

Twice-daily pre-mixed insulin rather than basal insulin therapy alone results in better overall glycaemic control in patients with Type 2 diabetes

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Abstract

Aims To compare the glycaemic control of an insulin lispro mixture (25% insulin lispro and 75% NPL) twice daily in combination with metformin to that of once-daily insulin glargine plus metformin in patients with Type 2 diabetes inadequately controlled with intermediate insulin, or insulin plus oral agent(s) combination therapy.

Research design and methods Ninety-seven patients were randomized in a multicentre, open-label, 32-week crossover study. Primary variables evaluated: haemoglobin A_{1c} (A_{1c}), 2-h post-prandial blood glucose (BG), hypoglycaemia rate (episodes/patient/30 days), incidence (% patients experiencing ≥ 1 episode) of overall and nocturnal hypoglycaemia.

Results At endpoint, A_{1c} was lower with the insulin lispro mixture plus metformin compared with glargine plus metformin (7.54% ± 0.87% vs. 8.14% ± 1.03%, $P < 0.001$). Change in A_{1c} from baseline to endpoint was greater with the insulin lispro mixture plus metformin (−1.00% vs. −0.42%; $P < 0.001$). Two-hour post-prandial BG was lower after morning, midday, and evening meals ($P < 0.001$) during treatment with the insulin lispro mixture plus metformin. The fasting BG values were lower with glargine plus metformin ($P = 0.007$). Despite lower BG at 03.00 hours ($P < 0.01$), patients treated with the insulin lispro mixture plus metformin had a lower rate of nocturnal hypoglycaemia (0.14 ± 0.49 vs. 0.34 ± 0.85 episodes/patient/30 days; $P = 0.002$), although the overall hypoglycaemia rate was not different between treatments (0.61 ± 1.41 vs. 0.44 ± 1.07 episodes/patient/30 days; $P = 0.477$).

Conclusion In patients with Type 2 diabetes and inadequate glucose control while on insulin or insulin and oral agent(s) combination therapy, treatment with a twice-daily insulin lispro mixture plus metformin, which targets both post-prandial and pre-meal BG, provided clinically significant improvements in A_{1c}, significantly reduced post-prandial BG after each meal, and reduced nocturnal hypoglycaemia as compared with once-daily glargine plus metformin, a treatment that targets fasting BG.

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Keywords lispro mixture, glargine, oral agents, Type 2 diabetes

Abbreviations FBG, fasting blood glucose; A_{1c}, haemoglobin A_{1c}; BG, blood glucose; HPLC, high-performance liquid chromatography; MODD, mean of daily differences; ITT, intent-to-treat; LOCF, last observation carried forward

Introduction

Preventing or slowing the progression of diabetes-related complications is a major goal of diabetes management. Clinical investigations in patients with Type 1 or Type 2 diabetes have demonstrated that the development of long-term microvascular complications of diabetes and the level of glycaemic control are closely related [1–3]. Although not yet confirmed by prospective clinical trials, increasing evidence suggests that improving control of post-prandial blood glucose (BG) in patients with Type 2 diabetes may be associated with a reduced risk of macrovascular complications [4–6].

Patients with Type 2 diabetes treated with an oral agent as monotherapy (e.g. sulphonylurea or metformin) often will experience inadequate glycaemic control even when maintained at maximum doses. An effective approach to sulphonylurea therapy failure is to add metformin [7]. However, adding metformin to sulphonylurea therapy does not adequately control post-prandial hyperglycaemia, a well-recognized metabolic defect in Type 2 diabetes. When an acceptable level of glycaemic control cannot be achieved or maintained with oral agents, the addition of insulin therapy is a generally accepted treatment option. Alternatively, another approach is to add one of the newer oral agents, particularly a glitazone, although triple agent therapy is not licensed in all countries. In contrast to insulin therapy alone or insulin plus sulphonylurea, insulin therapy in combination with metformin is becoming increasingly popular. Adding an insulin that controls both post-prandial and pre-meal hyperglycaemia would be expected to provide a more physiologic blood glucose profile than the addition of basal insulin alone.

