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Insulin glargine-based therapy improves glycemic control in patients with type 2 diabetes sub-optimally controlled on premixed insulin therapies☆

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ABSTRACT

The AT.LANTUS trial recently demonstrated the efficacy and safety of insulin glargine initiation and maintenance using two different treatment algorithms in poorly controlled type 2 diabetes mellitus (T2DM). This sub-analysis investigated glycemic control and safety in 686 patients switching from premixed insulin (premix) with or without (±OADs) to once-daily glargine (±OADs/prandial insulin). A 24-week, multinational ($n = 59$), multicenter ($n = 611$), randomized study comparing two algorithms (Algorithm 1: clinic-driven titration; Algorithm 2: patient-driven titration) in four glargine ± OADs treatment groups: alone, once- (OD), twice- (BD) or >twice- (>BD) daily prandial insulin. After switching to the glargine regimen, HbA_{1c} levels significantly improved in the overall group (9.0 ± 1.3 to 8.0 ± 1.2%; $p < 0.001$) and in all subgroups; fasting blood glucose levels also improved in all subgroups (overall: 167.1 ± 50.0 to 106.9 ± 27.2 mg/dL [9.3 ± 2.8 to 5.9 ± 1.5 mmol/L]; $p < 0.001$). The incidence of severe hypoglycemia was also low in all four subgroups (≤1.7%). Patients with T2DM switching from premix ± OADs to glargine ± OADs had significant reductions in glycemic control with a low incidence of severe hypoglycemia. The addition of prandial (OD, BD or >BD) insulin was associated with further improvements in glycemic control. These data provide support for the stepwise introduction of prandial insulin to a more physiologic basal–bolus regimen, which is under investigation.

1. Introduction

The progressive nature of type 2 diabetes mellitus (T2DM) means that insulin therapy is usually required to maintain good metabolic control [1]. However, there are barriers to initiating insulin [2,3], including fear of hypoglycemia, fear of multiple injections, and weight gain. The new generation of insulin analogs enables many of these barriers to be overcome

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but the best method of initiating insulin remains a subject of debate.

Premixed insulins (premix) combine long- and short-acting insulins in a single preparation injected once or twice daily. They do not mimic physiologic insulin profiles and are relatively inflexible, although newer analog mixtures may offer a closer equivalent [4]. Optimizing fasting blood glucose (FBG) levels with premix, even the newer analog mixtures, may result in an increased risk of hypoglycemia [5,6] and may not provide enough flexibility for patients to achieve optimal glycemic control. Furthermore, there is little information available regarding next-step therapeutic strategies for patients with inadequate glycemic control with premix.

Insulin glargine (LANTUS®; glargine) was the first long-acting basal insulin analog for once-daily administration [7]. In patients with T2DM, glargine is associated with a lower risk of hypoglycemic events versus NPH insulin [8–14] with at least equivalent glycemic control [11,12,14–16].

Two small studies have reported that transferring patients sub-optimally controlled with premix with or without oral antidiabetics (±OADs) to insulin glargine ± OADs improved glycemic control [17,18]. This is likely to be due to the ability to use glargine to optimize the basal component and further reduce fasting hyperglycemia without the risk of hypoglycemia occurring mid-morning and during the night. However, this area requires further investigation.

The AT.LANTUS study compared glargine initiation and maintenance using one of two treatment algorithms; full results are reported elsewhere [19]. Given the large-scale nature of the study (59 countries, 4961 T2DM patients) and the diversity of prior treatment, it has been possible to carry out sub-population analyses to help inform on possible therapeutic strategies in patients grouped according to their previous therapy. Here we report the findings of a sub-population of patients who were treated with premixed insulin (±OADs) and who switched to insulin glargine ± prandial insulin ± OADs.

2. Materials and methods

2.1. Study design

All patients gave informed consent and the study had full ethical approval [19]. Patients with T2DM sub-optimally controlled (HbA_{1c} 7–12%) on their previous insulin therapy were randomized to one of the two treatment algorithms, with the aim of optimizing glargine over 24 weeks to achieve a target FBG level of ≤100 mg/dL (≤5.5 mmol/L) [19]. Algorithm 1 was a clinic-driven titration: glargine dose adjustments of 0–8 U were made at every clinic visit depending on the mean FBG levels for the previous three consecutive days. Algorithm 2 was predominantly a patient-driven titration (reviewed by a physician at each visit); glargine dose adjustments of 0–2 U were made every 3 days depending on mean FBG levels for the previous three consecutive days.

