Advancing Insulin Therapy in Type 2 Diabetes Previously Treated With Glargine Plus Oral Agents

Prandial premixed (insulin lispro protamine suspension/lispro) versus basal/bolus (glargine/lispro) therapy

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OBJECTIVE — The purpose of this study was to compare two analog insulin therapies (prandial premixed therapy [PPT] versus basal/bolus therapy [BBT]) in type 2 diabetic patients previously treated with insulin glargine (≥30 units/day) plus oral agents, with the aim of demonstrating noninferiority of PPT to BBT.

RESEARCH DESIGN AND METHODS — Patients were randomly assigned to PPT (lispro mix 50/50: 50% insulin lispro protamine suspension and 50% lispro; $n = 187$) t.i.d. with meals or BBT (glargine at bedtime plus mealtime lispro; $n = 187$) in a 24-week, multicenter, open-label, noninferiority trial. Investigators could replace lispro mix 50/50 with lispro mix 75/25 at the evening meal if the fasting plasma glucose target was unachievable.

RESULTS — Baseline A1C was similar (PPT 8.8%; BBT 8.9%; $P = 0.598$). At week 24, A1C was lower with BBT (6.78 vs. 6.95%, $P = 0.021$). A1C was reduced significantly from baseline for both therapies ($P < 0.0001$). The difference in A1C change from baseline to the end point (BBT minus PPT) was −0.22% (90% CI −0.38 to −0.07). Noninferiority of PPT to BBT was not demonstrated based on the prespecified noninferiority margin of 0.3%. The percentages of patients achieving target A1C <7.0% (PPT versus BBT, respectively) were 54 vs. 69% ($P = 0.009$) and for target ≤6.5% were 35 vs. 50% ($P = 0.01$) but did not differ for target ≤6.0% or <7.5%. Rates of hypoglycemia were similar for both groups.

CONCLUSIONS — Although noninferiority of PPT to BBT was not demonstrated, findings for A1C reduction, percentage of patients achieving A1C targets, hypoglycemia, and number of required injections should be considered in the individual decision-making process of advancing insulin replacement to PPT versus BBT in type 2 diabetes.

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The progressive deterioration of pancreatic β-cell function in type 2 diabetes necessitates the advancement of treatment over time for most patients (1,2). For patients in whom treatment with oral antihyperglycemic agents (OHAs) has failed, basal insulin is often initiated (3–10). When glycemic control can no longer be achieved or maintained with this therapy, then prandial insulin is added (11).

Potential options for advancement of insulin therapy to include prandial insulin are prandial premixed therapy (PPT) (12–15) or basal/bolus therapy (BBT) (16–18). BBT is the recommended regimen for insulin intensification (11). However, PPT is a more convenient regimen that has the potential to work as effectively as BBT (12–15). There have been no previous head-to-head studies assessing the effectiveness of analog PPT plus OHAs compared with analog BBT plus OHAs in patients with type 2 diabetes. Thus, in this study we tested the hypothesis that an analog PPT regimen (insulin lispro mixtures three times daily with meals) in combination with OHAs is noninferior in overall glycemic control (A1C) at end point compared with analog BBT (insulin glargine plus mealtime insulin lispro) in combination with OHAs in patients with type 2 diabetes who have failed to achieve glycemic targets with once-daily insulin glargine in combination with OHAs.

RESEARCH DESIGN AND METHODS

— This 24-week, randomized, open-label, active-controlled trial was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical

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Abbreviations: BBT, basal/bolus therapy; FPG, fasting plasma glucose; OHA, oral antihyperglycemic agent; PPT, prandial premixed therapy; SAE, severe adverse event; SMPG, self-monitored plasma glucose; TDI, total daily insulin.

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

Practice and the Declaration of Helsinki (19) at 58 centers in the U.S. and Puerto Rico from May 2004 to June 2006. All patients provided written informed consent.

Men and women, aged 30–75 years, with type 2 diabetes (World Health Organization classification) and inadequate glycemic control (A1C ≥7.5 and ≤12%) while taking insulin glargine for at least 90 days (≥30 units/day) in combination with OHAs as monotherapy, dual therapy, or triple therapy (sulfonylurea or glinide, metformin, and thiazolidinedione) were eligible to be randomly assigned.

