

# Relative Contribution of Fasting and Postprandial Blood Glucose in Overall Glycemic Control: Post Hoc Analysis of a Phase IV Randomized Trial

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## ABSTRACT

**Introduction:** Few prospective clinical trials have investigated the role of fasting blood glucose (FBG) and/or postprandial glucose (PPG) in assessing overall glycemic control by using different insulin regimens. In the present post hoc analysis, we assessed the contribution of FBG and/or PPG in overall glycemic control in Chinese patients under insulin treatment.

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**Methods:** CLASSIFY is a phase IV, randomized, open-label, 26-week, parallel-arm, treat-to-target, multinational, controlled study in patients with type 2 diabetes mellitus to compare the efficacy and safety of insulin lispro mix 25 (LM25) and insulin lispro mix 50 (LM50) as starter insulins. Insulin was titrated with an aim to target pre-meal blood glucose (BG) levels at  $> 3.9$  and  $\leq 6.1$  mmol/L before breakfast and dinner. The primary outcome assessed was the change in HbA1c from baseline.

**Results:** Chinese patients contributed 38.7% ( $N = 156$ ) of the total population. The majority of patients were male (52.6%). The mean (SD) body mass index was 24.54 (3.04) kg/m<sup>2</sup> and mean (SD) HbA1c was 8.54 (1.10) % at baseline. At week 26, LM50 showed a significantly greater reduction from baseline in HbA1c ( $-2.03\%$  vs  $-1.55\%$ ,  $P < 0.001$ ), average daily BG ( $-3.21$  vs  $-2.34$  mmol/L,  $P < 0.001$ ), average post-meal BG ( $-3.58$  vs  $-2.39$  mmol/L,  $P < 0.001$ ), and average prandial BG excursion ( $-1.01$  vs  $-0.22$  mmol/L,  $P = 0.006$ ) than the LM25 group. The reductions in average pre-meal BG ( $-2.59$  vs  $-2.28$  mmol/L,  $P = 0.137$ ) were not significantly different between the groups. The proportion of patients achieving HbA1c targets ( $< 7\%$  or  $\leq 6.5\%$ ) without nocturnal hypoglycemia or weight gain was greater ( $P < 0.05$ ) with LM50 compared with LM25.

**Conclusion:** LM50 achieved better overall glycemic control than LM25 as a starter insulin in

Chinese patients, which may be due to greater improvement in PPG levels.

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**Keywords:** China; Glycosylated hemoglobin; Mixed insulins; Postprandial hyperglycemia; Type 2 diabetes mellitus

## INTRODUCTION

Onset of type 2 diabetes mellitus (T2DM) is noticed in Asian patients at an early age and at a much lower body mass index compared with the Western population because of greater visceral adiposity, fragile beta cell function, and insulin resistance [1–4]. In addition, postprandial glucose (PPG) and blood glucose (BG) excursions are more pronounced in Asian patients because of their carbohydrate-rich diets [5], which are high in glycemic index and glycemic load [6–10]. As a result of these unique genetic, clinical, and dietary characteristics, Asian patients with T2DM need customized treatment strategies.

Although the relationship between glycemic control and macroscopic complications is still unclear, there is evidence that both type 1 and type 2 diabetes patients could benefit from tight glycemic control owing to the resulting reduction in microvascular complications [11–16]. Control of plasma glucose is assessed by measurement of glycated hemoglobin (HbA1c), fasting blood glucose (FBG), and PPG. In recent years, glycemic variability has been deemed an emerging and more reliable target to assess BG control [17, 18], especially in patients with acceptable HbA1c levels who are still in need of optimization because of postprandial spikes and hypoglycemic events. However, HbA1c measurement remains the standard and preferred marker in assessing glycemic control and estimating the success of long-term diabetes-related therapies. According to the US Food and Drug Administration [19], the efficacy of glucose-lowering agents should be confirmed by a reduction in HbA1c as the primary endpoint. In the absence of HbA1c estimation, it

is controversial whether FBG or PPG serves as a better predictor of glycemic control, although American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) guidelines [20] recommend the use of basal insulin, which mainly targets FBG, as a starter insulin. In China, premixed insulin that targets both FBG and PPG is recommended as a starter insulin besides basal insulin [21].