At randomization, patients were transferred from their previous insulin therapy to receive once-daily glargine at bedtime (9 p.m.–12 a.m.) with or without prandial insulin and with or without OADs. A prandial insulin could be added in a step-wise fashion from Week 12, based on HbA_{1c} and FBG data, and titrated at the investigator's discretion. For patients previously on a regimen including OADs, the decision to continue OADs was at the investigators' discretion. Full details of the study methodology, including the inclusion and exclusion criteria, can be found elsewhere [19].

Biochemistry and hematology measurements were taken at screening. HbA_{1c} and body weight were measured at screening, baseline, and Weeks 12 and 24.

Safety assessments in each treatment algorithm included adverse event (AE) reporting, excluding the primary and secondary outcomes. All AEs, including non-treatment-emergent AEs (TEAEs), were recorded.

2.2. Objectives

In this group of patients who switched from premix to a glargine-based regimen (Population 1), the primary objective was to compare the two algorithms in terms of the incidence of severe hypoglycemia as defined by the Diabetes Control and Complications Trial criteria [20] (an event with symptoms of hypoglycemia for which the patient required the assistance of another person and was associated with either a blood glucose level < 2.8 mmol/L [<50 mg/dL] or a prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration). Secondary objectives included the analysis of: baseline to endpoint change in glycemic control (HbA_{1c} and FBG), rates of symptomatic and nocturnal hypoglycemia, and changes in body weight and insulin dose.

Symptomatic hypoglycemia was defined as an event where symptoms consistent with hypoglycemia are experienced and either the subject responds to ingestion of carbohydrate/meal/snack or the episode is associated with a blood glucose <2.8 mmol/L (<50 mg/dL). Nocturnal hypoglycemia was defined as hypoglycemia which occurs while the subject is asleep (i.e. between bedtime [after the evening injection] and before getting up in the morning [before the morning determination of fasting blood glucose, before the morning injection]), and associated with a blood glucose level <2.8 mmol/L (<50 mg/dL) but without any symptoms.

The study endpoint was defined by the patient's last evaluation during treatment Week 24, for those completing the study, or at the last evaluation, for those missing data on Week 24.

Since the protocol allowed some flexibility in treatment (i.e. the introduction of prandial insulin from Week 12), patients with a stable treatment regimen (i.e. the same number of prandial insulin injections) were also analyzed (Population 2). This analysis aimed at evaluating how safely and effectively prandial insulin (once- (OD), twice- (BD), or more than twice- (>BD) daily) can be initiated, in conjunction with glargine.

2.3. Study populations

Population 1 consists of patients who received premix (±OADs) prior to the start of the study and who switched to glargine (±prandial insulin ± OADs). Population 2 is the subpopulation of patients that remained throughout the study on the same prandial insulin regimen. Four subgroups of patients were identified: no prandial insulin ($n = 384$), OD

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($n = 21$), BD ($n = 116$) and >BD ($n = 165$) prandial insulin injections.

2.4. Initiation of insulin glargine

When transferring patients to glargine from once-daily premix, an initial glargine dose equivalent to the basal component of the premix was used. When transferring patients from ≥twice-daily premix, a reduction of 20–30% was applied to the premixed basal insulin component [21].

2.5. Statistical methods

The statistical methods used in this sub-analysis were as employed in the main AT.LANTUS study [19]. In brief, the primary efficacy analysis was the comparison of the proportion of patients with severe hypoglycemia in each algorithm during the whole study period plus 5 days, using all patients who completed the study as planned (completed population). Full intention-to-treat analysis was also performed and reported for the main outcomes, and if different from the per-protocol analysis (completed population, Week 24). Patients treated at baseline with premix (±OADs) were isolated and a descriptive analysis produced. Analyses were performed for four specific subgroups defined according to the number of daily prandial insulin injections received at randomization (none, OD, BD and >BD injections) and who remained on the same treatment regimen throughout the study. All endpoints defined for the main study were analysed in the sub-analyses. All analyses presented here were performed on an exploratory basis and were undertaken on non-randomized subgroups of patients without adjustment for multiple testing.

