Efficacy and Safety of Combination Therapy

Repaglinide plus metformin versus nateglinide plus metformin

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OBJECTIVE — An open-label, parallel-group, randomized, multicenter trial was conducted to compare efficacy and safety of repaglinide versus nateglinide, when used in a combination regimen with metformin for treatment of type 2 diabetes.

RESEARCH DESIGN AND METHODS — Enrolled patients (n = 192) had HbA_{1c} >7% and ≤12% during previous treatment with a sulfonylurea, metformin, or low-dose Glucovance (glyburide ≤2.5 mg, metformin ≤500 mg). After a 4-week metformin run-in therapy period (doses escalated to 1,000 mg b.i.d.), patients were randomized to addition of repaglinide (n = 96) (1 mg/meal, maximum 4 mg/meal) or nateglinide (n = 96) (120 mg/meal, reduced to 60 mg if needed) to the regimen for 16 weeks. Glucose, insulin, and glucagon were assessed after a liquid test meal at baseline and week 16.

RESULTS — Final HbA_{1c} values were lower for repaglinide/metformin treatment than for nateglinide/metformin (7.1 vs. 7.5%). Repaglinide/metformin therapy showed significantly greater mean reductions of HbA_{1c} (–1.28 vs. –0.67%; $P < 0.001$) and of fasting plasma glucose (FPG) (–39 vs. –21 mg/dl; $P = 0.002$). Self-monitoring of blood glucose profiles were significantly lower for repaglinide/metformin before breakfast, before lunch, and at 2:00 A.M. Changes in the area under the curve of postprandial glucose, insulin, or glucagon peaks after a test meal were not significantly different for the two treatment groups during this study. Median final doses were 5.0 mg/day for repaglinide and 360 mg/day for nateglinide. Safety assessments were comparable for the two regimens.

CONCLUSIONS — The addition of repaglinide to metformin therapy resulted in reductions of HbA_{1c} and FPG values that were significantly greater than the reductions observed for addition of nateglinide.

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Repaglinide (Prandin, NovoNorm) and nateglinide (Starlix) are mealtime insulin secretagogues approved for treatment of type 2 diabetes. By reducing postprandial blood glucose peaks, these drugs lower 24-h blood glucose profiles and reduce HbA_{1c} levels. Both agents stimulate insulin secretion via closure of ATP-dependent potassium channels (K_{ATP} channels) of the outer membrane of β-cells (1–3). The molecular binding sites of the two drugs are not identical (4).

To date, no clinical trial has compared the efficacy and safety of repaglinide and nateglinide in a "head-to-head" design. In a combination therapy trial of up to 5 months of treatment with repaglinide plus metformin, reductions of HbA_{1c} values were much greater for the combination than the respective monotherapies; in the patients who had previously failed to show adequate glycemic control using metformin alone (HbA_{1c} > 7.0%), reductions of HbA_{1c} values were 1.1% greater than in those who continued metformin monotherapy (5). A comparable study of 24-week treatment using nateglinide plus metformin reported a reduction of HbA_{1c} levels by up to 0.6% compared with metformin monotherapy (6). Both of these studies collected data in patients who had earlier shown unsatisfactory response to metformin, and metformin treatment was continued up to randomization to the combination treatments.

Preclinical research has indicated that nateglinide may have capabilities of stimulating certain glucose-elevating hormones (glucagon, growth hormone) that are not stimulated by repaglinide (7,8). Such drug actions could potentially reduce the efficacy of nateglinide used alone or in combination treatment, but the clinical significance of such observations remains to be determined.

A clinical trial was conducted to provide a direct head-to-head assessment of the relative efficacy and safety of repaglinide versus nateglinide, under conditions of combination therapy with metformin.

RESEARCH DESIGN AND METHODS

Enrolled subjects

Patients eligible for enrollment were adults (≥18 years old) who had type 2 diabetes for at least 3 months and BMI

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Abbreviations: $AUC_{0–240\ min}$, area under the time-concentration curve from 0 to 240 min; FPG, fasting plasma glucose; K_{ATP} channel, ATP-dependent potassium channel; IMI, incremental mean imputation; OAD, oral antidiabetic; SMBG, self-monitoring of blood glucose.

