PRESERVE-β

Two-year efficacy and safety of initial combination therapy with nateglinide or glyburide plus metformin

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OBJECTIVE — To compare long-term efficacy and safety of initial combination therapy with nateglinide/metformin versus glyburide/metformin.

RESEARCH DESIGN AND METHODS — We conducted a randomized, multicenter, double-masked, 2-year study of 428 drug-naïve patients with type 2 diabetes. Patients received 120 mg a.c. nateglinide or 1.25 mg q.d. glyburide plus 500 mg q.d. open-label metformin for the initial 4 weeks. During a subsequent 12-week titration period, glyburide and metformin were increased by 1.25- and 500-mg increments to maximum daily doses of 10 and 2,000 mg, respectively, if biweekly fasting plasma glucose (FPG) ≥6.7 mmol/l. Nateglinide was not titrated. Blinding was maintained by use of matching placebo for nateglinide and glyburide. An 88-week monitoring period followed, during which HbA_{1c} (A1C), FPG, and postprandial glucose excursions (PPGEs) during an oral glucose tolerance test were measured.

RESULTS — In nateglinide/metformin-treated patients, mean A1C was 8.4% at baseline and 6.9% at week 104. In glyburide/metformin-treated patients, mean A1C was 8.3% at baseline and 6.8% at week 104 ($P < 0.0001$ vs. baseline for both treatments, NS between treatments). The ΔPPGE averaged -96 ± 19 ($P < 0.0001$) and -57 ± 22 mmol · l^{-1} · min^{-1} ($P < 0.05$) in patients receiving nateglinide/metformin and glyburide/metformin, respectively, whereas ΔFPG was -1.6 ± 0.2 ($P < 0.0001$) and -2.4 ± 0.2 mmol/l ($P < 0.0001$) in patients receiving nateglinide/metformin and glyburide/metformin, respectively ($P < 0.01$ between groups). Thus, the two treatments achieved similar efficacy with differential effects on FPG versus PPGE. Hypoglycemia occurred in 8.2 and 17.7% of patients receiving nateglinide/metformin and glyburide/metformin, respectively.

CONCLUSIONS — Similar good glycemic control can be maintained for 2 years with either treatment regimen, but nateglinide/metformin may represent a safer approach to initial combination therapy.

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Abbreviations: AE, adverse event; FPG, fasting plasma glucose; ITT, intent to treat; PPGE, postprandial glucose excursion; SMBG, self-monitored blood glucose.

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

Type 2 diabetes is a highly prevalent, heterogeneous, and progressive disorder characterized by hyperglycemia caused by β-cell dysfunction and insulin resistance (1). The progressive deterioration of β-cell function over time often necessitates treatment with multiple agents to achieve and maintain good glycemic control (2). Since complications are present in upwards of 20% of patients at diagnosis (3), and there is no threshold below which added benefit is not derived from further reduction in HbA_{1c} (A1C) (4), early aggressive intervention with a combination of agents targeting both pathogenetic mechanisms is warranted, provided it can be safely done.

The Canadian Diabetes Association recently recommended combination therapy as a first-line approach to treating type 2 diabetes (5), and although current American Diabetes Association guidelines suggest a stepwise approach, they recommend that a target A1C <6.0% be considered, depending on the risk of hypoglycemia (6). Additionally, the potential benefit of agents that reduce postprandial glucose is noted (6).

Fixed combinations of metformin plus sulfonylureas are available for first-line therapy; however, long-term data are scarce. Although the reported efficacy in 16- to 52-week studies of initial combination with glyburide and metformin is promising (ΔA1C about −1.5%), a high incidence of hypoglycemia and substantial weight gain were noted, in addition to the gastrointestinal side effects commonly associated with the use of metformin (7–10). Some of the drawbacks of initiating therapy with a long-acting secretagogue and metformin might be ameliorated by an agent with a shorter and more glucose-dependent insulinotropic effect.

