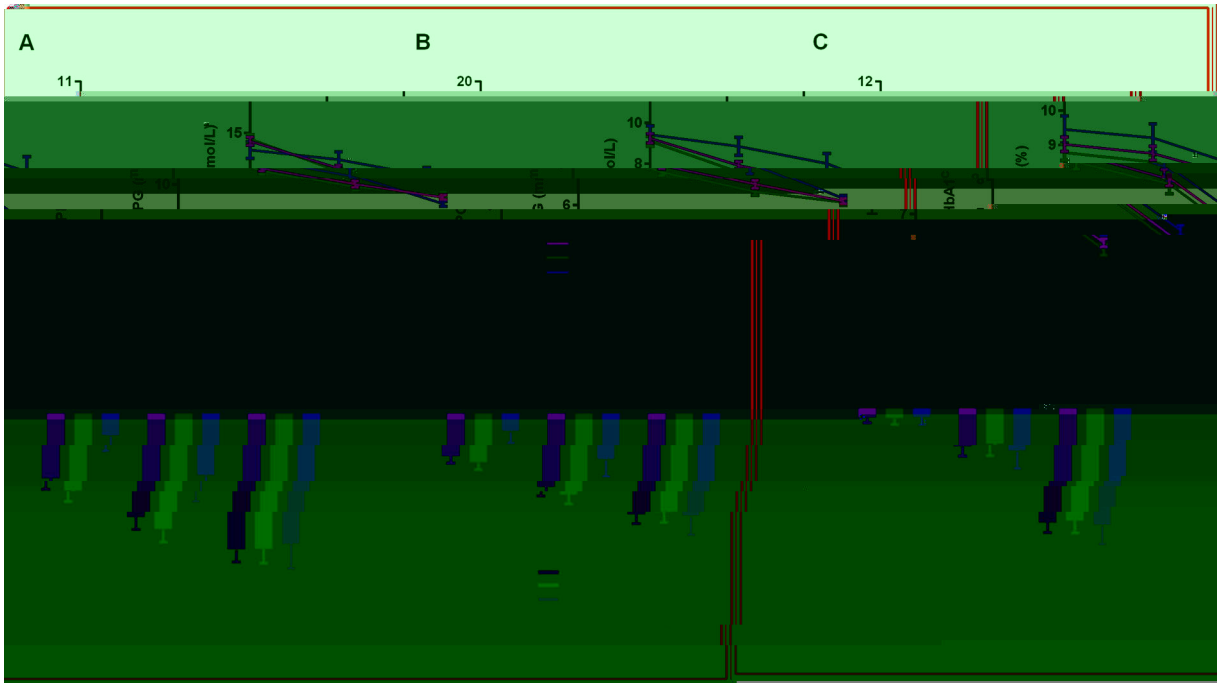
Clinical o comes af er 3 mon hs of beinagl ide

T e 2 Clinical parame ers compared i h baseline af er 3-mon h beinagl ide rea men

					S bgro p							
	To al (*N* = 314)				Beinagl ide (*N* = 215)				Beinagl ide + ins lin glargine (*N* = 96)			
Variables	*N*	Baseline	Af er rea men	*p*	*N*	Baseline	Af er rea men	*p*	*N*	Baseline	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	b3946400.001	3 (0.63)	9(4672)	<0.0001								



F e 2 Temporal rends in bod eigh be een baseline and 3 mon hs. (A) Absol e change in bod eigh (kg). (B) Rela i e change in bod eigh (%). (C) The propor ion of pa ien s i h eigh loss of ≥5%. (D) The propor ion of pa ien s i h eigh loss of ≥10%. The bars sho lo er limi s of 95% CIs. Significan changes from baseline are indica ed (*$p < 0.01$, $p < 0.0001$). [Correc ion added on 10 J l 2019, af er firs online p blica ion: Fig re 2 has been replaced in his ersion.]



F e 3 Temporal rends of gl caemic parame ers be een baseline and 3 mon hs. (A) Mean al es of HbA_{1c}. (B) Mean al es of PPG. (C) Mean al es of FPG. (D) Mean change in HbA_{1c}. (E) Mean change in PPG. (F) Mean change in FPG. The bars sho lo er limi s of 95% CIs. Significan changes from baseline are indica ed (*$p < 0.01$, $p < 0.0001$). FPG, fas ing plasma gl cose; HbA_{1c}, gl ca ed haemoglobin; PPG, pos prandial gl cose.

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changes in 2-h PPG and FPG af er 3 mon hs reached −5.46 mmol L^{-1} (−4.96 o −5.95) and −3.04 mmol L^{-1} (−2.78 o −3.31) (all $p < 0.0001$), respec i el . The s a is- ical res l s of he s bgro ps sho ed a similar rend. For pa ien s recei ing beinagl ide mono herap , he a erage change in HbA_{1c}, 2-h PPG and FPG grad all decreased o er 3 mon hs and reached −2.83% (−2.53 o −3.12), −5.44 mmol L^{-1} (−4.88 o −5.99) and −2.97 mmol L^{-1} (−2.67 o −3.27) (all $p < 0.0001$) af er 3 mon hs of rea - men , respec i el . For pa ien s recei ing combina ion herap i h beinagl ide and ins lin glargine, he a er- age change in HbA_{1c}, 2-h PPG and FPG af er 3 mon hs reached −2.94% (−2.49 o −3.39), −5.24 mmol L^{-1} (−4.27 o −6.21) and −3.10 mmol L^{-1} (−2.55 o −3.64) (all $p < 0.0001$), respec i el .