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

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values of 24–42 kg/m^2. Subjects were stratified by baseline HbA_{1c} value (<9% or ≥9%). Enrolled patients had HbA_{1c} values >7% and ≤12% in previous monotherapy with a sulfonylurea (at ≥25% of the maximum dose), metformin (>1,000 mg/day), or low-dose Glucovance (glyburide ≤2.5 mg and metformin ≤500 mg).

Study protocol

This clinical trial was conducted in accordance with the provisions of the Declaration of Helsinki for participation of subjects in human research. The protocol received approval of relevant institutional review boards before initiation of any trial-related activities.

This clinical trial was a multicenter, randomized, parallel-group, open-label comparison of repaglinide plus metformin versus nateglinide plus metformin treatment for a period of 16 weeks.

Subjects previously treated with a sulfonylurea had a 4-week run-in period of metformin treatment (500 mg b.i.d. for 2 weeks, followed by metformin 1,000 mg b.i.d. for 2 weeks and thereafter doses taken with meals). Those previously treated with metformin or low-dose Glucovance received 1,000 mg metformin b.i.d. for 4 weeks. Subjects were then randomly assigned to addition of either mealtime repaglinide (n = 96) or mealtime nateglinide (n = 96) to their metformin regimen. Repaglinide or nateglinide was to be administered 1–30 min before mealtimes. Dose titration was carried out according to product labeling of each secretagogue. During a 2-week titration period, the dosage of repaglinide was increased stepwise from 1.0 to 2.0 and to 4.0 mg per meal at weekly visits based on the results of 8-point self-monitoring of blood glucose (SMBG) (maximum dose, 16 mg/day). Targets for glycemic control during the 2-week dose titration period were SMBG preprandial values of 80–140 mg/dl. Starting nateglinide dose was 120 mg per meal (the maximum daily dose), which could be reduced to 60 mg/meal in response to hypoglycemia episodes. An additional 14 weeks of maintenance therapy followed, during which secretagogue dosage adjustment was still possible as needed.

Liquid meal challenge testing (two cans of Boost = 480 kcal) was performed at baseline and the 16-week visit. Plasma glucose (hexokinase assay), insulin (immunometric assay), and glucagon (radioimmunoassay) levels were determined by sampling for up to 4 h postchallenge (assays by Icon Laboratories). At the 16-week visit, repaglinide or nateglinide was given 10 min before the liquid test meal.

Efficacy end points

The primary efficacy end points of this trial were final HbA_{1c} values (HPLC assay, Icon Laboratories; HbA_{1c} values for nondiabetic individuals, 4.7–6.4%) and changes in HbA_{1c} from baseline. Secondary efficacy end points included fasting plasma glucose (FPG), and assessment of glucose area under the time-concentration curves from 0 to 240 min ($AUC_{0-240\ min}$), insulin $AUC_{0-240\ min}$, and glucagon $AUC_{0-240\ min}$ after a liquid test meal (at baseline and at end of study).

Safety end points

Adverse events and reports of hypoglycemic episodes were recorded at all study visits. Subjects were asked to conduct SMBG from the randomization visit onward. For the purposes of this clinical trial, hypoglycemic episodes were defined as follows. Major hypoglycemic episodes were events having severe central nervous system symptoms consistent with hypoglycemia in which the subject was unable to treat him- or herself, having blood glucose readings <50 mg/dl and/or reversal of symptoms by treatment (food intake, glucagon, or intravenous glucose). Minor hypoglycemic episodes included events with symptoms that were consistent with hypoglycemia symptoms and confirmed blood glucose levels <50 mg/dl, or a blood glucose level <50 mg/dl, even if there were no symptoms of hypoglycemia.

Statistical methods

In the event of patient withdrawal or missing data after baseline, missing values of HbA_{1c} and FPG were substituted by imputed data (calculated by the incremental mean imputation [IMI] method) (9). Appropriate simulations have indicated that the IMI method is more precise than the last observation carried forward (LOCF) method for datasets resembling this clinical trial (9). The IMI results were used because this method is considered to be more precise and more conservative for comparison of treatment groups. Differences between the combination therapy groups in the change in HbA_{1c} or FPG values were compared by ANOVA (with and without adjustment for baseline imbalance).

