# Combination Therapy With Nateglinide and a Thiazolidinedione Improves Glycemic Control in Type 2 Diabetes

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**OBJECTIVE** — To compare the effects of monotherapy using nateglinide and the thiazolidinedione troglitazone with initial combination of the two agents on glycated hemoglobin ($HbA_{1c}$) in patients with type 2 diabetes inadequately controlled by diet alone.

**RESEARCH DESIGN AND METHODS** — This study consisted of a 28-week, double-blind, randomized, multicenter study that included a 4-week, single-blind, placebo, run-in period and a 24-week (shortened to 16 weeks), double-blind, active treatment period.

**RESULTS** — At the 16-week end point, nateglinide 120 mg, troglitazone 600 mg, and the combination of the agents achieved statistically significant decreases in $HbA_{1c}$ in comparison with placebo and a baseline $HbA_{1c}$ of 8.1–8.4% ($P < 0.001$). The reductions in $HbA_{1c}$ were similar in the nateglinide (0.6%) and troglitazone (0.8%) monotherapy groups. The reduction in $HbA_{1c}$ (1.7%) was greatest in the combination group; 79% of patients in the combination group achieved $HbA_{1c}$ levels of <7%. The combination group had a higher number of adverse events, primarily due to an increased incidence of mild hypoglycemia in this treatment group.

**CONCLUSIONS** — Nateglinide and troglitazone are equally effective in decreasing $HbA_{1c}$ levels. However, these reductions from baseline $HbA_{1c}$ values of >8% are not adequate to achieve $HbA_{1c}$ levels of <7%. In contrast, the combination of nateglinide and of a thiazolidinedione shows an additive effect that is highly effective in reducing $HbA_{1c}$ levels to the target of <7% in 66% of patients, from a baseline $HbA_{1c}$ that is just above 8%.

*Diabetes Care* 25:1529–1533, 2002

The major defects of type 2 diabetes—insulin resistance and impaired insulin secretion—occur early in the pathogenesis of the disease (1). These abnormalities are chronic and progressive, resulting initially in impaired glucose tolerance and eventually in type 2 diabetes. As most patients with type 2 diabetes have both insulin deficiency and insulin resistance, it is of interest to target the dual defects with a combination of agents. It is well known that monotherapy with oral agents is insufficient with a high secondary failure rate as the pathophysiological defects worsen (2). Thus, it is important to consider beginning a combination regimen at the earliest possible stage of the disease, before responsiveness to monotherapy begins to decline.

Nateglinide is a derivative of the amino acid D-phenylalanine, which acts directly on the pancreatic β-cells to stimulate insulin secretion. This stimulation of insulin secretion is rapid, dependent on ambient glucose levels, and is rapidly reversible when glucose levels drop (3–6). Nateglinide taken just before meals controls mealtime hyperglycemia, resulting in improved overall glycemic control in patients with type 2 diabetes (7,8). Metformin taken two times or three times a day reduces glucose levels by improving insulin action, primarily in the liver. Previously we have shown that initial combination therapy with nateglinide and metformin resulted in reductions in $HbA_{1c}$ that were at least as great as those seen with the addition of the two agents alone (8). Troglitazone was a thiazolidinedione taken four times or two times a day, which reduces glucose levels by enhancing insulin sensitivity in liver and muscle (9). At the time of the initiation of this study, troglitazone was the only thiazolidinedione approved for use in the U.S.

This study was designed to test whether combination therapy with nateglinide and troglitazone in order to target the two major pathophysiological defects of type 2 diabetes, is more effective than monotherapy with either drug alone in patients with type 2 diabetes who have an $HbA_{1c}$ >6% on diet alone. In addition, the relative contribution of each monotherapy to the overall combination therapy effect was assessed.

## RESEARCH DESIGN AND METHODS

### Patients

Men or women diagnosed with type 2 diabetes for at least 3 months who were not controlled on diet and exercise alone were enrolled into the study. Patients were aged ≥30 years with a BMI of 20–35 $kg/m^2$. Patients were excluded if they had received oral hypoglycemic treatment within 4 weeks before enrollment, or had chronic insulin treatment within 6 months of the start of the run-in period. The use of oral corticosteroids and cholestyramine was not permitted, as they could interfere with study evaluations.

