



Efficacy of Dulaglutide in Chinese Patients with Type 2 Diabetes and Different Glycemic Patterns: a Post-hoc Analysis of the Phase 3 AWARD-CHN2 Trial

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ABSTRACT

Introduction: We evaluated the effect of dulaglutide on the relative contributions of fasting glucose (FG) and postprandial glucose (PPG) to overall hyperglycemia in patients with type 2 diabetes (T2D), and assessed responses to dulaglutide versus insulin glargine (glargine) in patients with different baseline glycemic patterns.

Methods: This post-hoc analysis of the phase 3 AWARD-CHN2 trial included data from 560 Chinese patients with uncontrolled T2D who received once-weekly dulaglutide (1.5 or 0.75 mg) or once-daily glargine for 26 weeks. The

relative contributions of FG and PPG to overall hyperglycemia across different glycated hemoglobin (HbA1c) categories were calculated using the area under the curve of 7-point self-monitored blood glucose profiles. Patients were also categorized into four subgroups according to median baseline FG (cutoff 8.9 mmol/L) and PPG (cutoff 12.5 mmol/L): low FG/low PPG, low FG/high PPG, high FG/low PPG and high FG/high PPG. Changes in glycemic parameters and body weight were calculated for patients in each subgroup.

Results: Among patients receiving dulaglutide, higher HbA1c was associated with higher relative contributions of FG and lower relative contributions of PPG to overall hyperglycemia at baseline and week 26 of dulaglutide treatment. After 26 weeks, dulaglutide 1.5 mg led to statistically greater decreases in HbA1c from baseline versus glargine in most subgroups, including the high FG subgroups, and a numerically greater decrease in HbA1c was observed in the low FG/high PPG subgroup. Across all subgroups, higher proportions of patients achieved $HbA1c \leq 6.5\%$ with dulaglutide 1.5 mg than with glargine (all $P < 0.05$). Dulaglutide 1.5 mg showed better control of body weight than glargine in all subgroups (all $P < 0.05$).

Conclusions: Dulaglutide reduced HbA1c through reductions in both FG and PPG across HbA1c categories in T2D patients with uncontrolled hyperglycemia. Furthermore, treatment

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with dulaglutide provided a greater reduction in HbA1c than glargine, regardless of baseline FG and PPG levels.

Keywords: Dulaglutide; GLP-1 receptor agonist; Basal insulin; Type 2 diabetes; Glycemic pattern

Key Summary Points

Why carry out this study?

In patients with type 2 diabetes (T2D), the interrelationship of glycated hemoglobin (HbA1c) with fasting glucose (FG) and postprandial glucose (PPG) levels changes with the degree of glycemic control, and there is a need for drugs that impact both fasting and postprandial hyperglycemia.

Limited clinical evidence is currently available to determine the relative contributions of FG and PPG to the overall glucose-lowering effects of glucagon-like peptide-1 receptor agonists, such as dulaglutide.

This study of Chinese patients with T2D included in the phase 3 AWARD-CHN2 trial evaluated the effect of dulaglutide on the relative contributions of FG and PPG to overall hyperglycemia across HbA1c categories and assessed treatment responses across patients with different baseline glycemic patterns based on FG and PPG levels.

What was learned from the study?

Dulaglutide reduced HbA1c through reductions in both FG and PPG across HbA1c categories and provided a greater reduction in HbA1c than insulin glargine, regardless of baseline FG and PPG levels.

The findings of this study support once-weekly dulaglutide as an effective therapeutic option for Chinese patients with T2D inadequately controlled by oral anti-hyperglycemic medications.

INTRODUCTION

Type 2 diabetes (T2D) is a chronic progressive metabolic disorder characterized by a combination of varied degrees of insulin resistance and secretion deficiency. Since the 1980s, there has been a remarkable increase in the prevalence of diabetes in China—from 0.67% in 1980 to 11.2% in 2017—in association with aging of the population and westernization of diets and lifestyles [1–3]. Diabetes therefore represents a critical health concern in China. It is well established that achieving optimal control of hyperglycemia reduces the risk of long-term diabetes-related complications. Widely accepted treatment guidelines for T2D in both China and other countries are consistent in recommending an individualized treatment approach to achieve target glycated hemoglobin (HbA1c) levels (commonly defined as HbA1c < 7%), based upon duration of diabetes, life expectancy, comorbidities, vascular complications and other patient-related factors [3–5].

HbA1c reflects an average of overall glycemia during both fasting and postprandial states. The interrelationship of HbA1c with fasting glucose (FG) and postprandial glucose (PPG) levels changes during the progression of T2D [6–8]. A study of non-insulin-using patients with T2D showed that the contribution of PPG to overall hyperglycemia decreased across quintiles of HbA1c, increasing from < 7.3% to > 10.2%, whereas the contribution from FG increased with increasing HbA1c. In patients with HbA1c ranging from 7.3% to 10.2%, the relative contributions of PPG to overall hyperglycemia ranged approximately from 50% to 60% [6]. These data indicate that all components of the glucose triad (HbA1c, FG and PPG) should be considered for optimal management of patients with T2D and highlight the need for drugs that impact both FG and PPG.

