*Journal of Clinical Pharmacy and Therapeutics* (2009) **34**, 13–23 doi:10.1111/j.1365-2710.2008.00984.x

ORIGINAL ARTICLE

# Nateglinide and glibenclamide metabolic effects in naïve type 2 diabetic patients treated with metformin

G. Derosa* MD PhD, A. D'Angelo* BD PhD, E. Fogari* MD, S. Salvadeo* MD, A. Gravina* MD, I. Ferrari† MD and A. F. G. Cicero* MD

**Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy and †G. Descovich Atherosclerosis Study Center, ''D. Campanacci'' Clinical Medicine and Applied Biotechnology Department, University of Bologna, Bologna, Italy*

## SUMMARY

***Background and objective:*** **Most antidiabetic agents target only one of several underlying causes of diabetes. The complementary actions of the glinides and the biguanides may give optimal glycemic control in patients with type 2 diabetes mellitus. The aim of the present study was to compare the effects of nateglinide plus metformin with glibenclamide plus metformin on glucose and lipid metabolism, and haemodynamic parameters in patients with type 2 diabetes mellitus.**

***Methods:*** **We enrolled 248 type 2 diabetic patients. Patients were randomly assigned to receive nateglinide ($n$ = 124) or glibenclamide ($n$ = 124), after 6 months of run-in, in which we titrated nateglinide (starting dose 180 mg/day), glibenclamide (starting dose 7·5 mg/day), and metformin (starting dose 1500 mg/day). The final doses were (mean ± standard deviation), 300 ± 60, 12·5 ± 2·5, and 2500 ± 500 mg/day, respectively. We followed these patients for 1 year after titration. We assessed body mass index (BMI), fasting (FPG) and post-prandial (PPG) plasma glucose, glycosylated haemoglobin ($HbA_{1c}$), fasting (FPI) and post-prandial (PPI) plasma insulin, homeostasis model assessment (HOMA) index, and lipid profile [total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), triglycerides (Tg), apolipoprotein A-I (Apo A-I), and apolipoprotein B (Apo B)], systolic blood pressure (SBP), and diastolic blood pressure (DBP). All variables were evaluated at baseline and after 3 and 6 months in the run-in period, and at baseline, and after 3, 6, 9 and 12 months for both treatment groups.**

***Results and discussion:*** **Body mass index did not show any significant change during the study. We observed a significant improvement from baseline to 1 year on $HbA_{1c}$ ($P < 0{\cdot}01$ vs. baseline and vs. glibenclamide group, respectively), FPG ($P < 0{\cdot}01$ vs. baseline), PPG ($P < 0{\cdot}01$ vs. baseline), and on HOMA index ($P < 0{\cdot}05$ vs. baseline) in the nateglinide group. In the glibenclamide group, we found significant changes in $HbA_{1c}$ ($P < 0{\cdot}05$ vs. baseline), FPG ($P < 0{\cdot}01$ vs. baseline), PPG ($P < 0{\cdot}05$ vs. baseline), and HOMA index ($P < 0{\cdot}05$ vs. baseline). No significant change was observed in TC, LDL-C, HDL-C, Tg, Apo A-I, Apo B, SBP, DBP and HR in either group after 3, 6, 9 and 12 months. These effects of nateglinide and glibenclamide on insulin-resistance parameters are in agreement with previous reports. Contrarily to previous reports, we did not observe any significant BP change in patients treated with glibenclamide. Although both nateglinide and glibenclamide attenuated PPG and HOMA index, they did not have significant effects on lipid metabolism, as already shown in subjects with type 2 diabetes and good glycemic control.**

***Conclusion:*** **Nateglinide improved glycemic control better than glibenclamide in combination with metformin.**

*Keywords*: **glibenclamide, insulin-resistance, metformin, nateglinide, oral antidiabetic agents**

Received 18 June 2007, Accepted 24 July 2007

Correspondence: G. Derosa, MD, PhD, Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, P.le C. Golgi, 19-27100 Pavia, Italy. Tel.: +39 0382 526217; fax: +39 0382 526259; e-mail: giuseppe.derosa@uni.pv.it.

 

## INTRODUCTION

Metformin is a biguanide antihyperglycemic drug used for the treatment of type 2 diabetes mellitus for over 40 years and its main mechanism of action is to counteract peripheral insulin-resistance (1). Moreover, metformin is the only antihyperglycemic drug that has been shown to have relevant positive effects on hard clinical outcomes: it prevented 40% of vascular events in a large retrospective Canadian study of more than 12000 patients (2), significantly reduced any diabetes-related endpoint in the United Kingdom Prospective Diabetes Study (3), and it decreased the incidence of diabetes by the 31% in the large Diabetes Prevention Program (4). However, type 2 diabetes mellitus is a progressive disorder, and although oral monotherapy is often initially successful, it is associated with a high secondary failure rate, which contributes to the development of long-term diabetes complications resulting from persistent hyperglycemia (5). For patients not taking insulin, accumulating evidence suggests that combination therapy using oral antidiabetic agents with different mechanisms of action may be highly effective in achieving and maintaining target blood glucose levels (6). In the course of the disease, the use of combinations of oral agents may delay the need for insulin while maintaining glycemic control, thus making aggressive oral treatment more acceptable for many patients (7).

Sulphonylureas (SUs) are widely used to treat type 2 diabetes because they stimulate insulin secretion from pancreatic beta-cells. They primarily act by binding to the SUR subunit of the ATP-sensitive potassium channel and inducing channel closure (8). Glibenclamide is a well-known first generation sulphanylurea. As all SUs, it binds a specific site on the adenosine triphosphate (ATP)-sensitive potassium channels, subsequently opening calcium channels and thus triggering insulin exocytosis from the pancreatic beta cell (9).

Nateglinide, a D-phenylalanine derivative lacking either a SU or benzamido moiety, stimulates insulin release via closure of (ATP)-sensitive potassium channels in pancreatic beta-cell, a primary mechanism of action it shares with glibenclamide and other SUs (10). Nateglinide binds rapidly to the SU SUR1 receptor with a relatively low affinity, and it dissociates from it extremely rapidly in a manner of seconds. This rapid association and dissociation gives nateglinide a unique 'fast on-fast off' effect (11). Thus, nateglinide has a rapid onset and short duration of action stimulating insulin secretion *in vivo* and providing good control of post-prandial hyperglycemia when taken immediately prior to meals. The rapid action of nateglinide on the beta cells stimulates and restores the normal physiological first and early phase of insulin secretion, consequently reducing post-prandial hyperglycemia (12). This hypoglycemic effect of nateglinide leads to improved glycemic control, and the short duration avoids delayed hyperinsulinemia and hypoglycemia after meals (13).

