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ORIGINAL RESEARCH

Efficacy and Safety of Dulaglutide by Baseline HbA1c in Chinese Patients with Type 2 Diabetes: A Post Hoc Analysis

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ABSTRACT

Introduction: To evaluate the efficacy and safety of dulaglutide 0.75 and 1.5 mg in patients with type 2 diabetes mellitus (T2DM) by baseline glycated hemoglobin (HbA1c) < 8.5% or ≥ 8.5% after 26 weeks of treatment.

Methods: Assessment of the Weekly AdministRation of dulaglutide in Diabetes (AWARD) China 1 (CHN1) study (NCT01644500, *n* = 556) included patients on dulaglutide vs. glimepiride who were treatment naïve or on monotherapy but discontinued therapy. AWARD-CHN2 (NCT01648582, *n* = 591) patients were on dulaglutide vs. insulin glargine and continued on metformin and/or sulfonylurea. Mean daily dose of glimepiride and insulin glargine was 2.51 mg and 21.0 IU, respectively. Post hoc analyses were conducted based on mixed-model repeated measures using a modified intent-to-treat analysis set with only the Chinese population. Change from baseline in HbA1c and body weight was analyzed by individual study.

Results: In the two studies, 70.1% of patients in AWARD-CHN1 and 59.7% in AWARD-CHN2 had baseline HbA1c < 8.5% (mean HbA1c 7.4% and 7.6%, respectively) and 29.9% in AWARD-CHN1 and 40.3% in AWARD-CHN2 had baseline HbA1c ≥ 8.5% (mean HbA1c 9.2% and 9.4%, respectively). In AWARD-CHN1, the HbA1c reductions at 26 weeks with baseline HbA1c < 8.5% and ≥ 8.5%, respectively, were dulaglutide 1.5 mg: − 1.1% and − 2.2%; dulaglutide 0.75 mg: − 0.9% and − 2.0%; glimepiride: − 0.7% and − 1.4%. In AWARD-CHN2, the HbA1c reductions at 26 weeks with baseline HbA1c < 8.5% and ≥ 8.5%, respectively, were dulaglutide 1.5 mg: − 1.2% and − 2.3%; dulaglutide 0.75 mg: − 1.0% and − 1.7%; and insulin glargine: − 0.6% and − 1.7%. Irrespective of baseline HbA1c, body

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weight decreased with both dulaglutide doses and increased with either glimepiride or insulin glargine at 26 weeks. Dulaglutide demonstrated low incidence of hypoglycemia in both doses in the two trials. Hypoglycemia incidence was generally lower in patients with baseline HbA1c $\geq$ 8.5%.
Conclusions: Dulaglutide demonstrated significantly greater HbA1c reduction with weight loss and lower risk of hypoglycemia compared with active comparators in Chinese patients with T2DM irrespective of baseline HbA1c, with much greater HbA1c reductions in patients with a higher baseline HbA1c.
Trial registration: ClinicalTrials.gov identifier, NCT01644500 and NCT01648582.

Keywords: Baseline HbA1c; Dulaglutide; Glimepiride; Hypoglycemia; Insulin glargine; Type 2 diabetes mellitus

Key Summary Points

Why carry out this study?

Efficacy and safety of dulaglutide were studied in two phase III randomized trials (AWARD-CHN1 and AWARD-CHN2 study) in Chinese adult patients with type 2 diabetes mellitus (T2DM), which demonstrated significant glycated hemoglobin (HbA1c) reduction.

The effects of dulaglutide in Chinese patients with T2DM and different baseline HbA1c levels (< 8.5% and $\geq$ 8.5%) have not yet been reported.

Thus, the present post hoc analysis of two phase III randomized trials is designed to evaluate the efficacy and safety of dulaglutide 1.5 mg and dulaglutide 0.75 mg in Chinese patients with T2DM by baseline HbA1c (< 8.5% and $\geq$ 8.5%) after 26 weeks of treatment. Also, the present post hoc analysis helps in understanding the efficacy and safety of dulaglutide in patients with T2DM and a higher HbA1c level.

What was learned from the study?

In the present post hoc analysis of two studies, dulaglutide demonstrated significantly greater HbA1c reduction with greater weight loss and less hypoglycemia in Chinese patients with T2DM irrespective of baseline HbA1c, with greater HbA1c reductions in patients with a higher baseline HbA1c.

Dulaglutide was well tolerated, with a safety profile similar to other GLP-1RAs.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is the most common form of diabetes and a chronic metabolic disorder with increasing worldwide prevalence [1]. Insulin resistance and a progressive decline in β-cell function [2] characterize it. China has the world's largest diabetes epidemic, with the estimated overall prevalence of 10.9% among adults as reported in a survey conducted in 2013 [3].

