Initiation and Gradual Intensification of Premixed Insulin Lispro Therapy Versus Basal ± Mealtime Insulin in Patients With Type 2 Diabetes Eating Light Breakfasts

Dario Giugliano,[1] Mariusz Tracz,[2] Sanjiv Shah,[3] Alfonso Calle-Pascual,[4] Cristina Mistodie,[5] Rui Duarte,[6] Ramazan Sari,[7] Vincent Woo,[8] Alina O. Jiletcovici,[9] Jürgen Deinhard,[10] Simone A. Wille,[11] and Jacek Kiljański[12]

OBJECTIVE

We compared two strategies initiating and intensifying insulin treatment and tested for noninferiority of premixed insulin to basal ± mealtime insulin analog in patients eating light breakfasts.

RESEARCH DESIGN AND METHODS

This randomized, open-label, 48-week study compared two algorithms. Up to three injections of insulin lispro mix 25 and/or insulin lispro mix 50 (premix; premixed insulin lispro) or basal insulin glargine plus up to three injections of insulin lispro (basal+; glargine + insulin lispro) were used in type 2 diabetic patients uncontrolled with oral antihyperglycemic medication and consuming <15% daily calories at breakfast. The hypothesis was to test noninferiority of premix to basal+ for glycemic control measured by HbA_{1c} after 48 weeks, assessed using ANCOVA with a 0.4% margin.

RESULTS

Patients (*n* = 344; 176 [51%] females; mean [SD] age 54.3 [8.8] years; BMI 29.4 [4.6] kg/m^2; baseline HbA_{1c} 9.02 [0.97]%) were randomized to premix (*n* = 171) or basal+ (*n* = 173). In the per-protocol analysis (*n* = 230), least squares means (95% CI) end point HbA_{1c} were 7.40% (7.15–7.65) and 7.55% (7.27–7.82) in respective arms. Between-treatment difference was −0.14% (−0.42 to 0.13), with noninferiority met. Significantly more patients in premix achieved HbA_{1c} targets of <7.0% compared with basal+ (48.2 vs. 36.2%; *P* = 0.024). Self-monitored blood glucose profiles, body weight changes, total insulin doses, and overall hypoglycemia (65 vs. 60%) were similar in premix and basal+ (*P* = 0.494), except nocturnal episodes (34.3 vs. 23.7%; *P* = 0.018) were more common in premix.

CONCLUSIONS

Both intensive insulin strategies improved glycemic control; however, final HbA_{1c} levels were seen above those achieved in previous treat-to-target trials, likely due to the inadequate insulin titrations and probably due to the complexity of tested insulin regimens. A higher percentage of patients achieved target HbA_{1c} <7% with multiple premixed insulins, but this treatment resulted in more nocturnal hypoglycemia than a basal–bolus regimen.

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[1]Department of Geriatrics and Metabolic Diseases, Second University of Naples, Naples, Italy
[2]Department of Gastroenterology and Metabolic Diseases, Medical University, Warsaw, Poland
[3]Diabetes Action Centre, Mumbai, India
[4]Hospital Clinico San Carlos, Servicio Endocrinologia, Madrid, Spain
[5]Spitalul Clinic Judetean de Urgenta "Sf. Apostol Andrei" Galati, Galati, Romania
[6]Associacao Dos Diabeticos de Portugal, Lisboa, Portugal
[7]Faculty of Medicine, Akdeniz University, Antalya, Turkey
[8]University of Manitoba Health Sciences Center, Winnipeg, Manitoba, Canada
[9]Diabetes Medical Affairs Europe, Eli Lilly and Company, Bucharest, Romania
[10]Accovion GmbH, Eschborn, Germany
[11]Diabetes Medical Affairs Europe, Eli Lilly and Company, Vienna, Austria
[12]Diabetes Medical Affairs Europe, Eli Lilly and Company, Warsaw, Poland

Corresponding author: Dario Giugliano, dario.giugliano@unina2.it.

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Eating light breakfast or even skipping it altogether is an increasingly common dietary habit among children and adults in the U.S., Europe, Middle East Asia, the Persian Gulf, and Japan (1–5). It has been demonstrated in various ethnic groups that skipping breakfast may be associated with obesity (4–7), increased visceral fat, and increased prevalence of diabetes mellitus (5).

Limited data are available about the dietary habits in patients with type 2 diabetes mellitus initiating insulin treatment. Studies in patients with type 1 diabetes report that eating practices are remarkably resistant to change, even in younger patients who initiate insulin therapy (8). Most people choose the same kinds of food because of their preferences and meal routines developed during childhood (9,10). Many patients with type 2 diabetes may therefore continue to consume light breakfasts or skip breakfasts, which could have considerable metabolic consequences. In patients with diabetes, skipping breakfast is associated with poorer metabolic control (11,12) and may increase the risk of hypoglycemia in the morning hours if conventional insulin therapy is applied. There is also evidence that patients who skip breakfast altogether increase food intake with other meals and snacks, which may contribute to poorer glycemic control (13,14), but consequences of eating light breakfasts in patients with diabetes are not well studied. The individual needs of these patients should be considered in treatment decisions leading to individualized therapy models to achieve glycemic targets safely.

