# Initiate Insulin by Aggressive Titration and Education (INITIATE)

## A randomized study to compare initiation of insulin combination therapy in type 2 diabetic patients individually and in groups

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**OBJECTIVE** — Insulin is often postponed for years because initiation is time-consuming. We sought to compare initiation of insulin individually and in groups with respect to change in A1C and several other parameters in type 2 diabetic patients.

**RESEARCH DESIGN AND METHODS** — A randomized (1:1), multicenter, two-arm, parallel design study with a recruiting period of up to 14 weeks and a 24-week treatment period. Either in groups of 4–8 or individually, using the same personnel and education program, 121 insulin-naive type 2 diabetic patients with an A1C of 7.0–12.0% were randomized to initiate bedtime insulin glargine. The patients visited the treatment center before and at the time of insulin initiation and at 6, 12, and 24 weeks. Patients self-adjusted the insulin dose to achieve a fasting plasma glucose 4.0–5.5 mmol/l.

**RESULTS** — At 24 weeks, mean ± SE A1C had decreased from 8.7 ± 0.2 to 6.9 ± 0.1% in those treated individually and from 8.8 ± 0.2 to 6.8 ± 0.1% in those in groups (not significant [NS]). Insulin doses averaged 62 ± 5 IU and 56 ± 5 IU at 24 weeks (NS), respectively. The frequency of hypoglycemia was similar. The total time (visits and phone calls) spent in initiating insulin in the patients in groups (2.2 ± 0.1 h) was 48% less than in those treated individually (4.2 ± 0.2 h). Diabetes treatment satisfaction improved significantly in both sets of patients.

**CONCLUSIONS** — Similar glycemic control and treatment satisfaction can be achieved by initiating insulin in groups and individually. Starting insulin in groups takes one-half as much time as individual initiation.

*Diabetes Care* 30:1364–1369, 2007

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Received for publication 6 November 2006 and accepted in revised form 13 March 2007.

Published ahead of print at http://care.diabetesjournals.org on 23 March 2007. DOI: 10.2337/dc06-1357. Clinical trial reg. no. ISRTN09079822, clinicaltrials.gov.

H.Y.-J. has acted as a consultant or speaker for Amylin, Astra-Zeneca, Aventis, Lilly, Merck, MSD, Pfizer, and Sanofi-Aventis and has received grant support for investigator-initiated trials from Astra-Zeneca, Aventis, Eli Lilly, Novartis, and Roche. M.D. has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, and Eli Lilly and has received grants in support of investigator and internal trials from Servier, Novartis, Novo Nordisk, Pfizer, and Sanofi-Aventis.

**Abbreviations:** ALT, alanine aminotransferase; DTSQ, Diabetes Treatment Satisfaction Questionnaire; FPG, fasting plasma glucose.

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



Despite new guidelines with strict glycemic targets, a recent survey of 157,000 type 2 diabetic patients indicated that over two-thirds have A1C concentrations >6.5% (1). In the 2005 guidelines by the International Diabetes Federation, insulin therapy is recommended when A1C exceeds 7.5% despite other therapies (2). This is because large trials have shown that it is feasible to achieve an A1C target of 7.0% using insulin combination therapy regimens (3–6). However, reluctance to initiate insulin is still common, in part because of lack of time and resources. There is thus a need for innovative strategies to facilitate the transition to insulin therapy.

Simple addition of basal insulin to existing oral agents is an attractive way to start insulin therapy as it involves only one injection of insulin, the dose of which can be adjusted based on measurement of fasting plasma glucose (FPG) (4,7–9). In studies where an A1C of ~7.0% was achieved, the insulin dose was aggressively titrated by daily measurement of FPG and frequent self-adjustment of insulin dose (4,6,9). Recent comparison of titration algorithms in 4,961 patients with type 2 diabetes showed that a simple subject-administered titration conferred significantly improved glycemic control with a low incidence of severe hypoglycemia compared with physician-managed titration (10).