The aim of our study is to directly compare the long-term metabolic effects of nateglinide and glibenclamide in naïve type 2 diabetic patients treated with metformin.

## PATIENTS AND METHODS

### *Study design*

This 12-month, multicenter, double-blind, randomized, controlled, parallel-group trial was conducted at the Department of Internal Medicine and Therapeutics, University of Pavia (Pavia, Italy); the 'G. Descovich' Atherosclerosis Study Center, 'D. Campanacci' Clinical Medicine and Applied Biotechnology Department, University of Bologna (Bologna, Italy); and in the Diabetes Care Unit at S. Carlo Hospital of Milano (Milano, Italy).

The study protocol was approved at each site by institutional review boards and was conducted in accordance with the 1994 Declaration of Helsinki and its amendments (14), and the Code of Good Clinical Practice.

### *Patients*

Two hundred and thirty-three (116 males and 117 females) Caucasian patients aged ≥ 18 of either sex were eligible for inclusion in the study if they had type 2 diabetes mellitus according to the American Diabetes Association (ADA) criteria (15) (duration, ≥ 6 months), and if they had poor glycemic control (glycosylated hemoglobin [$HbA_{1c}$] level, > 7·0%) and hypertension according to the World Health Organization criteria (16) (systolic/diastolic blood

pressure, ≥ 130/≥ 85 mm Hg). They were overweight (body mass index [BMI], 25·0–28·0 kg/m$^2$) (17). None of the selected subjects of this study were taking hypolipidemic drugs, diuretics, β-blockers or thyroxin. Suitable patients, identified from review of case notes and/or computerized clinic registers, were contacted by the investigators in person or by telephone.

Patients were excluded if they had a history of ketoacidosis or had unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy; impaired hepatic function (defined as plasma aminotransferase and/or gamma-glutamyltransferase level higher than the upper limit of normal [ULN] for age and sex), impaired renal function (defined as serum creatinine level higher than the ULN for age and sex), or severe anemia. Patients with serious cardiovascular disease (CVD) (eg, New York Heart Association class I–IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months before study enrollment also were excluded. Women who were pregnant or breast-feeding or of childbearing potential and not taking adequate contraceptive precautions were also excluded. All patients provided written informed consent to participate.

## METHODS

### *Treatment*

Patients were randomly assigned to receive nateglinide or glibenclamide after 6 months of run-in, in which patients were titrated to nateglinide (starting dose 180 mg/day), glibenclamide (starting dose 7·5 mg/day). Metformin (starting dose 1500 mg/day) was added in each arm independently of the glycemic control after 1 month of run-in (Fig. 1). The final doses were 300 ± 60, 12·5 ± 2·5, and 2500 ± 500 mg/day, respectively.

Patients were randomized using envelopes containing randomization codes prepared by a statistician. A copy of the randomization code was provided only to the person responsible for performing the statistical analysis. The code was only broken after database lock, but could have been broken for individual patients in cases of emer-

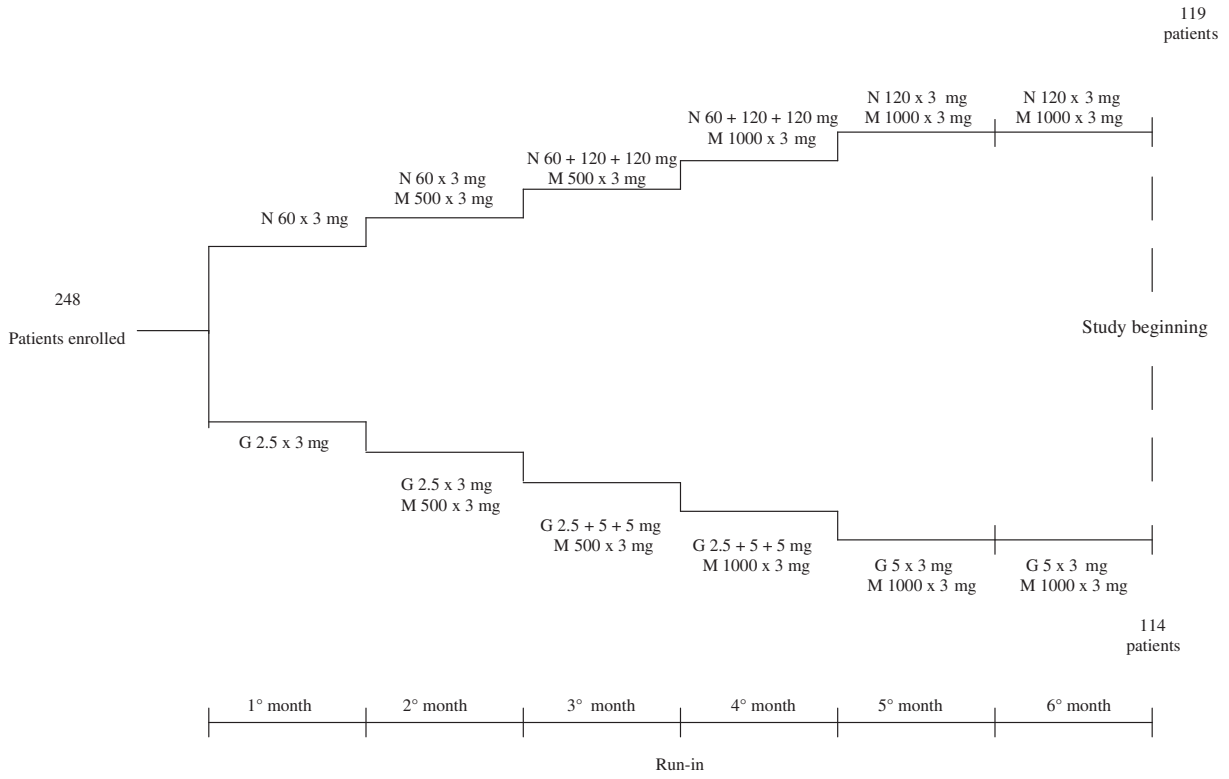


**Fig. 1.** Scheme of the study. N, nateglinide; G, glibenclamide; M, metformin.

gency, such as hospitalization or suspect of a serious adverse event.

Nateglinide, glibenclamide and metformin were supplied as identical, opaque, white capsules in coded bottles to ensure the double-blind status of the study. At baseline, we weighed participants and gave them a bottle containing a 100-day supply of study medication. Throughout the study, we instructed patients to take their first dose of new medication on the day after they were given the study medication. A bottle containing the study medication for the next treatment period was given to participants at the 3-month visit. At the same time, all unused medication was retrieved for inventory. All medications were provided free of charge.

