

# Improvement of Glycemic Control in Subjects With Poorly Controlled Type 2 Diabetes

## Comparison of two treatment algorithms using insulin glargine

MELANIE DAVIES, MD<sup>1</sup>  
 FRED STORMS, MD<sup>2</sup>  
 SIMON SHUTLER, BSC<sup>3</sup>

MONIQUE BIANCHI-BISCAY, MD<sup>4</sup>  
 RAMON GOMIS, MD, PHD<sup>5</sup>  
 FOR THE AT.LANTUS STUDY GROUP

**OBJECTIVE** — Large prospective studies have demonstrated that optimum glycemic control is not routinely achieved in clinical practice. Barriers to optimal insulin therapy include hypoglycemia, weight gain, and suboptimal initiation and dose titration. This study compared two treatment algorithms for insulin glargine initiation and titration: algorithm 1 (investigator led) versus algorithm 2 (performed by study subjects).

**RESEARCH DESIGN AND METHODS** — A prospective, multicenter ( $n = 611$ ), multinational ( $n = 59$ ), open-label, 24-week randomized trial in 4,961 (algorithm 1,  $n = 2,493$ ; algorithm 2,  $n = 2,468$ ) suboptimally controlled type 2 diabetic subjects.

**RESULTS** — At baseline, mean diabetes duration was  $12.3 \pm 7.2$  years, and 72% of subjects were pretreated with insulin. At end point, there was no significant difference in the incidence of severe hypoglycemia between algorithms 1 and 2 (0.9 vs. 1.1%). There was a significant reduction in HbA<sub>1c</sub> from  $8.9 \pm 1.3$  to  $7.8 \pm 1.2\%$ , with a greater decrease ( $P < 0.001$ ) with algorithm 2 ( $-1.22\%$ ) versus algorithm 1 ( $-1.08\%$ ). Fasting blood glucose decreased from 170 to 110 mg/dl, with a greater decrease ( $P < 0.001$ ) with algorithm 2 ( $-62$  mg/dl) versus algorithm 1 ( $-57$  mg/dl). Mean basal insulin dose increased from  $22.9 \pm 15.5$  to  $43.0 \pm 25.5$  IU, with a significant difference ( $P < 0.003$ ) between algorithm 2 (21.6 IU) and algorithm 1 (18.7 IU).

**CONCLUSIONS** — Glargine is safe and effective in improving glycemic control in a large, diverse population with longstanding type 2 diabetes. A simple subject-administered titration algorithm conferred significantly improved glycemic control with a low incidence of severe hypoglycemia compared with physician-managed titration.

*Diabetes Care* 28:1282–1288, 2005

From the <sup>1</sup>University Hospitals of Leicester, Leicester, U.K.; <sup>2</sup>Mesos Diabetes Centrum, Bilthoven, the Netherlands; <sup>3</sup>Sanofi-Aventis, Guildford, U.K.; the <sup>4</sup>Medical Department, Sanofi-Aventis Intercontinental, Paris, France; and <sup>5</sup>Hospital Clínic Universitari, Barcelona, Spain.

Address correspondence and reprint requests to Dr. Melanie Davies, University Hospitals of Leicester, Leicester Royal Infirmary, Infirmary Close, Leicester LE1 5WW, U.K. E-mail: melanie.davies@uhl-tr.nhs.uk. Received for publication 1 November 2004 and accepted in revised form 11 March 2005.

M.D. serves on advisory boards for and has received honoraria from Sanofi-Aventis. F.S. serves on an advisory board for Sanofi-Aventis.

**Abbreviations:** AE, adverse event; DCCT, Diabetes Control and Complications Trial; FBG, fasting blood glucose; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

© 2005 by the American Diabetes Association.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

The U.K. Prospective Diabetes Study (UKPDS) demonstrated that good glycemic control in type 2 diabetes is associated with a reduced risk of diabetes complications (1). However, achieving and maintaining tight glycemic targets represent a major challenge. Initial intervention is largely based around lifestyle modification; pharmacologic intervention, including insulin therapy, becomes necessary as the progressive decline in  $\beta$ -cell function leads to deterioration in glycemic control (2). One key barrier to initiating and optimizing insulin therapy is hypoglycemia (3–5). Indeed, fear of hypoglycemia often prevents subjects and physicians from actively treating to the stringent HbA<sub>1c</sub> targets (3) defined by many national organizations (6–8).

Some limitations surrounding insulin therapy have arisen as a result of using intermediate-acting insulin, such as NPH insulin and insulin ultralente (9), which are limited by their peak-action profiles (10) and large day-to-day variability in absorption after injection (11). However, the advent of basal insulin analogs has conferred benefits in terms of improved glycemic control, as well as a lower risk of hypoglycemia in both type 1 and type 2 diabetes (12–15).