Generally, patients with T2D inadequately controlled by comprehensive lifestyle modification and oral anti-hyperglycemic medications (OAMs) require initiation of injectable therapy to achieve optimal glycemic control [9]. The phase 3 AWARD-CHN2 trial was conducted to

compare the efficacy and safety of dulaglutide versus insulin glargine (glargine) in a population of predominantly Chinese patients with T2D and included assessment of HbA1c, PPG and FG. The primary results of the AWARD-CHN2 trial showed that dulaglutide 1.5 mg led to greater reductions in HbA1c with better weight control and a lower incidence of hypoglycemia than glargine [8]. Dulaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA), stimulates insulin secretion and inhibits glucagon release in a glucose-dependent manner in both fasted and postprandial states, and reduces both FG and PPG levels [10]. Other pharmacological effects of GLP-1 RAs include delayed gastric emptying and diminished appetite [11]. Despite these considerations, clinical evidence on the relative contributions of FG and PPG to the overall glucose-lowering effects of GLP-1 RAs is still limited. By contrast, glargine primarily functions by inhibiting hepatic glucose production, consequently lowering FG levels, with only minor effects on PPG [12]. Given these distinct modes of action, it has been hypothesized that patients with different glycemic profiles may respond differently to dulaglutide and glargine treatment. However, there are currently only limited published data to validate this hypothesis in Chinese patients with T2D, and further investigation would be of high value to inform clinical decision-making.

The aims of this post-hoc analysis of the AWARD-CHN2 trial were to evaluate the effect of dulaglutide on the relative contributions of FG and PPG to overall hyperglycemia in Chinese patients with different levels of HbA1c at baseline and at 26 weeks post treatment, and to compare the effect of dulaglutide versus glargine on the relative contribution of FG and PPG to overall hyperglycemia. In addition, the efficacy of dulaglutide versus glargine at 26 weeks was investigated in patients with different baseline FG and PPG categories.

METHODS

Study Design and Participants

This was a post-hoc analysis of Chinese patients with T2D randomized in AWARD-CHN2, a phase 3, open-label (blinded to dulaglutide dose), multicenter, non-inferiority study (ClinicalTrials.gov identifier: NCT01648582). The design and primary results of the AWARD-CHN2 study have been published [8]. Briefly, the study evaluated the efficacy and safety of once-weekly dulaglutide versus once-daily glargine in adult patients (aged ≥ 18 years) with a diagnosis of T2D for at least 6 months before screening, uncontrolled hyperglycemia with metformin and/or a sulphonylurea (HbA1c ≥ 7.0 and $\leq 11.0\%$) and a body mass index (BMI) of ≥ 19.0 and ≤ 35.0 kg/m². Key exclusion criteria were type 1 diabetes, previous receipt of a GLP-1 RA or insulin within 3 months of enrollment, clinically significant gastric emptying abnormalities, history of pancreatitis or serum calcitonin concentration ≥ 20 ng/L. Eligible patients were randomly assigned (1:1:1) to receive once-weekly dulaglutide (1.5 or 0.75 mg) or once-daily glargine, for 26 weeks. The AWARD-CHN2 study protocol was approved by the ethics review board of each trial site, including the master ethics review board at Ruijin Hospital Affiliated to Shanghai Jiao Tong University. The study was conducted in line with the ethical principles outlined in the Declaration of Helsinki of 1964 and its later amendments and with local regulations, and all patients provided written informed consent before randomization.

In this post-hoc analysis, the Chinese patients with T2D were categorized according to self-monitored blood glucose (SMBG) levels into four subgroups: low FG/low PPG, low FG/high PPG, high FG/low PPG and high FG/high PPG. The median baseline values of self-monitored

FG (8.9 mmol/L) and PPG (12.5 mmol/L) among the Chinese patients included in this analysis were used to define the subgroup thresholds (Electronic Supplementary Material [ESM] Fig. 1). It should be noted that these median glucose levels were used as subgroup thresholds because the clinical thresholds of FG (< 7.2 mmol/L) and PPG (< 10.0 mmol/L) commonly used to define glycemic control in patients with T2DM [4] led to unbalanced patient numbers in the subgroups.

Measurements

Efficacy assessments included changes from baseline in HbA1c, FG (central laboratory values), PPG (SMBG values) and the proportion of patients achieving HbA1c targets at week 26. Safety assessments included change in body weight and incidences of overall (plasma glucose \leq 3.9 mmol/L), severe (requiring assistance from another person) and nocturnal hypoglycemia.