Historically, insulin therapy has been started individually in patients with type 2 diabetes. Considering limited resources, the large numbers of patients, and that patients with type 2 diabetes by definition "survive without insulin," it would seem worthwhile to establish whether insulin can be started in groups. The present study was designed to test in a randomized fashion in poorly controlled insulin-naive patients with type 2 diabetes whether this is the case.

## RESEARCH DESIGN AND METHODS

### Study design

This was a multicenter, open, randomized, parallel-group study to compare ini-

tiation of insulin in groups versus individually in insulin-naive type 2 diabetic patients who were poorly controlled on oral hypoglycemic agents.

The study consisted of a 3- to 14-week run-in phase and a 24-week treatment phase. It was performed in Finland, Sweden, the U.K., and the Netherlands in accordance with the Declaration of Helsinki and good clinical practice (GCP) as described by Note for Guidance CPMP/ICH/135/95. Approval by institutional ethics committees was obtained for each site. All patients provided written informed consent before study entry. The study design was investigator-initiated (H.Y.). Sanofi-aventis provided funding and helped in conducting the study according to GCP guidelines (S.L.) but did not participate in data analysis, interpretation of the data, or writing the manuscript.

### Patients

Male or female patients aged ≥18 years of age with type 2 diabetes treated with a stable dose (any dose) of sulfonylurea and metformin (≥1.5 g) or either drug alone for at least 6 months were recruited. Further inclusion criteria included BMI <45 kg/m$^2$, A1C between 7.0 and 12%, and willingness and ability to inject insulin, perform self-monitoring of blood glucose, and share some health information (glycemic control and body weight) with other members. Main exclusion criteria were as previously described (9).

### Screening visit at −14 to −3 weeks (individual)

Informed consent was obtained, and the inclusion and exclusion criteria were reviewed. After a history and physical examination, a fasting blood sample was taken for measurement of A1C (central measurement), FPG, sodium, potassium, creatinine, alanine aminotransferase (ALT), and blood counts. Body weight and height were measured. Other tests included electrocardiogram, urine analysis, and a pregnancy test. A retinal examination was scheduled if not performed within the last 12 months. Oral antidiabetes drugs were continued unchanged. The importance of dietary and lifestyle approaches was reinforced.

After visit 1, eligible patients were randomized to either an individual or a group education program. Randomization was performed centrally, using the minimization of differences method (11). The following variables were included (relative weight is given in parentheses): age (1×), gender (0.5×), BMI (1.5×), A1C (1.5×), duration of diabetes (0.5×), previous oral agents (1×), history of macrovascular disease (0.5×), and education (1×).

### Preinitiation visit at −2 weeks (group or individual)

The group size was four to eight subjects. The same nurse led group and individual sessions. After screening visits, education was entirely taken care of by the nurse. The participants received counseling on pathogenesis and treatment (especially insulin treatment) of type 2 diabetes. All educational materials for each visit were similar in all centers. The participants were taught and asked to perform self-monitoring of FPG every morning and to send glucose values to the treatment center using a modem before the next visit. In the U.K., the patients sent glucose values recorded on a diary card to the study center by mail.

### Initiation of insulin visit at 0 weeks (group or individual)

At this visit, participants were taught how to inject insulin, use the insulin pen (OptiSet; Aventis Pharma, Germany), and self-adjust insulin dose. Symptoms and signs of hypoglycemia were discussed. Treatment satisfaction was assessed by asking the patients to fill in a Diabetes Treatment Satisfaction Questionnaire (DTSQ) form (12). The participants were told to inject 10 IU s.c. of insulin glargine (Lantus; Sanofi-Aventis, Germany) daily at bedtime and to measure FPG every morning. The patients were asked to increase the dose of insulin glargine by 2–4 IU when FPG exceeded 5.5 mmol/l for 3 consecutive days. The target FPG was 4.0–5.5 mmol/l. If FPGs were <4.0 mmol/l and symptomatic hypoglycemia occurred without an identifiable reason, the patients were asked to decrease the insulin dose by 2 IU/day. Participants were also asked to record glucose values and insulin doses daily in a diary to facilitate self-adjustment. They recorded symptoms of hypoglycemia and the glucose concentration at the time of hypoglycemia in the diary. At this and all subsequent visits, body weight and blood pressure were recorded. A blood sample was taken for measurement of serum lipids and A1C.