It is useful to identify the role of FBG and PPG in glycemic control from a clinical perspective. A prospective interventional trial showed that PPG is essential for achieving recommended HbA1c goals [22]. In the DECODE study, an increase in PPG resulted in a significant increase in mortality irrespective of FBG levels [23]. Similar results were shown in a diabetes intervention study [24].

After treatment with oral antihyperglycemic medications (OAMs), most patients eventually need to start on insulin therapy to stop further deterioration of glycemic control caused by beta cell dysfunction. Insulin therapy can be initiated as a basal, basal-bolus, prandial, or premixed regimen [25]. Any insulin with aggressive titration enables patients to reach overall glycemic control. However, different regimens will result in various nonglycemic outcomes like hypoglycemia and weight gain. To evaluate the therapeutic potential of different insulins, treat-to-target trials were introduced to establish the risk–benefit profile of each. These trials evaluate secondary outcomes at similar HbA1c level improvements [26].

Premixed insulins contain both rapid- and intermediate-acting components and are the preferred starter insulins in Asian patients because they are effective on PPG and are more convenient to use [27, 28]. Premixed insulins vary according to the ratio of rapid- and intermediate-acting components. The most commonly used premixed insulins are low mixtures and mid mixtures. Low-mixture insulins are widely used as starter insulin in patients with OAM failure [29, 30], while mid-mixture insulins are used in patients with higher BG excursions or in patients who need a simplified intensive insulin treatment regimen [31, 32]. Recently, a subgroup analysis of a treat-to-target, phase IV, randomized, open-label, 26-week study [33] showed that low- and mid-mixture

insulins were a viable treatment option as starter insulins in Chinese patients who had inadequate glycemic control with OAMs [34]. The aim of the present post hoc analysis was to assess the significance of FBG and/or PPG in achieving overall glycemic control in Chinese patients who were on premixed insulin treatments.

## METHODS

### Study Design

The present results are from a post hoc analysis of a phase IV, randomized, open-label, 26-week, parallel-arm, multinational, controlled study in Chinese patients with T2DM comparing insulin lispro mix 25 (LM25) and insulin lispro mix 50 (LM50) twice daily for change in HbA1c from baseline to 26 weeks [34].

The study included a 2- to 4-week screening and lead-in period, followed by a 26-week treatment period (12-week, weekly intensive, dose-adjustment period and 14-week maintenance period). The 26-week treatment duration was chosen because it allows sufficient time to stabilize glycemic control as measured by HbA1c and to explore the suitable insulin regimen for patients following initiation of insulin treatment. During the dose-adjustment period, the insulin dose was titrated to bring hyperglycemia on target. During the dose-maintenance period, the dosage of insulin remained stable.

### Study Population

Major inclusion criteria included male or female Chinese patients aged  $\geq 18$  years with a diagnosis of T2DM for at least 6 months before the screening visit based on the World Health Organization's diagnostic and classification criteria, with a body mass index of  $\geq 18.5$  and  $< 35.0$  kg/m<sup>2</sup>, and qualifying HbA1c values of  $\geq 7.0\%$  and  $\leq 11.0\%$  based on the National Glycohemoglobin Standardization Program at the screening visit. Patients had been taking a stable dose of sulfonylurea, biguanide,  $\alpha$ -

glucosidase inhibitor, glinide, or dipeptidyl peptidase IV inhibitors, or any combination of these, during the 8 weeks before screening, or a stable dose of thiazolidinedione for 12 weeks prior to screening [33, 34].

Major exclusion criteria included patients having type 1 diabetes mellitus, currently taking insulin or having previous insulin treatment more than 7 days continuously within the 6 months before the screening visit, having more than one episode of severe hypoglycemia within 6 months prior to the screening visit, receiving chronic ( $> 14$  days) systemic glucocorticoid therapy or receiving such therapy within 4 weeks prior to the screening visit, having an estimated creatinine clearance (Cockcroft–Gault formula)  $< 30$  mL/min, as determined by a central laboratory at visit 1, or having any hematologic condition that could interfere with HbA1c measurement [33, 34].