Nateglinide is a rapid-onset insulinotropic agent unrelated to sulfonylureas (11). Because its effect on insulin secretion subsides when glucose levels fall, nateglinide has less potential to elicit hypoglycemia than sulfonylureas (12,13). Even in patients with only modest hyperglycemia (fasting plasma glucose [FPG]

~7.6 mmol/l), nateglinide monotherapy effectively improved glycemic control with a low incidence of hypoglycemia (14). Further, nateglinide has minimal effects on body weight and does not require titration (15).

The purpose of this study was to address the hypothesis that by reducing both fasting and postprandial hyperglycemia, the combination of nateglinide and metformin will provide long-term glycemic control with less hypoglycemia and weight gain than the combination of glyburide and metformin. Accordingly, this study compared the 2-year efficacy and safety of nateglinide/metformin and glyburide/metformin in drug-naïve patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— This was a randomized, multicenter, double-masked, 104-week study comparing initial combination therapy with nateglinide/metformin (Nate/Met group) and glyburide/metformin (Glyb/Met group) in drug-naïve patients with type 2 diabetes whose A1C was between 7 and 11%. Eligibility was assessed during a 2-week screening period. Patients were then randomized to either 120 mg a.c. nateglinide or 1.25 mg glyburide before breakfast and 500 mg open-label metformin before the evening meal (dose level 1) for 4 weeks. The dose level was not adjusted during this 4-week maintenance period, unless hypoglycemia required downward titration to dose level 0 (60 mg a.c. nateglinide, all other medications as above). The blind was maintained by the use of matching placebo for nateglinide and glyburide.

The maintenance period was followed by a 12-week titration period, during which patients received either 120 mg a.c. nateglinide or glyburide (titrated in 1.25-mg increments to a maximum of 10 mg daily) and open-label metformin (titrated in 500-mg increments to a maximum of 2,000 mg daily). Titration was performed at biweekly visits if FPG ≥6.7 mmol/l, according to the schedule in Table 1.

An 88-week monitoring period followed the titration period, during which the doses of study medication remained constant, unless protocol-specified criteria for rescue therapy were met. The dose level was increased to the next highest level or to the "rescue dose level 9" if FPG

Table 1—*Details of dose regimens*

Dose level	Nateglinide (120-mg tablets or matching placebo)		Glyburide or matching placebo (number of tablets of 1.25-mg strength [a] and/or 2.5-mg strength [b])		Open-label metformin (500-mg tablets)		Total daily dose of nateglinide or glyburide and metformin (mg)		
	Number of tablets before breakfast	Number of tablets before lunch	Number of tablets before breakfast	Number of tablets before dinner	Number of tablets before breakfast	Number of tablets before dinner	Nateglinide or glyburide		Metformin
1	1	1	1a	—	—	1	360	1.25	500
2	1	1	1a	1a	—	1	360	2.5	500
3	1	1	2a	1a	1	1	360	3.75	1,000
4	1	1	2a	2a	1	1	360	5	1,000
5	1	1	1a, 1b	1b	1	2	360	6.25	1,500
6	1	1	2b	1b	1	2	360	7.5	1,500
7	1	1	2b	1a, 1b	2	2	360	8.75	2,000
8	1	1	2b	2b	2	2	360	10	2,000
0*	1 (60 mg)	1 (60 mg)	1a	—	—	1	180	1.25	500
9†	1 (180 mg)	1 (180 mg)	2 (5 mg)	1 (5 mg)	2	2	540	15	2,000

*Downward dose adjustment to nateglinide, 60 mg a.c. †Rescue dose using 180-mg tablets of nateglinide (a.c.) or 15 mg of glyburide given in divided daily doses.

≥13.3 mmol/l, A1C ≥9.0%, or the patient had symptomatic hyperglycemia.

