ORIGINAL ARTICLE doi: 10.1111/j.1463-1326.2006.00632.x

Nateglinide or gliclazide in combination with metformin for treatment of patients with type 2 diabetes mellitus inadequately controlled on maximum doses of metformin alone: 1-year trial results

S. Ristic, C. Collober-Maugeais, F. Cressier, P. Tang and E. Pecher

Novartis Pharma, Basel, Switzerland

Aim: To compare long-term efficacy and safety of nateglinide plus metformin with those of gliclazide plus metformin in patients with type 2 diabetes not adequately controlled with metformin monotherapy.
Methods: Double-blind, double-dummy, multicentre study extended to a total of 52 weeks. Patients with inadequate glucose control on maximal doses of metformin were randomized to nateglinide (N = 133) or gliclazide (N = 129) add-on treatment. After the initial 6-month study, the majority of patients in the nateglinide group [n = 112 (93.3%)] and in the gliclazide group [n = 101 (92.7%)] entered a 6-month, double-blind, extension study.
Results: There was no significant difference between treatment regimens in haemoglobin Alc (HbA1c) change from baseline to 52 weeks (−0.14% for nateglinide vs. −0.27% for gliclazide; p = 0.396). Proportions of patients achieving an endpoint HbA1c of <7% were similar (40 vs. 47.4%) for nateglinide and gliclazide groups. There was no significant between-treatment difference in fasting plasma glucose change from baseline to 52 weeks (nateglinide: −0.2 mmol/l and gliclazide: −0.7 mmol/l; p = 0.096). The decreases in prandial plasma glucose area under the curve$_{0-4\ h}$ from baseline were −3.26 and −1.86 h × mmol/l in the nateglinide and the gliclazide groups respectively, and the change was statistically significant in the nateglinide group only (p = 0.006). Initial insulin response to a meal was augmented with nateglinide treatment only, without between-treatment difference in 2-h insulin response. The overall rate of hypoglycaemic events was similar with nateglinide and gliclazide combinations with metformin. Nateglinide plus metformin treatment was not associated with weight gain.
Conclusions: No significant difference was seen between nateglinide plus metformin and gliclazide plus metformin in terms of HbA1c. Treatment with nateglinide plus metformin for up to 12 months was not associated with weight gain.
Keywords: gliclazide, HbA1c, metformin, nateglinide, type 2 diabetes mellitus
Received 4 April 2006; revised version accepted 18 April 2006

Introduction

Type 2 diabetes is characterized by insulin resistance and a decrease in insulin secretion from the pancreatic islets [1]. It is a severe, progressive disease that is increasing in prevalence worldwide, along with a rise in obesity [2]. The most frequently used initial pharmacological agent for the treatment of diabetes is metformin. Metformin works as an insulin sensitizer, predominantly by reducing glucose production from the liver [3]. Due to the progressive deterioration of β-cell function, treatment with more than one agent, with complementary modes of

Correspondence:
Dr Smiljana Ristic, Novartis Pharma AG, WSJ-202.2.14a, CH-4002 Basel, Switzerland.
E-mail:
smiliana.ristic@novartis.com

action, is required to maintain good glycaemic control over time. There is paucity of data about long-term efficacy of combination therapy, although there is initial evidence that even combination therapy gradually fails over time [4].

Sulphonylurea agents, such as gliclazide, are the most commonly used add-on treatment in patients not adequately controlled with metformin monotherapy. They augment insulin secretion from pancreatic β cells, irrespective of blood glucose level. Nateglinide belongs to the new generation of more physiological insulin secretagogues that stimulate β cells in a glucose-sensitive fashion at meal periods.

A previous study [5] evaluated and compared the efficacy and safety of an individually titrated dose of nateglinide with those of an individually titrated dose of gliclazide, each in combination with the highest individually tolerated dose of metformin. The study was carried out in patients with type 2 diabetes, who were inadequately controlled with metformin monotherapy and diet prior to the start of the study over a period of 24 weeks. At the end of the initial 6-month study, both treatments resulted in significant and clinically meaningful reductions in haemoglobin Alc (HbA1c), with little difference between the treatments. A 6-month extension study was carried out with the objective being to evaluate the effect of nateglinide compared with that of gliclazide in combination with metformin on HbA1c, fasting plasma glucose (FPG), body weight and postprandial insulin and glucose, after 12 months of treatment.