So far, no studies have been reported that evaluate insulin treatment strategies in type 2 diabetic patients routinely consuming light breakfasts. We report the results of a noninferiority trial comparing two strategies of initiating and gradually intensifying insulin therapy in this group of patients: premixed insulin lispro (premix arm) versus basal insulin glargine therapy ± mealtime insulin lispro (basal+ arm).

RESEARCH DESIGN AND METHODS

This was a multicountry, multicenter, randomized, open-label, active-controlled, parallel 48-week trial. The study was conducted in accordance with the ethical principles that originated in the Declaration of Helsinki and consistent with good clinical practices and applicable laws and regulations of participating countries. All patients gave written informed consent.

Patients

Patients with type 2 diabetes aged 30–74 years with HbA_{1c} ≥7% (≥53 mmol/mol) and <11.0% (<97 mmol/mol) who had BMIs ≤40 kg/m^2 and were treated with metformin and at least one other oral antihyperglycemic medication (OAM; sulfonylureas and/or thiazolidinediones) for at least 3 months before the study were enrolled if they routinely consumed <15% of their daily caloric intake at breakfast (5:00–10:00 A.M.) based on their routine practice (15), confirmed by 1-day dietary recall. Exclusion criteria were treatment with other glucose-lowering medications or with pioglitazone at doses higher than approved for combination with insulin, having more than one episode of severe hypoglycemia within 6 months, use of systemic glucocorticoids, advanced cardiac disease, history of renal transplantation, liver disease, active malignancy, or conditions affecting reliability of HbA_{1c} assessment. Patients were also excluded if during screening they had a self-monitored blood glucose (SMBG) reading ≤70 mg/dL (3.9 mmol/L) without a diet- or activity-related cause or both a fasting glucose and a before-dinner SMBG ≤130 mg/dL (7.2 mmol/L) for 3 nonconsecutive days.

Randomization and Interventions

After a 2-week screening period, patients were randomized (stratified by baseline HbA_{1c} ≤8.5 [≤69 mmol/mol] and >8.5% [>69 mmol/mol]) to either premixed insulin lispro (premix; 1, 2, or 3 injections of insulin lispro mix 25 [25% insulin lispro, 75% insulin lispro protamine suspension (ILPS; LM25)] and/or insulin lispro mix 50 [50% insulin, 50% ILPS (LM50)]) in one arm or basal insulin glargine ±1, 2, or 3 mealtime injections of insulin lispro (basal+) in another arm in a 1:1 ratio, using an interactive voice response system. In both arms, patients continued their prestudy OAM regimens except for rosiglitazone (discontinued at visit 1) and sulfonylurea (reduced or discontinued in the presence of hypoglycemia and stopped when the second injection of insulin was added). Dietary and lifestyle counseling and interventions were at the discretion of investigators.

After randomization, visits were scheduled at 2, 6, 10, 16, 20, 26, 32, 36, 42, and 48 weeks, and additional weekly contacts by telephone occurred between the visits for the first 12 weeks and then every second week to help patients adjust and optimize their insulin regimens.

Insulin Dosing Algorithm

Patients in both arms started treatment with a single insulin injection of 10 units of glargine in the morning or at bedtime (basal+ arm) or 10 units of either LM50 before lunch or LM25 before dinner (premix arm), depending on the higher 2-h postprandial blood glucose (BG) measures. Insulin doses were titrated according to the dosing algorithm (Table 1). In the premix arm, treatment could start with LM25 dose before dinner despite higher postlunch BG levels if fasting BG levels were ≥144 mg/dL (8.0 mmol/L). If the target of HbA_{1c} <7% (<53 mmol/mol) was not achieved after 16 or 32 weeks and/or 2-h postprandial BG target of <144 mg/dL (8.0 mmol/L) despite effective titration of existing doses, subsequent injections of insulin lispro or LM50/LM25 were added. In the basal+ arm, the initial insulin lispro dose equal to approximately 10% of the daily dose of glargine was added before either lunch or dinner depending on higher 2-h postprandial BG. In the premix arm, the previous total insulin lispro LM50/LM25 dose was split equally into two doses. Half of the dose was administered as LM50 before lunch and half as LM25 before dinner. Additional injections of insulin lispro (in basal+ arm) or LM25 (5 units in the premix arm) before breakfast could be added as a last step in the intensification process. LM25 before breakfast was replaced with LM50 if prelunch BG was high (although maintaining small breakfast) despite normal/low predinner BG values or hypoglycemia due to the protracted action of insulin developed. No additional insulin doses were to be

Table 1—Insulin dosing algorithm

LM25, LM50, and insulin lispro fasting/ predinner/prelunch BG mg/dL (mmol/L)	Dose change (units)	Glargine fasting BG mg/dL (mmol/L)
<55 (<3.0)	−4	
55–84 (3.0–4.6)	−2	<85 (<4.7)
85–114 (4.7–6.3)	0	85–114 (4.7–6.3)
115–144 (6.4–8.0)	+2	115–125 (6.4–6.9)
145–204 (8.1–11.3)	+4	126–145 (7.0–8.0)
>204 (>11.3)†	+6	146–165 (8.1–9.1)
	+8	≥166 (≥9.2)

Dose adjustments were based on the average of the following SMBG values: fasting BG to adjust doses of glargine and predinner LM25; fasting, bedtime, or other lowest BG (at investigator's discretion) to adjust predinner insulin lispro dose; predinner and prelunch BG values to adjust prelunch and prebreakfast doses of insulin lispro and LM25 and LM50, respectively. †Applicable to initial dose adjustment for LM25/LM50 in premix arm.

introduced within 4 weeks after the last dose adjustment or in the last 12 weeks before study end, even if previous insulin dose was still unstable.