### Treatment

Eligible patients were randomized in a 1:1 ratio to receive either LM25 or LM50 twice daily. The treatments were injected daily within 15 min before breakfast and within 15 min before dinner. The dose was chosen to have a target pre-meal blood glucose level of  $> 3.9$  and  $\leq 6.1$  mmol/L ( $> 70$  and  $\leq 110$  mg/dL), and was adjusted on the basis of the average pre-breakfast BG/pre-dinner BG values from the previous 3 days, including the day of injection. Details of the algorithm followed to choose insulin dose adjustments have been described previously [34].

### Compliance with Ethical Guidelines

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 1964 Declaration of Helsinki, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

## Statistical Analyses

The present analyses were post hoc in nature. Efficacy and safety analyses were conducted on the full analysis set which included data from all randomized subjects receiving at least one dose of the investigational product and was analyzed according to the treatment the subjects were assigned, regardless of what study drug was received. Missing data were not imputed, as all the available post-baseline data were used in the mixed-model repeated measures analyses. The detailed statistical analyses followed for this study and for the Chinese subgroup analysis have been presented previously [33, 34]. At baseline and at the end of the trial, all patients were asked to collect the seven-point self-monitored blood glucose (SMBG) measurements (before and after three meals and bedtime) on two non-consecutive days. The average of the 2 day's data was used to determine the SMBG measurements for baseline and week 26, and was used for the analyses. Change in blood glucose was assessed using daily average BG (average of SMBG readings), average pre-meal BG (average of three pre-meal BG measurements, i.e., before breakfast [fasting], lunch, and dinner), average post-meal BG (average of three post-meal BG measurements, i.e., approximately 2 h after breakfast, lunch, and dinner), SMBG average excursion (average post-meal BG minus average pre-meal BG), and FBG (evaluated using serum sample). All tests of treatment effects were conducted at a two-sided alpha level of 0.05. All analyses were performed using SAS Version 9.2 (Cary, NC, USA).

## RESULTS

Of 487 patients who entered the study, 403 patients were randomized to LM25 and LM50 and 368 patients completed the study. Most of the patients enrolled and randomized were from China ( $n = 156$ ) and Japan ( $n = 172$ ). The rest were from Korea ( $n = 46$ ) and Turkey ( $n = 29$ ) [33]. Of 156 patients who were randomized from China (LM25,  $n = 80$ ; LM50,

$n = 76$ ), 141 patients (LM25,  $n = 72$ ; LM50,  $n = 69$ ) completed the study [34].

The patients' baseline characteristics have been presented previously [34] and were comparable between the treatment groups (Table 1). A total of 23 (28.8%) patients in the LM25 treatment group and 19 (25.0%) patients in the LM50 treatment group did not take any OAMs after randomization.

A statistically significantly ( $P < 0.001$ ) greater decrease in HbA1c (%) was noted in the LM50 treatment group compared with the LM25 treatment group at the end of the 26-week treatment period (Fig. 1). A significantly greater number of patients also achieved the HbA1c target of  $< 7.0\%$  (72.4% vs 45.0%;  $P = 0.001$ ) and  $\leq 6.5\%$  (52.6% vs 20.0%;  $P < 0.001$ ) in the LM50 treatment group compared with the LM25 treatment group [34].

A greater proportion of patients achieved the target FBG and pre-breakfast BG of  $< 7.0$  mmol/L ( $< 126$  mg/dL) and  $< 6.1$  mmol/L ( $< 109.8$  mg/dL), respectively, in the LM25 treatment group compared with the LM50 treatment group; however, no significant differences were noted between the treatment groups (Fig. 2).

