Initiating Insulin Therapy in Type 2 Diabetes

A comparison of biphasic and basal insulin analogs

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OBJECTIVE — Safety and efficacy of biphasic insulin aspart 70/30 (BIAsp 70/30, prebreakfast and presupper) were compared with once-daily insulin glargine in type 2 diabetic subjects inadequately controlled on oral antidiabetic drugs (OADs).

RESEARCH DESIGN AND METHODS — This 28-week parallel-group study randomized 233 insulin-naive patients with HbA_{1c} values ≥8.0% on >1,000 mg/day metformin alone or in combination with other OADs. Metformin was adjusted up to 2,550 mg/day before insulin therapy was initiated with 5–6 units BIAsp 70/30 twice daily or 10–12 units glargine at bedtime and titrated to target blood glucose (80–110 mg/dl) by algorithm-directed titration.

RESULTS — A total of 209 subjects completed the study. At study end, the mean HbA_{1c} value was lower in the BIAsp 70/30 group than in the glargine group (6.91 ± 1.17 vs. 7.41 ± 1.24%, $P < 0.01$). The HbA_{1c} reduction was greater in the BIAsp 70/30 group than in the glargine group (−2.79 ± 0.11 vs. −2.36 ± 0.11%, respectively; $P < 0.01$), especially for subjects with baseline HbA_{1c} >8.5% (−3.13 ± 1.63 vs. −2.60 ± 1.50%, respectively; $P < 0.05$). More BIAsp 70/30–treated subjects reached target HbA_{1c} values than glargine-treated subjects (HbA_{1c} ≤6.5%: 42 vs. 28%, $P < 0.05$; HbA_{1c} <7.0%: 66 vs. 40%, $P < 0.001$). Minor hypoglycemia (episodes/year) was greater in the BIAsp 70/30 group than in the glargine group (3.4 ± 6.6 and 0.7 ± 2.0, respectively; $P < 0.05$). Weight gain and daily insulin dose at study end were greater for BIAsp 70/30–treated subjects than for glargine-treated subjects (weight gain: 5.4 ± 4.8 vs. 3.5 ± 4.5 kg, $P < 0.01$; insulin dose: 78.5 ± 39.5 and 51.3 ± 26.7 units/day, respectively).

CONCLUSIONS — In subjects with type 2 diabetes poorly controlled on OADs, initiating insulin therapy with twice-daily BIAsp 70/30 was more effective in achieving HbA_{1c} targets than once-daily glargine, especially in subjects with HbA_{1c} >8.5%.

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The U.K. Prospective Diabetes Study demonstrated that most patients with type 2 diabetes will need treatment with exogenous insulin at some point during their lifetimes (1,2). Diminished insulin secretion due to declining β-cell function eventually results in a loss of glycemic control obtainable with oral antidiabetic drugs (OADs) (3). Common options for insulin initiation include treatment with an intermediate- or long-acting basal insulin (4) or with a biphasic insulin formulation containing both basal and rapid-acting components (5).

Monnier et al. (6) have shown that postprandial glycemic control accounts for ~70% of overall glycemic control in patients with HbA_{1c} values <7.3% and for ~50% of overall glycemic control in patients with HbA_{1c} values between 7.3 and 8.4%. The impact of postprandial glycemic control on overall glycemic control increases as HbA_{1c} values get closer to the American Diabetes Association and American College of Endocrinology recommended HbA_{1c} targets of <7% and ≤6.5%, respectively (7,8). The Treat-to-Target trial, using a once-daily basal insulin algorithm based on target fasting plasma glucose (FPG) levels, has clearly demonstrated that patients can achieve the recommended American Diabetes Association HbA_{1c} target of 7% in 24 weeks (4). According to Monnier et al., the addition of a fast-acting insulin component to such a basal regimen might allow even more patients to achieve recommended HbA_{1c} targets by further controlling the postprandial glucose. This is more likely to be true in diabetic patients who have diminished endogenous insulin secretion (9).

NovoLog Mix 70/30 (BIAsp 70/30) is

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Abbreviations: FPG, fasting plasma glucose; OAD, oral antidiabetic drug; TZD, thiazolidinedione; SMPG, self-measured plasma glucose.