Patients were excluded if they had a history of scheduled mealtime insulin use or more than one episode of severe hypoglycemia within the prior 6 months, BMI >45 kg/m^2, or excessive insulin resistance (total daily insulin [TDI] dose >2.0 units/kg). Patients with congestive heart failure requiring pharmacological treatment, functional status of New York Heart Association class III or IV, a history of renal insufficiency (serum creatinine ≥1.5 mg/dl for men and ≥1.2 mg/dl for women), or liver disease were excluded.

Study medications and treatments

Eligible patients were randomly assigned through an interactive telephone system to either PPT or BBT and were assigned to either a more aggressive dosing algorithm based on plasma glucose levels as well as TDI requirement (insulin doses increased by 2–10 units if TDI was <100 IU and by 4–20 units if TDI was >100 IU). The more conservative dosing algorithm was based only on plasma glucose levels, and insulin doses were increased by 2–4 units if mean preprandial plasma glucose was >110 mg/dl (6.1 mmol/l) (Table 1 of the online appendix [available at http://dx.doi.org/10.2337/dc07–1122]). The randomization was 1:1:1:1 to regimen and algorithm, with sex stratification. PPT consisted of lispro mix 50/50 (Humalog Mix 50/50: 50% insulin lispro protamine suspension and 50% insulin lispro) administered three times daily with meals. The starting dose was based on the insulin glargine total dose at study entry divided into three equal doses of lispro mix 50/50 before meals. Because it was not known whether lispro mix 50/50 at the evening meal could effectively and safely achieve a fasting plasma glucose (FPG) target, investigators were allowed to switch this dose to lispro mix 75/25 (Humalog Mix 75/25: 75% insulin lispro protamine suspension and 25% insulin lispro) if FPG remained >110 mg/dl during the study. BBT consisted of insulin glargine (Lantus) administered at bedtime and insulin lispro (Humalog) with meals. The starting dose of this regimen was also based on the total glargine dose at study entry, with 50% administered as glargine and the other 50% given in three equal doses of lispro. Patients continued to take their prestudy OHAs, excluding sulfonylureas and glinides, which were discontinued upon random assignment.

In addition to scheduled 6-week office visits, patients were contacted weekly during the initial 3 months with adjustment of insulin doses to achieve target preprandial plasma glucose levels <110 mg/dl (<6.1 mmol/l). Insulin doses, self-monitored plasma glucose (SMPG) values, and any events associated with signs or symptoms of hypoglycemia were recorded in diaries.

Safety and tolerability were monitored throughout the study. Events related to hypoglycemia were assessed as to incidence, rate, and severity. Hypoglycemia was reported as any symptomatic event with classic cognitive and/or adrenergic signs with or without plasma glucose confirmation. Confirmed symptomatic hypoglycemia was reported as symptoms of hypoglycemia with plasma glucose levels ≤72 mg/dl (4 mmol/l), <60 mg/dl (≤3.3 mmol/l), and ≤50 mg/dl (≤2.8 mmol/l). Severe hypoglycemia was defined as any symptomatic event requiring assistance by another individual.

Outcome measures

The primary efficacy measure was change in A1C from baseline to end point for each treatment group. Secondary outcome measures included incidence of self-reported hypoglycemic episodes, comparison of SMPG values from 8-point profiles, insulin doses, and body weight. The percentage of patients achieving A1C goals was determined by a post hoc analysis based on current professional guidelines and trial design targets (20–22). All laboratory tests were analyzed by a central laboratory (Covance, Indianapolis, IN).

Statistical methods

All statistical analyses, except for percentage of patients achieving A1C goals and insulin formulation switching comparison, were performed in accordance with a predetermined statistical plan. The sample size for the primary analysis was calculated on the basis of a one-sided *t* test for noninferiority with a 5% significance level. Assuming SD of 1% for A1C change, 150 patients completing the study per treatment group provided 80% power to meet the prespecified noninferiority criterion of a 0.3% A1C difference. Use of the intent-to-treat population is generally not conservative in a noninferiority study; therefore, patients who completed the study with a 24-week A1C measurement constituted the primary efficacy analysis population (23).