Methods

This is a 6-month, double-blind, extension study of the previously reported 24-week, multicentre, double-blind, parallel group, randomized study [5]. Patients were eligible for the initial study if they had type 2 diabetes for a minimum of 6 months and had received metformin monotherapy for at least 3 months, with a minimum metformin dose of 1000 mg/day for at least 2 months prior to study entry. Inadequate glycaemic control on metformin monotherapy was defined as HbA1c level of 6.8–9%, and body mass index inclusion criterion was 20–35 kg/m^2. The original study and the extension study were carried out according to Good Clinical Practice guidelines and the Declaration of Helsinki.

Patients continued to receive their individual highest nateglinide or gliclazide treatment in combination with metformin monotherapy. The three dose levels for each treatment group were nateglinide 60, 120 and 180 mg three times a day before meals (t.i.d.) and gliclazide 80, 160 and 240 mg once daily. If the individual dose of nateglinide or gliclazide reached at the end of the 24-week study was not maximal, the study medication was uptitrated during the course of extension treatment, provided that the FPG level was >7 mmol/l [equivalent to fasting blood glucose; self-monitored blood glucose (SMBG) >6.3 mmol/l] and the patient had not experienced any confirmed hypoglycaemic events [symptomatic events with plasma glucose concentration of ≤4.0 mmol/l (≤72 mg/dl)] or the patient had not experienced more than three events with symptoms suggestive of hypoglycaemia in the previous month.

If significant hypoglycaemia occurred, the patient was downtitrated to a lower dose of study medication. Patients experiencing frequent (greater than or equal to three events a week) clinical grade 1 hypoglycaemic events, frequent (greater than or equal to three events a week) asymptomatic SMBG levels of ≤65 mg/dl (≤3.6 mmol/l) or three plasma glucose results of ≤72 mg/dl (≤4.0 mmol/l) during the course of the study on the lowest dose of study medication were discontinued from the study. Patients experiencing grade 2 hypoglycaemia (hypoglycaemic events that required the assistance of another person) were also discontinued from the study. Medication instruction, dispensing and the use of concomitant therapy were the same as for the initial 24-week study [5].

Patients completed a standard meal challenge [5] after 52 weeks of treatment, with measurement of glucose and insulin prior to and after meal ingestion. Levels of HbA1c, fasting glucose and insulin were measured after 52 weeks of study treatment using standard methods at a central laboratory. The primary efficacy evaluation was based on HbA1c changes from baseline to endpoint at week 52 or the final visit, using the last observation carried forward (LOCF) approach. Baseline was calculated as the average of the measurements obtained from the evaluations for HbA1c on weeks 2 and 0. If one of these measurements was missing, the remaining measurement was used as the baseline; if both were missing, then the patient was excluded from the analysis. The primary population in this assessment was the extension ITT population.

The study tested the null hypothesis H_0: $\tau_1 = \tau_2$ vs. the alternative hypothesis H_a: $\tau_1 \neq \tau_2$ using an analysis of covariance (ANCOVA) model, where τ_1 is the effect of nateglinide plus metformin combination therapy and τ_2 is the effect of gliclazide plus metformin combination therapy on HbA1c change from baseline at 52 weeks or last observation carried forward. The statistical test was conducted at the two-sided significance level of 0.05, and 95% confidence intervals are presented for the treatment comparison. The primary ancova model included effects for treatment, centre, baseline HbA1c and treatment

by baseline–HbA1c interaction. Small centres were pooled for this analysis to ensure at least one patient is present in each treatment arm. Analogous ANCOVA models were performed for secondary efficacy parameters.

Safety assessments consisted of monitoring and recording all adverse events and serious adverse events, hypoglycaemic events, the regular monitoring of haematology, blood chemistry and measurement of vital signs, as previously described [5].

Results

Of the 262 patients originally enrolled in the study, 229 completed the initial phase: 120 patients in the nateglinide group and 109 in the gliclazide group. The majority of the patients who completed the initial study agreed to continue with double-blind extended treatment: 112 (93.3%) in the nateglinide plus metformin group and 101 (89.1%) in the gliclazide plus metformin group. The proportion of patients who discontinued during the extension study period was small and similar in both treatment groups: four (3.6%) in the nateglinide group (one due to adverse events and three due to unsatisfactory therapeutic effect) and three (3.0%) in the gliclazide group (two due to adverse events and one who withdrew consent). Key demographic characteristics and background disease characteristics are shown in table 1; there were no evident differences between the two treatment groups.