Men and women with type 2 diabetes inadequately controlled by diet and exercise were eligible to participate if they met the following inclusion criteria: *1*) drug-naïve, *2*) aged 18–77 years, *3*) baseline A1C ≥7.0 and ≤11.0%, *4*) FPG ≤15 mmol/l, and *5*) BMI between 22 and 45 kg/m^2. Female subjects of childbearing potential were required to practice a medically approved birth control method.

Patients meeting any of the following criteria were excluded: *1*) type 1 diabetes or any secondary forms of diabetes, *2*) symptomatic hyperglycemia with >10% weight loss in the previous 8 weeks, *3*) abnormal renal function or significant diabetes complications, *4*) history of lactic acidosis or congestive heart failure requiring pharmacologic treatment, and *5*) liver disease or persistent elevations (two times upper limit of normal) of liver enzymes or other medical conditions that could interfere with interpretation of results or pose significant risk to the subject.

The protocol was approved by the independent ethics committee/institutional review board at each study site, and written informed consent was obtained from all participants. The study was performed with good clinical practice according to the Declaration of Helsinki.

Measurements and data analysis

A1C and FPG were measured at weeks −2, 0, and 4. FPG was assessed at biweekly intervals during the titration period, and A1C and FPG were measured at every study visit throughout the monitoring period (weeks 20, 28, 40, 52, 64, 76, 88, 96, and 104). Plasma lipids were measured and oral glucose tolerance tests were performed at baseline (week 0) and at weeks 28, 52, and 104 or study end point. The oral glucose tolerance tests were performed after an overnight fast, and the breakfast dose of study medication was administered 5 min before a 75-g oral glucose load. Efficacy parameters were measured at the diabetes diagnostic laboratory (Columbia, MO) (16). All other analyses were processed through a central laboratory (clinical reference laboratory, Lenexa, KS).

All patients were provided with a glucose monitor and supplies and instructed on their use. Hypoglycemia was defined as symptoms consistent with low blood glucose confirmed by a self-monitored blood glucose determination (SMBG) of <3.3 mmol/l plasma glucose equivalents. All adverse events were assessed as to severity and possible relationship to study medication. Safety laboratory assessments were made at weeks −2, 52, and 104.

The primary efficacy variable was the change from baseline (average of weeks −2 and 0) to week 104 in A1C in the intent-to-treat (ITT) population with last observation carried forward. Inferential tests for between-group and within-group differences in the primary efficacy variable were performed with Wilcoxon rank-sum and Wilcoxon signed-rank tests, respectively. In addition, exploratory analyses were performed on subgroups to examine the influence on efficacy of baseline A1C, BMI, age, sex, and race.

Secondary efficacy variables included the change from baseline to week 104 in FPG, body weight, and the incremental area under the curve ($AUC_{0-120min}$) of glucose during oral glucose tolerance tests in the ITT population, with last observation carried forward. For statistical analysis of secondary efficacy variables, as appropriate, either Wilcoxon tests or ANCOVA and paired *t* tests were used. Unless stated otherwise, data are presented as means ± SE of the ITT population.

RESULTS

Patient disposition and baseline characteristics of the ITT population

A total of 908 patients were screened and 428 patients were randomized. Table 2 reports the disposition and baseline characteristics of the 208 patients treated with nateglinide/metformin and 198 patients treated with glyburide/metformin who comprised the ITT population (randomized patients with at least one postbaseline efficacy assessment). The groups were well balanced with respect to demographic and metabolic characteristics, with baseline A1C averaging 8.35%.

At the end of study, the mean daily doses of nateglinide and metformin in the ITT population were 357 and 1,459 mg, respectively, compared with 5.1 and 1,105 mg glyburide and metformin, respectively. Of the patients randomized to the Nate/Met group, 17 (8.2%) were receiving the rescue dose, and 5 patients (2.4%) were receiving dose level 0. In the cohort randomized to the Glyb/Met group, five patients (2.5%) were on the rescue dose and eight patients (4.0%) were receiving dose level 0.