### Phone calls at weeks 1, 2, 4, 8, 16, and 20

The patients sent FPGs using a modem or by mail before calling the study center. During the call, the study nurse reviewed glucose measurements received at a Web site (www.prowellness.com), encouraged self-adjustment of insulin dose, and asked for possible adverse events, incidents of hypoglycemia, and changes in medication.

### Six-week visit (group or individual)

The patients examined their FPGs, which had been sent via modem to the treatment center, and discussed self-adjustment of insulin dose. Body weight and vital signs were recorded, and a blood sample for measurement of A1C was obtained. Effects of insulin therapy on body weight and the importance of a healthy lifestyle (diet and exercise) were discussed. Adverse events were recorded.

### Twelve-week visit (group or individual)

As the 6-week visit. In addition, the importance of A1C measurement and causes for a variation of insulin requirements in type 2 diabetes were discussed.

### Twenty-four–week visit (group or individual, end of study)

As the 6-week visit. In addition, a blood sample for measurement of fasting serum lipids, A1C (central measurement), FPG, sodium, potassium, creatinine, ALT, and blood counts were obtained. The participants were asked to fill in forms for the DTSQ, status version, and DTSQ, change version (13).

### Analytical procedures

A1C was measured by high-pressure liquid chromatography using the fully automated Glycosylated Hemoglobin Analyzer System (BioRad, CA), traceable to the Diabetes Control and Complications Trial reference method, with a reference range of 4.0–6.0%. Lipids, electrolytes, ALT, blood counts, creatinine concentrations, pregnancy tests, and urine analyses were performed using methods in local laboratories.

### Statistical analyses

The primary end point was difference in A1C between the education programs. The educational programs were defined as equally successful if A1C at the end of the study differed by <0.5%. In a previous study where insulin regimen consisted of basal insulin (glargine or NPH)

combined with metformin (9), the A1C at the end of the study averaged 7.19 ± 0.91%. Assuming a common SD of 0.91% and a −0.5%, 0.5% equivalence region, equivalence between the two education programs can be demonstrated with 53 patients per group at the 0.05 level of significance and 80% power. The goal was to recruit at least 120 patients to allow for drop-outs.

Secondary objectives included comparison of the two educational methods with respect to the following: *1*) time spent by a nurse on education, physician's time, and number and duration of phone calls; *2*) change in the concentrations of serum HDL and LDL cholesterol and serum triglycerides; *3*) change in body weight and blood pressure; *4*) change in FPG; *5*) insulin dose at study end, *6*) change in subject's treatment satisfaction; and *7*) incidence of hypoglycemic episodes, as previously defined (9), during the study.

All statistical analyses were performed on an intent-to-treat basis, defined as randomized patients who received at least one injection of insulin. Statistical testing was performed at a two-sided significance level of $\alpha = 0.05$. The primary end point was evaluated by using an ANCOVA model with A1C change from baseline to the end of the study as a response variable. The method of education and center were included as fixed effects, with the baseline value of A1C as a covariate in the ANCOVA model. A similar ANCOVA model was used for LDL and HDL cholesterol (log transformed), triglycerides (log transformed), body weight, blood pressure, and fasting glucose concentration. The change in a subjects' treatment satisfaction was compared between the groups using Mann-Whitney *U* test. The proportion of patients with hypoglycemic events and the number of events were compared using Cochran-Mantel-Haenszel test stratified by center. All statistical analyses were performed by 4Pharma (Kista, Sweden).

