ORIGINAL ARTICLE

[illegible]

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Aims

The e f hi d a e a i e he effec i e e f bei agl ide b d eigh , gl ca ed hae gl bi (HbA1c), bl d e e a d li id file i a ie i h e 2 diabe e elli (T2DM) i a eal- ld e i g i Chi a.

Materials and methods

Thi a a l ice e, b e a i al, e ec i e, e -label d c d c ed i Chi a. Da a e e c llec ed f T2DM a ie h a ed ea e i h bei agl ide be ee 2017 a d 2018.

Results

A al f 314 a ie e e i cl ded i he d . Af e 3 h f ea e i h bei agl ide, he e e e ig ifica ed c i i b d eigh (−10.05 kg [95% c fi-de ce i e al −9.29 −10.80]), HbA1c (−2.87% [−2.62 −3.11]), 2-h a dial la a gl c e (−5.46 l L−1 [−4.96 −

ic ea i g a e i ig hei c ehe i e effec b h gl cae ic c l a d eigh l ih l h gl cae ia i cide ce.

Bei agl ide (f e l k a be agl ide), a GLP-1RA, i ec bi a h a gl cag -like e ide-1 a d ha e 100% h l g ih h a GLP-1(7-36) (5). The d g a a ed b he Chi a F d a d D g Ad- i i a i f he ea e f T2DM i Dece be 2016. Bei agl ide i e f he GLP-1RA ec e ded f he ea e f T2DM b he Chi e e g ideli e f he e e i a d ea e f e 2 diabe e (2017 edi i) (6). The efficac a d afe f bei agl ide ha e bee a e ed i a d i ed c lled ial (RCT) i Chi a (7–9). Si ila he GLP-1RA , bei agl ide a effec- i e i l e i g gl ca ed hae gl bi (HbA_{1c}), fa i g la a gl c e (FPG) a d a dial la a gl c e (PPG) i a ie ih T2DM (7,8). I addi i , bei agl ide ed ced b d eigh a d b d a i de (BMI) i T2DM a ie ih e eigh a d be i (7,9). The e RCT ided e ide ce f he effec i e e f bei agl ide i a ell-defi ed a ie la i de a ic l c lled e i e , e i i ce ai ha e he e l ca be a la ed eal- ld cli ical ac ice he e a e ge e al a ie la i i ea ed ih he e i e e i i a ie cli ic .

Real- ld die a e e i a f he eal- a e he e f a ce f e d g ce he each he a ke . S ch die ca c le e RCT a d a e hei e l i a e ge e al a ie la i . The eal- ld effec f bei agl ide ha e bee e ed da e. Th , he e f hi d a e a i e he effec i e e f bei agl ide HbA_{1c}, b d eigh , bl d e e, a d li id file i a eal- ld e i g i Chi a. The a h h e i ed ha he efficac f bei agl ide i RCT ill al be b e ed i he eal- ld d .

M e , e a

Thi a a lice e, be e a i al, e ec i e, e e -label d c d c ed i h i al i Hebei P ice (he Chi a). The GLP-1RA bei agl ide a la ched i Feb a 2017 i Chi a. Si ce he , da a f T2DM a ie ea ed ih bei agl ide de i e cli ical ac ice c di i e e c ec i el c llec ed il Ma ch 2018, i.e. e a i e f a e f 14 h . Da a e e e ac ed f he elec ic edical ec d e a d ga he ed i a E cel da a hee b he e ea che . Ad l T2DM a ie (≥18 ea) e e eligible f he d . The e cl i ci e ia e e a ie ih e 1 diabe e elli a d h e h ef ed ide i f ed c e . The f ll ig da a e e c llec ed a ba eli e a d/ h ee b e e i i (afe 1, 2 a d 3 h f ea e): age, e , diabe e d a i , HbA_{1c}, 2-h PPG, FPG, b d eigh , BMI, ai ci c fe e ce (WC), C e ide, hea a e, lic bl d e e (SBP), dia lic bl d e e (DBP), igl ce ide , l -de i li ei ch le e l (LDL-C), high-de i li ei ch le e l (HDL-C), a i- h e e i e a d li id-l e i g he a ie a d hi f e i a i-diabe ic edica i . M e e, he d age f bei agl ide a d c c i a a i-diabe ic he a ie a ec ded. The al e f HbA_{1c}, FPG, 2-h PPG, C- e ide, igl ce ide , LDL-C a d HDL-C e e e ac ed f a da di ed lab a e e l . B d eigh , WC, hea a e, SBP a d DBP e e ea ed b fi- cie e ig a da de i e .