### *Diet and exercise*

At baseline, patients began a controlled-energy diet (~600 kcal daily deficit), based on ADA recommendations (18), that contained 50% of calories from carbohydrates, 30% from fat (6% saturated), and 20% from proteins, with a maximum cholesterol content of 300 mg/d, and 35 g/d of fiber. Each center's standard diet advice was given by a dietitian and/or specialist physician. Dietitians and/or specialists each two weeks provided instruction on dietary intake–recording procedures as part of a behavior-modification program and then from month 1 used the patients' food diaries for counseling. During the study, behavior-modification sessions on weight-loss strategies were given to individual patients at baseline, one at 6 months, and four with all patients at 3, 6, 9 and 12 months. Individuals were also encouraged to increase their physical activity by walking briskly or riding a stationary bicycle for 20 to 30 min, 3–5 times per week. The recommended changes in physical activity throughout the study were not assessed.

### *Efficacy, Tolerability, and Compliance Assessments*

Before starting the study, all patients underwent an initial screening assessment that included a medical history; physical examination; vital signs; a 12-lead electrocardiogram; measurements of height and body weight; calculation of BMI; assessment of glycemic control ($HbA_{1c}$, fasting and post-prandial plasma glucose, fasting and post-prandial plasma insulin levels [FPG, PPG, FPI, and PPI, respectively], homeostasis model assessment [HOMA] index), and lipid profile [total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), triglycerides (Tg), apolipoprotein A-I (Apo A-I), and apolipoprotein B (Apo B)], systolic blood pressure (SBP), and diastolic blood pressure (DBP). Body Mass Index, $HbA_{1c}$, FPG, PPG, FPI, PPI, HOMA index, TC, LDL-C, HDL-C, Tg, Apo A-I, Apo-B, SBP, and DBP values were also assessed at 3, 6, 9 and 12 months.

All plasmatic variables were determined after a 12-h overnight fast, except PPG and PPI, which were determined 2 h after lunch. Venous blood samples were drawn by a research nurse for all patients between 8:00 AM and 9:00 AM. We used plasma obtained by addition of $Na_2$-EDTA, 1 mg/mL, and centrifuged at 3000 *g* for 15 min at 4°C. Immediately after centrifugation, the plasma samples were frozen and stored at –80°C for ≤ 3 months. All measurements were performed in a central laboratory and the biologist responsible for the laboratory performed the assays.

BMI was calculated by the investigators as weight in kilograms divided by the square of height in meters. The estimate of insulin-resistance was calculated using the HOMA index, with the following formula:

Insulin-resistance = FPI ($\mu$U/mL) ' FPG (mmol/L)/ 22·5, as described by Matthews *et al*. (19) (Normal if < 2·5, marker of insulin-resistance if ≥ 2·5).

Blood pressure (BP) measurements were obtained from each patient (using the right arm) in the seated position, using a standard mercury sphygmomanometer (Erkameter 3000, ERKA, Bad Tolz, Germany) (Korotkoff I and V) with a cuff of appropriate size. BP was measured by the same investigator at each visit, in the morning before daily drug intake and after the patient had rested for ≥ 10 min in a quiet room. Three successive BP readings were obtained at 1-min intervals, and the mean of the three readings was calculated.

$HbA_{1c}$ level was measured using high-performance liquid chromatography (DIAMAT, Bio-Rad Laboratories, Inc., Hercules, CA, USA; normal value, 4·2–6·2%), with intra- and interassay coefficients of variation (CsV) of< 2% (20). Plasma

glucose was assayed using a glucose-oxidase method (GOD/PAP, Roche Diagnostics, Mannheim, Germany) with intra- and interassay CsV< 2% (21). Plasma insulin was assayed with Phadiaseph Insulin Radioimmunoassay (Pharmacia, Uppsala, Sweden) using a second antibody to separate the free and antibody-bound 125 I-insulin (intra- and interassay CsV, 4·6% and 7·3%, respectively) (22).

Total cholesterol and Tg levels were determined using fully enzymatic techniques (23, 24) on a clinical chemistry analyzer (HITACHI 737; Hitachi, Tokyo, Japan); intra- and interassay CsV were 1·0% and 2·1% for TC measurement, and 0·9% and 2·4% for Tg measurement, respectively. HDL-C level was measured after precipitation of plasma apo B-containing lipoproteins with phosphotungstic acid (25) intra- and interassay CsV were 1·0% and 1·9%, respectively; LDL-C level was calculated by the Friedewald formula (26). Apo A-I and Apo B were measured by immuno-turbidimetric assays (Boehringer-Mannheim, Mannheim, Germany); the inter- and intrassay CsV were 3–5%, respectively (27, 28). Treatment tolerability was assessed at each study visit using an accurate interview of patients by the investigators, and comparisons of clinical and laboratory values with baseline levels. Medication compliance was assessed by the investigators by counting the number of pills returned at the time of specified clinic visits.

## STATISTICAL ANALYSIS

An intention-to-treat analysis was conducted in patients who had received ≥ 1 dose of study medication and had a subsequent efficacy observation. Patients were included in the tolerability analysis if they had received ≥ 1 dose of trial medication after randomization and had undergone a subsequent tolerability observation. The null hypothesis that the expected mean $HbA_{1c}$, FPG, PPG, FPI, PPI, HOMA index change from baseline to 12 months of double-blind treatment did not differ significantly between nateglinide and glibenclamide treatments was tested using analysis of variance and analysis of covariance (ANCOVA) models (29). Similar analyses were applied to the other variables. The statistical significance of the independent effects of treatments on the other variables was determined using ANCOVA. A 1-sample *t*-test was used to compare values obtained before and after treatment administration; 2-sample *t*-tests were used for between-group comparisons. The Bonferroni correction for multiple comparison was also carried out. Statistical analysis of data was performed using the Statistical Package for Social Sciences software version 11·0 (SPSS Inc., Chicago, IL, USA). Data are presented as mean (SD). For all statistical analyses, $P < 0{\cdot}05$ was considered statistically significant.

## RESULTS

### *Study sample*

248 patients (124 males and 124 females) were enrolled in the trial. One hundred and twenty-four (60 males and 64 females) (50·0%) were randomized to double-blind treatment with nateglinide and 124 (62 males and 62 females) (50·0%) with glibenclamide. Two hundred thirty-three patients (94·0%) completed the study (119 patients in the nateglinide arm, 58 males and 61 females, and 114 patients in the glibenclamide arm, 58 males and 56 females).

There were 15 patients (6·0%) (six males and nine females) who did not complete the study and the reasons for premature withdrawal included protocol violation, loss to follow-up, non-compliance (Fig. 2). The characteristics of the patient population at study entry, shown in Tables 1 and 2, were similar in the two treatment group.

