

# Repaglinide Versus Metformin in Combination With Bedtime NPH Insulin in Patients With Type 2 Diabetes Established on Insulin/Metformin Combination Therapy

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**OBJECTIVE** — To compare the effect on glycemic control and weight gain of repaglinide versus metformin combined with bedtime NPH insulin in patients with type 2 diabetes.

**RESEARCH DESIGN AND METHODS** — A total of 80 subjects treated with 850 or 1,000 mg t.i.d. metformin combined with bedtime NPH insulin were randomized to 13 weeks of open-label treatment with 4 mg t.i.d. repaglinide ( $n = 39$ ) or metformin (dose unchanged) ( $n = 41$ ). Insulin dose was titrated at the clinician's discretion, aiming for a fasting blood glucose (FBG)  $\leq 6.0$  mmol/L.

**RESULTS** — Baseline age, diabetes duration, insulin requirement, weight, BMI, FBG, and HbA<sub>1c</sub> (Diabetes Control and Complications Trial-aligned assay, normal range 4.6–6.2%) were similar. Glycemic control improved (nonsignificantly) with insulin/metformin by (mean) 0.4%, from 8.4 to 8.1% ( $P = 0.09$ ) but deteriorated with insulin/repaglinide by (mean) 0.4%, from 8.1 to 8.6% ( $P = 0.03$ ;  $P = 0.005$  between groups). Weight gain was less with insulin/metformin:  $0.9 \pm 0.4$  kg (means  $\pm$  SE) ( $P = 0.01$ ) versus  $2.7 \pm 0.4$  kg ( $P < 0.0001$ ) ( $P = 0.002$  between groups). The Diabetes Treatment Satisfaction Questionnaire score (potential range 0 [minimum] to 36 [maximum]) increased from  $32.4 \pm 0.8$  to  $34.1 \pm 0.5$  ( $P = 0.01$ ) with insulin/metformin but decreased from  $32.5 \pm 0.9$  to  $29.1 \pm 1.3$  ( $P < 0.002$ ) with insulin/repaglinide.

**CONCLUSIONS** — Combined with bedtime NPH insulin, metformin provides superior glycemic control to repaglinide with less weight gain and improved diabetes treatment satisfaction.

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The U.K. Prospective Diabetes Study (1) confirmed that good glycemic control prevents and retards development of complications in patients with type 2 diabetes. It also demonstrated an inexorable decline in  $\beta$ -cell function, with many patients ultimately requiring insulin therapy. Insulin therapy in type 2 diabetes improves glycemic control but

causes weight gain and increases the risk of hypoglycemia, both of which are major concerns for patients. Many studies demonstrate that compared with insulin monotherapy, combining bedtime NPH insulin with oral agents results in similar glycemic control but with less weight gain and less hypoglycemia (2–6), particularly when metformin is used (3). Combina-

tion therapy regimens primarily target fasting rather than prandial glycemia, but controlling meal-related glycemic spikes may also be important (7). Combining a prandial blood glucose regulator such as repaglinide with bedtime NPH insulin may address this issue. Repaglinide (a meglitinide) is a short-acting  $\beta$ -cell stimulator that mediates insulin release in a glucose-dependent manner. It is as efficacious as metformin in monotherapy (8) and provides similar glycemic control to sulfonylureas with lower postprandial blood glucose excursions (9,10) and comparable (or less) hypoglycemia (11–14). The combination of repaglinide with bedtime NPH insulin has been reported to provide superior control to repaglinide or insulin therapy alone (15), suggesting that this may be a useful regimen for managing insulin-requiring type 2 diabetic patients.

The aim of this study was to compare the effect on glycemic control, weight gain, and frequency of hypoglycemia of repaglinide versus metformin combined with bedtime NPH insulin in patients with type 2 diabetes established on insulin/metformin combination therapy. Secondary end points were well-being and diabetes treatment satisfaction.