The i a d bjec i e a a e he effec- i e e f bei agl ide i c lli g gl cae ia af e 3 h f ea e . Sec da bjec i e i cl ded a e i g cha ge i b d eigh , he i f a ie ih eigh l ≥ 5% a d ≥10% a d he cli ical a a e e ela ed diabe e af e 3 h f ea e . Ad e e e e , h gl cae ic e e a d di c i a i f bei agl ide e e al acked.

Thi d a a ed b he l cal e hical c i- ee a d e f ed i acc da ce ih he Decla a i f Hel i ki (e i ed i 2013).

S a i ical a al i

The K l g –S i e a ed de e i e if al e e e all di ib ed. Da a f c i a iable e e e e ed a he ea (a da d de ia- i [SD]). Da a f ca eg ical a iable e e e e ed a e ce age (%). Ba eli e cha ac e i ic a e e ed he ba i f he f ll a al i e (FAS), hich i cl ded all a ie h e he eligibili ci e ia a d had ba eli e ea e f HbA_{1c} eigh . Efficac a al i i cl ded all a ie h ece ied a lea e d e f bei agl ide a d had a lea e ba eli e ea e- e f HbA_{1c} b d eigh . Mi i g al e e i ed i g he la b e a i ca ied f a d (LOCF) e h d. F ai ed a le , he ai ed *t*- e Wilc a ched ai ig ed- a k e a ed f i e i , a d e ea ed- ea e a al i f a ia ce he F ied a e f ll ed b D ' li le- c a i e a ed f li le i e i . The ea (SD), ea diffe e ce, a da d e (SE) a d 95% c fide ce i e al (CI) e e calc la ed f each i e i . S bg a al e f a ied a le e e e f ed ih he a e a i ical e h d. The cha ge i HbA_{1c} a d eigh e e a e ed b a al i f c a ia ce, adj i g f ba eli e ea e a d he d e f bei agl ide a c a ia e. A li a ia eli- ea eg e i del a lied ide if de e i a