The primary outcome (change from baseline in A1C) was analyzed by ANCOVA with treatment, dosing algorithm, sex, and baseline A1C as fixed effects. Noninferiority would be claimed if the lower limit of the two-sided 90% CI for the difference in change from baseline A1C did not exceed −0.3%. Secondary outcomes (SMPG, TDI dose, and change in weight) were analyzed by ANCOVA with treatment, dosing algorithm, and sex as fixed effects. Percentage of patients achieving A1C goals (<7.5, <7.0, ≤6.5, and ≤6.0%) was analyzed using Fisher's exact test.

In contrast with analysis of the primary outcome, safety assessments were based on the entire randomly assigned population. The proportions of patients in each group reporting at least one hypoglycemic event or a severe hypoglycemic event were compared with Fisher's exact test. Hypoglycemic rate and severe hypoglycemic rate were analyzed using ANCOVA with treatment, dose algorithm, and sex as fixed effects. Categorical safety variables were compared between groups with Fisher's exact test.

RESULTS

Patient disposition

Of the 547 patients who were screened, 374 were randomly assigned to receive the study treatment (PPT, $n = 187$; BBT, $n = 187$). All randomly assigned patients received at least one dose of study medication. A total of 158 patients in each treatment group (84%) completed the protocol. Reasons for early discontinuation are provided in Table 2 of the online appendix. Baseline characteristics were similar between groups (Table 1). The average duration of diabetes was 11 years, baseline weight was ~99 kg, and 45% of the study population was non-Caucasian. The numbers of patients taking various combinations of concomitant OHAs at study entry and during the study are shown in Table 2. At study entry, the only difference between groups was that the OHA combination of sulfonylurea and thiazolidinedione was more frequently

Table 1—*Baseline demographics and characteristics of randomly assigned patients*

	PPT	BBT	*P*
n	187	187	
Age (years)	55.4 ± 9.8	54.0 ± 9.2	0.163
Sex (male:female)	99 (53):88 (47)	98 (52):89 (48)	1.000
Race/ethnicity			
Caucasian	103 (55.1)	102 (54.6)	1.000
Hispanic	49 (26.2)	53 (28.3)	0.728
Black/African descent	25 (13.4)	18 (9.6)	0.331
Other	10 (5.3)	14 (7.5)	0.528
Weight (kg)	99.1 ± 19.8	99.8 ± 21.3	0.676
BMI (kg/m^2)	34.1 ± 5.3	34.8 ± 5.5	0.227
Diabetes duration (years)	10.9 ± 6.3	11.2 ± 6.2	0.625
A1C (%)	8.83 ± 1.04	8.89 ± 1.09	0.598
FPG [mg/dl (mmol/l)]	171.81 ± 59.79 (9.54 ± 3.32)	181.48 ± 59.74 (10.08 ± 3.32)	0.119
Total daily glargine dose at study entry [units (units/kg)]	52.5 ± 24.1 (0.53 ± 0.21)	54.9 ± 27.8 (0.56 ± 0.27)	0.382
Concomitant OHAs at study entry			
Met/Sulf/TZD	25 (13.4)	23 (12.3)	0.877
Met/Sulf	79 (42.2)	68 (36.4)	0.290
Met/TZD	19 (10.2)	16 (8.6)	0.723
Sulf/TZD	3 (1.6)	12 (6.4)	0.032
Metformin	30 (16.0)	29 (15.5)	1.000
Sulfonylurea	23 (12.3)	28 (15.0)	0.547
TZD	6 (3.2)	8 (4.3)	0.786
Concomitant OHAs during the study			
Met/TZD	37 (19.8)	36 (19.3)	1.000
Metformin	101 (54.0)	89 (47.6)	0.255
TZD	10 (5.3)	17 (9.1)	0.230

Data are means ± SD or *n* (%) unless otherwise indicated. Met, metformin; Sulf, sulfonylurea; TZD, thiazolidinedione.

used in the BBT group (BBT $n = 12$; PPT $n = 3$; $P = 0.032$); however, an equal number of patients in both groups discontinued sulfonylurea treatment upon random assignment (BBT $n = 131$; PPT $n = 130$).