### *Efficacy*

*Body mass index* No BMI change was observed after 3, 6, 9 and 12 months in both groups. Results are reported in details in Tables 1 and 2.

*Glycemic control* No $HbA_{1c}$ change was observed after 3 and 6 months in nateglinide group, while a significant $HbA_{1c}$ decrease was obtained after 9 ($P < 0{\cdot}05$), and 12 ($P < 0{\cdot}01$) months in nateglinide group compared to the baseline value and this change was significant after 12 ($P < 0{\cdot}05$) months with respect to the glibenclamide group. No significant $HbA_{1c}$ variation was present at 3, 6, and 9 months in the glibenclamide group, while a significant $HbA_{1c}$ decrease was obtained after 12 ($P < 0{\cdot}05$) months in this group compared to the

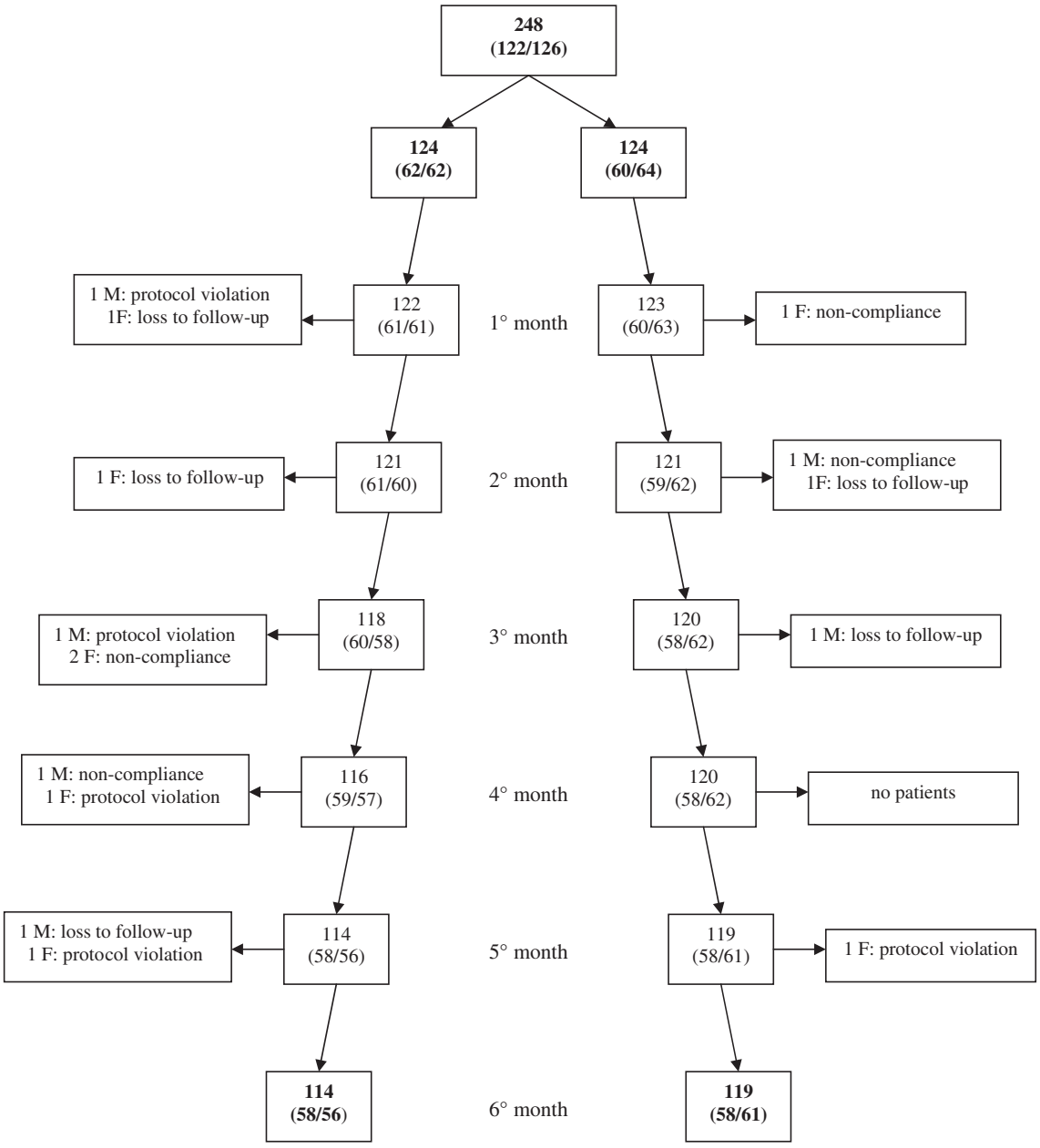


**Fig. 2.** patients flow (males/females) and withdrawals during the study; G or G + M on the left, N or N + M on the right. N: nateglinide. G: glibenclamide. M: metformin.

baseline value (Table 2) (Fig. 3). No significant FPG change was present at 3 and 6 month in both groups. After 9 and 12 months, mean FPG levels were significantly decreased in both groups ($P < 0{\cdot}05$ and $P < 0{\cdot}01$, respectively) (Tables 1 and 2) compared to baseline (Fig. 4). Post-prandial glucose did not show any significant change after 3 and 6 months in nateglinide group, and after 3, 6 and 9 months in glibenclamide group. Significant PPG decrease was obtained only at 9 months ($P < 0{\cdot}05$) in nateglinide group, and after 12 months in glibenclamide and nateglinide group ($P < 0{\cdot}05$ and $P < 0{\cdot}01$, respectively) with respect to the baseline (Tables 1 and 2) (Fig. 5). Fasting plasma insulin and PPI did not show any significant change after 3, 6, 9 and 12 months in both groups compared to the baseline value (Figs 6 and 7). Furthermore, HOMA index decrease was