## RESULTS

### Patient characteristics

A total of 128 patients were eligible at randomization visit. Seven patients dropped out during the recruitment phase while waiting for start of insulin therapy (metastasis of papillary thyroid carcinoma, retinal neovascularization, and unwillingness to continue: $n = 2$; group formation took too long: $n = 1$; other: $n = 2$). A total of 121 patients started insulin therapy and comprised the intention-to-treat population. Five dropped out from the individual education arm (poor compliance, $n = 2$; hypoglycemia, $n = 1$; protocol violation, $n = 1$; new adverse event, $n = 1$). No patients dropped out from the group education arm. The mean group size was 5.3 individuals. Of scheduled visits, 95.6 and 90.3% were attended in the individual and the group education arms, respectively (NS). Baseline demographic and clinical characteristics were similar between the treatment groups (Table 1).

**Table 1—*Baseline demographics and characteristics of the study groups (intention-to-treat groups)***

| Characteristic | Individualized treatment | Group treatment |
|---|---|---|
| Patients (*n*) | 63 | 58 |
| Sex (male/female) | 65/35 | 59/41 |
| Age (years) | 58 ± 1 | 58 ± 1 |
| Weight (kg) | 93.8 ± 2.6 | 90.1 ± 2.8 |
| BMI (kg/m$^2$) | 31.5 ± 0.7 | 31.2 ± 0.9 |
| Duration of diabetes (years) | 8 ± 1 | 7 ± 1 |
| A1C (%) | 8.65 ± 0.18 | 8.79 ± 0.20 |
| Complications/other conditions | | |
| Hypertension | 55 | 50 |
| Macrovascular disease | 14 | 16 |
| Microvascular disease | 47 | 55 |
| Oral agents before insulin | | |
| Sulfonylurea and metformin | 84 | 79 |
| Metformin only | 10 | 10 |
| Sulfonylurea only | 6 | 10 |
| Education | | |
| Elementary school | 41 | 43 |
| Vocational education | 44 | 48 |
| Academic | 14 | 9 |

Data are means ± SE or percentages unless otherwise indicated.

### Glycemic control

A1C decreased from 8.65 ± 0.18% at 0 weeks to 6.89 ± 0.14% at 24 weeks in patients individually treated ($P < 0.001$) and from 8.79 ± 0.20% to 6.81 ± 0.12% in those in the group education arm ($P < 0.001$), with no difference between the two arms (Fig. 1).

FPG averaged 9.0 ± 0.1, 7.1 ± 0.1, and 6.3 ± 0.1 mmol/l in those individually treated and 8.7 ± 0.1, 6.9 ± 0.1 and 6.4 ± 0.1 mmol/l in the group treatment patients during weeks 0–7, 8–15, and 16–23. The cumulative percentage of patients achieving target (weekly mean FPG within the target range 4.0–5.5 mmol/l) was 47% by week 12 and 66% by study end in the group treatment arm. The corresponding fractions were 41 and 70% in the individualized treatment arm (NS between arms).

### Hypoglycemia

The number of symptomatic hypoglycemia incidents averaged 3.5 and 3.1 episodes/patient year in the individual and group treatment arms, respectively (NS). The percentage of patients experiencing symptomatic hypoglycemia was 44 and 40%, respectively (NS). Of those experiencing symptomatic hypoglycemia, 13 and 10% were nocturnal in the individual and group treatment arms, respectively (NS). There were no incidents of severe hypoglycemia. The number of fasting hypoglycemia incidents, defined as FPG <2.5, 3.2, and 4.0 mmol/l, averaged 0.73, 3.6, and 19.5 episodes/patient-year in those individually treated and 0.53, 4.4, and 20.1 episodes/patient-year in the group arm (NS). The percentage of patients with FPG <2.5, 3.2, and 4.0 mmol/l averaged 13, 33, and 60% in those individually treated and 12, 38, and 66% in the group arm (NS) (Fig. *1*).