Many limitations of intermediate-acting insulins are addressed by insulin glargine (LANTUS), the first clinically available basal analog with a prolonged absorption and activity profile (16). Studies show that glargine has a 24-h duration of action, no pronounced peak, and lower between-subject variability versus NPH or insulin ultralente (16). In type 2 diabetes, glargine has been shown to confer at least equivalent glycemic control (17,18) with a lower incidence of hypoglycemia (18–20) compared with NPH. Therefore, glargine can be used as part of a more intensive treatment algorithm to achieve HbA<sub>1c</sub> targets (21) with a lower risk of hypoglycemia.

There is still much to learn regarding

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

Mean FBG for the previous 3 consecutive days	Increase in daily basal insulin glargine dose (IU)*	
	Algorithm 1: titration at every visit; managed by physician†	Algorithm 2: titration every 3 days; managed by subject‡
≥100 mg/dl and <120 mg/dl (≥5.5 mmol/l and <6.7 mmol/l)	0–2 (at the discretion of the investigator)‡	0–2 (at the discretion of the investigator)‡
≥120 mg/dl and <140 mg/dl (≥6.7 mmol/l and <7.8 mmol/l)	2	2
≥140 mg/dl and <180 mg/dl (≥7.8 mmol/l and <10 mmol/l)	4	2
≥180 mg/dl (≥10 mmol/l)	6–8 (at the discretion of the investigator)‡	2

\*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.

the optimal method for initiating and titrating basal analog insulin. Two approaches (17,19,22), which differed in the initiation dose, titration algorithm, and extent to which the subject can engage in self-management, have been used. While these approaches provided valuable information in terms of the way insulin therapy should be initiated in type 2 subjects, no prior investigation has compared or confirmed whether such methods are successful in more general clinical practice. Thus, the current study objectively compares algorithms based on these two different approaches.

## RESEARCH DESIGN AND METHODS

Subjects with type 2 diabetes suboptimally controlled on their previous antidiabetic treatment were included. Inclusion criteria included: age ≥18 years; on antidiabetic treatment (any oral and/or insulin therapy) for >6 months requiring, in the opinion of the investigating physician, basal long-acting insulin therapy for the control of hyperglycemia; HbA<sub>1c</sub> levels >7.0 and <12.0%; BMI values <40 kg/m<sup>2</sup>; and confirmed written informed consent.

Exclusion criteria included: impaired renal function (serum creatinine >2.0 mg/dl [ $>177 \mu\text{mol/l}$ ] and current renal dialysis); acute or chronic metabolic acidosis; active liver disease or serum alanine aminotransferase or aspartate aminotransferase >2.5 times the upper limit of the normal range; history of hypoglycemia unawareness; diabetic retinopathy with surgery in the previous 3 months or planned within 3 months after study entry; and pregnancy. Other exclusion criteria were in accordance with the manufacturers' prescribing information.

This was a prospective, multinational (611 centers in 59 countries in Western and Eastern Europe, South America, Asia, and Africa/Middle East), randomized controlled, parallel-design study (1:1). It included 12 contacts (of which at least 4 were face-to-face, and not more than 3 consecutive contacts were by telephone) over 24 weeks. To help ensure that the study results could be translated into clinical practice, a variety of centers were involved. Investigational staff had at least some previous insulin therapy experience.

To ensure a consistently high level of quality throughout the study, international, regional, and local meetings were conducted with investigators and study monitors. Compliance with treatment algorithms was regularly reviewed through the mandatory use of standard data collection tools including electronic case report forms. An audit plan was used to ensure adherence to the study protocol and internationally recognized quality standards. In addition to internal quality inspections, 15 investigator site audits were conducted during the study. The study was set up and conducted in accordance with the International Conference on Harmonisation–Good Clinical Practice standard operating procedures (23).

Glargine was administered once daily at bedtime (9 P.M. till 12 A.M.). The starting dose for insulin-naïve subjects was 10 IU/day for algorithm 1 and numerically equivalent to the highest fasting blood glucose (FBG) value in millimoles per liter over the previous 7 days for algorithm 2 (for example, if the FBG measure was 12 mmol/l, the initial dose would be 12 IU).

For subjects on oral agents, the investigator decided whether to continue each agent. Dose and regimen of oral agents

remained fixed and stable throughout the study.

Subjects insulin pretreated at study entry had their previous basal insulin discontinued. When switching from once-daily intermediate- or long-acting insulin to glargine, an equivalent dose was recommended. For subjects switching from twice-daily NPH, a reduction by 20–30% from the total NPH dose was recommended (24). The main aim of the study was to optimize basal insulin; however, a prandial treatment could be added in a stepwise fashion based on week 12 HbA<sub>1c</sub> and FBG profiles. For those on premix insulin at inclusion, the same change applied to the basal component. Prandial treatment could be added at the same time and titrated at the discretion of the investigator. This included oral agents and/or short-acting or regular insulin, administered once, twice, or three times daily.