Insulin lispro, a rapid-acting insulin analogue, results in lower post-prandial BG levels and decreases the risk of nocturnal hypoglycaemia compared with regular human insulin [8,9]. A pre-mixed insulin containing 25% insulin lispro and 75% insulin lispro protamine suspension (NPL) (Humalog® Mix25™, Eli Lilly and Company, Indianapolis, IN, USA) is currently available in many countries. Compared with regular human insulin mixtures, insulin lispro mixtures twice daily results in improved post-prandial BG levels, a lower risk of nocturnal hypoglycaemia and similar overall glycaemic control (A_{1c}), with the added convenience of immediate pre-meal dosing [10,11]. In addition, compared with twice-daily NPH, an insulin lispro mixture given twice daily before breakfast and dinner has been shown to reduce haemoglobin A_{1c} (A_{1c}) by 0.23% to 0.32% [12,13].

Insulin glargine (Lantus®, Aventis Pharmaceuticals, Frankfurt, Germany), a human insulin analogue with low solubility at a physiological pH, is designed to have a long duration of action. After subcutaneous injection, the acidic insulin glargine solution is neutralized and forms microprecipitates, resulting in its gradual release throughout a 24-h period. After reaching maximum levels in approximately 4 h, the ensuing insulin profile is relatively flat [14]. In a study of patients with Type 2

diabetes, once-daily NPH given at bedtime was compared with bedtime insulin glargine [15]. Patients receiving insulin glargine had less nocturnal hypoglycaemia and a lower post-prandial BG after the evening meal. Although the extended duration of action of insulin glargine supports a convenient once-daily injection, its efficacy in adequately controlling post-prandial hyperglycaemia throughout the day in a manner consistent with the European Diabetes Policy Group Guidelines [16] remains to be established.

To date, there have been no reported studies comparing a rapid-acting insulin analogue mixture, a formulation that focuses on post-prandial and pre-meal hyperglycaemia, with the long-acting insulin analogue insulin glargine, a formulation that focuses primarily on fasting blood glucose (FBG). The current study was designed to examine whether treatment with a twice-daily insulin lispro mixture results in improved overall glycaemic control compared with once-daily insulin glargine, when both are used in combination with metformin in patients with Type 2 diabetes inadequately controlled with intermediate insulin or insulin plus oral agent(s) combination therapy. The primary measures of efficacy were haemoglobin A_{1c} , post-prandial BG, and hypoglycaemia rate.

Research design and methods

Patient population

This study was conducted at 12 study centres in Spain and France and included 119 patients (ages 30–75 years) with Type 2 diabetes, as defined by World Health Organization criteria [17]. To be included in the study, patients must have demonstrated inadequate glycaemic control, as determined by an A_{1c} value between 1.3 and 2.0 times the upper limit of normal by a local laboratory within 30 days prior to inclusion in the study. Patients were excluded from the study if they had used glitazones within 30 days prior to the study. Patients were required to be using NPH once or twice daily, alone or in combination with an oral-antidiabetic agent(s), or a once-daily human insulin mixture with an oral agent(s), for at least 30 days before entering the study. These patients were selected because they would be expected to benefit from prandial control not provided by their previous insulin. The ethical review boards of the participating centres approved the protocol and the informed consent document used in the study. Patients gave written informed consent to participate in the study, which was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines.

Study design

This was a multicentre, randomized, prospective, open-label, crossover study. After a 6-week lead-in period, patients were randomly assigned to treatment with either the insulin lispro mixture before breakfast and dinner plus metformin (1500–2550 mg per day) or insulin glargine at bedtime plus metformin (1500–2550 mg per day) for 16 weeks, followed by 16 weeks of the opposite treatment.

Lead-in period

The lead-in period consisted of 6 (\pm 2) weeks between study entry and randomization. At entry, each patient's medical history was recorded and a physical examination was performed. Patients were asked to record hypoglycaemic episodes and insulin dosages in written diaries. In addition, patients were taught to properly use the pre-filled insulin injection device for NPH insulin (Humulin® N Pen, Eli Lilly and Company) and were asked to record one 7-point BG profile (before and 2 h after each meal and at 03.00 hours) and two 4-point BG profiles (before and 2 h after breakfast and dinner only) during the 2 weeks before randomization. Patients were given no special dietary instructions, but were expected to follow their usual diabetic diets during the trial.