Efficacy

Figure 1*A* depicts the mean A1C throughout the 2-year treatment period in the ITT population. Both treatments maintained similar reductions in A1C. The mean change in A1C from baseline to week 104 in patients randomized to the Nate/Met group (−1.2 ± 0.1%) was similar (P = 0.1730) to that in patients randomized to the Glyb/Met group (−1.5 ± 0.1%). The nadir in mean A1C occurred at week 28 in both treatment groups and increased thereafter at a rate of ~0.025% per month. Figure 1*B* and *C* show the change from baseline in A1C at week 52 and week 104 in the completer population. The mean A1C was 6.6 and 6.4% at week 52 (Δ = −1.8 ± 0.1 and −1.9 ± 0.1%) and 7.0 and 6.7% (Δ = −1.4 ± 0.1 and −1.6 ± 0.1%) at week 104 in patients receiving nateglinide/metformin and glyburide/metformin, respectively. Although the change relative to baseline was highly significant (P < 0.0001) in both groups of patients, both after 1- and 2-year treatment, there was no significant difference between treatments in the efficacy of combination therapy.

After 2 years of treatment, a reduction in A1C of 1.0, 2.0, and 3.0% was maintained in 88 (42%), 39 (19%), and 19 (9%) patients in the ITT population receiving nateglinide/metformin compared with 84 (42%), 38 (19%), and 13 (7%) in the population receiving glyburide/metformin. After 2 years of treatment, 80 (39%) and 86 (43%) ITT patients randomized to the Nate/Met and Glyb/Met groups, respectively, had maintained the American Diabetes Association goal of A1C <7.0%. Furthermore, 29 (14%) and 25 (13%) patients randomized to the Nate/Met and Glyb/Met groups, respectively, had achieved A1C values within the normal range (≤6.0%).

Subgroup analyses were performed to explore the influence of baseline A1C, age, BMI, sex, and race on efficacy. Only baseline A1C (<9, ≥9%) had a substantial influence on the efficacy of either treatment. In the 70 patients with high baseline A1C randomized to the Nate/Met group, the ΔA1C at week 104 was −2.3 ± 0.2% compared with −1.1 ± 0.1% in the 138 patients with the lower baseline A1C. Similarly, in the 54 patients with high baseline A1C randomized to

Table 2—*Patient disposition and baseline characteristics of the ITT population*

Patient disposition		
n		908
Did not meet inclusion criteria		410 (45.2)
Met exclusion criteria		23 (2.5)
Other		47 (5.2)
	Nateglinide/metformin	Glyburide/metformin
Randomized (randomized population)	219 (100.0)	209 (100.0)
Received study drug (safety population)	219 (100.0)	209 (100.0)
ITT population*	208 (95.0)	198 (94.7)
Completed (completer population)	141 (64.4)	122 (58.4)
Discontinued	78 (35.6)	87 (41.6)
Reasons for discontinuation		
AE (any AE)†	27 (12.3)	28 (13.4)
Abdominal pain	0	4 (1.9)
Diarrhea	3 (1.4)	4 (1.9)
Hypoglycemia	1 (0.5)	4 (1.9)
Subject withdrew consent	22 (10.1)	31 (14.8)
Lost to follow-up	15 (6.9)	16 (7.7)
Protocol violation	7 (3.2)	8 (3.8)
Unsatisfactory therapeutic effect	3 (1.4)	3 (1.4)
Abnormal lab value 2 (0.9)	0	
Administrative problem 1 (0.5)	0	
Death	1 (0.5)	1 (0.5)
Baseline characteristics of ITT population		
Age (years)	52.6 ± 11.6	53.5 ± 11.6
Sex		
Men	106 (51.0)	95 (48.0)
Women	102 (49.0)	103 (52.0)
Race		
Caucasian	134 (64.4)	129 (65.2)
Black	27 (13.0)	33 (16.7)
Asian	5 (2.4)	1 (0.5)
Other	42 (20.2)	35 (17.7)
BMI (kg/m^2)	33.3 ± 6.0	33.5 ± 5.6
Duration of diabetes (years)	1.5 ± 2.9	2.0 ± 4.3
A1C (%)	8.4 ± 1.2	8.3 ± 1.1
FPG (mmol/l)	10.0 ± 2.5	9.9 ± 2.3