Calculation of Glycemic Exposure Over Diurnal Period

The relative contribution of FG and PPG to overall hyperglycemia was evaluated by calculating fasting hyperglycemia and postprandial hyperglycemia, respectively. Overall hyperglycemia, postprandial hyperglycemia and fasting hyperglycemia were calculated using methods reported previously [13]. In brief, overall hyperglycemia (AUC_{overall}) was based on glycemic exposure from the pre-breakfast glucose measurement up to the bedtime glucose measurement and calculated as the area under the curve (AUC) of the 7-point SMBG profiles and above the 5.6 mmol/L level. Postprandial hyperglycemia ($AUC_{\text{postprandial}}$) was calculated as the sum of the AUC of the 7-point SMBG after each meal, taking each pre-meal level as the baseline. Fasting hyperglycemia (AUC_{fasting}) was then calculated as AUC_{overall} minus $AUC_{\text{postprandial}}$. The relative contributions of postprandial and fasting hyperglycemia to overall hyperglycemia were calculated across HbA1c categories (< 7%, 7 to < 7.5%, 7.5 to <

8%, 8 to < 8.5%, 8.5 to < 9% and \geq 9% for the baseline measurements and < 6%, 6 to < 6.5%, 6.5 to < 7%, 7 to < 7.5%, 7.5 to < 8% and \geq 8% for measurements at week 26). The relative contributions of postprandial or fasting hyperglycemia were also compared for patients receiving dulaglutide versus glargine across HbA1c quartiles.

Statistical Analysis

Changes in glycemic outcomes and body weight were calculated in a modified intention-to-treat (mITT) population including all randomized patients with a baseline HbA1c measurement and at least one post-baseline HbA1c measurement and who received at least one dose of study drug. Incidence of hypoglycemia was evaluated in the safety population (all patients receiving at least 1 dose of study drug).

Baseline characteristics were listed in subgroups of patients stratified by median baseline FG/PPG levels. Glycemic and safety outcomes were compared among the baseline FG/PPG subgroups. Continuous variables were presented as mean \pm standard deviation (SD), and discrete variables were presented as the number (percentage), unless otherwise specified. The relative contributions of fasting hyperglycemia and postprandial hyperglycemia within each HbA1c category was compared using a paired Student's *t* test. The correlation between glycemic outcomes (AUC_{overall} and relative contributions of fasting hyperglycemia and postprandial hyperglycemia) and HbA1c at baseline and week 26, respectively, were evaluated using a Pearson correlation test. Changes in glycemic outcomes (HbA1c, FG and PPG) at week 26 were analyzed using analysis of covariance (ANCOVA), with treatment, subgroup and treatment by subgroup interaction as fixed effects. Changes in body weight were analyzed using ANCOVA with treatment, subgroup and treatment by subgroup interaction as fixed effects and baseline body weight as a covariate. Results from ANCOVA are summarized as least-squares mean (LSM) with standard error (SE). Missing post-baseline data were imputed using last observation carried forward

(LOCF). All analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC, USA).

RESULTS

Patient Disposition and Baseline Characteristics

A total of 560 patients were included in this analysis (low FG/low PPG, $n = 205$; low FG/high PPG, $n = 77$; high FG/low PPG, $n = 77$; high FG/high PPG, $n = 201$). Overall, around 60% of patients were male. Mean BMI was 26.03 kg/m^2 and mean age was 54.79 years. The mean baseline HbA1c level was 8.35%, and the mean duration of diabetes was 8.01 years (Table 1). Demographics and baseline characteristics for the patients further stratified by treatment are presented in ESM Table 1.

Relative Contributions of Fasting and Postprandial Hyperglycemia

At baseline, there was a significant positive correlation between AUC_{overall} (mean \pm SD: $1374.02 \pm 699.18 \text{ mg h/dL}$) and HbA1c ($r^2 = 0.43$; $P < 0.001$) among patients receiving dulaglutide 1.5 mg. In addition, the relative contribution of fasting hyperglycemia increased (from 40% to 67%) from the lowest to the highest HbA1c category (< 7 to $\geq 9\%$) ($r^2 = 0.20$; $P < 0.001$), with a corresponding decrease in the relative contribution of postprandial hyperglycemia (from 60% to 33%; Fig. 1a).

After 26 weeks of treatment with dulaglutide 1.5 mg, the mean AUC_{overall} (\pm SD) was $793.94 \pm 452.83 \text{ mg h/dL}$, which is a reduction from baseline (difference [mean \pm SE]: $-580.07 \pm 56.43 \text{ mg h/dL}$; $P < 0.001$). Similarly, both AUC_{fasting} and $AUC_{\text{postprandial}}$ (mean \pm SD) were lower at week 26 compared to baseline

Table 1 Demographics and baseline characteristics of Chinese patients with type 2 diabetes stratified by glycemic pattern

Variables	Low FG/low PPG ($n = 205$)	Low FG/high PPG ($n = 77$)	High FG/low PPG ($n = 77$)	High FG/high PPG ($n = 201$)	Overall ($n = 560$)
Age, years	55.62 ± 9.49	56.57 ± 10.33	52.64 ± 9.04	54.07 ± 9.67	54.79 ± 9.67
Male	128 (62.4%)	46 (59.7%)	40 (51.9%)	120 (59.7%)	334 (59.6%)
Weight, kg	73.21 ± 12.32	70.59 ± 11.70	74.12 ± 12.82	71.87 ± 11.87	72.50 ± 12.17
Body mass index, kg/m^2	26.13 ± 3.21	25.42 ± 3.16	26.69 ± 3.28	25.91 ± 3.07	26.03 ± 3.17
Duration of diabetes, years	7.28 ± 4.80	8.73 ± 5.00	7.85 ± 4.73	8.54 ± 5.22	8.01 ± 5.00
HbA1c, %	7.68 ± 0.75	8.17 ± 0.90	8.23 ± 0.88	9.14 ± 1.01	8.35 ± 1.08
FG, mmol/L	8.22 ± 1.58	8.82 ± 1.60	10.14 ± 1.90	11.48 ± 2.22	9.74 ± 2.37
PPG ^a , mmol/L	10.47 ± 1.28	13.80 ± 1.13	11.40 ± 0.85	15.68 ± 2.49	12.93 ± 2.91

