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Initiation of insulin glargine therapy in type 2 diabetes subjects suboptimally controlled on oral antidiabetic agents: results from the AT.LANTUS trial*

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Objective: For many patients with type 2 diabetes, oral antidiabetic agents (OADs) do not provide optimal glycaemic control, necessitating insulin therapy. Fear of hypoglycaemia is a major barrier to initiating insulin therapy. The AT.LANTUS study investigated optimal methods to initiate and maintain insulin glargine (LANTUS®, glargine, Sanofi-aventis, Paris, France) therapy using two treatment algorithms. This subgroup analysis investigated the initiation of once-daily glargine therapy in patients suboptimally controlled on multiple OADs.

Research Design and Methods: This study was a 24-week, multinational (59 countries), multicenter (611), randomized study. Algorithm 1 was a clinic-driven titration and algorithm 2 was a patient-driven titration. Titration was based on target fasting blood glucose $\leq$100 mg/dl ($\leq$5.5 mmol/l). Algorithms were compared for incidence of severe hypoglycaemia [requiring assistance and blood glucose <50 mg/dl (<2.8 mmol/l)] and baseline to end-point change in haemoglobin A_{1c} (HbA_{1c}).

Results: Of the 4961 patients enrolled in the study, 865 were included in this subgroup analysis: 340 received glargine plus 1 OAD and 525 received glargine plus >1 OAD. Incidence of severe hypoglycaemia was <1%. HbA_{1c} decreased significantly between baseline and end-point for patients receiving glargine plus 1 OAD (−1.4%, $p < 0.001$; algorithm 1 −1.3% vs. algorithm 2 −1.5%; $p = 0.03$) and glargine plus >1 OAD (−1.7%, $p < 0.001$; algorithm 1 −1.5% vs. algorithm 2 −1.8%; $p = 0.001$).

Conclusions: This study shows that initiation of once-daily glargine with OADs results in significant reduction of HbA_{1c} with a low risk of hypoglycaemia. The greater reduction in HbA_{1c} was seen in patients randomized to the patient-driven algorithm (algorithm 2) on 1 or >1 OAD.

Keywords: basal insulin analogues, insulin glargine, oral antidiabetic agents, titration, type 2 diabetes, treatment algorithms
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†Duality 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. F. S. has served on advisory boards for sanofi-aventis.

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Achieving and maintaining tight glycaemic control for patients with type 2 diabetes is essential to delay progression of micro- and macrovascular complications [1]. Targets for haemoglobin A_{1c} (HbA_{1c}) have been set as <7.0, 6.5–7.5 and <6.5% by the American Diabetes Association [2], National Institute for Health and Clinical Excellence in the UK [3] and the International Diabetes Federation [4], respectively. However, the majority of patients with type 2 diabetes are unable to reach target HbA_{1c} levels [5,6].

Following diagnosis, patients are generally advised to make a number of lifestyle changes, focussed on increasing physical activity levels [7] and diet [8]. However, such programmes are usually insufficient by this stage of the diabetes [9]. The progressive nature of type 2 diabetes mellitus, characterized by a decline in β-cell function [10,11] and deterioration in glycaemic control [12], means that pharmacologic interventions are usually required [13]. Oral antidiabetic agents (OADs), for example sulfonylureas, metformin and glitazones, are therapeutic interventions used in monotherapy or in combination. However, to achieve and maintain good glycaemic control, OADs, even in combination, are insufficient [14] and insulin therapy is often required [13].

Both patients and physicians may be reluctant to start insulin therapy [6,15,16]. The fear of hypoglycaemia, needle anxiety and weight gain are among the reasons cited that actively discourage insulin therapy. Therefore, it is important that for insulin therapy to be effective in patients with type 2 diabetes, these barriers must be overcome.

Insulin glargine (LANTUS®, glargine) is the first clinically available basal analogue with no pronounced peak in activity and a 24-h duration of action following once-daily administration [17]. In type 2 diabetes, insulin glargine has at least equivalent glycaemic control [18–20] with a lower incidence of hypoglycaemia compared with NPH insulin [20–25]. Therefore, insulin glargine could potentially be used as part of a more intensive treatment regimen to achieve target HbA_{1c} levels $\leq$7%, with a lower risk of hypoglycaemia. Combination therapy of insulin glargine in conjunction with one or more OADs is an effective and simple regimen in patients with type 2 diabetes who have suboptimal control on OADs alone [26,27].

