ORIGINAL ARTICLE

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Aims

The p rpo e of hi d a o e amine he effec i ene of beinagl 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 beinagl 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 beinagl 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

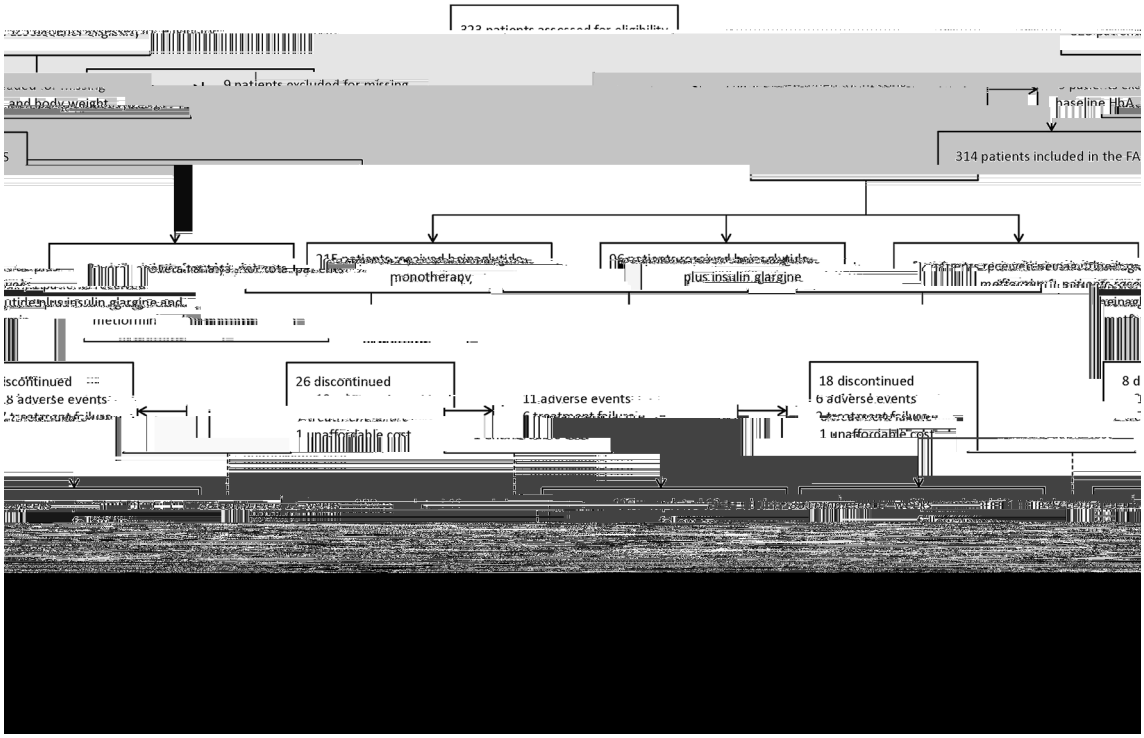
of HbA_{1c} red c ion and eigh lo . Independen ari- able incl ded age, e , diabe e d ra ion, ba eline HbA_{1c}, BMI, SBP, rigl ceride , LDL-C, HDL-C and he do e of beinagl ide. $p < 0.05$ a con idered a i i- call ignifican (o ailed). Da a ere anal ed ing SPSS 23 of are (IBM SPSS, USA).

Ba ed on he da a i ho imp a ion for mi ing al e (i.e. ob er ed da a onl), a en i i i anal i a cond c ed o a e he her he LOCF me hod for handling mi ing da a migh ha e infl enced an cri ical concl ion .

R e .