During the lead-in period, patients were required to use NPH once daily at bedtime and metformin two or three times daily. All other oral antidiabetic agents were discontinued. The purpose of the lead-in period was to stabilize patients on a common insulin regimen. The daily dose of metformin used at the end of the lead-in period was continued throughout the study. Patients whose daily metformin dose was outside the acceptable therapeutic range of 1500–2550 mg were discontinued.

Treatment period

The 16-week treatment period allowed for 4 weeks of insulin dose adjustment and 3 months for stabilization of overall glycaemic control. The dose of the insulin lispro mixture or insulin glargine was adjusted by the investigators throughout the study in an attempt to achieve targets for fasting and pre-meal BG concentrations of 5–7 mmol/l (90–126 mg/dl). During treatment with the insulin lispro mixture plus metformin, an additional BG target for 2-h post-prandial BG of 8–10 mmol/l (144–180 mg/dl) was established. The recommended initial dose of insulin glargine was equal to or greater than the final dose of bedtime NPH during the lead-in period.

Patients returned to the study centre monthly for routine assessments. At each visit, patients' diaries were reviewed. Body weight, adverse events including hypoglycaemia, and insulin doses were recorded. A_{1c} was measured at randomization and after 12 and 16 weeks into each treatment period. The A_{1c} assay was performed by ion-exchange high-performance liquid chromatography (HPLC) on a Bio-Rad Variant Analyser (Bio-Rad Clinical Diagnostics Group, Hercules, CA, USA; certified by the National Glycohemoglobin Standardization Program) at a central laboratory (Covance, Geneva, Switzerland reference range, 4.3% to 6.1%).

Two different insulin delivery devices, a pre-filled pen (Humalog® Mix25 Pen and Humulin® N Pen) for use with the insulin lispro mixture and NPH, and a reusable insulin delivery device (OptiPen® Pro; Aventis, Frankfurt, Germany) for insulin glargine, were given to participating patients. At the beginning and endpoint of each treatment period, patients were asked to complete an insulin delivery device questionnaire indicating their level of satisfaction with the insulin injection device(s). Patients performed three BG profiles on separate days in the 2 weeks prior to randomization, and at 12 and 16 weeks of each treatment, which included one 7-point profile and two 4-point

profiles. On days that these profiles were performed, patients recorded BG measurements and insulin doses in their diaries.

Primary efficacy measures included: A_{1c} ; 2-h post-prandial BG after the morning, midday, and evening meals; BG before the morning and evening meals; and the frequency, rate, and severity of hypoglycaemia [defined as BG < 3.5 mmol/l (63 mg/dl) or symptoms of hypoglycaemia], as well as the rate of nocturnal hypoglycaemia. Nocturnal was defined as the time interval between bedtime and breakfast for each patient. Secondary measures included mean daily BG level; M-value (measure of the intraday variability in BG values averaged over 3 days and their deviation from euglycaemia. Higher M-values correspond to greater fluctuations in BG indicating a propensity toward hypo- or hyperglycaemia), which is an index of overall glycaemia [18], and MODD, (mean of daily differences of paired BG values, an index of day-to-day BG variability. Higher values demonstrate greater fluctuations in the BG profile over time); body weight; responses to two patient questionnaires (insulin injection device satisfaction and acceptability); BG profiles; and insulin dosage information from patient diaries.

Study drugs

Mix25 (Humalog® Mix25™) was provided in 3-ml pre-filled pens. NPH (Humulin® N) was also supplied in 3-ml pre-filled pens. Insulin glargine (Lantus®) was provided in 3-ml cartridges for use in the OptiPen® Pro reusable injection device. Metformin hydrochloride was provided in 500 and 850 mg tablets.

Statistical methods

The study was designed to have 80% power to detect a treatment difference of 0.3% for A_{1c} . The rate of early discontinuations was expected to approach 10%. Therefore, approximately 100 patients were planned for randomization to one of the two sequence groups with approximately 50 patients per group. Analysis methods for a crossover design were used to evaluate both the carryover and treatment effects. If a carryover effect was present, analyses and interpretation of the treatment effect followed the recommendation by Lehmacher [19]. A crossover model was used to evaluate both the carryover and treatment effects. No evidence of a statistically significant carryover effect was observed. All analyses were based on the intent-to-treat (ITT) population, which included all randomized patients who received insulin. The last observation carried forward (LOCF) method was used for missing values.