Glycemic control

Baseline A1C was similar in both groups (PPT 8.8 ± 1.0%; BBT 8.9 ± 1.1%; $P = 0.598$). Significant decreases in mean A1C values were observed within 6 weeks of therapy initiation for both groups ($P < 0.001$), and A1C continued to decline throughout the duration of the study. At study end (24 weeks), mean A1C was reduced from baseline by 1.87% in the PPT group to 6.95% and by 2.09% in the BBT group to 6.78% ($P = 0.021$ for comparison of end point A1C values) (Fig. 1*A*). The difference in A1C change from baseline to end point (BBT minus PPT) was −0.22%, with a 90% CI of −0.38 to −0.07 (Fig. 1*A*). The protocol-specified lower limit of the CI required for noninferiority was −0.3%. Thus, noninferiority of PPT was not demonstrated.

The cumulative percentage of patients across A1C values was analyzed. At baseline, the distribution was similar between the two groups (data not shown). By visit 4 (12 weeks), the BBT group began to show a trend toward a greater number of patients achieving target A1C values of <7.0 and ≤6.5% (data not shown). This trend became statistically significant by the study conclusion; 101

Table 2—*Incidence and rate of symptomatic hypoglycemia in patients receiving PPT versus BBT*

Type of symptomatic hypoglycemia	PPT	BBT	*P*
Overall hypoglycemia			
Incidence	169 (90.37)	166 (88.77)	0.736
Rate (number of episodes · patient^{-1} · year^{-1})	51.20 ± 50.08	48.70 ± 48.41	0.619
Nocturnal hypoglycemia			
Incidence	109 (58.29)	110 (58.82)	1.000
Rate (number of episodes · patient^{-1} · year^{-1})	4.78 ± 7.15	6.17 ± 10.68	0.139
Severe hypoglycemia			
Incidence	6 (3.21)	4 (2.14)	0.751
Rate (number of episodes · patient^{-1} · year^{-1})	0.10 ± 0.65	0.04 ± 0.31	0.266
Hypoglycemia confirmed by PG values			
PG <72 mg/dl (<4.0 mmol/l)			
Incidence	165 (88.24)	165 (88.24)	1.000
Rate (number of episodes · patient^{-1} · year^{-1})	46.50 ± 48.00	44.95 ± 46.80	0.747
PG <60 mg/dl (<3.3 mmol/l)			
Incidence	148 (79.14)	150 (80.21)	0.898
Rate (number of episodes · patient^{-1} · year^{-1})	20.75 ± 26.86	19.26 ± 24.51	0.574
PG <50 mg/day (<2.8 mmol/l)			
Incidence	104 (55.61)	115 (61.50)	0.294
Rate (number of episodes · patient^{-1} · year^{-1})	7.34 ± 12.88	5.93 ± 9.92	0.230

Data are means ± SD or *n* (%) unless otherwise indicated. PG, plasma glucose.