## RESEARCH DESIGN AND METHODS

This was a single-center open-label randomized parallel group study conducted at Whiston Hospital, Prescot, Merseyside, U.K. It was approved by the local research ethics committee in accordance with the Declaration of Helsinki, and all subjects gave written informed consent to participate in the study.

## Subjects

Men and women  $>18$  years of age with type 2 diabetes as defined by the World

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**Abbreviations:** DTSQ, Diabetes Treatment Satisfaction Questionnaire; FBG, fasting blood glucose; WBQ, Well-Being Questionnaire.

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

Health Organization (16), treated with 850 or 1,000 mg t.i.d. (maximum tolerated dose) metformin combined with bedtime NPH insulin, were included. There was no minimum duration of insulin therapy required for inclusion, and all subjects needed to be willing and able to perform home blood glucose monitoring. Exclusion criteria were as follows: type 1 diabetes, pregnancy or lactation, hypoglycemic unawareness, recurrent severe hypoglycemia (four or more episodes in the previous year), hepatic impairment (aspartate or alanine aminotransferase more than three times the upper limit of normal), renal impairment (creatinine  $>120 \mu\text{mol/l}$ ), decompensated (New York Health Association grade III/IV) heart failure, unstable angina, known or suspected allergy to any trial medications, or a known or suspected history of alcohol or drug abuse. Subjects were also excluded if they were taking other medications likely to affect glycemic control or drugs known to interact with trial medication (systemic corticosteroids, monoamine oxidase inhibitors, octreotide, anabolic steroids, danazol, sympathomimetics, ketoconazole, itraconazole, erythromycin, phenytoin, or rifampicin). We also excluded individuals with any illness rendering them unable to fully understand and participate in the study. The use of other oral hypoglycemic agents (including sulfonylureas or thiazolidinediones) was not permitted.

## Design

**Visit 1 (screening, 4 weeks before study entry).** After gaining written informed consent, subjects underwent a medical history and physical examination, and blood was drawn for HbA<sub>1c</sub>, renal function, and liver function tests. A pregnancy test was performed in female subjects of childbearing potential. Subjects were provided with (and instructed in the use of) a calibrated blood glucose meter (Precision Q-I-D; Medisense, Abbott Laboratories, Maidenhead, Berks, U.K.) and were given a diary for recording home blood glucose values, episodes of hypoglycemia, and seven-point blood glucose profiles. The latter consisted of measurements of blood glucose before and 90 min after breakfast, lunch, and the evening meal and before bed. Subjects were asked to perform a seven-point blood glucose profile in the week after

visit 1 and 1 week before visit 2 (randomization).

All subjects received dietetic and lifestyle advice regarding hypoglycemia prevention and were provided with a contact number for the project leader, diabetes nurse specialist, and a 24-h emergency phone line. Diabetes therapy (insulin/metformin) was continued unchanged throughout the run-in period.

**Visit 2 (randomization).** Investigation results were reviewed to confirm study eligibility. Current diabetes therapy, fasting blood glucose (FBG), HbA<sub>1c</sub>, weight, blood pressure, adverse events, and changes to any medication were recorded. All subjects completed two validated questionnaires to assess well-being (Well-Being Questionnaire [WBQ], Professor Clare Bradley, September 1993) and diabetes treatment satisfaction (Diabetes Treatment Satisfaction Questionnaire [DTSQ], Professor Clare Bradley, September 1993). Subjects were then individually randomized by way of concealed random numbers in sequenced envelopes to 4 mg t.i.d. repaglinide (NovoNorm) and bedtime NPH insulin (Insulatard; Novo Nordisk, Crawley, West Sussex, U.K.) or continued metformin therapy (dose unchanged) with bedtime NPH insulin. Repaglinide was initiated at a dose of 4 mg t.i.d., administered 15 min preprandially, and reduced only if subjects suffered recurrent hypoglycemia related to repaglinide therapy. Metformin was administered with meals. At randomization, the bedtime insulin dose was increased to  $\geq 0.5$  units/kg body wt (providing no risk of hypoglycemia as judged by the study coordinator) and subsequently increased after 1 week to  $\geq 0.7$  units/kg providing no (risk of) hypoglycemia. Insulin doses were then titrated at the clinician's discretion at each subsequent visit (with increments typically between 4 and 20 units), aiming for a target FBG of 4.0–6.0 mmol/l. The insulin dose was increased if FBG was  $>6.0$  mmol/l on  $>50\%$  of occasions in any 2-week period and was reduced (generally by 2–4 units) if more than two minor hypoglycemic episodes/week or one major hypoglycemic episode occurred. All subjects were asked to monitor blood glucose levels before meals and bed twice weekly and additionally if they felt symptoms of hypoglycemia.

