

Nateglinide Alone and in Combination With Metformin Improves Glycemic Control by Reducing Mealtime Glucose Levels in Type 2 Diabetes

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OBJECTIVE — To evaluate the efficacy and tolerability of nateglinide and metformin alone and in combination in type 2 diabetic patients inadequately controlled by diet, focusing on changes in HbA_{1c}, fasting plasma glucose (FPG), and mealtime glucose excursions.

RESEARCH DESIGN AND METHODS — In this randomized double-blind study, patients with an HbA_{1c} level between 6.8 and 11.0% during a 4-week placebo run-in received 24 weeks' treatment with 120 mg nateglinide before meals (*n* = 179), 500 mg metformin three times a day (*n* = 178), combination therapy (*n* = 172), or placebo (*n* = 172). HbA_{1c} and FPG were evaluated regularly, and plasma glucose levels were determined after Sustacal challenge at weeks 0, 12, and 24. Hypoglycemia and other adverse events were recorded.

RESULTS — At study end point, HbA_{1c} was reduced from baseline with nateglinide and metformin but was increased with placebo (−0.5, −0.8, and +0.5%, respectively; *P* ≤ 0.0001). Changes in FPG followed the same pattern (−0.7, −1.6, and +0.4 mmol/l; *P* ≤ 0.0001). Combination therapy was additive (HbA_{1c} −1.4% and FPG −2.4 mmol/l; *P* ≤ 0.01 vs. monotherapy). After Sustacal challenge, there was a greater reduction in mealtime glucose with nateglinide monotherapy compared with metformin monotherapy or placebo (adjusted area under the curve [AUC]_{0–130min} −2.1, −1.1, and −0.6 mmol · h^{−1} · l^{−1}; *P* ≤ 0.0001). An even greater effect was observed with combination therapy (AUC_{0–130min} −2.5 mmol · h^{−1} · l^{−1}; *P* ≤ 0.0001 vs. metformin and placebo). All regimens were well tolerated.

CONCLUSIONS — Nateglinide and metformin monotherapy each improved overall glycemic control but by different mechanisms. Nateglinide decreased mealtime glucose excursions, whereas metformin primarily affected FPG. In combination, nateglinide and metformin had complementary effects, improving HbA_{1c}, FPG, and postprandial hyperglycemia.

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It is well established that glycemic control in type 2 diabetes reduces long-term complications (1). The earliest determinants of progression to type 2 diabetes are both progressive insulin resistance and

loss of early insulin secretion (2). These defects result in postprandial hyperglycemia. This development first manifests itself as impaired glucose tolerance, which may progress to the even higher postpran-

dial hyperglycemia associated with type 2 diabetes. Eventually, fasting hepatic glucose production increases, leading to the elevated fasting glucose levels characteristic of symptomatic diabetes (2). Thus, an important and early component of hyperglycemia is postprandial hyperglycemia. An increased incidence of postprandial hyperglycemia has been observed in the elderly; therefore, control of this aspect of diabetes is especially warranted in the elderly patient (3). Furthermore, almost all patients with type 2 diabetes will eventually require combination therapy to control both fasting and postprandial hyperglycemia. Currently available therapies either do not target postprandial hyperglycemia or have troublesome side effects in some patients (4).

Nateglinide is a derivative of the amino acid D-phenylalanine (5,6), which is chemically and pharmacologically unique among oral antidiabetic agents. It acts directly on the pancreatic β-cells to stimulate insulin secretion that is rapid, of short duration, and dependent on ambient glucose levels (7,8). Nateglinide taken just before meals controls mealtime hyperglycemia, resulting in improved overall glycemic control in patients with type 2 diabetes with minimal risk of hypoglycemia (9).

Metformin is the most widely used oral antidiabetic agent for the treatment of type 2 diabetes. Metformin improves glycemic control as monotherapy and in combination with other oral antidiabetic agents, such as sulfonylureas and thiazolidinediones (10–12). Metformin does not affect insulin secretion, and its effects on overall glycemic control are achieved mainly by the reduction of fasting plasma glucose (FPG) (10). The primary objectives of this study were to evaluate the effects of nateglinide, as monotherapy and in combination with metformin, on glycemic control, including postprandial glucose control, and to assess the tolerability and safety of these treatment regimens in patients with type 2 diabetes. A previous acute clinical study demonstrated that the combination of nateglinide and metformin produced additive effects in reducing over-

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Abbreviations: AUC, area under the curve; FPG, fasting plasma glucose; ITT, intention-to-treat.