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

See accompanying editorial, p. 494.

a biphasic insulin analog formulation of insulin aspart containing 30% soluble insulin aspart and 70% insulin aspart crystallized with protamine. When injected at mealtime, BIAsp 70/30 results in improved postprandial glucose levels compared with biphasic human insulin 70/30 (10–12). In type 2 diabetic patients beginning insulin therapy, once-daily suppertime (evening) injection of BIAsp 70/30 used in combination with metformin was effective in decreasing HbA_{1c} values in type 2 diabetic patients with inadequate glycemic control on previous OAD therapy (5). With the growing recognition of postprandial glucose control for achieving glycemic targets and the ability of BIAsp 70/30 to control both fasting and postprandial hyperglycemia, we conducted a treat-to-target trial to compare the safety and efficacy of twice-daily BIAsp 70/30 and once-daily insulin glargine therapy in insulin-naive type 2 diabetic subjects.

RESEARCH DESIGN AND METHODS

— This was a 28-week randomized, multicenter, open-label, parallel-group, treat-to-target study with a 4-week metformin optimization period (with or without thiazolidinediones [TZDs]). Subjects were randomized to either twice-daily BIAsp 70/30 before breakfast and supper or once-daily glargine at bedtime. The lowest available randomization number was used within each center to provide a balanced treatment assignment. Subjects were also stratified based on TZD use. Subjects and investigators were masked to treatment sequence up to the point of subject randomization. The study was conducted at 25 centers in the U.S., in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines (13). All subjects provided written informed consent.

The study randomized 233 insulin-naive subjects with type 2 diabetes who were 18–75 years old and had a BMI ≤40 kg/m^2, body weight <125 kg (275 lbs), and an HbA_{1c} value ≥8%. All subjects were previously treated with metformin, at least 1,000 mg/day, as a single agent or in combination therapy for at least 3 months before the trial. Women of childbearing age were excluded if they were pregnant, breast-feeding, or not practicing contraception.

During the 4-week metformin run-in period, metformin was optimized to 1,500–2,550 mg/day and subjects discontinued secretagogues and α-glucosidase inhibitors. Pioglitazone was continued (up to 30 mg) if taken prestudy. Subjects taking rosiglitazone were changed to pioglitazone because, at the time of this study, rosiglitazone did not have an approved indication in the U.S. for combination use with insulin. Subjects taking ≤4 mg rosiglitazone were changed to 15 mg pioglitazone, whereas those taking >4 mg received 30 mg pioglitazone. Pioglitazone doses remained constant throughout the trial. Subjects with any self-measured plasma glucose (SMPG) (blood glucose meters calibrated to plasma glucose) value ≤70 mg/dl or with both FPG and presupper plasma glucose values ≤140 mg/dl at the end of the metformin optimization period were considered run-in failures and were not randomized into the study.

Insulin therapy was initiated at a total daily dose of 10 units for subjects with FPG values <180 mg/dl or 12 units for subjects with FPG values ≥180 mg/dl. The BIAsp 70/30 (NovoLog Mix 70/30; Novo Nordisk, Bagsvaerd, Denmark) dose was administered within 15 min before breakfast and supper (evening meal) using the FlexPen insulin delivery device and, for the initiation dose, was divided equally between the two meals. The entire dose of glargine (Lantus; Sanofi-Aventis Pharmaceuticals, Paris, France) was administered at bedtime using a vial and syringe.