In China, patients with T2DM have poor glycemic control prior to the initiation of insulin [4]. According to the 2017 Chinese Diabetes Society guidance, insulin therapy is recommended in patients with T2DM when lifestyle modifications and oral antihyperglycemic medications (OAM) fail to achieve adequate glycated hemoglobin (HbA1c) < 7% [5]. However, in Chinese clinical practice, real-world observational studies [4, 6] have demonstrated that insulin treatment is only initiated when HbA1c is about 9% and the rate of achieving glycemic control is relatively low. In addition, hypoglycemia [7] and weight increase [8] associated with insulin therapy remain barriers to overcome. Patient-centered diabetes management must balance the benefits of glycemic control and potential weight effects against the risk of adverse events (AEs), particularly hypoglycemia and weight gain [9]. Unlike therapy with insulin and sulfonylureas, glucagon-like peptide-1 receptor agonists (GLP-1RAs)

stimulate insulin secretion in a glucose-dependent pattern, improving glucose control with weight loss and a lower risk of hypoglycemia [10]. Several lines of clinical evidences suggest a better risk-to-benefit ratio of GLP-1RAs compared with traditional antidiabetic drugs, such as glimepiride, which is widely used across East Asia. GLP-1RAs are generally well tolerated, although gastrointestinal (GI) AEs are commonly observed across the class [11–14].

Dulaglutide, a long-acting glucagon-like peptide-1 receptor agonist, was approved in 2014 for the treatment of T2DM [12]. Dulaglutide has been evaluated across the diabetes treatment continuum in the Assessment of Weekly AdministRation of LY2189265 in Diabetes (AWARD) trials in mainly Caucasians patients with T2DM [9]. In AWARD studies, dulaglutide demonstrated significant improvements in glycemic control irrespective of gender, duration of diabetes (< 5, ≥ 5 years and < 10, ≥ 10 years) or baseline HbA1c ($< 8.5\%$, $\geq 8.5\%$), with greater HbA1c and fasting blood glucose (FBG) reductions in patients with a higher baseline HbA1c [9]. Moreover, lower risk of weight gain or hypoglycemia was observed with dulaglutide compared with active comparators such as metformin, sitagliptin, exenatide twice daily, and insulin glargine. Efficacy and safety of dulaglutide were also studied in two phase III randomized trials (AWARD-China 1 [CHN1] and AWARD-CHN2 study) in Chinese adult patients with T2DM, which demonstrated significant HbA1c reduction [11, 12]. However, the effects of dulaglutide in Chinese patients with T2DM and different baseline HbA1c levels ($< 8.5\%$ and $\geq 8.5\%$) have not yet been reported. Hence, this post hoc analysis of two trials aimed to evaluate the efficacy and safety of dulaglutide 1.5 mg and 0.75 mg in Chinese patients with T2DM with a baseline HbA1c ($< 8.5\%$ and $\geq 8.5\%$) after 26 weeks of treatment.

METHODS

Study Design and Patients

The present analysis included patients from two randomized, phase III clinical trials from the AWARD program, AWARD-CHN1 (NCT01644500) and AWARD-CHN2 (NCT01648582). The primary end point of both studies was to assess the change in HbA1c from baseline at week 26. Individual trial results were previously published [11, 12]. In AWARD-CHN1, the enrolled patients were treatment naïve or on monotherapy but discontinued therapy. In AWARD-CHN2, the enrolled patients were on metformin with or without sulfonylurea. Both studies assessed the efficacy and safety of once weekly dulaglutide (1.5 mg and 0.75 mg) vs. active comparators [glimepiride (GLIM) in AWARD-CHN1 and glargine (GLAR) in AWARD-CHN2] in Chinese adult patients with T2DM. Institutional ethics committee approval was obtained for the studies, and written informed consent was taken from each patient before participation. Both studies were conducted in consensus with the Declaration of Helsinki, good clinical practice guidelines, and applicable laws and regulations.

End Points and Statistical Analysis

The primary end point of this analysis was conducted based on a modified intent-to-treat analysis set with only the Chinese population, consisting of all randomized patients who had a baseline HbA1c measurement with at least one post-baseline HbA1c measurement and received at least one dose of study drug. All efficacy and safety analyses were conducted at 26 weeks, as this was a common primary efficacy time point for both AWARD-CHN studies. Efficacy analyses of changes from baseline in HbA1c and FBG, proportion of patients achieving HbA1c targets of $< 7\%$ and $\leq 6.5\%$, and self-monitored blood glucose (SMBG) level at baseline and at week 26 after dulaglutide 0.75 mg and 1.5 mg treatments were analyzed by individual study. Safety end points included change in body weight, incidence and rate of all hypoglycemia (total hypoglycemia, plasma glucose ≤ 3.9 mmol/l), severe hypoglycemia episodes (defined as requiring treatment), nocturnal hypoglycemia, and documented symptomatic hypoglycemia, which were summarized by individual study. In addition, GI AEs (occurring in $\geq 5\%$ of patients)