Data are means ± SD or n (%). *ITT population: randomized patients who had a least one postbaseline efficacy assessment. †Specific AEs leading to premature discontinuation that occurred in three or more patients are detailed.

the Glyb/Met group, the ΔA1C at week 104 was −2.4 ± 0.3% compared with −1.3 ± 0.1% in the 144 patients with the lower baseline A1C.

Fasting and postprandial glucose

At the first visit after the titration period (week 20) in the ITT population, the FPG averaged 7.2 ± 0.1 and 6.6 ± 0.1 mmol/l in patients randomized to the Nate/Met and Glyb/Met groups, respectively. The percentage of patients achieving the FPG target (<6.7 mmol/l) at this time was 41.4 vs. 60.8 in patients receiving nateglinide/metformin vs. glyburide/metformin ($P = 0.003$). The change in FPG from baseline to week 52 was −2.2 ± 0.2 mmol/l in patients randomized to the Nate/Met group ($P < 0.0001$) and −2.8 ± 0.2 mmol/l in patients randomized to the Glyb/Met group ($P < 0.0001$ vs. baseline, $P = 0.0435$ vs. Nate/Met). At week 104, the mean change in FPG was −1.6 ± 0.2 mmol/l in patients randomized to the Nate/Met group ($P < 0.0001$) and −2.4 ± 0.2 mmol/l in patients randomized to the Glyb/Met group ($P < 0.0001$ vs. baseline, $P = 0.0078$ vs. Nate/Met).

In the ITT population at week 52, the mean change in PPGE was −97 ± 21 in patients receiving nateglinide/metformin ($P < 0.0001$) and −64 ± 21 mmol · l^{-1} · min^{-1} in patients receiving glyburide/metformin ($P = 0.0022$ vs. baseline, $P = 0.0742$ vs. Nate/Met). At week 104, the mean change in PPGE was −94 ± 19 mmol · l^{-1} · min^{-1} in patients randomized to the Nate/Met group ($P < 0.0001$) and −57 ± 22 mmol · l^{-1} · min^{-1} in patients randomized to the Glyb/Met group ($P = 0.0112$ vs. baseline, $P = 0.0592$ vs. Nate/Met).

Plasma lipid parameters were not formal efficacy variables; however, there was a similar small (~5%) increase in HDL cholesterol and a similar modest (~10%) decrease in triglycerides in both treatment groups. Total and LDL cholesterol decreased by <5% in both groups.

Body weight decreased slightly in patients randomized to the Nate/Met group (Δ = −0.4 ± 0.4 kg) and increased slightly in patients randomized to the Glyb/Met group (Δ = 0.8 ± 0.5 kg). The change in body weight was only statistically significant relative to baseline for the Glyb/Met group ($P = 0.8143$ and $P = 0.0011$ for Nate/Met and Glyb/Met, respectively), but the between-group difference was statistically significant (Nate/Met − Glyb/Met = −1.2 kg, $P = 0.0115$).

Safety and tolerability

As expected for a 2-year study of patients with type 2 diabetes, one or more adverse events (AEs) was experienced by most of the subjects: 91.8% of those randomized to the Nate/Met group and 90.9% of patients randomized to the Glyb/Met group. The majority were classified as mild or moderate, and other than gastrointestinal symptoms and those often associated with falling blood glucose, the AE profile was consistent with common ailments seen in the general population, such as influenza (12.3% Nate/Met, 10.0% Glyb/Met) or headache (16.4% Nate/Met, 17.7% Glyb/Met) or those expected to occur at an increased frequency in an aging overweight population, such as arthralgia (10.5% of both treatment groups) or hypertension (8.7% Nate/Met, 14.8% Glyb/Met). Nausea, vomiting, diarrhea, or abdominal pain occurred in 6–20% of patients, with a similar frequency in both treatment groups. Hyperhidrosis, asthenia, dizziness, fatigue, or feeling jittery occurred in 9–16% of patients, again with a similar frequency in both groups. The