3. Results

Results of independent audits performed in accordance with Good Clinical Practice concluded that the trial data were reliable, verifiable and retrievable. All data presented are for the completed population; results of the full population did not differ clinically or statistically (data not shown). The results are presented according to algorithm (Algorithm 1 vs. Algorithm 2) and according to the study treatment (OAD-only, prandial OD, prandial BD and prandial >BD).

3.1. Total group according to algorithm

3.1.1. Patients

A total of 686 patients in the completed population were previously treated with premix at baseline and remained on a stable prandial regimen throughout the study period (Algorithm 1, $n = 357$; Algorithm 2, $n = 329$). There were no significant differences in patient demographics with Algorithm 1 versus Algorithm 2. Baseline characteristics are given in Table 1.

3.1.2. Severe hypoglycemia

The proportion of patients experiencing severe hypoglycemia was <1% in the total population studied, with no significant difference between algorithms (1.1% vs. <1%, Algorithm 1 vs. Algorithm 2). The incidence of severe hypoglycemia was 1.8 events per 100 patient-years, again with no significant difference between algorithms (2.31 events per 100 patient vs. 1.24 events per 100 patient-years).

3.1.3. Other hypoglycemia

The proportion of patients experiencing nocturnal hypoglycemia was 2.9%, which was similar in the Algorithm 1 versus Algorithm 2 groups (3.1% vs. 2.7%), with similar incidence in both groups (6.4 events per 100 patient-years vs. 5.6 events per 100 patient-years). However, there was a significant difference ($p = 0.02$) between the algorithms in terms of symptomatic hypoglycemia: 19.6% with Algorithm 1 versus 27.1% with Algorithm 2 (23.2% in the overall group). Therefore, the risk of symptomatic hypoglycemia was lower with Algorithm 1 (46.1 events per 100 patient-years) compared with Algorithm 2 (66.6 events per 100 patient-years; risk reduction [Algorithm 1/Algorithm 2]: 0.69; 95% confidence interval: 0.51, 0.94).

3.1.4. Glycemic control

Mean HbA_{1c} decreased significantly from 9.0 ± 1.3 to $8.0 \pm 1.2\%$ (-1.0%; $p < 0.001$) in the total group during

Table 1 – Demographics at baseline according to treatment algorithm

	All patients	Algorithm 1	Algorithm 2
Number	686	357	329
Age (years)	57.7 ± 9.6	58.1 ± 9.6	57.2 ± 9.6
Female/male (%)	50.9/49.1	53.2/46.8	48.3/51.7
Weight (kg)	81.0 ± 15.5	79.8 ± 14.8	82.4 ± 16.2
BMI (kg/m^2)	29.4 ± 4.7	29.2 ± 4.6	29.6 ± 4.8
Duration since diagnosis (years)	12.8 ± 7.0	13.0 ± 7.5	12.5 ± 6.4
Time since start insulin (years)	4.3 ± 4.7	4.2 ± 4.7	4.4 ± 4.6
HbA_{1c} baseline (%)	8.97 ± 1.25	8.96 ± 1.25	8.98 ± 1.25
FBG baseline			
(mg/dL)	169.3 ± 47.6	170.1 ± 48.5	167.9 ± 46.7
(mmol/L)	9.4 ± 2.6	9.4 ± 2.7	9.3 ± 2.6
Premixed insulin only (%)	42.3	40.3	44.4
Premixed insulin with OADs (%)	57.7	59.7	55.6

Data are mean ± standard deviation unless otherwise stated; OAD, oral antidiabetic agent; BMI, body mass index; FBG, fasting blood glucose.