## Basal insulin algorithms

The treatment algorithms are outlined in Table 1. The differences are in starting dose for insulin-naïve subjects, frequency of titration, and extent of dose adjustments. The first algorithm was primarily physician-led dose titration, whereas in the second algorithm subjects were encouraged to self-manage dose adjustments. Subjects randomized to algorithm 1 initially had their basal insulin dose adjusted weekly during visits or telephone contacts. In comparison, subjects randomized to algorithm 2 self-adjusted their basal insulin every 3 days. Subject dose adjustments were reviewed by the investigator at clinical visits or over the telephone.

## Objectives

The primary objective was to compare the two algorithms in terms of incidence of severe hypoglycemia, defined according to criteria used in the Diabetes Control and Complications Trial (DCCT) (25).

Secondary objectives included baseline to end point change in glycemic control (HbA<sub>1c</sub> and FBG); incidence of symptomatic (symptoms of hypoglycemia responding to ingestion of carbohydrate or an episode associated with a blood glucose level <50 mg/dl [ $<2.8$  mmol/l]), nocturnal (hypoglycemia occurring while the subject was asleep and associated with a blood glucose level <50 mg/dl [ $<2.8$  mmol/l] but without symptoms), and asymptomatic hypoglycemia (associated with a blood glucose level <50 mg/dl [ $<2.8$  mmol/l]); change in body weight; and insulin dose. The study end point was defined by the subject's last evaluation during treatment (visit 12 for those completing the study or last evaluation for those missing data on visit 12). If a subject discontinued treatment permanently before the planned study end, the last evaluation before discontinuation was considered for the end point analysis.

## Measurements and safety

At screening, biochemistry and hematology measurements were taken. HbA<sub>1c</sub> and weight were measured at screening, baseline, and weeks 12 and 24. Analyses of HbA<sub>1c</sub> were performed by the laboratory of each participating site, either according to the DCCT standard method or a DCCT-aligned method within a documented quality controlled system. Subjects were encouraged to capture and record FBG with a minimum of two 8-point 24-h profiles before each visit/contact with their study center. Glucose monitors were provided for subject determination of home blood glucose values. The glucose meters (Glucotrend; Roche) used a standardized platform for the entire study and reported results in whole blood. Data and calibration of blood glucose meters was verified at clinical visits.

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

## Statistical methods

The primary efficacy analysis was comparison of the proportion of subjects with

severe hypoglycemia in each algorithm during the whole study period plus 5 days, using the 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). Analyses were performed using both the last observation carried forward and data at week 24 and reported if different. The expected rate of severe hypoglycemia with each algorithm was 3%. A two-sided 90% confidence interval (CI) for the difference between algorithms in the proportion of subjects who experienced severe hypoglycemia was calculated. The two algorithms were declared equivalent if this CI was contained within the equivalence interval ( $-1.5$  to  $1.5\%$ , based on 2,216 subjects per group). It is worth noting that the actual rate of hypoglycemia observed in the study was 1% and not the expected 3%. However, had the trial been planned around a 1% rate of hypoglycemia, the same number of subjects and the same equivalence interval, the study would have had in excess of 99% power. This emphasizes the robust nature of the study results and indicates that the same results would be obtained had a 95% CI been applied.

The changes from baseline in HbA<sub>1c</sub>, FBG, body weight, and insulin dose were analyzed using an ANCOVA. Corresponding 95% CI values for the estimated treatment effect were calculated. Statistical analyses were performed using SAS statistical software package version 8.

**RESULTS**— Results of audits concluded that the trial data were reliable, verifiable, and retrievable. Of the 5,677 subjects screened, 5,033 were eligible for inclusion and randomized to one of two algorithms (algorithm 1: 2,529 subjects; algorithm 2: 2,504 subjects). Of these (algorithm 1 vs. 2), 31 vs. 35 subjects were not treated and 5 vs. 1 subject had no outcome measure. Therefore, the full analysis population consisted of 2,493 subjects in algorithm 1 and 2,468 in algorithm 2. Of these, 119 subjects in algorithm 1 and 141 subjects in algorithm 2 prematurely discontinued the study. Reasons for discontinuation (algorithm 1 vs. 2) were consent withdrawal (46 vs. 57 subjects); protocol violation (9 vs. 25 subjects); AEs (17 vs. 15 subjects); lost to follow-up (13 vs. 11 subjects); entry criteria no longer met (9 vs. 5 subjects);

death (5 vs. 5 subjects); hypoglycemia (3 vs. 1 subject); other (15 vs. 21 subjects); and unknown (2 vs. 1 subject). Major protocol violations occurred in 59 subjects treated with algorithm 1 and 54 with algorithm 2. Therefore, the per-protocol population consisted of 2,315 subjects receiving algorithm 1 and 2,273 receiving algorithm 2. Compliance to treatment was high, with 97.1% of subjects receiving algorithm 1 and 97.4% receiving algorithm 2 using study medication for  $\geq 22$  weeks (per-protocol analysis).