De ailed res l s (mean differences, s andard error and 95% CI) of he emporal rends in HbA_{1c}, 2-h PPG, FPG and bod eigh are repor ed in Tables S1–S3.

Changes in bod eigh and HbA_{1c} according o baseline charac eris ics and he dose of beinagl ide

The changes in bod eigh did no ar significan l b se ($p = 0.097$), age ($p = 0.157$), diabe es d ra ion ($p = 0.157$) or baseline HbA_{1c} ca egories ($p = 0.949$). The changes in HbA_{1c} also did no ar significan l b se ($p = 0.471$), age ($p = 0.249$), diabe es d ra ion ($p = 0.169$) or baseline BMI ca egories ($p = 0.964$). Ho e er, he changes in bod eigh ere significan l grea er in pa ien s i h ≥28 kg m^{-2} of baseline BMI and in pa ien s recei ing beinagl ide 0.60 mg ($p = 0.007$ and $p < 0.0001$, respec i el); and he changes in HbA_{1c} ere significan l grea er in pa ien s i h ≥9.0% baseline HbA_{1c} and in pa ien s recei ing beinagl ide of 0.40–0.48 mg (all $p < 0.0001$) (Fig re S1).

De erminan s of eigh loss and HbA_{1c} red c ion

The res l s of m l iple linear regression models sho ed ha eigh loss from baseline o 3 mon hs posi i el correla ed i h baseline BMI le els and he dose of beinagl ide, and he HbA_{1c} red c ion from baseline o 3 mon hs posi i el correla ed i h baseline HbA_{1c} le els and he dose of beinagl ide (Table S4 and S5).

Ad erse e en s, h pogl caemic e en s and discon in a ion

Among pa ien s in he FAS, he mos common ad erse e en s ere gas roin es inal s mp oms, incl ding na sea (51.0%) and omi ing (18.2%). O her repor ed ad erse e en s ere di iness (17.2%) and headache (8.3%). These ad erse e en s anoainl occ rred in he firs mon h af er ini ia ion of rea men , and mos ere mild o moder- a e. A o al of 14 s mp oma ic h pogl caemic e en s ere recorded i hin he 3 mon hs prior o beinagl ide rea men , b no s ch e en s ere repor ed af er beinagl ide rea men . A o al of 26 pa ien s (8.3%) discon in ed beinagl ide herap i hin 3 mon hs o ing o gas roin es inal side effec s (5.7%), rea men fail re (2.2%) or naffordable cos (0.3%).

Sensi i i anal sis performed on he comple er's da a i ho LOCF imp a ion as generall consis en i h he concl sions of he aforemen ioned s d res l s (da a no sho n).

D sc i ss

The presen s d is he firs m l icen re, obser a ional, re rospec i e, open-label anal sis of beinagl ide effec- i eness in T2DM pa ien s, mos l i h o er eigh and obesi , in China. These da a demons ra ed a mean eigh loss of 10.05 kg and a mean red c ion of 2.87% in HbA_{1c} af er 3 mon hs of rea men . These obser a ions confirmed he effec i eness of beinagl ide in a real- orld se ing.

The pa ien s incl ded in he presen s d represen ed a general T2DM pop la ion in a real- orld se ing in China. Baseline da a indica ed ha beinagl ide herap as commonl prescribed for pa ien s i h o er eigh and obesi ho had a rela i el shor disease d ra ion. No abl , 27.7% of he pa ien s ere ne l diagnosed i h T2DM, indica ing ha beinagl ide as generall accep ed as a second-line rea men .

For he Chinese people, a BMI be een 24.0 and 27.9 kg m^{-2} is defined as o er eigh , and a BMI ≥ 28.0 kg m^{-2} is ca egori ed as obese (10). In he presen s d , 56.5% of pa ien s ere o er eigh , 41.2% ere obese and onl 2.3% ere normal eigh . When anal sing he eigh -loss effec of beinagl ide on he basis of baseline BMI, pa ien s i h o er eigh and obesi e perienced grea er eigh -loss effec s. This BMI-dependen effec as similar o ha in a pre io s s d of liragl ide (11,12). Da a for normal eigh Chinese pa ien s ere onl a ailable for si indi id als, making es ima es for his s bgro p nreliable. Similar o o her s dies of GLP- 1RAs (13,14), he eigh -loss effec of beinagl ide as dose dependen , i h he highes dose (0.6 mg) pro iding he grea es eigh loss. In addi ion, based on o r res l s, se , age and disease d ra ion had no impac on dr g ef- ficac i h regard o ei her gl caemic con rol or eigh loss, hich as consis en i h pre io s s dies of GLP-1RAs (11,15).

The mean red c ion in HbA_{1c} in his s d as higher han mean red c ions repor ed in he pre io s RCTs of

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beinagl ide, in hich mean red c ions from baseline be-

S e e - ss s ce

The a hors ackno ledge Yale D an, Ning D and G i Zhao (Shanghai Benemae Pharmace ical Corpora ion) for s a is ical and edi orial assis ance.

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This s d as s ppor ed b he Na ral Science Fo nda ion of Hebei Pro ince (gran no. H2013209053). The English-lang age edi ing fee and p blica ion charge ere f nded b Shanghai Benemae Pharmace ical Corpora ion.

C -c s - e ,e s s e e

The a hors ha e declared ha he ha e no conflic s of in eres associa ed i h his s d .

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