**Table 1.** Baseline characteristics and parameter changes at 3, 6, 9 and 12 month of the study in nateglinide group

| | Nateglinide + metformin | | | | |
|---|---|---|---|---|---|
| | Baseline | 3 months | 6 months | 9 months | 12 months |
| *n* | 119 | – | – | – | – |
| Sex (M/F) | 58/61 | – | – | – | – |
| Age (years) | 55 ± 5 | – | – | – | – |
| Diab. Dur. (years) | 5 ± 2 | – | – | – | – |
| BMI (kg/m$^2$) | 26·4 ± 1·4 | 26·2 ± 1·2 | 26·6 ± 1·3 | 26·5 ± 1·3 | 26·8 ± 1·6 |
| $HbA_{1c}$ (%) | 8·1 ± 1·0 | 7·3 ± 0·8 | 7·1 ± 0·7 | 6·7 ± 0·5* | 6·4 ± 0·4**,*** |
| FPG (mg/dL) | 174 ± 21 | 165 ± 20 | 156 ± 19 | 144 ± 18* | 138 ± 17** |
| PPG (mg/dL) | 191 ± 28 | 184 ± 25 | 176 ± 24 | 162 ± 22* | 150 ± 21** |
| FPI ($\mu$U/mL) | 26·6 ± 4·8 | 26·1 ± 4·6 | 26·3 ± 4·6 | 25·9 ± 4·4 | 24·7 ± 4·2 |
| PPI ($\mu$U/mL) | 68·2 ± 9·3 | 67·5 ± 9·1 | 66·4 ± 8·9 | 67·3 ± 9·0 | 65·3 ± 8·7 |
| HOMA index | 11·4 ± 4·8 | 11·1 ± 4·6 | 10·5 ± 4·3 | 9·8 ± 4·0 | 8·5 ± 3·9* |
| TC (mg/dL) | 196 ± 18 | 192 ± 17 | 190 ± 16 | 186 ± 15 | 181 ± 14 |
| LDL-C (mg/dL) | 121 ± 13 | 120 ± 13 | 118 ± 12 | 115 ± 12 | 113 ± 11 |
| HDL-C (mg/dL) | 42 ± 5 | 42 ± 5 | 44 ± 8 | 45 ± 7 | 43 ± 6 |
| Tg (mg/dL) | 156 ± 40 | 150 ± 37 | 146 ± 36 | 142 ± 34 | 141 ± 33 |
| Apo A-I (mg/dL) | 127 ± 20 | 125 ± 19 | 126 ± 21 | 12 ± 20 | 128 ± 20 |
| Apo B (mg/dL) | 116 ± 18 | 116 ± 19 | 115 ± 18 | 117 ± 20 | 115 ± 16 |
| SBP (mmHg) | 136·8 ± 4·4 | 136·1 ± 4·2 | 135·3 ± 4·0 | 136·1 ± 3·9 | 134·5 ± 3·6 |
| DBP (mmHg) | 87·3 ± 3·8 | 86·8 ± 3·7 | 86·1 ± 3·5 | 85·8 ± 3·5 | 85·4 ± 3·4 |
| HR (b/min) | 78 ± 7 | 76 ± 6 | 76 ± 7 | 74 ± 6 | 72 ± 5 |

BMI, body mass index; $HbA_{1c}$, glycated haemoglobin; FPG, fasting plasma glucose; PPG, post-prandial plasma glucose; FPI, fasting plasma insulin; PPI, post-prandial plasma insulin; HOMA index, homeostasis model assessment index; TC, total cholesterol; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; Tg, triglycerides; Apo A-I, apolipoprotein A-I; Apo B, apolipoprotein B; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.
Data are mean ± SD; *$P < 0{\cdot}05$ vs. baseline; **$P < 0{\cdot}01$ vs. baseline; ***$P < 0{\cdot}05$ vs. glibenclamide + metformin.

obtained only at 12 months ($P < 0{\cdot}05$) compared to the baseline value in both groups (Fig. 8).

*Lipid profile and lipoprotein variables* No TC, LDL-C, HDL-C, Tg, apo A-I, and apo B change were obtained during the study in both groups (Tables 1 and 2).

*Blood pressure effects* No SBP and DBP change were obtained in either group after 3, 6, 9 and 12 months. No significant heart rate (HR) variation was observed during the study in both groups (Tables 1 and 2).

## DISCUSSION

The metabolic control of type 2 diabetes with an oral monotherapy is often difficult and consequently a combined treatment is required. Metformin may be the first therapeutic option in type 2 diabetes mellitus patients who are overweight or obese. SUs, alpha-glucosidase inhibitors, thiazolidinediones, meglitinides, insulin, and diet fail to show greater beneficial effect on glycemia control, body weight, or lipids, than metformin alone (30).

The association of nateglinide and metformin has already been shown to be an efficacious and safe antidiabetic treatment in type 2 diabetic patients (31, 32). Its efficacy and safety has also been shown in elderly diabetic patients (33) and as a first line-therapy in treatment-naïve patients with recently developed type 2 diabetes (34). The PRESERVE-beta trial compared the effect of the nateglinide-metformin combination with that of glibenclamide-metformin for the long-term metabolic control of 428 newly diagnosed type 2 diabetics. Both protocols appeared to be efficacious in achieving good glucose homeostasis, but the

**Table 2.** Baseline characteristics and parameter changes at 3°, 6°, 9°, and 12 month of the study in glibenclamide group

| | Glibenclamide + metformin | | | | |
|---|---|---|---|---|---|
| | Baseline | 3 months | 6 months | 9 months | 12 months |
| *n* | 114 | – | – | – | – |
| Sex (M/F) | 58/56 | – | – | – | – |
| Age (years) | 56 ± 4 | – | – | – | – |
| Diab. Dur. (years) | 4 ± 2 | – | – | – | – |
| BMI (Kg/m$^2$) | 26·5 ± 1·5 | 26·5 ± 1·5 | 26·7 ± 1·6 | 26·8 ± 1·7 | 26·9 ± 1·7 |
| $HbA_{1c}$ (%) | 8·2 ± 1·1 | 7·9 ± 0·8 | 7·7 ± 0·8 | 7·6 ± 0·7 | 7·3 ± 0·6* |
| FPG (mg/dL) | 177 ± 24 | 168 ± 21 | 160 ± 18 | 147 ± 17* | 136 ± 15** |
| PPG (mg/dL) | 187 ± 24 | 182 ± 23 | 174 ± 22 | 169 ± 21 | 166 ± 20* |
| FPI ($\mu$U/mL) | 27·1 ± 5·0 | 26·9 ± 4·8 | 26·5 ± 4·7 | 26·8 ± 4·7 | 25·7 ± 4·4 |
| PPI ($\mu$U/mL) | 67·0 ± 9·2 | 66·8 ± 9·0 | 66·2 ± 8·8 | 66·0 ± 8·7 | 65·5 ± 8·6 |
| HOMA index | 11·7 ± 4·9 | 11·2 ± 4·8 | 10·6 ± 4·6 | 9·7 ± 4·5 | 8·9 ± 4·1* |
| TC (mg/dL) | 193 ± 17 | 189 ± 17 | 188 ± 16 | 186 ± 16 | 185 ± 15 |
| LDL-C (mg/dL) | 119 ± 12 | 115 ± 12 | 110 ± 11 | 108 ± 10 | 104 ± 10 |
| HDL-C (mg/dL) | 42 ± 5 | 40 ± 4 | 41 ± 5 | 42 ± 5 | 41 ± 4 |
| Tg (mg/dL) | 161 ± 42 | 157 ± 40 | 151 ± 37 | 145 ± 33 | 140 ± 31 |
| Apo A-I (mg/dL) | 130 ± 21 | 132 ± 23 | 132 ± 22 | 130 ± 22 | 131 ± 21 |
| Apo B (mg/dL) | 117 ± 19 | 116 ± 18 | 115 ± 17 | 116 ± 19 | 114 ± 15 |
| SBP (mmHg) | 137·4 ± 4·6 | 136·8 ± 4·5 | 136·2 ± 4·3 | 135·7 ± 4·0 | 135·4 ± 3·8 |
| DBP (mmHg) | 88·1 ± 3·5 | 88·8 ± 3·7 | 88·3 ± 3·6 | 87·5 ± 3·5 | 86·8 ± 3·5 |
| HR (b/min) | 76 ± 6 | 74 ± 5 | 76 ± 6 | 76 ± 6 | 75 ± 6 |