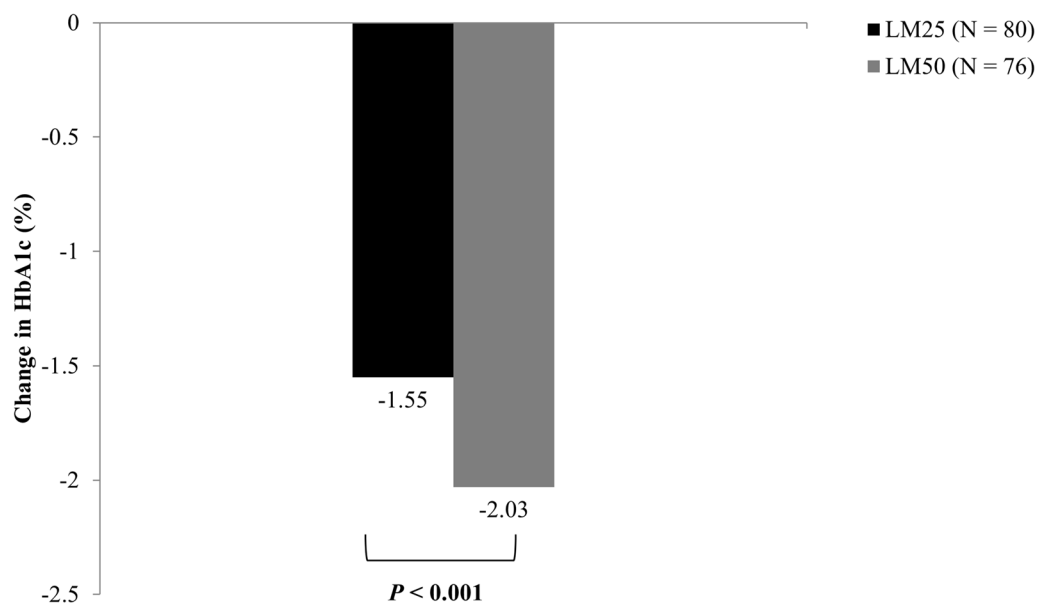
Statistically significant decreases in daily average BG LS mean change [95% confidence interval, CI] (LM50,  $-3.21$  [ $-3.55$ ,  $-2.86$ ] mmol/L vs LM25,  $-2.34$  [ $-2.67$ ,  $-2.01$ ] mmol/L), average post-meal BG average of three post-meal BG measurements, i.e., approximately 2 h after breakfast, lunch, and dinner; (LM50,  $-3.58$  [ $-4.06$ ,  $-3.11$ ] mmol/L vs LM25,  $-2.39$  [ $-2.84$ ,  $-1.93$ ] mmol/L), and SMBG average excursion (LM50,  $-1.01$  [ $-1.41$ ,  $-0.61$ ] mmol/L vs LM25,  $-0.22$  [ $-0.62$ ,  $0.17$ ] mmol/L) were noted in the LM50 treatment group compared with the LM25 treatment group ( $P < 0.05$ ). Also, a greater decrease in average pre-meal BG (average of three pre-meal BG measurements, i.e., before breakfast [fasting], lunch, and dinner) was reported in patients treated with LM50 compared with LM25 (LM50,  $-2.59$  [ $-2.89$ ,  $-2.29$ ] mmol/L vs LM25,  $-2.28$  [ $-2.57$ ,  $-1.99$ ] mmol/L); however, the difference was not statistically significant between the treatment groups. A greater decrease in FBG was reported in the LM25 treatment group compared with the LM50

**Table 1** Baseline patient characteristics

Characteristics	LM25 N = 80	LM50 N = 76
Gender		
Female, n (%)	39 (48.80)	35 (46.10)
Age, years	56.93 (9.24)	58.61 (9.05)
BMI, kg/m <sup>2</sup>	24.41 (2.67)	24.68 (3.40)
HbA1c, %	8.60 (1.11)	8.48 (1.10)
Duration of T2DM, years	8.68 (5.57)	7.33 (4.65)
Baseline FBG, mmol/L	9.61 (2.30)	9.68 (2.27)
Baseline 2-h PPG, mmol/L	13.70 (3.41)	13.55 (3.28)