Statistical analyses were performed using the endpoint value defined as the last value observed for each patient during each period of the crossover study. Data were analysed with SAS version 6.09 (SAS, Cary, NC, USA) using two-sided tests at a 0.05 level of significance. Haemoglobin A_{1c} and BG values were analysed using the method of Grizzle for a crossover design [20]. The treatment, country, and treatment-by-country interaction were the factors included in the analyses. Hypoglycaemia rate (episodes/patient/30 days) was analysed using the same crossover model as described above according to the method suggested by Koch [21]. Binary response data were analysed using a method reported by Nagelkerke, Hart and Oosting [22]. All continuous

variables are reported as mean \pm standard deviation (SD) in the text and tables, and mean \pm standard error of the mean (SEM) in the figures.

Results

Of the 119 patients entering the study, 97 were randomized; 50 were initially assigned to receive the insulin lispro mixture plus metformin, and 47 were assigned to begin glargine plus metformin. Reasons patients discontinued prior to randomization included: 15 failed to meet entry criteria, 3 patient decisions, 2 physician decisions, and 2 adverse events. Prior to the study, 54 patients had used oral agents and 33 patients had used two or more oral agents. Five patients used alpha-glucosidase inhibitors, 49 biguanides, 30 sulphonylureas, and 7 meglitinides. In addition, over 90% of patients used NPH prior to entering the study. A total of 84 patients completed the study; 3 dropped out while receiving the insulin lispro mixture plus metformin: 1 lack of efficacy (patient decision), 1 adverse event (not related to study drug), 1 death (myocardial infarction, not related to study drug). Ten patients discontinued while receiving glargine plus metformin: 1 death (not related to study drug), 1 adverse event (not related to study drug), 2 lack of efficacy (1 patient decision, 1 patient and physician decision), 1 lost to follow-up, 1 patient decision, 3 entry criteria not met, 1 physician decision. No differences in baseline characteristics were observed between treatment sequence groups (Table 1).

Haemoglobin A_{1c}

At endpoint, A_{1c} was lower after treatment with the insulin lispro mixture plus metformin compared with glargine plus metformin (7.54% \pm 0.87% vs. 8.14% \pm 1.03%; $P < 0.001$), and the reduction in A_{1c} from baseline to endpoint was greater for the insulin lispro mixture plus metformin (-1.00% \pm 0.85% vs. -0.42% \pm 0.92%, $P < 0.001$) (Fig. 1 and Table 2). A higher percentage of patients treated with the insulin lispro mixture

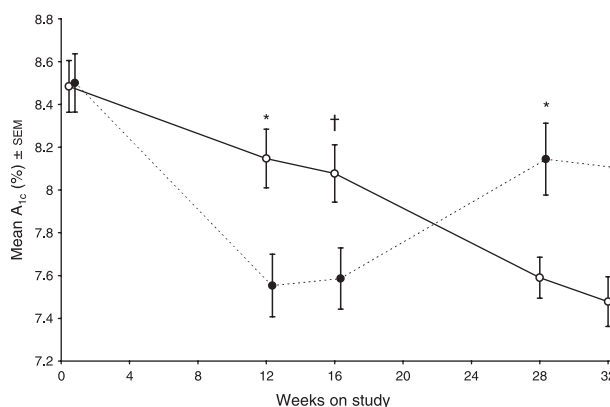


Figure 1 Mean (\pm SEM) A_{1c} values by treatment sequence [lispro mixture plus metformin then glargine plus metformin (●) and glargine plus metformin then lispro mixture plus metformin (○)] and weeks on study. * $P < 0.01$, † $P = 0.02$.

plus metformin were at or below an A_{1c} of 7% at endpoint (30% vs. 12%; $P = 0.002$), while there was no difference between treatments for the percentage of patients achieving an A_{1c} \leq 6.5% A_{1c} target ($P = 0.100$).