Ba eline charac eri ic of pa ien

From Jan ar 2017 o March 2018, da a from 323 pa ien rea ed i h beinagl ide ere e rac ed from he elec ronic medical record em. Of ho e, nine pa- ien lacked ba eline da a for HbA_{1c} and bod eigh (nkno n rea on) and ere e cl ded from he anal i . The remaining 314 pa ien ere incl ded in he FAS (ee 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) ear . Mo pa ien (60.3%) had a diabe e d ra ion < 5 ear . On a erage, ba eline bod eigh a 77.94 (10.91) kg, BMI a 27.95 (4.07) kg m^{-2}, HbA_{1c} a 9.05 (1.48)%, 2-h PPG a 14.23 (3.23) mmol L^{-1} and FPG a 9.25 (1.77) mmol L^{-1}. Ba eline charac eri - ic of he FAS pop la ion are mmari ed in Table 1. Appro ima el 27.7% of he FAS pop la ion ere dr g-na e pa ien ho ere ne l diagno ed i h T2DM. Regarding he hi or of pre io an i-diabe ic medica ion before ini ia ing beinagl ide, 30.3% of pa ien had been rea ed pre io l i h me formin, 14.0% i h repaglinide, 12.7% i h acarbo e, 10.8% i h lfon l rea, 8.6% i h hor -ac ing in lin, 7.0% i h ba al in lin, 1.9% i h DPP4 inhibi or and 1.0% i h liragl ide. In addi ion, 48.1% of pa ien had recei ed one an i-diabe ic agen , 21.0% recei ed o an i-diabe ic agen and a mall propor ion (3.2%) recei ed hree an i-diabe ic agen prior o beinagl ide rea men . Regarding diabe ic complica ion , 12.7% and 1.3% of pa ien pre en ed i h a per onal hi or of coronar hear di ea e and brain infarc ion, re pec i el . Diabe ic peripheral ne ropa h , nephropa h and re inop- a h ere pre en in 40.4%, 13.7% and 2.2% of pa ien , re pec i el . A o al of 10.5% of pa ien pre en ed i h bo h diabe ic peripheral ne ropa h and nephropa h , and a mall propor ion (0.1%) pre en ed i h diabe ic pe- ripheral ne ropa h , nephropa h and re inopa h . H per- en ion a pre en in 51.9% of pa ien , 84.0% of hom



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

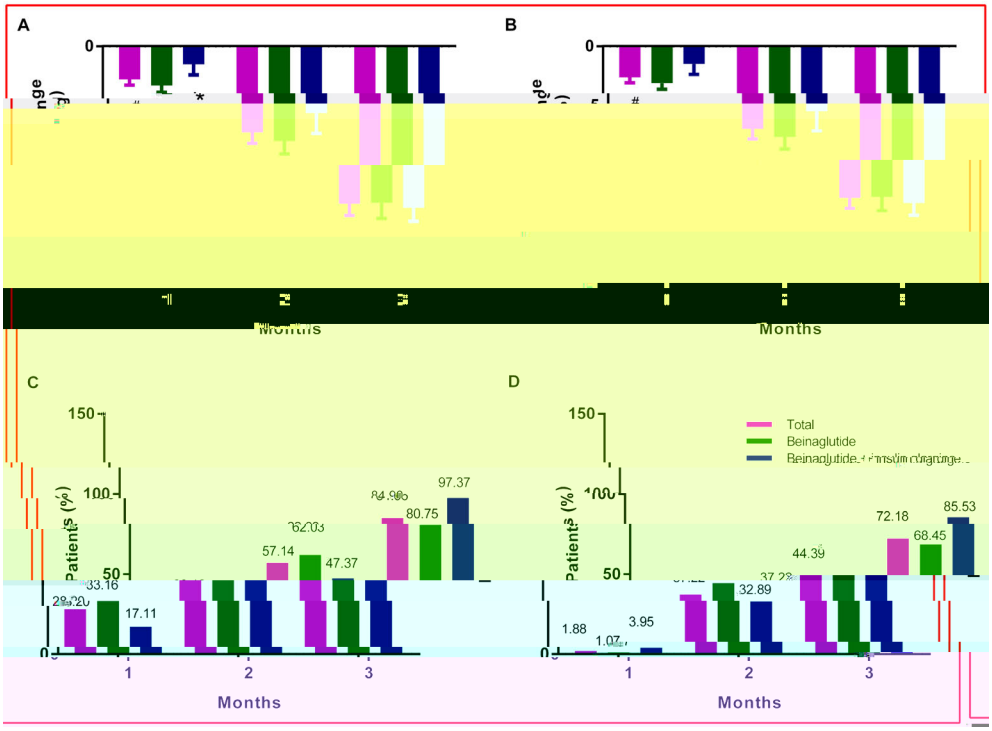
Beinagl ide admini ra ion

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 .

