Diabetes Ther (2017) 8:887–898
DOI 10.1007/s13300-017-0284-1

ORIGINAL RESEARCH

Which Patients Will Benefit from a Switch in Therapy from Premixed Insulin to Insulin Glargine plus Oral Antidiabetic Drugs? Further Analysis of the Lantus Registry Study

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Received: April 5, 2017 / Published online: June 16, 2017

ABSTRACT

Introduction: This subgroup analysis of data from the 16-week Lantus Registry Study in China investigated the characteristics of patients with type 2 diabetes mellitus (T2DM) associated with clinical benefits of transitioning therapy from premixed insulin to insulin glargine (100 U/ml) plus oral antidiabetic drugs (OADs).

Methods: The modified intention-to-treat population of the Lantus Registry Study, comprising 1847 patients with T2DM, were included in the current subgroup analyses. Enrolled patients were divided into subgroups based on efficacy variables of endpoint glycated hemoglobin (HbA_{1c}), endpoint fasting plasma glucose (FPG), and change in HbA_{1c} from baseline. The baseline characteristics of those who did and did not achieve HbA_{1c} <7.0% were compared, as were those with improvement, no change, or deterioration in HbA_{1c}. Characteristics of patients who were unable to achieve HbA_{1c} <7.0%, further grouped according to whether or not they achieved FPG ≤6.1 mmol/L, were also compared. Logistic regression analysis was used to identify factors associated with achieving HbA_{1c} <7.0%.

Results: Comparison between subgroups demonstrated that patients with endpoint HbA_{1c} <7.0% were significantly younger, with a shorter duration of diabetes and lower baseline FPG, HbA_{1c}, body mass index, and dose of premixed insulin than patients with endpoint HbA_{1c} ≥7.0%. Logistic regression analysis revealed a negative correlation between baseline age, HbA_{1c}, FPG, and duration of diabetes with achieving HbA_{1c} <7.0%. When stratified according to change in HbA_{1c}, the improvement group was younger, with higher baseline HbA_{1c} and a greater number of patients with duration of diabetes ≤5 years. Three-quarters of patients unable to achieve HbA_{1c} <7.0% also failed to reach FPG ≤6.1 mmol/L.

Conclusion: Younger patients with a shorter duration of diabetes and lower HbA_{1c}, FPG, and premixed insulin dose following a switch in treatment to insulin glargine (100 U/ml) plus OADs from premixed insulin have greater potential to achieve HbA_{1c} <7.0%. Poorly controlled patients with higher baseline HbA_{1c} are most likely to experience an improvement in HbA_{1c} following the switch in therapy. The majority of patients unable to achieve HbA_{1c} <7.0% also failed to reach FPG ≤6.1 mmol/L, highlighting the importance of adequate titration of insulin glargine to achieve adequate FPG

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control, which can enable achievement of target HbA_{1c}.
Funding: Sanofi.

Keywords: Insulin glargine; Oral antidiabetic drugs; Premixed insulin; Type 2 diabetes mellitus

INTRODUCTION

The selection of appropriate therapy for the treatment of type 2 diabetes mellitus (T2DM) can often be challenging given the availability of a wide variety of therapeutic options. However, it is recognized that most patients with long-standing T2DM will need to incorporate insulin into their treatment regimen at some point because of the progressive nature of the condition [1]. Early initiation of insulin is increasingly advocated to enable patients to achieve adequate glycemic control. Several international guidelines, as well as the Chinese treatment guidelines, recommend that insulin should be considered if the initiation of lifestyle modifications and metformin or combination therapy of two to three oral antidiabetic drugs (OADs) is unable to achieve and maintain target glycemic levels [2–5]. While some guidelines recommend initiation with basal insulin [3, 5], a long-acting insulin analogue that maintains basal glycemic levels throughout the day, others recommend initiation with basal or premixed insulin [2, 4]. Premixed insulin, a combination of rapid-acting bolus insulin and intermediate-acting basal insulin, was developed to mimic physiological endogenous insulin secretion [6, 7]. Premixed insulin is typically prescribed and initiated in approximately 70.0% of Chinese patients with T2DM, while only around 10.0% receive basal insulin [8]. This is partly because premixed insulin was available in China earlier than basal insulin analogues, and is considerably cheaper [7]. While premixed insulins are considered to be a good option for patients who require both basal and prandial insulin but wish to limit the number of daily injections, the fixed dose combination of basal and rapid-acting insulins means that the dose of insulins cannot be conveniently adjusted to meet individual patient requirements [9]. Additionally, in comparison to treatment with basal insulin, premixed insulin has been associated with inadequate glycemic control, as well as an increased risk of hypoglycemia [10, 11].