Data are presented as mean (SD), except where indicated otherwise

*BMI* body mass index, *FBG* fasting blood glucose (serum sample), *HbA1c* glycated hemoglobin, *LM25* insulin lispro mix 25, *LM50* insulin lispro mix 50, *PPG* postprandial glucose (capillary blood glucose), *SD* standard deviation, *T2DM* type 2 diabetes mellitus

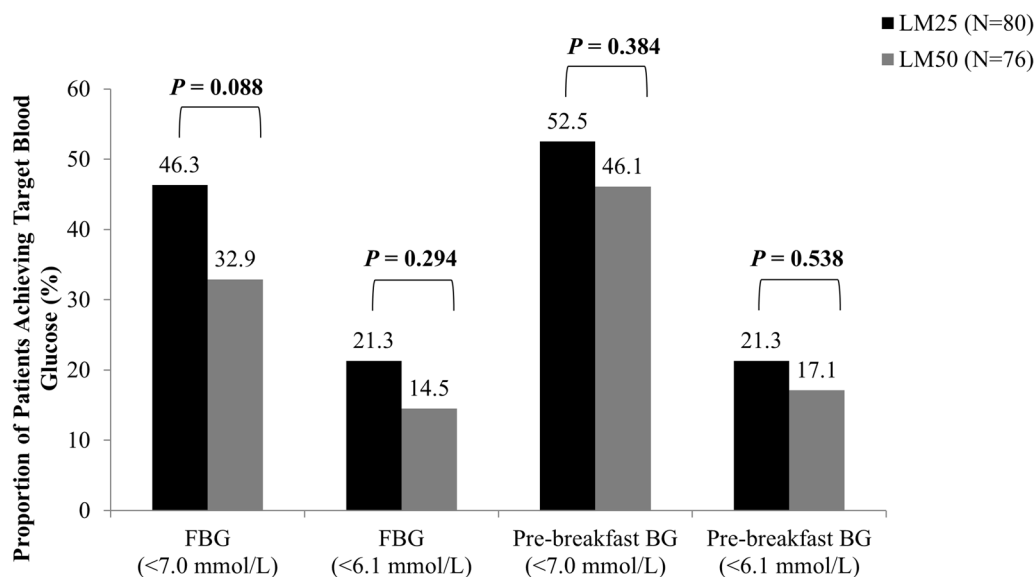


**Fig. 1** Change from baseline in HbA1c at week 26. HbA1c glycated hemoglobin, LM25 insulin lispro mix 25, LM50 insulin lispro mix 50. Data of 80 patients in LM25 and 76 patients in LM50 were available at week 26

treatment group (LM50,  $-2.12$  [ $-2.53, -1.72$ ] mmol/L vs LM25,  $-2.50$  [ $-2.89, -2.11$ ] mmol/L); however, the difference was not statistically significant (Table 2).

The proportion of patients achieving the targets HbA1c of  $< 7.0\%$  and  $\leq 6.5\%$  without

conditions like nocturnal hypoglycemia or weight gain was significantly higher ( $P < 0.05$ ) in the LM50 treatment group compared with the LM25 treatment group (Table 3).



**Fig. 2** Proportion of patients with target pre-breakfast blood glucose and fasting blood glucose at endpoint (< 7.0 mmol/L [ $< 126$  mg/dL] and < 6.1 mmol/L [ $< 109.8$  mg/dL], respectively). BG blood glucose, FBG fasting blood glucose, LM25 insulin lispro mix 25, LM50 insulin lispro mix 50, SMBG self-monitored blood glucose.

FBG is fasting reading before the patient eats/drinks. Pre-breakfast reading is a baseline reading of blood sugar before the patient has breakfast at a standard time. Pre-breakfast blood glucose is part of SMBG measurement while FBG is evaluated using serum sample

## DISCUSSION

The relative contribution of FBG and/or PPG in achieving glycemic control has been a subject of interest in the past decade because there is no consensus among clinicians due to conflicting reports. Multiple studies have shown contradictory conclusions about the positive contribution of FBG and/or PPG in overall glycemic control [35–39].