Efficacy and Safety Measures

The primary objective was to test the hypothesis that the premix treatment provides noninferior glycemic control compared with the basal+ regimen based on the HbA_{1c} at week 48 (adjusted on baseline HbA_{1c}, noninferiority margin of 0.4%). Secondary objectives included efficacy end points such as change in HbA_{1c}; proportions of patients achieving HbA_{1c} ≤6.5% (≤48 mmol/mol) and <7% (<53 mmol/mol); seven-point SMBG profiles; 1.5 anhydroglucitol levels reflecting postprandial BG levels over the period of 1–2 weeks (16); insulin dose; body weight change; and proportions of caloric intake consumed at breakfast, lunch, and dinner.

Safety end points included treatment-emergent adverse events (TEAEs) and self-reported hypoglycemic episodes (all, non-nocturnal, and nocturnal) defined as signs or symptoms associated with hypoglycemia or BG level of ≤75 mg/dL (4.2 mmol/L), International Federation of Clinical Chemistry (IFCC) plasma values corresponding to ≤70 mg/dL (3.9 mmol/L), Roche plasma glucose, irrespective of signs and symptoms (17). A severe hypoglycemic episode was defined as an episode requiring third-party assistance and associated with a BG level of <55 mg/dL (3.0 mmol/L); IFCC plasma values corresponding to <50 mg/dL (2.8 mmol/L); Roche plasma glucose; or prompt recovery after oral carbohydrate, glucagon, or intravenous glucose. We report in this article IFCC measures.

Health outcome measures were assessed by the EuroQol instrument (EQ-5D) (18) and the Diabetes Treatment Satisfaction Questionnaire (DTSQ) (19).

Statistical Analysis

The primary efficacy analysis was performed on the per-protocol (PP) population, which is defined as those patients completing the study with no major protocol violations. A linear regression model was fitted that included treatment, country, baseline HbA_{1c} (continuous), and a variable indicating whether Ramadan occurred between visits 10 and 12 as independent variables. The CI for the difference of HbA_{1c} between the two treatment arms (LS means of premix arm to basal+ arm) was based on a t distribution using the mean square error from the model. The noninferiority margin was defined as 0.4%. If the upper limit of the CI was below 0.4%, the premix arm was concluded to be noninferior to the basal+ arm.

Secondary efficacy analyses were performed on the full analysis set (FAS; all randomized patients with postbaseline HbA_{1c} measurements). For handling incomplete data, mixed-model repeated measures (MMRM) for continuous and generalized linear mixed models for discrete variables were used. CIs and *P* values at the visits were obtained from contrast analysis between treatment regimens. The continuous variables were analyzed using MMRM analysis similar to the one used for the HbA_{1c} changes. LS means for the two treatment regimens, differences, and *P* values for the difference were reported at visits from contrast analysis between the treatment regimens. For subgroup analysis, the same MMRM model was calculated by subgroup.

Changes of body weight from baseline to 48 weeks were analyzed by MMRM, including treatment, country, and baseline weight as independent variables. Safety analyses were performed on the safety population (patients treated with at least 1 dose), including hypoglycemic episodes, TEAEs, and body weight. Unless otherwise specified, statistical analyses to compare treatments for continuous and discrete data were performed using similar random-effects models as for secondary efficacy variables.

Incidence of hypoglycemia was analyzed by logistic regression and the rate of hypoglycemia per patient/year by ANCOVA, with baseline value, treatment, country, and Ramadan as explanatory factors.

EQ-5D scores were analyzed using MMRM. Patients' satisfaction with their diabetes therapy was evaluated by the DTSQ and summarized at week 48.

The planned overall sample size of 300 patients in the PP population had 80% power to confirm noninferiority at a one-sided significance level of 2.5% with a noninferiority limit of 0.4% (premix–basal+), using the upper limit of a two-sided 95% CI.

RESULTS

The trial was conducted in nine countries from April 2008 to November 2010. From 553 screened patients, 344 patients were recruited (*n*; %) from Brazil (13; 3.8), Canada (7; 2.0), Egypt (64; 18.6), India (58; 16.9), Mexico (71; 20.6), Portugal (15; 4.4), Romania (50; 14.5), Spain (40; 11.6), and Turkey (26; 7.6).

Patients were randomized to the premix (*n* = 171) or to the basal+ (*n* = 173)

treatment arm (patient flow available in Supplementary Fig. 1). Altogether, 342 treated patients (premix 169, basal+ 173) were included in the safety set, 321 patients (premix 158, basal+ 163) in the FAS, and 230 patients (premix 119, basal+ 111) in the PP set. Overall, 74 patients (22%) discontinued the study (premix 33 [19]%, basal+ 41 [24]%). No relevant differences in patient demographics and baseline characteristics were observed between treatment groups (Table 2).