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Table 2 – Demographics at baseline according to study treatment group

	Insulin glargine ± OAD	Insulin glargine ± OAD + OD prandial	Insulin glargine ± OAD + BD prandial	Insulin glargine ± OAD + >BD prandial
Number	384	21	116	165
Age (years)	58.8 ± 9.6	58.1 ± 9.0	54.9 ± 9.7	56.8 ± 9.2
Female/male (%)	51.3/48.7	47.6/52.4	45.7/54.3	53.9/46.1
Weight (kg)	81.1 ± 15.4	80.4 ± 12.8	78.5 ± 15.1	82.7 ± 16.3
BMI (kg/m^2)	29.4 ± 4.7	29.6 ± 4.9	28.5 ± 4.8	30.0 ± 4.6
Duration since diagnosis (years)	12.7 ± 7.1	13.6 ± 5.4	13.2 ± 7.4	12.5 ± 6.8
Time since start insulin (years)	3.8 ± 4.4	4.3 ± 2.9	4.2 ± 4.4	5.5 ± 5.4
HbA_{1c} baseline (%)	8.8 ± 1.3	9.0 ± 1.2	9.3 ± 1.3	9.2 ± 1.2
FBG baseline				
(mg/dL)	161.9 ± 45.8	178.5 ± 65.9	172.5 ± 53.7	174.0 ± 49.2
(mmol/L)	(9.0 ± 2.5)	(9.9 ± 3.7)	(9.6 ± 3.0)	(9.7 ± 2.7)
Premixed insulin only (%)	34.6	52.4	51.7	52.1
Premixed insulin with OADs (%)	65.4	47.6	48.3	47.9

Data are mean ± standard deviation unless otherwise stated; OAD, oral antidiabetic agent; OD, once daily; BD, twice daily; >BD, more than twice daily; BMI, body mass index; FBG, fasting blood glucose.

difference between Algorithms (Algorithm 1: 9.0 ± 1.3 to 8.0 ± 1.3% [−1.0%]; Algorithm 2: 9.0 ± 1.3 to 7.9 ± 1.2% [−1.1%]).

Mean FBG decreased significantly by 60.2 ± 50.3 mg/dL (3.3 ± 2.8 mmol/L; $p = 0.009$) from 167.1 ± 50.0 to 106.9 ± 27.2 mg/dL (9.3 ± 2.8 to 5.9 ± 1.5 mmol/L). When FBG was analysed according to algorithm, a significant decrease was observed with both algorithms ($p < 0.001$); although, the decrease was significantly greater with Algorithm 2 versus Algorithm 1 (−60.7 ± 48.1 mg/dL vs. −59.7 ± 52.3 mg/dL [3.4 ± 2.7 mmol/L vs. 3.3 ± 2.9 mmol/L]; $p = 0.02$), it is unlikely to be clinically relevant. The proportion of patients achieving FBG ≤100 mg/dL (≤5.5 mmol/L) was 47.5% (Algorithm 1: 44.3%; Algorithm 2: 51.1%).

3.1.5. *Insulin glargine dose*

The glargine dose increased by 20.2 ± 19.3 U in the total group; from 28.4 ± 15.2 U at the start of glargine therapy to 48.6 ± 26.6 U at the study endpoint. This increase was significant with both algorithms ($p < 0.001$) and significantly greater with Algorithm 2 versus Algorithm 1 (22.1 ± 21.7 U vs. 18.5 ± 16.6 U; $p = 0.03$).

3.1.6. *Daily prandial insulin dose*

Daily prandial insulin dose increased significantly (both $p < 0.001$) from 20.0 ± 11.8 U at the start of glargine therapy to 25.4 ± 17.5 U at endpoint, in Algorithm 1 (5.4 ± 10.3 U) and from 22.7 ± 14.2 at start of glargine therapy to 28.3 ± 16.8 U at endpoint, with Algorithm 2 (5.3 ± 11.8 U), with no significant difference between algorithms.

3.1.7. *Daily total (insulin glargine + prandial) insulin dose*

Daily total (glargine + prandial) insulin dose increased significantly (both $p < 0.001$) from 36.5 ± 23.7 U at the start of glargine therapy to 57.2 ± 34.8 U at endpoint in Algorithm 1 (20.8 ± 18.8 U) and from 39.2 ± 23.5 U at the start of glargine therapy to 63.6 ± 35.5 U at endpoint with Algorithm 2 (24.4 ± 23.7 U). The change in total insulin dose was significantly greater for Algorithm 2 compared with Algorithm 1 ($p = 0.05$).