### Insulin dose

Insulin doses were similarly titrated by both study arms. At 24 weeks, the insulin doses averaged 62 ± 5 and 56 ± 5 IU/day

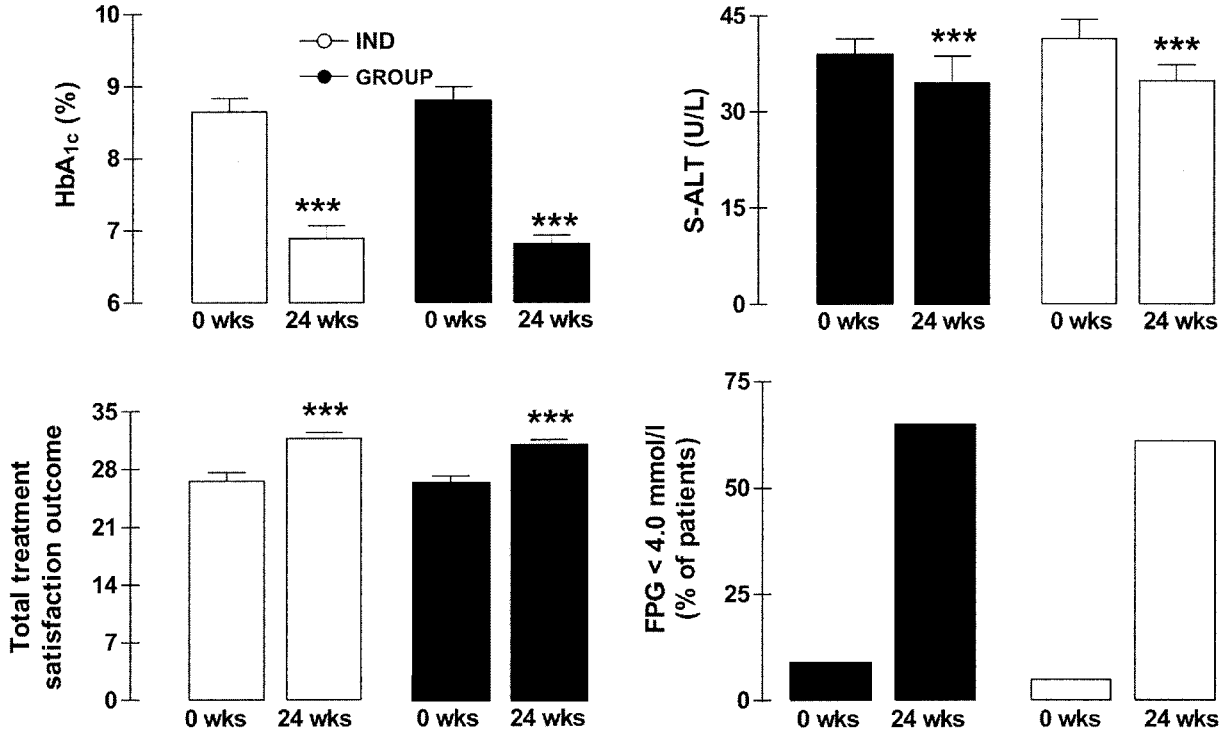


**Figure 1**—*A1C, serum ALT activities, total diabetes treatment satisfaction score, and the percentage of patients with FPGs <4.0 mmol/l in the individual and group arms at baseline (0 weeks) and after 24 weeks of treatment. The FPGs <4.0 mmol/l at 24 weeks denote the percentage of patients during the entire 24-week period. IND, individualized treatment.*

(NS) (0.64 ± 0.05 and 0.60 ± 0.05 IU · $kg^{-1}$ · $day^{-1}$, NS) in the individual and group treatment arms.

### Body weight

The mean weight gain during 24 weeks was significantly lower in the individual (2.2 ± 0.4 kg) than in the group (3.7 ± 0.6 kg, $P < 0.02$) arm.