It was projected that 64 randomized patients per group who had at least one postdosing efficacy evaluation would be required to detect 0.6% units of difference in HbA_{1c} values with 80% power. Liquid meal testing postprandial values of glucose, insulin, and glucagon were analyzed in terms of $AUC_{0-240\ min}$, where these values were adjusted for the baseline level at time 0 (meal initiation).

RESULTS — Demographic characteristics and baseline values of enrolled patients are summarized in Table 1. The treatment groups were generally comparable in such variables as duration of diabetes, previous diabetes treatment, age, and BMI. The repaglinide group had a somewhat higher number of women and persons of Hispanic ethnic background than the nateglinide treatment group. Inclusion of race or sex as variables in this model indicated that these variables were associated with no significant differences in response to treatment.

The primary efficacy parameter of this study, HbA_{1c}, showed significant divergence between the treatment groups from week 4 onward (Fig. 1*A*). Final HbA_{1c} values were lower for repaglinide/metformin combination therapy than nateglinide/metformin treatment (Table 2). Mean end-of-study changes in HbA_{1c} values from baseline were significantly greater for the repaglinide/metformin combination regimen than for nateglinide/metformin (–1.28 vs. –0.67%; P < 0.001). The percentage of patients who achieved final HbA_{1c} values ≤7% was also higher for repaglinide/metformin therapy (59 vs. 47% for nateglinide/metformin). Of the 47 repaglinide-treated patients having initial HbA_{1c} values >8%, there were 17 (36%) who achieved final HbA_{1c} values ≤7%. By contrast, only 7 of 34 (21%) comparable nateglinide-treated patients showed the same improvement in final HbA_{1c} values.

FPG values were significantly different for the two treatment groups within a week of therapy, with this treatment difference persisting to the end of the study (Fig. 1*B*). FPG values reached a steady state after ~4 weeks of therapy. Mean end-of-study reductions of FPG values from baseline were significantly greater for the repaglinide/metformin group (–39 vs. –21 mg/dl for nateglinide/metformin;

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Table 1—*Characteristics of randomized population at baseline and completion status*

Population characteristics	Repaglinide/ metformin	Nateglinide/ metformin
n	96	96
Age (years)	55.8 ± 10.7	55.0 ± 10.6
Male/female	50/46	60/36
BMI (kg/m^2)	32.9 ± 5.7	33.4 ± 5.7
Race (C/B/H/A/O)	63/15/16/1/1	68/20/4/2/2
Mean time since diabetes diagnosis (years)	6.7 ± 6.4	7.1 ± 6.2
Previous diabetes treatment		
Low dose glucovance	11	10
Metformin monotherapy	59	63
Sulfonylurea monotherapy	26	23
Completion status		
Completed week 16	89 (93)	79 (82)
Did not complete week 16	7 (7)	17 (18)
Reasons for discontinuation		
Adverse event	0	1 (1)
Lack of efficacy	0	7 (7)
Noncompliance	2 (2)	2 (2)
Other	5 (5)	7 (7)

Data are means ± SD or *n* (%). C, Caucasian; B, Black; H, Hispanic; A, Asian; O, Other.

$P = 0.002$) (Table 2). At the end of the 16-week maintenance therapy, 48% of repaglinide/metformin group patients had reductions of FPG values by >40 mg/dl, whereas only 26% of nateglinide/metformin group patients had a glycemic response of this magnitude.

The mean 8-point SMBG profiles of the two treatment groups are summarized in Fig. 2. Repaglinide/metformin therapy was associated with mean SMBG values that were consistently lower than those of the nateglinide/metformin group at all times measured. Such treatment-related differences were significant at several times during the day: before breakfast, before lunch, and at 2:00 A.M.

At the end of 16-week treatment period, liquid meal challenge testing demonstrated slightly lower postmealtime glucose levels in the repaglinide/metformin group than in the nateglinide/metformin group (Fig. 3*A*). Mean end-of-study reductions in postprandial glucose levels from baseline were not significantly different between the groups (glucose $AUC_{0-240\ min}$ in Table 2). The treatments were also comparable for changes in insulin $AUC_{0-240\ min}$ and glucagon $AUC_{0-240\ min}$ during the study (Fig. 3*B* and Table 2).