Exclusion criteria included a history of type 1 diabetes, diabetes that was the result of pancreatic injury, secondary

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Received for publication 8 March 2002 and accepted in revised form 6 June 2002.

**Abbreviations:** LFT, liver function test.

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

forms of diabetes, or a history of acute metabolic or significant diabetic complications, or cardiac or liver conditions. Patients with liver function tests (LFTs) >1.5× the upper limit of normal range on screening were also excluded. Individuals were eligible for randomization into the double-blind treatment phase if they had a mean $HbA_{1c}$ of 6.8–11%, based on values obtained during the run-in period, and a fasting plasma glucose <15 mmol/l.

### Study design

This double-blind, randomized, parallel-group study comprised a 4-week, single-blind, placebo, run-in period and a 24-week, double-blind treatment period. The double-blind period was shortened to 16 weeks when the Food and Drug Administration restricted monotherapy use of troglitazone. Some patients had already completed 24 weeks of treatment. Study blinding was maintained through the use of double-dummy blinding of the study medications. During the run-in period, patients received one nateglinide placebo tablet three times daily before meals and three troglitazone placebo tablets with breakfast only. Eligible patients who completed the run-in period were randomized into one of four treatment groups for the double-blind treatment period, *1*) nateglinide 120 mg plus troglitazone placebo ("nateglinide monotherapy"); *2*) troglitazone 600 mg plus nateglinide placebo ("troglitazone monotherapy"); *3*) nateglinide 120 mg plus troglitazone 600 mg ("combination therapy"); and *4*) nateglinide placebo plus troglitazone placebo ("placebo").

Patients were instructed to take one tablet from the nateglinide (120 mg) bottle (nateglinide or matching placebo) before each of three main meals and three 200 mg tablets from the troglitazone bottle (troglitazone or matching placebo) with breakfast throughout the double-blind treatment period. If a meal had been missed, patients were advised not to take the study medication at that mealtime and to resume the normal regimen at the next meal.

Evaluations were conducted at weeks –4, –2, and 0, then once every 4 weeks, except standard biochemistry tests, which were carried out once every 2 weeks. Safety assessments included laboratory tests (hematology, blood chemistry, urinalysis), vital signs, electrocardiogram, and physical examination. Patients fasted for at least 7 h before an assessment visit.

The primary efficacy variable measured was $HbA_{1c}$. Secondary efficacy parameters were fasting plasma glucose; fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels; body weight; and hip and waist circumference. Tolerability variables included adverse experiences, laboratory results, and measures of hypoglycemia.

The study was designed to ensure adherence to Good Clinical Practice, and was carried out in accordance with the principles of the Declaration of Helsinki as revised in 1996 (10).

### Statistics

Changes from baseline in both primary and secondary efficacy variables at the week-16 end point were analyzed using the ANCOVA model, which included effects for treatment, center, baseline efficacy measure, treatment by center interaction, and treatment by baseline efficacy measure interaction. Small centers with fewer than two patients per treatment group were pooled and used in the model. For each treatment the least squares mean (±SEM) along with its 95% CI was obtained from this ANCOVA model. The 95% CI was constructed for each pairwise treatment comparison using the least squares means.

The week-16 intent-to-treat population (ITT16) was the primary population assessed. This included all randomized patients who received trial medication and who had documented evidence of at least one post-baseline efficacy evaluation on or before week 16. The last observation carried forward approach was used to measure changes from baseline in all primary and secondary efficacy variables for those individuals who did not complete the week-16 efficacy assessment.

## RESULTS

### Patient population

A total of 1,320 patients were screened into the single-blind run-in period (Fig. 1). Of these individuals, 599 were subsequently randomized. Demographics for the randomized patients are shown in Table 1.

Of the 599 patients randomized, the majority were male (60.4%), Caucasian (79.1%), and under 65 years of age (67.1%). There were no statistically significant differences between treatment groups for any demographic variable. We were not able to identify truly drug-naïve patients as the information collected only allowed us to tell if a patient was drug naïve during the 3 months before study entry; 62.9% of patients fit that category. Among the 37.1% who received antidiabetic drug therapy during the 3 months before study entry, 75.7% were on sulfonylureas. In any case, all patients were drug naïve at least 4 months before randomization.

### $HbA_{1c}$ concentration

At baseline, mean $HbA_{1c}$ levels were similar across the four treatment groups. Throughout the study, mean $HbA_{1c}$ levels in the three active treatment groups steadily declined, while values in the placebo group essentially remained constant.

