0013-7227/02/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 87(9):4171–4176

doi: 10.1210/jc.2002-020068

Efficacy and Safety of Nateglinide in Type 2 Diabetic Patients with Modest Fasting Hyperglycemia

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Nateglinide is a fast-acting insulin secretion agent that specifically targets postprandial hyperglycemia in patients with type 2 diabetes. The recent reduction in the diagnostic criteria for diabetes and improved understanding of the importance of early insulin secretion served as the rationale for this multicenter, double-blind, randomized, parallel-group, 24-wk study performed in 675 patients with type 2 diabetes but only moderately elevated fasting plasma glucose (FPG) (FPG = 7.0–8.3 mmol/liter) to assess the efficacy and safety of three fixed doses of nateglinide (30, 60, or 120 mg, with meals). A substudy of the effects on early insulin release and prandial glucose excursions following a standardized breakfast was performed in 127 subjects. Nateglinide was well tolerated and elicited a dose-dependent reduction of placebo-adjusted hemoglobin A_{1c} ($\Delta = -0.26$ to -0.39%) and FPG ($\Delta = -0.51$ to -0.73 mmol/liter) accompanied by a dose-related increase in suspected hypoglycemic episodes. However, confirmed hypoglycemia occurred in only 5.3% of patients treated with the highest dose, compared with 1.2% in placebo-treated patients ($P < 0.05$). Nateglinide increased early insulin release and reduced prandial glucose excursions ($P < 0.05$ *vs.* placebo). In sum, nateglinide is a safe and effective therapeutic option for treatment of patients with mild to moderate fasting hyperglycemia. (*J Clin Endocrinol Metab* 87: 4171–4176, 2002)

THE DIABETES CONTROL and Complications Trial (DCCT) in patients with type 1 diabetes mellitus and the United Kingdom Prospective Diabetes Study in patients with type 2 diabetes mellitus (T2DM) have convincingly established that intensive therapy to reduce overall glycemic exposure, as reflected by hemoglobin A_{1c} (HbA_{1c}) reduces the incidence and progression of the microvascular complications of diabetes (1, 2). Because there is no threshold for the reduction of risk, it has been suggested that the therapeutic goal for treating diabetes should be normalization of glucose levels. However, as this target is approached, the incidence of serious hypoglycemia increases dramatically (3, 4) and limits attainment of the therapeutic goal.

Based on increasing understanding of the pathogenesis of diabetes and its complications, in 1997 the American Diabetes Association (ADA) lowered the recommended fasting plasma glucose (FPG) level at which diabetes should be diagnosed from 7.8 to 7.0 mmol/liter (140 to 126 mg/dl) (5). Although many patients with only modestly elevated FPG can achieve good glycemic control through diet and exercise, many also require pharmacologic intervention, mandated by the ADA if preprandial (*i.e.* fasting) blood glucose levels exceed 7.8 mmol/liter (140 mg/dl) or if HbA_{1c} levels exceed 8.0% (6).

Nateglinide (Starlix, Novartis Pharmaceuticals, East Hanover, NJ) is a recent addition to the therapeutic armamentarium available for the treatment of T2DM (7), which may be particularly suited for use in patients with only modestly elevated FPG. Nateglinide is a rapid-onset and rapidly reversible insulinotropic agent that restores early prandial insulin secretion in a glucose-dependent fashion and thereby specifically targets postprandial hyperglycemia (8). Because of its short-lived and glucose-dependent insulinotropic action, nateglinide has a low hypoglycemic potential (9) and may therefore allow more aggressive therapeutic goals. Because defective early insulin secretion occurs very early in the progression of T2DM and indeed loss of early insulin secretion determines whether an individual with impaired glucose tolerance develops T2DM (10), an agent that restores early insulin secretion may be an attractive option for use in recently diagnosed, mildly hyperglycemic patients.

The present work describes a double-blind, fixed-dose, randomized, parallel group, dose-ranging study designed to assess the efficacy and safety of nateglinide in patients with T2DM and only modestly elevated FPG (7.0–8.3 mmol/liter = 126–150 mg/dl). A substudy was performed to examine prandial glucose and insulin profiles to verify the primary mechanism of action in this patient group.