Blood glucose profiles

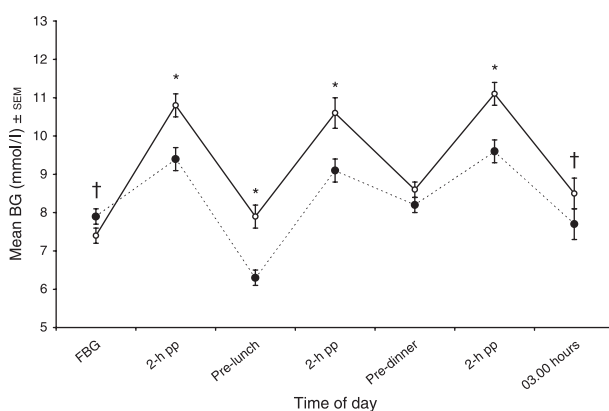
Although the FBG was higher during treatment with Mix25 plus metformin (7.90 \pm 1.92 vs. 7.39 \pm 1.96 mmol/l, $P = 0.007$), the 2-h post-prandial BG levels after each meal were lower with Mix25+M (Fig. 2). Mean morning (9.44 \pm 2.56 vs. 10.83 \pm 2.74 mmol/l), midday (9.14 \pm 2.92 vs. 10.65 \pm 3.67 mmol/l), and evening post-prandial BG levels (9.59 \pm 2.50 vs. 11.15 \pm 2.52 mmol/l) ($P < 0.001$) and 03.00 hour BG levels (7.75 \pm 3.44 vs. 8.53 \pm 3.54 mmol/l; $P = 0.01$) were lower with the insulin lispro mixture plus metformin (Fig. 2). The M-value was significantly lower with the insulin lispro mixture plus metformin (23.18 \pm 20.92 vs. 31.44 \pm 23.93; $P = 0.001$) at endpoint, while the MODD was not different between treatments (2.01 \pm 1.25 vs. 1.96 \pm 1.02 mmol/l; $P = 0.484$).

Variable	Lispro mixture then glargine (n = 50)	Glargine then lispro mixture (n = 47)	P-value
Age (year)	59.18 \pm 8.58	59.63 \pm 8.03	0.788
Males	25 (50%)	18 (38%)	0.246
Females	25 (50%)	29 (62%)	
Weight (kg)	77.82 \pm 13.61	77.21 \pm 15.91	0.840
BMI (kg/m ²)	29.41 \pm 4.57	29.64 \pm 5.16	0.816
FBG (mmol/l)	8.63 \pm 2.93	8.21 \pm 2.09	0.369
A _{1c} (%)	8.50 \pm 0.95	8.48 \pm 0.80	0.758
Diabetes duration (year)	13.52 \pm 8.18	11.90 \pm 6.27	0.278
Previous treatment			
NPH 1–2/day without oral agent(s)	24	19	
One insulin + oral agent(s)	26	28	
Sulphonylureas	14	16	

Table 1 Patients' baseline characteristics by treatment sequence (mean \pm SD)

Table 2 Selected clinical characteristics of patients by treatment group at baseline endpoint (mean \pm SD)

Variable	<i>n</i>	NPH + metformin baseline	Lispro mixture + metformin endpoint	Glargine + metformin endpoint	Endpoint <i>P</i> -value
A _{1c} (%)	93	8.49 \pm 0.88	7.54 \pm 0.87	8.14 \pm 1.03	< 0.001
Change in A _{1c} (%)			-1.00 \pm 0.85	-0.42 \pm 0.92	< 0.001
FBG (mmol/l)	97	8.42 \pm 2.55	7.90 \pm 1.92	7.39 \pm 1.96	0.007
Overall hypoglycaemia rate (episodes/patient/30 days)	97	0.32 \pm 0.80	0.61 \pm 1.41	0.44 \pm 1.07	0.477
Nocturnal hypoglycaemia rate (episodes/patient/30 days)	97	0.19 \pm 0.54	0.14 \pm 0.49	0.34 \pm 0.85	0.002
Body weight (kg)	97	77.53 \pm 14.69	78.31 \pm 15.13	77.05 \pm 14.38	0.001
Change in weight (kg)			0.82 \pm 2.56	0.06 \pm 2.49	0.001
Insulin dose (U/kg)	97	0.27 \pm 0.11	0.42 \pm 0.20	0.36 \pm 0.18	< 0.001

**Figure 2** Mean (\pm SEM) 7-point blood glucose (BG) profiles at endpoint. [glargine plus metformin (\circ) and lispro mixture plus metformin (\bullet)]. * $P \leq 0.001$, † $P \leq 0.01$.