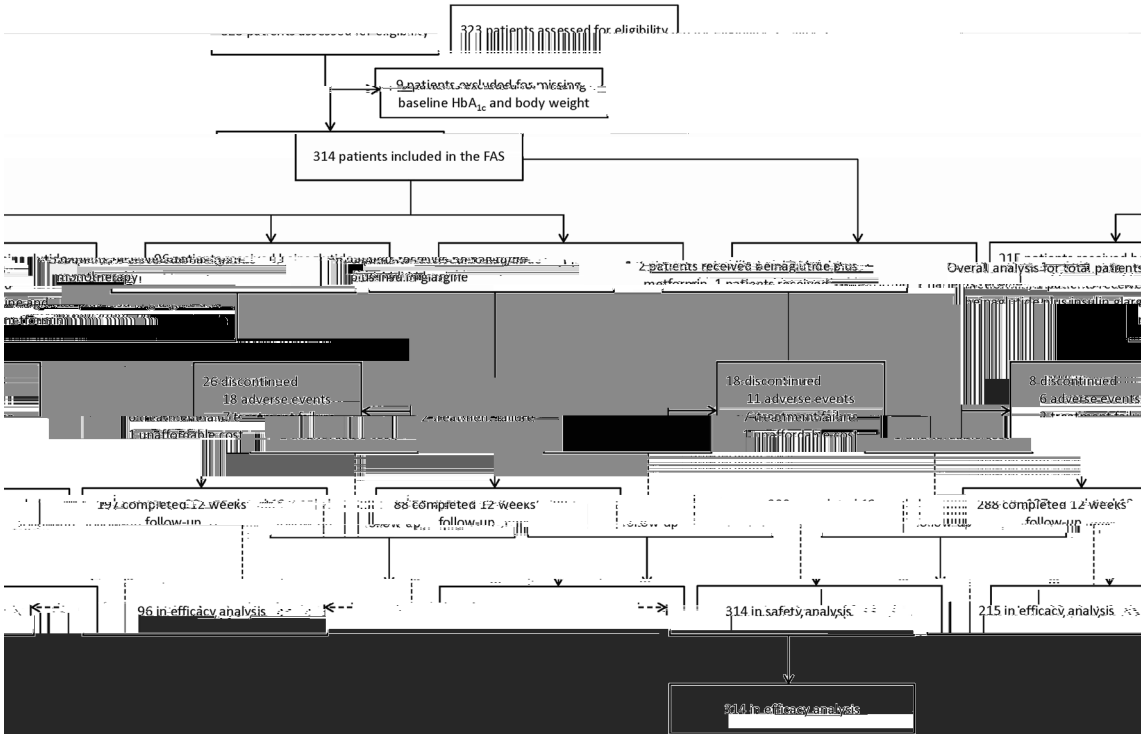
of HbA_{1c} ed ci ad eigh l . I de ede ai able i cl ded age, e , diabe e d a i , ba eli e HbA_{1c}, BMI, SBP, igl ce ide , LDL-C, HDL-C a d he d e f bei agl ide. $p < 0.05$ a c ide ed a i i call ig ifica (ailed). Da a e e a al ed i g SPSS 23 f a e (IBM SPSS, USA).

Ba ed he da a ih i ai f i ig al e (i.e. b e ed da a l), a e ii i a al i a c d c ed a e he he he LOCF eh d f ha dli g i i g da a igh ha e i fl e ced a c ical c cl i .

R

Ba eli e cha ac e i ic f a ie

F Ja a 2017 Ma ch 2018, da a f 323 a ie ea ed ih bei agl ide e e e ac ed f he elec ic edical ec d e . Of h e, i e a ie lacked ba eli e da a f HbA_{1c} a d b d eigh (k ea) a d e e e cl ded f he a al i . The e ai i g 314 a ie e e i cl ded i he FAS (ee fl cha i Fig e 1). The e e e 163 (51.9%) e a d 151 (48.1%) e , ih a e all ea age f 47.6 (10.5) ea . M a ie (60.3%) had a diabe e d a i < 5 ea . O a e age, ba eli e b d eigh a 77.94 (10.91) kg, BMI a 27.95 (4.07) kg $^{-2}$, HbA_{1c} a 9.05 (1.48)%, 2-h PPG a 14.23 (3.23) l L^{-1} a d FPG a 9.25 (1.77) l L^{-1}. Ba eli e cha ac e i ic f he FAS e la i a e a i ed i Table 1. A i a el 27.7% f he FAS e la i e e d g- a e a ie h e e l diag ed ih T2DM. Rega di g he hi f e i a i-diabe ic edica i bef e i ii a i g bei agl ide, 30.3% f a ie had bee ea ed e i l ih e f i , 14.0% ih agli ide, 12.7% ih aca b e, 10.8% ih lf l ea, 8.6% ih h -ac i g i li , 7.0% ih ba al i li , 1.9% ih DPP4 i hibi a d 1.0% ih li agl ide. I addi i , 48.1% f a ie had ece ied e a i-diabe ic age , 21.0% ece ied a i-diabe ic age a d a all i (3.2%) ece ied h ee a i-diabe ic age i bei agl ide ea e . Rega di g diabe ic c lica i , 12.7% a d 1.3% f a ie e e ed ih a e al hi f c a hea di ea e a d b ai i fac i , e ec iel . Diabe ic e i he al e ah , h ah a d e i - ah e e e i 40.4%, 13.7% a d 2.2% f a ie , e ec iel . A al f 10.5% f a ie e e ed ih b h diabe ic e i he al e ah a d h ah , a d a all i (0.1%) e e ed ih diabe ic e i he al e ah , h ah a d e i ah . H e e i a e e i 51.9% f a ie , 84.0% f h



F e 1 S d fl cha . FAS, f ll a al i e ; HbA_{1c}, gl ca ed hae gl bi .

ecei ed a i-h e e ie ea e . D ji idae ia a e e i 33.4% f a ie , 79.0% f h ecei ed ji id-l ei g ea e .