**Treatment period (13 weeks of duration).** Subjects were seen by the trial investigator at 2, 4, 6, and 13 weeks after randomization. At each visit, current diabetes therapy, FBG, weight, hypoglycemic episodes, blood pressure, adverse events, and changes to medication were recorded. Insulin doses were altered as described above. HbA<sub>1c</sub> was measured at 6 and 13 weeks. Subjects were asked to complete a seven-point blood glucose profile in the week before the penultimate and final visits. At the end of the study, all subjects again completed the WBQ and DTSQ.

The primary end points were HbA<sub>1c</sub>, weight change, and frequency of hypoglycemia. Secondary end points were quality of life and treatment satisfaction.

## Analytical methods

FBG and seven-point blood glucose profiles were measured using Precision Q-I-D. HbA<sub>1c</sub> was analyzed using an HA 8121 high-performance liquid chromatography assay (Menarini Diagnostics) and a DCA 2000 Analyzer (Bayer Diagnostics). Both assays were U.K. Diabetes Control and Complications Trial-aligned (normal range 4.6–6.2%) and quality assured weekly to ensure reproducible standardized accuracy. Clinical chemistry analyses of renal and liver function tests were made using an AXON autoanalyzer (Bayer Diagnostics).

Hypoglycemia was defined as a blood glucose reading  $<3.5$  mmol/l with or without symptoms. Nocturnal hypoglycemia was defined as that occurring while the subject was asleep between bedtime after the injection of insulin and before prebreakfast blood glucose determination. Severe hypoglycemia was defined as that requiring third-party assistance.

## WBQ

The WBQ consisted of 22 statements about the patient's feelings (including four subscales: Depression (six items), Anxiety (six items), Energy (four items), and Well-Being (six items)). Each statement was scored 0–3 on a Likert scale, indicating whether the patient felt that the statement applied to him or her all the time (3) or not at all (0) over the preceding few weeks. Scoring the questionnaire for "general well-being" could provide a potential range of 0 (low) to 66 (high).

Table 1—Baseline characteristics at randomization

	Metformin	Repaglinide	P
n	41	39	—
Sex (M/F)	15/26	24/15	—
Age	61.6 ± 1.6	57.4 ± 1.6	0.07
Diabetes duration (months)	120 (9–306)	120 (10–240)	0.9
Duration of insulin therapy (months)	10 (1–45)	6 (1–40)	0.5
HbA <sub>1c</sub> (%)	8.4 ± 0.2	8.1 ± 0.2	0.35
Weight (kg)	91.2 ± 2.8	97.5 ± 3.5	0.2
BMI (kg/m <sup>2</sup> )	33.0 ± 0.7	33.7 ± 1.0	0.5
Insulin (units/kg)	0.47 ± 0.03	0.5 ± 0.03	0.43
Metformin dose (mg/day)	2,824 ± 35	2,850 ± 34	0.6
FBG (mmol/l)	7.6 ± 0.4	7.6 ± 0.5	0.9
Creatinine (μmol/l)	88.5 ± 2.1	90.0 ± 2.0	0.6
WBQ score	50.4 ± 2	47.5 ± 1.8	0.23
DTSQ score	32.2 ± 0.8	32.5 ± 0.9	0.97

Data are means ± SE or medians (range) unless otherwise indicated.