The CLASSIFY study [33] and its subgroup analysis of Chinese patients [34] showed that both LM25 and LM50 improved glycemic control at the end of 26 weeks of treatment and were well tolerated. In the present post hoc analysis, an attempt was made to determine the contribution of FBG and/or PPG in achieving overall glycemic control in Chinese patients. We assessed FBG, pre-meal BG, daily average BG, post-meal BG, and BG excursions to identify the relative contribution of FBG and/or PPG in achieving HbA1c targets.

Multiple efforts have been made to target HbA1c and FBG in achieving glycemic control

without positive outcomes. In recent years, some studies have shown a positive correlation between HbA1c and FBG [35, 36]. In fact, the 4-T Study [40] demonstrated that mealtime insulin was more efficacious than basal insulin but required more injections and was associated with pronounced weight gain and greater hypoglycemia risk. It is now generally accepted that antihyperglycemia treatment targeting PPG is slightly more efficacious than that targeting FBG, although this type of more aggressive approach increases the likelihood of side effects like hypoglycemia and weight gain. Considering the lower hypoglycemia rates, lower weight gain, and greater simplicity and convenience associated with basal insulin [41], the current treatment algorithm of the ADA [42], EASD [20], and American Association of Clinical Endocrinologists (AACE) [43] recommends the use of basal insulin as starter insulin in patients failing on OAMs and the addition of bolus insulin on further progression. However, the Glycemic Optimization Treatment (GOT) Study, which assessed the glycemic control and

**Table 2** Change in blood glucose compared with baseline after treatment

Variable	Baseline, mean (SD)	Endpoint, mean (SD)	LS mean change from baseline (95% CI)	Difference in LS means of change from baseline at endpoint (95% CI)	<i>P</i> value
Daily average BG (mmol/L) <sup>a</sup>					
LM25 ( <i>N</i> = 80)	11.29 (2.78)	8.71 (1.54)	− 2.34 (− 2.67, − 2.01)	0.87 (0.40, 1.34)	< 0.001**
LM50 ( <i>N</i> = 76)	11.02 (2.45)	7.81 (1.17)	− 3.21 (− 3.55, − 2.86)		
Average pre-meal BG (mmol/L) <sup>b</sup>					
LM25 ( <i>N</i> = 80)	9.74 (2.63)	7.38 (1.26)	− 2.28 (− 2.57, − 1.99)	0.31 (− 0.10, 0.73)	0.137
LM50 ( <i>N</i> = 76)	9.68 (2.37)	7.06 (1.15)	− 2.59 (− 2.89, − 2.29)		
Average post-meal BG (mmol/L) <sup>c</sup>					
LM25 ( <i>N</i> = 80)	12.78 (3.16)	10.07 (2.14)	− 2.39 (− 2.84, − 1.93)	1.20 (0.55, 1.85)	< 0.001**
LM50 ( <i>N</i> = 76)	12.44 (2.82)	8.83 (1.61)	− 3.58 (− 4.06, − 3.11)		
SMBG average excursion (mmol/L) <sup>d</sup>					
LM25 ( <i>N</i> = 80)	3.04 (1.80)	2.68 (1.85)	− 0.22 (− 0.62, 0.17)	0.78 (0.23, 1.33)	0.006*
LM50 ( <i>N</i> = 76)	2.76 (1.77)	1.77 (1.45)	− 1.01 (− 1.41, − 0.61)		
FBG (mmol/L) <sup>e</sup>					
LM25 ( <i>N</i> = 80)	9.61 (2.30)	7.20 (1.64)	− 2.50 (− 2.89, − 2.11)	− 0.38 (− 0.94, 0.18)	0.179
LM50 ( <i>N</i> = 76)	9.68 (2.27)	7.60 (1.76)	− 2.12 (− 2.53, − 1.72)		

BG blood glucose, CI confidence interval, FBG fasting blood glucose, LM25 insulin lispro mix 25, LM50 insulin lispro mix 50, LS least squares, SD standard deviation, SMBG self-monitored blood glucose