Bei agl ide ad i i a i

A ba eli e, 215 a ie (68.5%) ed bei agl ide he a , 96 (30.6%) ed bei agl ide i c bi a- i ih i li gla gi e, (0.6%) i c bi a i ih e f i a d e (0.3%) i c bi a i ih i li gla gi e a d e f i . A ba eli e, 37.6% f he a ie e e c ibed a dail d e f 0.2 g, 52.3% ecei ed 0.3 g, 5.5% ecei ed 0.4 g, 0.5% ecei ed 0.45 g a d 4.1% ecei ed 0.6 g f bei agl ide. F ll i g a e i d f d e e cala i f 1–2 ek , e c i f 0.2, 0.3, 0.4, 0.42, 0.48 a d 0.6 g f bei agl ide e e gi e 31.2%, 5.7%, 2.1%, 11.3%, 22.7% a d 27.1% f he a ie , e ec i el . I addi- i , 96.0% f a ie ca ied le e al life le i e e i .

Cli ical c e af e 3 h f bei agl ide ea e

Cli ical a a e e a ba eli e a d he 3- h f ll - a e e e ed i Table 2. C a ed ih ba eli e, af e 3 h f ea e , he a ie h ed ig ifica ed c i i b d eigh , HbA_{1c}, 2-h PPG, FPG, BMI, WC, hea a e, SBP, DBP, igl ce ide a d LDL-C a d a ig ifica ele a i i HDL-C (all $p < 0.0001$). I bg a ie ecei i g bei agl ide he a bei agl ide i c bi a i ih i li gla gi e h ed i ila e l ($p < 0.001$). C e ide h ed a ig ifica ed c i f ba eli e 3 h i he al la i f a ie ($p = 0.0016$) a d he a ie h ecei ed he a ($p < 0.0001$), b i h e- cei i g bei agl ide i c bi a i ih i li gla gi e ($p = 0.4464$).

Te al e d i b d eigh cha ge a e h i Fig e 2. Sig ifica eigh l a b e ed a all i e i . F he al la i f a ie , b d eigh a dec ea ed b −10.05 kg (−9.29 −10.80) a d −12.90% (−12.02 −13.78) af e 3 h (all $p < 0.0001$). Af e 3 h , 84.96% a d 72.18% f a ie a ai ed eigh l f ≥5% a d ≥10%, e ec i el . S bg a al e h ed i ila e l . Af e 3 h , b d eigh a dec ea ed b −9.98 kg (−8.97 −10.99) a d −12.81% (−11.64 −13.97) i bei agl ide he a a ie a d b −10.30 kg (−9.43 −11.16) a d 13.33% (−12.28 −14.38) he ad i i e ed i c bi a i ih i li gla gi e (all $p < 0.0001$). F he e, a 3 h , he i f a- ie ih eigh l f ≥5% a d ≥10% e e 80.75% a d 68.45% f he a a d 97.37% a d 85.53% f he c bi a i he a ih i li gla gi e, e ec i el .