Insulin doses were titrated weekly for the first 12 weeks and then every 2 weeks thereafter to achieve target FPG and presupper plasma glucose values of 80–110 mg/dl. Presupper BIAsp 70/30 and bedtime glargine doses were titrated based on FPG values. The prebreakfast BIAsp 70/30 dose was titrated based on presupper SMPG values. Dose titration was based on plasma glucose values from the preceding 3 days (measured with a One-Touch Ultra blood glucose meter; LifeScan). If two of the three readings for a specified time period (prebreakfast or presupper) were not within target, the insulin dose was adjusted based on the lower of the two plasma glucose readings unless hypoglycemia was occurring. Prebreakfast and presupper BIAsp 70/30 doses were adjusted independently of each other as follows: decreased by 2 units if plasma glucose was <80 mg/dl, no change if plasma glucose was 80–110 mg/dl, increased by 2 units if plasma glucose was 111–140 mg/dl, increased by 4 units if plasma glucose was 141–180 mg/dl, and increased by 6 units if plasma glucose was >180 mg/dl. Glargine was adjusted according to FPG with an algorithm similar to that used in the Treat-to-Target study (4): decreased by 2 units if plasma glucose was <80 mg/dl, no change if plasma glucose was 80–110 mg/dl, increased by 2–4 units if plasma glucose was 111–140 mg/dl, increased by 4–6 units if plasma glucose was 141–180 mg/dl, and increased by 6–8 units if plasma glucose was >180 mg/dl. The increase in the total daily dose was not to exceed the greater of 10 units or 10% of the current total daily dose.

Efficacy assessments

The primary end point was the reduction in HbA_{1c} values from baseline to the end of the study. Values for HbA_{1c}, FPG, and eight-point (immediately before and 90 min after breakfast, lunch, and supper; at bedtime; and at 3:00 A.M.) self-monitored plasma glucose profiles were obtained at randomization and at study weeks 12 and 28. Postprandial glycemic control and plasma glucose increments at each meal were assessed by comparison of eight-point SMPG profiles.

Safety assessments

Safety was assessed by physical examination findings, clinical laboratory evaluations, and reporting of adverse events and hypoglycemic episodes. Minor hypoglycemic episodes were defined as blood glucose values of <56 mg/dl (3.1 mmol/l) with or without symptoms that were self-treated. Major hypoglycemia was an episode with neurological symptoms consistent with hypoglycemia that required assistance and had either a plasma glucose value <56 mg/dl or reversal of symptoms after food intake, glucagon, or intravenous glucose.

Statistical analysis

The analysis of data were performed on the intent-to-treat population, defined as the set of subjects for which any efficacy data were available. The primary and secondary variables were analyzed for the full analysis set. Accordingly, end-of-study values represent mean values for the last observation carried forward. An ANCOVA model was used in the analysis for HbA_{1c} with HbA_{1c} change from base-

Table 1—*Characteristics of enrolled population and subject disposition*

	BIAsp 70/30	Glargine
Subjects randomized (*n*)	117	116
Age (years)	52.6 ± 10.6	52.3 ± 9.8
Sex (%) (M/F)	53/47	56/44
Ethnicity (%) (C/B/H/A/O)*	55/15/27/2/2	52/17/26/4/1
Weight (kg)	90.6 ± 18.8	89.9 ± 19.0
BMI (kg/m^2)	31.5 ± 5.5	31.4 ± 5.3
Prior TZD use (yes/no)	38 (32)/79 (68)	38 (33)/78 (67)
Diabetes duration (years)	9.5 ± 5.9	8.9 ± 4.8
HbA_{1c} (%) (all subjects)	9.7 ± 1.5	9.8 ± 1.4
Subjects with HbA_{1c} >8.5% at baseline (*n*)	10.2 ± 1.3 (89)	10.1 ± 1.3 (99)
Subjects with A1C ≤8.5% at baseline (*n*)	8.0 ± 0.4 (28)	8.1 ± 0.3 (17)
Subjects on prestudy TZD† (*n*)	9.3 ± 1.5 (38)	9.7 ± 1.1 (38)
Subjects not on prestudy TZD (*n*)	9.9 ± 1.5 (79)	9.9 ± 1.6 (78)
Completed study	100 (85)	109 (94)
Discontinuation from study‡	17 (15)	7 (6)
For adverse event	4 (3)	1 (1)
For noncompliance	5 (4)	3 (3)
For ineffective therapy	1 (1)	0
For "other"	7 (6)	3 (3)