Table 2—Patient baseline demographics (randomized patients)

	Premix (*n* = 171)	Basal+ (*n* = 173)	Overall (*n* = 344)
Age, years	54.3 (8.9)	54.2 (8.6)	54.3 (8.8)
Median (range)	54.9 (31–75)	54.3 (30–74)	54.8 (30–75)
>65 years, *n* (%)	24 (14)	17 (10)	41 (12)
Sex, *n* (%)			
Female	84 (49)	92 (53)	176 (51)
Male	87 (51)	81 (47)	168 (49)
Race, *n* (%)			
Caucasian	101 (59)	97 (56)	198 (58)
African	1 (0.6)	2 (1)	3 (1)
Hispanic	40 (23)	44 (25)	84 (24)
Asian	29 (17)	30 (17)	59 (17)
Weight, kg	79.7 (15.6)	78.7 (16.8)	79.2 (16.2)
BMI, kg/m^2	29.6 (4.7)	29.1 (4.5)	29.4 (4.6)
Median (range)	29.4 (20–40)	28.9 (20–40)	29.3 (20–40)
HbA_{1c}, %	8.98 (0.95)	9.07 (0.99)	9.02 (0.97)
HbA_{1c}, mmol/mol	75	76	75
Median (range), %	9.00 (7.0–11.0)	9.20 (7.0–11.0)	9.10 (7.0–11.0)
Median (range), mmol/mol	75 (53–97)	77 (53–97)	76 (53–97)
HbA_{1c} >8.5% (>69 mmol/mol), *n* (%)	109 (63.7)	111 (64.2)	220 (64.0)
GlycoMark test, μg/mL	5.7 (4.5)	6.3 (5.8)	6.0 (5.2)
Fasting BG, mmol/L*	9.4 (2.2)	9.6 (2.2)	9.5 (2.2)
Postprandial BG levels, mmol/L*			
After breakfast	12.0 (2.8)	12.6 (2.8)	12.3 (2.8)
After lunch	11.9 (2.8)	12.2 (2.9)	12.0 (2.8)
After dinner	12.2 (2.7)	12.2 (3.2)	12.2 (2.9)
Total caloric intake, kcal			1,704 (456)
At breakfast	294 (254)	278 (199)	286 (227)
Proportion at breakfast, %	14 (16)	13 (13)	13 (15)
At lunch	832 (331)	822 (318)	827 (324)
At dinner	572 (281)	597 (255)	585 (268)
Concomitant OAM, *n* (%)			
Metformin	167 (97.7)	171 (98.8)	338 (98.3)
Sulfonylurea	157 (91.8)	164 (94.8)	321 (93.3)
Thiazolidinedione	26 (15.2)	24 (13.9)	50 (14.5)
Dipeptidyl peptidase-4 inhibitor**	1 (0.6)	4 (2.3)	5 (1.5)
Daily dose of OAM, mg			
Metformin	2,011 (448)	1,922 (437)	1,966 (444)
Sulfonylurea (gliclazide)	103 (42)	94 (43)	99 (42)
Sulfonylurea (glimepiride)	4.8 (1.4)	4.6 (1.4)	4.7 (1.4)
Sulfonylurea (glibenclamide)	13.1 (3.76)	13.2 (3.45)	13.1 (3.57)
Pioglitazone*	28.8 (7.25)	28.1 (7.49)	28.4 (7.33)

Data are presented as mean (SD) unless otherwise indicated. *From SMBG reading. **Protocol violation.

Treatment Regimen

At the visit after initiation, the majority of patients (105; 66.5%) in the premix arm followed the LM25 injection before dinner scheme and 45 patients (28.5%) with the LM50 injection before lunch scheme. Eight patients (5%) could not be classified into one of the treatment arms. At study end, mean (SD) number of insulin injections was 1.96 (0.829) and 1.99 (1.060) in the premix and basal+ arms, respectively. The number of insulin injections is shown in Supplementary Table 1. In the premix arm, all patients needed LM50 at lunch and LM25 at dinner, and fewer patients needed some insulin at breakfast (Supplementary Table 2). Mean (SD) total daily insulin dose for the premix and basal+ arms at week 48 was 0.56 (0.32) and 0.57 (0.39) units/kg, respectively (P = 0.774). Basal insulin dose was 0.37 (0.21) and 0.39 (0.21) units/kg (P = 0.235), and the rapid-acting insulin analog dose was 0.20 (0.12) and 0.18 (0.23) units/kg (P = 0.414), respectively. Treatment compliance as observed by the investigator throughout the study was premix 82.3% and basal+ 86.5% (P = 0.580).