While little is known regarding the optimal titration regimen for initiating basal insulin therapy, the Treat-to-Target study [25] demonstrated that aggressive titration, in the context of an intensive and fully resourced clinical trial setting, can result in ~60% of patients achieving target HbA_{1c} of $\leq$7%.

We recently showed that two treatment algorithms, one largely clinic driven and the other primarily patient driven, can be introduced to a large cohort of subjects [28]. Given the large-scale nature of the AT.LANTUS study (59 countries, 4961 patients) and the diversity of prior treatment, it has been possible to perform a number of *post hoc* subanalyses on different subpopulations. One of the most likely clinical contexts in which basal insulin is initiated in type 2 diabetes is in those with suboptimal glycaemic control on OADs; thus, results in this particular subgroup are of particular relevance. Here, we report the findings of a subgroup analysis of insulin-naive patients suboptimally controlled with OADs who took part in the AT.LANTUS study.

Research Design and Methods

Study Design

This was a prospective, multinational (611 centres in 59 countries in Western and Eastern Europe, South America, Asia and Africa/Middle East), randomized controlled, parallel-design study of 24 weeks duration of 4961 type 2 diabetes patients. This study included only four mandatory clinical visits, similar to standard clinical practice. All patients gave informed consent in accordance with the Declaration of Helsinki, and the study was performed in accordance with Good Clinical Practice. Full details are available elsewhere [28].

Inclusion criteria for the total population [28] included subjects aged $\geq$18 years on antidiabetic treatment (any oral and/or insulin therapy) for >6 months, HbA_{1c} levels >7.0 and <12.0%, body mass index values <40 kg/m^2 and a willingness to perform self-monitored blood glucose. Additional subgroup analysis criteria included insulin-naive patients suboptimally controlled with >1 OAD. Exclusion criteria were in accordance with the manufacturer's prescribing information.

In this paper, we discuss the subgroup analysis of subjects who were previously taking only OADs. At baseline, subjects were randomized (1 : 1) to receive insulin glargine according to algorithm 1 (clinic-driven titration) or algorithm 2 (patient-driven titration) (table 1).

At baseline, the investigator decided whether to continue each OAD, in line with the prescribing information. Once it was decided whether the subject should take 1 or >1 OAD, the dose of OAD(s) remained fixed and stable for the duration of the study. As thiazolidinediones were not licensed for use in combination with insulin at the time this study was conducted, for any patients using a thiazolidinedione during screening, the investigators were asked to switch therapy, in line with the prescribing information.

Table 1 Summary of the two treatment titration regimens for insulin glargine

	Increase in daily basal insulin glargine dose (U)*	
Mean FBG for the previous 3 consecutive days	**Algorithm 1†: titration at every visit; physician-driven**	**Algorithm 2†: titration every 3 days; subject-driven and reviewed by physicians at each visit**
Starting dose	10 U/day	Numerically equivalent to FBG in preceding 7 days (e.g. FBG = 12 mmol/l, insulin dose = 12 U/day)
≥100 and <120 mg/dl (≥5.6 and <6.7 mmol/l)	0–2 (at the discretion of the investigator)‡	0–2 (at the discretion of the investigator)‡
≥120 and <140 mg/dl (≥6.7 and <7.8 mmol/l)	2	2
≥140 and <180 mg/dl (≥7.8 and <10 mmol/l)	4	2
≥180 mg/dl (≥10 mmol/l)	6–8 (at the discretion of the investigator)‡	2

FBG = fasting blood glucose.
*Target FBG ≤ 100 mg/dl (≤5.5 mmol/l).
†Reviewed by physician at each visit, either in person or over the telephone; titration occurred only in the absence of blood glucose levels <72 mg/dl (<4.0 mmol/l).
‡Magnitude of daily basal dose was at the discretion of the investigator.

Objectives

The primary objective of the full study was to compare the two treatment algorithms for the initiation and maintenance of insulin glargine based on the incidence of severe hypoglycaemia, defined according to criteria used in the Diabetes Control and Complications Trial (DCCT) [29,30].