## DTSQ

The DTSQ consists of eight questions (e.g., “How satisfied are you with your current treatment?”), each of which was answered on a seven-point scale from 0 to 6 (e.g., 0 = very dissatisfied, 6 = very satisfied). The answers for six of the eight questions were summed to produce a measure of satisfaction with diabetes treatment providing a potential range of 0 (low) to 36 (high). Both questionnaires are appropriate validated measures for subjects included in this study (17) and are advocated by the World Health Organization (18).

## Statistical methods

Power calculations indicated 90% power to detect a difference of 1% in HbA<sub>1c</sub> at the 5% level of statistical significance, should such a difference arise between the interventions, if there were 36 patients in each group. Assuming a 10% dropout rate, we aimed to recruit 40 patients into each group. All data were summarized using an intention-to-treat analysis (all subjects who received at least one dose of the study medication and returned for at least one visit after randomization.) The end point was defined as the last measurement available during the treatment phase. Data were tested for normality using the Shapiro-Wilk test. If the normality test was not rejected, the parametric approach was used. For parametric data, within-patient comparisons were made using paired two-tailed *t* tests and between-group comparisons two-tailed unpaired *t* tests. For nonparametric data, within-

patient comparisons were made using Wilcoxon's signed-rank test; between-group comparisons were made using the Mann-Whitney *U* test. The  $\chi^2$  test was used for analyzing proportions of discontinuous variables. All statistical tests were two sided and performed at a significance level of  $\alpha = 5\%$ . Analyses were carried out using SPSS version 10 for Windows.

## RESULTS

### Subjects

A total of 94 subjects were screened, of whom 80 were randomized. Of the 14 not randomized, 5 withdrew consent and 9 were excluded because of impaired renal function ( $n = 5$ ) or noncompliance with treatment ( $n = 1$ ), and 1 was excluded after systemic corticosteroid therapy for an exacerbation of chronic obstructive pulmonary disease. Two subjects complained of significant gastrointestinal side effects during the run-in period, necessitating the withdrawal of metformin therapy (with subsequent resolution of symptoms) and thus exclusion from the study. There were 41 and 39 subjects who received insulin/metformin and insulin/repaglinide therapy, respectively. All received at least one dose of study medication and returned for at least one visit; hence, all subjects were included in the final analysis.

There were 39 subjects in the insulin/metformin group and 36 in the insulin/repaglinide group who completed the study. Of the two noncompleters in the insulin/metformin group, one withdrew

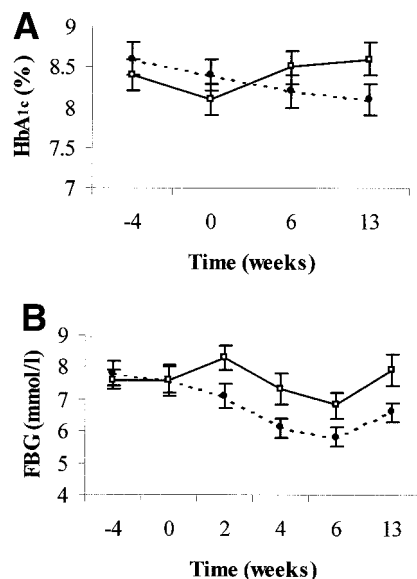
because of gastrointestinal side effects at 2 weeks, and one did not attend the final visit. In the repaglinide/insulin group, two subjects were withdrawn at 1 and 2 weeks, respectively, after ineffective therapy (symptomatic hyperglycemia), and one was withdrawn after 12 weeks of therapy because of severe hypertension. These subjects were converted to alternative insulin regimens.

Baseline characteristics of all patients at randomization are summarized in Table 1. The metformin group contained more females; however, no other significant differences were detected between the groups at baseline.