Various studies, including the recent Lantus Registry Study in China, have shown that switching to insulin glargine-based therapy can improve glycemic control in patients with T2DM who are poorly controlled on premixed insulin [7, 9, 12–15]. These studies have demonstrated that a switch in therapy can lead to a significant reduction in glycated hemoglobin (HbA_{1c}) and an improvement in treatment satisfaction, along with a low incidence of hypoglycemic events [7, 9, 12–15]. Once-daily insulin glargine is also considered to be a more flexible regimen with lower healthcare costs than premixed insulin, providing further evidence of the benefits of switching therapy [12, 16].

The current study, a subgroup analysis of the Lantus Registry Study [12], aims to identify independent factors associated with changes in blood glucose for patients with T2DM who have switched their treatment from premixed insulin therapy to insulin glargine plus OADs. In doing so, this study aims to determine the characteristics of patients who are more likely to obtain real-life clinical benefits from this switch in treatment.

METHODS

Patients and Study Design

The Lantus Registry Study was a 16-week, open label, prospective, observational multicenter study conducted across China from September 2010 to June 2012 [12].

In brief, patients were eligible for enrollment if they were 18 to 75 years of age, had received premixed insulin with or without OADs for at least 3 months, and had an HbA_{1c} level $\leq$10.0%. The main exclusion criteria included diagnosis of type 1 diabetes mellitus, temporary insulin treatment for gestational diabetes or surgery, allergy to insulin glargine (100 U/ml)/OAD or its excipients, and acute diabetes-related

complications such as hyperglycemic hyperosmolar state or diabetic ketoacidosis. The study protocol was conducted in accordance with the Declaration of Helsinki, and approved by the local ethical committees or institutional review boards at each participating institution. All patients or their legally acceptable surrogates gave written informed consent.

Study Treatment

Eligible participants were switched from their previous premixed insulin therapy (with or without OADs) to insulin glargine plus OADs at the discretion of both the physician and the patient, and in accordance with local product labels. Insulin glargine was initiated at a dose equivalent to 60.0% (in patients with baseline HbA_{1c} ≤8.0%) or 80.0% (in patients with baseline HbA_{1c} >8.0%) of the total dose of the intermediate insulin component of the patient's previous premixed dose. Insulin glargine was up-titrated every 3 days by 2, 4, 6, and 8 U for a fasting plasma glucose (FPG) of 5.5–6.6, 6.7–7.7, 7.8–9.9, and ≥10.0 mmol/L, respectively, until an FPG level of ≤5.6 mmol/L was achieved. This titration algorithm was in line with the Treat-to-Target algorithm [17]. The OAD type and dosage were adjusted at the physicians' discretion according to the label and standard practice.

Data Collection

At baseline (week 1), patient demographic data were obtained together with the disease history and details of diabetes treatment prior to participation in the study. Visits subsequently took place at weeks 2, 4, 8, and 16. Physical examinations were carried out at all visits, and FPG, 2-h postprandial glucose (PPG), safety data, and details of current treatment were recorded. For 2-h PPG, at least the latest recording from the laboratory test or self-monitoring was collected at each visit. However, patients could provide further recordings to assist the treating physician's decision. HbA_{1c} measurements were collected at weeks 1 and 16. Hypoglycemic events were also recorded, and were defined as all events in which patients showed symptoms of hypoglycemia for which their symptoms could be relieved by ingestion of carbohydrates or their symptoms occurred when blood glucose was ≤3.9 mmol/L. The number of patients who had experienced at least one hypoglycemic event since their last visit was recorded from visit 2 (week 2) to visit 5 (week 16).

Data Assessment

The primary endpoint of the Lantus Registry Study was change in HbA_{1c} from baseline to week 16. Secondary endpoints included FPG, 2-h PPG, and body weight changes from baseline to week 16, as well as treatment satisfaction score changes from baseline to week 16 based on the Diabetes Treatment Satisfaction Questionnaire status version [18]. The current subgroup analyses were performed to assess the characteristics of patients who successfully achieved or sustained HbA_{1c} <7.0% (target HbA_{1c}). This was evaluated by comparing characteristics of patients who did and did not achieve HbA_{1c} <7.0%, as well as by conducting logistic regression analysis. Characteristics of patients who showed improvement, deterioration, or no change in glycemic control following the transition from premixed insulin to insulin glargine plus OADs were also assessed. Improvement of glycemic control was defined as a reduction in HbA_{1c} of ≥0.3%. Unchanged glycemic control was defined as a –0.3% to +0.3% change in HbA_{1c}, and deterioration of HbA_{1c} was defined as an increase in HbA_{1c} of ≥0.3%. Characteristics of patients who were unable to reach HbA_{1c} <7.0% were further analyzed by stratifying these patients into subgroups based on their FPG at endpoint (>6.1 or ≤6.1 mmol/L) and comparing these subgroups.