BMI, body mass index; $HbA_{1c}$, glycated haemoglobin; FPG, fasting plasma glucose; PPG, post-prandial plasma glucose; FPI, fasting plasma insulin; PPI, post-prandial plasma insulin; HOMA index, homeostasis model assessment index; TC, total cholesterol; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; Tg, triglycerides; Apo A-I, apolipoprotein A-I; Apo B, apolipoprotein B; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.
Data are mean ± SD; *$P < 0·05$ vs. baseline; **$P < 0·01$ vs. baseline.

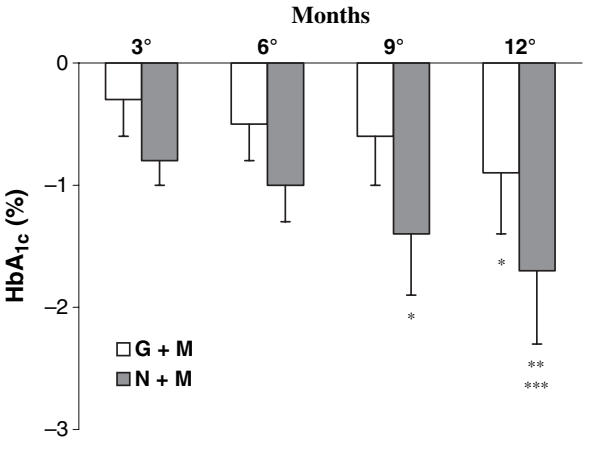


**Fig. 3.** Change in $HbA_{1c}$ from baseline to 3, 6, 9 and 12 months in patients receiving glibenclamide (G) or nateglinide (N). $HbA_{1c}$: glycated haemoglobin.*$P < 0·05$, change from baseline; **$P < 0·05$, change from baseline; ***$P < 0·05$ between treatments.

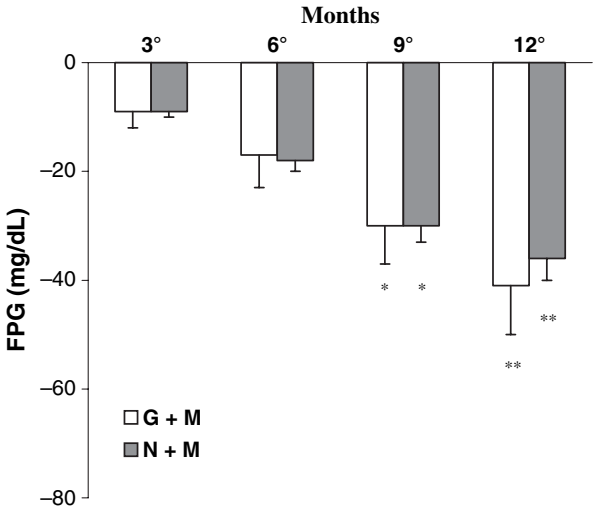


**Fig. 4.** Change in FPG from baseline to 3, 6, 9 and 12 months in patients receiving glibenclamide (G) or nateglinide (N). FPG: fasting plasma glucose. *$P < 0·05$, change from baseline; **$P < 0·05$, change from baseline.

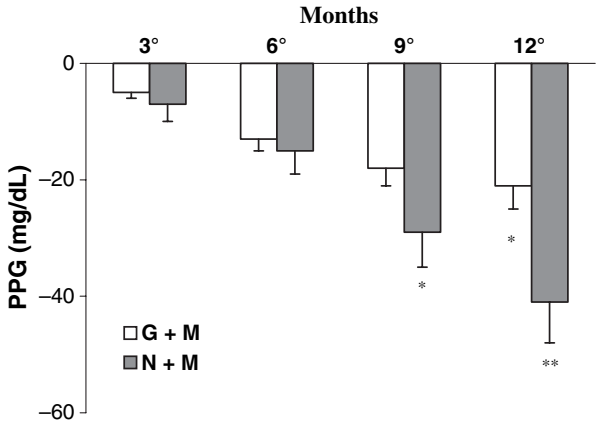


**Fig. 5.** Change in PPG from baseline to 3, 6, 9 and 12 months in patients receiving glibenclamide (G) or nateglinide (N). PPG: post-prandial plasma glucose. *$P < 0{\cdot}05$, change from baseline; **$P < 0{\cdot}05$, change from baseline.

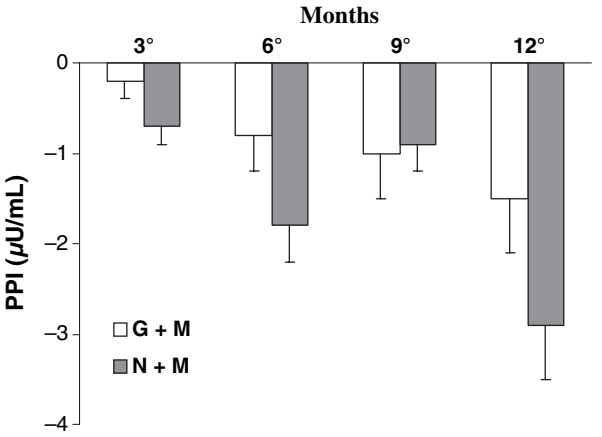


**Fig. 7.** Change in PPI from baseline to 3, 6, 9 and 12 months in patients receiving glibenclamide (G) or nateglinide (N). PPI: post-prandial plasma insulin.

nateglinide-metformin group had fewer episodes of hypoglycemia (8·8% vs. 17·7%) (35). Other trials have also shown the glibenclamide-metformin combination to be efficacious and safe for type 2 diabetes mellitus (36, 37).