Subject demographics and baseline characteristics were similar between the two treatment groups (Table 2). Subjects had long-standing diabetes, with a mean duration of disease of 12 years and a 5-year mean duration of insulin pretreatment. It is noteworthy that 72% of subjects were insulin pretreated at inclusion (of these, 40.5% with NPH and 23.2% with premixed insulin).

While data presented are based on the per-protocol analysis unless otherwise stated, the results of the full population or intention-to-treat population were virtually identical and, therefore, did not differ clinically or statistically.

## Primary outcome (per-protocol analysis)

The incidence of severe hypoglycemia in the total per-protocol population was 1.0%. There was no significant difference between algorithms 1 and 2 (Fig. 1A). The calculated incidence of severe hypoglycemia was 1.87 events per 100 patient-years for algorithm 1 and 2.36 per 100 patient-years for algorithm 2. Similarly, in the intention-to-treat population, there was no significant difference between algorithms 1 and 2 (1.0 vs. 1.3%, difference 0.3% [90% CI  $-0.03$  to  $0.007\%$ ]). The calculated incidence of severe hypoglycemia was 2.21 events per 100 patient-years for algorithm 1 and 2.68 per 100 patient-years for algorithm 2.

## Secondary outcomes (per-protocol analysis)

**Hypoglycemia.** The overall incidence of hypoglycemia was significantly lower with algorithm 1 than 2 (29.8 vs. 33.3%;  $P < 0.01$ ). The incidence of symptomatic hypoglycemia was also lower with algorithm 1 versus 2 (Fig. 1A). The incidence of asymptomatic hypoglycemia (10.3% for both algorithms [90% CI  $-1.5$  to  $1.5\%$ ]) and nocturnal hypoglycemia (Fig.

Table 2—Baseline demographics and characteristics of subjects treated with insulin glargine by algorithms 1 and 2 (per-protocol population)

Demographics and characteristics	Algorithm 1	Algorithm 2	Total
<i>n</i>	2,315	2,273	4,588
Age (years)	57.6 ± 10.0	57.5 ± 10.1	57.5 ± 10.0
BMI (kg/m <sup>2</sup> )	29.0 ± 4.7	29.0 ± 4.7	29.0 ± 4.7
Sex (%)			
Male	47.3	49.7	48.5
Female	52.7	50.3	51.5
Age at onset of diabetes (years)	45.3 ± 10.3	45.1 ± 10.3	45.2 ± 10.3
Diabetes duration (years)	12.3 ± 7.3	12.3 ± 7.0	12.3 ± 7.2
HbA <sub>1c</sub> (%)	8.9 ± 1.3	8.9 ± 1.3	8.9 ± 1.3
Fasting blood glucose [mg/dl (mmol/l)]	169.8 ± 50.0 (9.4 ± 2.8)	169.4 ± 50.8 (9.4 ± 2.8)	169.6 ± 50.4 (9.4 ± 2.8)
Duration of antidiabetic treatment (years)	11.2 ± 7.0	11.2 ± 6.9	11.2 ± 7.0
Duration of treatment with insulin (years)	5.1 ± 5.3	5.0 ± 5.4	5.1 ± 5.3
Previous treatment (%)			
NPH insulin	39.4	41.7	40.5
Premixed insulin	23.5	22.8	23.2
Prandial insulin (%) (mean daily dose, IU/kg)	25.1 (0.37 ± 0.25)	23.6 (0.40 ± 0.30)	24.4 (0.39 ± 0.27)
Any oral antidiabetic agents	65.7	66.0	65.9
Sulfonylureas	36.0	37.4	36.7
Biguanides	51.8	50.9	51.4
α-Glucosidase inhibitors	4.4	4.9	4.7
Glitazones	4.4	4.4	4.4
Others	4.4	3.8	4.1

Data are mean ± SD unless otherwise indicated.

1A) was low with both algorithms 1 and 2, with no significant difference between the groups.

**HbA<sub>1c</sub>.** Overall, in the per-protocol population there was a significant reduction in HbA<sub>1c</sub> from 8.9 ± 1.3 to 7.8 ± 1.2% ( $P < 0.001$ ). When the results were analyzed according to treatment algorithm, a significantly greater ( $P < 0.001$ ) baseline to end point reduction in HbA<sub>1c</sub> was observed with algorithm 2 (8.9 ± 1.3 to 7.7 ± 1.2%) than with algorithm 1 (8.9 ± 1.3 to 7.9 ± 1.2%) (Fig. 1B). Results were similar for the intention-to-treat population (8.9 ± 1.3 to 7.9 ± 1.2% and 8.9 ± 1.3 to 7.8 ± 1.2%, respectively). At end point, 26% of subjects had reached target HbA<sub>1c</sub> levels <7% with algorithm 1 compared with 30% of subjects with algorithm 2 ( $P = 0.004$ ). The incidence of severe hypoglycemia in subjects achieving target HbA<sub>1c</sub> levels <7% was 1.2% with algorithm 1 and 0.7% with algorithm 2 ( $P = 0.57$ ).