Subjects and Methods

Male and female patients aged 30 yr or older with a medical history of T2DM for at least 6 wk and maintained on diet alone for at least 6 wk before screening were recruited in 103 study centers in 12 countries. Patients agreed to maintain their prior diet and exercise habits during the study. Patients were excluded from the study if they had a history of type 1 diabetes mellitus, diabetes that resulted from pancreatic injury, or acute metabolic or significant diabetic complications. Patients who had received oral antidiabetic treatment during the previous 3 months or intense insulin treatment within the past 6 months or with known

Abbreviations: a.c., With meals; ADA, American Diabetes Association; AE, adverse event; AUC, area under the curve; BMI, body mass index; DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c}; ITT, intention to treat; PPG, postprandial glucose; SMBG, self-monitoring blood glucose; T2DM, type 2 diabetes mellitus.

sensitivity to drugs similar to nateglinide were excluded, as were patients with a history of cardiovascular events within the past 6 months; chronic liver disease; persistent elevations of alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase more than 2 times the upper limit of normal; direct bilirubin more than 1.3 times upper limit of normal; or fasting triglycerides more than 7.9 mmol/liter within the past 3 months.

Patients were included in the double-blind active treatment period if the mean of FPG measurements at study entry and after 2 wk was in the range of 7.0–8.3 mmol/liter but excluded if either FPG was less than 6.1 mmol/liter or more than 10 mmol/liter. However, 49 subjects with a mean baseline FPG less than 6.9 mmol/liter and 32 subjects with a mean baseline FPG more than 8.3 mmol/liter were included in the intention-to-treat (ITT) population and analysis despite the protocol violation. Patients were also excluded if body weight had changed by more than 5% between study entry and randomization, the serum creatinine was more than 220 μmol/liter, thyroid hormone replacement therapy had been initiated less then 3 months before study entry, or the thyroid stimulating hormone level was abnormal. Informed consent was obtained from all participants, and the study was performed in accordance with the Declaration of Helsinki and the Rules Governing Medicinal Products in the European Community following Institutional Review Board approvals.

Materials and methods

Study design. This was a randomized, double-blind, parallel group study to evaluate the efficacy, safety, and tolerability of nateglinide *vs.* placebo in patients with T2DM and an FPG between 7.0 and 8.3 mmol/liter (126–150 mg/dl). A total of 675 patients were randomized in approximately equal numbers at wk 0 to receive nateglinide 30 mg, 60 mg, 120 mg, or placebo taken up to 30 min before breakfast, lunch, and dinner [with meals (a.c.)] for 24 wk. This was preceded by a 4-wk single-blind run-in period during which all patients took placebo before the three main meals.

A substudy to assess the effect of nateglinide on prandial glucose excursions and insulin secretion was performed in 127 subjects with approximately 32 patients per arm. In this substudy following an overnight fast, a standard 475-kcal breakfast was administered immediately before initiation of treatment and after 24 wk of treatment. The breakfast consisted of 180 ml orange juice, two slices of toast with butter/margarine (10 g) and preserves (20 g), and 120 ml whole milk.

Efficacy and safety assessments. The primary efficacy variable was HbA_{1c} (change from baseline at end of study). Body weight and FPG were secondary efficacy variables. Blood samples for HbA_{1c} and FPG measurements were obtained between 0700 and 1000 h from patients fasted for at least 7 h at wk 0, 4, 8, 12, 16, and 24. Patients also underwent physical examination, electrocardiogram assessment, measurement of vital signs, and determination of standard laboratory parameters (hematology, biochemistry, and urinalysis). For the substudy, predose blood samples were drawn following an overnight fast after which the study medication was given. Ten minutes later, patients were given a standard 475-kcal breakfast, and blood samples were obtained at seven time points after the meal (15, 30, 60, 90, 120, 180, and 240 min). Blood HbA_{1c} levels were measured with the Diamat (Bio-Rad Laboratories, Inc., Hercules, CA) ion-exchange method (normal range 4.0–6.0%), plasma glucose levels were measured by a hexokinase method, and insulin was measured by RIA. Laboratory samples were processed through central laboratories (CRL, DDL, Medinet, and Sydpath).

Adverse events were recorded throughout the study and were rated by the investigator as to their severity and relationship to study medication. All patients were provided with a self-monitoring blood glucose (SMBG) device at study entry and instructed to take a blood glucose measurement for all episodes of suspected hypoglycemia. All suspected symptomatic hypoglycemic episodes were recorded as adverse events, with or without the presence of an SMBG value. Confirmed hypoglycemia was defined as symptoms accompanied by an SMBG plasma equivalent value of 3.3 mmol/liter or less. Compliance was assessed by pill count at each visit.