\**P* ≤ 0.01, \*\**P* ≤ 0.001

<sup>a</sup> Average of SMBG readings

<sup>b</sup> Average of three pre-meal BG measurements, i.e., before breakfast [fasting], lunch, and dinner

<sup>c</sup> Average of three post-meal BG measurements, i.e., approximately 2 h after breakfast, lunch, and dinner

<sup>d</sup> SMBG excursion is average post-meal BG minus average pre-meal BG

<sup>e</sup> FBG is evaluated using serum sample

rate of severe hypoglycemia for five different dosing algorithms of insulin glargine, showed that targeting greater FBG reduction required

higher doses and resulted in a higher rate of hypoglycemia; this indicates that 5.56–6.11 mmol/L (100–110 mg/dL) is an ideal target

**Table 3** Proportion of patients achieving HbA1c < 7.0% and ≤ 6.5% targets without hypoglycemia or weight gain

Patients achieving target HbA1c with	HbA1c < 7.0%			HbA1c ≤ 6.5%		
	LM25	LM50	<i>P</i> value	LM25	LM50	<i>P</i> value
	( <i>N</i> = 80) <i>n</i> (%)	( <i>N</i> = 76) <i>n</i> (%)		( <i>N</i> = 80) <i>n</i> (%)	( <i>N</i> = 76) <i>n</i> (%)	
No weight gain	15 (18.8)	25 (32.9)	0.0463*	7 (8.8)	18 (23.7)	0.0154*
No hypoglycemic episode <sup>a</sup>	16 (20.0)	26 (34.2)	0.0725	8 (10.0)	16 (21.1)	0.0561
No nocturnal hypoglycemic episode <sup>b</sup>	32 (40.0)	53 (69.7)	0.0002***	13 (16.3)	38 (50.0)	< 0.0001***
Neither weight gain nor hypoglycemic episode <sup>a</sup>	5 (6.3)	13 (17.1)	0.0446*	2 (2.5)	9 (11.8)	0.0245*
Neither weight gain nor nocturnal hypoglycemic episode <sup>b</sup>	12 (15.0)	24 (31.6)	0.0218*	5 (6.3)	18 (23.7)	0.0028**

HbA1c glycated hemoglobin, LM25 insulin lispro mix 25, LM50 insulin lispro mix 50, *n* number of patients who achieved HbA1c goal with the specified condition

\**P* ≤ 0.05, \*\**P* ≤ 0.01, \*\*\**P* ≤ 0.001

<sup>a</sup> Hypoglycemic episode is defined as a combination of the following: an episode with blood glucose concentration of ≤ 70 mg/dL (≤ 3.9 mmol/L) with or without symptoms, an episode during which symptoms are indicative of hypoglycemia but are not accompanied by a blood glucose concentration of ≤ 70 mg/dL (≤ 3.9 mmol/L), or a severe hypoglycemic episode (requiring medical assistance as determined by the investigator)

<sup>b</sup> Any hypoglycemic event that occurs between bedtime and waking

to achieve with insulin glargine treatment, and it is not advisable to aggressively titrate the insulin to meet the goal of < 5.56 mmol/L (< 100 mg/dL) considering the adverse effects such as severe hypoglycemia [44]. This finding reveals that FBG targets should be realistic with insulin glargine treatment rather than aggressive.

In most diabetic clinical studies, the importance and consistence of FBG and SMBG have not been fully discussed. Although FBG (measured by serum sample) was more reliable and accurate as the endpoint, SMBG (capillary blood glucose) was more clinically relevant to evaluate the efficacy of the insulin regimen as the BG target used in the treatment algorithm was based on SMBG rather than FBG. Interestingly, in the CLASSIFY substudy [34], a treat-to-target trial, the morning pre-meal BG at endpoint in both the LM25 and LM50 treatment groups was well controlled (< 126 mg/dL, which is recommended by the Chinese Diabetes Society as a

target value for morning pre-meal BG), and no significant difference was reported between the treatment groups. The insulin dose was comparable between the LM25 and LM50 treatment groups for the complete duration of the study.

