Rapid and Short-Acting Mealtime Insulin Secretion With Nateglinide Controls Both Prandial and Mean Glycemia

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OBJECTIVE — The objective of the study was to assess the efficacy and safety of four fixed doses of nateglinide compared with placebo in the treatment of patients with type 2 diabetes with focus on the prandial state.

RESEARCH DESIGN AND METHODS — This randomized double-blind placebo-controlled multicenter study was conducted in 289 patients who received either nateglinide at doses of 30 mg (n = 51), 60 mg (n = 58), 120 mg (n = 63), or 180 mg (n = 57) or placebo (n = 60) before three main meals for 12 weeks. Levels of HbA_{1c}, fasting plasma glucose (FPG), fructosamine, and plasma lipids were measured at predetermined intervals, and the effects of nateglinide on prandial glucose insulin, C-peptide, and triglyceride levels were measured after a liquid standard meal (Sustacal; Mead Johnson, Evansville, IN). Adverse events and hypoglycemic episodes were recorded.

RESULTS — After a liquid meal challenge, nateglinide rapidly increased mealtime insulin levels within 30 min of drug intake and reduced mealtime glucose excursions without affecting triglyceride levels. At study end point, reduction of HbA_{1c} levels was statistically significantly greater with nateglinide at doses of 60, 120, and 180 mg than placebo (−0.45, −0.62, and −0.64%, respectively; $P < 0.05$). The mean level of FPG was significantly reduced versus placebo in the nateglinide 120-mg group only (−1.14 mmol/l; $P < 0.01$). Overall, nateglinide was well tolerated.

CONCLUSIONS — This study demonstrated that nateglinide improves mealtime and mean glycemic control in a dose-dependent manner by restoring early insulin secretion phase. Nateglinide was well tolerated and is suitable for the treatment of patients with type 2 diabetes.

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The Diabetes Intervention Study, a prospective population-based multicenter trial of newly detected cases of type 2 diabetes, has indicated that good control of postprandial blood glucose, blood pressure, and triglycerides is associated with a lower incidence of coronary heart disease and death (1). In addition, the U.K. Prospective Diabetes Study (UKPDS) has confirmed that intensive control of HbA_{1c} and fasting plasma glucose (FPG) in type 2 diabetic patients treated with sulfonylureas or insulin for >10 years substantially decreased the risk of microvascular complications (2). However, such beneficial effects were not observed in macrovascular disease or diabetes-related mortality (2). Although fasting insulin and glucose levels were measured throughout the UKPDS, no prandial (mealtime) insulin or glucose data were available from this study. Recent publications have shown that 2-h postchallenge hyperglycemia is also associated with increased total mortality (3) and coronary heart disease mortality (4). A recent study has suggested that prandial plasma glucose concentrations contribute to and are significantly better predictors of long-term glycemic control in diabetes than FPG (5). Furthermore, a study of the correlations of the 30-min and 2-h plasma insulin concentrations with the 2-h plasma glucose concentration has shown that impaired early insulin release during a meal leads to impaired suppression of hepatic glucose production and augmented mealtime glucose excursions (6).

Thus, there is a clear need to achieve good control of prandial glucose excursions and FPG if overall diabetic morbidity and mortality are to be reduced. Currently available oral antidiabetic agents that stimulate insulin secretion do so by enhancing late insulin secretion that may induce moderate-to-severe hypoglycemia. In contrast, nateglinide is a derivative of the amino acid D-phenylalanine (7), which is chemically distinct from other oral antidiabetic agents and acts directly on the pancreatic β-cells to stimulate insulin release that is rapid and of short duration (8). Because chronic hyperinsulinemia may affect body weight, plasma lipid profile, and blood pressure and may thereby increase the risk of cardiovascular disease (9), maintaining glucose control by increasing early postchallenge insulin secretion without incurring chronic hyperinsulinemia is potentially advantageous.

The primary objectives of this study were to evaluate the effects of nateglinide versus placebo on glycemic control, including prandial insulin and glucose control, and to assess the tolerability and safety of nateglinide in patients with type 2 diabetes.