Statistical analysis. The ITT population was used for assessment of change from baseline of HbA_{1c} at wk 24 and for the secondary efficacy parameters using last observation carried forward for patients who did not complete the 24-wk trial. Baseline comparability among the treatment groups for demographic and baseline efficacy variables was examined using the Cochran-Matel-Haenszel test for qualitative variables and an F test for quantitative variables. An analysis of covariance model that included effects for treatment, center, baseline measure, and treatment by center interaction and baseline interaction was used to compare the effects of the four treatments. Analyses were carried out using two-sided tests and a statistical significance level of 0.05. Subanalyses of efficacy data (without statistical testing) were carried out according to demographic characteristics to identify patient groups most appropriate for nateglinide monotherapy. Accordingly, change from baseline of HbA_{1c} was compared between males and females, patients with body mass index (BMI) less than 30 or 30 kg/m^2 or more, patients aged less than 65 yr or 65 yr of age or more, and patients with baseline HbA_{1c} levels less than 6.5% or 6.5% or more. Because a high ratio of baseline HbA_{1c} to FPG might serve to identify patients with predominantly prandial hyperglycemia, the change in HbA_{1c} was correlated with this baseline ratio to determine whether this factor influenced the response to treatment. The responder rate was also calculated, response being defined as achieving HbA_{1c} of less than 6.0%, the upper limit of normal of the assay. In the substudy, 4-h areas under the curve (AUCs) were calculated for the prandial data using the trapezoidal method. Statistical comparisons were made only on these parameters and on the 30-min incremental insulin value and the 2-h postprandial glucose (PPG) value.

Results

Study subjects

Table 1 reports the baseline demographic and background characteristics of the randomized population. There were no differences among treatment groups in any of the demographic or baseline characteristics. The majority of patients were Caucasian, approximately 60% were male, and 36% of patients were 65 yr of age or older. Just under 40% of patients were obese (BMI 30 kg/m^2 or more), and baseline FPG and HbA_{1c} levels were very similar among the treatment groups and only modestly elevated.

Efficacy

In placebo-treated patients, glycemic control deteriorated modestly over the 24 wk of study (Δ HbA_{1c} = +0.16 ± 0.05%), whereas nateglinide produced a dose-related reduction of HbA_{1c}. The least square mean changes of HbA_{1c} from baseline relative to placebo (−0.26 ± 0.05, −0.31 ± 0.04, −0.39 ± 0.05 for 30 mg, 60 mg, and 120 mg, respectively) were highly significant ($P < 0.001$) and may be considered clinically meaningful in light of the very modest elevation of HbA_{1c} at baseline seen in these moderately hyperglycemic patients. Figure 1 depicts the time course of the change from baseline in HbA_{1c} that occurred in the four cohorts. The maximum effect of nateglinide was seen after 16 wk of treatment; HbA_{1c} levels appeared to increase slightly thereafter. Responder analysis revealed that at the end of study, normal HbA_{1c} levels (<6.0%) were achieved by 22.2%, 24.8%, 25.9%, and 37.9% of the patients in the placebo, nateglinide 30 mg, 60 mg, and 120 mg arms, respectively.

To attempt to identify patient populations most appropriate for nateglinide monotherapy, several subanalyses were performed. Gender and age did not appear to influence the efficacy of nateglinide (data not shown). However, nateglinide (120 mg, a.c.) was somewhat more effective in patients with baseline HbA_{1c} 6.5% or more (placebo-adjusted ΔHbA_{1c} = −0.51%) than in patients with baseline HbA_{1c} levels less than

TABLE 1. Baseline demographic and background characteristics of randomized subjects

Variable	Nateglinide 30 mg (n = 166)	Nateglinide 60 mg (n = 175)	Nateglinide 120 mg (n = 171)	Placebo (n = 163)	Total (n = 675)
Sex, n (%)					
Male	105 (63.3)	107 (61.1)	112 (65.5)	98 (60.1)	422 (62.5)
Female	61 (36.7)	68 (38.9)	59 (34.5)	65 (39.9)	253 (37.5)
Race, n (%)					
Caucasian	162 (97.6)	163 (93.1)	163 (95.3)	157 (96.3)	645 (95.6)
Black	2 (1.2)	1 (0.6)	2 (1.2)	2 (1.2)	7 (1.0)
Asian/Oriental	1 (0.6)	3 (1.7)	4 (2.3)	1 (0.6)	9 (1.3)
Other	1 (0.6)	8 (4.6)	2 (1.2)	3 (1.8)	14 (2.1)
Age (yr)	61.0 (10.1)	61.1 (9.3)	59.6 (9.9)	59.1 (10.6)	60.2 (10.0)
Age group n (%)					
<65 yr	104 (62.7)	106 (60.6)	115 (67.3)	108 (66.3)	433 (64.1)
≥65 yr	62 (37.3)	69 (39.4)	56 (32.7)	55 (33.7)	242 (35.9)
BMI (kg/m^2)	28.95 (3.59)	28.92 (3.70)	29.12 (3.67)	28.78 (3.54)	28.94 (3.62)
BMI group, n (%)					
<30 kg/m^2	101 (60.8)	112 (64.0)	104 (60.8)	106 (65.0)	423 (62.7)
≥30 kg/m^2	65 (39.2)	63 (36.0)	67 (39.2)	57 (35.0)	252 (37.3)
Diabetes duration (yr)	3.8 (5.12)	3.6 (4.93)	3.7 (4.76)	3.2 (3.66)	3.6 (4.66)
HbA_{1c} (%)	6.55 (0.63)	6.53 (0.60)	6.57 (0.69)	6.45 (0.60)	6.53 (0.63)
FPG (mmol/liter)	7.6 (0.70)	7.5 (0.77)	7.6 (0.60)	7.5 (0.59)	7.6 (0.67)

