

Efficacy and Safety of Acarbose in Metformin-Treated Patients With Type 2 Diabetes

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OBJECTIVE — To demonstrate the efficacy, tolerability, and safety of acarbose compared with placebo in patients with type 2 diabetes inadequately controlled with diet and metformin (2,000 or 2,500 mg/day in divided doses).

RESEARCH DESIGN AND METHODS — This study had a multicenter randomized double-blind placebo-controlled parallel-group comparison design. The trial lasted 31 weeks and consisted of a 1-week screening period, a 6-week placebo pretreatment period, and a 24-week period of acarbose or placebo, with a forced titration from 25–50 mg t.i.d. and a titration of 50–100 mg tid that was based on glucose control. The primary efficacy variable was the mean change from baseline in HbA_{1c}. Secondary efficacy variables included mean changes from baseline in fasting and postprandial plasma glucose, serum insulin, and triglyceride levels.

RESULTS — The addition of acarbose to patients on background metformin and diet therapy showed a statistically significant reduction in mean HbA_{1c} of 0.65%. There were statistically significant reductions in fasting and postprandial plasma glucose and serum insulin levels compared with placebo. Gastrointestinal side effects were more frequently reported in the acarbose-treated patients. No significant differences in liver transaminase elevations were observed between patients treated with acarbose and those treated with placebo.

CONCLUSIONS — The results of this study demonstrate that the addition of acarbose to patients with type 2 diabetes who are inadequately controlled with metformin and diet is safe and generally well tolerated and that it significantly lowers HbA_{1c} and fasting and postprandial glucose and insulin levels.

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Abbreviations: ANCOVA, analysis of covariance; AUC, area under the curve; SGPT, serum glutamic-pyruvic transaminase.

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

The aim of all strategies for the metabolic control of diabetes is to achieve normoglycemia. In patients with type 2 diabetes with milder elevations in fasting plasma glucose, an initial attempt to control blood glucose is usually undertaken through diet, that is, through restricting the composition and caloric content of the patients' meals. This dietary intervention is the foundation of all metabolic therapy for type 2 diabetes (1,2). If blood glucose levels remain elevated despite attempts at dietary control and the introduction of exercise, treatment with oral medication is usually begun. Oral agents currently available for the treatment of type 2 diabetes are the sulfonylurea compounds, acarbose, metformin, troglitazone, and repaglinide.

A common and difficult problem in controlling diabetes is the large increase in blood glucose that occurs after meals. In many patients with type 2 diabetes, adequate control of postprandial hyperglycemia is not achieved, despite dietary modification, sulfonylureas, biguanides, and even insulin therapy.

A new therapeutic principle for the control of postprandial hyperglycemia is available with the use of α -glucosidase inhibitors, which reduce or delay carbohydrate digestion by competitive enzyme inhibition at the ciliated border of the small intestine. Because carbohydrate is digested and subsequently absorbed more slowly with these agents, the large postprandial increases in blood glucose levels observed in diabetes are prevented or reduced. Acarbose, a pseudotetrasaccharide, has been shown to reduce postprandial glycemia and glycosylated hemoglobin levels in numerous clinical trials involving patients with type 1 and type 2 diabetes (3–11). Acarbose has been approved by the Food and Drug Administration for use as monotherapy in patients with type 2 diabetes that is inadequately controlled by diet and as adjunctive therapy in combination with sulfonylureas and diet.

Metformin decreases hepatic glucose output and improves, to some degree, insulin sensitivity. It does not cause hypoglycemia, nor does it stimulate insulin

secretion by the pancreas. Metformin and acarbose, having distinct and complementary modes of action, should be additive in combination and may be effective in patients with diabetes that is not adequately controlled by either agent alone. In a 1-year Canadian study during which patients receiving background therapy with metformin were given acarbose, the placebo-subtracted treatment effect on the parameter of HbA_{1c} showed an improvement of 0.8% (7). In that study, the dosage of metformin was kept constant for each patient but was variable from patient to patient, depending on the dosage used at study entry, and acarbose was titrated to a higher dosage than is approved in the U.S. The present study used approved doses of acarbose to examine its effect in patients taking either 2,000 or 2,500 mg of metformin daily in divided doses to determine the added benefit of adding acarbose to a maximum dosage of metformin.

RESEARCH DESIGN AND METHODS

This multicenter randomized double-blind placebo-controlled parallel-group comparison study was 31 weeks in duration and consisted of a 1-week screening period, a 6-week single-blind placebo pretreatment period, and a 24-week double-blind parallel treatment period of acarbose and metformin or placebo and metformin. Men and women who were ≥ 30 years of age, who had type 2 diabetes as defined by the National Diabetes Data Group (1), who were inadequately controlled on diet plus 2,000 or 2,500 mg metformin daily were eligible for enrollment. No other pharmacological therapy for type 2 diabetes was allowed for at least 56 days before screening. Patients had to be willing to follow a diet appropriate for people with diabetes, with at least 50% of calories derived from carbohydrates (2). Patients eligible for study enrollment were required to have an HbA_{1c} between 7 and 10%, inclusive. Patients had to have a stable body weight (within 3 kg) for at least 4 weeks before screening. The patients enrolled in the study were generally healthy except for their having diabetes.