Values are expressed as mean \pm SD, with the exception of male sex which is expressed as n (%)

FG Fasting glucose, HbA1c glycated hemoglobin, PPG postprandial glucose, SD standard deviation, SMBG self-monitored blood glucose, T2D type 2 diabetes

^aPPG was based on SMBG

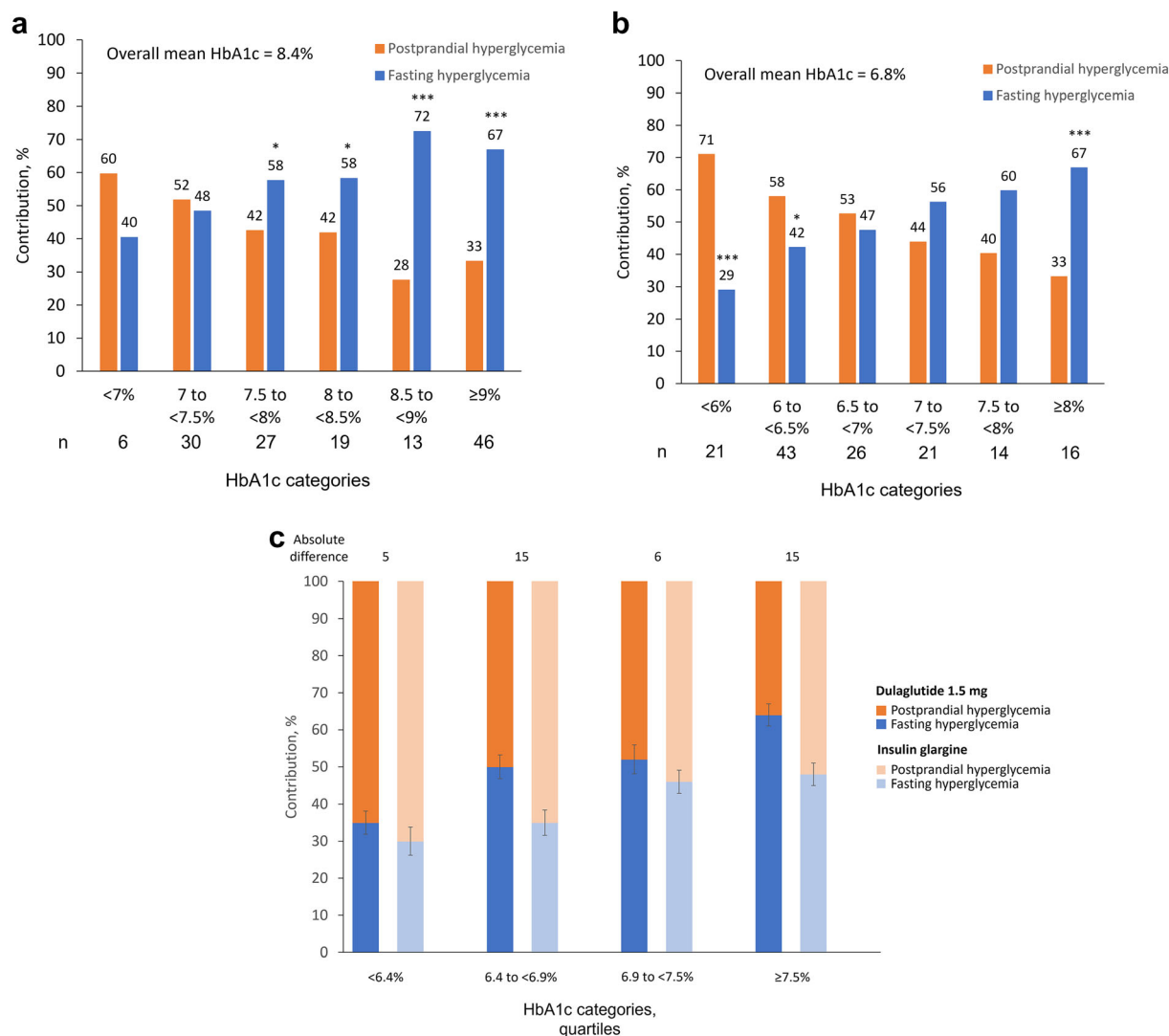


Fig. 1 Relative contributions of fasting glucose and postprandial glucose to overall hyperglycemia stratified by HbA1c categories in Chinese patients receiving dulaglutide 1.5 mg at baseline (**a**) and week 26 (**b**). **c** Comparison of patients receiving dulaglutide 1.5 mg and those receiving

glargine, at week 26. Asterisks denote significant difference between fasting and postprandial hyperglycemia within each HbA1c category at * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$. *HbA1c* Glycated hemoglobin