### Glycemic control

**HbA<sub>1c</sub> and FBG.** HbA<sub>1c</sub> and FBG were similar in both groups at baseline. HbA<sub>1c</sub> improved (nonsignificantly) with insulin/metformin by (mean) 0.4%, from 8.4 to 8.1% ( $P = 0.09$ ), but deteriorated with insulin/repaglinide by (mean) 0.4%, from 8.1 to 8.6% ( $P = 0.03$ ;  $P = 0.005$  between groups). FBG improved from 7.6 to 6.6 mmol/l ( $P = 0.03$ ) with insulin/metformin but rose (nonsignificantly) in the insulin/repaglinide group from 7.6 to 7.9 mmol/l ( $P = 0.4$ ;  $P = 0.04$  between groups) (Fig. 1).

**Seven-point blood glucose profile.** Seven-point blood glucose profiles were broadly similar at baseline, but by 13 weeks, poorer fasting control was demonstrated in the insulin/repaglinide group (6.4 mmol/l [insulin/metformin] vs. 7.6 mmol/l [insulin/repaglinide] [ $P =$

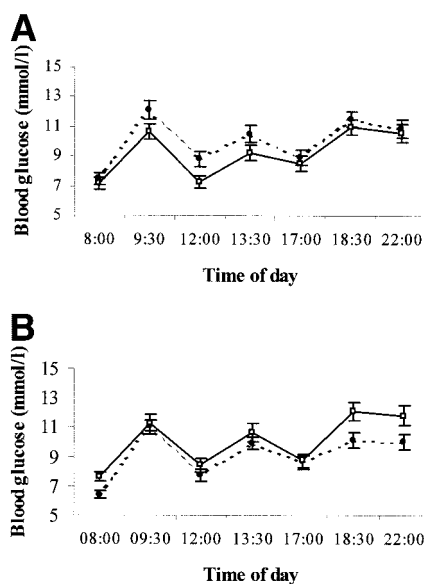


**Figure 1**—Glycemic control: HbA<sub>1c</sub> (A) and FBG (B). Data are expressed as means  $\pm$  SE. ●, Metformin; □, repaglinide.

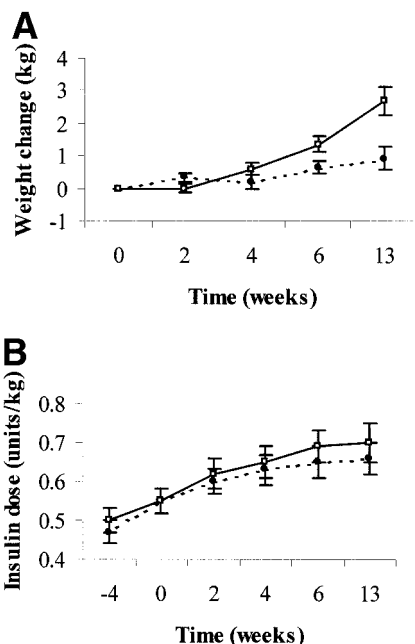
0.009]). The postevening meal (10.1 vs. 12.1 mmol/l [ $P = 0.03$ ]) and bedtime (10.0 vs. 12.8 mmol/l [ $P = 0.04$ ]) levels were also higher in the insulin/repaglinide group (Fig. 2).

### Weight gain and insulin requirement

Weight gain during the treatment period was  $0.9 \pm 0.4$  kg (mean  $\pm$  SE) for the insulin/metformin group ( $P = 0.01$ ) and  $2.7 \pm 0.4$  kg for the insulin/repaglinide



**Figure 2**—Seven-point profiles at baseline (A) and 13 weeks (B). ●, Metformin; □, repaglinide.



**Figure 3**—Weight change (A) and insulin requirement (B). Data are expressed as means  $\pm$  SE. ●, Metformin; □, repaglinide.

group ( $P < 0.0001$ ) ( $P = 0.002$  between groups). Insulin requirements at baseline were  $0.47 \pm 0.03$  and  $0.5 \pm 0.03$  units/kg for the insulin/metformin and insulin/repaglinide groups, respectively ( $P = 0.43$ ). Insulin dose increased by  $0.19 \pm 0.03$  to  $0.66 \pm 0.04$  units/kg in the insulin/metformin group and by  $0.21 \pm 0.03$  to  $0.7 \pm 0.05$  units/kg in the insulin/repaglinide group ( $P < 0.0001$  for both groups from baseline;  $P = 0.74$  between groups). The range of bedtime insulin requirement was 20–180 units (Fig. 3).