Statistical Analysis

A modified intention-to-treat (mITT) analysis was used for reporting patient characteristics and demographics at baseline and study endpoint. The subgroup analyses were conducted using different efficacy variables: HbA_{1c} level at endpoint, change in HbA_{1c} from baseline, and

FPG level at endpoint. Data were summarized using mean and standard deviation for continuous parameters, and counts plus percentages for categorical parameters. The *t* test was used for comparison between subgroups. In addition, the Wilcoxon signed-rank test and the Chi-squared test were used for continuous and dichotomous variables, respectively. Logistic regression analysis was used to explore the factors associated with achieving HbA_{1c} <7.0%. The following variables were included in the analyses: baseline and endpoint HbA_{1c} (%); baseline and endpoint FPG (mmol/L); duration of diabetes at baseline (years); premixed insulin dose prior to study entry (U/kg and U/kg/day); age at baseline (years); body mass index (BMI) at baseline (kg/m^2); gender; dose of insulin glargine at study end (U/kg and U/kg/day); number of OADs at baseline; baseline and endpoint 2-h PPG; diabetic complications at baseline; comorbidities at baseline; hypoglycemia. A *P* value less than 0.05 (two-sided tests) was considered statistically significant. All statistical analyses were carried out using the SAS 9.1.3 software package (SAS Institute, Cary, NC, USA).

Information on the patients, study design, intervention, data collection, clinical assessment, and statistical analysis of the Lantus Registry Study have been reported previously [12].

RESULTS

Patient Disposition and Baseline Characteristics

The Lantus Registry Study was conducted between September 28, 2010 and June 18, 2012 at 53 hospitals across China. The mITT population comprised 1847 patients, who were included in the following subgroup analyses. The mean duration of diabetes of the mITT population was 8.4 years, mean HbA_{1c} was 7.8%, and mean FPG was 8.1 mmol/L. At study entry, 28.6% of patients had an HbA_{1c} level <7.0%. Details of the baseline characteristics of the mITT population have been reported previously [12].

OAD Treatment Before and After the Switch

The types and number of OADs used before and after the switch have also been described previously [12]. The overall pattern of OAD usage was similar before and after the switch. Before the switch, the most common regimen was premixed insulin plus one OAD (41.4%), followed by no OAD (40.4%), two OADs (15.9%) and more than two OADs (2.2%). Overall, the most common OADs used were biguanides (35.5%), followed by α-glucosidase inhibitors (26.2%), glinides (6.7%), sulfonylureas (6.0%), thiazolidinediones (TZDs) (4.8%), and others (0.9%).

After the switch, the types and number of OADs used in combination with insulin glargine demonstrated a trend of being stable after 8 weeks' treatment. One OAD in combination with insulin glargine was used by more than 45.0% of the patients at all visits after the switch and remained the most common regimen, followed by insulin glargine plus two types of OADs. Biguanides remained the most common OAD used after the switch (over 48.0% at all visits), followed by α-glucosidase inhibitors, glinides, sulfonylureas, TZDs, and others.

Baseline Characteristics of the Patients Stratified by Endpoint HbA_{1c}

Patients were stratified according to an endpoint HbA_{1c} level of either <7.0% or ≥7.0%. Among them, 1019 patients (55.2%) reached HbA_{1c} <7.0% and 828 patients (44.8%) did not. Patient demographics and characteristics of the two groups at baseline are shown in Table 1. Patients with an endpoint HbA_{1c} <7.0% were younger (55.10 ± 11.16 vs 57.90 ± 10.61 years; $P < 0.001$) and had lower baseline BMI (24.94 ± 2.94 vs 25.34 ± 3.58 kg/m^2; $P < 0.05$), shorter mean duration of diabetes (6.05 ± 5.60 vs 9.14 ± 6.49 years; $P < 0.001$), and lower baseline HbA_{1c} (7.34 ± 1.16% vs 8.28 ± 1.06%; $P < 0.001$) and FPG (7.60 ± 1.87 vs 8.70 ± 2.19 mmol/L; $P < 0.001$) than patients with an endpoint HbA_{1c} of ≥7.0%. The HbA_{1c} <7.0% group also had a lower proportion of