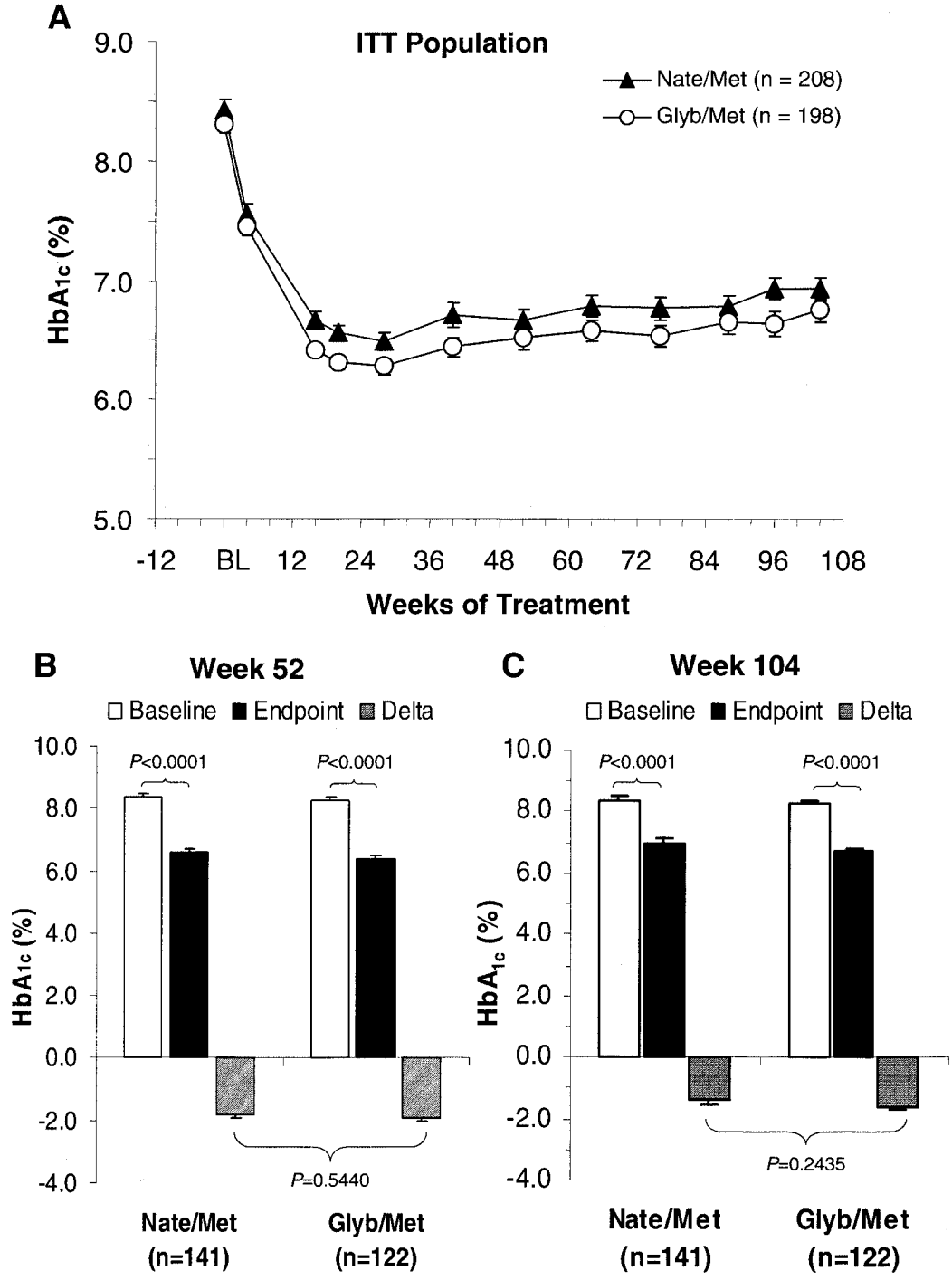

Figure 1—A: *Time course of A1C in patients randomized to the Nate/Met (▲) and Glyb/Met (○) groups. Means ± SE of available observations, ITT population.* n = *208 and 198 at baseline (BL) and decreased progressively to 136 and 120 at week 104 for the Nate/Met and Glyb/Met groups, respectively.* B: *Baseline (□), end point (■), and change from baseline to end point (▨) in A1C after 1-year treatment with nateglinide/metformin and glyburide/metformin. Means ± SE, completer population.* C: *Baseline (□), end point (■), and change from baseline to end point (▨) in A1C after 2-year treatment with nateglinide/metformin and glyburide/metformin. Means ± SE, completer population.*

only AEs that occurred frequently (in >10% of patients) in a preponderance in one treatment group (more than a twofold difference in prevalence) was hypoglycemia. One or more episodes of confirmed hypoglycemia was reported by 17.7% of patients receiving glyburide/metformin vs. 8.2% of those receiving nateglinide/metformin ($P = 0.003$).

Serious adverse events were experienced by 25 (11.4%) patients receiving nateglinide/metformin and by 27 (12.9%) patients receiving glyburide/metformin. No specific serious AEs occurred in >1.5% of patients in either treatment

group. The only serious AE suspected to be related to the study drug was severe hypoglycemia (grade 2, requiring assistance from an outside party), which occurred in two patients receiving glyburide/metformin and in no patients treated with nateglinide/metformin. One death occurred in each treatment group.

CONCLUSIONS — The main findings of this study were that *1*) initial combination therapy with an insulinotropic agent and an insulin-sensitizing agent is effective at maintaining good glycemic control for 2 years in patients with type 2 diabetes, *2*) the nateglinide/metformin combination is as effective as the glyburide/metformin combination, and *3*) the glyburide/metformin combination is associated with more than twofold increased risk of hypoglycemia relative to nateglinide/metformin.