Patients were excluded from the study for any of the following reasons: presence of significant diseases or conditions likely to alter the course of the diabetes or the patient's ability to complete the study; acute or chronic acidosis, persistent ketonuria, or a history of ketoacidosis (suggesting the need for insulin therapy); documented gas-

trointestinal diseases likely to be associated with abnormal gut motility, altered absorption of nutrients, chronic diarrheal states or chronic enteropathies; chronic liver or kidney disease; inadequately controlled hypertension (sitting blood pressure $>160/90$ mmHg); a myocardial infarction within 2 months before screening; history of excessive alcohol consumption; serum creatinine levels ≥ 1.5 mg/dl for men and ≥ 1.4 mg/dl for women; aspartate aminotransferase or alanine aminotransferase elevated >1.8 times the normal level; low vitamin B-12 levels; hemoglobin <11 g/dl, or any hemoglobin variant. Patients were not allowed concomitant therapy with glucocorticoids, other investigational drugs (during the study or within 30 days before screening), medications to lower serum lipids or blood pressure (unless on a stable dose for at least 28 days before screening), or medications that might significantly alter gastrointestinal motility or absorption. Women of childbearing age who were pregnant, who were unable or unwilling to use effective birth control measures, or who were nursing a child during the study were also excluded. Patients with known hypersensitivity to metformin or acarbose were not allowed in the study. All patients had to give written informed consent before entering the study.

All patients were stabilized on diet plus metformin therapy at 2,000 or 2,500 mg daily in divided doses for a minimum of 56 days before screening. Metformin therapy was to be maintained at a constant dosage level throughout the study. During the 1-week screening phase, patients had a complete medical history, physical examination, electrocardiogram, and specific laboratory tests to determine their eligibility for the study. Patients whose treatment consisted of diet therapy received metformin and placebo during the 6-week pretreatment period. Patients were required to have had an HbA_{1c} between 7 and 10%, inclusive, as measured during the pretreatment period, and to have taken at least 80% of their prescribed metformin during the pretreatment period to be eligible for randomization in the double-blind portion of the study. At randomization (week 0), patients received either placebo or 25 mg acarbose three times daily, taken orally at the beginning of each meal. Four weeks after randomization, patients underwent forced titration to 50 mg acarbose three times daily. After 8 weeks, dosages of acarbose were titrated to 100 mg t.i.d. if the 1-h postprandial capillary blood

glucose was >160 mg/dl. Patients who were unable to tolerate the study medication dosage of 100 mg t.i.d. could have it reduced to 50 mg t.i.d. Patients who were unable to tolerate the 50 mg t.i.d. dosage were withdrawn from the study.

Test meals were to be given at randomization, and at postrandomization weeks 4, 12, and 24, or at end point, while the patient was in the fasting state. The test meal consisted of two cans (total, 16 oz) of Ensure With Fiber (total, 520 calories; 54% of calories from carbohydrates), which was to be consumed over a period of ~ 15 min. Blood samples were obtained at 0, 60, 90, and 120 min after the meal to determine plasma glucose, serum insulin, and triglyceride levels. A blood sample for determination of HbA_{1c} was also obtained during screening, randomization, and all post-baseline visits (weeks 4, 8, 12, 18, and 24). HbA_{1c} levels were assayed at the University of Missouri at Columbia, using the DIAMAT method (Bio-Rad, Richmond, CA) (normal range, 4.0–6.0%). A complete laboratory evaluation (hematology, chemistry profile, and urinalysis) was performed at screening, randomization, and all post-baseline visits.

The primary efficacy variable was the mean change from baseline in HbA_{1c} at double-blind end point, defined as the last valid observation after at least 56 days of double-blind treatment. Patients were considered invalid for the following reasons: the patient's background metformin regimen was not the same as the baseline regimen; the end-of-treatment visit was >10 days after the stop date of study medication; the patient began or modified chronic glucocorticoid treatment; the incorrect study medication was dispensed to the patient at the previous visit. Secondary efficacy variables included the mean changes from baseline in HbA_{1c} at weeks 4–24 of double-blind therapy and the mean changes from baseline at weeks 4, 12, and 24 and at end point in fasting plasma glucose and serum insulin levels and in plasma glucose, serum insulin, and triglyceride levels 60, 90, and 120 min after meals. Additional efficacy variables included changes from baseline in area under the plasma glucose, serum insulin, and serum triglyceride concentration-time curves and changes from baseline in fasting serum lipid levels at weeks 4, 12, and 24 and at end point. Total area under the curve (AUC) from 0 to 120 min for glucose, insulin, and triglycerides was computed using the trapezoidal rule.

Table 1—Baseline demographic and disease characteristics for patients valid for efficacy

Characteristics	Placebo	Acarbose
n	74	74
Age (years)	55.9	57.2
Sex (M/F) (%)	49/51	61/39
Caucasian (%)	80	86
Black (%)	9	5
Hispanic (%)	7	8
Other ethnic group (%)	4	0
Body weight (kg)	91.5	94.4
BMI (kg/m ²)	32.3	32.4
Duration of diabetes (years)	7.8	7.2
HbA _{1c} (%)	8.17	8.46

Data are means, unless otherwise indicated.