Data represent mean (SD).

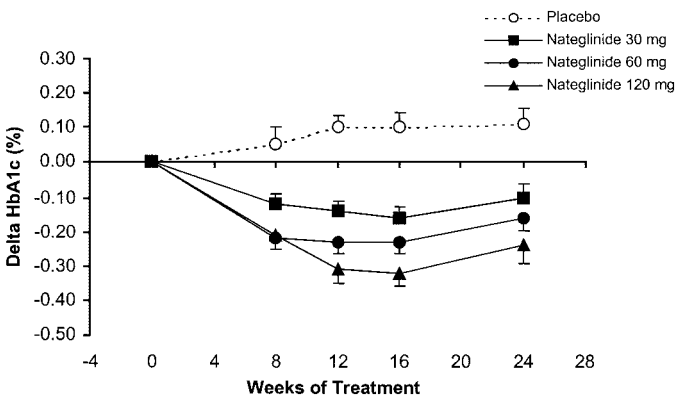

FIG. 1. Change from baseline in HbA_{1c} during 24-wk treatment with placebo (*dotted line*) or nateglinide 30 mg (*boxes*), 60 mg (*filled circles*), or 120 mg (*triangles*) a.c. in patients with T2DM and only modestly elevated fasting plasma glucose ($P < 0.001$, nateglinide *vs.* placebo). Mean ± SEM, n ranges from 138 to 166 patients per data point.

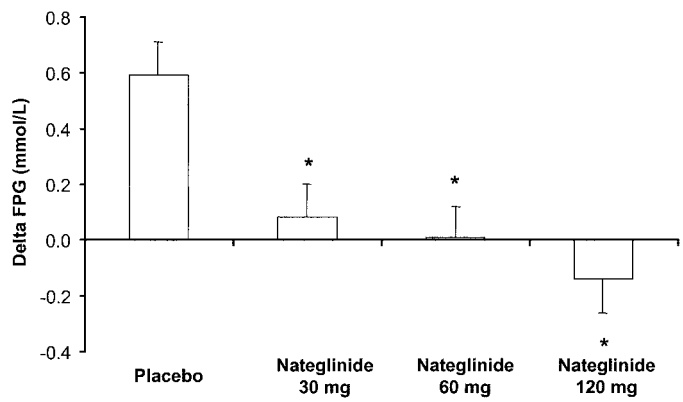

FIG. 2. Change from baseline in FPG after 24-wk treatment with placebo or nateglinide (30, 60, or 120 mg, a.c.) in patients with T2DM and only modestly elevated fasting plasma glucose. Mean ± SEM. *, $P < 0.001$ *vs.* placebo.

6.5% (placebo-adjusted $\Delta HbA_{1c} = -0.26\%$). Nateglinide (120 mg, a.c.) also appeared to be more effective in obese patients (BMI 30 kg/m^2 or more: placebo-adjusted $\Delta HbA_{1c} = -0.59\%$) than in patients with BMIs less than 30 kg/m^2 (placebo-adjusted $\Delta HbA_{1c} = -0.27\%$). Furthermore, a significant correlation was observed between the baseline ratio of HbA_{1c} to FPG (with a high ratio indicating predominant postprandial hyperglycemia) and the change of HbA_{1c}. The best fit line is represented by the equation: $\Delta\ HbA_{1c} = 0.52 - 0.6944 \times \text{ratio}$ ($P < 0.003$).