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Abbreviations: AUC, area under the plasma concentration-time curve; FPG, fasting plasma glucose; UKPDS, U.K. Prospective Diabetes Study.

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

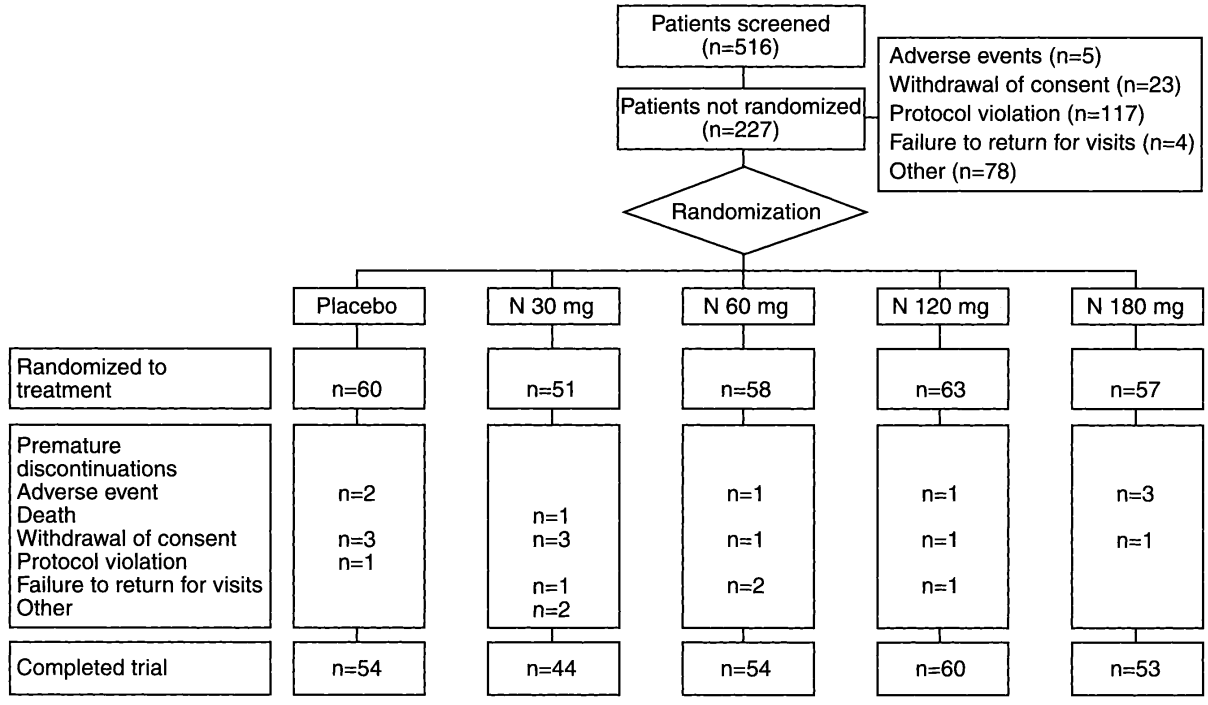

Figure 1—*Study completion status. N, nateglinide.*

RESEARCH DESIGN AND METHODS

Study protocol

This multicenter prospective randomized double-blind parallel-group study included a 4-week single-blind placebo run-in screening period after which patients were randomized to receive double-blind treatment with either placebo or nateglinide at doses of 30, 60, 120, and 180 mg taken 10 min before breakfast, lunch, and dinner for 12 weeks.

Men and women aged 30–75 years with type 2 diabetes without complications who were treated with diet and exercise were eligible for inclusion. Patients were randomized if their mean FPG level was ≥7.8 mmol/l and the mean level of two HbA_{1c} measurements was in the range of 6.8–10.5%. Patients were excluded from randomization and double-blind treatment if they had confirmed FPG >15 mmol/l and complications or concomitant treatment affecting the efficacy or safety assessments. All other antidiabetic agents were discontinued at least 3 months before randomization.

Visits were performed at weeks −4, −2, 0, 2, 4, 8, and 12. Patients were maintained on their normal antidiabetic diets throughout the study. At baseline (week 0) and at weeks 4 and 12, a Sustacal liquid meal replaced the normal breakfast. Sustacal liquid meal was ingested 10 min after the administration of nateglinide or placebo.