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

all glycemia without affecting the pharmacokinetic parameters of either agent (13).

RESEARCH DESIGN AND METHODS

Study design

This was a prospective, double-blind, randomized placebo-controlled study. Patients underwent a 4-week washout period and were then screened during a 4-week, single-blind, placebo run-in period. Eligible patients were subsequently equally randomized via a computerized system to one of four groups for 24 weeks' treatment. The treatment groups were randomized to the following regimens: 120 mg nateglinide (taken 1–30 min before each of three main meals), metformin titrated according to the approved package labeling to 500 mg (immediately after the start each of three main meals), 120 mg nateglinide (taken 1–30 min before each of three main meals) plus 500 mg metformin (immediately after the start each of three main meals), or placebo. To maintain the blind, the double-dummy technique was used; patients in the monotherapy groups received their assigned active treatment plus identical placebo for the alternative therapy, whereas patients in the placebo group received both dummy nateglinide and metformin tablets. All patients, therefore, received six tablets each day.

Patients could be included in the study if they were aged ≥ 30 years and had been diagnosed with type 2 diabetes for at least 3 months. BMI was required to be 20–35 kg/m², and all patients had to have been treated with diet alone during the 4-week washout period before enrollment in the 4-week placebo run-in phase. Those subjects with HbA_{1c} levels between 6.8 and 11.0% (despite dietary intervention) during run-in and with an FPG level ≤ 15 mmol/l were able to proceed to treatment randomization. Exclusion criteria included type 1 diabetes, secondary forms of diabetes, a history of significant diabetic complications, or renal impairment. In addition, all oral hypoglycemic agents had to be discontinued for at least 4 weeks before placebo run-in. Other medications could be taken if their use had been instituted before study entry, but agents that could interfere with study evaluations, including other oral antidiabetic agents and corticosteroids, were not allowed.

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.

Interventions

Clinic visits were scheduled for weeks –4 and –2 during the run-in period, at randomization (week 0), and weeks 4, 8, 12, 16, and 24 during the treatment phase. Patients were expected to maintain a constant diet throughout both phases of the study.

Study assessments were made after a minimum of 7 h fasting (overnight) before each scheduled visit. The primary efficacy measurement was change in HbA_{1c} from baseline, because this parameter is the single most reliable indicator of glycemic control. HbA_{1c} was assessed at each visit (except week 4) by high-performance liquid chromatography using the Bio-Rad Diamat ion-exchange method. Secondary efficacy variables were FPG, measured at each visit using the hexokinase method, and plasma glucose levels after liquid meal challenges of Sustacal (containing 35 g carbohydrate, 8.3 g fat, and 8.8 g protein in 240 ml) at weeks 0, 12, and 24. Change from baseline in body weight was also assessed.

Adverse events were recorded throughout the study and were rated by the investigator as to their severity and relationship to study medication. Suspected hypoglycemia was determined by self-monitoring of blood glucose; patients were taught how to recognize, treat, and monitor hypoglycemia and were instructed to note all symptomatic and asymptomatic events in a study diary. All suspected symptomatic hypoglycemic episodes were recorded as adverse events, even in the absence of a confirmatory blood glucose measurement. Patients also underwent physical examination, electrocardiogram assessment, measurement of vital signs, and determination of standard laboratory parameters (hematology, biochemistry, and urinalysis). Compliance was assessed by counting patients' remaining medication at each visit.

Statistical analysis

The intention-to-treat (ITT) population was used for assessment of change from baseline in HbA_{1c} at week 24 and for all secondary efficacy parameters, using the last observation carried forward method for patients who did not complete the week 24 efficacy assessment. Computation of area under the curve (AUC)_{0–130min} for plasma glucose after Sustacal ingestion was com-

puted using the trapezoidal rule with and without adjustment for the pre-Sustacal challenge measurement. An analysis of covariance model that included effects for treatment, center, baseline measure, treatment by center interaction, and treatment by baseline interaction was used to compare the effects of the four treatment groups. A sample size of 680 subjects was required (170 per group) to detect a difference of 0.5% absolute unit for change in HbA_{1c} between nateglinide monotherapy and placebo, with a type 1 error of 5%, a power of 90%, and the allowance of an 18% dropout rate.