In the overall ITT population, nateglinide treatment produced a modest but statistically significant and dose-related reduction of FPG relative to placebo ($P < 0.001$ *vs.* placebo for all dose strengths). However, as illustrated in Fig. 2, the difference between active treatment groups and placebo largely reflects the increase of FPG accompanying deterioration of glycemic control in the placebo-treated patients rather than an absolute reduction relative to baseline in the nateglinide-treated patients. Body weight increased modestly in each treatment group, ranging from +0.31 kg in the placebo-treated cohort to +0.65 kg in the patients that received 30 mg nateglinide, although there were no statistically significant differences in weight gain among the four treatment groups.

Substudy: mechanism of action

To assess the mechanism by which nateglinide influences overall glycemic control, standardized meal challenges were performed before the first test dose and after 24 wk of treatment. As predicted from animal studies and clinical trials in other patient populations, nateglinide increased early insulin release and reduced prandial glucose excursions. Each dose of nateglinide increased the 30-min incremental insulin response (Δ from pretreatment = +234 ± 55, +118 ± 51, and +228 ± 59 pmol/liter for 30 mg, 60 mg, and 120 mg, respectively) although the response to 60 mg failed to achieve statistical significance (for 30 mg and 120 mg, $P < 0.05$). Thus, the insulin responses to nateglinide were not strictly dose related. In contrast, the nateglinide-induced reductions of prandial glucose excursions did appear to be dose related (Δ 2 h PPG = −0.56 ± 0.37, −0.94 ± 0.44, and −1.11 ± 0.41

mmol/liter for 30 mg, 60 mg, and 120 mg, respectively, $P < 0.05$).

To assess the overall effects of nateglinide on prandial glucose and insulin, the 4-h AUCs were calculated and are presented in Fig. 3. Each dose of nateglinide modestly increased overall insulin secretion although again, the 60 mg dose failed to achieve statistical significance, and the response did not appear to be dose related. However, the baseline incremental insulin AUCs varied somewhat among groups. Thus, the changes from baseline (wk 0) of the total (unadjusted) insulin AUCs depicted in Fig. 3A represent percent changes of incremental insulin AUCs of −6%, +18%, +14%, and +22% for placebo, 30 mg, 60 mg, and 120 mg nateglinide, respectively. As illustrated in Fig. 3B, nateglinide significantly and dose dependently reduced overall prandial glycemia. The changes from baseline of total glucose AUCs represent percent changes of incremental glucose AUCs of +17%, −21%, −53%, and −45% for placebo, 30 mg, 60 mg, and 120 mg nateglinide, respectively.

To allow a clearer appreciation of the nature of nateglinide's insulinotropic and glucose-lowering effects, Fig. 4 depicts the insulin and glucose profiles during the standardized meal challenges at wk 0 and wk 24 of treatment with nateglinide (120 mg, a.c.). Nateglinide selectively increased early insulin release and markedly reduced prandial glucose excursions.

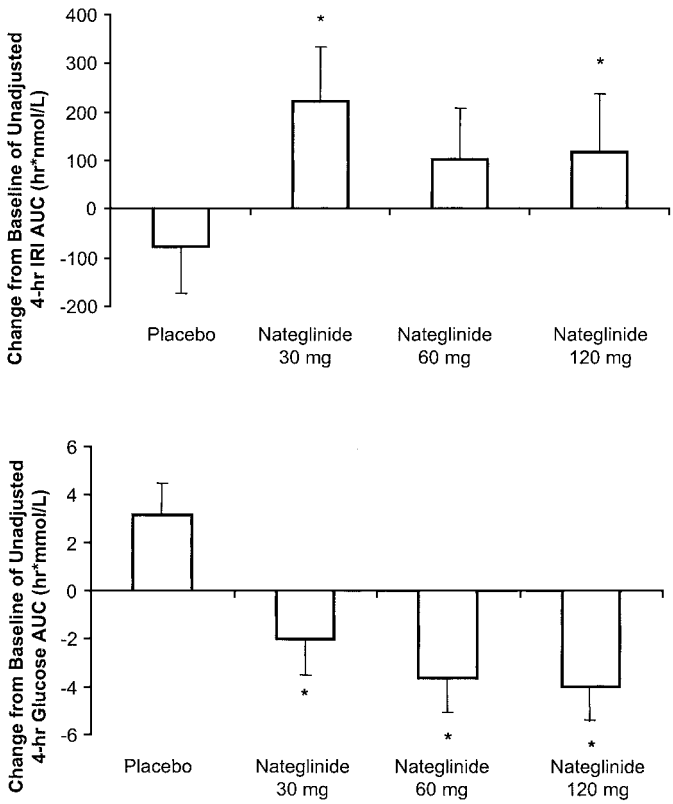

FIG. 3. Change from baseline in insulin (IRI, *top*) and glucose (*bottom*) 4-h AUC during a standard meal challenge performed in patients with T2DM and only modestly elevated fasting plasma glucose following 24-wk treatment with placebo or nateglinide (30, 60, or 120 mg, a.c.). Mean ± SEM. *, $P < 0.05$ or better *vs.* placebo.