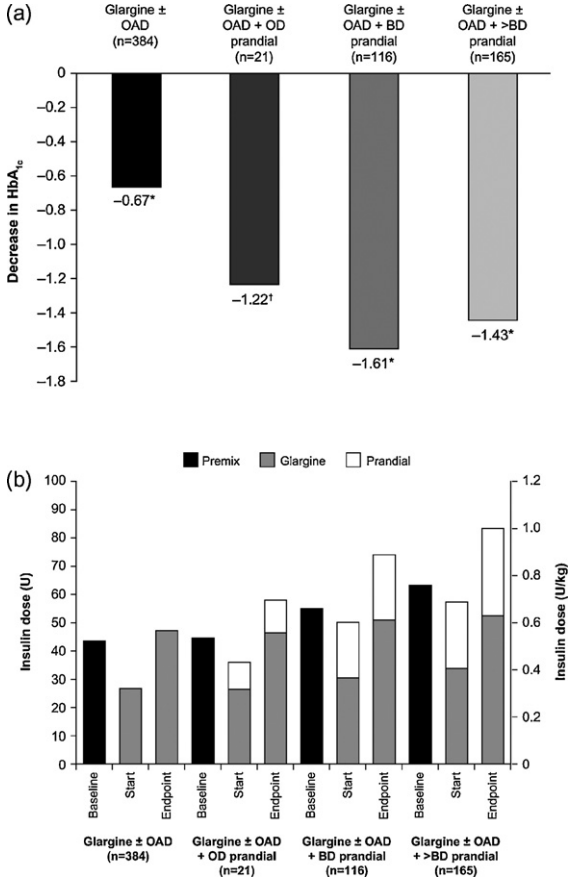

Fig. 1 – (A) Baseline to endpoint decrease in HbA_{1c} levels for patients who had previously received premixed insulin ± OADs before transferring to a regimen including once-daily insulin glargine. *$p < 0.001$ and †$p = 0.004$ for baseline to endpoint change; Glargine, insulin glargine; OAD, oral antidiabetic agent; OD, once daily; BD, twice daily; >BD, more than twice daily. (B) Premixed insulin dose at baseline and insulin glargine and prandial insulin dose at endpoint. Glargine, insulin glargine; OAD, oral antidiabetic agent; OD, once daily; BD, twice daily; >BD, more than twice daily.

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3.1.8. Body weight

Body weight increased modestly by 0.8 kg, from 81.2 ± 15.6 to 82.0 ± 15.7 kg, in the total group ($p < 0.001$), with no significant difference between algorithms.

3.1.9. Safety

The safety population comprised 391 patients treated according to Algorithm 1 and 361 patients treated according to Algorithm 2. TEAEs were reported in 42.2% of patients in Algorithm 1 and 44.6% of patients in Algorithm 2, with no difference between the frequencies of TEAEs between groups. The most frequently reported AEs were respiratory tract infections ($n = 15$ and 17, respectively) and injection site reactions ($n = 27$ and 23, respectively); in >95% of episodes, the AE was rated as mild or moderate. Treatment discontinuation due to an AE occurred in four patients treated according to Algorithm 1 and three patients treated according to Algorithm 2. In total, two patients died (both in the Algorithm 2 group); however, the deaths were not considered related to the study medication. Full details can be found elsewhere [19].

3.2. Groups according to study treatment

3.2.1. Patients

Of the 686 patients in the completed population who were previously treated with premix at baseline and remained on a stable prandial regimen throughout the study period; 384 patients received glargine ± OADs alone (Group: OAD), 21 patients received glargine ± OADs plus once-daily prandial insulin (Group: prandial OD), 116 patients received glargine ± OADs plus twice-daily prandial insulin (Group: prandial BD) and 165 patients received glargine ± OADs plus >twice-daily prandial insulin (Group: prandial >BD). There were no significant differences in patient demographics between the four treatment groups (Table 2) or between treatment algorithms (data not shown).

3.2.2. Severe hypoglycemia

The proportion of patients experiencing an episode of severe hypoglycemia was low in all four treatment groups during the glargine treatment phase: OAD group <1%, prandial OD group 0%, prandial BD group 1.7% and prandial >BD group <1%. The incidence of severe hypoglycemia was 1.6 events per 100 patient-years in the OAD group, 0 events per 100 patient-years in the prandial OD group, 3.6 events per 100 patient-years in the prandial BD group and 1.2 events per 100 patient-years in the prandial >BD group.