The primary outcome measure for this subgroup analysis was the comparison between algorithms for the incidence of severe, symptomatic and nocturnal hypoglycaemia. Secondary outcomes included glycaemic control [HbA_{1c} and fasting blood glucose (FBG)] and change in insulin dose from baseline. The study end-point was defined by the subject's last observation (visit 12 for those completing the study, or last clinic for those missing data on visit 12). If a subject discontinued treatment permanently before the planned study ends, the last evaluation before discontinuation was considered for the end-point analysis.

Measurements and Safety

At screening, biochemistry and haematology measurements were taken. HbA_{1c} and weight were measured at screening, baseline and weeks 12 and 24. Analyses of HbA_{1c} were performed by the laboratory of each participating site, either according to the DCCT standard method or according to a DCCT-aligned method within a documented quality controlled system. FBG levels on 6 consecutive days before and on the day of a visit were measured by subjects weekly from baseline to week 24. Glucose monitors were provided for self-monitored blood glucose. The glucose meters used a standardized platform for the entire study and reported results in whole blood. Data and calibration of blood glucose meters were verified at clinical visits.

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

Statistical Methods

The statistical and reporting methods used in this subanalysis were similar to those used in the main AT. LANTUS study [28]. In the full study population, the primary efficacy variable (frequency of severe hypoglycaemia) was evaluated using a two-sided 90% confidence interval (CI), with equivalence declared if the 90% CI was contained in the pre-defined equivalence boundaries (−1.5, 1.5%). For analyses presented here, patients treated at baseline with >1 OAD were isolated and a descriptive analysis was produced. Analyses were performed for two subgroups defined according to the number of OADs received at randomization (1 or >1 OAD) and who remained on the same treatment regimen throughout the study. All analyses presented here were performed on an exploratory basis. The analyses were undertaken on non-randomized subgroups of patients without adjustment for multiple testing and were based on the per-protocol population. Changes from baseline in HbA_{1c}, FBG, body weight and insulin dose were analysed using analysis of covariance. Student's *t*-test and the chi-squared test were also used as appropriate. A p value of <0.05 was considered statistically significant. Statistical analyses were performed using SAS version 8 (SAS, Cary, NC, USA).

Results

Results of independent audits performed in accordance with Good Clinical Practice concluded that the trial data

were reliable, verifiable and retrievable. The results from the full study population (n = 4961) can be found elsewhere [28]. A total of 865 subjects with type 2 diabetes, previously suboptimally controlled on multiple OADs, were included in this subgroup analysis; of these patients, 340 received insulin glargine plus 1 OAD and 525 received insulin glargine plus >1 OAD (intention-to-treat population of this subgroup). Of patients receiving 1 OAD, 316 (algorithm 1: 170 and algorithm 2: 146) completed the study to form the per-protocol population; reasons for discontinuation, algorithm 1 vs. algorithm 2, were patient not followed to final visit (four vs. eight subjects) and major protocol violations (six vs. six subjects). In patients receiving >1 OAD, 499 (algorithm 1: 256 and algorithm 2: 243) completed the study to form the per-protocol population; reasons for discontinuation, algorithm 1 vs. algorithm 2, were patient not followed to final visit (five vs. seven subjects) and major protocol violations (eight vs. six subjects).

Subject demographics and baseline characteristics were broadly similar between the two treatment groups and within each algorithm, although patients in the >1 OAD treatment group tended to have a longer duration of OAD treatment compared with those in the 1 OAD treatment group (table 2).

While data presented are based on the per-protocol analysis, full intention-to-treat analyses were performed. The results were virtually identical and, therefore, did not differ clinically or statistically and are not presented here.

Hypoglycaemia

The incidence of severe, symptomatic and nocturnal hypoglycaemia in patients receiving insulin glargine via either treatment algorithm plus either 1 OAD or >1 OAD is summarized in table 3. The incidence of severe hypoglycaemia was <1% in both treatment groups, with no significant difference between the treatment algorithms.