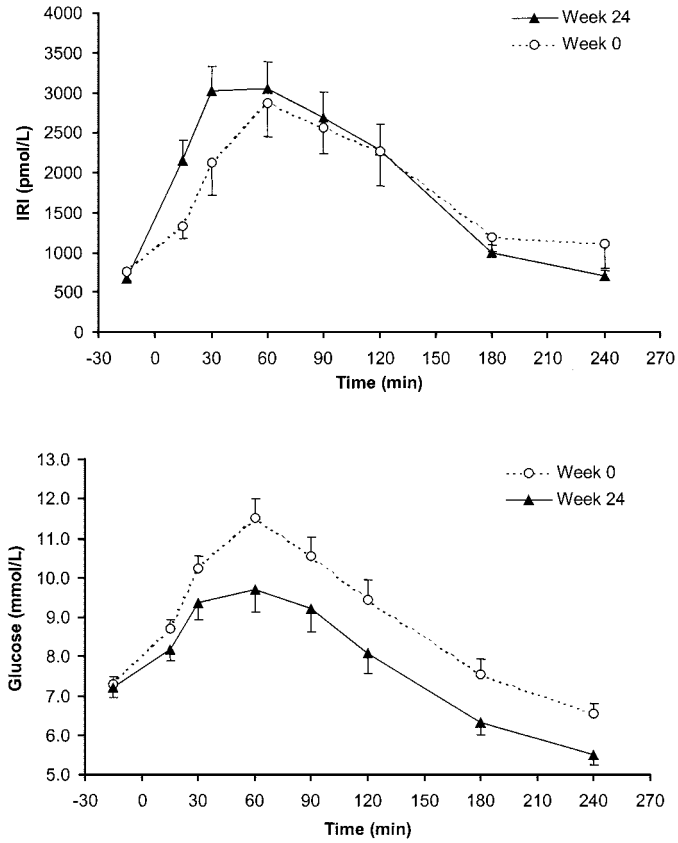

FIG. 4. Plasma insulin (IRI, *top*) and glucose (*bottom*) profiles during a standard meal challenge performed in patients with T2DM but only modestly elevated fasting plasma glucose before the first dose (*dotted line*) and after 24 wk (*solid line*) of treatment with nateglinide (120 mg, a.c.). Mean ± SEM.

Safety and tolerability

There were no deaths during the study. The incidence of serious adverse events (AEs) during the active treatment period was low and comparable across the treatment groups, and none were suspected to be related to the study medication. A total of 7 (4.3%), 9 (5.4%), 6 (3.4%), and 13 (7.6%) patients treated with placebo or nateglinide (30 mg to 120 mg), respectively, withdrew from the study due to AEs.

Nateglinide was generally well tolerated. The most frequently reported AEs were hypoglycemia, upper respiratory tract infection, headache, and influenzalike symptoms. However, the frequency of AEs was evenly distributed among treatment groups, with the exception of metabolic disorders (primarily hypoglycemia) and central nervous system disorders (primarily tremor), which occurred with greater frequency in the nateglinide 120 mg cohort.

During the study, patients were provided with glucose monitors and instructed to perform SMBG during any suspected hypoglycemic episode to confirm hypoglycemic events and allow assessment of their severity. As depicted in Fig. 5, there was a dose-related increase in symptomatic hypoglycemia, but the incidence of confirmed hypoglycemia in nateglinide-treated patients was much lower than symptomatic hypoglycemia, ranging from 2.4% in the 30-mg group to 5.3% in the 120-mg group. Furthermore, serious

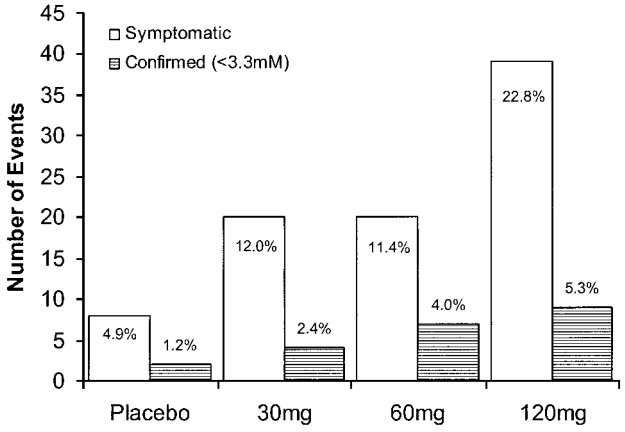

FIG. 5. Number of events of symptomatic hypoglycemia (*open bars*) and confirmed hypoglycemia (with SMBG <3.3 mmol/liter, *hatched bars*) during 24 wk of treatment with placebo (n = 163), 30 mg nateglinide (n = 166), 60 mg nateglinide (n = 175), or 120 mg nateglinide (n = 171).