This observation suggests that in Chinese patients, LM50 with smaller amounts of basal insulin may have a similar effect on pre-meal BG and FBG levels compared with LM25, which has relatively more basal insulin. In fact, in a Chinese study, Humalog mix 50/50 showed significantly improved FBG levels compared with Humalog mix 75/25 [45].

This observation suggests that Asian patients may not need much basal insulin to achieve target FBG. In a recently conducted study in Japanese patients, the maximum mean (SD) basal insulin dose needed to achieve significant improvement in HbA1c was 19 (8.5) units (U)/day [46]. However, in Caucasians, the total daily basal insulin usually needed to achieve target HbA1c was > 40 U/day [47]. Also, in a



recently concluded study in Chinese and Japanese insulin-naïve patients, once-daily biphasic insulin aspart 30 showed similar improvements in HbA1c and FBG levels compared with insulin glargine [48]. These findings support our observation of the need for low-dose basal insulin in Asian patients. In a treat-to-target study conducted by Pan et al. [49], aggressive titration of insulin glargine in Chinese patients to achieve target FBG levels (6.67 mmol/L [120 mg/dL]) did not guarantee achieving target HbA1c levels (< 7.5%), even when the average insulin dose was titrated to 32 U/day, which is relatively high considering the low body mass index of Chinese patients.

This finding suggests that the development of beta cell impairment varies in East Asians and Caucasians: East Asians may have impaired insulin secretion due to beta cell dysfunction after ingestion of a meal, whereas Caucasians have more impaired insulin secretion during fasting [50].

In the present study, significantly greater reduction in HbA1c was noted in patients treated with LM50 compared with LM25; also, a significantly greater number of patients treated with LM50 achieved target HbA1c levels of < 7% and  $\leq$  6.5%. At the same time, statistically significant decreases in daily average BG, average post-meal BG, and SMBG average excursion were noted in patients treated with LM50 compared with patients treated with LM25, suggesting that PPG may contribute to reaching target HbA1c levels.

A greater number of patients treated with LM25 achieved < 7.0 mmol/L (< 126 mg/dL) and < 6.1 mmol/L (< 109.8 mg/dL) FBG and pre-breakfast BG levels, respectively, compared with patients treated with LM50; however, the difference was not statistically significant between the treatment groups. This result shows that the role of FBG may be of limited clinical significance in achieving target HbA1c levels in Chinese patients in the CLASSIFY study and that a decrease in PPG may have accounted for a decrease in HbA1c levels compared with FBG levels. Similar results were also shown in patients who were not previously treated with insulin [51].

In the present treat-to-target study, a greater proportion of patients achieved specified HbA1c targets of < 7.0% and  $\leq$  6.5% without side effects like weight gain, hypoglycemia, or nocturnal hypoglycemic episodes in the LM50 treatment group compared with the LM25 treatment group, indicating LM50 as a better treatment option.

A recently published pooled analysis in insulin-naïve patients who failed on OAMs showed that East Asian and Caucasian patients have different BG excursions. This may be due to lower pre-meal BG levels in East Asian patients because post-meal BG levels were almost similar in both groups after treatment with insulin lispro [52]. This result suggests that ethnicity may play a role in FBG and PPG reductions in insulin treatment.

### Limitations

The present post hoc analysis was a subgroup analysis of the CLASSIFY study in Chinese patients with T2DM. Also, as a result of its open-label study design, the present analysis may have been subject to bias. In the present study, randomization was determined by a computer-generated random sequence using an interactive voice-response system. Additionally, because of the post hoc nature of the analysis, the results should be interpreted cautiously. Further analyses should be conducted in order to adequately consider the role of ethnicity when concluding the relative contribution of various BG in glycemic control.

### CONCLUSION

In this post hoc analysis, patients in the LM50 treatment group showed an improvement in overall glycemic control, which may be due to greater improvements in PPG levels compared with FBG. The role of PPG in achieving better glycemic control needs to be confirmed in a prospective, large-scale, randomized clinical trial.

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**Compliance with Ethics Guidelines.** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 1964 Declaration of Helsinki, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

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

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