Haemoglobin A_{1c}

In subjects receiving insulin glargine plus 1 OAD, there was a significant baseline to end-point decrease in HbA_{1c} in both algorithms (figure 1A). Algorithm 2 was associated with a greater reduction compared with algorithm 1 (−1.5 vs. −1.3%, p = 0.03). Significant reductions in HbA_{1c} from baseline to end-point were also observed in patients receiving insulin glargine plus >1 OAD in both algorithms (figure 1A). Algorithm 2 was associated with

Table 2 Baseline demographics and characteristics of the subgroup analysis subjects treated with insulin glargine by algorithm 1 and algorithm 2 (per-protocol population)

	Insulin glargine + 1 OAD (n = 316)		Insulin glargine + >1 OAD (n = 499)	
Demographics and characteristics	**Algorithm 1 (n = 170)**	**Algorithm 2 (n = 146)**	**Algorithm 1 (n = 256)**	**Algorithm 2 (n = 243)**
Age (years)	57.9 ± 10.2	56.6 ± 11.0	57.2 ± 10.3	57.3 ± 10.5
Body mass index (kg/m^2)	29.3 ± 4.6	29.2 ± 4.6	29.3 ± 4.6	28.9 ± 4.3
Sex				
Male (%)	51.2	58.9	50.8	52.7
Female (%)	48.8	41.1	49.2	47.3
Age at onset of diabetes (years)	48.6 ± 9.5	46.8 ± 10.7	46.8 ± 10.1	46.7 ± 10.3
Diabetes duration (years)	9.3 ± 5.5	9.7 ± 6.5	10.4 ± 5.7	10.5 ± 6.6
Duration of OAD therapy (years)	7.9 ± 5.7	7.7 ± 5.8	9.2 ± 5.1	9.4 ± 6.2
HbA_{1c} (%)	9.1 ± 1.3	9.1 ± 1.3	9.1 ± 1.3	9.2 ± 1.2
Fasting blood glucose, mg/dl (mmol/l)	180.7 ± 45.8 (10.0 ± 2.5)	186.2 ± 55.3 (10.3 ± 3.1)	180.4 ± 46.5 (10.0 ± 2.6)	183.7 ± 47.8 (10.2 ± 2.7)

HbA_{1c}, haemoglobin A_{1c}; OAD, oral antidiabetic agent.
Data are mean ± s.d. unless otherwise stated.

Table 3 Incidence of severe, symptomatic and nocturnal hypoglycaemia

	Insulin glargine + 1 OAD (n = 316)			Insulin glargine + >1 OAD (n = 499)		
	Algorithm 1 (n = 170)	**Algorithm 2 (n = 146)**	**p**	**Algorithm 1 (n = 256)**	**Algorithm 2 (n = 243)**	**p**
Severe hypoglycaemia (% <2.8 mmol/l)	0	0	N/S	<1	<1	N/S
Symptomatic hypoglycaemia (%)	13.5	15.1	N/S	18.8	16	N/S
Nocturnal hypoglycaemia (%)	<1	2.1	N/S	2.7	4.5	N/S

OAD, oral antidiabetic agent; N/S, non-significant.