Glycemic Control

LS mean HbA_{1c} at end point was 7.40% (95% CI 7.15–7.65) in the premix arm (n = 119) and 7.55% (95% CI 7.27–7.82) in the basal+ arm (n = 111); the between-treatment difference was −0.14% (95% CI −0.42 to 0.13), thus confirming the primary hypothesis of noninferiority of premix versus basal+. These results were confirmed in the FAS population. The mean (SD) HbA_{1c} at baseline was 8.93 (0.94)% in the premix arm and 9.08 (0.99)% in the basal+ arm, and the values at end point were 7.27 (1.16)% in the premix arm and 7.49 (1.18)% in the basal+ arm (FAS with last observation carried forward). The baseline-adjusted LS mean HbA_{1c} at end point was 7.40% (95% CI 7.20–7.60) in the premix arm and 7.58% (95% CI 7.38–7.78) in the basal+ arm; the between-treatment difference was −0.18% (95% CI −0.42 to 0.07; P = 0.155). The LS mean (SEM) HbA_{1c} change from baseline to week 48 was not significantly different between both arms (premix −1.65 [0.10]% and basal+ −1.57 [0.10]% HbA_{1c}; P = 0.556; Supplementary Fig. 2). The mean change within the groups was statistically significant different, with $P < 0.001$. Significantly more patients in the premix arm achieved HbA_{1c} targets of <7.0% compared with the basal+ arm (48.2 vs. 36.2%; odds ratio = 1.87; P = 0.024), and 24.8% patients in the premix arm achieved target HbA_{1c} ≤6.5% compared with 18.5% patients in the basal+ arm (odds ratio = 1.59; P = 0.138; Fig. 1). No difference was seen in HbA_{1c} change

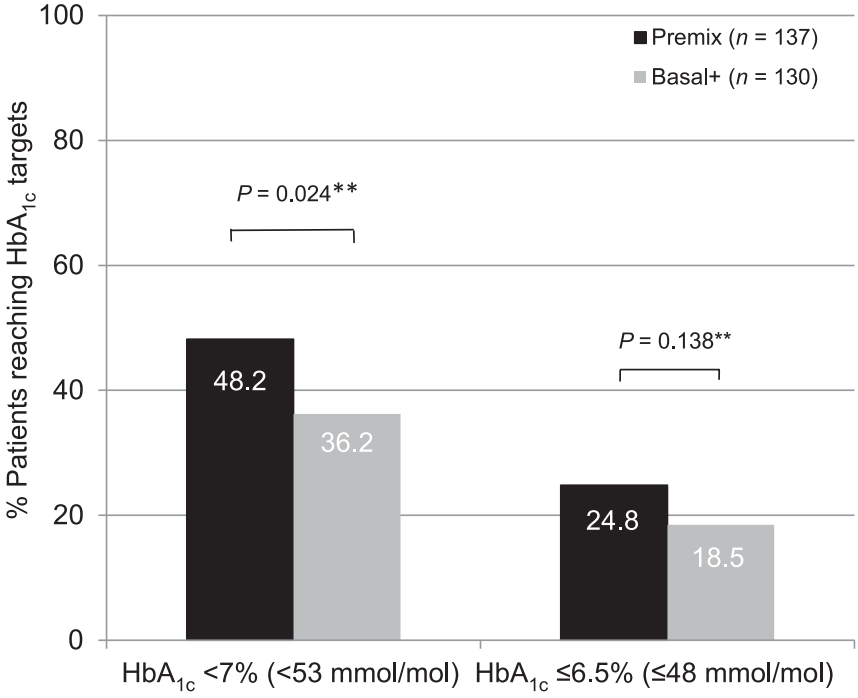

Figure 1—Percentage of patients reaching HbA_{1c} targets at week 48 (FAS; only patients attending the 48-week visit were taken into account). ***P* values derived from the generalized mixed model.

from baseline between both treatment arms for patients with a baseline HbA_{1c} level below or above 8.5%. Proportions of patients achieving HbA_{1c} targets with different final treatment regimens are presented in Fig. 2. At week 48, the mean (SD) daily BG level from SMBG was premix 7.26 (1.34) mmol/L and basal+ 7.30 (1.24) mmol/L ($P = 0.579$). Mean (SD) seven-point SMBG values are presented in Fig. 3, with the only statistically significant difference between arms at postdinner SMBG readings ($P = 0.001$). Levels of 1.5 anhydroglucitol at 48 weeks were 11.4 and 10.9 μg/mL in the premix and basal+ arms, respectively ($P = 0.104$).

Body Weight and Caloric Intake

Body weight increased by a mean (SD) 2.31 (3.3) kg in premix and by 2.32 (3.7) kg in basal+ ($P = 0.819$) at 48 weeks. The self-reported mean (SD) total daily caloric consumption at week 48 was premix 1,656 (426) kcal and basal+ 1,693 (411) kcal ($P = 0.411$). Breakfast constituted 15 and 13% of the total caloric intake, lunch 48% for both arms, and dinner 33 and 35% of the total for premix and basal+, respectively.

Health outcomes measures improved statistically significantly in both arms ($P < 0.001$). The mean baseline DTSQ score was 29 in both arms, and at 48 weeks, the scores had increased by mean (SD) 5 (9) in the premix arm and 5 (7) in the basal+ arm; the EQ-5D health state score increased from a mean (SD) baseline value of 73 (17) and 75 (15) by 8 (17) and 6 (15), respectively.