Te al e d i HbA_{1c}, 2-h PPG a d FPG a e h i Fig e 3. F he al la i f a ie , he a e age cha ge i HbA_{1c}

T e 2 Cli ica a a e e c a ed i h ba eli e af e 3- h bei agl ide ea e

					Subgroups							
		Total (N = 314)			Beiagl ide (N = 215)				Beiagl ide + i li gla gi e (N = 96)			
Va iable	N	Ba eli e	Af e ea e	p	N	Ba eli e	Af e ea e	p	N	Ba eli e	Af e ea e	p
B d 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, l 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, l 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 (0.59TD()Tj/F21Tf.7710TD(0.0001)Tj-81	
								<0.0001				
<			<0.0001	67			<0.0001					

cha ge i 2-h PPG a d FPG af e 3 h eached -5.46 l L^{-1} (-4.96, -5.95) a d -3.04 l L^{-1} (-2.78, -3.31) (all $p < 0.0001$), e ec i el . The a i - ical e l f he bg h ed a i ila e d. F a ie ecei i g bei agl ide he , he a e age cha ge i HbA_{1c}, 2-h PPG a d FPG g ad all dec ea ed e 3 h a d eached -2.83% (-2.53, -3.12), -5.44 l L^{-1} (-4.88, -5.99) a d -2.97 l L^{-1} (-2.67, -3.27) (all $p < 0.0001$) af e 3 h f ea - e , e ec i el . F a ie ecei i g c bi a i he i h bei agl ide a d i li gla gi e, he a e - age cha ge i HbA_{1c}, 2-h PPG a d FPG af e 3 h eached -2.94% (-2.49, -3.39), -5.24 l L^{-1} (-4.27, -6.21) a d -3.10 l L^{-1} (-2.55, -3.64) (all $p < 0.0001$), e ec i el .

De ailed e l (ea diffe e ce , a da d e a d 95% CI) f he e al e d i HbA_{1c}, 2-h PPG, FPG a d b d eigh a e ed i Table S1–S3.

Cha ge i b d eigh a d HbA_{1c} acc di g ba eli e cha ac e i ic a d he d e f bei agl ide

The cha ge i b d eigh did a ig ifica l b e ($p = 0.097$), age ($p = 0.157$), diabe e d a i ($p = 0.157$) ba eli e HbA_{1c} ca eg ie ($p = 0.949$). The cha ge i HbA_{1c} al did a ig ifica l b e ($p = 0.471$), age ($p = 0.249$), diabe e d a i ($p = 0.169$) ba eli e BMI ca eg ie ($p = 0.964$). H e e , he cha ge i b d eigh e e ig ifica l g ea e i a ie i h ≥28 kg $^{-2}$ f ba eli e BMI a d i a ie ecei i g bei agl ide 0.60 g ($p = 0.007$ a d $p < 0.0001$, e ec i el); a d he cha ge i HbA_{1c} e e ig ifica l g ea e i a ie i h ≥9.0% ba eli e HbA_{1c} a d i a ie ecei i g bei agl ide f 0.40–0.48 g (all $p < 0.0001$) (Fig e S1).

De e i a f eigh l a d HbA_{1c} ed c i

The e l f l le li ea eg e i del h ed ha eigh l f ba eli e 3 h i i el c ela ed i h ba eli e BMI le el a d he d e f bei agl ide, a d he HbA_{1c} ed c i f ba eli e 3 h i i el c ela ed i h ba eli e HbA_{1c} le el a d he d e f bei agl ide (Table S4 a d S5).

Ad e e e e , h gl cae ic e e a d di c i a i

A g a ie i he FAS, he c ad e e e e e e ga i e i al , i cl di g a ea (51.0%) a d i i g (18.2%). O he ed ad e e e e e e di i e (17.2%) a d headache (8.3%). The e ad e e e e ai l cc ed i he fi h af e i i ia i f ea e , a d e e ild de - a e. A al f 14 a ic h gl cae ic e e e e ec ded i hi he 3 h i bei agl ide ea e , b ch e e e e ed af e bei agl ide ea e . A al f 26 a ie (8.3%) di c i ed bei agl ide he i hi 3 h i g ga i e i al ide effec (5.7%), ea e fail e (2.2%) aff dable c (0.3%).

Se i i i a al i e f ed he c le e' da a i h LOCF i a i a ge e all c i e i h he c cl i f he af e e i ed d e l (da a h).