Data are means ± SD or *n* (%) unless otherwise indicated. *A, Asian; B, black; C, Caucasian; H, Hispanic; O, other. †Baseline HbA_{1c} values for subjects on a prestudy TZD are not significantly different ($P = 0.1441$). ‡Adverse event withdrawals in the BIAsp 70/30 group were unrelated to treatment: stroke, adenocarcinoma, chest pain, and gastrointestinal bleeding. Adverse event withdrawal in the glargine group had a possible study drug relationship: injection site stinging. Reasons for "other" included lost to follow-up, failure to return, and subject withdrawing consent.

line to end of study as the dependent variable, treatment as the fixed effect, and HbA_{1c} at baseline as the covariate. Change-from-baseline HbA_{1c} values were calculated as least-square mean values ± SE. Mean rates of hypoglycemia were compared using a Wilcoxon's two-sample test. Values are expressed as means ± SD unless otherwise noted.

RESULTS

Subjects

A total of 263 subjects were enrolled into the 4-week metformin run-in period. There were 30 subjects who failed the run-in period, and 233 were randomized to insulin treatment. Baseline demographic characteristics were similar between treatment groups (Table 1). Most ($n = 209$, 90%) subjects completed the study. A total of 24 subjects discontinued the study; 17 subjects from the BIAsp 70/30 group and 7 from the glargine group (Table 1). The intent-to-treat population included 108 subjects in the BIAsp 70/30 group and 114 subjects in the glargine group.

Efficacy

At the end of the study, the mean HbA_{1c} values were lower for the BIAsp 70/30 group compared with the glargine group (6.91 ± 1.17 vs. 7.41 ± 1.24%, $P < 0.01$), and the overall reduction in HbA_{1c} for subjects in the BIAsp 70/30 group was significantly greater than for subjects in the glargine group (−2.79 ± 0.11 vs. −2.36 ± 0.11%, respectively; $P < 0.01$). The HbA_{1c} reduction was even larger for subjects whose baseline HbA_{1c} values were >8.5% (−3.13 ± 1.63 vs. −2.60 ± 1.50%, $P < 0.05$, BIAsp 70/30 vs. glargine, respectively). In subjects with baseline HbA_{1c} ≤8.5%, the absolute HbA_{1c} reductions were less pronounced and were comparable between treatment groups (−1.40 ± 0.53 vs. −1.42 ± 0.59%, BIAsp 70/30 vs. glargine, $P > 0.05$). For all subjects in each treatment group, a greater percentage of the BIAsp 70/30 group achieved target HbA_{1c} values <7.0 and ≤6.5% than in the glargine group (Fig. 1).

The similar percentage of subjects in each group (32 vs. 33%) was taking pioglitazone before and during the study (Table 1). Subjects treated with a TZD before the study had slightly lower baseline HbA_{1c} values than subjects not treated with a TZD (Table 1). The end-of-study HbA_{1c} values (±SD) were significantly lower in the BIAsp 70/30 group regardless of pioglitazone use during the study (with pioglitazone: 6.8 ± 0.9 vs. 7.4 ± 1.1%, $P = 0.014$; without pioglitazone: 7.0 ± 1.3 vs. 7.4 ± 1.3%, $P = 0.037$, for BIAsp 70/30 vs. glargine, respectively). The end-of-study HbA_{1c} reductions from baseline were significantly greater for the BIAsp 70/30 group regardless of pioglitazone use (with pioglitazone: −2.60 ± 0.16 vs. −2.13 ± 0.16%, $P < 0.05$; without pioglitazone: −2.89 ± 0.15 vs. −2.46 ± 0.14%, $P < 0.05$, BIAsp 70/30 vs. glargine, respectively).

FPG values were similar at baseline (252 ± 67.4 vs. 243 ± 68.8 mg/dl, BIAsp 70/30 vs. glargine, respectively; $P > 0.05$) and at the end of the study (127 ± 40.6 vs. 117 ± 44.3 mg/dl, $P > 0.05$). The FPG in the glargine group was similar to the 116 mg/dl found in the Treat-to-Target study (4). Target FPG (80–110 mg/dl) at the end of the study was achieved by 57