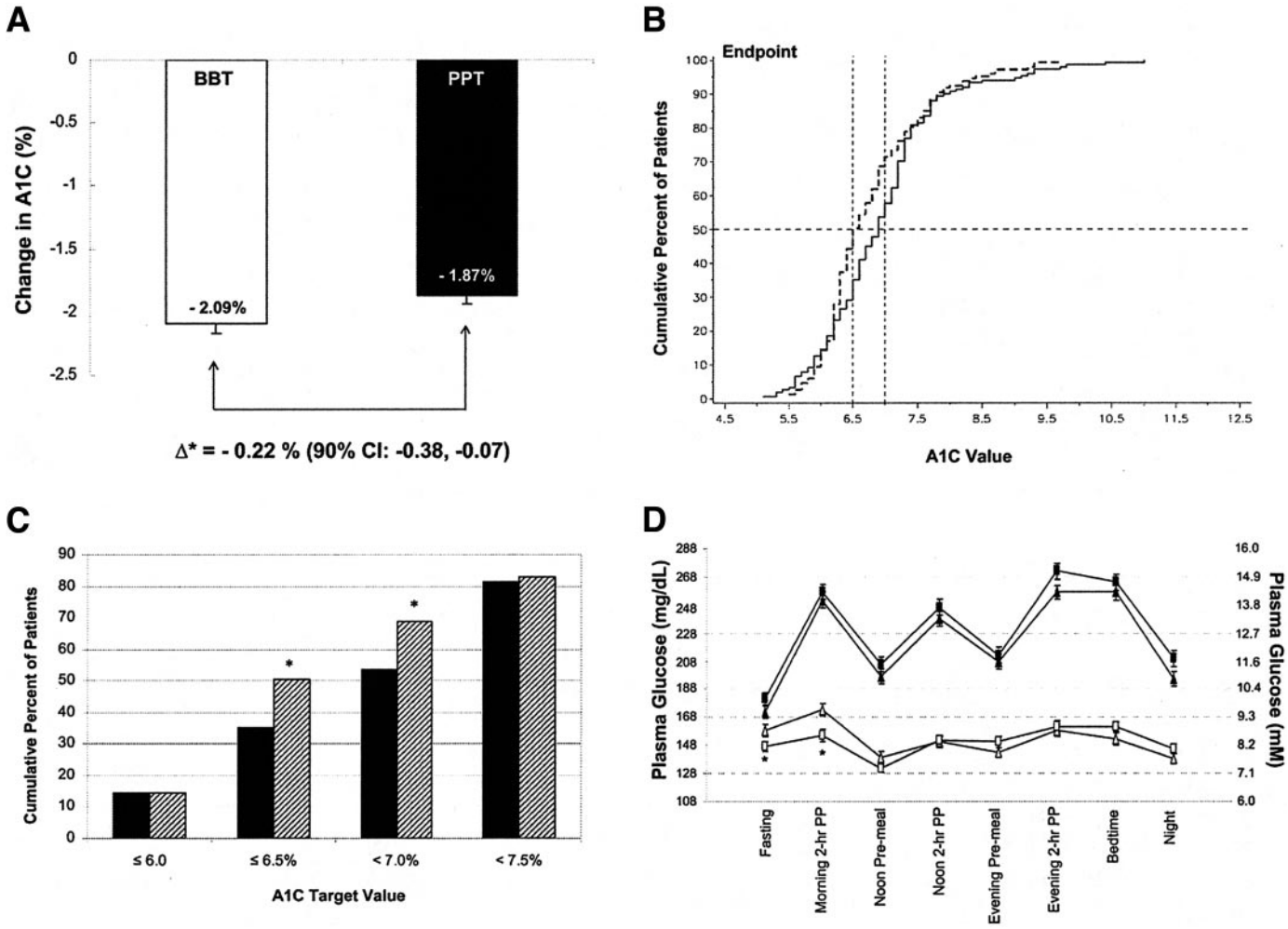

Figure 1—A: *Change in mean A1C ± SEM from baseline to end point for the BBT (□) and PPT (■) groups and the difference (BBT − PPT) in A1C change, with the 90% CI.* B: *Distribution of the cumulative percentage of patients across A1C values after 24 weeks of treatment with PPT (——) or BBT (– – –).* C: *Cumulative percentage of patients achieving specific target A1C values after 24 weeks of treatment with PPT (■) or BBT (▨).* *P < *0.05.* D: *SMPG 8-point profiles at baseline and end point for patients treated with PPT (▲, baseline; △, end point) or BBT (■, baseline; □, end point).* *P < *0.05 for comparison of end point values between treatment groups. PP, postprandial.*

patients (69%) in the BBT group achieved an A1C <7.0% vs. 81 patients (54%) in the PPT group, whereas 74 patients (50%) in the BBT group achieved an A1C ≤6.5% vs. 53 patients (35%) in the PPT group (Fig. 1*B*). High percentages of patients receiving both insulin regimens were able to achieve an A1C <7.5% (BBT 83%; PPT 82%). The percentage of patients at specific A1C values is shown in Fig. 1*C*. Two patients in the PPT group and none in the BBT group had an A1C ≥10% at 24 weeks.

SMPG 8-point profiles, collected at baseline and end point, are shown in Fig. 1*D*. Both therapies significantly reduced plasma glucose values from baseline at all time points measured. End point profiles collected were similar between the two groups at all time points except fasting and morning 2-h postprandial, for which BBT produced significantly lower plasma glucose (147 ± 43 mg/dl [8.2 ± 2.4 mmol/l] vs. 159 ± 55 mg/dl [8.8 ± 3.0 mmol/l], $P = 0.013$; and 155 ± 53 mg/dl [8.6 ± 3.0 mmol/l] vs. 174 ± 56 mg/dl [9.6 ± 3.1 mmol/l], $P = 0.002$).