At the week-16 end point, there were statistically significant reductions from baseline in $HbA_{1c}$ in all active treatment groups. Compared with a 0.5% increase in the placebo group, $HbA_{1c}$ was significantly decreased from baseline by 0.6% in the nateglinide group, by 0.8% in the troglitazone group, and by 1.7% in the combination therapy group ($P < 0.001$ for all). There was no statistically significant difference in the magnitude of the $HbA_{1c}$ response between the nateglinide and troglitazone monotherapy groups. In addition, $HbA_{1c}$ was significantly decreased in the combination group compared with nateglinide and troglitazone monotherapy ($P < 0.0001$ for both) (Fig. 2). Similarly, at the originally planned scheduled study end point (week 24), $HbA_{1c}$ was increased by 0.3% in the placebo group, and was decreased by 0.7, 1.0, and 1.8% in the nateglinide, troglitazone, and combination groups, respectively. This 1.8% decrease in $HbA_{1c}$ in the combination group resulted in 82% of patients getting below the $HbA_{1c}$ target of 7%.

### Secondary efficacy results

At week 16, statistically significant reductions in fasting plasma glucose, compared with baseline, were observed in each of the active treatment groups ($P < 0.01$), whereas the placebo group experienced a 0.7 mmol/l increase. The greatest reduction in fasting plasma glucose observed was in the nateglinide/troglitazone combination group (–3.2 mmol/l); this was statistically significant when compared

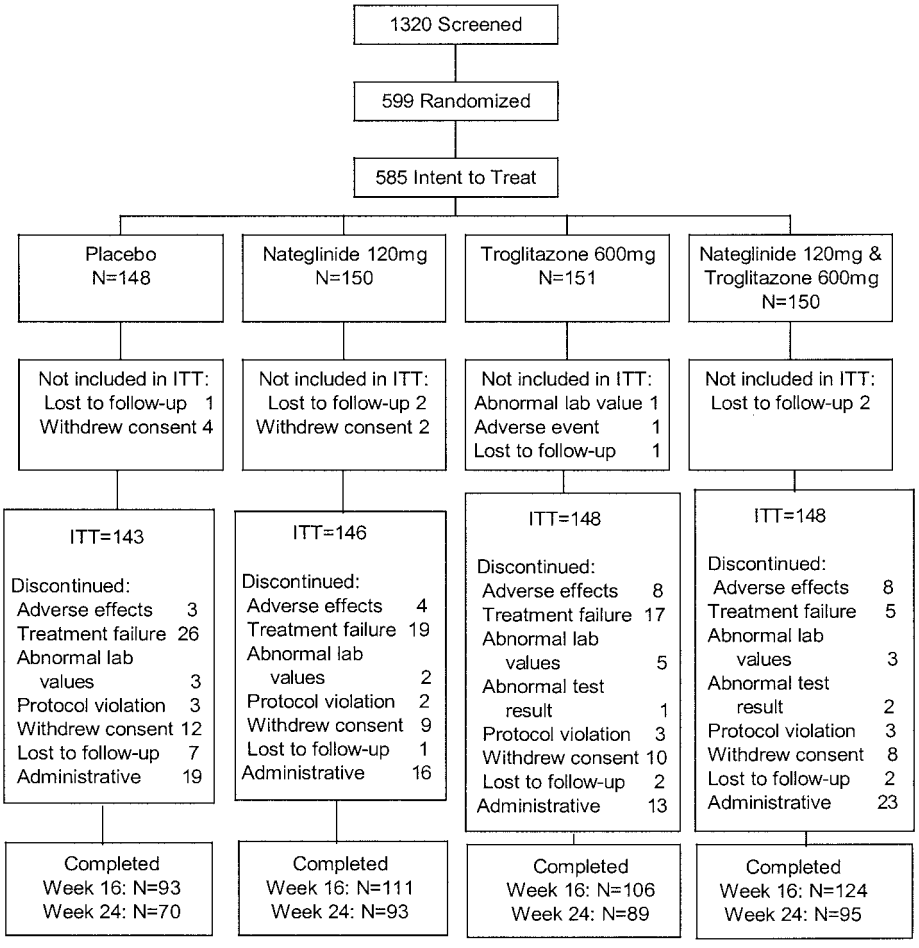


**Figure 1—***Patient disposition. ITT, intent-to-treat population.*

with placebo and nateglinide (0.5 mmol/l) or troglitazone (−2.0 mmol/l) monotherapy ($P < 0.001$).