Most nateglinide-treated patients did not require dose reduction from the maximal recommended dose to prevent hypoglycemic events, whereas most repaglinide-treated patients did not reach maximal recommended doses. At the end of 16 weeks of treatment, median final doses of mealtime secretagogues were 5.0 mg/day for repaglinide and 360 mg/day for nateglinide. For the nateglinide/metformin group, 82% of patients received the daily maximal dose of nateglinide, whereas only 7% of repaglinide-treated patients received the maximal daily dosage. In both groups, the median dose of metformin was 2,000 mg/day.

The fraction of patients who discontinued study treatment was slightly higher for the nateglinide/metformin regimen than for the repaglinide/metformin regimen (18 vs. 7%, respectively) (Table 1). The single most frequently cited reason for the higher rate of discontinuation of therapy among nateglinide/metformin group patients was lack of efficacy, as assessed by the investigator (Table 1).

There were no patients in either treatment group who experienced major hypoglycemic episodes (requiring the assistance of another person). Minor hypoglycemic episodes occurred in 7% of the patients of the repaglinide/metformin group compared with 2% of the patients in the nateglinide/metformin group. Most of these minor hypoglycemic events were accompanied by symptoms (five of seven events for repaglinide/metformin and all events for nateglinide/metformin). The

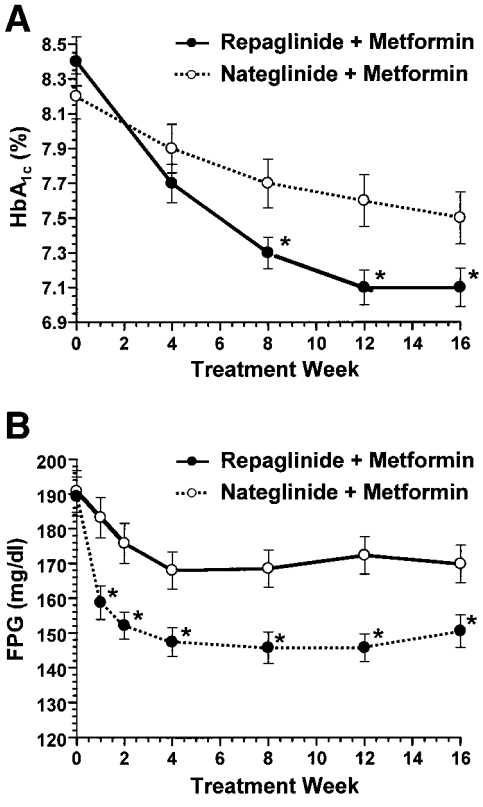

Figure 1—*A: Mean HBA_{1c} values during treatment. SE values are indicated by bars. *HbA_{1c} values in the two treatment groups were significantly different* ($P < 0.05$). B: *Mean FPG values during treatment. SE values are indicated by bars. *FPG values in the two treatment groups were significantly different* ($P < 0.05$).

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Table 2—*Changes in glycemic control during 16 weeks of treatment*

	Repaglinide/metformin	Nateglinide/metformin
HbA_{1c} (%)		
n	92	89
Baseline	8.4 ± 1.3	8.2 ± 1.3
16 weeks	7.1 ± 1.1	7.5 ± 1.4
Change in 16 weeks	−1.28 ± 0.1*	−0.67 ± 0.1
FPG (mg/dl)		
n	92	93
Baseline	189 ± 54.3	191 ± 58.5
16 weeks	150 ± 45.1	170 ± 52.0
Change in 16 weeks	−39 ± 5.7†	−21 ± 4.5
Mealtime test glucose AUC ($mg \cdot min^{-1} \cdot dl^{-1}$)		
n	86	80
Baseline	15.2×10^3 (7.7×10^3)	12.2×10^3 (7.9×10^3)
End of study	10.1×10^3 (7.7×10^3)	8.8×10^3 (6.9×10^3)
Change by end of study	-4.2×10^3 (0.7×10^3)	-4.4×10^3 (0.8×10^3)
Mealtime test insulin AUC ($\mu IU \cdot min^{-1} \cdot ml^{-1}$)		
n	79	72
Baseline	5.6×10^3 (3.7×10^3)	5.9×10^3 (5.0×10^3)
End of study	8.0×10^3 (5.8×10^3)	8.5×10^3 (5.8×10^3)
Change by end of study	2.4×10^3 (0.6×10^3)	2.6×10^3 (0.6×10^3)
Mealtime test glucagon AUC ($pg \cdot min^{-1} \cdot ml^{-1}$)		
n	75	68
Baseline	3.4×10^3 (4.1×10^3)	3.1×10^3 (3.9×10^3)
End of study	3.5×10^3 (4.7×10^3)	3.7×10^3 (5.2×10^3)
Change by end of study	0.3×10^3 (0.6×10^3)	0.5×10^3 (0.6×10^3)