hypoglycemia (glucose 2.2 mmol/liter or less = 40 mg/dl) was a rarity, and the majority of suspected hypoglycemic episodes was accompanied by a blood glucose measurement of 3.3 mmol/liter or more = 60 mg/dl. In the subpopulation with BMI of 30 kg/m^2 or more confirmed hypoglycemia occurred in 0%, 3.1%, 1.6%, and 6.0% of patients receiving placebo or nateglinide 30 mg, 60 mg, and 120 mg, respectively. The corresponding incidence of hypoglycemia in patients with BMI less than 30 kg/m^2 was 1.9%, 2.0%, 5.4%, and 4.8%. No hypoglycemic episode in any patient required assistance from an outside party.

Discussion

The purpose of this study was to assess the efficacy and safety of nateglinide monotherapy in patients with T2DM but only modest fasting hyperglycemia, a rapidly growing but infrequently studied patient population. It was found that nateglinide produced a dose-related reduction of HbA_{1c} in these previously diet-treated patients with mean baseline HbA_{1c} levels of approximately 6.5% and mean baseline FPG of approximately 7.6 mmol/liter (137 mg/dl). This is in general agreement with an earlier 12-wk dose-ranging study in patients with initial HbA_{1c} levels averaging 8.4%. In that study the placebo-adjusted reduction of HbA_{1c} ranged from −0.27 to −0.64% for nateglinide 30 mg to 180 mg, a.c (11).

Although the patients participating in the present study exceed the diagnostic criteria for diabetes, at this time many physicians follow the ADA mandate of "taking additional action" (beyond prescribing diet and exercise) only if FPG levels exceed 8.3 mmol/liter (150 mg/dl) or HbA_{1c} exceeds 8.0% (6), rather than attempting to achieve the ADA-recommended goal of reducing HbA_{1c} levels to less than 7%. Thus, many of the patients represented by the present study population are not receiving appropriate pharmacotherapy despite the clear demonstration that they are at increased risk for both microvascular and macrovascular complications of diabetes (5).

The questions may then arise, first, whether the magnitude of the reduction of HbA_{1c} seen in this study (−0.23 relative to baseline and −0.39 relative to placebo for nateglinide, 120 mg, a.c.) is clinically meaningful, and, second, whether the risk/benefit ratio of nateglinide monotherapy in this population with modest fasting hyperglycemia merits implementation of pharmacotherapy.

It is usually observed that the magnitude of decrement of HbA_{1c} levels induced by a therapeutic intervention is proportional to the baseline levels of HbA_{1c}. For example, in one recent study of patients (n = 179) with T2DM and mean baseline HbA_{1c} of 8.3%, 24 wk of monotherapy with nateglinide (120 mg, a.c.) elicited a placebo-adjusted decrease of HbA_{1c} of 0.9%, but in a subset of these patients with baseline HbA_{1c} more than 9.5%, the nateglinide-induced reduction was 1.5% (12). Accordingly, it is not surprising that the overall efficacy of nateglinide found in the present study was modest and that it was greater in patients with higher HbA_{1c} (6.5% or more). However, it was noted that in the overall study population, 40% of the patients receiving 120 mg nateglinide achieved normalization of HbA_{1c} levels (*i.e.* <6.0%). In contrast, 22% of placebo-treated patients had HbA_{1c} levels less than 6.0% at study end point.

The observed effects of nateglinide on FPG may also merit particular attention. Although an absolute reduction from baseline was seen only in the 120-mg cohort, there was a modest but significant effect of each dose relative to placebo as FPG levels in this group increased over the 24-wk study by 0.6 mmol/liter. One possible interpretation of this finding is that nateglinide prevents the metabolic deterioration seen in the absence of intervention. However, whether this agent could actually slow the progression of disease would need to be directly tested in a longer-term prospective study.