This is the first long-term controlled clinical study of the effects of initial combination therapy, but the findings, with regard to both efficacy and safety/tolerability, are consistent with previous results from a 24-week study combining nateglinide with metformin in drug-naïve patients (17) and a 32-week study combining glyburide with metformin in drug-naïve patients with type 2 diabetes (7). In the former, the mean change in A1C from baseline (8.2%) to week 24 in 89 patients receiving nateglinide (120 mg a.c.) and metformin (500 mg t.i.d.) was −1.6%, with 70% of patients achieving a target level <7.0%, 3.4% of patients experiencing hypoglycemia confirmed by SMBG ≤2.8 mmol/l, and no significant effect on body weight relative to placebo. In the latter, the mean change in A1C from baseline (8.2%) to week 32 in 165 patients treated with glyburide/metformin tablets (2.5 mg/500 mg titrated based on mean daily glucose level) was −1.5%, with 72% of patients achieving a target level of <7.0%, 16.0% of patients experiencing hypoglycemia confirmed by SMBG <2.8 mmol/l, and a modest (1.9 kg) but significant increase of body weight.

The present study provides important information about the long-term efficacy and safety of initial combination treatment with nateglinide/metformin relative to glyburide/metformin. After 2 years of treatment, each combination maintained similar statistically and clinically significant improvements of glycemic control, with 42% of patients in the ITT population maintaining a target A1C <7.0% and, importantly, 13–14% of patients in both treatment groups achieving an A1C within the normal range. Since there is no A1C threshold below which added benefit is not derived (4), the present findings argue strongly in favor of instituting early aggressive treatment with a combination of agents that act by complementary mechanisms rather than taking a stepwise approach that allows periods of poor glycemic control (18). This concept is further reinforced by recent findings of the Epidemiology of Diabetes Interventions and Complications trial, which suggest the benefit of early aggressive treatment to reduce both microvascular complications (19) and markers of cardiovascular disease (20) are long-lasting and extend well beyond the time at which patients may have relaxed glycemic control. Thus, analogous to the recommendations of Joint National Committee 7, to institute initial drug therapy with a combination of agents in hypertensive patients clearly above blood pressure goals (21), a compelling argument can be made for initial combination therapy in patients with type 2 diabetes, provided that the approach does not impose undue risk.