Although statistically significant increases in mean total cholesterol, LDL cholesterol, and HDL cholesterol were observed in the nateglinide/troglitazone combination and troglitazone monotherapy groups, they were small and were not clinically meaningful (Table 2). Furthermore, changes from baseline or differences between treatment groups in waist and hip circumference had no clinical relevance. Statistically significant increases from baseline in mean body weight were observed for the active treatment groups, but not for the placebo treatment group. The mean increase was greatest in the combination therapy group (2.31 kg) but was similar for the nateglinide and troglitazone monotherapy treatment groups (0.53 and 0.50 kg, respectively) (Table 2).

### Adverse events

Of the 599 evaluated patients, 438 experienced at least one adverse event during the randomized period. The nateglinide/troglitazone combination group had the greatest number of patients with adverse events (81%) compared with the placebo, nateglinide and troglitazone groups, (67, 68, and 77%, respectively). The most frequent adverse events were events suggestive of mild hypoglycemia and upper respiratory tract infection.

Events suggestive of mild hypoglycemia occurred in 16.4% of patients, most commonly in the combination therapy group (32.7%). Confirmed hypoglycemic episodes were rare. Confirmed hypoglycemia was defined as the presence of symptoms and a plasma glucose reading <60 mg/dl. These events occurred in 6.7% of patients in the combination therapy group, and in 2.0% of the placebo group. The monotherapy groups had event rates of 0.7% for nateglinide and 1.3% for troglitazone. Only three patients discontinued due to hypoglycemia. Two of these individuals were in the combination group, while the other was on troglitazone monotherapy. None of the patients with hypoglycemic events required the assistance of another person.

Adverse events led to only 27 individuals (4.5%) withdrawing from the study, 5.3% in the combination therapy group, 2.7% in the nateglinide group, 7.9% in the troglitazone group, and 2.0% in the placebo group. The majority of the events that caused withdrawals in the troglitazone and combination groups were consistent with the known effects of troglitazone, i.e., increased hepatic enzymes and weight gain. Thirteen patients in total withdrew from the study as a result of LFTs above predefined changes from baseline (SGOT [serum glutamic oxaloacetic transaminase] and SGPT [serum glutamic pyruvic transaminase] >200%, alkaline phosphatase and total bilirubin >100%) and were outside the normal range. These included seven patients receiving troglitazone monotherapy, four who received combination therapy, and one who received placebo. During the study, one patient died from cardiac arrest subsequent to acute myocardial infarction. This individual was in the nateglinide treatment group and had a history of hypertension and hypercholesterolemia. The event was judged to be unrelated to trial medication.

**CONCLUSIONS** — The use of initial combination of agents that target the two defects of type 2 diabetes—insulin resistance and impaired insulin secretion—appears to be a logical approach to the management of this condition. This study demonstrated that the combination of nateglinide and troglitazone (agents with complementary mechanisms of action, which in this study were equally effective in decreasing $HbA_{1c}$ levels) is efficacious in patients with type 2 diabetes inadequately controlled on diet alone. Indeed, when used in combination, they significantly improved both measures of glycemic control $HbA_{1c}$ and fasting plasma glucose, after 16 weeks of treatment compared with monotherapy or placebo. These reductions are at least as great as those reported earlier using a similar protocol in which initial combination therapy of nateglinide and metformin was