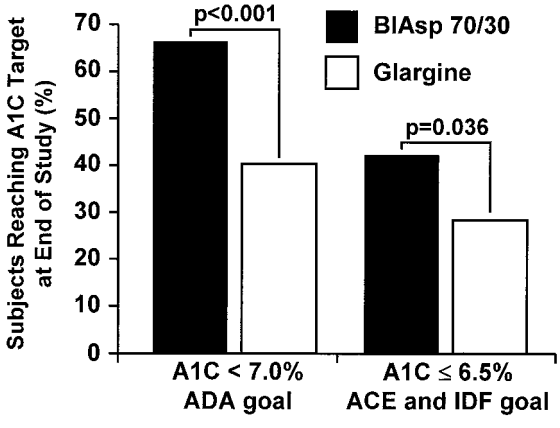

Figure 1—*Percentage of subjects achieving HbA_{1c} target values at the end of the study.* P *values were calculated from Fisher's exact test. ADA, American Diabetes Association; ACE, American College of Endocrinology; IDF, International Diabetes Federation.*

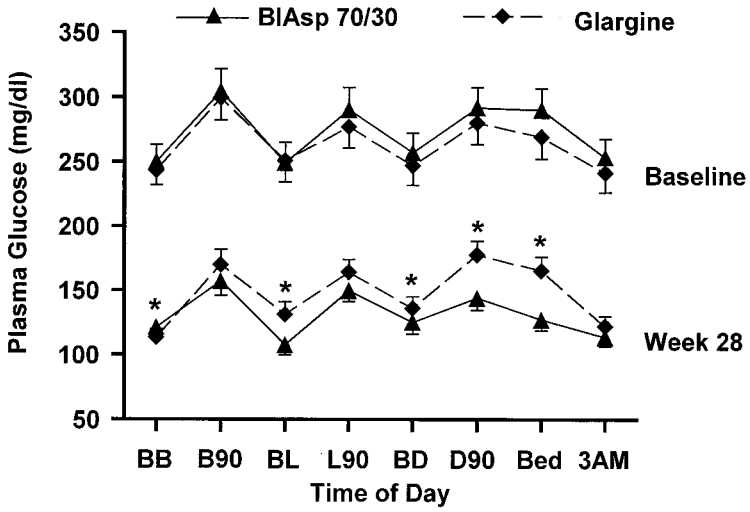

Figure 2—*Eight-point SMPG readings before breakfast, lunch, and supper [BB, BL, and BD] and 90 min after breakfast, lunch, and supper [B90, L90, and D90]; at bedtime [Bed]; and at 3:00 A.M.). Number of data points at each time point at baseline, 114–116; at week 28, BIAsp 70/30, 97–99; glargine, 105–106. Statistically significant differences (*P *< 0.05) between treatment groups at specific time points are indicated with an asterisk. Error bars represent 2 SE.*

and 36% of the subjects in the glargine and BIAsp 70/30 groups, respectively. The change-from-baseline FPG values were the same for each treatment group (125 ± 72.9 vs. 125 ± 74.4 mg/dl, BIAsp 70/30 vs. glargine, respectively).

Both treatment groups had improvements from baseline in their eight-point SMPG profile (Fig. 2). At the end of the study, SMPG values before lunch and supper, after supper, and at bedtime were significantly less for the BIAsp 70/30 group (Fig. 2). Except for lunch, mean prandial plasma glucose increments (postprandial plasma glucose minus preprandial plasma glucose values) were less for BIAsp 70/30 than for glargine (breakfast: 33.9 ± 46.9 vs. 55.3 ± 49.9 mg/dl, $P < 0.01$; lunch: 44.5 ± 48.8 vs. 32.5 ± 53.9 mg/dl, $P > 0.05$; supper: 19.0 ± 62.7 vs. 41.8 ± 52.8 mg/dl, $P < 0.05$). Overall postprandial glycemic exposure was ~25% less for the BIAsp 70/30 group than for the glargine group, as demonstrated by a lower cumulative SMPG value (sum of the three mealtime plasma glucose increments) for the BIAsp 70/30 group (97.4 ± 90.4 vs. 129.6 ± 102 mg/dl, $P < 0.05$).