In a previous cross-over study, Barnett *et al.* compared the acute metabolic effect of nateglinide and glibenclamide with a cross-over study. They demonstrated that nateglinide significantly improved early prandial measures of insulin and glucose response to a standard meal when compared to glibenclamide (38).

Other authors have compared the hypoglycemic potential of nateglinide and glibenclamide, concluding that nateglinide has a lower hypoglycemic potential, because of its better insulinotropic effect (39). Its safety has also recently been confirmed by post-marketing surveys (40).

In our study, we observed that at 9 months both drug combinations produced a significant reduction in FPG (nateglinide, 17·2%; glibenclamide, 16·9%) compared to the baseline, but only in the nateglinide group was there a significant reduction of $HbA_{1c}$ (−17·3%) and PPG (−15·2%). After one year of treatment, compared to the baseline the nateglinide group experienced a significant reduction in $HbA_{1c}$ (−21%), FPG (−20·7%), PPG (−21·5%), HOMA index (−25·4%); the glibencla-

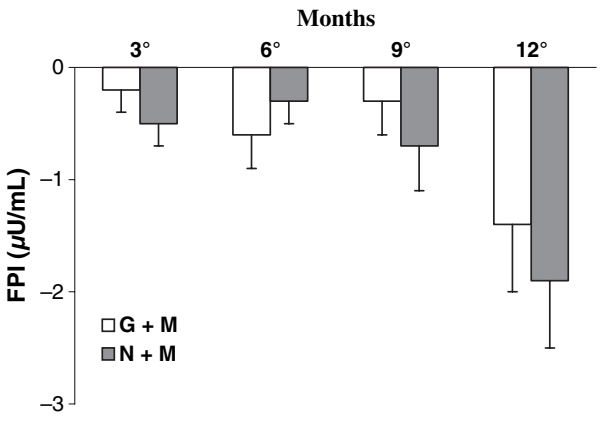


**Fig. 6.** Change in FPI from baseline to 3, 6, 9 and 12 months in patients receiving glibenclamide (G) or nateglinide (N). FPI: fasting plasma insulin.

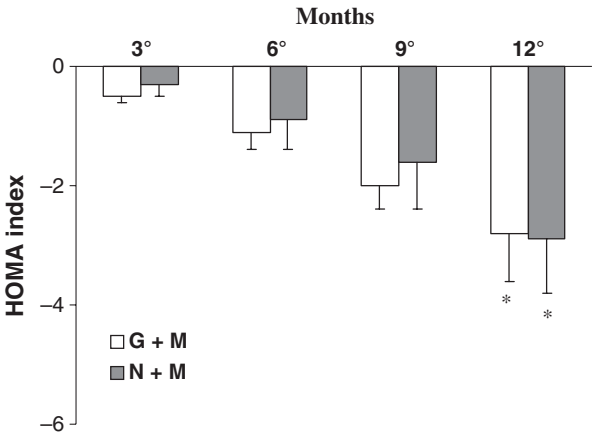


**Fig. 8.** Change in HOMA index from baseline to 3, 6, 9 and 12 months in patients receiving glibenclamide (G) or nateglinide (N). HOMA index: homeostasis model assessment index. *$P < 0{\cdot}05$, change from baseline.

mide group, on the contrary experienced only a significant reduction in $HbA_{1c}$ (−11%), FPG (−23·2%), PPG (−11·2%), and HOMA index (−15·4%). Moreover, the decrease in $HbA_{1c}$ observed in the nateglinide treated group was significantly higher than with glibenclamide.

These effects of nateglinide and glibenclamide on insulin-resistance parameters are in agreement with previous reports (41, 42).

Contrarily to what has been reported by other authors (43), we did not observe any significant BP change in patients treated with glibenclamide. Although both nateglinide and glibenclamide attenuated PPG and HOMA index, they did not have any significant effect on lipid metabolism, as has been reported by Vakkilainen *et al*. (44) in subjects with type 2 diabetes and good glycemic control.

In conclusion, nateglinide improved glycemic control better than glibenclamide in combination with metformin. Because of the relatively small sample of selected patients in this study, the results should be extrapolated cautiously, especially with respect to treatment tolerability.

## REFERENCES


1. Vague P (2003) Is metformin more than an oral hypoglycaemic agent? *Diabetes & Metabolism*, **29,** 5–7.
2. Johnson JA, Simpson SH, Majumdar SR, Toth EL (2002) Decreased mortality associated with the use of metformin compared with sulphanylurea monotherapy in type 2 diabetes. *Diabetes Care*, **25,** 2244–2248.
3. UK Prospective Diabetes Study (UKPDS) Group. (1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes. *Lancet*, **253,** 854–865.
4. The Diabetes Prevention Program Research Group (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *The New England Journal of Medicine*, **346,** 393–403.
5. American Diabetes Association (2002) American Diabetes Association: clinical practice recommendations 2002. *Diabetes Care*, **25** (Suppl. 1), S1–147.
6. Van Gaal LF, De Leeuw IH (2003) Rationale and options for combination therapy in the treatment of Type 2 diabetes. *Diabetologia*, **46** (Suppl. 1), 44–50.
7. Riddle M (2000) Combining sulfonylureas and other oral agents. *The American Journal of Medicine*, **108** (Suppl. 6), 15–22.
8. Proks P, Reimann F, Green N, Gribble F, Ashcroft F (2002) Sulfonylurea stimulation of insulin secretion. *Diabetes*, **51** (Suppl. 3), S368–376.
9. Rendell M (2004) The role of sulphonylureas in the management of type 2 diabetes mellitus. *Drugs*, **64,** 1339–1358.
10. Hu S, Wang S, Dunning BE (2001) Glucose-dependent and glucose-sensitizing insulinotropic effect of nateglinide: comparison to sulfonylureas and repaglinide. *International Journal of Experimental Diabetes Research*, **2,** 63–72.
11. Norman P, Rabasseda X (2001) Nateglinide: A structurally novel, short-acting, hypoglycemic agent. *Drugs Today*, **37,** 411–426.
12. Ball AJ, Flatt PR, McClenaghan NH (2004) Acute and long-term effects of nateglinide on insulin secretory pathways. *British Journal of Pharmacology*, **142,** 367–373.
13. McLeod JF (2004) Clinical pharmacokinetics of nateglinide: a rapidly-absorbed, short-acting insulinotropic agent. *Clinical Pharmacokinetics*, **43,** 97–120.
14. The Council for International Organisation of Medical Sciences (1982) *Proposed International Guidelines for Biomedical Research Involving Human Subjects*. Geneva: The Council for International Organisation of Medical Sciences.
15. American Diabetes Association (2001) Screening for diabetes (Position Statement). *Diabetes Care*, **24** (Supp. l), S21–S24.
16. World Health Organization–International Society of Hypertension Guidelines for the Management of Hypertension (1999) Guidelines Subcommittee. *Journal of Hypertension*, **17,** 151–183.
17. World Health Organization (1997) Obesity: Preventing and Managing the Global Epidemic. *Report of WHO Consultation on Obesity*. Geneva: WHO.
18. American Diabetes Association (2001) Nutrition recommendations and principles for people with diabetes mellitus (Position Statement). *Diabetes Care*, **24** (Supp. l), S44–S47.
19. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC (1985) Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*, **28,** 412–419.
20. Bunn HF, Gabbay HK, Gallop PM (1978) The glycosylation of haemoglobin. Relevance to diabetes mellitus. *Science*, **200,** 21–27.
21. European Diabetes Policy Group (1999) A desktop guide to type 2 diabetes mellitus. *Diabetic Medicine*, **16,** 716–730.
22. Heding LG (1972) Determination of total serum insulin (IRI) in insulin-treated diabetic patients. *Diabetologia*, **8,** 260–266.