Drug treatment and evaluation

Nateglinide was administered as either 30- or 60-mg oral tablets that were identical to the placebo tablets. In all treatment groups, three tablets were taken 10 min before each main meal (breakfast, lunch, and dinner), using the double-dummy method to maintain blinding.

The laboratory measurements performed to assess the overall metabolic impact of different doses of nateglinide included HbA_{1c} (results standardized to the high-performance liquid chromatography Diamat ion-exchange method), FPG (the primary end points of the study), and fructosamine. Blood samples were obtained before medication and at 15, 30, 60, 120, 180, and 240 min after Sustacal ingestion. Levels of glucose, insulin, C-peptide, and nateglinide were measured in all samples, and triglycerides were determined in the premedication and 120-min samples. A fasting lipid profile (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides) was also measured. Glucose was measured by an enzymatic method (Boehringer Mannheim, Mannheim, Germany) and a Cobas Bio analyzer (Roche Diagnostics, Basel, Switzerland). Fructosamine was measured by a spectrophotometric method (Roche, Basel) and a Cobas Bio analyzer. Triglyceride levels were measured with an enzymatic-refectometric method (Johnson and Johnson, Rochester, NY) using a Vitros 750 XR analyzer (Ortho Clinical Systems, Rochester, NY). Levels of insulin and C-peptides were measured by radioimmunoassays (Pharmacia, Uppsala, Sweden, and DPC, Los Angeles, CA, respectively) using a Gamma-counter (Wallace, Turku, Finland) and Multicalc (Wallace). Safety parameters included physical examination, vital signs, electrocardiograms, laboratory evaluations (hematology, chemistry, and urinalysis), adverse events, and self-monitoring of blood glucose levels for suspected hypoglycemia. Symptomatic suspected hypoglycemic episodes were recorded even if not confirmed by a low blood glucose measurement. Also, asymptomatic low fingerstick blood glucose values <2.8 mmol/l that corresponded to a plasma level <3.3 mmol/l were recorded.

Statistical analysis

The analysis of the HbA_{1c}, FPG, Sustacal challenge data, fructosamine, and lipid variables was carried out in the intention-

Table 1—*Demographic and glycemic parameters at baseline*

	Placebo	Nateglinide (mg)			
		30	60	120	180
n	60	51	58	63	57
Sex					
M	36	36	41	44	36
F	24	15	17	19	21
Mean age (years)	57.4 ± 9.6	58.0 ± 9.8	56.1 ± 9.7	54.4 ± 11.6	56.5 ± 9.9
<65	45	34	45	50	42
≥65	15	17	13	13	15
BMI (kg/m^2)	28.3 ± 3.2	29.0 ± 3.3	28.1 ± 3.2	28.6 ± 3.7	28.8 ± 3.4
Duration of type 2 diabetes (years)	5.4 ± 5.0	4.5 ± 4.8	6.2 ± 6.4	4.4 ± 4.0	3.7 ± 3.3
Baseline FPG (mmol/l)	10.0 ± 2.0	10.3 ± 2.2	9.9 ± 2.1	10.3 ± 1.9	10.1 ± 2.1
Baseline fructosamine (μmol/l)	328.1 ± 55.3	321.8 ± 53.8	313.1 ± 46.0	316.6 ± 55.1	319.6 ± 52.7
Baseline HbA_{1c} (%)	8.5 ± 1.0	8.4 ± 1.1	8.3 ± 1.1	8.3 ± 0.9	8.5 ± 1.1

Data are *n* or means ± SD.

to-treat population using the last observation carried forward approach for those subjects who did not have a week-12 assessment in change from baseline. An analysis of variance was used to assess treatment differences. The sample size of 60 patients per treatment group was sufficient to detect a 1% change in levels of HbA_{1c} versus placebo with a type 1 error of 5%, a power of 80%, and a drop-out rate of 20%.