The present study did not compare the safety and efficacy of initial combination therapy with stepwise treatment, and comparisons to published studies performed with a different patient population must be done with caution. However, the present findings are consistent with the concept that early aggressive intervention with initial combination treatment may be more effective than an add-on approach. In a recent 52-week study, the addition of metformin or pioglitazone to ongoing sulfonylurea treatment resulted in a mean reduction in A1C of −1.36 and −1.20%, respectively, with 40 and 39% of patients achieving a target A1C of <7.0%, respectively (22). In the present study, treatment with nateglinide/metformin and glyburide/metformin resulted in a mean reduction in A1C of −1.8% and −1.9%, respectively at week 52, with 69 and 75% of patients achieving a target A1C of <7.0%, respectively. In addition, the rate of deterioration in A1C from nadir to end point in the add-on study was ~0.05% per month, twice the rate observed over 2 years with either regimen in the present study. Most importantly, it should be recognized that many, perhaps most, physicians allow years of poor glycemic control (A1C >8.0%) before adding a second agent (18).

It is of interest to note that when combined with metformin, essentially equivalent efficacy was achieved with an agent targeting primarily postprandial glucose and an agent that targets primarily FPG, highlighting the importance of the postprandial period in overall glycemic exposure. Indeed, despite studies demonstrating that lowering PPGE is at least as effective in reducing A1C as is lowering FPG (23), and the accumulating evidence that postprandial hyperglycemia may be an independent risk factor for cardiovascular disease (24,25), the benefit of reducing PPGE is often underappreciated.

The difference in mechanism of action of nateglinide (a rapid-onset insulinotropic agent whose effect subsides as glucose levels fall) and glyburide (a long-acting agent that raises insulin levels throughout the day) (12,15) appears to underlie the substantially improved safety profile of nateglinide/metformin relative to glyburide/metformin in terms of hypoglycemia. In patients receiving glyburide/metformin, the incidence of hypoglycemia confirmed by SMBG <3.3 mmol/l was 17.7%, with two patients experiencing severe hypoglycemia. In contrast, the incidence of confirmed hypoglycemia in patients treated with nateglinide/metformin was 8.2%, with no severe hypoglycemia. The incidence of hypoglycemia in patients receiving nateglinide/metformin in the present study is somewhat higher than that reported in the earlier study discussed above. This could be due either to the longer treatment period or, more likely, the difference in SMBG level used to confirm/define hypoglycemia (3.3 mmol/l in this study vs. 2.8 mmol/l in the earlier study).

Other than hypoglycemia, the incidence of any specific AE was similar in the two treatment groups. The prevalence of gastrointestinal symptoms in either treatment group was similar to those reported for all metformin-containing products (26–30), and these AEs were generally mild to moderate. They tend to occur early in the course of treatment and subside with continued use. Serious AEs were infrequent and only the two episodes of severe hypoglycemia were suspected to be related to study medication.

In summary, initial combination therapy with an insulinotropic agent (nateglinide or glyburide) plus metformin is an

effective approach to maintaining good glycemic control for at least 2 years in drug-naïve patients with type 2 diabetes. In view of the statistically indistinguishable efficacy of the two treatment regimens but the greatly reduced risk of hypoglycemia with nateglinide/metformin versus glyburide/metformin, we conclude that combining nateglinide with metformin is a more appropriate approach to instituting early and aggressive treatment of patients with type 2 diabetes.

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