**FBG.** Overall, FBG significantly decreased ( $P < 0.001$ ) from 170 mg/dl (9.4

mmol/l) to 110 mg/dl (6.1 mmol/l). The reduction in FBG was greater ( $P < 0.001$ ) with algorithm 2 (169.4 ± 50.8 mg/dl [9.4 ± 2.8 mmol/l] to 107.7 ± 28.7 mg/dl [6.0 ± 1.6 mmol/l]) than with algorithm 1 (169.8 ± 50.0 mg/dl [9.4 ± 2.8 mmol/l] to 112.9 ± 31.4 mg/dl [6.3 ± 1.7 mmol/l]) (Fig. 1C).

**Additional analysis of low blood glucose.** Hypoglycemia in the main analysis was associated with blood glucose values <50 mg/dl (<2.8 mmol/l) and <36 mg/dl (<2.0 mmol/l). Consequently, non-protocol-defined hypoglycemia may have been included where the blood glucose value was not recorded. However, there were a number of events reported where the blood glucose value was above that stipulated for the statistical analysis of hypoglycemia. The total number of events outside of the study protocol definitions was 3,675 or 0.8 events/subject, with no evident difference between the algorithms.

**Glargine dose.** Figure 1C shows the pattern of titration performed during the study and the corresponding reduction in

FBG over 24 weeks. Maximal dosing was approached between weeks 12 and 14, when FBG was close to 120 mg/dl (6.7 mmol/l). According to the algorithms, once a subject had achieved an FBG of 120 mg/dl (6.7 mmol/l), titration was optional. The baseline to end point increase in mean basal glargine dose was significantly greater ( $P < 0.003$ ) with algorithm 2 than 1 (18.7 vs. 21.6 IU) (Fig. 1D).

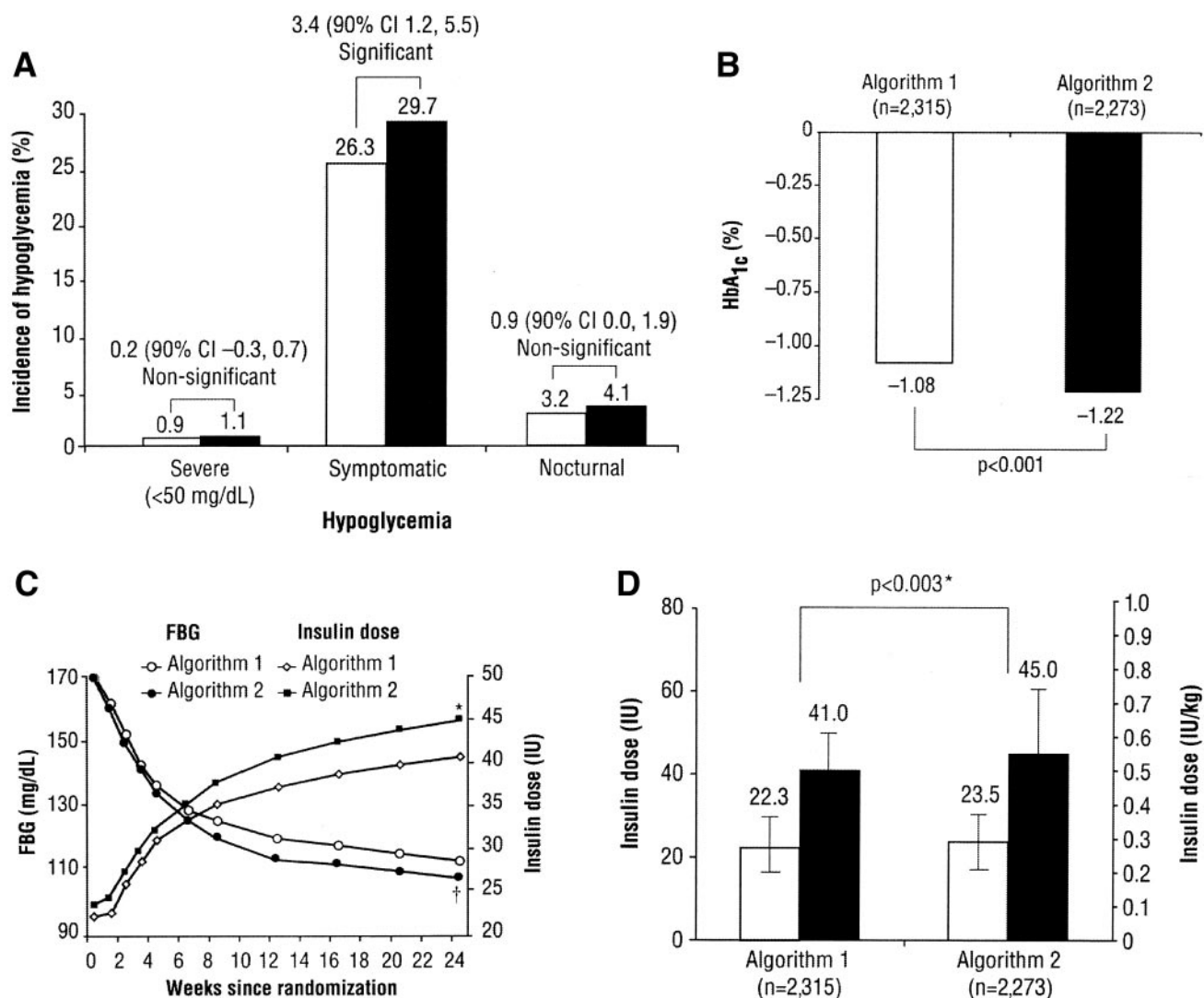
**Prandial treatment.** A small but overall nonsignificant change in the dose of prandial insulin was noted (29.7 ± 22.2 IU at baseline to 30.2 ± 25.8 IU at end point).