### Lipids, blood pressure, and liver enzymes

There were no within–education arm differences in serum triglycerides, HDL, or LDL cholesterol. Serum triglycerides decreased from 2.4 ± 0.2 to 1.7 ± 0.1 mmol/l ($P < 0.001$ for 24 vs. 0 weeks) in those individually treated and from 2.1 ± 0.1 mmol/l to 1.8 ± 0.1 mmol/l ($P < 0.001$ for 24 vs. 0 weeks) in the group arm (NS). Serum HDL cholesterol averaged 1.26 ± 0.05 vs. 1.27 ± 0.04 mmol/l (NS) in those individually treated and 1.28 ± 0.05 vs. 1.34 ± 0.05 mmol/l ($P < 0.05$ for 24 vs. 0 weeks) in the group arm at 0 vs. 24 weeks (NS). Serum LDL cholesterol remained unchanged and averaged 2.78 ± 0.10 vs. 2.77 ± 0.10 mmol/l in the individual treatment arm and 2.58 ± 0.12 vs. 2.71 ± 0.11 mmol/l in the group arm at 0 vs. 24 weeks (NS).

Systolic (at 0 vs. 24 weeks, individual treatment 140 ± 2 vs. 142 ± 3 mmHg and group treatment 140 ± 2 vs. 142 ± 3 mmHg) and diastolic (at 0 vs. 24 weeks, individual treatment 83 ± 1 vs. 82 ± 1 mmHg and group treatment 85 ± 1 vs. 83 ± 1 mmHg) blood pressures remained unchanged. Serum ALT decreased highly significantly in both the individual and the group education arms (Fig. 1).

### Treatment satisfaction and time spent on patient education

Total treatment satisfaction outcome improved significantly and similarly in both education arms (Fig. 1). There were no significant differences between the groups in responses to the individual questions of the DTSQ (data not shown).

The total time (scheduled and extra) over 24 weeks spent starting insulin was 48% lower in the group than in the individual education arm (Fig. 2). There was no correlation between class time or total time and the A1C achieved, the change in A1C, or the percentage of decrease in A1C (data not shown) within the educational arms.

### Adverse events

The incidence of adverse events considered not to be related to treatment was similar between groups: 31 patients (49%) in the individual and 28 patients (48%) in the group arms reported at least one adverse event. Most common were infections and musculoskeletal disorders, with no differences between the arms. There was one side effect considered to be related to treatment: one injection site reaction in the individual treatment arm. Four patients (group, $n = 1$; individual, $n = 3$) had serious adverse events during the course of the study. All serious adverse events recovered without sequelae.

**CONCLUSIONS** — The present study is to our knowledge the first attempt to compare, in a randomized fashion, initiation of insulin therapy by adding basal insulin to existing oral agents individually and in groups. We found that both education methods were equally effective with respect to improvement of glycemic control. There were also no differences in the time course of titration of the insulin doses, in symptomatic or biochemical hypoglycemia, or in treatment satisfaction. Individual initiation took twice the amount of the nurse educator's time compared with initiation of insulin in groups. Weight gain was slightly greater when insulin was started in groups compared with patients treated individually.

We chose to start insulin therapy by

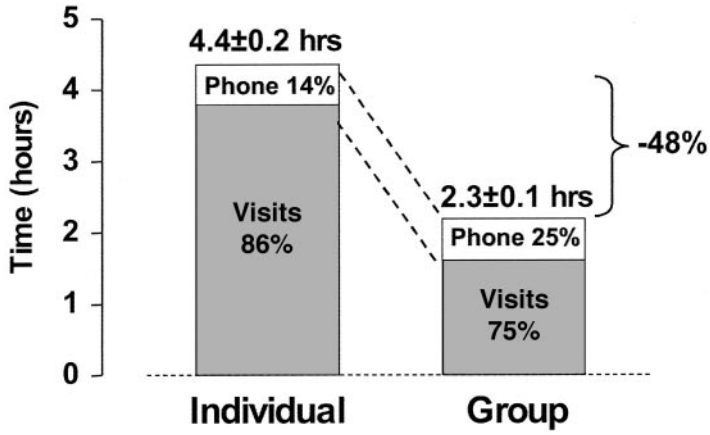


**Figure 2—***Total time spent to initiate insulin during the study. The total (scheduled in-class or over-the-phone and extra) time for the group arm was 2.3 ± 0.1 h* (n = *58): 1.6 ± 0.1 h for scheduled visits, 0.59 ± 0.03 h for scheduled phone calls, and 0.73 ± 0.24 h for extra visits* (n = *10) and 0.17 ± 0.05 h for extra phone calls* (n = *11). The corresponding times in the individual arm were as follows: 4.4 ± 0.2* (n = *63), 3.6 ± 0.2, 0.59 ± 0.03, 0.59 ± 0.2* (n = *14), and 0.14 ± 0.03 h* (n = *11).*