Table 1 Demographic and baseline characteristics of the study participants stratified by endpoint HbA_{1c}

Variables	Endpoint HbA_{1c} <7.0%	Endpoint HbA_{1c} ≥7.0%
No. of patients (%)	1019 (55.2)	828 (44.8)
Age (years)		
Mean (SD)[a]	55.10 (11.16)	57.90 (10.61)
Female sex		
n (%)[b]	421 (41.3)	395 (47.7)
BMI (kg/m^2)		
Mean (SD)[c]	24.94 (2.94)	25.34 (3.58)
Baseline HbA_{1c} (%)		
Mean (SD)[a]	7.34 (1.16)	8.28 (1.06)
Baseline FPG (mmol/L)		
Mean (SD)[a]	7.60 (1.87)	8.70 (2.19)
Duration of diabetes (years)		
Mean (SD)[a]	6.05 (5.60)	9.14 (6.49)
Presence of diabetic complications		
n (%)[a]	369 (36.2)	376 (45.4)
Presence of comorbidities		
n (%)[b]	583 (57.2)	527 (63.6)
Baseline dose of premixed insulin		
Mean (SD), U/day[a]	27.74 (9.71)	31.68 (11.07)
Mean (SD), U/kg/day[a]	0.41 (0.14)	0.46 (0.16)
Baseline OADs, *n* (%)[a]		
1	646 (63.6)	408 (49.3)
2	311 (30.6)	328 (39.6)
≥3	59 (5.8)	92 (11.1)

Wilcoxon signed-rank, Chi-square, and Cochran–Mantel–Haenszel tests were used for between-group comparison of continuous, dichotomous, and categorical variables, respectively

BMI body mass index, *FPG* fasting plasma glucose, *HbA_{1c}* glycated hemoglobin, *OADs* oral antidiabetic drugs, *SD* standard deviation

[a] $P < 0.001$; [b] $P < 0.01$; [c] $P < 0.05$

patients with diabetes complications (36.2% vs 45.4%; $P < 0.001$) and comorbidities (57.2% vs 63.6%; $P < 0.01$). A lower proportion of female patients achieved HbA_{1c} <7.0% compared with those who achieved HbA_{1c} ≥7% (41.3% vs 47.7%; $P < 0.05$). Furthermore, patients with an endpoint HbA_{1c} of <7.0% received a markedly lower dose of premixed insulin prior to treatment switch (0.41 ± 0.14 vs 0.46 ± 0.16 U/kg/day; $P < 0.001$). There was also a difference in the number OADs taken at baseline between patients who achieved HbA_{1c} <7.0% and those who did not ($P < 0.001$); a higher proportion of patients who achieved HbA_{1c} <7.0% took only one OAD at baseline (63.6% vs 49.3%).

In terms of hypoglycemic events, 16.4% and 15.7% of patients with endpoint HbA_{1c} <7% and endpoint HbA_{1c} ≥7%, respectively, experienced hypoglycemia during the study ($P = 0.6889$). Details of other safety events have been previously reported [12].

Factors Associated with Achieving Target HbA_{1c} <7.0%

Logistic regression analysis revealed that age, baseline FPG, baseline HbA_{1c}, endpoint insulin glargine dose, the number of OADs at endpoint, and duration of diabetes were all negatively associated with patients being able to reach HbA_{1c} <7.0% (all $P < 0.05$; Table 2).

Characteristics of Patients with Improved, Unchanged, or Deteriorated Levels of HbA_{1c}

Patients in the mITT population were also stratified according to whether their HbA_{1c} levels improved, unchanged, or deteriorated at the end of the study. The numbers of patients in the improved, unchanged, and deteriorated groups were 1168 (63.2%), 412 (22.3%), and 267 (14.5%) patients, respectively. Characteristics of patients in the different HbA_{1c} groups are shown in Table 3. Baseline HbA_{1c} was lowest in the unchanged group (6.90 ± 0.91%) and

Table 2 Factors associated with achieving target $HbA_{1c} < 7.0\%$

Variables	Parameter estimates	OR (95% CI)	*P*
Age (years)	−0.02	0.981 (0.970, 0.991)	0.0003
Baseline FPG (mmol/L)	−0.07	0.935 (0.882, 0.992)	0.0251
Baseline HbA_{1c} (%)	−0.60	0.547 (0.492, 0.607)	<0.0001
Endpoint insulin glargine dose (U/kg/day)	−0.06	0.943 (0.926, 0.960)	<0.0001
Number of OADs at endpoint	−0.29	0.746 (0.638, 0.872)	0.0002
Duration of diabetes (years)	−0.05	0.949 (0.931, 0.967)	<0.0001