### Hypoglycemia

All reported episodes of hypoglycemia were mild. A total of 19 (46%) subjects in the insulin/metformin group and 23 (59%) subjects in the insulin/repaglinide group remained free from hypoglycemia throughout the study ( $P = 0.4$  between groups). Over the 13-week study period, the mean number of hypoglycemic episodes experienced per patient was  $1.56 \pm 0.4$  and  $0.97 \pm 0.26$  for the insulin/metformin and insulin/repaglinide groups, respectively ( $P = 0.28$  between groups).

Most recorded hypoglycemic episodes occurred before breakfast (86% for the insulin/metformin group and 72% for the insulin/repaglinide group [ $P = 0.6$ ]). Only five episodes of nocturnal hypogly-

cemia were recorded, all in the insulin/repaglinide group.

### Well-being and diabetes treatment satisfaction

Well-being (WBQ) and diabetes treatment satisfaction (DTSQ) scores were similar at baseline. Well-being scores improved (nonsignificantly) from  $50.4 \pm 2.0$  to  $50.9 \pm 2.1$  ( $P = 0.78$ ) in the insulin/metformin group and from  $47.5 \pm 1.8$  to  $48.5 \pm 1.8$  ( $P = 0.54$ ) in the insulin/repaglinide group. There were statistically significant changes in DTSQ scores in both groups. DTSQ scores increased from  $32.4 \pm 0.8$  to  $34.1 \pm 0.5$  ( $P < 0.01$ ) in the insulin/metformin group but fell from  $32.5 \pm 0.9$  to  $29.1 \pm 1.3$  ( $P = 0.002$ ) in the insulin/repaglinide group. Between the groups, this change in DTSQ scores was highly statistically significant ( $P = 0.0003$ ).

### Adverse events

A total of 93 adverse events were recorded throughout the study: 43 in the insulin/metformin group and 50 in the insulin/repaglinide group. Five serious adverse events occurred, and all were in the insulin/repaglinide group; one subject suffered a myocardial infarction, and another was hospitalized with chest pain (myocardial infarction excluded) on three separate occasions. One female subject was found to have an adrenal tumor (benign at surgical excision). Most commonly reported adverse events constituted gastrointestinal side effects, respiratory and urinary tract infections, headache, and itch. Of the 93 adverse events recorded, 10 were considered possibly or probably related to trial treatment. Hypoglycemia was recorded separately.

**CONCLUSIONS**—The aim of our study was to compare the effect on glycemic control, weight gain, and frequency of hypoglycemia of the short-acting meglitinide repaglinide versus metformin combined with bedtime NPH insulin in type 2 diabetic patients. After 13 weeks of treatment, subjects randomized to receive repaglinide (4 mg t.i.d.) with bedtime NPH insulin experienced a small deterioration in glycemic control (HbA<sub>1c</sub> +0.4%), and metformin/insulin-treated patients experienced a small improvement (HbA<sub>1c</sub> -0.4%). Both groups gained weight, but gain was significantly



less ( $\sim 2$  kg less) in individuals who remained on insulin/metformin therapy. Frequency of hypoglycemia was similar with both treatments; all were mild and self-treated.