The mean metformin doses at study entry were comparable (1931 and 1834 mg/day in the nateglinide and gliclazide groups respectively). In the nateglinide group, 64.3% of patients were on the highest dose level (180 mg t.i.d.) at the end of extension study compared with 40.6% of patients in the gliclazide group, who attained the highest dose level (240 mg/day) at the end of the 52-week period.

Glycaemic Control

Changes in HbA1c concentrations over 12 months are shown in figure 1. HbA1c decreased significantly ($p < 0.001$) in both groups over the first 24 weeks, but then tended to increase again over the following 24 weeks, with no significant difference between treatments at week 52 ($p = 0.396$). Similar percentages of patients achieved endpoint HbA1c levels below 7% (table 2).

Changes in FPG levels mirrored changes in HbA1c levels. The decrease from baseline in FPG was statistically significant only in the gliclazide plus metformin treatment arm, but the difference from baseline between the two treatment groups was not statistically significant (table 2).

Table 1 Demographic and background characteristics of treatment groups

	Nateglinide + metformin (n = 112)	Gliclazide + metformin (n = 101)
Age (years)		
Mean (s.d.)	61.9 (11.1)	61.5 (10.2)
Range	28–84	38–80
Age group, n (%)		
<65 years	60 (53.6)	54 (53.5)
≥65 years	52 (46.4)	47 (46.5)
Sex, n (%)		
Male	63 (56.3)	51 (50.5)
Female	49 (43.8)	50 (49.5)
Race, n (%)		
Caucasian	110 (98.2)	98 (97.0)
Non-Caucasian	2 (1.8)	3 (3.0)
BMI (kg/m^2), mean (s.d.)	28.6 (3.5)	30.0 (3.2)
Duration of diabetes (years), mean (s.d.)	7.28 (6.34)	6.31 (5.40)
Baseline HbA1c (%), mean (s.d.)	7.65 (0.60)	7.55 (0.57)
Baseline FPG (mmol/l), mean (s.d.)	9.04 (1.53)	8.54 (1.45)

BMI, body mass index; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c.

Reductions in postprandial glucose after a standard meal were significantly different for the nateglinide group than for the gliclazide group at 24 weeks (−0.7 vs. −0.1; $p = 0.037$), but during the extended study, the differences narrowed and no longer reached statistical significance at the 52-week endpoint (table 3). The observed decreases in glucose area under the curve $(AUC)_{0–4\ h}$ from baseline at the 52-week endpoint were −3.26 and −1.86 h × mmol/l in the nateglinide and the gliclazide groups respectively. This change from baseline was statistically significant in the nateglinide group only ($p = 0.006$), but the difference between groups was not statistically significant. These decreases were smaller than those observed at the 24-week study endpoint (−5.96 vs. −3.93 h × mmol/l).

Nateglinide plus metformin treatment augmented the acute plasma insulin response at 30 min after a meal to a greater degree than gliclazide plus metformin treatment (table 3). The difference between the treatment arms for the 2-h plasma insulin concentration was not statistically different. The insulin secretion index, as measured by HOMA-B, was greater than at baseline for the gliclazide arm but lower than at baseline for the nateglinide group. In contrast to the results at 24 weeks, the difference between treatments was statistically significant.

A statistically significant ($p = 0.009$) increase of 0.91 kg in body weight during the 52-week study period was