3.2.3. Other hypoglycemia

Episodes of symptomatic and nocturnal hypoglycemia were also low in all four treatment groups during the glargine treatment phase: OAD group 22.4 and 3.1% (53.3 and 6.5 events per 100 patient-years), prandial OD group 9.5 and 0% (20.0 and <1 events per 100 patient-years), prandial BD group 25.0 and <1% (62.1 and 1.8 events per 100 patient-years), and prandial >BD group 25.5 and 4.2%, respectively (62.3 and 8.8 events per 100 patient-years).

Table 3 – Efficacy data according to treatment group

	Insulin glargine ± OAD	Insulin glargine ± OAD + OD prandial	Insulin glargine ± OAD + BD prandial	Insulin glargine ± OAD + >BD prandial
Number	384	21	116	165
HbA_{1c} (%)				
Baseline	8.80 ± 1.26	9.02 ± 1.18	9.26 ± 1.25	9.15 ± 1.19
Endpoint	8.17 ± 1.31	7.80 ± 0.94	7.65 ± 1.15	7.70 ± 1.08
Change	−0.67 ± 1.44	−1.22 ± 1.73	−1.61 ± 1.38	−1.43 ± 1.27
p-Value	<0.001	0.004	<0.001	<0.001
FBG (mg/dL)				
Baseline	161.9 ± 45.8	178.5 ± 65.9	172.5 ± 53.7	174.0 ± 49.2
Endpoint	106.9 ± 27.3	99.5 ± 16.4	105.0 ± 24.6	109.1 ± 29.7
Change	−55.0 ± 47.9	−79.0 ± 67.0	−67.1 ± 55.2	−64.9 ± 48.5
p-Value	<0.001	<0.001	<0.001	<0.001
FBG (mmol/L)				
Baseline	9.0 ± 2.5	9.9 ± 3.7	9.6 ± 3.0	9.7 ± 2.7
Endpoint	5.9 ± 1.5	5.5 ± 0.9	5.8 ± 1.4	6.1 ± 1.6
Change	−3.1 ± 2.7	−4.4 ± 3.7	−3.7 ± 3.1	−3.6 ± 2.7
p-Value	<0.001	<0.001	<0.001	<0.001
Body weight (kg)				
Baseline	81.4 ± 15.5	80.2 ± 12.6	78.5 ± 15.0	82.9 ± 16.5
Endpoint	81.7 ± 15.7	81.5 ± 14.1	80.1 ± 14.8	84.2 ± 16.6
Change	+0.3 ± 3.1	+1.4 ± 3.1	+1.6 ± 3.1	+1.5 ± 3.6
p-Value	0.076	0.059	<0.001	<0.001

Data are mean ± standard deviation unless otherwise stated; OAD, oral antidiabetic agent; OD, once daily; BD, twice daily; >BD, more than twice daily; FBG, fasting blood glucose.

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3.2.4. *Glycemic control*

Mean HbA_{1c} levels decreased significantly over the course of the study for all treatment groups (Fig. 1A). In the OAD group, HbA_{1c} levels decreased from $8.8 \pm 1.3\%$ at the start to $8.2 \pm 1.3\%$ at endpoint. In the prandial OD group, HbA_{1c} levels decreased from 9.0 ± 1.2 to $7.8 \pm 0.9\%$. In the prandial BD group, HbA_{1c} levels decreased from 9.3 ± 1.3 to $7.7 \pm 1.2\%$. In the prandial >BD group, HbA_{1c} levels decreased from 9.2 ± 1.2 to $7.7 \pm 1.1\%$. There was no significant difference between the algorithms. There were also significant baseline to endpoint decreases in FBG (Table 3) over the course of the study in all treatment groups ($p < 0.001$ for baseline to endpoint change for all groups).