($AUC_{fasting}$ at week 26: 417.83 ± 354.05 mg h/dL; difference [mean \pm SE]: -440.60 ± 47.00 mg h/dL, $P < 0.001$; $AUC_{postprandial}$ at week 26: 376.11 ± 204.77 mg h/dL, difference [mean \pm SE]: -139.48 ± 23.00 mg h/dL, $P < 0.001$). In line with the baseline observations, $AUC_{overall}$ showed a significant positive correlation with HbA1c ($r^2 = 0.42$; $P < 0.001$) after treatment with dulaglutide 1.5 mg. Also consistent with the trend observed at baseline,

after dulaglutide treatment, the relative contribution of fasting hyperglycemia to overall hyperglycemia increased (from 29 to 67%) from the lowest to highest HbA1c categories (< 6 to $\geq 8\%$; $r^2 = 0.27$, $P < 0.001$) with a reciprocal decrease in the contribution of postprandial hyperglycemia (from 71 to 33%) (Fig. 1b).

Patients receiving dulaglutide 1.5 mg and glargine achieved significant reductions in mean HbA1c from baseline to week 26. After 26

weeks of treatment with glargine, the mean AUC_{overall} (\pm SD) was 887.07 ± 444.53 mg h/dL. Consistent with the known basal-preferential effect of glargine, patients receiving glargine had a lower relative contribution to overall hyperglycemia from fasting hyperglycemia but a higher relative contribution from postprandial hyperglycemia across all quartiles of HbA1c following 26 weeks of treatment (Fig. 1c). Similar results were observed for patients receiving dulaglutide 0.75 mg (ESM Fig. 2; ESM Table 2).

Changes in HbA1c from Baseline

At week 26, significant reductions in LSM HbA1c from baseline were observed for patients receiving dulaglutide 1.5 mg and glargine across all subgroups (all $P < 0.05$) (Fig. 2a). Overall, the greatest reductions were observed in the high FG/high PPG subgroup (dulaglutide 1.5 mg: -2.22% ; glargine: -1.55%). A significantly greater reduction in LSM HbA1c from baseline was observed for patients receiving dulaglutide 1.5 mg versus glargine in the low FG/low PPG (LSM difference: -0.70% , 95% confidence interval [95% CI] $-1.04, -0.37$; $P < 0.001$), high FG/low PPG (LSM difference: -0.85% , 95% CI $-1.42, -0.28$; $P = 0.003$) and high FG/high PPG (LSM difference: -0.67% , 95% CI $-1.00, -0.34$; $P < 0.001$) subgroups (Fig. 2a). Among patients receiving dulaglutide 0.75 mg, a significant reduction in LSM HbA1c from baseline was also observed across all subgroups. Patients receiving dulaglutide 0.75 mg had a numerically higher reduction in HbA1c from baseline than patients receiving glargine, although the differences did not reach statistical significance (ESM Fig. 3a).

Proportion of Patients Achieving HbA1c Targets

At week 26, HbA1c $< 7\%$ was achieved by a greater proportion of patients receiving dulaglutide 1.5 mg versus glargine across all subgroups, and the difference reached statistical significance in the low FG/low PPG, low FG/

high PPG and high FG/high PPG subgroups (Fig. 2b). In addition, a significantly higher proportion of patients receiving dulaglutide 1.5 mg achieved HbA1c $\leq 6.5\%$ versus glargine across all subgroups (Fig. 2c). Similar trends were observed for patients receiving dulaglutide 0.75 mg, with significantly higher proportions of patients achieving HbA1c $< 7.0\%$ and $\leq 6.5\%$ in the low FG/low PPG subgroup (ESM Fig. 3b, c).

Changes in FG and PPG from Baseline

Statistically significant LSM reductions in FG from baseline to week 26 were observed for patients receiving dulaglutide 1.5 mg and glargine across all subgroups (Fig. 2d). The greatest reductions in FG were achieved in patients belonging to the high FG/high PPG subgroup and the smallest reductions in those belonging to the low FG/low PPG subgroup. Differences in reduction of FG from baseline to week 26 between the dulaglutide 1.5 mg and glargine treatment groups did not reach statistical significance across all subgroups.

Statistically significant LSM reductions in PPG were observed at week 26 for patients receiving dulaglutide 1.5 mg and glargine across all subgroups, with the exception of patients receiving glargine in the low FG/low PPG subgroup (Fig. 2e). The greatest and smallest reductions in PPG were achieved in patients belonging to the high FG/high PPG subgroup and low FG/low PPG subgroup, respectively. Overall, patients treated with dulaglutide 1.5 mg tended to achieve a greater reduction in PPG than those receiving glargine across all subgroups, and the difference reached statistical significance in the high FG/high PPG subgroup (LSM difference: -1.43 mmol/L, 95% CI $-2.24, -0.62$; $P < 0.001$).

A consistent trend was observed among patients receiving dulaglutide 0.75 mg, with a significantly greater reduction in PPG at week 26 versus patients receiving glargine in the low FG/low PPG subgroup (-1.35 vs. -0.45 mmol/L; LSM difference: -0.90 mmol/L, 95% CI $-1.71, -0.10$; $P = 0.028$; ESM Fig. 3d, e).