D c

The e e d i he fi l ice e, b e a i al, e ec i e, e -label a al i f bei agl ide effec- i e e i T2DM a ie , l i h e eigh a d be i , i Chi a. The e da a de a ed a ea eigh l f 10.05 kg a d a ea ed c i f 2.87% i HbA_{1c} af e 3 h f ea e . The e b e a i c fi ed he effec i e e f bei agl ide i a eal- ld e i g.

The a ie i cl ded i he e e d e e ed a ge e al T2DM la i i a eal- ld e i g i Chi a. Ba eli e da a i dica ed ha bei agl ide he a c l e c ibed f a ie i h e eigh a d be i h had a ela i el h di ea e d a i . N abl , 27.7% f he a ie e e e l diag ed i h T2DM, i dica i g ha bei agl ide a ge e all acc ed a a ec d-li e ea e .

F he Chi e e le, a BMI be ee 24.0 a d 27.9 kg $^{-2}$ i defi ed a e eigh , a d a BMI ≥ 28.0 kg $^{-2}$ i ca eg i ed a be e (10). I he e e d, 56.5% f a ie e e e eigh , 41.2% e e be e a d l 2.3% e e al eigh . Whe a al i g he eigh -l effec f bei agl ide he ba i f ba eli e BMI a ie i h e eigh a d be i e e ie ced g ea e eigh -l effec . Thi BMI-de e de effec a i ila ha i a e i d f li agl ide (11,12). Da a f al eigh Chi e a ie e e l a ailable f i i di id al , aki g e i a e f hi bg eliable. Si ila he die f GLP-1RA (13,14), he eigh -l effec f bei agl ide a d e de e de , i h he highe d e (0.6 g) idi g he g ea e eigh l . I addi i , ba ed e l , e , age a d di ea e d a i had i ac d g ef-ficac i h ega d ei he gl cae ic c l eigh l , hich a c i e i h e i die f GLP-1RA (11,15).

The ea ed c i i HbA_{1c} i hi d a highe ha ea ed c i ed i he e i RCT f

bei agl ide, i hich ea ed c i f ba eli e be- ee 0.7% a d 1.2% ha e bee e ed (7,9). Thi e- l a e i e e ig beca e HbA_{1c} ed c i i eal- ld g ha e all bee alle ha h e i RCT acc di g Edel a a d P l k' d (16). P e i die ha e e ed ha ba eli e HbA_{1c} le el igh edic a ea l e e GLP-1RA i e f HbA_{1c} ed c i (15,17). I he e e d, HbA_{1c} ed c i a i i el c ela ed i h ba eli e HbA_{1c} le el ; ha i, i.e. a ie i h highe ba eli e HbA_{1c} le el had a g ea e HbA_{1c} ed c i af e 3 h f ea e . C a ed i h e i RCT f bei agl ide (ea ba eli e HbA_{1c} be ee 7.97% a d 8.05%) (7,9), he highe ba eli e HbA_{1c} le el (9.02%) i hi d a be a i a ea f he ic ea ed efficac b e ed i h bei agl ide ea e .

Thi di c a c igh al be e lai ed b a cha ge i he f la i f bei agl ide. I e i RCT , bei agl ide l hili ed de a ed f i jec i ; ha i, i.e. he de had be di l ed a d he bc a e l i jec ed i h a di able e ile i ge (7–9). Thi f la i ic ea ed he diffic l f a ie e he d g, a d he acc ac f he d g d ea de a ie c lia ce e e affec ed. H e e, a e f la i (bei agl ide i jec i) a de el ed bef e e i g he a ke. I cli ical ac ice a ie ca ea il e a i jec i e f bc a e ad i i a i idi g gea c e ie ce f a ie e c ibed bei agl ide. Th , he cha ge i he f la- i a be a he ea f he ic ea ed efficac f bei agl ide ea e i he eal- ld e i g. I addi- i , he HbA_{1c} ed c i e e e ig ifica i he ela i el high-d e g (0.40–0.48 a d 0.60 g), a d hi fi di g a c i e i h ha f e i die f GLP-1RA (18,19).