Logistic regression analysis was used
CI confidence interval, *FPG* fasting plasma glucose, *HbA_{1c}* glycated hemoglobin, *OADs* oral antidiabetic drugs, *OR* odds ratio

Table 3 Characteristics of patients with improvement, no change, or deterioration in endpoint HbA_{1c}

Variables	Improvement	No change	Deterioration	*P*
No. of patients (%)	1168 (63.2)	412 (22.3)	267 (14.5)	
Baseline HbA_{1c} (%)				
Mean (SD)	8.25 (1.04)	6.90 (0.91)	6.98 (1.15)	<0.001
Age (years)				
Mean (SD)	55.50 (11.14)	57.60 (10.69)	58.10 (10.53)	0.077
BMI (kg/m^2)				
Mean (SD)	25.26 (3.24)	24.88 (3.25)	24.85 (3.26)	0.054
Duration of diabetes (years)				
Mean (SD)	7.24 (6.15)	7.00 (6.08)	8.98 (6.45)	<0.001
No. of patients with ≤5 years of diabetes	507	192	81	<0.001
No. of patients with 5–10 years of diabetes	312	98	75	
No. of patients with >10 years of diabetes	349	122	111	

The Cochran–Mantel–Haenszel test was used
BMI body mass index, *HbA_{1c}* glycated hemoglobin, *SD* standard deviation

highest in the improvement group ($8.25 \pm 1.04\%$; $P < 0.001$). There was a trend toward older age at baseline when moving from the HbA_{1c} improvement (55.50 ± 11.14 years) to deterioration group (58.10 ± 10.53 years), although this difference was not statistically significant. BMI levels were similar across all three groups ($P = 0.054$). The number of patients with a mean duration of diabetes ≤5 years, 5–10 years, and >10 years differed significantly between all three groups ($P < 0.001$). The number of patients with mean duration of diabetes ≤5 years was the highest for the improvement group compared with the unchanged and deterioration groups (507 vs 192 vs 81, respectively).

Characteristics of Patients Unable to Achieve Target HbA_{1c} Stratified by Endpoint FPG

Further analysis of patients unable to achieve HbA_{1c} <7.0% was conducted according to whether or not they were able to achieve an FPG of ≤6.1 mmol/L (Table 4). The majority of patients unable to achieve target HbA_{1c} also failed to reach an FPG of ≤6.1 mmol/L (74.5% vs 25.5%). Patients with an endpoint FPG of ≤6.1 mmol/L had significantly lower endpoint HbA_{1c} (7.60 ± 0.88% vs 7.90 ± 0.89%; $P < 0.0001$), baseline FPG (8.01 ± 1.82 vs 8.97 ± 2.25 mmol/L; $P < 0.0001$), endpoint FPG (5.46 ± 0.57 vs 8.01 ± 2.32 mmol/L; $P < 0.0001$), baseline 2-h PPG (11.67 ± 3.09 vs 12.81 ± 3.86 mmol/L; $P < 0.0001$), endpoint 2-h PPG (9.24 ± 2.66 vs 10.89 ± 2.68 mmol/L; $P < 0.0001$), BMI (24.12 ± 3.04 vs 25.76 ± 3.67 kg/m^2; $P < 0.0001$), dose of endpoint insulin glargine in U/day (16.42 ± 6.15 vs 18.39 ± 6.62 U/day; $P = 0.0002$), and baseline dose of premixed insulin in U/day (29.78 ± 9.28 vs 32.33 ± 11.55 U/day; $P = 0.0013$) than patients with an endpoint FPG of >6.1 mmol/L. Other characteristics such as age, baseline HbA_{1c}, duration of diabetes, dose of endpoint insulin glargine in U/kg/day, and baseline dose of premixed insulin in U/kg/day were similar between both groups.

DISCUSSION

The Lantus Registry Study in China was a prospective, observational study that reported improved glycemic control and treatment satisfaction with a low incidence of hypoglycemia in adult Chinese patients with T2DM who switched from premixed insulin to insulin glargine plus OADs [12]. This subgroup analysis of the Lantus Registry Study aimed to identify the characteristics of patients who may gain the greatest benefit by transitioning therapy from premixed insulin to insulin glargine plus OADs.