Table 1 Demographics and baseline characteristics

Variable	AWARD-CHN1 (N = 556)						AWARD-CHN2 (*N* = 591)					
	DU 1.5 mg		DU 0.75 mg		GLIM		DU 1.5 mg		DU 0.75 mg		GLAR	
	HbA1c < 8.5% (*n* = 129)	HbA1c ≥ 8.5% (*n* = 55)	HbA1c < 8.5% (*n* = 127)	HbA1c ≥ 8.5% (*n* = 59)	HbA1c < 8.5% (*n* = 134)	HbA1c ≥ 8.5% (*n* = 52)	HbA1c < 8.5% (*n* = 120)	HbA1c ≥ 8.5% (*n* = 80)	HbA1c < 8.5% (*n* = 118)	HbA1c ≥ 8.5% (*n* = 78)	HbA1c < 8.5% (*n* = 115)	HbA1c ≥ 8.5% (*n* = 80)
Age, years Mean (SD)	54.2 (9.7)	49.6 (11.3)	53.4 (10.5)	54.6 (8.4)	53.1 (9.3)	51.6 (10.5)	55.8 (10.2)	52.7 (9.6)	53.8 (10.3)	54.5 (9.5)	54.7 (8.6)	55.5 (9.9)
Gender												
Male, n (%)	67 (51.9)	42 (76.4)	68 (53.5)	39 (66.1)	75 (56.0)	34 (65.4)	63 (52.5)	54 (67.5)	77 (65.3)	43 (55.1)	71 (61.7)	52 (65.0)
Female, n (%)	62 (48.1)	13 (23.6)	59 (46.5)	20 (33.9)	59 (44.0)	18 (34.6)	57 (47.5)	26 (32.5)	41 (34.7)	35 (44.9)	44 (38.3)	28 (35.0)
Weight, kg Mean (SD)	68.2 (9.8)	73.0 (12.3)	70.8 (12.1)	70.7 (12.0)	69.1 (10.6)	69.3 (10.6)	71.9 (12.6)	72.0 (11.6)	74.6 (12.1)	71.1 (11.6)	72.7 (12.0)	72.2 (13.2)
BMI, kg/m^2 Mean (SD)	25.5 (3.0)	25.7 (3.6)	26.1 (3.3)	25.8 (3.4)	25.2 (2.8)	25.6 (3.2)	26.0 (3.2)	25.7 (3.2)	26.5 (3.3)	25.9 (3.2)	26.1 (3.3)	25.9 (3.0)
Diabetes duration, years Mean (SD)	3.8 (4.6)	4.5 (4.9)	3.1 (4.1)	3.4 (3.7)	3.8 (4.3)	3.3 (3.6)	8.1 (4.5)	7.2 (4.7)	7.6 (5.1)	8.2 (5.7)	7.9 (5.2)	8.5 (4.8)
HbA1c, % Mean (SD)	7.5 (0.6)	9.2 (0.6)	7.5 (0.6)	9.3 (0.6)	7.4 (0.6)	9.2 (0.5)	7.6 (0.5)	9.6 (0.8)	7.6 (0.5)	9.4 (0.6)	7.6 (0.5)	9.3 (0.7)
FBG (mmol/l) Mean (SD)	8.7 (2.0)	11.3 (2.7)	8.4 (1.8)	11.2 (2.6)	8.7 (1.8)	11.3 (2.3)	8.6 (2.1)	11.1 (2.6)	8.8 (2.0)	11.0 (2.2)	9.0 (1.7)	11.2 (2.3)

Data are presented for modified intent-to-treat Chinese population

BMI = body mass index; DU = dulaglutide; FBG = fasting blood glucose; GLAR = insulin glargine; GLIM = glimepiride; HbA1c = glycated hemoglobin; SD = standard deviation

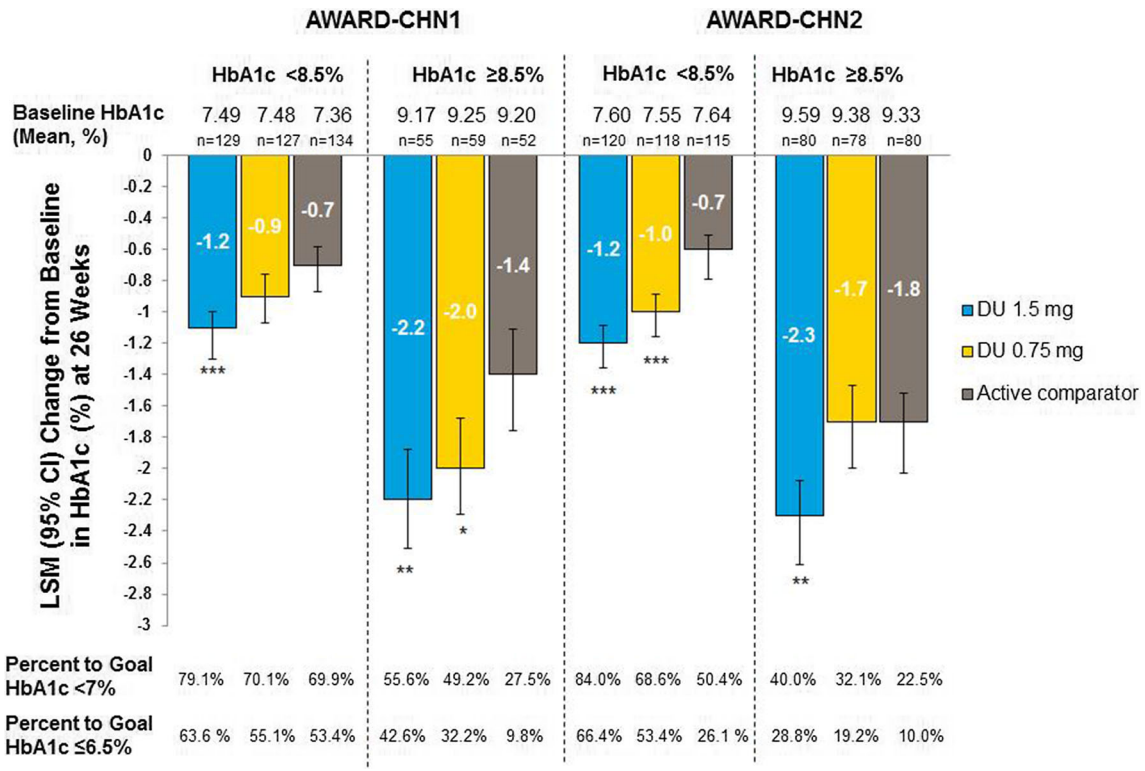

Fig. 1 HbA1c reduction at week 26 with baseline HbA1c < 8.5% and ≥ 8.5%. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, dulaglutide vs. active comparator. *DU* dulaglutide, *HbA1c* glycated hemoglobin, *LSM* least-squares mean