**Table 1—*Baseline demographics and background characteristics of the randomized patient population***

| Variable | Placebo | Nateglinide 120 mg | Troglitazone 600 mg | Nateglinide 120 mg and Troglitazone 600 mg |
|---|---|---|---|---|
| *n* | 148 | 150 | 151 | 150 |
| Sex (M/F %) | 59/41 | 59/41 | 63/37 | 61/39 |
| Race (%) | | | | |
| Caucasian | 74.3 | 79.3 | 80.1 | 82.7 |
| Black | 10.1 | 6.0 | 7.9 | 2.7 |
| Asian/Oriental | 0.7 | 1.3 | 1.3 | 1.3 |
| Other | 14.9 | 13.3 | 10.6 | 13.3 |
| Mean age (years) | 58 | 58 | 57 | 59 |
| Range | 32–83 | 34–83 | 33–86 | 31–82 |
| Mean BMI (kg/m$^2$) | | | | |
| Range | 20–38 | 21–38 | 19–37 | 21–45 |
| Mean duration of diabetes (years) | 4.7 | 5.1 | 4.2 | 4.2 |
| Range | 0.2–37.9 | 0.1–33.4 | 0–20.4 | 0.3–26.2 |
| Mean $HbA_{1c}$ (%) | 8.2 | 8.4 | 8.1 | 8.3 |
| SD | 1.2 | 1.1 | 1.0 | 1.3 |
| Mean fasting plasma glucose (mmol/l) | 10.4 | 10.9 | 10.3 | 10.5 |
| SD | 2.5 | 2.3 | 2.3 | 2.4 |

demonstrated to be efficacious in patients with type 2 diabetes inadequately controlled on diet alone (8).

The additive glucose-lowering effect observed in this study has been demonstrated previously when thiazolidinediones have been combined with metformin, sulfonylureas, repaglinide, and insulin (11–14). In addition, monotherapies with sulfonylureas and metformin can achieve comparable results to those seen in this combination study (19). However, there are limitations to all of these therapies (19) that make the combination of nateglinide with either a thiazolidinedione or metformin (8) an attractive alternative therapy when one or more of the possible therapeutic regimens is not appropriate.

There were no clinically meaningful changes from baseline or between treatment groups in fasting serum lipids. Weight gain has been found to be a side effect of troglitazone monotherapy in previous studies (11,15–17), which may explain the 2.3-kg increase in weight gain seen in the individuals in the combination group of this study. The pattern and distribution of adverse events observed in the study were consistent with diabetes, its associated comorbidities, and the known effects of the study drugs. The majority of adverse events were mild to moderate in severity, and no hypoglycemic events were considered severe or serious. Increased hepatic enzymes can be associated with troglitazone therapy (18). In this study, however, only two patients withdrew for this reason—one in the troglitazone group and the other in the placebo group. It is conceivable that the results of this study can be extrapolated to the current thiazolidinediones pioglitazone and rosiglitazone but studies will need to confirm the findings.

This study has shown that a combination of agents can optimize antidiabetic therapy in type 2 diabetic subjects with mild hyperglycemia who need further glycemic control. The approach was to use a combination of nateglinide and troglitazone to target the major pathophysiological defects of type 2 diabetes—insulin resistance and impaired insulin secretion. Nateglinide was chosen based on its unique ability to stimulate early insulin secretion (3–6) and the glitazone (9) to potentiate insulin sensitivity. By this approach, we have shown that combination therapy with nateglinide and troglitazone, agents with complementary mechanisms of action, produce additive reductions in fasting plasma glucose and $HbA_{1c}$, resulting in many more patients reaching the therapeutic goal of a $HbA_{1c}$ $<7\%$.

Future studies are certainly warranted to explore the beneficial effects of initial combination therapy with nateglinide and with safer thiazolidinediones such as rosiglitazone and pioglitazone.