Fasting glycemia was similar at baseline, but despite similar aggressive insulin dose titration in both groups, only 18 subjects in the metformin group and 10 in the repaglinide group achieved the target FBG ( $\leq 6.0$  mmol/l) at the final visit. Final HbA<sub>1c</sub> for these subjects was (mean) 8.0% (reference range 4.6–6.2%). Yki-Järvinen (19) suggested that achieving a fasting plasma glucose of  $< 6.0$  mmol/l with combination therapy corresponds with an HbA<sub>1c</sub> of  $\sim 7.5\%$ . Our results do not entirely support this, but our patients practiced home blood glucose monitoring with meters referenced for whole blood, not plasma. Plasma-referenced readings are  $\sim 10$ –15% above corresponding values for whole blood. Thus, it is likely that titrating to a similar fasting glucose target with plasma-referenced meters would provide further improvements in glycemic control, as measured by HbA<sub>1c</sub>. If “good” glycemic control (HbA<sub>1c</sub>  $< 7\%$ ) is to be achieved, however, it is likely that even lower target fasting glucose levels ( $< 5.5$  mmol/l) will be required. Also, our study was of a relatively short duration (13 weeks), with only three visits between randomization and completion of the study (at 2, 4, and 6 weeks), when the investigator was able to review blood glucose values and titrate insulin doses. More frequent insulin dose increments would be preferable. We have since adopted a patient-led insulin dose titration regimen according to a predetermined algorithm (3), with patients monitoring fasting glucose daily and increasing bedtime insulin by 2 or 4 units if three successive readings are  $> 6$  or 8 mmol/l, respectively. It is likely that the use of such an approach will provide better glycemic control than that observed in our study. With this algorithm, metformin combined with bedtime NPH insulin has been shown to improve glycemic control (to an HbA<sub>1c</sub> of 7.2% [reference range 4–6%]) while preventing weight gain in type 2 diabetic patients initiated on insulin therapy (3). However, our study suggests that metformin may only limit rather than prevent weight gain, although it is possible that the aggressive physician-led escalation of insulin dose (up to 20-unit increases at a

time) used in our study may have exacerbated weight gain.

Baseline WBQ scores were similar and improved (nonsignificantly) in both groups with no differences between the groups. DTSQ scores were also similar at baseline, but the insulin/metformin group showed a significant improvement of  $1.7 \pm 0.6$  points, whereas there was a significant reduction of  $-3.4 \pm 1.1$  points in the insulin/repaglinide group. This result suggests that the subjects favored treatment with insulin/metformin over insulin/repaglinide. It is possible, however, that the study design favored metformin because patients were preselected by their tolerance of metformin, and more frequent adverse events in the repaglinide group might have accounted for less favorable DTSQ scores. The number of subjects reporting adverse events during the study was, however, similar (30 patients in each group;  $P = 0.8$ ).

Repaglinide when used as monotherapy is as efficacious as metformin (8) and provides similar glycemic control to sulfonylureas with lower postprandial blood glucose excursions (9,10) and comparable (or less) hypoglycemia (11–14). In our study (in which the median diabetes duration was 120 months), no superiority was demonstrated by repaglinide with respect to prandial or overall glycemic control. This may reflect inadequate  $\beta$ -cell reserve at this stage of the disease when insulin secretagogues might be expected to be less efficacious. Patients intolerant of metformin frequently require insulin at an earlier stage (when the pancreatic insulin secretory capacity is greater), often given in combination with a sulfonylurea. Repaglinide combined with bedtime NPH insulin in patients with type 2 diabetes (median duration 96 months) poorly controlled with oral agents alone has been shown to be as efficacious as insulin/gliclazide (20), suggesting that this regimen may be useful if used earlier. Thus, the results of our study cannot be generalized to all insulin-requiring patients with type 2 diabetes.

In conclusion, despite theoretical advantages for short-acting meglitinide therapy combined with bedtime NPH insulin in type 2 diabetic patients who require insulin, in this study, metformin/insulin proved superior to repaglinide/insulin, providing better glycemic control with less weight gain, comparable hypo-

glycemia, and improved diabetes treatment satisfaction.

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We accept full responsibility for design, statistical analysis, interpretation of results, and the subsequent writing-up of this study.

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