Hypoglycemia

Incidences and rates (episodes/patient/year) of all categories of hypoglycemia studied are shown in Table 3. Patients on glargine +3 injections of insulin lispro had the lowest chance to develop hypoglycemia over time (Supplementary Fig. 3). Nocturnal hypoglycemia was reported more frequently in the premix arm. However, proportions of patients in the premix arm reaching glycemic targets without nocturnal hypoglycemic events were not statistically different compared with the basal+ arm (40 [29]% patients and 8 [6]% patients reaching $HbA_{1c} < 7$ and ≤6.5%, compared with 26 [20]% and 4 [3]% patients, respectively; $P = 0.104$ and $P = 0.300$). Three patients (two in the premix arm and one in the basal+ arm) required hospitalization because of hypoglycemia, and one patient in the premix arm had a hypoglycemic episode treated in the emergency room. No coma associated with hypoglycemia was reported.

Adverse Events

A total of 32% of patients in each arm (54 in premix, 55 in basal+) reported at least one TEAE. Most TEAEs were unrelated to the insulin treatment. Seven (4.1%) and three (1.7%) patients in the premix and basal+ arms, respectively, reported serious TEAEs occurring once. No deaths occurred.

CONCLUSIONS

This is the first trial to evaluate two strategies of initiating and advancing insulin treatment in patients with type 2 diabetes who have a habit of eating light breakfasts. Both strategies (premixed insulin analog versus basal insulin with or without mealtime rapid-acting analog) started with a single injection of insulin and advanced to a more complex regimen if HbA_{1c} and/or postprandial BG targets were not met. The current study showed a significant improvement in glycemic control with both of the two strategies. Mean HbA_{1c} decreased significantly in both arms, from 9% (75 mmol/mol) to 7.4% (57 mmol/mol) and 7.6% (60 mmol/mol) in the premix and basal+ arms, respectively. Significantly more patients from premix arm achieved the glycemic target of <7.0% (<53 mmol/mol). In both arms, observed proportions of patients reaching treatment targets were highest among patients using one or two injections (Fig. 2). We observed similar proportions of patients meeting the HbA_{1c} target of <7.0% (<53 mmol/mol) with insulin glargine +1 injection of insulin lispro compared with patients with two or three injections of premixed insulin lispro. Notably, the observed proportions of patients reaching targets appeared to be lower among those who used the highest number of insulin lispro injections at end point, and these patients had the lowest chance to develop hypoglycemia over time. This could reflect the difficulty following a more complex treatment regimen, the reluctance to titrate insulin more aggressively, or some other factors

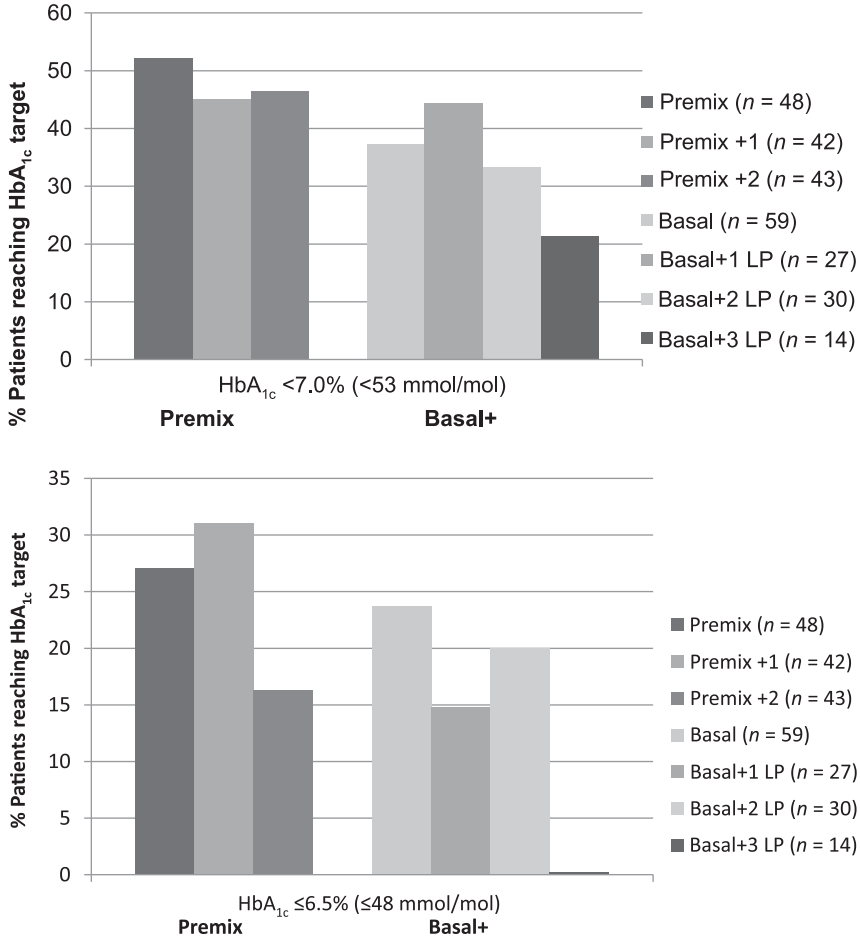

Figure 2—Proportion of patients reaching target HbA_{1c} <7.0 and ≤6.5% by final treatment regimen (FAS; only patients attending the 48-week visit were taken into account). LP, insulin lispro.

making successful treatment in this subgroup more difficult.