were summarized by individual study. Changes from baseline in HbA1c, FBG, SMBG, and weight were analyzed using mixed-model repeated measures with model terms including treatment group, OAM stratum, visits, treatment by visit interaction, and baseline value. Least squares (LS) means and corresponding 95% confidence intervals (CIs) are presented. All analyses were conducted using SAS 9.2 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Patient Disposition and Baseline Characteristics

In the AWARD-CHN1 study, 70.1% (390/556) of patients had baseline HbA1c < 8.5% and 29.9% (166/556) had baseline HbA1c ≥ 8.5%, whereas 59.7% (353/591) of patients in the AWARD-CHN2 study had baseline HbA1c < 8.5% and 40.3% (238/591) had baseline HbA1c ≥ 8.5%. The demographics and baseline characteristics of all 1147 patients were stratified by baseline HbA1c and are listed in Table 1. Overall, patient characteristics were comparable between the treatment groups for each subgroup. Patients with higher baseline HbA1c (≥ 8.5%) had higher mean FBG than patients with lower baseline HbA1c (< 8.5%).

Efficacy

In both HbA1c subgroups, dulaglutide 1.5 mg and 0.75 mg treatments resulted in significantly greater HbA1c reductions compared with active comparators, with much greater HbA1c reductions observed for patients with HbA1c ≥ 8.5% than for patients with HbA1c < 8.5% (Fig. 1). Moreover, dulaglutide 1.5 mg and 0.75 mg treatments resulted in a greater proportion of patients achieving HbA1c values of less than both 6.5% and 7% at 26 weeks compared with active comparators (GLIM/GLAR) in both the

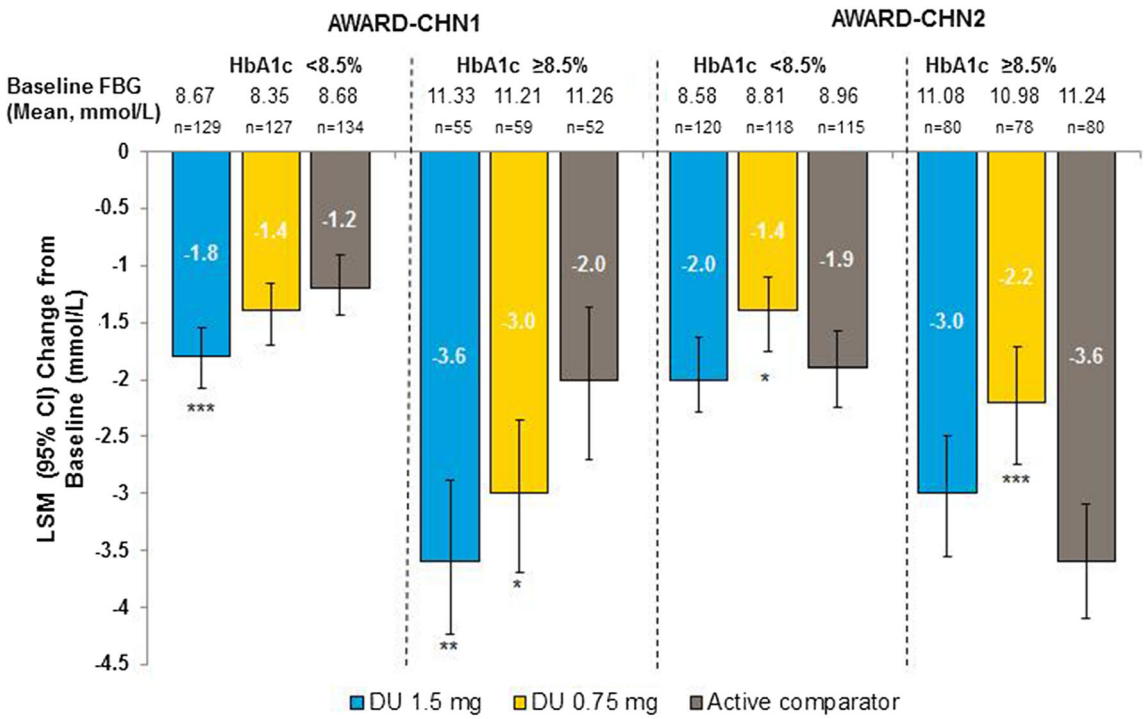

Fig. 2 Change in fasting blood glucose from baseline to week 26. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, dulaglutide vs. active comparator. *DU* dulaglutide, *FBG* fasting blood glucose, *HbA1c* glycated hemoglobin, *LSM* least squares mean