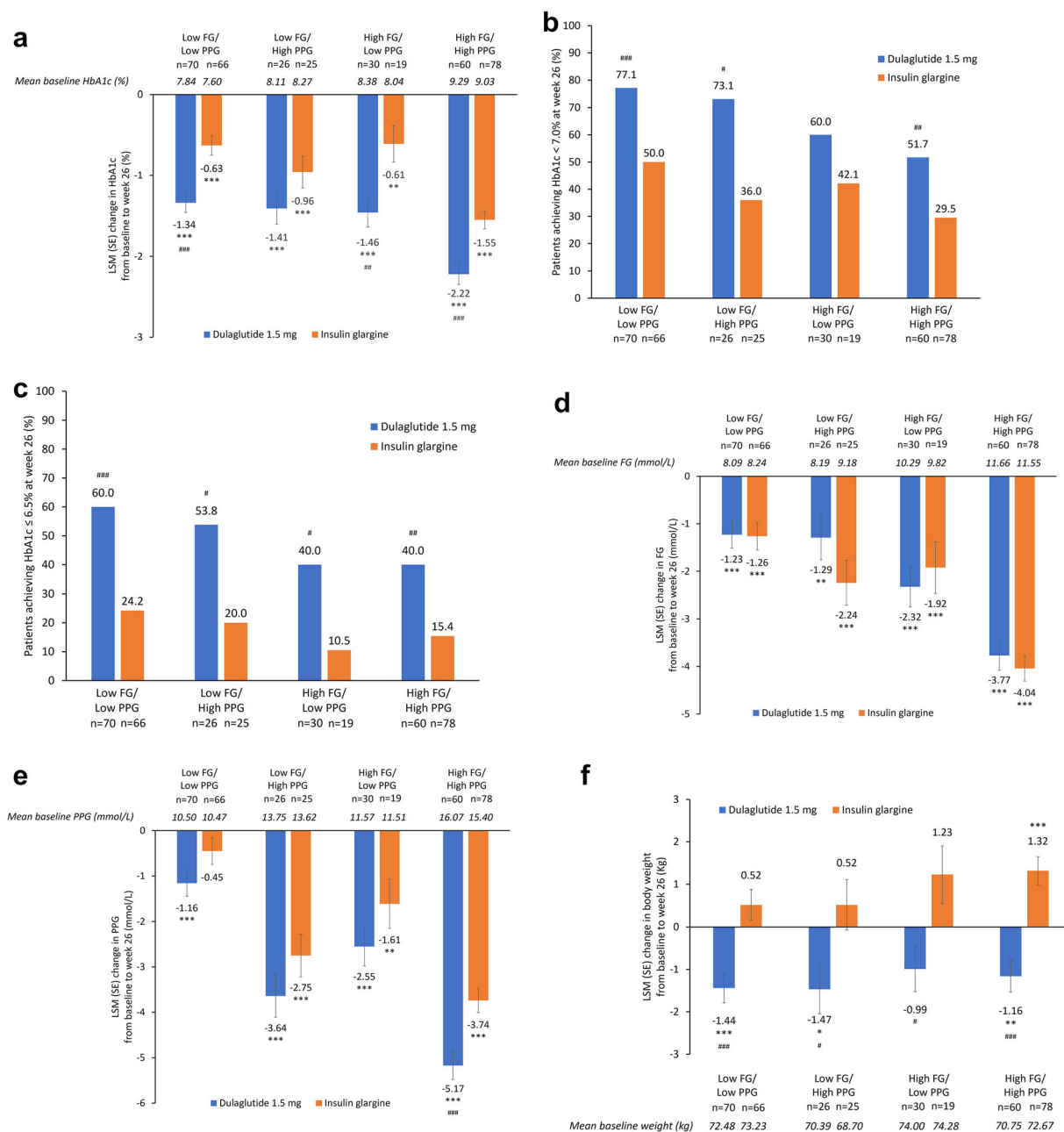


Fig. 2 Glycemic control and body weight change at week 26 stratified by glycemic pattern in Chinese patients with T2D treated with dulaglutide 1.5 mg or glargine. **a** Change in HbA1c from baseline, **b** proportion of patients with HbA1c < 7.0%, **c** proportion of patients with HbA1c ≤ 6.5%, **d** change in FG from baseline, **e** change in PPG glucose from baseline, **f** change in body weight from baseline. Asterisks denote significant difference

from baseline at * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$. Hash signs indicate significant difference between dulaglutide 1.5 mg and glargine within each glycemic pattern category at # $P < 0.05$, ## $P < 0.01$ and ### $P < 0.001$. FG fasting glucose, LSM least-squares mean, PPG postprandial glucose, SE standard error, T2D type 2 diabetes

Change in Body Weight from Baseline

Dulaglutide 1.5 mg led to significantly better control of body weight than glargine in all subgroups: low FG/low PPG (LSM difference: -1.97 kg, 95% CI $-2.96, -0.98$; $P < 0.001$), low FG/high PPG (LSM difference: -1.98 kg, 95% CI $-3.60, -0.37$; $P = 0.016$), high FG/low PPG (LSM difference: -2.22 kg, 95% CI $-3.91, -0.53$; $P = 0.010$) and high FG/high PPG (LSM difference: -2.49 kg, 95% CI $-3.48, -1.50$; $P < 0.001$) subgroups (Fig. 2f). A similar trend was observed in patients treated with dulaglutide 0.75 mg, with significant treatment differences observed in the low FG/low PPG, high FG/low PPG and high FG/high PPG subgroups (ESM Fig. 3f).