Incidence and rates of overall and daytime hypoglycemia were similar in both arms; however, the incidence of nocturnal hypoglycemia was higher with premixed insulin analog treatment.

Treatment options for patients with type 2 diabetes who have a habit of eating light breakfasts and require insulin therapy have not been evaluated in clinical trials so far. Therapeutic recommendations given to these patients have to be based on results of clinical studies conducted in general populations, which tend to exclude patients with atypical dietary habits. The proposed strategies of gradual intensification of insulin treatment begin with the simplest once-daily injection model and proceed to more complex multiple daily injections treatment if targets are not met.

Starting insulin therapy with a single injection of basal insulin is a common way of initiating insulin therapy in patients with type 2 diabetes, taking into consideration that complexity of the injection regimen and the numbers of injections are a major concern and barrier to insulin therapy (20). A recent European Association for the Study of Diabetes/American Diabetes Association position statement recommends this approach for most patients as the optimal and most convenient option (21). An alternative approach is to initiate insulin therapy with premixed insulin analogs (22). Recent meta-analyses (23–25) comparing basal-only and premixed insulin strategies as first line insulin therapy in type 2 diabetes have indicated that treatment with premixed insulin formulations once daily results in a greater overall efficacy, but at the cost of increased hypoglycemia risk and weight gain.

There is no consensus on how therapy should be intensified in patients failing on either basal or premixed insulins (21). Targeting postprandial hyperglycemia with mealtime insulins is a logical choice in these patients, as high postmeal BG values significantly contribute to the overall glycemic burden (26). In patients on basal insulin only, addition of mealtime insulin before the main meal (basal+) is considered the most logical step (21,27). Stepwise escalation of this treatment with additional mealtime insulin doses was applied if target glycemic control was not achieved with the basal+ treatment regimen (28). In patients not achieving target glycemic control with one or two injections of premixed insulin, increasing the number of injections could further improve the glycemic control (29). Premixed insulin analog formulations with a higher proportion (e.g., 50%) of rapid-acting insulin seem to be particularly useful for the thrice-daily regimen in patients failing twice-daily premixed therapy (30) and in patients failing basal insulin (31).

Results of one head-to-head clinical trial indicated that both treatment strategies, progressive advancing therapy with premixed insulin lispro or basal plus mealtime insulin, significantly improved glycemic control with similar risk of overall and nocturnal hypoglycemia and similar weight gain (32). However, in contrast to our study, the noninferiority of the premixed insulin strategy to the basal glargine was not demonstrated. The findings from our study, using a stepwise insulin treatment intensification approach in patients with the habit of eating a light breakfast, indicated that patients were able to improve glycemic control comparable to results from other trials. Interestingly, studied patients did not modify their dietary habits and continued to consume light breakfasts.

In this trial, the prebreakfast injection of insulin was the last to be added. We found that at baseline, mean SMBG values after breakfast were actually not much different from the mean SMBG values after lunch and dinner. Whether

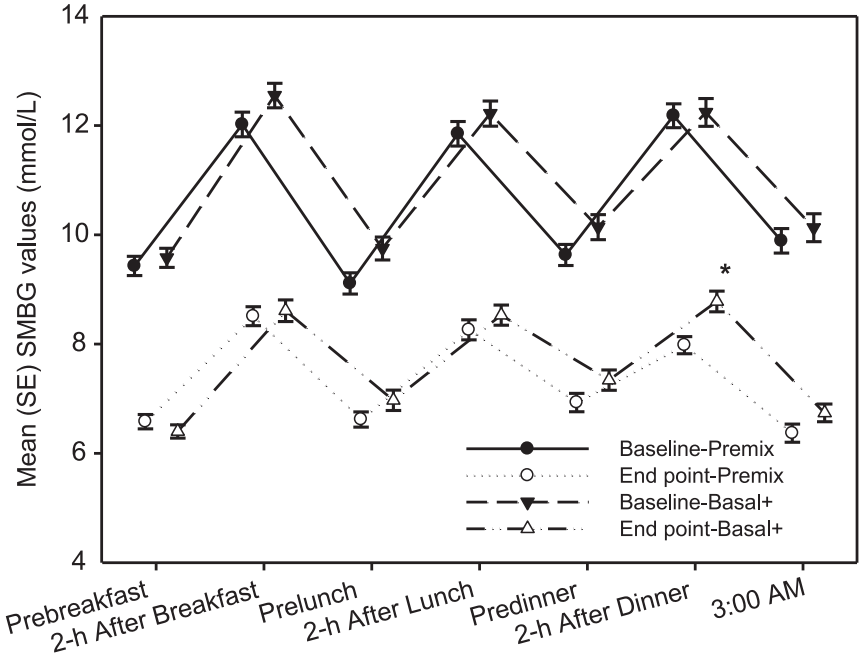

Figure 3—Mean (SE) seven-point SMBG values at baseline and week 48 (FAS; only patients attending the 48-week visit were taken into account). *P = 0.0012 between treatment arms at postdinner BG (MMRM analysis).