In this study, following a switch in treatment from premixed insulin to insulin glargine plus OADs, 55.2% of patients achieved an endpoint HbA_{1c} level of <7.0% in comparison to the 28.6% of patients at baseline. Additionally, 63.2% demonstrated an improvement in HbA_{1c}. These results indicate the benefits of this transition in treatment.

Patient characteristics influencing treatment outcomes identified in this study were baseline duration of diabetes, HbA_{1c}, FPG, and age. Logistic regression analysis revealed that baseline duration of diabetes, HbA_{1c}, FPG, and age were negatively associated with achieving target HbA_{1c} levels of <7.0%. This was reflected in patients with endpoint HbA_{1c} <7.0% having a shorter mean duration of diabetes, lower HbA_{1c} and FPG, and younger age at baseline than patients with endpoint HbA_{1c} ≥7.0%. Additionally, a higher proportion of patients with mean duration of diabetes ≤5 years were found in the HbA_{1c} improvement group compared with the unchanged and deterioration groups. The mean age from the HbA_{1c} improvement to deterioration groups also increased numerically.

The above results suggest that switching treatment to insulin glargine plus OADs in patients earlier, while they are younger, with a shorter duration of diabetes and with lower levels of HbA_{1c} and FPG, can provide them with a better chance of achieving target glycemic control. Given that islet beta cell function has been shown to progressively deteriorate over time in patients with T2DM [19], an early transition in treatment for patients inadequately controlled on premixed insulin is more desirable. The above results have also been observed in two real-world Chinese studies which, similar to this study, have evaluated patient characteristics that aid in identifying patients who can benefit the most from a switch in treatment from premixed insulin to insulin glargine plus OADs. One of the studies by Zhang et al. demonstrated, through comparison of patient groups who did and did not reach HbA_{1c} targets (HbA_{1c} ≤6.5%, 6.5% < HbA_{1c} < 7.0%, or HbA_{1c} >7.0%) by the study end, that duration of diabetes and baseline HbA_{1c} were two factors closely associated with the success of the treatment transition [7]. The other study by Yang et al. also demonstrated, through logistic regression analysis, that the probability of achieving a HbA_{1c} target of <7.0% is lower with increased disease duration (odds ratio [OR] = 0.785) and higher baseline HbA_{1c}

Table 4 Demographic and baseline and endpoint characteristics of the study participants unable to reach target HbA_{1c} stratified by FPG at endpoint (> or ≤6.1 mmol/L)

Variables	FPG ≤6.1 mmol/L	FPG >6.1 mmol/L	*P*
Age (years), *n*	211	615	
Mean (SD)	59.13 (11.22)	57.52 (10.35)	0.0564
BMI (kg/m^2), *n*	211	615	
Mean (SD)	24.12 (3.04)	25.76 (3.67)	<0.0001
Duration of diabetes (years), *n*	211	615	
Mean (SD)	9.32 (6.95)	9.08 (6.34)	0.6488
Endpoint insulin glargine dose (U/day), *n*	211	615	
Mean (SD)	16.42 (6.15)	18.39 (6.62)	0.0002
Endpoint insulin glargine dose (U/kg/day), *n*	211	615	
Mean (SD)	0.25 (0.09)	0.26 (0.09)	0.3275
Baseline dose of premixed insulin (U/day), *n*	211	615	
Mean (SD)	29.78 (9.28)	32.33 (11.55)	0.0013
Baseline dose of premixed insulin (U/kg/day), *n*	211	615	
Mean (SD)	0.46 (0.14)	0.46 (0.16)	0.7265
FPG at baseline (mmol/L), *n*	211	614	
Mean (SD)	8.01 (1.82)	8.97 (2.25)	<0.0001
FPG at endpoint (mmol/L), *n*	211	615	
Mean (SD)	5.46 (0.57)	8.01 (2.32)	<0.0001
HbA_{1c} at baseline (%), *n*	211	615	
Mean (SD)	8.24 (1.05)	8.29 (1.06)	0.5162
HbA_{1c} at endpoint (%), *n*	211	615	
Mean (SD)	7.60 (0.88)	7.90 (0.89)	<0.0001
2-h PPG at baseline (mmol/L), *n*	207	609	
Mean (SD)	11.67 (3.09)	12.81 (3.86)	<0.0001
2-h PPG at endpoint (mmol/L), *n*	211	611	
Mean (SD)	9.24 (2.66)	10.89 (2.68)	<0.0001