Incidence of Hypoglycemia

At week 26, the incidence of overall and nocturnal hypoglycemia was lower among patients receiving dulaglutide 1.5 mg versus glargine across all glycemic pattern subgroups, apart from the low FG/high PPG subgroup in which the incidence of overall and nocturnal hypoglycemia was comparable for the two treatments (29.6 vs. 28.0% and 7.4 vs. 8.0%, respectively) (Table 2). No patient experienced severe hypoglycemia during the trial. Similar results were observed for patients receiving dulaglutide 0.75 mg (ESM Table 3). The mean glargine dose at week 26 was higher in the high FG groups (high FG/low PPG: 27.42 U; high FG/high PPG: 24.80 U) than in the low FG groups (low FG/low PPG: 16.21 U; low FG/high PPG: 18.00 U).

DISCUSSION

This post-hoc analysis of the AWARD-CHN2 trial is the first study to investigate the effect of a GLP-1 RA on glycemic control deep-dived from glycemic patterns in a population of Chinese patients with T2D. The results of this analysis showed that the relative contribution of FG to overall hyperglycemia increased, and

the relative contribution of PPG decreased, with increasing baseline HbA1c levels, and that this trend was maintained after 26 weeks of treatment with dulaglutide. This finding suggests that dulaglutide lowers both fasting and postprandial hyperglycemia to reduce HbA1c levels. Furthermore, dulaglutide provided a greater reduction in HbA1c than glargine, regardless of baseline FG and PPG levels. Taken together, these data indicate that dulaglutide is an effective glucose-lowering therapeutic option for Chinese patients with T2D.

As reported in a previous study conducted in French patients with T2D inadequately controlled by OAMs, the relative contribution of postprandial hyperglycemia to overall glycemic load varies according to the degree of glycemic control [6]. The relative contribution of PPG is predominant in patients with fairly well controlled glycemia, whereas the relative contribution of FG increases gradually with worsening of glycemic control [6]. For example, in patients with HbA1c $< 7.3\%$, PPG contributed to 69.7% of overall hyperglycemia, and in patients with HbA1c of 7.3–10.2%, the relative contributions of FG and PPG to overall hyperglycemia were balanced (approx. 50% each); in contrast, in poorly controlled patients with HbA1c $> 10.2\%$, the relative contribution of PPG decreased to 30.5% [6]. This post-hoc analysis showed that dulaglutide 1.5 mg reduced HbA1c, and the relative contribution of PPG to overall hyperglycemia after 26 weeks of treatment ranged from 71 to 33% across HbA1c categories (< 6.0 to $\geq 8.0\%$). This finding indicates that dulaglutide has a proportional impact on both FG and PPG across different HbA1c levels. In addition, patients receiving dulaglutide showed a higher FG contribution and lower PPG contribution than those receiving glargine, across all HbA1c quartiles. Our findings are consistent with a pooled analysis of five phase 3 trials conducted in predominantly Caucasian patients with T2D inadequately controlled by one to two OAMs [13]. Furthermore, in line with previous findings in predominantly Caucasian patients with T2D [7], the basal preferential effect of glargine in Chinese patients with T2D was evident from the narrow range of relative contributions of FG to overall

Table 2 Hypoglycemia in Chinese patients with T2D treated with dulaglutide 1.5 mg or glargine and daily glargine dose at week 26 stratified by glycemic pattern

Variables	Low FG/low PPG		Low FG/high PPG		High FG/low PPG		High FG/high PPG	
	Dulaglutide (n = 72)	IGlar (n = 68)	Dulaglutide (n = 27)	IGlar (n = 25)	Dulaglutide (n = 30)	IGlar (n = 19)	Dulaglutide (n = 60)	IGlar (n = 79)
Overall hypoglycemia	14 (19.4%)	21 (30.9%)	8 (29.6%)	7 (28.0%)	1 (3.3%)	7 (36.8%)	7 (11.7%)	17 (21.5%)
Nocturnal hypoglycemia	7 (9.7%)	10 (14.7%)	2 (7.4%)	2 (8.0%)	0 (0.0)	2 (10.5%)	2 (3.3%)	6 (7.6%)
IGlar dose, U/kg	-	0.22 ± 0.13	-	0.26 ± 0.13	-	0.36 ± 0.17	-	0.33 ± 0.15
IGlar dose, U	-	16.21 ± 10.10	-	18.00 ± 11.16	-	27.42 ± 15.02	-	24.80 ± 12.17

IGlar Insulin glargine

Values are reported as number of patients with hypoglycemic events (%) or as the mean ± SD

hyperglycemia (30–48%) observed across HbA1c categories (< 6.4 to ≥ 7.5%).