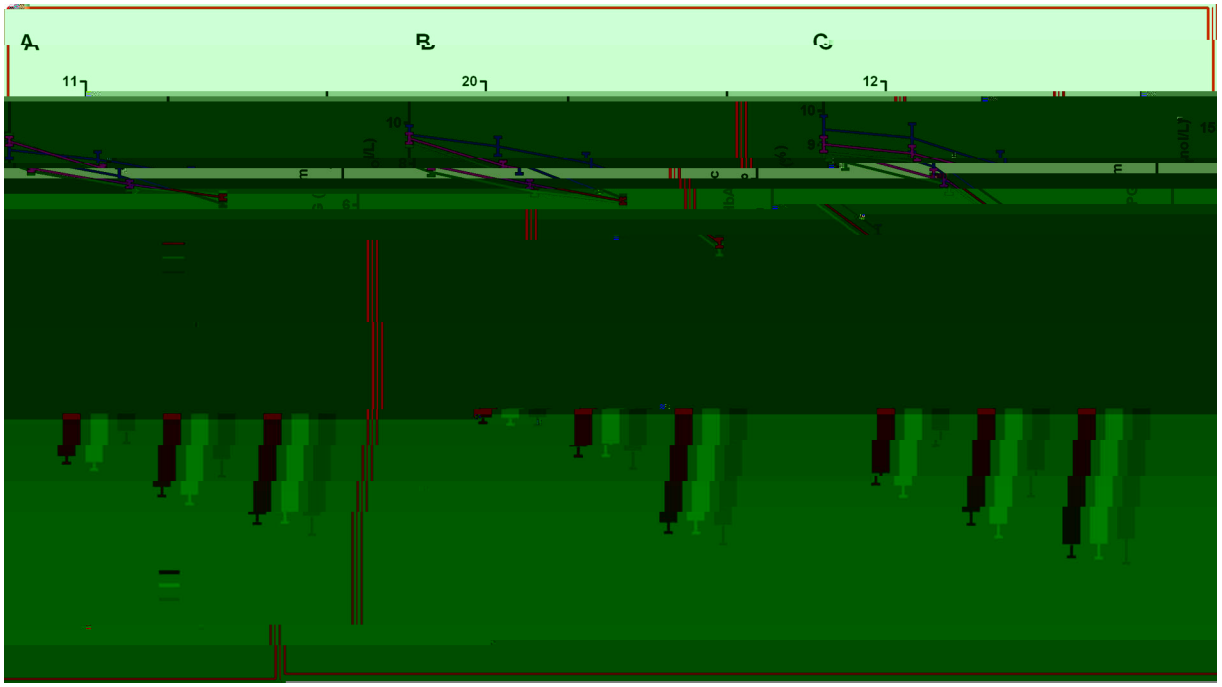
Clinical o come af er 3 mon h of beinagl ide

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

					S 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((119.04.7(bpm64))	(1617)	
<0.0001	b3944640.0013 (0.67)		9(4672)	<0.0001								



F e 2 Temporal rend in bod eigh be een ba eline and 3 mon h . (A) Ab ol 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 J l 2019, af er fir online p blica ion: Fig re 2 ha been replaced in hi er ion.]



F e 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.

change in 2-h PPG and FPG af er 3 mon h reached −5.46 mmol L^{-1} (−4.96 o −5.95) and −3.04 mmol L^{-1} (−2.78 o −3.31) (all $p < 0.0001$), re pec i el . The a i - ical re l of he bgro p ho ed a imilar rend. For pa ien recei ing beinagl ide mono herap , he a erage change in HbA_{1c}, 2-h PPG and FPG grad all decrea ed o er 3 mon h 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 h of rea - men , re pec i el . For pa ien recei ing combina ion herap i h beinagl ide and in lin glargine, he a er- age change in HbA_{1c}, 2-h PPG and FPG af er 3 mon h 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 $p < 0.0001$), re pec i el .