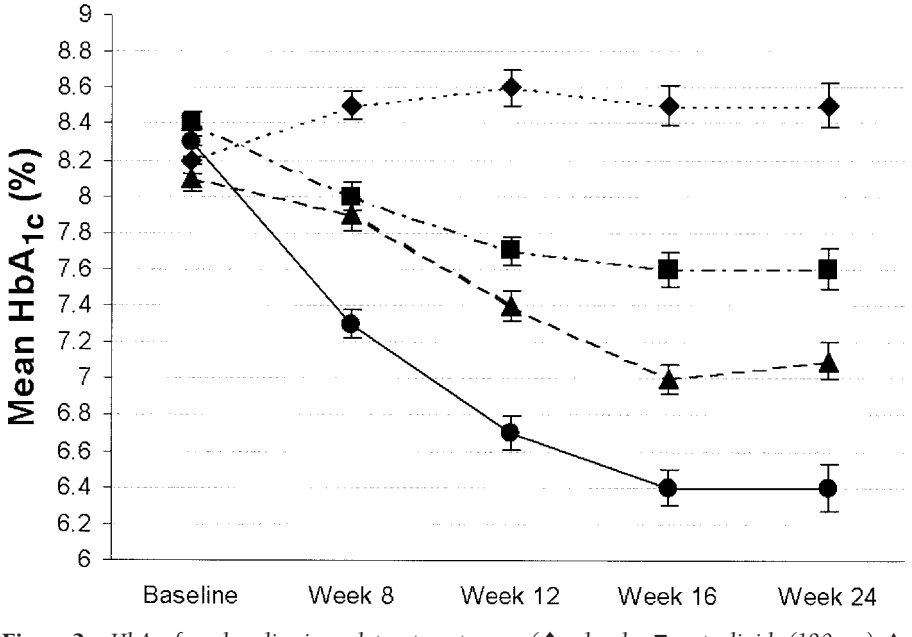


**Figure 2—*$HbA_{1c}$ from baseline in each treatment group (◆, placebo; ■, nateglinide (120 mg); ▲, troglitazone (600 mg); ●, nateglinide (120 mg) and troglitazone (600 mg).***

**Table 2—*Effects of therapeutic regimes***

| | Placebo | Nateglinide 120 mg | Troglitazone 600 mg | Nateglinide 120 mg and Troglitazone 600 mg |
|---|---|---|---|---|
| Lipid parameters* | | | | |
| Total cholesterol | + 0.05 | − 0.03 | + 0.35 | + 0.30 |
| LDL cholesterol | − 0.05 | − 0.01 | + 0.19 | + 0.17 |
| HDL cholesterol | + 0.02 | + 0.02 | + 0.12 | + 0.11 |
| Triglycerides | + 0.12 | − 0.2 | − 0.37 | − 0.29 |
| Weight* | − 0.23 | + 0.53 | + 0.50 | + 2.31 |
| Number discontinued | 0 | 0 | 1 | 0 |
| Suggestive hypoglycemia | 7 | 24 | 18 | 49 |
| Percent of total | 4.7 | 16 | 11.9 | 32.7 |
| Confirmed hypoglycemia | 3 | 1 | 2 | 10 |
| Percent of total | 2.0 | 0.7 | 1.3 | 6.7 |
| Changes in liver enzymes | 2 | 1 | 8 | 7 |
| Number discontinued | 2 | 0 | 7 | 4 |
| Hematocrit >20% decrease | 0 | 1.3 | 2.0 | 0 |

*Adjusted mean changes from baseline.

**Acknowledgments**— This study was supported by a grant from Novartis Pharmaceuticals. The authors would like to thank Susan Mallows for logistical support, Dr. Christopher Bush for statistical support, and the following investigators: Steven Aronoff, Michael Azorr, Joseph Barrera, Harold Bays, Charles Booras, Joan Brigham, Richard Castaldo, Harold Cathcart, Sid Clevinger, Cynthia Clinkingbeard, Kathleen Collins, Lydia Corn, Adnan Dahdul, Carlos de la Garza, Ron Degarno, Joseph Dehaven, George Dennish, Adrian Dobs, Jerry Drucker, Arcot Dwarakanathan, Daniel Einhorn, Jose Jeffrey Enejosa, William Ervin, James Farrell, Anthony Fiorillo, Zachary Freedman, John Frost, Gumaro Garza, Edward Gillie, G. Murthy Gollapudi, Maria Gutierez, Burritt Haag, Karen Hall, Scott Heatley, Kenneth Hershon, Gary Hunt, Robert Hutchins, David Jennings, William Keating, James Kern, Charles Kilo, David Klachko, Terry Klein, Ronica Kluge, Kevin Knopf, Edward LaCava, Francis Lee, Theodore Lefton, Andrew Lewin, Thomas Littlejohn, J. Paul Lock, Peter Lodewick, Antoinette Mangione, Luigi Meneghini, David Morin, Jeffrey Morton, William Mullican, James Mumper, Oscar Oandasan, Carl Ott, Thomas Parker, Jan Perloff, Gregory Peterson, Lawrence Phillips, Robert Plasko, Philip Raskin, Marc Rendell, John Robbins, Steven Rosansky, Herman Rose, Marshall Sack, Douglas Schumacher, Sherwyn Schwartz, Louis Shane, Rajesh Sharma, William Smith, Diane Smith, Ronald Sockolov, Scott Soerries, Roger Steinbrenner, Greg Sullivan, Rudee Suwannasri, Alain Taylon, Jalal Thwainey, Timothy Truitt, Jacob Vadakekalam, Jeffrey Wayne, Richard Weinstein, Ned Weiss, Peter Weissman, David Williams, and Barry Winston.