studies (AWARD-CHN1 and AWARD-CHN2) (Fig. 1). Also, in both studies, the HbA1c < 8.5% subgroup had a greater proportion of patients achieving HbA1c values of less than both 6.5% and 7% at 26 weeks compared with the HbA1c ≥ 8.5% subgroup. Consistent with HbA1c reduction, the FBG reductions (mmol/l) from baseline were greater in patients with ≥ 8.5% than in patients with HbA1c < 8.5% for both dulaglutide 1.5 mg and 0.75 mg treatments at 26 weeks compared with active comparators (GLIM/GLAR) (Fig. 2). Mean 7-point SMBG profiles by treatment groups at baseline and week 26 are shown in Fig. 3 for patients with HbA1c < 8.5% and HbA1c ≥ 8.5%, respectively. In the HbA1c < 8.5% and HbA1c ≥ 8.5% subgroups, dulaglutide demonstrated greater reduction in SMBG values from baseline after 26 weeks compared with active comparators (GLIM/GLAR) for all time points, except morning pre-meal (Fig. 3, Supplementary Table S1). Dulaglutide achieved a similar effect on weight in patients with HbA1c ≥ 8.5% and those with < 8.5% (Fig. 4). In AWARD-CHN1, for both subgroups, LS mean body weight was decreased from baseline in dulaglutide-treated patients and increased from baseline in glimepiride-treated patients after 26 weeks (Fig. 4). In AWARD-CHN2, for both subgroups, LS mean body weight was decreased from baseline in dulaglutide-treated patients and increased from baseline in insulin glargine-treated patients after 26 weeks (Fig. 4). For both subgroups, the differences in change in body weight between the treatment groups (dulaglutide vs. GLIM/GLAR) were statistically significant ($p < 0.001$).

Safety

The incidence and rate of hypoglycemia (symptomatic, nocturnal, and severe) events in AWARD-CHN1 and AWARD-CHN2 by HbA1c levels (< 8.5% vs. ≥ 8.5%) are shown in Table 2. In AWARD-CHN1 and AWARD-CHN2, dulaglutide demonstrated a low incidence of hypoglycemia in both doses. Hypoglycemia

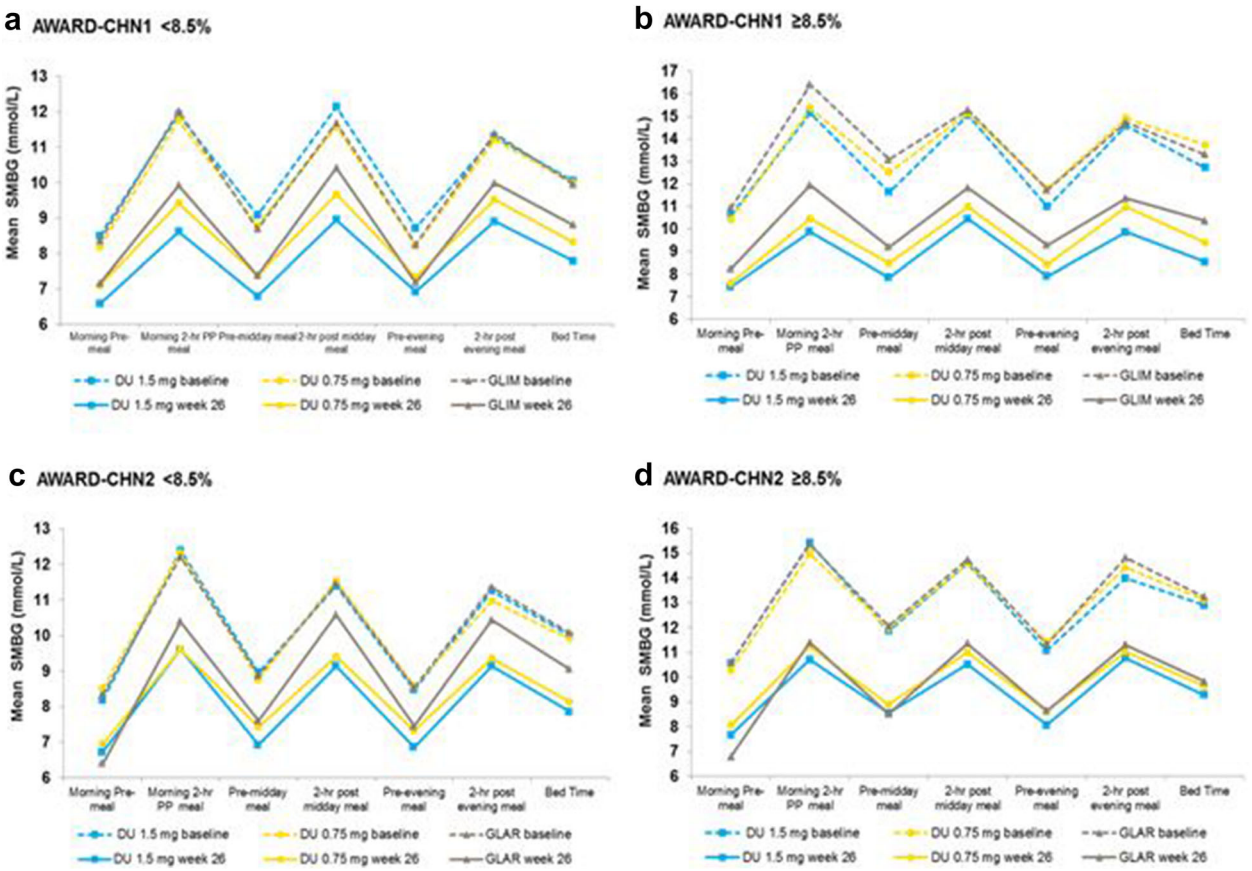

Fig. 3 Seven-point self-monitored blood glucose (smbg) profiles by time of day. *DU* dulaglutide, *GLAR* glargine, *GLIM* glimepiride, *PP* postprandial