Baseline, 16 week, and end of study data are means ± SD; changes from baseline (least squared mean) are means ± SE. *$P < 0.001$ vs. nateglinide/metformin; †$P = 0.002$ vs. nateglinide/metformin.

most frequent adverse event in both groups was upper respiratory tract infection (21% of repaglinide/metformin group vs. 12% of nateglinide/metformin group). Adverse events occurring in 3–8% of patients in both groups included nausea, viral infection, accidental injury, sinusitis, diarrhea, and headache. The repaglinide/metformin group had 5% incidence of arthralgia and 5% incidence of chest pain, as compared with 1% for each in the nateglinide/metformin group. In general, the treatment groups showed no noteworthy differences in safety measures during 16 weeks of therapy.

Both repaglinide and nateglinide showed small weight changes from baseline during 16 weeks of therapy (mean changes were 0.6-kg gain vs. 0.5-kg loss, respectively).

CONCLUSIONS — Repaglinide and nateglinide are insulin secretagogues that are administered at mealtimes, and both are approved in the U.S. for use in a combination regimen with metformin. No controlled clinical trial has been previously reported that would provide a direct comparison of efficacy and safety of repaglinide/metformin versus nateglinide/metformin.

The repaglinide/metformin combination therapy regimen rapidly reduced FPG values to a steady state in 4 weeks and had a stable effect on HbA_{1c} values by 12 weeks. Reductions of HbA_{1c} values differed by ~0.6% between treatment groups, a difference that is clinically and statistically significant ($P < 0.001$). From the results of this clinical trial, it would be estimated that ~22% more patients achieved FPG reductions of >40 mg/dl by using repaglinide/metformin rather than nateglinide/metformin. A lesser efficacy response for nateglinide/metformin therapy cannot be attributed to dosage of the mealtime secretagogues: median final daily dosage of repaglinide was 5.0 mg/day (only 31% of recommended maximum dose), whereas the median daily dosage of nateglinide was 360 mg/day (100% of the recommended maximum dose). Most patients did not reach the maximal recommended dose of repaglinide during dose titration, for the most part because glycemic goals were achieved. The dose adjustment regimen (based on product labeling) dictated that all nateglinide doses began at the maximal dose,

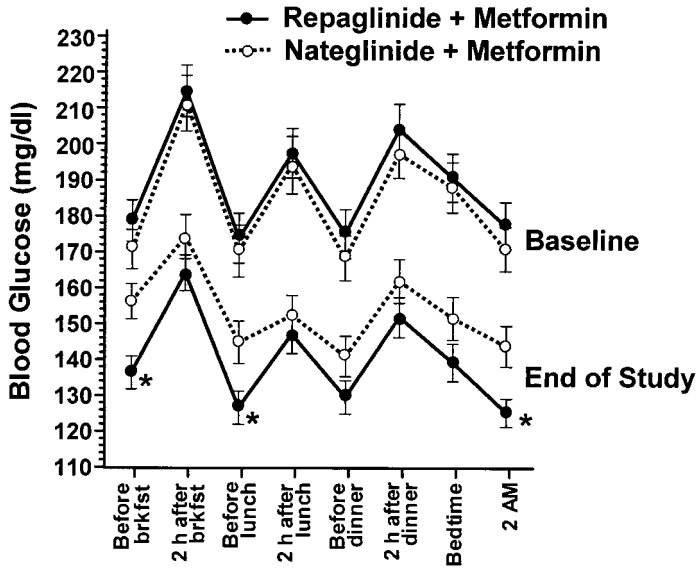

Figure 2— *Mean 8-point blood glucose profiles at baseline and end of study. SE values are indicated by bars. *Blood glucose values in the two treatment groups were significantly different ($P < 0.05$).*