Blood glucose targets

A greater proportion of patients treated with the insulin lispro mixture plus metformin achieved the morning and evening 2-h post-prandial BG targets of ≤ 10 mmol/l (66% vs. 42%; $P < 0.001$ and 64% vs. 40%; $P < 0.001$, respectively). In contrast, a greater proportion of patients treated with glargine plus metformin achieved the FBG target (≤ 7 mmol/l) at endpoint (34% vs. 51%; $P = 0.01$). There was no significant difference between treatments in the proportion of patients achieving the midday 2-h post-prandial BG target (59% vs. 49%; $P = 0.182$).

Hypoglycaemia

The overall hypoglycaemia rate was not different between treatments (0.61 \pm 1.41 vs. 0.44 \pm 1.07 episodes/patient/30 days; $P = 0.477$) (Table 2). At endpoint, patients treated with the insulin lispro mixture plus metformin experienced a lower rate of nocturnal hypoglycaemia (0.14 \pm 0.49 vs. 0.34 \pm 0.85 episodes/patient/30 days; $P = 0.002$). Daytime hypoglycaemia

rate was higher with the insulin lispro mixture plus metformin at endpoint (0.46 \pm 1.28 vs. 0.10 \pm 0.51 episodes/patient/30 days; $P = 0.003$). There was no difference in the incidence of hypoglycaemia between treatments and no episodes of severe hypoglycaemia occurred in either group.

Body weight, insulin and metformin doses

Patients in the insulin lispro mixture plus metformin group experienced more weight gain than those treated with glargine plus metformin ($P = 0.001$), and required a slightly higher daily insulin dose ($P < 0.001$) (Table 2). Metformin dose at endpoint was similar for the two treatment groups (2128 \pm 425 vs. 2146 \pm 424).

Insulin delivery devices

Most (78%) participants preferred the Humalog® Mix25 Pen device compared with the Optipen® Pro (14%) ($P < 0.001$) at endpoint, while 8% expressed no preference. For overall ease of use, 71% of patients preferred the Humalog Mix25 Pen, while 14% preferred the OptiPen Pro, and 13% had no preference. Forty-five per cent of subjects preferred the insulin lispro mixture, 28% preferred glargine, and 27% had no preference. Most indicated both the insulin pen and insulin therapy were important to them.

Adverse events

There was no difference between treatments in the overall incidence of adverse events [54 (60%) patients; 49 (52%) patients]. The most frequently reported adverse events were flu syndrome (7%), diarrhoea (5%), urinary tract infection (5%), and insomnia (4%). Three serious adverse events were reported with the insulin lispro mixture plus metformin, and three with glargine plus metformin; none were related to insulin or metformin treatment.

Discussion

This study reports the first direct comparison of glycaemic response between a regimen containing a twice-daily insulin lispro mixture and a regimen containing once-daily insulin glargine. In patients treated with the insulin lispro mixture plus metformin, the A_{1c} at endpoint (7.54%) was closer to the target A_{1c} of < 7% recommended by the American Diabetes Association [23]. Patients treated with the insulin lispro mixture plus metformin exhibited a clinically significant ($P < 0.001$) decrease in A_{1c} from baseline (-1.00%) compared with glargine plus metformin (-0.42%). In the UKPDS, a 1% decrease in A_{1c} was associated with an overall risk reduction of 21%, including a 14% risk reduction in myocardial infarction, 21% decrease in deaths, and 37% decrease in microvascular complications [24]. Thus, the absolute decrease of 1% in A_{1c} observed in the present study in patients treated with the insulin lispro mixture plus metformin, if maintained, would be expected to reduce the risk of diabetes complications.

Though the present study was not designed to exam diabetic vascular complications, emerging evidence indicates that acute hyperglycaemia is associated with physiological alterations similar to those observed during the early pathogenesis of diabetic vascular complications [6,25]. Although not yet confirmed by prospective studies, from an epidemiological standpoint, elevated post-prandial BG has been associated with an increased risk of cardiovascular disease in individuals with and without diabetes [5,25,26]. In the current study, the insulin lispro mixture plus metformin, which contributes both basal and post-prandial insulin action, resulted in the combined effects of improved A_{1c} , lower post-prandial BG, and less nocturnal hypoglycaemia compared with insulin glargine plus metformin. This suggests a possible improvement in long-term health outcomes may be possible. However, other variables that would support improved health outcomes such as blood lipids, blood pressure, and other markers of vascular disease were not included in the present study. Therefore, the relationship of post-prandial BG control and vascular outcomes remains speculative and requires further study.