incidence was generally lower in patients with baseline HbA1c ≥ 8.5%. The incidences of total, symptomatic, and nocturnal hypoglycemia were considerably less frequent with dulaglutide than with GLIM/GLAR in both subgroups (Table 2). In patients with baseline HbA1c ≥ 8.5%, the incidence of total, symptomatic, and nocturnal hypoglycemia was generally lower than in patients with baseline HbA1c < 8.5% in either treatment group. Severe hypoglycemia was not reported in any of the subgroups. In AWARD-CHN1 and AWARD-CHN2, GI AEs occurred more frequently with dulaglutide than GLIM/GLAR in both subgroups. Dulaglutide-treated patients with HbA1c < 8.5% had higher incidences of GI treatment-emergent AEs (TEAEs) such as diarrhea, nausea, vomiting, abdominal distension, and upper abdominal pain compared with the patients with HbA1c ≥ 8.5% in either treatment arm (Table 3).

DISCUSSION

This is the first analysis designed to explore the efficacy and safety of once weekly dulaglutide 1.5 mg and 0.75 mg compared with glimepiride or insulin glargine by subgroups of HbA1c (< 8.5% or ≥ 8.5%) in Chinese patients with T2DM. In this subgroup analysis, dulaglutide 1.5 mg and 0.75 mg treatments resulted in clinically meaningful reductions in HbA1c compared with GLIM/GLAR, with greater HbA1c reductions in patients with higher baseline HbA1c (≥ 8.5%) compared with patients with lower baseline HbA1c (< 8.5%). Our observation that poorly glycemic-controlled patients with HbA1c ≥ 8.5% had greater

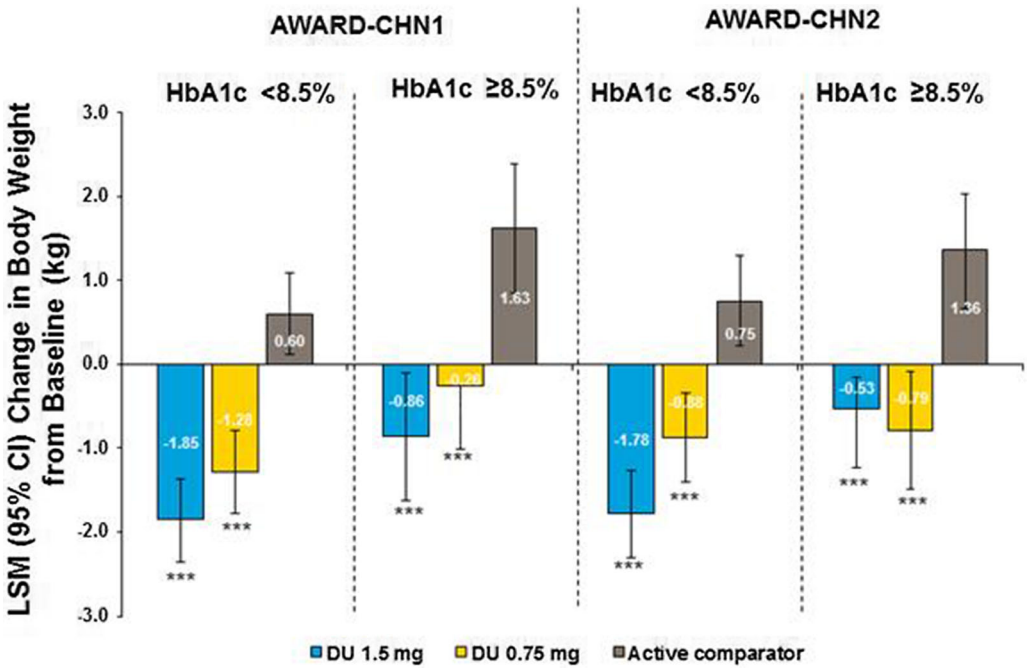

Fig. 4 Change in body weight from baseline to week 26. ***$p < 0.001$, dulaglutide vs. active comparator

HbA1c reductions compared with patients with HbA1c < 8.5% is consistent with published data that patients with lower HbA1c tend to experience smaller treatment-induced changes in HbA1c than those with higher HbA1c at baseline [13–15]. This was also reported for liraglutide by Henry et al. [16]. In that post hoc analysis of phase III randomized controlled trials, patients with T2DM were stratified by HbA1c values into five categories (≤ 5%, > 7.5–8.0%, > 8.0–8.5%, > 8.5–9.0%, and > 9.0%), and reductions in HbA1c levels with liraglutide were generally greater in groups with higher baseline HbA1c [16]. Similar findings were also reported for lixisenatide, with greater reductions in HbA1c in patients with higher baseline HbA1c levels, as shown in a pooled analysis of the lixisenatide GetGoal studies [17]. The observed effect is due to the greater potential for improvement in glycemic control in patients with higher baseline HbA1c. Similar relationships between HbA1c levels and improvements in glycemic control have also been identified in previous reports of meta-analyses of various glucose-lowering therapies [18], meta-analyses of GLP-1RAs other than dulaglutide [19], and global phase III studies of dulaglutide [9]. Similarly, the FBG reductions were consistent with HbA1c reductions in both dulaglutide doses.