Insulin dose and weight gain

At study entry, patients had similar total daily glargine doses (PPT 52 ± 24 units [0.5 ± 0.2 units/kg]; BBT 55 ± 28 units [0.6 ± 0.3 units/kg]) (Table 1). At the end of the study, the mean TDI dose was significantly greater for the BBT group (146 ± 85 units [1.4 ± 0.8 units/kg] vs. the PPT group (123 ± 69 units [1.2 ± 0.5 units/kg]; $P = 0.002$). In the BBT group, 48% of the TDI dose was administered as glargine and the remainder was lispro. By the study end, 87 patients (55%) in the PPT group were switched from an evening meal injection of lispro mix 50/50 to lispro mix 75/25. There was no difference in end point FPG between patients who continued to receive the lispro mix 50/50 and those who were switched to lispro mix 75/25 (160 ± 45 mg/dl [8.9 ± 2.5 mmol/l] vs. 158 ± 62 mg/dl [8.8 ± 3.4 mmol/l]; $P = 0.862$). The mean end point A1C was reduced significantly from baseline for both groups but was lower in the group of patients who were switched than in those who were not switched (6.9 vs. 7.1%; $P = 0.032$). Patients in the PPT and BBT groups experienced similar weight gains (PPT 4.0 ± 4.2 kg; BBT 4.5 ± 4.4 kg; $P = 0.224$).

Safety: hypoglycemia and adverse events

During the study, there was no difference between groups in the rate or incidence of

overall, nocturnal, or severe hypoglycemia or in any hypoglycemia confirmed by plasma glucose (Table 2). The incidence (patients with at least one self-reported episode) of overall hypoglycemia was ~90% for both regimens. However, rates (number of episodes per patient per year) of severe hypoglycemia were very low (BBT 0.05 ± 0.31; PPT 0.10 ± 0.65; P = 0.266).

There were a total of 9 serious adverse events (SAEs) reported in the PPT group and 13 in the BBT group, and no difference in the incidence of SAEs (6 [3.2%] for PPT vs. 9 [4.8%] for BBT; P = 0.600). No SAEs were identified as potentially being related to the study drug other than hypoglycemia (one event: BBT group).

CONCLUSIONS — We report the first head-to-head comparison of two basal/prandial insulin analog regimens (PPT versus BBT) designed to optimize glycemic control in type 2 diabetic patients previously treated with insulin glargine plus oral agents. The difference in A1C change from baseline to end point (BBT minus PPT) was −0.22% (90% CI −0.38 to −0.07); thus, noninferiority of PPT to BBT was not demonstrated based on a prespecified noninferiority margin of 0.3%. More patients in the BBT group reached A1C targets of <7.0 and ≤6.5%; however, mean end point A1C values for both groups were <7.0%. The slightly lower A1C results in the BBT group compared with the PPT group may be partially accounted for by the significantly lower FPG and morning 2-h postprandial plasma glucose results observed in the BBT group. This result may have reflected the lack of prior clinical experience with titration of lispro mix 50/50.

Both insulin regimens caused a modest weight gain of 4–5 kg in conjunction with significant A1C reduction. Intensive insulin therapy is also known to be associated with hypoglycemia, although severe events are infrequent in type 2 diabetes (11,24). This study, using downloadable glucose meter data and patient diaries to capture any occurrence of hypoglycemia, showed that with both insulin regimens the majority of patients experienced at least one episode of self-reported hypoglycemia. In contrast, among all patients, there was a maximum of 6 nocturnal events and 0.1 severe event per patient per year.

Clinical studies have been conducted to compare PPT with basal insulin therapy, and other studies have evaluated the safety and efficacy of BBT, but trials evaluating the efficacy of three-times-daily PPT in type 2 diabetic patients previously treated with insulin are few (12,15), as are analog BBT studies (17,18). Differences in insulin titration algorithms and glycemic targets may limit potential theoretical comparisons with these studies. Furthermore, previous trials assessing the efficacy of PPT in type 2 diabetic patients have not used BBT as a comparator.