**Body weight.** There was a small increase in body weight from baseline to end point with both algorithm 1 (79.8 ± 15.8 to 80.8 ± 16.0 kg) and algorithm 2 (79.8 ± 16.2 to 81.1 ± 16.5 kg;  $P < 0.001$  for both).

### Safety

Treatment-emergent AEs were reported in 48.7% of subjects, and their overall frequency was similar per algorithm. The most frequently encountered AEs were





**Figure 1**—A: Incidence of hypoglycemia in the per-protocol population receiving insulin glargine algorithm 1 (□; n = 2,315) or algorithm 2 (■; n = 2,273). B: Mean reduction in HbA<sub>1c</sub> levels from baseline to end point in the per-protocol population receiving insulin glargine algorithm 1 or algorithm 2. C: Mean FBG throughout the study compared with mean insulin glargine dose (IU) in the per-protocol population receiving algorithm 1 or algorithm 2. The decrease in FBG and increase in insulin dose from baseline to end point was significant for both algorithms (P < 0.001). \*P < 0.003 between algorithms at end point; †P < 0.001 between algorithms at end point. D: Insulin dose at baseline (□) and end point (■) in the per-protocol population receiving insulin glargine algorithm 1 or algorithm 2.

respiratory tract infections and injection site reactions. AEs were rated as mild to moderate in the majority (>95% of all treatment-emergent AEs). In total, 11% of AEs (principally injection site reactions) were considered potentially related to the study treatment (12% with algorithm 1 and 10% with algorithm 2). Treatment discontinuation due to AEs occurred in 47 subjects (26 with algorithm 1 and 21 with algorithm 2), corresponding to <1% of all AEs. Thirteen deaths occurred during the study (12 during the treatment phase: 6 subjects with algorithm 1 and 6 with algorithm 2), but none was considered related to the study medication.

**CONCLUSIONS**— This study represents one of the largest prospective, randomized studies of glycemic management performed in subjects with type 2 diabetes. With both algorithms there was a low incidence of severe hypoglycemia, with no incident difference. Indeed, overall incidence of severe hypoglycemia was only 1.0% with a calculated incidence per patient year of 2.11. Since results did not differ significantly between the analysis groups, it is evident that this result would remain unchanged by the small number of dropouts due to hypoglycemia (0.008%). These findings compare favorably with those from the UKPDS, where

the proportion of subjects with at least one incidence of severe hypoglycemia was 2.3% per year in insulin-treated subjects (1). Importantly, the UKPDS investigated newly diagnosed (insulin naive) subjects, whereas subjects in the current study had a longer duration of diabetes (~12 years) and the majority (72%) were already on insulin therapy at baseline.

Further, the introduction of glargine accompanied by a simple initiation and titration algorithm resulted in an improvement in metabolic control (measured by HbA<sub>1c</sub> and FBG), regardless of treatment algorithm. Of particular note is the finding that a reduction in HbA<sub>1c</sub> of

>1% was achieved despite 72% of the study population being insulin pretreated at baseline for an average of 5 years (confirmed by individual subanalyses reported elsewhere (26–31). Previous studies suggest that achieving HbA<sub>1c</sub> improvements is harder in subjects with longstanding diabetes (2). While a shortcoming of the current study may be the lack of a placebo arm, the HbA<sub>1c</sub> reduction (>1%) observed is greater than would be expected as a result of a placebo effect. More aggressive titration may have increased the proportion of subjects achieving target HbA<sub>1c</sub> ≤7%.