A *t* test was used for comparing the two subgroups

BMI body mass index, *FPG* fasting plasma glucose, *HbA_{1c}* glycated hemoglobin, *PPG* postprandial glucose, *OADs* oral antidiabetic drugs, *SD* standard deviation

(OR = 0.482) [9]. The study by Yang et al. also demonstrated that patients with endpoint HbA_{1c} <7.0% were younger than patients with HbA_{1c} ≥7.0% (54.67 ± 7.99 vs 57.42 ± 8.42 years; $P = 0.0265$) [9]. Studies have shown that there is impaired beta cell function and tissue sensitivity to insulin with aging [20, 21], which may be why younger patients are able to better respond to the

switch in treatment, and therefore reach glycemic targets or demonstrate an improvement in HbA_{1c}, in comparison to those who are older.

This study also demonstrates that BMI could be a factor influencing efficacy outcomes. Patients with endpoint HbA_{1c} <7.0% were shown to have lower baseline BMI than patients with endpoint HbA_{1c} ≥7.0%. Higher BMI has been shown to be associated with decreased insulin sensitivity [22, 23], which may be why patients with lower BMI exhibit greater glycemic control in response to insulin glargine.

Another factor of significance was the insulin glargine dose at endpoint, which was shown to be negatively associated with achieving HbA_{1c} <7.0%. This may have been on account of the suboptimal glycemic control of patients at baseline. At baseline, the mean HbA_{1c} of the mITT set was 7.8% and the mean FPG was 8.1 mmol/L [12].

Findings from this study demonstrate that FPG is an important factor influencing the HbA_{1c} level of patients. Patients with an improvement in HbA_{1c} had significantly higher baseline HbA_{1c} in comparison to the unchanged and deterioration groups. This reflects a more marked reduction in HbA_{1c} for poorly controlled patients, although this does not necessarily indicate their achievement of HbA_{1c} <7.0%. Fasting hyperglycemia is the main contributor to glycemic load for poorly controlled T2DM [7, 24, 25] and this suggests that for patients with poor glycemic control at baseline, treatment with insulin glargine, which targets FPG, has a greater impact on overall glycemic control. This has also been observed in the study by Zhang et al. [7]. Patients with higher baseline HbA_{1c} levels, as a result of the nature of their hyperglycemia, are therefore likely to experience improvements in glycemic control in comparison to those with lower baseline HbA_{1c} levels during treatment switching.

Approximately three-quarters (74.5%) of patients unable to achieve HbA_{1c} <7.0% in this study also failed to achieve FPG ≤6.1 mmol/L. The lack of adequate FPG control in patients unable to achieve HbA_{1c} <7.0% is not surprising given the increased contribution of fasting hyperglycemia to poorly controlled T2DM [24, 25]. Considering their high FPG levels, these patients would have a lower tendency to experience hypoglycemia. Our analysis also showed that the incidence of hypoglycemia did not increase in patients with endpoint HbA_{1c} ≥7.0% compared with patients achieving endpoint HbA_{1c} <7.0% ($P = 0.6889$), even though patients in the ≥7.0% group were older, with a longer duration of diabetes, and a higher proportion of complications and comorbidities. The average endpoint insulin glargine dose for patients who failed both HbA_{1c} and FPG targets was 0.26 ± 0.09 U/kg/day, which was approximately 40% lower than the doses (0.4–0.5 U/kg/day) required to achieve adequate glycemic control while maintaining a low risk of hypoglycemia reported by other studies [17, 26]. This indicates that there is still potential for up-titration of the dose of insulin glargine in patients who failed to reach both glycemic targets. Hence, further up-titration of the insulin glargine dose in patients who failed to reach both HbA_{1c} and FPG targets may not increase the risk of hypoglycemia, and improve the likelihood of achieving adequate FPG control and therefore target HbA_{1c}.

Optimally titrating the dose of insulin glargine is therefore a critical factor influencing achievement of adequate FPG control and therefore target HbA_{1c}. This finding holds particular significance as it demonstrates a mechanism by which patients can achieve target HbA_{1c} following a switch in therapy from premixed insulin to insulin glargine plus OADs. This finding is also relevant to Asia, given that physicians in Asia often have a cautious approach to the titration of insulin, especially as Asian patients with T2DM, who are leaner than Caucasian patients, are perceived to be at an increased risk of hypoglycemia [27, 28]. This fear is unfounded as several studies conducted in Asian patients with T2DM have shown that the rates of hypoglycemia are low with insulin glargine when taken as combination therapy with OADs in insulin-naïve patients or in patients switching from premixed insulin [7, 12, 27]. A study by Riddle et al. which sought to determine the relative contributions of basal hyperglycemia versus postprandial hyperglycemia in patients inadequately controlled on OADs prior to and following treatment

intensification with various therapies, demonstrated that symptomatic hypoglycemic events were greater with the other treatments than with basal insulin [25].