Although initial daily insulin doses were similar in both groups (0.14 ± 0.03 vs. 0.13 ± 0.03 units/kg for BIAsp 70/30 vs. glargine, respectively), insulin doses at the end of the study were greater for the BIAsp 70/30 group than for the glargine group (total units: 78.5 ± 39.5 vs. 51.3 ± 26.7 units; for units by weight, 0.82 ± 0.40 vs. 0.55 ± 0.27 units/kg, $P < 0.05$). Despite independent titration of the prebreakfast and presupper doses, the total daily dose of BIAsp 70/30 at the end of the study was equally divided between prebreakfast and presupper (38.7 ± 20.4 and 39.9 ± 20.7 units, respectively). The mean total daily insulin dose was ~21 units lower in subjects in the BIAsp 70/30 group taking pioglitazone (64.2 ± 33.8 units) compared with those not taking pioglitazone (85.4 ± 40.4 units). Mean total insulin doses of glargine were similar for subjects with or without pioglitazone treatment (53.0 ± 26.4 and 50.5 ± 26.9 units, respectively).

Mean body weight increased in both treatment groups at the end of the study (BIAsp 70/30, 5.4 ± 4.8 kg, vs. glargine, 3.5 ± 4.5 kg, $P < 0.01$). The weight gain was similar for both treatments when subjects were taking pioglitazone during the study (5.1 ± 5.1 vs. 4.5 ± 4.6 kg, BIAsp 70/30 vs. glargine, respectively, $P > 0.05$). However, in subjects not taking pioglitazone, weight gain was significantly greater in the BIAsp 70/30 group (5.6 ± 4.6 vs. 3.0 ± 4.3 kg, BIAsp 70/30 vs. glargine, respectively; $P < 0.01$).

Safety

The overall rate of minor hypoglycemia (documented plasma glucose <56 mg/dl, with or without symptoms) based on all subjects was greater in the BIAsp 70/30 group than in the glargine group (3.4 ± 6.6 vs. 0.7 ± 2.0 episodes per patient year, respectively; $P < 0.05$). Minor hypoglycemia was reported by 43% of subjects in the BIAsp 70/30 group and by 16% of subjects in the glargine group ($P < 0.05$). Only one major hypoglycemic episode occurred during the trial; a subject in the glargine group reported this episode. Subjects also reported symptoms suggestive of hypoglycemia but whose associated plasma glucose values were ≥56 mg/dl. The rates of these symptoms were 9.8 ± 17.1 and 4.7 ± 11.4 per patient-year for the BIAsp 70/30 and glargine groups, respectively ($P < 0.05$). Included in these rates are symptoms for which a plasma glucose reading was not taken (~4% of all reported episodes in each treatment group). No subjects discontinued treatment because of hypoglycemic episodes.

The number and type of reported adverse events were similar for the two treatment groups and were not unexpected for the trial population. No end-of-study differences in blood chemistry or hematology laboratory values were noted and mean values for vital signs at the end of the study were similar to baseline values.

CONCLUSIONS — This study evaluated two approaches for initiating insulin therapy in type 2 diabetic patients who have failed to achieve target glycemic control goals on OAD therapy. Initiating insulin therapy with twice-daily BIAsp 70/30 provided significantly improved overall glycemic control as measured by a lower end-of-study HbA_{1c} value compared with once-daily insulin glargine. The reductions in HbA_{1c} provided a significant and clinically relevant treatment improvement (HbA_{1c} difference of 0.43%) for subjects in the BIAsp 70/30 group, allowing significantly more BIAsp 70/30–treated subjects to achieve HbA_{1c} targets established by the American Diabetes Association. Notably, BIAsp 70/30 was significantly more effective than insulin glargine in reducing HbA_{1c} for subjects who entered the present study with HbA_{1c} values >8.5%. This is consistent with the fact that as β-cell function declines, HbA_{1c} rises, and basal insulin replacement alone is insufficient to control postprandial hyperglycemia.