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

Change in bod eigh and HbA_{1c} according o ba eline charac eri ic and he do e of beinagl ide

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

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

The re l of m l iple linear regre ion model ho ed ha eigh lo from ba eline o 3 mon h po i i el correla ed i h ba eline BMI le el and he do e of beinagl ide, and he HbA_{1c} red c ion from ba eline o 3 mon h po i i el correla ed i h ba eline HbA_{1c} le el and he do e of beinagl ide (Table S4 and S5).

Ad er e e en , h pogl caemic e en and di con in a ion

Among pa ien in he FAS, he mo common ad er e e en ere ga roin e inal mp om , incl ding na ea (51.0%) and omi ing (18.2%). O her repor ed ad er e e en ere di ine (17.2%) and headache (8.3%). The e ad er e e en anoainl occ rred in he fir mon h af er ini ia ion of rea men , and mo ere mild o moder- a e. A o al of 14 mp oma ic h pogl caemic e en ere recorded i hin he 3 mon h prior o beinagl ide rea men , b no ch e en ere repor ed af er beinagl ide rea men . A o al of 26 pa ien (8.3%) di con in ed beinagl ide herap i hin 3 mon h o ing o ga roin e inal ide effec (5.7%), rea men fail re (2.2%) or naffordable co (0.3%).

Sen i i i anal i performed on he comple er' da a i ho LOCF imp a ion a generall con i en i h he concl ion of he aforemen ioned d re l (da a no ho n).

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The pre en d i he fir m l icen re, ob er a ional, re ro pec i e, open-label anal i of beinagl ide effec- i ene in T2DM pa ien , mo l i h o er eigh and obe i , in China. The e da a demon ra ed a mean eigh lo of 10.05 kg and a mean red c ion of 2.87% in HbA_{1c} af er 3 mon h of rea men . The e ob er a ion confirmed he effec i ene of beinagl ide in a real- orld e ing.

The pa ien incl ded in he pre en d repre en ed a general T2DM pop la ion in a real- orld e ing in China. Ba eline da a indica ed ha beinagl ide herap a commonl pre cribed for pa ien i h o er eigh and obe i ho had a rela i el hor di ea e d ra ion. No abl , 27.7% of he pa ien ere ne l diagno ed i h T2DM, indica ing ha beinagl ide a generall accep ed a a econd-line rea men .

For he Chine e people, a BMI be een 24.0 and 27.9 kg m^{-2} i defined a o er eigh , and a BMI ≥ 28.0 kg m^{-2} i ca egori ed a obe e (10). In he pre en d , 56.5% of pa ien ere o er eigh , 41.2% ere obe e and onl 2.3% ere normal eigh . When anal ing he eigh -lo effec of beinagl ide on he ba i of ba eline BMI, pa ien i h o er eigh and obe i e perienced grea er eigh -lo effec . Thi BMI-dependen effec a imilar o ha in a pre io d of liragl ide (11,12). Da a for normal eigh Chine e pa ien ere onl a ailable for i indi id al , making e ima e for hi bgro p nreliable. Similar o o her die of GLP- 1RA (13,14), he eigh -lo effec of beinagl ide a do e dependen , i h he highe do e (0.6 mg) pro iding he grea e eigh lo . In addi ion, ba ed on o r re l , e , age and di ea e d ra ion had no impac on dr g ef- ficac i h regard o ei her gl caemic con rol or eigh lo , hich a con i en i h pre io die of GLP-1RA (11,15).

The mean red c ion in HbA_{1c} in hi d a higher han mean red c ion repor ed in he pre io RCT of

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

S e e - - e

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

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

C - - e,e - e e -

The a hor ha e declared ha he ha e no conflic of in ere a ocia ed i h hi d .

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