RESULTS

Demographics and participant flow

A total of 516 patients were screened, and 289 were randomized into the double-blind treatment period (Fig. 1). Of the 289 patients randomized, almost all patients were Caucasian, 193 (66.8%) were men, and 73 (25.3%) were aged 65 years or older. Treatment groups were comparable at baseline with respect to demographic characteristics (Table 1). Overall, 202 patients (69.9%) took at least one concomitant medication during the treatment period, mostly for diseases associated with diabetes, such as hypertension or hypercholesterolemia.

Meal challenge

A rapid increase in insulin secretion was observed during the liquid meal challenge. The increases were essentially dose-dependent, with maximal values observed 30 min postdose and a return to predose levels within 3–4 h (Fig. 2).

The increase from baseline (week 0) in total area under the plasma concentration-time curve ($AUC_{0-4\,h}$) for insulin and C-peptide was statistically significant in the nateglinide 60-, 120-, and 180-mg groups compared with the group administered placebo (Table 2). Corresponding reductions in mean plasma glucose were observed 1–4 h postdose compared with the group administered placebo (Fig. 3). The reductions from baseline (week 0) in total $AUC_{0-4\,h}$ for plasma glucose concentrations were statistically significant in all of the nateglinide groups compared with the group administered placebo (Table 2).

Nateglinide did not affect 2-h triglyceride levels after liquid meal challenge.

Fasting efficacy data

Mean HbA_{1c}, FPG, fructosamine, and fasting lipid concentrations (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) at baseline were similar in all treatment groups and remained essentially unchanged throughout the study in the placebo group. The reduction in HbA_{1c} at study end point (week 12 or last observation carried forward) was statistically significantly greater than placebo in the nateglinide 60- (−0.45%; $P < 0.05$) and 120- and 180-mg groups (−0.62 and −0.64%, respectively; $P < 0.001$). A reduction in the mean FPG concentration from baseline was observed throughout the study in each of the nateglinide treatment groups and was statistically significant in the nateglinide 120-mg group (−1.14 mmol/l; $P < 0.01$ vs. placebo). The reduction in mean fructosamine concentration was statistically significantly greater than with placebo in the nateglinide 60- (−24.0 μmol/l; $P < 0.01$ vs. placebo) and 120- and 180-mg groups (−31.4 and −35.1 μmol/l, respectively; $P < 0.001$ vs. placebo) at study end point (Table 2).

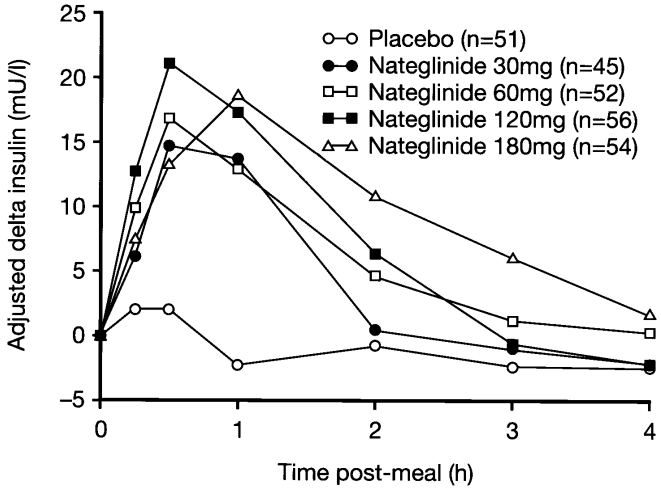

Figure 2—*Adjusted mean change versus baseline in prandial plasma insulin at week 12.*

Table 2—*Changes in meal challenge data and HbA_{1c}, FPG, and fructosamine concentrations at study end point*