RESULTS

Patients

In total, 701 of the 1,451 screened subjects were randomized to treatment (Fig. 1). Withdrawal rates and reasons for withdrawal were comparable across the treatment groups. Baseline characteristics of the randomized patients are detailed in Table 1 and did not differ among groups. The majority of patients were Caucasian (80.6%), 62.2% were men, and 71.0% of patients were aged < 65 years. The mean duration of diabetes was 4.6 years, ranging from 0 to 38.2 years, and almost half of the patients (48.1%) were obese (BMI ≥ 30 kg/m²). Concomitant therapies were taken by 89.3% of patients, with no difference among groups with respect to patient usage or medication classes. The most commonly used agents were for the treatment of hypertension, arthritis, and hyperlipidemia.

Efficacy parameters

There were no significant differences in baseline HbA_{1c} or FPG values among the four treatment groups (Table 1). Both parameters decreased from baseline with all active treatments during the 24-week treatment period ($P \leq 0.0001$ at study end point), whereas an increase was observed with placebo (Fig. 2). The decrease over time was similar for both monotherapy groups, with a larger effect being observed in the combination therapy arm (data not shown). At study end point, the adjusted mean change from baseline for HbA_{1c} and FPG was statistically significant with nateglinide and metformin monotherapy compared with placebo (Fig. 2). The difference in FPG between the two agents was 0.9 mmol/l ($P < 0.001$). The placebo-subtracted reduction in HbA_{1c} at end point was –0.9, –1.2, and –1.9% in the nateglinide, metformin, and combination groups,

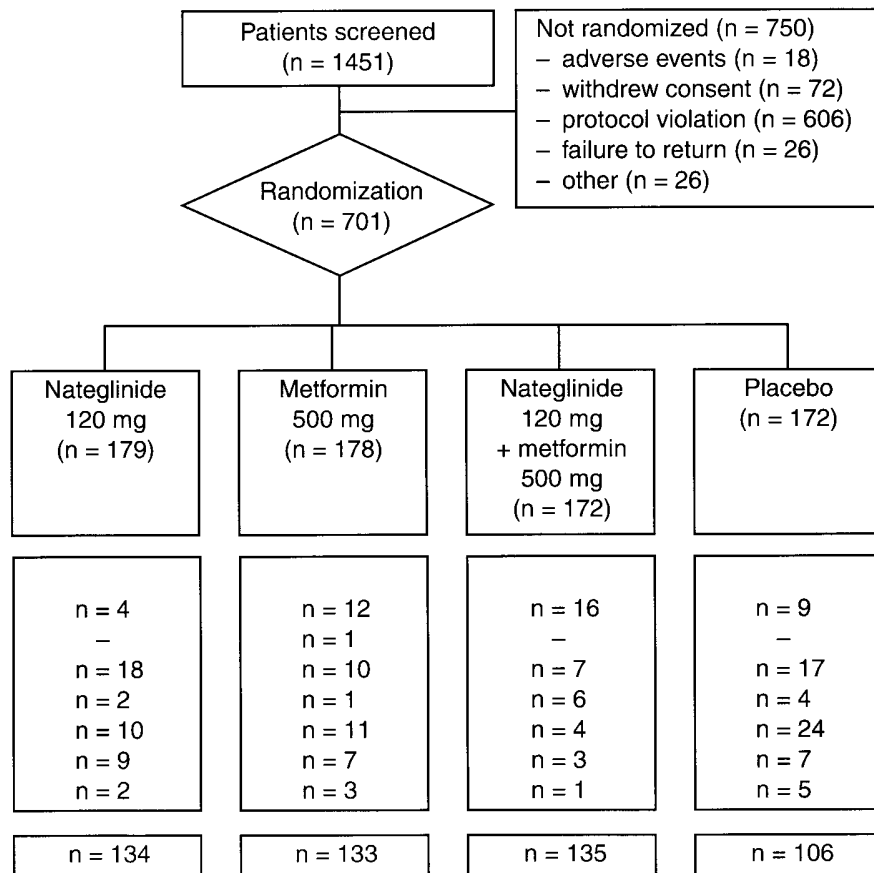


Figure 1—Number of patients screened and randomized to treatment, including reasons for withdrawal.