Bastyr *et al.* [27] compared the effects of combination therapies (insulin lispro plus glyburide, metformin plus glyburide, or NPH plus glyburide) on fasting and post-prandial BG. At endpoint, insulin lispro plus glyburide resulted in significantly lower A_{1c} compared with the other therapy groups ($P = 0.025$), suggesting that controlling post-prandial BG levels, despite increased fasting glucose levels, led to improved overall glycaemic control [27]. The results of the current study are in agreement with the findings of Bastyr and colleagues.

Insulin lispro mixtures have been shown to decrease post-prandial BG levels compared with an equal dose of NPH or human insulin 30/70 (soluble/NPH) when each insulin was given prior to a breakfast test meal in patients with Type 2 diabetes [28]. In longer-term clinical studies, twice-daily administration of insulin lispro mixtures, compared with twice-daily NPH, improved post-prandial BG after breakfast and dinner,

and significantly decreased A_{1c} [12,13]. In those studies, the improved glucose control was associated with similar or less frequency of hypoglycaemia [12,13]. Recently, Holcombe *et al.* reported significant decreases in A_{1c} with a twice-daily insulin lispro mixture in combination with metformin compared with twice-daily NPH plus metformin in patients with Type 2 diabetes [29].

Current treatment practice suggests adding a single bedtime dose of basal insulin (NPH or insulin glargine) to one or more oral agents. However, the present study provides strong evidence supporting the use of an alternative regimen: a fixed-mixture insulin lispro analogue before morning and evening meals to address both basal and post-prandial insulin demands. An earlier study comparing insulin glargine and NPH once- or twice-daily in patients with Type 2 diabetes showed similar reductions in FBG and A_{1c} , along with similar rates of overall hypoglycaemia [30]. While patients treated with insulin glargine had a lower incidence of nocturnal hypoglycaemia, as well as less weight gain than with NPH [30]. Another study has shown that insulin glargine, compared with NPH given once daily in combination with oral agents, is associated with lower post-dinner BG and less symptomatic and nocturnal (bedtime to waking) hypoglycaemia [15].

A large European study has been conducted examining the use of glimepiride combined with morning or bedtime insulin glargine or bedtime NPH in patients with Type 2 diabetes with the insulin doses titrated to achieve a target FBG of ≤ 5.56 mmol/l (≤ 100 mg/dl) [31]. A_{1c} decreased for each of the treatments, although morning insulin glargine resulted in a significantly greater improvement than bedtime insulin glargine or NPH [31]. Endpoint A_{1c} was 7.8% with morning insulin glargine, 8.3% with bedtime NPH, and 8.1% with bedtime insulin glargine. Less nocturnal hypoglycaemia was noted with insulin glargine administered at either time compared with NPH at bedtime [31]. Riddle *et al.* compared bedtime insulin glargine with bedtime NPH added to oral agent therapy and ability to attain a target A_{1c} of 7% [32]. At endpoint, fasting plasma glucose and A_{1c} were similar between treatments. A majority of patients (60%) attained an $A_{1c} \leq 7\%$ with either insulin; however, 25% more patients treated with insulin glargine achieved this without documented nocturnal hypoglycaemia [BG ≤ 4.0 mmol/l (≤ 72 mg/dl)]. Our endpoint A_{1c} results were similar to the European study with bedtime insulin glargine [31]; however, they were higher than those achieved by Riddle *et al.* where more intensive study monitoring was performed to achieve glycaemic targets [32]. In the current study, a lower percentage of patients achieved A_{1c} targets in either treatment group compared with the study of Riddle *et al.* [32]. Had patients been treated more aggressively to reach lower BG targets, more patients would probably have achieved the target A_{1c} , but with an increased risk of nocturnal hypoglycaemia. In a recent study comparing the same insulin lispro mixture plus metformin with insulin glargine plus metformin, Malone *et al.* followed the same study procedures as in current study, but in Type 2 patients just beginning insulin