3.2.5. *Insulin glargine dose*

In the OAD group, the daily glargine dose increased from 26.2 ± 14.0 U at the start of therapy to 46.7 ± 27.3 U at endpoint (Fig. 1B). The daily glargine dose increased from 25.9 ± 16.1 to 46.1 ± 22.2 U in the prandial OD group, from 29.7 ± 14.5 to 50.7 ± 22.8 U in the prandial BD group and from 33.1 ± 17.1 to 52.1 ± 27.6 U in the prandial >BD group (Fig. 1B).

3.2.6. *Daily prandial insulin dose*

Over the course of the study, the total daily prandial insulin dose increased from 10.1 ± 5.4 U at the start of therapy to 11.5 ± 6.2 U at endpoint in the OD group ($+0.8 \pm 2.2$ U), from 19.8 ± 14.3 to 23.2 ± 15.1 U in the BD group (3.4 ± 9.2 U) and from 23.8 ± 12.0 to 31.1 ± 17.9 U in the >BD group (7.3 ± 12.3 U) (Fig. 1B).

3.2.7. *Daily total (insulin glargine + prandial) insulin dose*

Over the course of the study, the daily total insulin dose increased from 26.2 ± 14.0 U at the start of therapy to 46.7 ± 27.3 U at endpoint in the OAD group, from 36.0 ± 19.8 to 56.5 ± 27.2 U in the prandial OD group, from 49.5 ± 24.7 to 73.6 ± 32.8 U in the prandial BD group and from 56.9 ± 24.7 to 83.2 ± 39.0 U in the prandial >BD group (Fig. 1B).

3.2.8. *Body weight*

Between the start and endpoint of the study, body weight increased by 0.3 kg in the OAD group, by 1.6 kg in the prandial OD group, by 1.6 kg in the prandial BD group and by 1.5 kg in the prandial >BD group (Table 3). Analysis of weight changes according to OAD treatment indicated a difference in weight change dependent on the use or non-use of metformin. Patients not receiving metformin ($n = 465$) experienced a mean weight change of 1.14 ± 3.3 kg whereas a mean increase of 0.23 ± 3.2 kg was seen in those patients who had received metformin ($n = 91$; $p = 0.036$).

4. Conclusions

The AT.LANTUS study was carried out in a large population ($n = 4961$ patients in 59 countries) and the results will be applicable to many patients in a clinical setting [19]. In this sub-analysis of 686 patients who were previously using premixed insulin, the switch from premix ± OADs to glargine ± OADs was associated with a low incidence of severe hypoglycemia, significant reductions in HbA_{1c} and FBG and only modest weight gain. The addition of prandial insulin treatment (OD, BD or >BD) produced further improvements in glycemic control without a corresponding increase in the incidence of hypoglycemia and only modest weight gain over 24 weeks. These results echo those achieved in a second study with glargine plus OADs in 5045 patients failing premix (OD, BD or >BD) ± OADs [17]. During the 12-week treatment period, glycemic control improved significantly with glargine (HbA_{1c} decreased from 8.3 to 7.1%; FBG −55.9 mg/dL [−3.10 mmol/L]; both $p \leq 0.001$) [17]. In addition, mean body weight decreased by 1.6 kg ($p \leq 0.001$). Although we have presented the results of the completed population, results of intention-to-treat analyses were consistent with those presented here.

As the present study was conducted as an exploratory analysis of a large subgroup ($n = 686$) of patients from the original AT.LANTUS study ($n = 4961$ patients), the analyses were mainly descriptive, without a control group of patients who continued their premix regimen. Furthermore, patients were not randomized to receive a specific number of prandial insulin doses, and thus the results may also reflect baseline characteristics. Further prospective studies, comparing intensification of premixed insulin versus initiation and intensification of glargine (±OADs/prandial insulin) are warranted to confirm the results presented here.