respectively. Although the decrease was greater with metformin than with nateglinide, the between-group difference for change in HbA_{1c} was small (HbA_{1c} 0.3% difference, $P < 0.01$). Furthermore, in the patients who were not treated with hypoglycemic drugs before study entry, the adjusted mean decrease from baseline was the same (0.8%) in the nateglinide and the metformin monotherapy groups. Efficacy parameters were similar in patients older and younger than 65 years of age (data not shown). With combination therapy, the decreases in HbA_{1c} were even more marked, being significantly greater than with either treatment alone (Fig. 2). However, a more robust reduction in HbA_{1c} relative to placebo was seen in patients with higher initial HbA_{1c} levels. In the nateglinide monotherapy group, there was a 1.4% relative reduction in patients with initial HbA_{1c} levels $\geq 9.5\%$ compared with a 1.5% relative reduction in the metformin monotherapy group; with combination therapy, the reduction in HbA_{1c} relative to placebo was 2.5%.

After Sustacal challenge (240 ml), nateglinide monotherapy resulted in a reduction from baseline in mealtime plasma glucose excursion (adjusted AUC_{0-130min})

compared with metformin monotherapy or placebo (Fig. 2). The effect of metformin on mealtime glucose excursion was not significantly different from placebo. The greatest reduction in mealtime glucose was observed in the combination therapy group, although this reduction did not differ significantly from the effect observed with nateglinide alone (Fig. 2).

There were no significant changes from baseline in body weight in any of the active treatment groups at the end of the study. In the nateglinide monotherapy group, the change from baseline was <1 kg.

Safety and tolerability

Adverse events led to 42 (6.0%) patient withdrawals from the study, around half being related to gastrointestinal events (predominantly diarrhea). These were judged by the investigator as definitely, probably, or possibly related to treatment in only 1 of 5 cases in the nateglinide group, 6 of 12 in the metformin group, 6 of 16 in the combination therapy group, and 3 of 9 subjects who received placebo. One death due to arteriosclerotic and hypertensive heart disease occurred in the metformin group, but the relationship to therapy was judged to be unlikely.

Overall, 541 of 701 (77.2%) patients experienced adverse events, with a slightly higher occurrence in the active treatment groups (77.7% nateglinide, 79.2% metformin, and 83.1% combination therapy) compared with placebo (68.6%). The most frequently observed adverse events were events suggestive of hypoglycemia (95 of

Table 1—Baseline demographics and background characteristics of randomized patients

	120 mg Nateglinide	500 mg Metformin	Nateglinide + metformin	Placebo
n	179	178	172	172
Sex (M/F)	110/69	121/57	101/71	104/68
Age (years)	58.6 ± 10.7	56.8 ± 10.9	58.4 ± 10.9	59.6 ± 10.9
<65	122	136	122	118
≥65	57	42	50	54
Race (%)				
Caucasian	82.1	79.2	82.6	78.5
African-American	9.5	9.6	11.6	16.9
Asian	2.8	2.2	0.6	0.6
Other	5.6	9.0	5.2	4.1
BMI (kg/m ²)	29.6 ± 3.8	29.6 ± 4.3	30.0 ± 3.7	29.2 ± 3.9
Duration of diabetes (years)	4.7 ± 5.5	4.5 ± 5.5	4.5 ± 5.3	4.6 ± 4.7
HbA _{1c} (%)	8.3 ± 1.0	8.4 ± 1.2	8.4 ± 1.1	8.3 ± 1.1
FPG (mmol/l)	10.8 ± 2.4	11.0 ± 2.6	11.0 ± 2.4	10.7 ± 2.3

Data are means ± SD unless otherwise indicated.