In the general diabetic population, a reduction of HbA_{1c} of 0.5% is considered to be clinically meaningful by the regulatory agencies and by most physicians, although clearly the ultimate goal of treatment is to normalize HbA_{1c}. From large prospective studies, such as the DCCT, it has been established that for every 10% reduction in HbA_{1c}, there is a 40% reduction in risk of microvascular complications and there is no threshold below which no added benefit ensues (13). Because the lowering achieved in our study (0.39%) represents a reduction of 6% relative to placebo, we speculated that it should lead to a reduction in risk that may indeed be considered to be meaningful and would merit institution of pharmacotherapy provided the safety profile (risk) would not outweigh the anticipated benefit.

From the various subanalyses performed, two subpopulations of the mildly hyperglycemic patients were identified that may be particularly well suited for nateglinide monotherapy, namely obese patients and those with a disproportionate elevation in PPG levels. Thus, in patients with a BMI over 30 kg/m^2, the efficacy of 120 mg nateglinide was more than twice that in the leaner subpopulation but with no corresponding increase in the frequency of hypoglycemia. The relationship between efficacy and the baseline ratio of HbA_{1c} to FPG would suggest that patients with disproportionately elevated postprandial hyperglycemia may also be good candidates for nateglinide monotherapy. It should be acknowledged that these subpopulations overlap; however, only 38% of the patients with a ratio of HbA_{1c} to FPG above the median were obese. Thus, it would appear that obesity

and disproportional elevation in PPG independently affect the efficacy of nateglinide.

In this study, as in all previous clinical trials with nateglinide, the agent was very well tolerated, and the only treatment-emergent side effect was an increased incidence of mild to moderate hypoglycemia. However, the incidence of confirmed hypoglycemia with the highest dose strength (120 mg, a.c.) was 5.3%, still considerably lower than that routinely seen with sulfonylureas in the general diabetic population with much higher HbA_{1c} levels than in the present study population (8). Because it is known from the DCCT (3) that the frequency of hypoglycemia increases dramatically as HbA_{1c} levels approach normalization, the low incidence of hypoglycemia reported in the present study in patients with only modest fasting hyperglycemia is remarkable. Furthermore, it is important to note that no patient required assistance of an outside party, the commonly used definition of severe hypoglycemia. In contrast, in the United Kingdom Prospective Diabetes Study, a population with a baseline HbA_{1c} more similar to the present study than that in the DCCT, the annual rate of severe hypoglycemia requiring assistance in the various sulfonylurea-treated subgroups ranged from 0.4% to 2.5% (14).

In earlier clinical trials in patients with more advanced disease, nateglinide was shown to preferentially augment the early prandial insulin response and substantially reduce mealtime glucose excursions (8, 12). This mechanism of action was confirmed in the present study in the mildly hyperglycemic patient population.

Whether the reductions of PPG seen in the substudy solely reflect increased insulin secretion is not altogether clear because the reductions of PPG were dose related, but the increases of insulin secretion were not. However, it is essential to consider the timing of insulin secretion as well as the overall amount of insulin released. Thus, it has been repeatedly demonstrated that a small amount of insulin administered at the onset of a meal is more effective to curb prandial glucose excursions than is more insulin administered at a later time (15, 16). Although an extrapancreatic action of nateglinide to directly enhance glucose uptake or to suppress glucose production cannot be ruled out, to date there is no direct evidence for such effects. The present results may then best be interpreted as evidence for the importance of early insulin secretion. Furthermore, the minimal and transient nature of nateglinide's insulinotropic effects may explain the lack of significant weight gain relative to placebo reported here. The current data also demonstrate that postprandial hyperglycemia makes a significant contribution to overall glycemic exposure as reflected by HbA_{1c}. Thus, in this mildly hyperglycemic population, nateglinide had minimal effects on FPG but substantially reduced HbA_{1c}.

In summary, in patients with T2DM but only modest fasting hyperglycemia, premeal administration of nateglinide augments early insulin release and curbs prandial glucose excursions. This results in a significant and clinically meaningful reduction of HbA_{1c} with minimal weight gain and a low incidence of hypoglycemia. It may be concluded that nateglinide is safe and effective in improving glucose control in patients with T2DM and that it may be a good option for first-line therapy in newly diagnosed mildly hyperglycemic patients.

Acknowledgments

We thank Shamita Gupta and Patricia Rumpelt for clinical study coordination and David Shaw for statistical input. Additionally, we thank the investigators and study personnel at the 103 clinical sites in Argentina, Australia, Belgium, Canada, Finland, France, Germany, Italy, the Netherlands, New Zealand, Sweden, and the United States for the contribution to the study.

Received January 22, 2002. Accepted June 12, 2002.

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This work was supported by funding from Novartis Pharmaceuticals and a grant from Novartis Pharma AG and in Finland by the Sigrid Juselius Foundation and Academy of Finland.

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