The main limitations of the Lantus Registry Study have been reported previously [12]. Briefly, the lack of comparator arm in the trial means that it is difficult to determine whether observed improvements in glycemic control following the switch in treatment are solely on account of treatment effectiveness or influenced by study design. This is because observation can alter the behavior of both patients and physicians involved in a clinical trial, which can influence outcome measures. Another general limitation of observational and single-arm studies is the strong likelihood of bias and confounding in study design. Treatment was at the discretion of the physicians, which further exposes the study to bias.

Additionally, the duration of the Lantus Registry Study was relatively short and did not allow proper evaluation of the clinical challenges associated with optimal titration of insulin glargine along with OAD dosage adjustments. A longer study is required for more robust evaluation of these clinical challenges and insulin glargine titration. As a result of the widespread use of premixed insulin in China, there is lack of clinical experience with insulin glargine, which may have led to insufficient titration and therefore a lower achievement of glycemic control than would have otherwise been seen. However, the current subgroup analysis of the Lantus Registry Study does provide insight into the characteristics of patients associated with the clinical benefits of transitioning therapy from premixed insulin to insulin glargine plus oral OADs, based on real-world data. It also highlights the need to improve the management of T2DM in clinical practice, especially with regard to titrating the dose of insulin glargine to enable patients to achieve adequate glycemic control. This study also raises the need for further investigation of the effects of switching therapy on the incidence of hypoglycemia in Asian populations to encourage optimal titration of the dose of insulin glargine.

CONCLUSIONS

This subgroup analysis of the Lantus Registry Study aimed to identify the characteristics of patients with T2DM in China who may potentially benefit from transitioning therapy from premixed insulin to insulin glargine (100 U/ml) plus OADs. Results of this study demonstrate that patients with T2DM who are younger, have a shorter duration of diabetes, lower baseline HbA_{1c} and FPG levels, and a lower dose of premixed insulin prior to the switch have a greater potential to achieve glycemic targets following a transition in therapy from premixed insulin to insulin glargine plus OADs. The group with improvement in HbA_{1c} had the highest baseline HbA_{1c} levels compared with those with no change or deterioration in HbA_{1c}. Therefore, this study demonstrates that while patients with lower baseline HbA_{1c} may be able to achieve glycemic targets following a switch in therapy, poorly controlled patients with higher baseline HbA_{1c} are most likely to demonstrate an improvement in glycemic control following a switch to insulin glargine plus OADs. The majority of patients who failed to achieve HbA_{1c} $<7.0\%$ also failed to reach an FPG of ≤ 6.1 mmol/L, and this highlights the importance of titrating the dose of insulin glargine to an appropriate level in order to achieve adequate FPG control, which can aid achievement of target HbA_{1c}.

ACKNOWLEDGEMENTS

Sponsorship of this study and article processing charges were funded by Sanofi, Shanghai, China. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published. Sanofi was responsible for the design of the study, collecting and managing data, and performing all statistical analyses. All authors had full access to all the data in this study, and were fully responsible for the data interpretation and all content and editorial

decisions relating to this manuscript. Wenying Yang participated in study concept and design, data analysis; Shi Bu provided acquisition, analysis, interpretation of data, and critical revision of the manuscript for important intellectual content. Xuelian Zhang, Zhu Haiqing, Ying Shuai and Xiaoyan Xing participated in the data collection and manuscript composing. All authors have read and approved the final manuscript. Medical editorial and writing assistance in the preparation of this manuscript was provided by Priya Shreedhar of MediTech Media Asia Pacific and was funded by Sanofi. The authors would like to thank all of investigators and patients for their participation.

Disclosures. Wenying Yang reported being a consultant and/or speaker for Sanofi outside the submitted work. Shi Bu, Xuelian Zhang, Haiqing Zhu, Ying Shuai, and Xiaoyan Xing have nothing to disclose.

Compliance with Ethics Guidelines. The Lantus Registry Study protocol was conducted in accordance with the Declaration of Helsinki, and approved by the local ethical committees or institutional review boards at each participating institution. All patients or their legally acceptable surrogates gave written informed consent. This article is based on the previously conducted Lantus Registry Study, and does not involve any new studies of human or animal subjects performed by any of the authors.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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