A recent 24-week, parallel-group study by Robbins et al. (15), compared overall glycemic control with lispro mix 50/50 three times daily (plus metformin) to once daily glargine (plus metformin) in type 2 diabetic patients previously treated with OHAs (metformin and/or sulfonylureas) and zero to two daily insulin injections. The end point mean A1C for the lispro mix 50/50 group was similar to our PPT value (7.1 and 6.9%, respectively). The change in A1C from baseline observed in our PPT group (−1.87%) was larger than the comparable value in the lispro mix 50/50 group (−0.7%). However, it should be noted that the Robbins et al. study had a 6-week lead-in period in which patients received twice-daily lispro mix 75/25 and metformin, which may have resulted in a lower baseline A1C of 7.8%.

Glycemic control using once-, twice-, or thrice-daily injections of biphasic insulin aspart 70/30 (NovoLog Mix 70/30) was assessed in type 2 diabetic patients in whom OHA treatment with or without basal insulin has failed (The 1-2-3 Study) (12). Treatment with biphasic insulin aspart 70/30 once daily for 16 weeks was started, which was then progressed to twice daily for 16 weeks and finally to thrice daily for 16 weeks if A1C exceeded 6.5% at the end of any phase. Patients were considered completers if they attained target A1C by the end of a phase and were then withdrawn from the study. By combining all three phases, 77% of patients achieved a target A1C <7% at the end point. In the PPT arm of our study, 54% of patients achieved this target. However, the 1-2-3 Study was an uncontrolled, nonrandomized trial with no comparator arm and is therefore of limited comparison value owing to these important methodological limitations. In addition, loss of glycemic control over time would not have been reflected in completer populations of the 1-2-3 Study because of withdrawal of patients upon achievement of the target A1C.

Other studies using basal/bolus insulin therapy (17,18) have demonstrated efficacy and safety findings similar to those observed in our trial. In a recent study, Bergenstal et al. (18) used BBT (glargine/glulisine) to test a premeal glucose pattern algorithm versus carbohydrate counting for dose adjustment of insulin glulisine (Apidra). Similar to our study, eligible subjects in the trial had type 2 diabetes inadequately controlled by previous insulin therapy plus OHAs, an average duration of diabetes of >10 years, and baseline BMI of 36.7 kg/m^2. These authors observed a 1.5–1.6% decrease in mean A1C from baseline to end point (8.2 to ~6.6%, respectively). Together with our study, these findings support the fact that patients with a longer duration of disease and higher BMI require large TDI doses (>1.0 unit/kg) to achieve targeted glycemic goals. Herman et al. (17) compared BBT (glargine/lispro) to a continuous subcutaneous insulin infusion using insulin lispro in older adults with type 2 diabetes. That study demonstrated a safety profile for the BBT group similar to what we observed for BBT patients in our trial (90% of the BBT patients in their study experienced at least one episode of self-treated hypoglycemia, with a rate of 0.23 severe event per person-year).

Potential limitations of the current study include the open-label design, the possibility that the glargine dose before the study entry was not optimized, and the chance that insulin doses were more aggressively titrated in the BBT arm than in the PPT arm. It should be noted that the average daily prestudy glargine dose for patients in our study was ≥53 units (0.53 unit · kg^{-1} · day^{-1}), which is higher than the optimized glargine therapy reported previously (47 units/day or 0.48 unit · kg^{-1} · day^{-1}) (6). Dose titration might have been more aggressive in the BBT group because of greater investigator familiarity with adjustment of BBT. This familiarity could explain the significantly higher insulin doses administered in the BBT arm, which would have favored glycemic outcomes for this group. However, data on how individual investigators titrated insulin in their patients were not collected, so this suggestion remains speculative.

Both insulin regimens demonstrated a clinically meaningful ability to improve glycemic control, although, based on the prespecified margin, noninferiority of PPT compared with BBT was not demonstrated. This study assessed multiple factors that need to be considered in the

individual decision-making process of selecting PPT versus BBT for type 2 diabetic patients requiring insulin advancement, such as the magnitude of desired A1C reduction from baseline, the percentage of patients achieving specific A1C targets, the incidence and severity of hypoglycemia, and the number of required injections. BBT was associated with a greater reduction in A1C from baseline and a larger proportion of patients who achieved A1C targets of <7.0 and $\leq 6.5\%$. However, both PPT and BBT (in combination with OHAs) can effectively lower A1C levels to $<7\%$ in patients with type 2 diabetes who have previously been treated with insulin glargine plus OHAs.

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