It has been estimated that nearly 40% of all insulin-treated patients with diabetes worldwide are treated with premix [22]. The popularity of premix is largely due to the perceived simplicity of the regimen. However, a significant proportion of patients on premix have sub-optimal glycemic control. This is probably because many patients on premix cannot optimize FBG levels without the risk of hypoglycemia, particularly mid-morning or during the night. Glargine has been shown to enable the achievement of good glycemic control with a significantly lower incidence of minor hypoglycemia and weight gain compared with premix [5,6]. In a study of insulin-naïve patients, mean HbA_{1c} levels decreased significantly in patients initiated on glargine plus OADs compared with 70/30 premix (−1.64% vs. −1.31%; $p = 0.0003$) as did FBG levels (adjusted mean difference: −17 mg/dL [−0.9 mmol/L]; $p < 0.0001$), and these improvements in glycemic control were associated with fewer confirmed hypoglycemic episodes (mean 4.07 per patient-year vs. 9.87 per patient-year; $p < 0.0001$) [6]. This is in contrast to studies that compared analog insulin mixtures (lispro 75/25 and aspart 70/30) with OD glargine and have shown more effective glycemic control with the premixed regimen but with greater risk of hypoglycemia and weight gain [5,23].

The results presented here demonstrate that patients with T2DM poorly controlled on premix can safely achieve improved glycemic control by transferring to a glargine-based regimen (±OADs). For some patients, optimization of basal insulin alone will significantly reduce HbA_{1c}. Optimization of FBG levels makes an important contribution to overall glycemic control, particularly if the HbA_{1c} is greater than 8.4% [24]. It is of interest that in this study the FBG in all groups previously on a long-term insulin regimen (over 4 years duration) was high—often over 170 mg/dL (9.4 mmol/L) and with a relatively low dose of basal insulin. This emphasises the dilemma that clinicians are faced with when seeing patients on premix regimens, when further increases in doses are often

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resisted by patients because of the risk of hypoglycemia and potential weight gain. However, it should be acknowledged that for some patients, even optimal titration of basal insulin is insufficient to reach or maintain optimal glycemic control and, therefore, prandial insulin requirements in these patients are an important consideration. It has been shown that post-prandial hyperglycemia makes an important contribution to HbA_{1c} the closer you get to the optimal HbA_{1c} target [24]. Even with aggressive titration of basal insulin analogs, a significant proportion of patients remain above the optimal target of 7% or experience hypoglycemia. In the treat-to-target trial, only 58% of patients reached the target HbA_{1c} of $\leq$7%, and 33% reached the target HbA_{1c} without experiencing an episode of nocturnal hypoglycemia in the glargine arm [11].

So what next for patients on OADs who have optimal basal insulin but remain above target HbA_{1c}? Strategies could include a switch to a premix regimen with aggressive dose titration, but as previously stated, this can lead to increased risk of hypoglycemia and weight gain [5,23].

A move to a formal basal–bolus regimen is often considered but this requires intensive support and four injections a day. Instead, this sub-analysis suggests that a switch from premixed insulin to once-daily glargine ± OADs can confer significant improvements in glycemic control. It can be argued that because no patients were continued on premixed insulin, the improvements observed with glargine may be a result of the increased health care received during the trial as opposed to treatment efficacy. However, the switch to glargine ± OADs offers the physician potential to further escalate therapy with the addition of one or more doses of prandial insulin. Indeed, further improvements in glycemic control were seen with the use of multiple doses of prandial insulin. The results of this study suggest that one additional prandial injection confers benefit in terms of lowering HbA_{1c}, albeit in a relatively small number of patients. The addition of prandial therapy was entirely at the investigator's discretion, without formal guidance on how this was implemented. However, our data also provide support for the stepwise introduction of prandial insulin to a more physiologic basal–bolus regimen. The concept of tailoring therapy to the changing needs of the patient as the disease inevitably deteriorates could begin with basal insulin followed by the addition of one prandial injection before the largest meal, titrating against post-prandial glucose levels, and stepwise introduction of further prandial injections as required. This concept of the main meal either in terms of the carbohydrate content or its ability to induce post-prandial hyperglycemia needs further clarity. However, this approach in terms of physiologic basis and flexibility it may offer to patients is an option, which clearly needs further investigation.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.diabres.2007.09.013.

Conflict of interest

M.D. has acted in a consultancy capacity and as a speaker for Novartis, Novo Nordisk, sanofi-aventis, Eli Lilly and Merck Sharpe Dohme. M.D. has also received grants in support of investigator-led and internal trials from Servier, Novartis, Novo Nordisk, Pfizer and sanofi-aventis. R.G. has received financial support from sanofi-aventis. F.S. has served on advisory boards for sanofi-aventis. P.S. is an employee of sanofi-aventis.

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