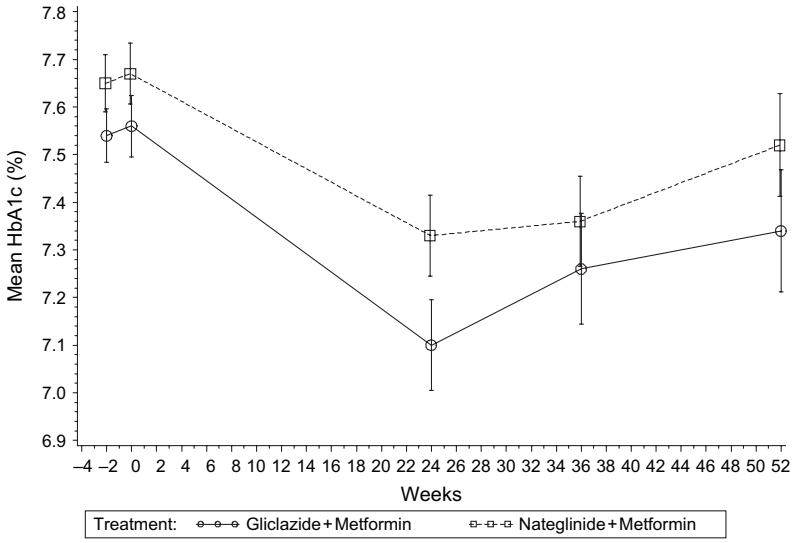

Fig. 1 Mean haemoglobin A1c (HbA1c) level over time of treatment with either nateglinide or gliclazide in combination with metformin in patients with type 2 diabetes.

observed in patients in the gliclazide plus metformin group. The change in the nateglinide plus metformin group was 0.42 kg and was not significantly different from baseline ($p = 0.201$).

Safety

There were no deaths during the study, and no clinically meaningful differences between the two treatment arms were observed in the rates of incidence of specific adverse events. Serious adverse events during the extension phase were infrequent (1.8 vs. 6.9% for nateglinide and gliclazide groups respectively). Serious adverse events in the nateglinide group were cardiac failure and unstable angina; in the gliclazide group, the serious events were prostate adenoma, chest pain, acute coronary syndrome, intervertebral disc protrusion, atrial fibrillation and two cases of myocardial infarction. No adverse events were attributed to the study drug in contrast to the 24-week study where a proportion of events experienced in the gliclazide group were attributed to study medication. The most frequent types of adverse events were nasopharyngitis, hypertension, influenza, diarrhoea and upper respiratory tract infections. Discontinuations due to adverse events were also infrequent (one and two patients in the nateglinide and the gliclazide groups respectively). There were no clinically relevant differences between treatments in clinical laboratory parameters and vital signs.

Table 2 Proportion of patients with positive responses to predefined HbA1c criteria and changes in fasting plasma glucose at the 52-week endpoint

	Nateglinide + metformin (n = 110)	Gliclazide + metformin (n = 99)
Response rates, n (%)		
Reduction of HbA1c ≥1% from baseline	22 (20.0)	24 (24.2)
Endpoint HbA1c <7%	44 (40.0)	47 (47.5)
Baseline FPG (mmol/l), mean ± s.d.	8.98 ± 1.52	8.51 ± 1.44
Change, least squares mean ± s.e.	−0.20 (0.22)	−0.69 (0.23)
p value for change	0.357	0.003
Treatment difference, mean ± s.d.	0.49 ± 0.29	
p value for treatment difference	0.096	

FPG, fasting plasma glucose; HbA1c, haemoglobin A1c.

Hypoglycaemic Events

The number of patients who experienced hypoglycaemic events (table 4), either symptomatic or asymptomatic, was similar in both treatment arms during the extension period and distinctly lower than that observed during the initial 24-week study. The overall rate of events suggestive of hypoglycaemia during the extension period was similar: 8.2 and 8.7 events/100 patients/month for the nateglinide and gliclazide groups respectively. These rates were considerably lower than those observed in the 24-week study (16.4 and 31.5 events/100 patients/month). In particular, the rates of symptomatic events were very low in both groups (1.8 and 1.4 events/100 patients/month in the nateglinide and gliclazide groups respectively). The rates of asymptomatic and confirmed events were also similar in both treatment groups.