The significant decrease in HbA<sub>1c</sub> was achieved with minimal incidence of hypoglycemia and a small increase in body weight. These findings have important implications: insulin therapy is often delayed in type 2 diabetes for various reasons, including fear of hypoglycemia, weight gain, and injection concerns (3–5), despite its obvious metabolic benefits. The notable improvement in HbA<sub>1c</sub>, with a low incidence of hypoglycemia and no clinically significant weight gain suggests that this therapy addresses many of the barriers to initiating insulin.

The growing prevalence of type 2 diabetes places an increasing burden on health care systems, particularly health-care professionals, a drain further exacerbated by evidence supporting earlier insulinization of these subjects (32), which requires the demanding exercise of switching from oral agents to insulin. Increasingly, insulin initiation is performed in community and group settings, emphasizing the need for a simple, safe, and effective regimen that can be initiated and titrated easily. Initiation of insulin therapy in type 2 diabetes can be relatively straightforward, but the follow-up care and essential need for titration can be hugely time consuming. Evidence suggests that in conventional regimens, subjects remain on low doses of insulin and are seldom titrated sufficiently to achieve treatment targets (1). Thus, any titration regimen that can be successfully undertaken by the subjects themselves is beneficial.

In the current study, subjects treated with glargine according to algorithm 2 achieved a significantly greater reduction in HbA<sub>1c</sub> and FBG versus those treated according to algorithm 1. This suggests that it is possible to obtain metabolic benefits (a low incidence of severe hypogly-

cemia) safely, using a titration regimen that facilitates subject participation in their treatment management. The high level of adherence to both algorithms (study medication used for ≥22 weeks: 97.1% [algorithm 1] and 97.4% [algorithm 2]) suggests that the regimens were easy to follow.

This study provides insight into two simple, widely applicable treatment algorithms for glargine, which can easily be translated into clinical practice in both primary (general practitioners) and secondary (hospital) health care settings. Results show that regardless of the previous treatment option, glargine titrated in small increments at short intervals allows subjects from diverse clinical settings with longstanding type 2 diabetes to safely and effectively participate in the management of their treatment, with the potential to significantly reduce the burden of care on health care professionals. The size and diversity of the study population has created the opportunity for further subanalyses to determine whether glycemic control can be improved in subjects switching from a variety of treatment regimens to glargine-based regimens and will be the focus of future studies.

**Acknowledgments**— This study was sponsored by Sanofi-Aventis. Data from this study were presented as one oral (Davies M, et al. *Diabetologia* 47 [Suppl. 2]:Abstract 146, 2004), four posters (Lavalle-Gonzalez F, et al. *Diabetes* 12-LB [late breaking], 2004; Fulcher G, et al. *Diabetologia* 47 [Suppl. 2]:Abstract 750, 2004; Lavalle-Gonzalez F, et al. *Diabetologia* 47 [Suppl. 2]:Abstract 751, 2004; Storms F, et al. *Diabetologia* 47 [Suppl. 2]:Abstract 910, 2004), and published in abstract form (Davies M, et al. *Diabetes* 53 [Suppl. 2]:A473, 2004).

We thank all 611 investigational sites from the 59 countries participating in the AT. LANTUS type 2 study program.

## References

1. UKPDS: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33): UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352: 837–853, 1998
2. Turner R, Cull C, Frighi V, Holmann R: Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS

- 49): UK Prospective Diabetes Study (UKPDS) Group. *JAMA* 281:2005–2012, 1999
3. Korytkowski M: When oral agents fail: practical barriers to starting insulin. *Int J Obes Relat Metab Disord* 26:S18–S24, 2002
4. Cryer P, Childs BP: Negotiating the barrier of hypoglycemia in diabetes. *Diabetes Spectrum* 15:20–27, 2002
5. Cryer P: Hypoglycemia is the limiting factor in the management of diabetes. *Diabetes Metab Res Rev* 15:42–46, 1999
6. AACE: The American Association of Clinical Endocrinologists medical guidelines for the management of diabetes mellitus: the AACE system of intensive diabetes self-management: 2000 update. *Endocrine Practice* 6:43–84, 2000
7. A desktop guide to type 2 diabetes mellitus: European Diabetes Policy Group 1999. *Diabet Med* 16:716–730, 1999
8. NICE: Clinical guidelines for type 2 diabetes: management of blood glucose [article online], 2002. London, NICE. Available from <http://www.nice.org.uk>
9. Barnett A: A review of basal insulins. *Diabet Med* 20:873–885, 2003
10. Bolli GB: The pharmacokinetic basis of insulin therapy in diabetes mellitus. *Diabetes Res Clin Pract* 6:S3–S16, 1989
11. Binder C, Lauritzen T, Faber O, Pramming S: Insulin pharmacokinetics. *Diabetes Care* 7:188–199, 1984
12. Yki-Jarvinen H: Insulin therapy in type 2 diabetes: role of the long-acting insulin glargine analogue. *Eur J Clin Invest* 34:410–416, 2004
13. Ratner R: Insulin glargine versus NPH insulin in patients with type 1 diabetes. *Drugs Today* 39:867–876, 2003
14. Hermansen K, Fontaine P, Kukolja K, Peterkova V, Leth G, Gall M: Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. *Diabetologia* 47:622–629, 2004
15. Chapman T, Noble S, Goa KL: Insulin aspart: a review of its use in the management of type 1 and 2 diabetes mellitus. *Drugs* 62:1945–1981, 2002
16. Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, Di Vincenzo A, Cordoni C, Costa E, Brunetti P, Bolli GB: Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes* 49:2142–2148, 2000
17. Yki-Jarvinen H, Haring H, Zeger S, Arbet-Engels C, Nguyen H, Riddle M: The relationship between HbA<sub>1c</sub>, fasting blood