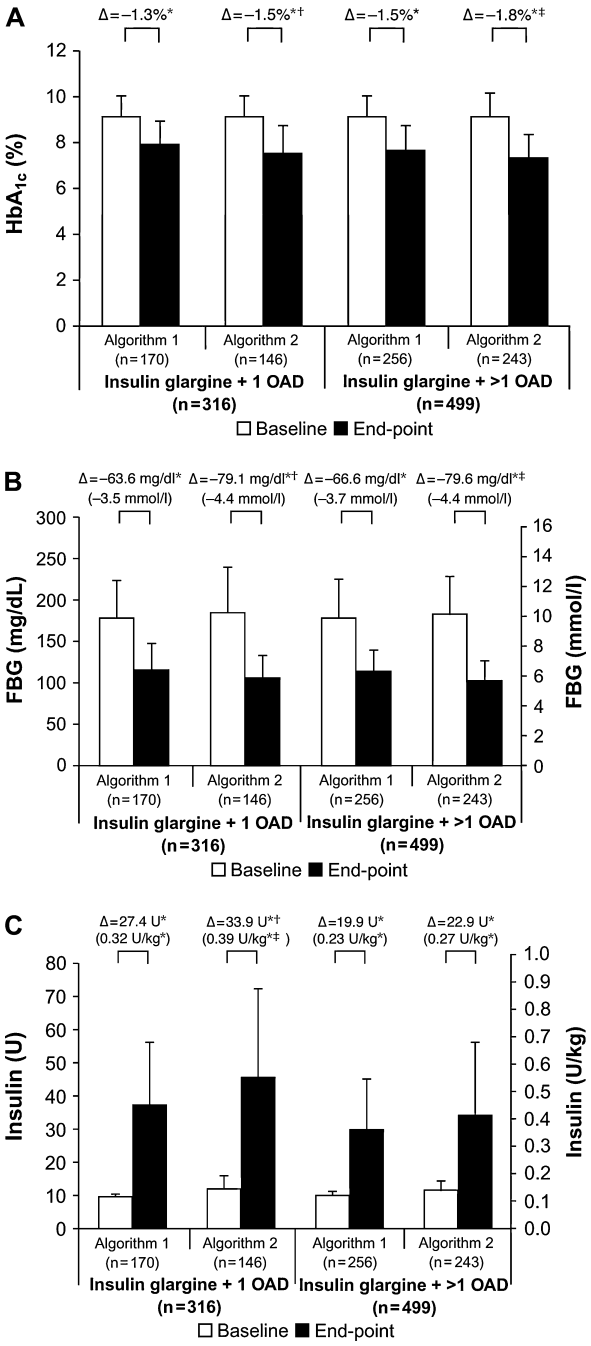

Fig. 1 (A) HbA_{1c} levels at baseline (open bars) and end-point (closed bars) in the per-protocol population receiving insulin glargine via algorithm 1 or algorithm 2 plus either 1 OAD or >1 OAD. *$p < 0.001$ for baseline to end-point change. †$p = 0.03$ and ‡$p = 0.001$ for difference between algorithms for baseline to end-point change. The magnitude of change in HbA_{1c} from baseline to end-point for algorithm 1 vs. Algorithm 2 in the intent-to-treat population was 1.9 and 1.6%, respectively. (B) FBG levels at baseline (open bars) and end-point (closed bars) in the per-protocol population receiving insulin glargine via algorithm 1 or algorithm 2 plus either 1 OAD or >1 OAD. *$p < 0.001$ for baseline to end-point change. †$p = 0.001$ and ‡$p < 0.001$ for difference between algorithms for baseline to end-point change. (C) Insulin dose at baseline (open bars) and end-point (closed bars) in the per-protocol population receiving insulin glargine via algorithm 1 or algorithm 2 plus either 1 OAD or >1 OAD. *$p < 0.001$ for baseline to end-point change. †$p = 0.04$ and ‡$p = 0.03$ for difference between treatment algorithms in baseline to end-point change in daily total insulin dose (†) and daily total weight-adjusted insulin dose (‡).HbA_{1c}, haemoglobin A_{1c}; FBG, fasting blood glucose; OAD, oral antidiabetic agent.

a greater reduction compared with algorithm 1 (−1.8 vs. −1.5%, $p = 0.001$).

At end-point, in subjects receiving insulin glargine plus 1 OAD, 24% had reached target HbA_{1c} levels ≤7% with algorithm 1 compared with 38% of subjects with algorithm 2 ($p = 0.009$), and in subjects receiving insulin glargine plus >1 OAD, 31% had reached target HbA_{1c} levels ≤7% with algorithm 1 compared with 43% of subjects with algorithm 2 ($p = 0.007$). Significantly more subjects achieved HbA_{1c} levels ≤7% without experiencing either severe or nocturnal hypoglycaemia in algorithm 2 vs. algorithm 1 in subjects receiving both insulin glargine plus 1 OAD (33 vs. 21%, $p = 0.02$) and insulin glargine plus >1 OAD (37 vs. 28%, $p = 0.03$).