		Nateglinide (mg)			
	Placebo	30	60	120	180
Meal challenge parameters (change from baseline)					
n	48	46	47	53	48
$AUC_{0-4\,h}$ glucose ($h \cdot mmol \cdot l^{-1}$)	3.2 (0.3 to 6.0)	−3.6* (−6.4 to −0.8)	−8.0* (−10.6 to −5.5)	−8.5* (−11.0 to –5.9)	−8.1* (−10.8 to −5.4)
$AUC_{0-4\,h}$ insulin ($h \cdot mU \cdot l^{-1}$)	6.0 (−8.7 to 20.7)	19.0 (4.2 to 33.9)	35.5† (22.3 to 48.8)	49.1* (35.8 to 62.3)	46.2* (32.4 to 59.9)
$AUC_{0-4\,h}$ C-peptide ($h \cdot pmol \cdot ml^{-1}$)	−0.2 (−0.7 to 0.4)	0.4 (−0.2 to 0.9)	1.2* (0.7 to 1.7)	1.8* (1.3 to 2.3)	1.6* (1.1 to 2.1)
Mean glycemia parameters					
n	60	51	58	63	57
HbA_{1c} (%)	0.07 (−0.18 to 0.32)	−0.20 (−0.48 to 0.07)	−0.38 (−0.62 to −0.13)	−0.55 (−0.79 to −0.30)	−0.56 (−0.81 to −0.31)
Difference from placebo	—	−0.27 (−0.65 to 0.10)	−0.45† (−0.80 to −0.10)	−0.62‡ (−0.97 to −0.27)	−0.64‡ (−0.99 to −0.28)
FPG (mmol/l)					
Change from baseline	0.22 (−0.27 to 0.72)	−0.42 (−0.95 to 0.12)	−0.46 (−0.94 to 0.02)	−0.92 (−1.40 to −0.44)	−0.56 (−1.05 to −0.08)
Difference from placebo	—	−0.64 (−1.37 to 0.08)	−0.69 (−1.37 to 0.00)	−1.14* (−1.83 to −0.46)	−0.79 (−1.48 to −0.10)
Fructosamine (μmol/l)					
Change from baseline	7.7 (−2.8 to 18.3)	0.4 (−11.0 to 11.8)	−16.2 (−26.9 to −5.6)	−23.7 (−33.8 to −13.6)	−27.3 (−37.4 to −17.3)
Difference from placebo	—	−7.4 (−22.9 to 8.14)	−24.0* (−38.9 to −9.06)	−31.4‡ (−46.0 to −16.8)	−35.1‡(−49.6 to −20.6)

Data are *n* or means (95% CI). Changes versus placebo (analysis of variance model): *$P < 0.01$, †$P < 0.05$, ‡$P < 0.001$.

No statistically significant differences between the nateglinide and placebo groups in the concentrations of any of the serum lipids were observed at study end point.

Safety

A total of 6 patients (10.0%) in the placebo group and 18 patients (7.9%) in the pooled nateglinide group did not complete the study. However, the discontinuation rates for adverse events were low in both groups (two patients [3.3%] in the placebo group and five patients [2.2%] in the pooled nateglinide group). One patient in the nateglinide 180-mg group was discontinued because of elevated liver function tests (gamma-glutamyl transferase, alanine aminotransferase, and aspartate aminotransferase) that were considered to be possibly related to the study drug and that returned to normal at the follow-up visit. One patient in the nateglinide 30-mg group with a history of chronic coronary artery disease died from myocardial infarction ascribed to coexistent disease; his death, therefore, is considered unlikely to be related to the study drug.

The incidence of adverse events for all randomized patients was higher in the pooled nateglinide group (49.3%) (*n* = 229) compared with the placebo group (35.0%) (*n* = 60). Although there were more adverse events judged as possibly or probably related to treatment reported for patients in the pooled nateglinide group than in the placebo group, the incidence of events was not dose dependent. Most of the events were mild symptoms suggestive of hypoglycemia, such as increased sweating (*n* = 16 [7.0%]), tremor (*n* = 14 [6.1%]), dizziness (*n* = 7 [3.1%]), increased appetite (*n* = 6 [2.6%]), and asthenia (*n* = 4 [1.7%]). Only three patients in the 120-mg group with events suggestive of hypoglycemia had a blood glucose value in the 2.7–3.3 mmol/l range, but no patients were discontinued for hypoglycemia. The predominant causes of symptoms suggestive of hypoglycemia were strenuous exercise or a missed or delayed meal. All such events occurred during the daytime, and most patients recovered within 15 min. A patient from the nateglinide 30-mg group with suspected serious hypoglycemia experienced a fall with a short loss of consciousness 5 h after medication and meal intake; however, she recovered spontaneously and