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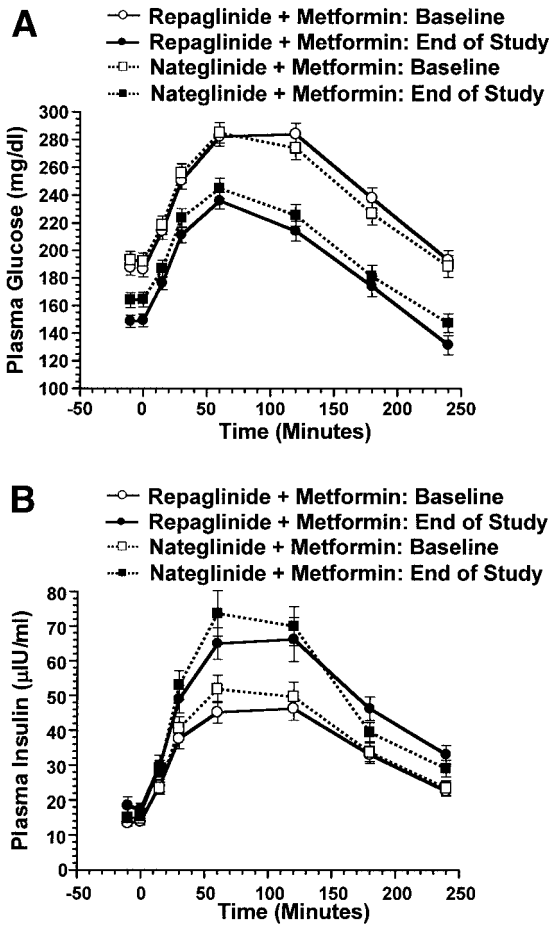

Figure 3—A: *Postprandial plasma glucose levels following a liquid meal challenge at baseline and end of study. SE values are indicated by bars.* B: *Postprandial plasma insulin levels following a liquid meal challenge at baseline and end of study. SE values are indicated by bars.*

while repaglinide was titrated upward from 1 mg/meal. It is possible that differences in efficacy of repaglinide and nateglinide would be even greater under conditions where both agents were used at the maximal dosage.

The efficacy of repaglinide/metformin observed in the current study is consistent with earlier clinical trials of this combination therapy (5). For nateglinide/metformin therapy, HbA_{1c} values were reduced by 0.67% relative to baseline in 16 weeks, whereas some studies have reported reductions of as much as 1.4% in 24 weeks (3). However, such differences may reflect study design, since the latter data were collected after a 2-month oral antidiabetic (OAD) washout period that would have resulted in a significant rise in HbA_{1c} values before initiation of combination therapy.

In assays following a single liquid test meal, the two treatments produced similar reductions of postprandial glucose peaks, stimulation of insulin, and effects on glucagon levels. This clinical trial did not detect any evidence that nateglinide has clinically significant differences in effects on the earliest stages of insulin secretion. The lesser clinical efficacy of nateglinide in the current trial (as measured by HbA_{1c} and FPG levels) may be a result of its lower affinity for the β-cell molecular target (half-maximal inhibitory concentration [IC_{50}] for K_{ATP} channels = 7.4 μmol/l for nateglinide vs. 5 nm for repaglinide) (10). It has been reported that the duration of repaglinide inhibitory actions at K_{ATP} channels is notably longer than that of nateglinide (10), indicating there may be small differences in the late postprandial actions of these two agents. Although such differences may not be apparent in a single meal challenge test, they may have cumulative impact during repeated dosing.

Safety parameters did not show any notable differences between the two treatments. There were no notable differences in weight changes, laboratory values, or hypoglycemic event frequency for repaglinide/metformin and nateglinide/metformin.

The current study provides a direct comparison that will obviate the need to draw comparisons between separate and potentially disparate clinical studies of the efficacy of the individual drugs. Such comparisons have previously implied that nateglinide has an efficacy that is somewhat less than sulfonylureas and repaglinide (11).

In conclusion, combination therapy of repaglinide plus metformin was a safe and effective therapy in the treatment of type 2 diabetes after unsatisfactory response to OAD monotherapy (sulfonylureas, metformin, low-dose Glucovance). The comparison regimen of nateglinide/metformin showed significantly less reduction of glycemic parameters, with comparable safety.

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APPENDIX

Repaglinide vs. Nateglinide Metformin Combination Study Group

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