adding basal insulin to existing oral agents, which mostly consisted of sulfonylureas combined with metformin. This regimen, compared with other options such as use of insulin mixtures or multiple insulin injection regimens, requires only one measurement of fasting glucose and one injection of insulin and is associated with less weight gain and hypoglycemia than multiple insulin injection regimens (5–8). Recommending only one fasting measurement for adjusting a single injection of insulin also facilitates interpretation of glucose values received by modem (9). One center did not use the modem but nevertheless managed to achieve good glycemic control in both education arms. We found use of the modem very helpful, as it allows immediate visualization of whether the FPG target has been reached. The modem also allowed accurate assessment of fasting hypoglycemia; however, symptomatic hypoglycemia is underestimated unless patients are strongly encouraged to also record hypoglycemia on a card. In keeping with this, we found almost twice the rate of confirmed hypoglycemia (episodes of FPG $<4.0$ mmol/l $\cdot$ patient$^{-1}$ $\cdot$ year$^{-1}$) than in the treat-to-target study but less symptomatic hypoglycemia (4). This could possibly be due to use of the modem, which allows accurate recording of all measured glucoses.

The A1C achieved at the end of 24 weeks in the group education arm (6.8%) is to our knowledge the best glycemic control achieved in any insulin treatment study in established type 2 diabetes (4–6,9,14–15). Compared with other studies, this cannot be attributed to differences in baseline BMI, glycemic control, duration of diabetes, lack of weight gain during insulin therapy, or choice of oral agents. We attribute the success to use of adequate titration of insulin doses and to not discontinuing the sulfonylurea. In the large treat-to-target study, where basal insulin was added to sulfonylurea and metformin combination therapy (4), FPG was higher than in the LANMET study (9), where only metformin was used—yet A1C was lower. Our patients were just as obese as those in the study of Riddle et al. (4) but used 55–62 IU of insulin, while the insulin doses in the latter study were 42–47 IU.

Body weight increased by 3.7 kg in the group arm, which was 1.5 kg more than in the individual treatment arm. We have previously shown that for every 1% decrease in A1C, body weight increases by 2 kg (16). This increase reflects the net effects of reduction in calories lost in the urine and of changes in energy expenditure due to an increase in fat-free mass that accompanies weight gain, as well as a decrease in the energy consumed for glucose production (16). Since A1C decreased by 2% in both arms, one would have predicted a 4 kg weight gain in both arms, but this was only observed in the group arm. The difference in weight gain between the two educational arms suggests that the patients may have received more dietary advice during the individual education sessions than in the group.

Treatment satisfaction improved similarly in both educational arms. While this implies that patients were equally satisfied with both educational methods, it is not possible to determine why treatment satisfaction improved. We have previously shown that treatment satisfaction improved with combination therapy compared with use of continued oral agents (7), suggesting that improved glycemic control rather than simply participating in a study improves general well-being. Of note, treatment satisfaction was similar, although participation in the group arm required more time of the patient than individual education.

In conclusion, starting insulin in type 2 diabetes in groups gives as good glycemic control as individual initiation. Group and individual education also appear similar with respect to hypoglycemia, lipid changes, and insulin doses. Body weight increased more in the group education than in the individual education arm. Given years of delay in initiating insulin and the growing number of patients needing intensified treatment, we recommend initiation of insulin therapy using the simple principles of the present study in groups rather than individually because this saves considerable amount of time and resources. Although not all patients will be eligible for this method of education, we believe a substantial proportion of the diabetic population will be eligible.

**Acknowledgments**— This study was investigator initiated and supported by Sanofi-Aventis.

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