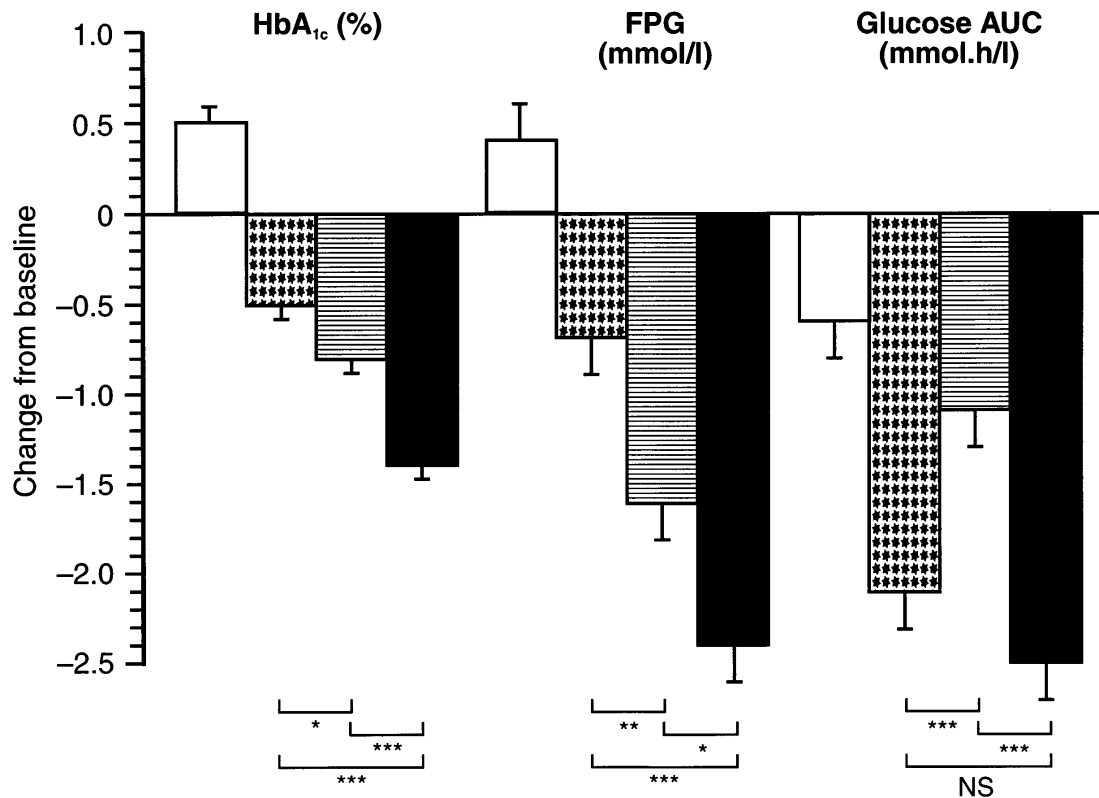


Figure 2—Adjusted mean change from baseline in HbA_{1c}, FPG, and glucose AUC after Sustacal challenge (ITT population). All parameters were significantly reduced from baseline ($P \leq 0.0001$) in the active treatment groups. All values were significantly reduced compared with placebo ($P \leq 0.0001$) except for glucose AUC with metformin monotherapy (NS). * $P \leq 0.01$; ** $P \leq 0.001$; *** $P \leq 0.0001$. □, Placebo; ▣, nateglinide; ▤, metformin; ■, nateglinide plus metformin.

701 [13.6%]); the highest occurrence was observed in the combination therapy group (45 of 172 [26.2%]), and no difference was observed between the nateglinide and metformin monotherapy groups (12.8 vs. 10.1%). Furthermore, there were no serious hypoglycemic events. On a 4-point grading scale, the events were predominantly symptomatic grade 1 events, with one grade 2 event in the placebo group. The number of patients with confirmed events, defined as symptomatic hypoglycemia with a plasma glucose measurement ≤ 3.3 mmol/l, was low (three nateglinide, one metformin, and five combination therapy patients). Events suggestive of hypoglycemia led to withdrawal in only one case in the nateglinide group and three in the combination therapy arm.

Diarrhea was more common in the groups receiving metformin alone (19.7%) or in combination (14.5%), the frequency being three to four times higher than with nateglinide alone or placebo. Other frequent adverse events were upper respiratory tract infection (14.3%), headache (7.1%), abdominal pain (6.3%), nausea (5.7%),

fatigue (5.1%), and sinusitis (5.0%). These were comparable between the four groups. Overall, 22 patients experienced serious adverse events, all of which were judged as “unlikely” or “not related” to treatment. There were no clinically meaningful changes from baseline or differences between treatment groups with respect to laboratory safety values. Of the 18 patients experiencing notable changes in vital signs (blood pressure and body weight), only one was documented as an adverse event (hypertension in the placebo group). Eight patients had electrocardiogram abnormalities that were regarded as adverse events, two (one on combination therapy and one on placebo) of which were considered as possibly related to the study drug.