- glucose (FBG), and hypoglycaemia using insulin glargine versus NPH insulin: a meta-regression analysis in type 2 diabetes (Abstract). *Diabetes* 52 (Suppl. 1): A149, 2003
18. Riddle M, Rosenstock J, Gerich J, Investigators IGS: The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetes patients. *Diabetes Care* 26:3080–3086, 2003
  19. Rosenstock J, Massi Benedetti M, Haring HU, Lin Z, Salzman A: Confirmed lower risk of hypoglycemia with insulin glargine versus NPH insulin: a meta-analysis of 2304 patients with type 2 diabetes. *Diabetologia* 46: A304, 2003
  20. Yki-Järvinen H, Dressler A, Ziemer M: Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes: HOE 901/3002 Study Group. *Diabetes Care* 23: 1130–1136, 2000
  21. American Diabetes Association: Clinical Practice Recommendations 2003. *Diabetes Care* 26 (Suppl. 1):S1–S156, 2003
  22. Yki-Järvinen H, Ryysy L, Nikkila K, Tuolkas T, Vanamo R, Heikkilä M: Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus: a randomized, controlled trial. *Ann Intern Med* 130:389–396, 1999
  23. International Conference on Harmonisation: Good clinical practice, consolidated guideline. *Federal Register* 62:25691–25709, 1997
  24. Aventis: *LANTUS prescribing information*. Bridgewater, NJ, Aventis, 2003
  25. DCCT: Epidemiology of severe hypoglycemia in the diabetes control and complications trial. *Am J Med* 90:450–459, 1991
  26. Davies M, Storms F, Shutler S, Bianchi-Biscay M, Gomis R: Insulin glargine in type 2 patients with suboptimal glycemic control on twice-daily premix insulin: AT.LANTUS Trial Results study (Abstract). *Diabetes* 53 (Suppl. 2):A473, 2004
  27. Lavalle-Gonzalez F, Storms F, Shutler S, Bianchi-Biscay M, Gomis R: Effect of basal insulin glargine therapy in type 2 patients inadequately controlled on oral antidiabetic agents: AT.LANTUS trial results. Abstract presented at the American Diabetes Association 64th Scientific Sessions, 4–8 June 2004, The Orange County Convention Center, Orlando, Florida:12-LB (late breaking), 2004
  28. Fulcher G, Storms F, Shutler S, Leperlier C, Gomis R, Davies M: Initiation of insulin glargine in patients with type 2 diabetes suboptimally controlled on once- or twice-daily NPH insulin: results from the AT.LANTUS trial. *Diabetologia* 47:A272, 2004
  29. Lavalle-Gonzalez F, Storms F, Shutler S, Bianchi-Biscay M, Gomis R, Davies M: Initiation of basal insulin glargine therapy in type 2 patients inadequately controlled on oral antidiabetic agents: results from the AT.LANTUS Trial. *Diabetologia* 47: Abstract 751, 2004
  30. Storms F, Shutler S, Rodriguez J, Gomis R, Davies M: The AT.LANTUS trial investigating treatment algorithms for insulin glargine (LANTUS) therapy: results in subjects with type 1 and type 2 diabetes. *Diabetologia* 47:Abstract 910, 2004
  31. Davies M, Storms F, Shutler S, Bianchi-Biscay M, Gomis R: Initiation of insulin glargine in type 2 patients with suboptimal glycaemic control on twice-daily premix insulin: results from the AT.LANTUS trial. *Diabetologia* 47:Abstract 146, 2004
  32. Riddle M: Timely addition of insulin to oral therapy for type 2 diabetes. *Diabetes Care* 25:395–396, 2002