Post hoc analyses of the dulaglutide clinical development program/global AWARD studies (AWARD-1 to -6 and -8 clinical trials), which included mainly Caucasian patients with T2DM, demonstrated significant improvements in glycemic control irrespective of HbA1c levels, with greater HbA1c and FBG reductions in patients with a higher baseline HbA1c [9]. The dulaglutide clinical development program showed that patients with HbA1c ≥ 8.5% had greater HbA1c reductions than patients with baseline HbA1c < 8.5%, (≥ 8.5%: LS mean − 1.86% [95% CI − 1.97, − 1.75]; < 8.5%: LS mean − 1.02% [95% CI − 1.12, − 0.93]) [9]. Also, global AWARD studies showed that reductions in FBG were consistent with HbA1c changes. The findings of this post hoc analysis of Chinese data are consistent with the global AWARD studies. In AWARD-CHN1, the HbA1c reductions at 26 weeks with baseline HbA1c < 8.5% and ≥ 8.5%, respectively, were dulaglutide 1.5 mg: − 1.1% and − 2.2%; dulaglutide

Table 2 Summary of hypoglycemia (incidence and rate) up to 26 weeks

Variable	AWARD-CHN1						AWARD-CHN2					
	DU 1.5 mg		DU 0.75 mg		GLIM		DU 1.5 mg		DU 0.75 mg		GLAR	
	HbA1c < 8.5% (*n* = 133)	HbA1c ≥ 8.5% (*n* = 56)	HbA1c < 8.5% (*n* = 132)	HbA1c ≥ 8.5% (*n* = 61)	HbA1c < 8.5% (*n* = 135)	HbA1c ≥ 8.5% (*n* = 52)	HbA1c < 8.5% (*n* = 123)	HbA1c ≥ 8.5% (*n* = 80)	HbA1c < 8.5% (*n* = 119)	HbA1c ≥ 8.5% (*n* = 82)	HbA1c < 8.5% (*n* = 117)	HbA1c ≥ 8.5% (*n* = 81)
All hypoglycemia												
Patients with episodes, *n* (%)	8 (6.0)	3 (5.4)	6 (4.5)	1 (1.6)	31 (23.0)	2 (3.8)	28 (22.8)	4 (5.0)	24 (20.2)	7 (8.5)	35 (29.9)	19 (23.5)
Rate, mean (SD)[a]	0.15 (0.64)	0.11 (0.45)	0.11 (0.51)	0.07 (0.51)	1.82 (9.38)	0.28 (1.54)	1.18 (3.63)	0.18 (0.97)	0.96 (2.75)	0.39 (1.57)	1.73 (4.72)	0.89 (2.07)
Documented symptomatic hypoglycemia												
Patients with episodes, *n* (%)	0 (0.0)	1 (1.8)	2 (1.5)	0 (0.0)	13 (9.6)	1 (1.9)	14 (11.4)	3 (3.8)	12 (10.1)	3 (3.7)	17 (14.5)	12 (14.8)
Rate, mean (SD)[a]	0.00 (0.00)	0.03 (0.25)	0.03 (0.25)	0	0.82 (4.82)	0.16 (1.16)	0.34 (1.05)	0.07 (0.38)	0.35 (1.50)	0.10 (0.53)	0.61 (1.98)	0.52 (1.61)
Nocturnal hypoglycemia												
Patients with episodes, *n* (%)	1 (0.8)	0	1 (0.8)	0	5 (3.7)	0	11 (8.9)	2 (2.5)	6 (5.0)	2 (2.4)	14 (12.0)	7 (8.6)
Rate, mean (SD)[a]	0.02 (0.18)	0	0.02 (0.18)	0	0.13 (0.92)	0	0.31 (1.20)	0.05 (0.32)	0.17 (0.84)	0.07 (0.49)	0.47 (1.79)	0.25 (1.02)

DU dulaglutide, *GLAR* insulin glargine, *GLIM* glimepiride, *HbA1c* glycated hemoglobin, *SD* standard deviation