application of the first injections of premixed insulin or mealtime insulin before any of the three main meals, including breakfast, might result in similar improvement of glycemic control remains to be established. As expected for gradual insulin dose escalation strategies, the main drawback of the therapy was hypoglycemia, which was reported by 65 and 60% of patients in the premix and basal+ arms, respectively. The incidence of hypoglycemia in our study was comparable to or lower than previously reported from studies evaluating two approaches to intensify basal insulin treatment with up to three injections of mealtime insulin (28,33,34), gradual intensification of premixed insulin analog treatment (29,30,32), or intensification of treatment to basal–bolus therapy (30,32) in patients with type 2 diabetes. Event rates were lower than those reported in the recent meta-analysis by Giugliano et al. (23). The only difference in terms of safety between the two arms was nocturnal hypoglycemia occurring in more patients in premix arm. Incidence of all categories of hypoglycemia, however, was similar in the two arms.

Weight gain is typically associated with insulin therapy, and patients treated according to the algorithms defined in our study were no exception. Mean weight gain of 2.3 kg was observed after 48 weeks, which was higher in patients taking more injections of insulin per day than in patients using simpler treatment schemes. Body weight change seen in our study is comparable to the findings from Meneghini et al. (34) but either lower (23,28,32) or slightly greater (30,33) than in other trials. Final insulin doses exceeding 0.56 units/kg body weight per day are in line with those in other studies evaluating initial insulin therapy algorithms in type 2 diabetes. This dosage was delivered with a similar mean number of injections per day. Interestingly, final proportions of basal and mealtime insulin components were the same in both treatment arms, with approximately 2/3 of insulin delivered as basal and 1/3 delivered as mealtime insulin. This may explain why similar glycemic control was achieved in the two arms even though patients in the basal+ arm received fewer injections of mealtime insulin than patients in the premix arm.

There were several limitations to this study. Dietary habits were evaluated using a 24-h recall, which is less objective than a dietary record. Patients could underreport caloric intake. The forced-titration insulin regimens evaluated in this study might not be suitable in some clinical practice settings, as health care providers and patients may find frequent BG monitoring, frequent dose escalation, and treatment intensification too complex. Many patients in both study arms eventually used two different insulins, which added to the treatment complexity. All these factors might affect the ability to adhere to the treatment algorithm, explaining why notable proportions of patients continued treatment with simpler regimens (e.g., single injection) despite glycemic targets not being met. Another limitation of this trial was the use of fasting/preprandial BG targets higher than those validated in the treat-to-target trials. The use of these higher targets may have prevented effective titration of basal insulin glargine and caused disadvantage to the basal–bolus arm. This could also increase the proportion of patients requiring additional injections of mealtime insulin in this arm. The results of our study

Table 3—Hypoglycemia over the treatment period (safety set)

	Premix (n = 169)		Basal+ (n = 173)		
Types	Incidence, n (%)	Rate, mean (SD)	Incidence, n (%)	Rate, mean (SD)	P value, incidence/rate
All hypoglycemia	109 (64.5)	9.63 (19.31)	104 (60.1)	8.13 (13.45)	0.379/0.435
Nocturnal episodes	58 (34.3)	1.91 (5.20)	41 (23.7)	1.09 (3.25)	0.018/0.068
Non-nocturnal episodes	102 (60.4)	7.72 (16.36)	98 (56.6)	7.04 (12.12)	0.472/0.733
Severe episodes	4 (2.4)	0.09 (0.74)	6 (3.5)	0.12 (0.80)	—/0.852

All treated patients with at least one dose of study medication. Incidence is the number/percentage of patients with a least one event between baseline and study end. Rate is per episode/patient/1 year.

indicate that in patients with type 2 diabetes who have a habit of consuming light breakfast, starting insulin therapy with either premixed insulin analog or basal insulin administration and subsequently advancing the treatment could be used to improve glycemic control. Noninferiority was confirmed of premix versus basal+ in the change of HbA_{1c}. Both intensive insulin strategies improved glycemic control; however, final HbA_{1c} levels were seen above those achieved in previous treat-to-target trials, likely due to the inadequate insulin titrations and probably due to the complexity of tested insulin regimens. The percentage of patients at HbA_{1c} target $<7\%$ (<53 mmol/mol) was higher in the premix insulin analog arm, while the incidence of nocturnal hypoglycemia was lower in the basal+ arm. This warrants cautious use of premix treatment strategy in patients at high risk for hypoglycemia. These findings may provide useful guidance to adapt treatment to individual patient needs.

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Author Contributions. D.G., M.T., and A.O.J. contributed and reviewed critically INTRODUCTION, RESULTS, and CONCLUSIONS. S.S. contributed and reviewed critically INTRODUCTION, RESULTS, and CONCLUSIONS and was involved in the acquisition of data. A.C.-P., C.M., R.D., R.S., and V.W. were involved in the acquisition of data. J.D. performed the statistical analysis and contributed to RESEARCH DESIGN AND METHODS. S.A.W. drafted the manuscript. J.K. contributed and reviewed critically INTRODUCTION, RESULTS, and CONCLUSIONS and drafted the manuscript. All authors were involved in the interpretation of data, critical revision, and approval of the manuscript. J.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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