In the present analysis, dulaglutide led to greater HbA1c reductions than glargine across the different baseline FG/PPG subgroups. As expected, the greatest reduction in mean HbA1c level was observed in the high FG/high PPG subgroup and a higher baseline HbA1c level was associated with greater HbA1c reductions. However, compared with glargine, dulaglutide was also associated with an increased HbA1c reduction in the high FG/low PPG subgroup. These data further support the premise that glycemic control can be improved by utilizing therapies targeting both PPG and FG. Previous observations indicate that particular attention should be paid to the management of PPG in patients with near-normal blood glucose concentrations in order to reach individualized HbA1c targets [6]. Thus, it seems reasonable to implement therapies with a PPG-lowering effect, especially when prandial hyperglycemic load is preminent.

Compared with a post-hoc analysis of the AWARD-2 trial conducted in predominantly Caucasian patients with T2D [14], this post-hoc analysis showed that dulaglutide led to greater reductions in HbA1c in Chinese patients across all baseline glycemic pattern subgroups. In addition, a meta-analysis of 15 clinical trials showed a greater reduction in HbA1c with GLP-1 RAs versus placebo among predominantly Asian patients compared to non-Asian patients (weighted mean difference: -1.16% [95% CI -1.48, -0.85] vs. -0.83% [95% CI -0.97, -0.70]; between group difference: -0.32%, 95% CI -0.64, -0.01; *P* = 0.04) [15]. However, the underlying explanation for differences in dulaglutide efficacy between Chinese patients with T2D and patients from other regions is not fully understood. Further studies are needed to investigate if dulaglutide is a preferred option for Chinese patients with T2D.

Consistent with prior findings in predominantly Caucasian patients with T2D [14], this post-hoc analysis in Chinese patients with T2D indicated that dulaglutide led to weight loss, versus weight gain with glargine, regardless of baseline FG and PPG levels. Compared with

patients treated with glargine, a lower incidence of overall and nocturnal hypoglycemia was observed in patients treated with dulaglutide across all subgroups except those with low FG/high PPG at baseline, in whom the incidence was comparable in patients receiving both treatments. In addition to the glucose-lowering and weight loss effects and low risk of hypoglycemia associated with dulaglutide that were supported by the present analysis, the primary and secondary cardiovascular benefits of dulaglutide [16] as well as frequency of administration and adherence are clinically relevant factors that should be considered when choosing anti-hyperglycemic therapies following a patient-centric approach [17, 18].

Given that glargine was titrated according to FG in the AWARD-CHN2 trial, higher doses were observed at 26 weeks in the high FG subgroups. As shown in the primary report of the AWARD-CHN2 trial, the mean daily dose of glargine at 26 weeks was 0.29 U/kg [8]. Accordingly, the mean daily doses of glargine (range 0.22–0.36 U/kg) observed in this post-hoc analysis were comparable to those reported in the phase III ABET trial (0.22 U/kg), in which Chinese patients with T2D inadequately controlled by ≥ 2 OAMs received glargine for 24 weeks [19], but were lower than reports from two similar international phase 3 trials conducted in Caucasian and multiracial patients with T2D (0.48–0.61 U/kg) [20, 21].

This study had several limitations, including the post hoc nature of the analysis. The relatively short duration of 26 weeks may not represent the long-term effects of dulaglutide, although consistent results were reported in the post hoc analysis of the AWARD-2 study with a 52-week duration [14]. A potential bias in the evaluation of fasting and postprandial hyperglycemia may have been caused by the single “point-in-time” measurement of SMBG and thus an inability to provide an accurate estimate of glucose exposure. In this regard, future studies using continuous glucose monitoring are warranted. Additionally, the use of median FG and PPG levels as cutoffs resulted in a less strict definition of glycemic patterns and may limit the generalizability of the results of this study. However, it was not possible to use the

clinically accepted cutoffs for FG and PPG as it would have resulted in very small patient numbers in the low FG/high PPG and high FG/low PPG subgroups. Finally, the generalizability of the findings of this analysis may be less robust in patients with HbA1c > 11% due to the characteristics of the pre-defined study population.

CONCLUSIONS

In summary, the present analysis further strengthens current evidence that dulaglutide reduces HbA1c by lowering both fasting and postprandial hyperglycemia across a wide range of HbA1c levels. Interestingly, a trend for better glycemia and weight control and lower risk of hypoglycemia was observed in patients treated with dulaglutide versus those receiving glargine regardless of baseline FG and PPG levels. Taken together with the potential cardioprotective effect of dulaglutide, these findings support the clinical use of once-weekly dulaglutide as an optimal option for Chinese patients with T2D inadequately controlled by 1–2 OAMs.

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Compliance with Ethics Guidelines. The AWARD-CHN2 study protocol was approved by the ethics review board of each trial site, including the master ethics review board at Ruijin Hospital Affiliated to Shanghai Jiao Tong University. The study was conducted in line with the ethical principles outlined in the Declaration of Helsinki of 1964 and its later amendments and with local regulations, and all patients provided written informed consent before randomization.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding authors on reasonable request.

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