[a] Rate is expressed as events/patient/year

Table 3 Gastrointestinal adverse events through 26 weeks

Variable	AWARD-CHN1						AWARD-CHN2					
	DU 1.5 mg		DU 0.75 mg		GLIM		DU 1.5 mg		DU 0.75 mg		GLAR	
	HbA1c < 8.5% (*n* = 133)	HbA1c ≥ 8.5% (*n* = 56)	HbA1c < 8.5% (*n* = 132)	HbA1c ≥ 8.5% (*n* = 62)	HbA1c < 8.5% (*n* = 135)	HbA1c ≥ 8.5% (*n* = 52)	HbA1c < 8.5% (*n* = 123)	HbA1c ≥ 8.5% (*n* = 80)	HbA1c < 8.5% (*n* = 119)	HbA1c ≥ 8.5% (*n* = 82)	HbA1c < 8.5% (*n* = 117)	HbA1c ≥ 8.5% (*n* = 81)
At least 1 GI TEAE, *n* (%)	54 (40.6)	16 (28.6)	28 (21.2)	12 (19.4)	13 (9.6)	3 (5.8)	43 (35.0)	21 (26.3)	29 (24.4)	22 (26.8)	10 (8.5)	5 (6.2)
Patients with ≥ 5% GI TEAE in any group, *n* (%)												
Diarrhea	25 (18.8)	10 (17.9)	12 (9.1)	6 (9.7)	6 (4.4)	1 (1.9)	23 (18.7)	8 (10.0)	10 (8.4)	9 (11.0)	3 (2.6)	3 (3.7)
Nausea	14 (10.5)	4 (7.1)	3 (2.3)	2 (3.2)	1 (0.7)	0(0.0)	15 (12.2)	5 (6.3)	6 (5.0)	3 (3.7)	2 (1.7)	0 (0)
Abdominal distension	11 (8.3)	4 (7.1)	5 (3.8)	0 (0.0)	3 (2.2)	1 (1.9)	10 (8.1)	8 (10.0)	8 (6.7)	4 (4.9)	0 (0)	0 (0)
Vomiting	10 (7.5)	2 (3.6)	1 (0.8)	0 (0)	0 (0.0)	0 (0)	9 (7.3)	1 (1.3)	1 (0.8)	0 (0)	1 (0.9)	0 (0)
Abdominal pain upper	4 (3.0)	0 (0)	5 (3.8)	0 (0)	1 (0.7)	0 (0)	1 (0.8)	4 (5.0)	1(0.8)	0 (0)	2(1.7)	1 (1.2)
Constipation	4 (3.0)	3 (5.4)	1 (0.8)	0 (0)	0 (0.0)	0 (0)	6 (4.9)	1 (1.3)	4 (3.4)	3 (3.7)	0 (0)	0 (0)

DU dulaglutide, *GI* gastrointestinal, *GLAR* insulin glargine, *GLIM* glimepiride, *HbA1c* glycated hemoglobin, *TEAE* treatment-emergent adverse event

0.75 mg: − 0.9% and − 2.0%; glimepiride: − 0.7% and − 1.4%. In AWARD-CHN2, the HbA1c reductions at 26 weeks with baseline HbA1c < 8.5% and ≥ 8.5%, respectively, were dulaglutide 1.5 mg: − 1.2% and − 2.3%; dulaglutide 0.75 mg: − 1.0% and − 1.7%; insulin glargine: − 0.6% and − 1.7%. In the dulaglutide and active comparator treatment groups (GLIM/GLAR), the patients with HbA1c ≥ 8.5% experienced greater reductions in HbA1c than patients with HbA1c < 8.5%. Moreover, the present analysis showed dulaglutide 1.5 and 0.75 mg treatments resulted in a greater proportion of patients achieving HbA1c values of less than both 6.5% and 7% at 26 weeks compared with active comparators (GLIM/GLAR). Also, in this post hoc analysis, the HbA1c < 8.5% subgroup had a greater proportion of patients achieving HbA1c values of less than both 6.5% and 7% at 26 weeks compared with the HbA1c ≥ 8.5% subgroup. This indicates that early initiation of dulaglutide treatment when the HbA1c target is not being met may lead to a better patient outcome.

In this post hoc analysis, dulaglutide-treated patients experienced GI AEs more frequently than active comparator-treated patients; however, all the observed GI AEs were reported as mild to moderate intensity and well tolerated. The incidences of total hypoglycemia, asymptomatic, and nocturnal hypoglycemia were lower with dulaglutide than GLIM/GLAR in both subgroups, with low incidence of hypoglycemia in patients with baseline HbA1c ≥ 8.5% compared with the patients with baseline HbA1c < 8.5%. Moreover, incidences of hypoglycemia were higher in insulin glargine-treated patients with lower HbA1c than in patients with higher HbA1c. Overall, in this post hoc analysis, both doses of dulaglutide were well tolerated and the safety profile of dulaglutide was similar to the GLP-1RA class of drugs, suggesting a favorable benefit-to-risk profile for dulaglutide. The findings of the present post hoc analysis are consistent with the findings from global studies (AWARD program) [9] with dulaglutide and with those from other studies with published data for other GLP-1RAs [20, 21]. The safety and tolerability profile of dulaglutide is similar to that of other agents in the GLP-1RA class [11, 12, 20, 21]. The most common side effects are GI related and include nausea, vomiting, diarrhea, and abdominal distension [11, 12]. Also consistent with the GLP-1RA class, GI side effects are mostly mild to moderate, occur early in the course of treatment, and are transient.

The present post hoc analysis has some limitations. Pooled analyses of data of both the included AWARD-CHN studies were not conducted to prevent the confounding effect of the various concomitant background medications used in each study. Additional limitations include: an imbalanced sample size and smaller number of patients with HbA1c ≥ 8.5% compared with HbA1c of ≤ 8.5%.

CONCLUSIONS

In the present post hoc analysis of two studies, dulaglutide demonstrated significantly greater HbA1c reduction with weight loss and lower risk of hypoglycemia than active comparators in Chinese patients with T2DM irrespective of baseline HbA1c, with much greater HbA1c reductions in patients with a higher baseline HbA1c. Dulaglutide was well tolerated, with a safety profile similar to other GLP-1RAs.

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Compliance with Ethics Guidelines. Institutional ethics committee approval was obtained from both the studies, and written informed consent was taken from each patient before participation. Both the studies were conducted in consensus with the Declaration of Helsinki, good clinical practice guidelines, and applicable laws and regulations.

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

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