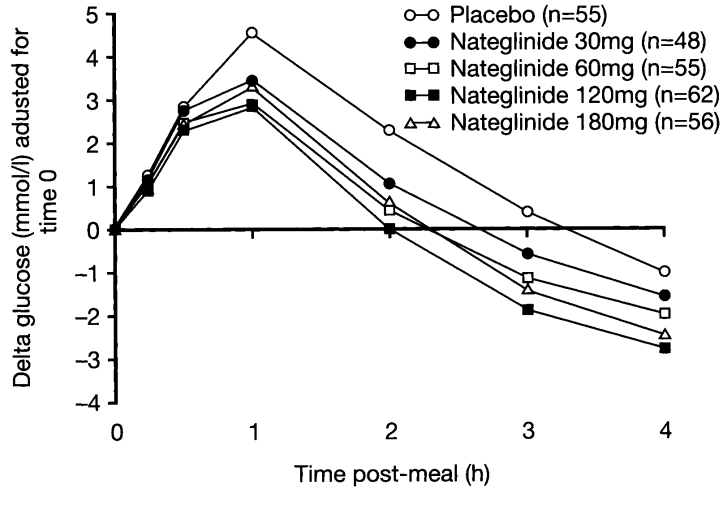

Figure 3—*Adjusted mean change in prandial glucose at week 12.*

completed the study uneventfully. A blood glucose measurement was not performed at the time of the event.

Hematologic and biochemical analyses did not reveal further differences between the treatment groups. There were no relevant electrocardiogram abnormalities or changes in vital signs. Changes in body weight ranged from −0.38 to 0.72 kg in the nateglinide 120-mg group.

CONCLUSIONS — The study population was representative of mild to moderately severe type 2 diabetes with mean baseline HbA_{1c} values of 8.3–8.5%. The mean FPG values at baseline were in the range between 9.9 and 10.3 mmol/l, and one-quarter of the study population was aged 65 years and older. Only small changes versus baseline were observed in the placebo group, because stable baseline levels of glycemic control were established by using a long washout period in patients previously on oral antidiabetic treatment (HbA_{1c} increase from baseline at study end point in the placebo group was only 0.07%).

Administration of 30–180 mg of nateglinide before meals consistently decreased all parameters of glycemic control, such as mealtime glycemia, FPG, fructosamine, and HbA_{1c}, compared with placebo at end point and from baseline. The results of the liquid meal challenge confirmed the rapid onset of prandial insulin secretion with high insulin levels present 15 min postdose and maximal plasma concentrations observed 30–60 min postdose.

Defects in early insulin secretion in patients with type 2 diabetes or at increased risk for diabetes were first identified in the 1960s (10). These abnormalities contribute to prandial hyperglycemia and late hyperglycemia, which lead to marked delay in the inhibition of hepatic glucose production (5,6). These defects were also observed in the patients of this study who were administered placebo. The administration of nateglinide induced a rapid stimulation of insulin secretion of short duration with relevant changes between placebo and active arms between 15 and 30 min after drug intake. Insulin levels returned to baseline values 3–4 h after drug intake. The induction of early insulin secretion with nateglimide offers an advantage over glyburide, which does not have any appreciable effect on early-phase insulin secretion but enhances late insulin secretion in patients with type 2 diabetes (11), and repaglinide, which produces a longer duration of insulin stimulation (12).

The rapid and relevant increase in insulin secretion after nateglinide administration blunted the sharp rise in glucose that follows a meal as indicated by the 1- to 4-h postmeal decreases in glucose excursions. The decreases in parameters assessing mean glucose exposure, such as HbA_{1c} and fructosamine, reflect decreases in mealtime glycemia. Nateglinide showed a relatively small effect on FPG. This might reflect an indirect rather than a direct effect on hepatic glucose production given the short duration of insulin stimulation that was observed with all tested doses of nateglinide.

Mealtime glucose excursions have been shown to make a major contribution to overall poor glycemic control in type 2 diabetes (5), and the rapid-onset/short-duration insulin-release profile seen with nateglinide after liquid meal challenge appears to mimic the physiological early phase of insulin release that is deficient in patients with type 2 diabetes. Similar observations have been made with a short-acting insulin (13).