Dec ea ed fa i g C e ide le el af e bei agl ide he a gge ed e ial efficac f i ig h e i li ae ia a d β-cell e . A a h -ac i g eal- i e GLP-1RA, bei agl ide ha a h half-life (15 i) a d d a i f aci (2 h) (6). Bei agl ide i la e a dial i li ec e i i a gl c e- de e de a e (20), b he i li ic effec i ai ai ed i he fa i g a e ig id deg a- da i f he d g. Thi c e i be eficial beca e β-cell e e e ec i le β-cell agai e i- la i a di ei le f ci (21,22). Thi he e- f β-cell e a al b e ed i e i die f GLP-1 (7-36) a d e e di -4 i he a dial a e (23–25). F a ie eceii g bei agl ide l i li gla gi e, he e a a dec ea e i C e ide le el , b he e a ig ifica diffe e ce, hich igh be d e l e ba eli e C e ide le el (i.e. β-cell f c- i) i hi g .

The e e d al ide e i f a i ab he be efi f bei agl ide he heal h i dica i a eal- ld e i g. Af e 3 h f ea e , ig ifica ed c i i hea a e, SBP, DBP, al ch le e l a d LDL-C e e b e ed, he ea HDL-C i c ea ed ig ifi- ca l . The e i e e i ca di a c la a d li id file e e ela ed bei agl ide ea e a d l a iall c ib ed b c c ia a i-h e e ie li id-l e i g ea e . The e be efi ge he i h eigh l i lied a i i e i ac f bei agl ide e all ca di a c la c e. H e e, hi c e- he i e be eficial efficac a e ec ed, a i di- ca ed b e i die f GLP-1RA (13,26).

The afe cha ac e i ic f bei agl ide e e al c i e ih e i fi di g f GLP-1RA (27–29). Ga i e i al ad e e e e ec b l a ie . N a ic h gl cae ic e e e ed d i g he 3- h ea e , hich a be e lai ed b he gl c e-de e de i li ic effec a d h half-life f bei agl ide. The ai ca e f bei agl ide di c i a i a ad e e e e (5.7%), hich a i ila e i die f GLP-1RA (30,31).

The e e d ha ig ifica e g h , ch a e e ie cli ical if a i ad i i al ec l i c ie ia, e l i g i e f if l da a gai ed f a ide a ge f T2DM a ie . A a b e a i al a d e- e ec i e d, he lack f a d i a i a dac l g a e he ai li i a i f hi d . I addi i , he f ll e e i d a li ied he fi 3 h f he a f bei agl ide. Addi i al RCT a d eal- ld die a e eeded e al a e he effec i e e a d afe f l g-e bei agl ide ea e .

I a , hi d c fi ed he effec i e e f bei agl ide Chi e e T2DM a ie i a eal- ld e i g. Sig ifica i e e ee b e ed i b d eigh, HbA_{1c}, bl d e e a d li id file af e 3 h f ea e i h bei agl ide. A e d f i e e i he ei li ae ia a d β-cell e al e e ged. S ch be efi e e b e ed de ie a ide a ge f a ie ba eli e cha ac e i ic . The e b e a- i al e l gge ha bei agl ide a be a effec- i e ea e f T2DM, e eciall f a ie i h e eigh a d be i , i cli ical ac ice.

A

S d de ig a e f ed b Y. Z. a d Y. J. Da a c llec i a d a al i e e c d c ed b C. Z., X. L., M. Y., L. T. a d X. Z. Ma c i i g a ca ied b Y. Z. a d Y. J. All a h e ie d a d ed he fi al e i f he a c i .

S e e - ce

The a h ack ledge Yale D a , Ni g D a d G i Zha (Sha ghai Be e ae Pha ace ical C a i) f a i ical a d edi ial a i a ce.

F

Thi d a ed b he Na al Scie ce F da i f Hebei P i ce (g a . H2013209053). The E gli h-la g age edi i g fee a d blica i cha ge e e f ded b Sha ghai Be e ae Pha ace ical C a i .

C - e e e e

The a h ha e decla ed ha he ha e c flic f i e e a cia ed i h hi d .

Re e e ce

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