CONCLUSIONS—Nateglinide is a fast-acting short-duration insulinotropic agent that improves mealtime glucose control by enhancing insulin secretion (7,14,15). The rapid action of nateglinide in enhancing early insulin secretion results in attenuation of postprandial hyperglycemia (7,14–16). This attenuation of the

initial glucose rise requires only a small burst of insulin to inhibit hepatic glucose production. In contrast, it takes a greater concentration of insulin to dispose of a glucose load into muscle once the glucose excursion has been generated (17). Furthermore, stimulation of insulin secretion by nateglinide is rapidly reversed when glucose levels fall (7,14–16), reducing the risk of hypoglycemia. Previous pharmacokinetic and pharmacodynamic studies have demonstrated that when nateglinide is taken orally immediately before meals, it is a safe and efficacious therapy for the treatment of type 2 diabetes (8,9).

This study demonstrates that nateglinide has a complementary mechanism of action to that of metformin in improving overall glycemic control in patients with type 2 diabetes. Nateglinide reduced postprandial hyperglycemia as reflected by a significant decrease in the adjusted glucose AUC_{0–130min} after Sustacal challenge. There was also a 0.7 mmol/l decrease in fasting glucose levels and a 0.5% drop in HbA_{1c} levels. This decrease in HbA_{1c} was nearly as great as that seen with metformin (–0.8%). In con-

trast, a 1.6 mmol/l drop in fasting glucose levels largely accounted for the improved glycemic control with metformin. There was a 1.4% reduction in HbA_{1c} with the combination of metformin and nateglinide. Previous studies with metformin and other oral antidiabetic agents have reported much larger decreases in HbA_{1c}, but the effects in those studies were relative to placebo in patients with higher starting HbA_{1c} levels or who had not been washed out from previous drug treatment (18–20). In the current study, patients were washed out for at least 8 weeks, resulting in a more modest placebo effect (0.5%). When patients with baseline HbA_{1c} >9.5% were evaluated relative to placebo, there was a 1.4% decrease in HbA_{1c} with nateglinide monotherapy and a 2.5% decrease with the combination of nateglinide and metformin. Because switching drug monotherapy is uncommon in type 2 diabetes, a more relevant comparison of efficacy of oral agents for monotherapy may be the change from baseline in patients not being treated with hypoglycemic drugs. Nateglinide and metformin showed an identical 0.8% reduction from baseline in HbA_{1c} in such patients. Nateglinide improves insulin secretion kinetics and attenuates mealtime glucose excursions, thereby leading to a reduction in overall glycemia. Defects in insulin secretion kinetics and excessive postprandial hyperglycemia occur at all levels of FPG, starting in the impaired glucose tolerance range (2,21). In addition to the microvascular risk of excessive glucose exposure (1,22) associated with postprandial hyperglycemia, there are now numerous studies showing that mortality is highly associated with postprandial hyperglycemia (21,23,24). Furthermore, defects in fasting hepatic glucose production occur later in the progression of diabetes (2). Thus, earlier identification and treatment of diabetes will require pharmacological agents, such as nateglinide, which focus on the early defects of insulin secretion kinetics and reduction of excessive mealtime glucose excursions.

This study, as well as those previously undertaken with nateglinide (7–9), indicates that nateglinide is safe and very well tolerated. The only treatment-emergent side effects of nateglinide that are greater than those with placebo are symptoms suggestive of hypoglycemia. The percentage of patients experiencing confirmed hypoglycemic events was <2% with monotherapy and <3% in combination with metformin. None of these patients required assistance, and there was no nocturnal hypoglycemia

with nateglinide. It is worth noting that we found that symptoms suggestive of hypoglycemia were no more common in the nateglinide monotherapy group than in the metformin monotherapy group.

In summary, this study demonstrates that both nateglinide and metformin treatments lead to clinically significant reductions in HbA_{1c} with minimal weight gain and a low incidence of hypoglycemic episodes. The nateglinide effect on HbA_{1c} is mostly via its effect on mealtime glucose excursions, whereas the metformin effect is via its effect on FPG. The combination of nateglinide and metformin leads to an additive reduction in HbA_{1c} with excellent overall safety and tolerability. The safety and convenience of nateglinide, coupled with its selective effect on postprandial hyperglycemia, makes it an attractive oral hypoglycemic monotherapy in patients with type 2 diabetes who have near-normal FPG, who are elderly, or who are unable to tolerate other oral hypoglycemic agents. It is also effective as combination therapy with metformin for patients with more advanced disease requiring therapy to reduce both fasting and postprandial hyperglycemia.

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