23. Klose S, Borner K (1978) Enzymatische Bestimmung des Gesamtcholesterins mit dem Greiner Selective Analyzer (GSA II). *Journal of Clinical Chemistry and Clinical Biochemistry*, **15,** 121–130.
24. Wahlefeld AW (1974) Triglycerides determination after enzymatic hydrolysis. In: Bermeyer HU, eds. *Methods of enzymatic analysis*, 2nd English ed. New York: Academic Press, Inc, 18–31.
25. Havel RJ, Edr HA, Bragdon JH (1955) The distribution and chemical composition of ultracentrifugally separated lipoproteins in human serum. *Journal of Clinical Investigation*, **34,** 1345–1353.
26. Friedewald WT, Levy RI, Fredrickson DS (1972) Estimation of the concentration of low density lipoprotein in plasma, without use of the preparative ultracentrifuge. *Clinical Chemistry*, **18,** 499–502.
27. Leblond L, Marcel YL (1991) The amphipathic a-helical repeats of apolipoprotein A-I are responsible for binding of high density lipoproteins to HepG2 cells. *Journal of Biological Chemistry*, **266,** 6058–6067.
28. De Loof H, Rosseneu M, Yang CY, Li WH, Gotto AM Jr, Chan L (1987) Human apolipoprotein: analysis of internal repeats and homology with other apolipoproteins. *Journal of Lipid Research*, **28,** 1455–1465.
29. Winer BJ. (1971) *Statistical principles in experimental design*. 2nd ed. New York: McGraw-Hill.
30. Saenz A, Fernandez-Esteban I, Mataix A, Ausejo M, Roque M, Moher D (2005) Metformin monotherapy for type 2 diabetes mellitus. *Cochrane Database Systematic Reviews*, **3,** CD002966.
31. Marre M, Van Gaal L, Usadel KH, Ball M, Whatmough I, Guitard C (2002) Nateglinide improves glycaemic control when added to metformin monotherapy: results of a randomized trial with type 2 diabetes patients. *Diabetes, Obesity and Metabolism*, **4,** 177–186.
32. Schatz H, Schoppel K, Lehwalder D, Schandry R (2003) Efficacy, tolerability and safety of nateglinide in combination with metformin Results from a study under general practice conditions. *Experimental and Clinical Endocrinology & Diabetes*, **111,** 262–266.
33. Weaver JU, Robertson D, Atkin SL (2004) Nateglinide alone or with metformin safely improves glycaemia to target in patients up to an age of 84. *Diabetes, Obesity and Metabolism*, **6,** 344–352.
34. Horton ES, Foley JE, Shen SG, Baron MA (2004) Efficacy and tolerability of initial combination therapy with nateglinide and metformin in treatment-naive patients with type 2 diabetes. *Current Medical Research and Opinion*, **20,** 883–889.
35. Gerich J, Raskin P, Jean-Louis L, Purkayastha D, Baron MA (2005) PRESERVE-beta: two-year efficacy and safety of initial combination therapy with nateglinide or glyburide plus metformin. *Diabetes Care*, **28,** 2093–2099.
36. Garber AJ, Larsen J, Schneider SH, Piper BA, Henry D. (2002) Glyburide/Metformin Initial Therapy Study Group. Simultaneous glyburide/metformin therapy is superior to component monotherapy as an initial pharmacological treatment for type 2 diabetes. *Diabetes, Obesity and Metabolism*, **4,** 201–208.
37. Tosi F, Muggeo M, Brun E *et al.* (2003) Combination treatment with metformin and glibenclamide versus single-drug therapies in type 2 diabetes mellitus: a randomized, double-blind, comparative study. *Metabolism*, **52,** 862–867.
38. Barnett AH, Anderson DM, Shelley S, Morgan R, Owens DR (2004) A placebo-controlled crossover study comparing the effects of nateglinide and glibenclamide on postprandial hyperglycaemia and hyperinsulinaemia in patients with type 2 diabetes. *Diabetes, Obesity and Metabolism*, **6,** 104–113.
39. Fonseca VA, Kelley DE, Cefalu W *et al.* (2004) Hypoglycemic potential of nateglinide versus glyburide in patients with type 2 diabetes mellitus. *Metabolism*, **53,** 1331–1335.
40. Taki H, Maki T, Iso T, Iwamoto K, Kajiura T (2005) Postmarketing surveillance study of nateglinide in Japan. *Advances in Therapy*, **22,** 513–526.
41. Shiba T (2003) Improvement of insulin resistance by a new insulin secretagogue, nateglinide-analysis based on the homeostasis model. *Diabetes Research and Clinical Practice*, **62,** 87–94.
42. Mortensen UM, Nielsen-Kudsk JE, Sondergaard HM, Jakobsen P, Jensen BS, Schmitz O, Nielsen TT (2006) Effect of the oral hypoglycaemic sulphonylurea glibenclamide, a blocker of ATP-sensitive potassium channels, on walking distance in patients with intermittent claudication. *Diabetic Medicine*, **23,** 327–330.
43. Yosefy C, Magen E, Kiselevich A, Priluk R, London D, Volchek L, Viskoper RJ Jr (2004) Rosiglitazone improves, while glibenclamide worsens blood pressure control in treated hypertensive diabetic and dyslipidemic subjects via modulation of insulin resistance and sympathetic activity. *Journal of Cardiovascular Pharmacology*, **44,** 215–222.
44. Vakkilainen J, Mero N, Schweizer A, Foley JE, Taskinen MR (2002) Effects of nateglinide and glibenclamide on postprandial lipid and glucose metabolism in type 2 diabetes. *Diabetes Metabolism Research and Reviews*, **18,** 484–490.