therapy [33]. In that study, the insulin lispro mixture provided a similar lowering of A_{1c} compared with insulin glargine as in the current study (7.39 vs. 7.78%; $P < 0.001$) but with an increase in overall (0.68 vs. 0.39 episodes/patient/30 days; $P = 0.041$), but not nocturnal, hypoglycemia [33]. Like the current study, a higher proportion of patients achieved A_{1c} targets $\leq 7.0\%$ with the insulin lispro mixture (41% vs. 22%; $P < 0.001$) [33].

Another difference in the current study was the observation of higher nocturnal hypoglycaemia with glargine plus metformin, whereas nocturnal hypoglycaemia was lower with glargine compared with NPH in the other two studies [31,32]. The difference between the current study and that of Riddle *et al.* may be because the insulin lispro mixture was administered before dinner while NPH in the other studies was given at bedtime. The lower rate of nocturnal hypoglycaemia with the insulin lispro mixture plus metformin could have been caused by the waning action of the evening dose of the insulin lispro mixture before breakfast, in contrast to the increasing action of bedtime insulin glargine overnight. A greater decline in overnight BG was observed with glargine plus metformin (Fig. 2), compared with the plateau in BG observed between 03.00 hours and breakfast with the insulin lispro mixture plus metformin.

Blood glucose goals have decreased in recent years and investigators in the current study were given a relatively wide range for BG targets to allow for individual patient needs. Providing both fasting and pre-meal targets for both insulin lispro mixture plus metformin and glargine plus metformin, and additional post-prandial BG targets for only the insulin lispro mixture plus metformin may have influenced the A_{1c} outcome. However, most studies with insulin glargine have also used only FBG targets [15,32]. Using a FBG target of 5–7 mmol/l and a post-prandial BG target of 8–10 mmol/l, our findings are not unexpected. If the FBG target had been more aggressive, such as 4–6 mmol/l, there would likely be a smaller difference in endpoint A_{1c} between the two treatments. In addition, attempting to target post-prandial BG with insulin glargine would probably increase the risk of hypoglycaemia later in the day. Therefore, a potential bias in the study exists because the two treatments were not targeting the same BG time points.

A slightly higher insulin dose (approximately 4–5 U based on the average patient weight) was observed with the insulin lispro mixture compared with insulin glargine; however, this absolute dose difference was small and would not completely explain the observed difference in A_{1c} between treatments. The insulin lispro mixture dose may have been higher because of need for the rapid-acting insulin component to manage post-prandial BG. Another possible reason for the dose difference could be that insulin glargine was new to most investigators, causing them to be more cautious in increasing the dose. In addition, the investigators may have been concerned about nocturnal hypoglycaemia, thus they were reluctant to increase the glargine dose. The concern over increasing nocturnal hypoglycaemia may have contributed to a lower percentage of patients achieving the A_{1c} target compared with Riddle *et al.* [32].

Data from a number of studies indicate that the treatment of Type 2 diabetes with exogenous insulin is associated with an increase in body weight of 3% to 9%, depending on study duration and extent of BG control [34]. The weight gain found in the present study with the insulin lispro mixture plus metformin represented approximately 1% of the mean baseline weight. The use of metformin in this study may have attenuated weight gain in both groups.

In conclusion, patients with Type 2 diabetes inadequately controlled on human insulin once or twice daily, with or without oral agents at study entry, showed treatment with a twice-daily insulin lispro mixture plus metformin provided clinically significant improvements in A_{1c} and post-prandial hyperglycaemia, while reducing nocturnal hypoglycaemia as compared with treatment with once-daily insulin glargine plus metformin. The insulin lispro mixture provided both basal and post-prandial insulin action without excessive weight gain when used in combination with metformin. Compared with basal-only insulin glargine plus metformin, a twice-daily insulin lispro mixture with metformin provides a more effective treatment option for patients with Type 2 diabetes who are not well controlled on once- or twice-daily insulin regimens.

Competing interests

J.K.M., S.B., B.N.C., B.A.-F., J.R. are employed by Eli Lilly and Company and hold stocks and shares in the Company.

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