Furthermore, mealtime and postchallenge glucose have been shown to be linked with an increased risk of overall mortality (3) and an increased risk of diabetic complications, such as nephropathy, retinopathy, neuropathy, atherosclerosis, and myocardial infarction (1,14,15). Treatments aimed at reducing mealtime glycemic excursions as monotherapy or in combination with drugs having a complementary mode of action may further contribute to alleviating the burden on patients with type 2 diabetes.

Overall, nateglinide was well tolerated. The most common adverse events were equally distributed among the different treatment groups with the exception of predominantly mild symptoms suggestive of hypoglycemia in the pooled nateglinide group. Most symptoms of hypoglycemia were not associated with low blood sugar values and can therefore be classified as relative hypoglycemia. Confirmed hypoglycemia (blood glucose value ≤3.3 mmol/l), was observed in three patients (1.3%).

In conclusion, this study has demonstrated that nateglinide improves glycemic control in a dose-dependent manner through increased mealtime insulin secretion. Nateglinide seems to be particularly effective in restoring early insulin secretion in response to a meal, which is of crucial importance for regulation of the postprandial state. Nateglinide was well tolerated and is suitable for the treatment of patients with type 2 diabetes.

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References

1. Hanefeld M, Fischer S, Julius U, Schulze J, Schwanebeck U, Schmechel H, Ziegelasch HJ, Lindner J: Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study. 11-year follow up. *Diabetologia* 39:1577–1583, 1996
2. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
3. The DECODE Study Group: Two-hour post-challenge glucose concentrations are better predictors of mortality than fasting glucose alone: the DECODE Study. *Lancet* 354:617–621, 1999
4. Barrett-Connor E, Ferrara A: Isolated postchallenge hyperglycemia and the risk of fatal cardiovascular disease in older women and men: the Rancho Bernardo Study. *Diabetes Care* 21:1236–1239, 1998
5. Avignon A, Radauceanu A, Monnier L: Nonfasting plasma glucose is a better marker of diabetic control than fasting plasma glucose in type 2 diabetes. *Diabetes Care* 20:1822–1826, 1997
6. Mitrakou A, Kelley D, Mokan M, Veneman T, Pangburn T, Reilly J, Gerich J: Role of reduced suppression of glucose production and diminished early insulin release in impaired glucose tolerance. *N Engl J Med* 326:22–29, 1992
7. Shinkai H, Toi K, Kumashiro I, Seto Y, Fukuma M, Dan K, Toyshima S: N-acylphenylalanines and related compounds: a new class of oral hypoglycemic agents. *J Med Chem* 31:2092–2097, 1988
8. Sato Y, Nishikawa M, Shinkai H, Sukegawa E: Possibility of ideal blood glucose control by a new oral hypoglycemic agent, N-[(trans-4-isopropylcyclohexyl)-carbonyl]-D-phenylalanine (A-4166), and its stimulatory effect on insulin secretion in animals. *Diabetes Res Clin Pract* 12:53–59, 1991
9. DeFronzo RA, Ferrannini E: Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 14:173–194, 1991
10. Yalow RS, Berson SA: Plasma insulin con-

centrations in nondiabetic and in early diabetic subjects: determinations by a new sensitive immuno-assay technique. *Diabetes* 9:254–260, 1960
11. Groop LC: Sulfonylureas in NIDDM. *Diabetes Care* 15:737–754, 1992
12. Leclerq-Meyer V, Ladriere L, Fuhlendorff J, Malaisse WJ: Stimulation of insulin and somatostatin release by two meglitinide analogs. *Endocrine* 7:311–317, 1997
13. Bruttomesso D, Pianta A, Mari A, Valerio A, Marescotti MC, Avogaro A, Tiengo A, Del Prato S: Restoration of early rise in plasma insulin levels improves the glucose tolerance of type 2 diabetes patients. *Diabetes* 48:99–105, 1999
14. Yamasaki Y, Kawamori R, Matsushima H, Nishizawa H, Kodama M, Kabota M, Kajimoto Y, Kamada T: Asymptomatic hyperglycaemia is associated with increased intimal plus medial thickness of the carotid artery. *Diabetologia* 38:585–591, 1995
15. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997