Fasting Blood Glucose

FBG decreased significantly from baseline to end-point in all subgroups ($p < 0.001$; figure 1B), but the reduction in FBG was significantly greater for subjects randomized to algorithm 2 compared with algorithm 1 for subjects receiving insulin glargine plus 1 OAD [−79.1 ± 55.3 (4.4 ± 3.1 mmol/l) vs. 63.6 ± 51.7 mg/dl (3.5 ± 2.9 mmol/l), $p = 0.001$] and subjects receiving insulin glargine plus >1 OAD [79.6 ± 48.3 (4.4 ± 2.7 mmol/l) vs. −66.6 ± 51.6 (3.7 ± 2.9 mmol/l), $p < 0.001$].

Insulin Glargine Dose

For patients receiving 1 OAD, the increases in insulin dose were significantly greater for patients randomized to algorithm 2 [+33.9 U, range: −8 to +128 U (+0.39 U/kg)] compared with algorithm 1 (+27.4 U, $p = 0.04$; range: −2 to +104 U (+0.32 U/kg, $p = 0.03$); figure 1C]. For patients receiving >1 OAD, the increases in insulin dose were not significantly different in the patients randomized to algorithm 1 [+19.9 U; range: −6 to +100 U (+0.23 U/kg)] or algorithm 2 [+22.8 U, $p = 0.57$; range: −16 to +114 U (+0.27 U/kg, $p = 0.20$); figure 1C].

Body Weight

In subjects receiving both 1 OAD and >1 OAD, there was a modest statistically significant ($p < 0.001$) increase in body weight from baseline to end-point with both algorithm 1 [81.2 ± 15.5 to 82.8 ± 15.9 (mean change +1.6 ± 3.3) kg and 81.3 ± 16.5 to 83.2 ± 16.8 (+1.9 ± 3.5) kg, respectively] and algorithm 2 [82.1 ± 15.3 to 83.5 ± 15.5 (+1.4 ± 3.4) kg and 78.5 ± 15.7 to 80.6 ± 16.2 (+2.1 ± 3.3) kg, respectively]. There was no significant difference in weight change between algorithms.

Safety

In the main study, treatment-emergent AEs were reported in 48.7% of patients; their overall frequency was similar between the algorithms [28]. In this subgroup analysis, the incidence of AEs was similar to that in the main study (data not shown).

Conclusions

The AT.LANTUS study is one of the largest randomized clinical studies (n = 4961 patients) of glycaemic management performed in subjects with type 2 diabetes, and the results will be applicable to many patients in a clinical setting [28]. This subgroup analysis, undertaken in 865 subjects, included all insulin-naive patients who were previously suboptimally controlled on multiple OADs. The results presented here demonstrate that two simple insulin initiation and treatment algorithms were highly effective in safely achieving and maintaining glycaemic control. Furthermore, these results were achieved regardless of concomitant OAD therapy (+1 OAD or >1 OAD) along with a very low incidence of severe hypoglycaemia.

We have previously published results from the overall population; changes in HbA_{1c} were −1.08 and −1.22% for algorithms 1 and 2, respectively [28]. Meanwhile, in this subgroup analysis, patient-driven titration of insulin dose achieved the greater improvement in HbA_{1c} (+1 OAD −1.5%, >1 OAD −1.8%) compared with physician-driven titration (+1 OAD: −1.3%; > 1 OAD: −1.5%). We also show that patient-driven titration of basal insulin with multiple OAD therapy is associated with the greatest improvement in HbA_{1c} without an increased risk of symptomatic hypoglycaemia. In separate subgroup analyses, initiation of insulin glargine achieved reductions of 0.8–0.9% in HbA_{1c} for patients previously on NPH insulin [31] and 1.5% for patients previously on twice-daily premixed insulin plus OADs [32].

The fears of weight gain and hypoglycaemia are significant barriers to the initiation of insulin therapy in type 2 diabetes [15,33]. In this subgroup analysis, weight gain was relatively modest (range 1.4–2.1 kg over 24 weeks) in the context of significant improvement in glycaemic control, with 24–43% of patients reaching target HbA_{1c} levels of ≤7.0%. This occurred with a comparatively low incidence of severe hypoglycaemia. Furthermore, these benefits were seen regardless of concomitant OAD therapy. Therefore, therapy with basal insulin glargine plus OADs may provide the impetus to overcome the fears of hypoglycaemia and weight gain.