**References**

1. Weyer C, Bogardus C, Mott DM, Pratley RE: The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 104:787–794, 1999
2. Riddle M: Combining sulfonylureas and other oral agents. *Am J Med* 108 (Suppl. 1):15S–22S, 2000
3. Pratley RE, Foley JE, Dunning BE: Rapid acting insulinotropic agents: restoration of early insulin secretion as a physiologic approach to improve glucose control. *Curr Pharm Des* 7:1175–1397, 2001
4. Keilson L, Mather S, Walter YH, Subramanian S, McLeod JF: Synergistic effects of nateglinide and meal administration on insulin secretion in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 85:1081–1086, 2000
5. Hollander PA, Schwartz SL, Gatlin MR, Haas SJ, Zheng H, Foley JE, Dunning BE: Importance of early insulin secretion: Comparison of nateglinide and glyburide in previously diet-treated patients with type 2 diabetes. *Diabetes Care* 24: 983–988, 2001
6. Kahn SE, Montgomery B, Howell W, Ligueros-Saylan M, Hsu CH, Devineni D, McLeod JF, Horowitz A, Foley JE: Importance of early phase insulin secretion to intravenous glucose tolerance in subjects with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 86:5824–5829, 2001
7. Hanefeld M, Bouter KP, Dickinson S, Guitard C: Rapid and short-acting mealtime insulin secretion with nateglinide controls both prandial and mean glycemia. *Diabetes Care* 23:202–207, 2000
8. Horton ES, Clinkingbeard C, Gatlin M, Foley JE, Mallows S, Shen S: Nateglinide alone or in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes. *Diabetes Care* 23:1660–11665, 2000
9. Maggs DG, Buchanan TA, Burant CF, Cline G, Gumbiner B, Hsueh WA, Inzucchi S, Kelley D, Nolan J, Olefsky JM, Polonsky KS, Silver D, Valiquett TR, Shulman GI: Metabolic effects of troglitazone monotherapy in type II diabetes mellitus: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 128:176–185, 1998
10. International Committee of Medical Journal Editors: Uniform requirements for manuscripts submitted to biomedical journals. *JAMA* 277:925–926, 1997
11. Schwartz S, Raskin P, Fonseca V, Graveline JF for the Troglitazone and Exogenous Insulin Study Group: Effect of troglitazone in insulin-treated patients with type II diabetes mellitus. Troglitazone and Exogenous Insulin Study Group. *N Engl J Med* 338:861–866, 1998
12. Inzucchi SE, Maggs DG, Spollett GR, Page SL, Rife FS, Walton V, Shulman GI: Efficacy and metabolic effects of metformin and troglitazone in type II diabetes. *N Engl J Med* 338:867–872, 1998
13. Raskin P, Jovanovic L, Berger S, Schwartz S, Woo V, Ratner R: Repaglinide/troglitazone combination therapy: improved glycemic control in type 2 diabetes. *Diabetes Care* 23:979–983, 2000
14. Fonseca V, Rosenstock J, Ptwardhan R, Salzman A: Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a ramdomized controlled trial. *JAMA* 283: 1695–1702, 2000
15. Gorson DM: Significant weight gain with rezulin therapy. *Arch Intern Med* 159:99, 1999
16. Iwamoto Y, Kosaka K, Kuzuya T, Akanuma Y, Shigeta Y, Kaneko T: Effects of troglitazone: a new hypoglycemic agent in patients with NIDDM poorly controlled by diet therapy. *Diabetes Care* 19: 151–156, 1996
17. Horton ES, Whitehouse F, Ghazzi M, Venable TC, Whitcomb RW: Troglitazone in combination with sulfonylurea restores glycemic control in patients with type 2 diabetes. The Troglitazone Study Group. *Diabetes Care* 21:1462–1469, 1998
18. Füchtenbusch M, Standl E, Schatz H: Clinical efficacy of new thiazolidinediones and glinides in the treatment of type 2 diabetes mellitus. *Exp Clin Endocrinol Diabetes* 108:151–163, 2000
19. Lebovitz H: Oral therapies for diabetic hyperglycemia. *Endocrinol Metab Clin North Am* 30: 909–933, 2001