The results of this study were comparable to a similar study where insulin therapy was initiated with either twice-

daily biphasic insulin lispro 75/25 or once-daily glargine, both taken concomitantly with metformin (14). Reduction in HbA_{1c} was greater in the lispro premix group, and more subjects reached target HbA_{1c} <7% in 16 weeks when treated with lispro premix than with glargine (41 vs. 22%, $P < 0.001$). In another study, therapy with once-daily glargine plus sulfonylureas and metformin was compared with twice-daily biphasic human insulin premix alone, without OADs (15). Although greater HbA_{1c} reduction was observed in the glargine group at 24 weeks, the human premix group may have been disadvantaged by the removal of OADs from the therapeutic regimen, specifically metformin, which has been shown to be very efficacious when used in combination with insulin therapy (16). Additionally, a biphasic human insulin mix formulation was used, not an analog mix that would have provided greater postprandial glycemic control than the human premix (10). In the present study, the withdrawal of secretagogues from both treatment arms may have disadvantaged insulin glargine. However, it is questionable whether secretagogues would provide significant benefit in subjects with baseline HbA_{1c} values >8.5%. Regardless of secretagogue use, this study used a treat-to-target regimen to optimize insulin therapy, such that the mean FPG in the glargine group at the end of the study was similar to that achieved with glargine in the Treat-to-Target study (4).

Biphasic analog insulin mixes have an advantage over basal insulin alone because they provide the rapid-acting insulin analog insulin aspart as the soluble component that covers mealtime glycemic needs (11,12,17). In this trial, the plasma glucose increments for breakfast and supper, as well as the overall plasma glucose increment for the three meals, were significantly less in the BIAsp 70/30 group. The proposed 50–70% contribution of postprandial glycemic control to overall glycemic control as subjects get closer to achieving glycemic targets would give subjects treated with BIAsp 70/30 an advantage in getting to HbA_{1c} target compared with subjects treated with only basal insulin (6).

The rate of hypoglycemia typically increases as patients use insulin to attain better glycemic control and defined glycemic targets. It is not surprising that the overall rate of minor hypoglycemia was greater in the BIAsp 70/30 group than in the glargine group considering that the BIAsp 70/30 group had better glycemic control than the glargine group. Importantly, hypoglycemia was not a barrier to achieving glycemic targets for the BIAsp 70/30 group. Because intensive glycemic control using insulin is associated with an increased risk of hypoglycemia (18), all patients initiating insulin therapy should always be referred to diabetes self-management training programs to help them prevent, recognize, and manage their hypoglycemic episodes.

Initiation of insulin therapy is often accompanied by an increase in weight as glycemic control improves. The BIAsp 70/30 group had its greatest increase in weight (1.3 kg) within the first month of therapy; lesser weight increases occurred during subsequent months until the increase was 0.8 and 0.4 kg in months 5 and 6 of the study. The glargine group had consistent weight increases during the study, ~0.7 kg per month. Because of the duration of this study (24 weeks), it was not possible to determine whether the weight increase had neared its plateau for either treatment group. A study of longer duration might be required to determine a realistic treatment difference.

Insulin therapy is typically begun only after lifestyle modification and OAD therapy fail to normalize HbA_{1c} values. In the authors' experience, most individuals with type 2 diabetes rarely are started on insulin with HbA_{1c} values <8.5%. Unfortunately, many subjects will have had type 2 diabetes for 10–15 years before diagnosis and may have already developed complications (19). Therefore, earlier introduction of the most effective insulin therapy should be encouraged despite the reluctance of patients and their physicians (20).

Based on the results of this study, biphasic insulin aspart 70/30 appears to be more effective than insulin glargine and a reasonable choice to initiate insulin therapy in insulin-naive subjects with type 2 diabetes that is not optimally controlled on OAD therapy, particularly for those subjects whose HbA_{1c} before insulin initiation is >8.5%.

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APPENDIX— The INITIATE Study Group includes the following investigators: Bruce Bode, Peter Bressler, Robert Gabbay, Alan Garber, G. Murthy Gollapudi, Brent Gooch, Priscilla Hollander, Roy Kaplan, William Kaye, Leslie Klaff, Wendy A. Lane, Andrew Lewin, John Liljenquist, Dennis Linden, Eric Maybach, Kwame Osei, Philip Raskin, Raymond Reynolds, Julio Rosenstock, Sherwyn Schwartz, Phillip Snell, Danny Sugimoto, Gregory Waser, Richard Weinstein, and Kevin Wietecha.

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