In our study, no patients in the insulin glargine +1 OAD group experienced severe hypoglycaemia and <1% of the patients in the >1 OAD group experienced severe hypoglycaemia, which compares favourably with that reported by the UK Prospective Diabetes Study (UKPDS; 2.3% for patients treated with insulin) [34]. Furthermore, our study was of the patients with long-standing type 2 diabetes, with a mean duration since diagnosis of 10 years and mean duration of OAD therapy of >7 years, whereas the UKPDS included only newly diagnosed (insulin and OAD naive) patients.

In the Treat-To-Target trial [25], which used a forced titration schedule with doses monitored by clinical staff, 36.2% of patients achieved a target HbA_{1c} of ≤7.0% without an episode of documented nocturnal hypoglycaemia. In our study, a similar proportion of patients achieved the target HbA_{1c} of ≤7.0% without experiencing nocturnal hypoglycaemia. The proportion of patients who achieved target HbA_{1c} without experiencing hypoglycaemia was statistically superior in the patient-driven titration group, regardless of concomitant OAD therapy (28.3 and 37.3% for patients in algorithms 1 and 2, respectively; intent-to-treat population). This occurred in conjunction with larger reductions in HbA_{1c} (1.9 vs. 1.6%; intent-to-treat population). Furthermore, the patients in our study had a lower rate of hypoglycaemia without including unlicensed thiazolidinedione use. In our study, the exclusion of thiazolidinediones may have limited the proportion of patients who achieved target HbA_{1c} (≤7%). In the past, and increasingly now, thiazolidinediones in combination with insulin have demonstrated good reductions in HbA_{1c} in type 2 diabetes [25,35,36]. A further reason for the lower proportion of patients reaching $HbA_{1c} < 7\%$ is that we did not force the titration of insulin glargine, whereas the Treat-to-Target study did. As a result, the rates of hypoglycaemia were lower in our study. This suggests that titration of insulin glargine dose could be more aggressive, to better reach treatment targets, although this must be balanced against the inevitable risk of hypoglycaemia.

While a shortcoming of the current study may be the lack of a placebo arm, the reduction in HbA_{1c} (>1%) observed in this study is greater than that might be expected as a result of a placebo effect.

The patients included in this analysis had relatively long-standing type 2 diabetes (>9 years) and HbA_{1c} > 9% on average. It is evident that a change in therapy was warranted. The addition of once-daily basal insulin to their oral antidiabetic regimen led to clinically important improvements in glycaemic control (including HbA_{1c} and FBG) with low risk of hypoglycaemia. Nevertheless, a number of patients had HbA_{1c} levels above the recommended levels (i.e. ≤7%). One option would be to use a more aggressive titration regimen, which may have increased the proportion of subjects achieving target $HbA_{1c} \leq 7\%$, as in the LANMET study [21], which is discussed below. Alternatively, the addition of one or several doses of a rapid-acting insulin at mealtime to the therapeutic regimen may be warranted for those patients who were not reaching target HbA_{1c} levels once the basal insulin dose is fully optimized. Indeed, such an approach was also suggested in the American Diabetes Association/European Association for the Study of Diabetes consensus statement [37]. Nevertheless, this concept will need objective testing.

A further shortcoming of the present study is that it was conducted as an exploratory analysis of a large subgroup (n = 865) of patients from the original AT.LANTUS study (n = 4961 patients). As such, the analyses were mainly descriptive. However, as a large proportion of patients from the original study were included in the analyses presented here and that the analysis includes a similar number of patients used in trials such as the Treat-to-Target study [25], one would expect that the results show a high degree of statistical power and support the need for confirmatory studies.

While additional prospective randomized studies may be necessary to further confirm the results reported, it is evident that the current subanalysis confirms the results of the Treat-to-Target study. The distinguishing feature here is that patient-driven titration appears to achieve greater HbA_{1c} benefits, with more patients reaching target HbA_{1c} at end-point, twice the percentage of patients reaching target FBG (72 vs. 36%) and a lower incidence of severe hypoglycaemia, all in the absence of the use of thiazolidinediones.