Table 3 Plasma glucose and insulin levels following a test meal, and insulin secretion index (HOMA-B), at study baseline and changes after 52 weeks of treatment of patients with type 2 diabetes*

	Nateglinide + metformin	Gliclazide + metformin	Treatment difference
Maximum postprandial plasma glucose (mmol/l)	n = 102	n = 93	
Baseline, mean ± s.d.	15.03 ± 3.37	13.59 ± 2.82	
Least squares mean change ± s.e.	−0.69 ± 0.40	−0.29 ± 0.43	−0.40 ± 0.55
p value	0.087	0.500	0.470
Thirty minutes' postprandial insulin (pmol/l)	n = 97	n = 92	
Baseline, mean ± s.d.	156.8 ± 127.4	161.8 ± 123.1	
Least squares mean change ± s.e.	131.7 ± 13.2	40.7 ± 13.6	91.0 ± 17.6
p value	<0.001	0.003	<0.001
Two hours postprandial insulin (pmol/l)	n = 95	n = 87	
Baseline, mean ± s.d.	213.4 ± 165.7	235.8 ± 197.7	
Least squares mean change ± s.e.	77.4 ± 14.7	49.1 ± 15.7	28.3 ± 20.2
p value	<0.001	0.002	0.163
HOMA-B	n = 95	n = 91	
Baseline, mean ± s.d.	48.2 ± 55.9	57.3 ± 70.5	
Least squares mean change ± s.e.	−1.83 ± 5.4	19.8 ± 5.6	−21.6 ± 7.3
p value	0.738	0.001	0.004

*The p values are within-group for changes from baseline and between-groups for treatment difference.

Discussion

A 6-month extension to the previously reported 24-week study was conducted to obtain long-term data on efficacy, safety and tolerability of nateglinide compared with those of gliclazide in combination with metformin in patients inadequately controlled on metformin monotherapy. HbA1c levels tended to be higher at the 52-week endpoint compared with the previously reported 24-week period for both combination treatments. This is in agreement with recent studies that compared combination treatment of gliclazide and metformin with pioglitazone and metformin and documented HbA1c increases by approximately 0.4% between the 24-week and 52-week follow up [6]. A progressive rise in HbA1c with monotherapy followed by add-on treatment has been confirmed during the UK Prospective Diabetes Study [4,7,8]. In the current trial, the two combination regimens were likewise unable to halt the progressive deterioration of metabolic control typical for type 2 diabetes.

Table 4 Number of patients reporting hypoglycaemic events during 52 weeks of treatment with nateglinide or gliclazide in combination with metformin

	Nateglinide + metformin (n = 112)	Gliclazide + metformin (n = 101)
Patients with at least one event suggestive of hypoglycaemia, n (%)	19 (17.0)	16 (15.8)
Patients with at least one confirmed event of hypoglycaemia, n (%)	17 (15.2)	15 (14.9)
Patients with greater than or equal to three events suggestive of hypoglycaemia, n (%)	7 (6.3)	7 (6.9)
Patients with greater than or equal to three events confirmed as hypoglycaemia, n (%)	7 (6.3)	7 (6.9)

Responder rate, as assessed by the number of patients showing an improvement in HbA1c greater than 1.0%, was similar for both treatments. Similar proportion of patients in both treatment combinations reached a HbA1c below 7.0%, which is the currently defined treatment goal [9]. The changes in FPG levels paralleled the changes observed in HbA1c levels. FPG concentrations at 52 weeks were slightly, but significantly, lower than at baseline in the gliclazide plus metformin treatment arm. However, there was no difference in FPG between the nateglinide plus metformin and gliclazide plus metformin groups.

The superior ability of nateglinide to reduce postprandial plasma glucose levels, observed in the previously reported 24-week study [5], was further confirmed in this follow-up study. Although the differences in postprandial plasma glucose AUC were smaller than at 24 weeks, they nevertheless reached statistical significance. Reduction in postprandial glucose with nateglinide was achieved through greater increase in early insulin secretion, documented by significantly higher insulin level at 30 min achieved with nateglinide than with gliclazide. Two-hour insulin levels indicate that there was no difference in later phase insulin secretion between nateglinide and gliclazide. This is consistent with the previously reported glucose-sensitive nature of insulin secretion with nateglinide treatment [10].

While there was a statistically significant increase in body weight in the gliclazide group, there was no increase in body weight in patients on the nateglinide plus metformin treatment, most likely due to more physiological pattern of insulin secretion with nateglinide.

Nateglinide plus metformin and gliclazide plus metformin were well tolerated during the extension study period, and no differences of note were observed for any specific adverse events. Serious adverse events were infrequent but tended to be more common in the gliclazide plus metformin group; however, none was considered to be related to the study drug. The number of patients who experienced hypoglycaemic events was similar in both treatment arms during the extension period and distinctly lower than observed during the 24-week study. The higher incidence of hypoglycaemia in this study in comparison to the other nateglinide studies could be ascribed to the utilization of broader criteria of hypoglycaemic events and to the frequent use of the highest dose of nateglinide. Definition of hypoglycaemic event included asymptomatic episodes of low blood glucose and events suggestive of hypoglycaemia without confirmation based on blood glucose measurement.

The results after 52 weeks are broadly similar to those after 24 weeks. With both treatment modalities, the initial improvement in metabolic control was attenuated during the extension period. The trend in favour of the gliclazide plus metformin combination in reduction of HbA1c weakened between the 24-week and 52-week follow up. Nateglinide plus metformin remained more potent at stimulating the acute insulin response to a meal until the end of the 52-week follow up. Postprandial plasma glucose control remained better in patients treated with nateglinide plus metformin, and statistical significance was maintained for the adjusted $AUC_{0-4\ h}$. Thus, the good safety and tolerability of both treatments demonstrated in the 24-week study were confirmed in this 6-month extension.

Acknowledgements

The authors thank Dr Peter Bates, Cambridge Medical Writing Services, CB10 1SH, UK, for help in preparation of the manuscript. The authors also thank the investigators involved in the study: Dr Keith Bowering, Alberta, Dr Chantal Godin, Quebec, Dr Irving Gottesman, Ontario, Dr David Lau, Alberta, Dr Alicia Schiffrin, Quebec, Dr Vincent Woo, Manitoba, Canada; Dr Pierre Cause, Saint Etienne, Dr Michel David, Fabregues, Dr Salam Farhat, St Pierre de Chandieu, Dr Alain Giacomino, Savigny en Veron, Dr Francois Lacoin, Albens, Dr Michele Pithon, Hyeres, France; Dr Maurizio Bevilacqua, Milan, Dr Laura Corsi, Chiavari, Prof Ottavio Giampietro, Pisa, Prof Italo Tanganelli, Sienna, Prof Giorgio Viviani, Genova, Italy; Dr Isabel Chico, Barcelona, Dr Francisca Fernandez, Girona, Dr Jose Miguel Gonzalez, Barcelona, Dr Joan Martorell, Lerida, Dr Andreu Nubiola, Barcelona, Dr Luis De Teresa, Alicante, Spain and Dr Gertrud Kacerovsky-Bielesz, Vienna, Austria. This study was sponsored by Novartis Pharma, Basel.

References

1 James DE. MUNC-ing around with insulin action. J Clin Invest 2005; **115:** 219–221.
2 Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2001; **414:** 782–787.
3 Goodarzi MO, Bryer-Ash M. Metformin revisited: re-evaluation of its properties and role in the pharmacopoeia of modern antidiabetic agents. Diabetes Obes Metab 2005; **7:** 654–665.
4 UK Prospective Diabetes Study Group. UKPDS 28: a randomized trial of efficacy of early addition of metformin in sulfonylurea-treated type 2 diabetes. Diabetes Care 1998; **21:** 87–92.
5 Ristic S, Collober-Maugeais C, Pecher E, Cressier F. Comparison of nateglinide and gliclazide in combination with metformin, for treatment of patients with type 2 diabetes inadequately controlled on maximum doses of metformin alone. Diabet Med 2006; **23:** 757–762.
6 Maher LJ, Edwards G, Lee CE *et al.* Long-term combination therapy with pioglitazone plus metformin for type 2 diabetes: a randomized comparative study with gliclazide plus metformin. Diabetologia 2003; **46** (Suppl. 2): A28.
7 UK Prospective Diabetes Study Group. UKPDS 13: relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed insulin-dependent diabetes followed for three years. Br Med J 1995; **310:** 83–88.
8 UK Prospective Diabetes Study Group. UKPDS 33: intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet 1998; **352:** 837–853.
9 American Diabetes Association. Standards of medical care in diabetes-2006. Diabetes Care 2006; **29** (Suppl. 1): S4–S42.
10 Mari A, Gastaldelli A., Foley JE *et al.* Beta-cell function in mild type 2 diabetic patients: effects of 6-month glucose lowering with nateglinide. Diabetes Care 2005; **28:** 1132–1138.