Physicians currently face a number of options for transferring patients from combination OAD therapy to insulin, including multiple daily or basal injections and whether to continue or change OAD therapy. In a recent meta-analysis [38] of four trials comparing insulin glargine with NPH insulin in patients with type 2 diabetes [22,24,25,39], insulin glargine was associated with significantly lower incidence of hypoglycaemia in conjunction with improved HbA_{1c}, and this occurred despite similar increases in dose from baseline to end-point (20–28 weeks) from 21 to 38 U for insulin glargine and 21 to 37 U for NPH insulin. The relative merits of twice-daily premixed insulin vs. once-daily basal insulin are often debated. One study has shown that once-daily insulin glargine plus metformin was more effective at lowering HbA_{1c} than a twice-daily premixed insulin regimen, but a criticism was that metformin was discontinued in the premixed insulin arm, and a conventional premixed insulin was used [40]. In comparison, in two studies, where OADs were continued and comparing biphasic analogue mixtures (Lispro Mix 75/25 or Aspart Mix 70/30) with insulin glargine, the premixed insulin regimens were associated with greater reductions in HbA_{1c} [35,41]. However, the premixed insulin regimens were also associated with significantly higher incidence of hypoglycaemia and greater weight gain compared with insulin glargine.

In the LANMET study [21], which investigated the addition of either insulin glargine or NPH insulin to metformin therapy, the percentages of patients in the insulin glargine group experiencing hypoglycaemia were 46 and 43% during weeks 0–12 and 13–24, respectively. By comparison, a smaller proportion of patients experienced symptomatic hypoglycaemia in our study (<19%). This may be because of the titration methods used in the two studies, insulin doses reached ~60 U by week 24 in the LANMET study, whereas in our study, the mean insulin dose was <46 U for all subanalysis groups. This balance between high insulin dose, change in HbA_{1c} and risk of hypoglycaemia is a trade-off that will need to be acceptable for the patient. In our study, we used algorithm based on avoidance of hypoglycaemia, with allowances for decreasing insulin dose in the event of regular hypoglycaemia, thus limiting the extent to which insulin doses can be increased.

In a study investigating continued sulphonylurea and metformin with either insulin glargine or rosiglitazone (patients previously treated with sulfonylurea and metformin), insulin glargine was associated with significantly improved glycaemic control (HbA_{1c} and FBG) [27]. While the incidence of hypoglycaemia was higher in the insulin glargine group, less weight gain and fewer AEs occurred in the insulin glargine group.

In studies with insulin glargine [25,27,40,41], the starting dose of insulin glargine was typically 10–20 U. By end-point (20–28 weeks), the dose had increased to 25–40 U. In our study, patients in both treatment algorithms with >1 OAD achieved similar doses at week

24. However, those patients on 1 OAD achieved a greater increase in basal insulin dose when encouraged to self-titrate.

Effective and efficient use of scarce healthcare resources is an important aspect of care. An approach that increases patient-driven management is as effective and reduces the need for face-to-face contact with healthcare professionals is thus potentially a more effective use of healthcare resources. However, it has been reported that healthcare providers underestimate the proportion of patients who would be willing to take part in decision making about their treatment [42].

The approach to insulin initiation and dose titration with a single injection of insulin titrated against an FBG level [37], as used here, is a simple and consistent approach, which is conducive to being taught in a group setting, and has also been shown to be a more effective use of healthcare professional time. Indeed, in a study by Yki-Jarvinen *et al.*, where patients were encouraged to self-adjust their insulin dose, with education delivered in either a group or an individual setting, improvements in HbA_{1c} were similar in both arms (group: 8.8–6.8%, individual: 8.7–6.9%). However, the time spent by the healthcare professional per patient was significantly less with group than with Individual education (2.2 vs. 4.2 h, $p < 0.001$) [43].

The findings presented here support those observed in the full cohort that two simple, widely applicable titration algorithms (either patient- or physician-driven) for the initiation of glargine can be implemented in clinical practice with low incidence of hypoglycaemia. We also show that patient-driven dose titration achieves more pronounced improvements in glycaemic control compared with physician-driven titration, and this improvement is not associated with an increased risk of hypoglycaemic episodes. Moreover, subjects with type 2 diabetes, suboptimally controlled with OADs, can safely and effectively participate in the management of their treatment if given simple information and support, with the potential to significantly reduce the burden of care on healthcare professionals. Further intensification of the insulin regimen would be expected to help more patients reach their recommended treatment targets.

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