Changes from baseline in 24-h urinary excretion of glucose and albumin after 24 weeks of therapy and at end point were also evaluated. The proportion of patients who were treatment responders was also determined at weeks 8–24. A patient was considered a responder at a particular visit if HbA_{1c} was ≤7% and the baseline HbA_{1c} had been reduced by ≥0.5%, or if the reduction from baseline in HbA_{1c} was ≥1.0%. The bioavailability of metformin was determined by the fasting and 2-hour postprandial metformin levels at weeks 4, 12, and 24. Safety was evaluated by examining vital signs, laboratory values, and reports of adverse events.

All significance studies were performed as two-tailed tests at an α-level of 0.05. The efficacy variables were analyzed using analysis of covariance (ANCOVA) models with the baseline value included as the covariate and with terms for center and treatment. The logarithms of the plasma metformin levels were analyzed using an ANCOVA model with terms for baseline metformin level (on the log scale), center, and treatment. A 90% two-sided CI for the ratio of the geometric means was provided. Fisher's exact test was used for the analyses of adverse events and laboratory abnormalities, except when fewer than one-quarter of the cells had expected counts of <5, in which case the χ² test was used for computational ease. Triglycerides and normalized urinary albumin excretion were analyzed on the log scale because of departures from normality. Because of this transformation, the results are presented as geometric means (i.e., means on the antilog scale).

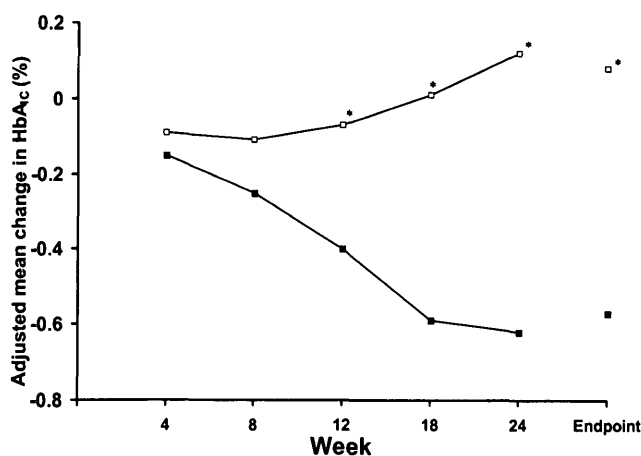


Figure 1—Adjusted mean percentage change from baseline in HbA_{1c} in patients receiving acarbose (■) or placebo (□) at 4, 8, 12, 18, and 24 weeks of treatment and at double-blind end point. Asterisks indicate significant difference from acarbose.

RESULTS— Of the 84 patients randomized to each of the treatment groups, 74 (88%) were valid for efficacy in each group; however, in the acarbose-treated group, only 73 patients could be used to evaluate efficacy in terms of HbA_{1c} because of a missing laboratory value in 1 patient. No clinically significant differences in demographic characteristics were found between the treatment groups (Table 1). The mean baseline HbA_{1c} levels differed for the placebo- and the acarbose-treated groups (8.17 and 8.46%, respectively). These data were analyzed using an ANCOVA model, with the mean HbA_{1c} values adjusted to a common baseline (8.33%). The 74 valid patients in the group treated with placebo and metformin demonstrated a mean increase in HbA_{1c} of 0.08%, whereas the 73 valid patients in the acarbose and metformin group demonstrated a mean decrease in HbA_{1c} of 0.57% (Fig. 1). Thus, the placebo-subtracted

mean change from baseline in HbA_{1c} caused by acarbose therapy was -0.65% at end point (P = 0.0001). In the intent-to-treat population, the placebo-subtracted difference was -0.71% (P = 0.0001). For patients valid for efficacy, acarbose therapy also caused a statistically significant decrease in HbA_{1c} from baseline at weeks 12, 18, and 24 compared with placebo (P ≤ 0.0036). The results were similar in the intent-to-treat analysis. For patients valid for efficacy at end point, there was a significantly greater proportion of responders in the acarbose group than in the placebo group (36 vs. 16%, respectively; P = 0.006).

The baseline values for the secondary efficacy variables are presented in Table 2. An analysis of secondary efficacy variables showed a favorable effect of acarbose on plasma glucose levels (Fig. 2). For patients valid for efficacy, the mean fasting plasma glucose at end point had increased 1.8 mg/dl in the placebo-treated patients but

Table 2—Baseline secondary efficacy variables for all valid patients

	Fasting	Postprandial (min)			AUC
		60	90	120	
Placebo					
Plasma glucose (mg/dl)	195.2	263.9	275.5	273.3	30,079.7
Serum insulin (μIU/ml)	16.33	40.55	46.30	50.76	4,463.9
Triglycerides*	175.9	198.3	212.7	223.6	24,100.8
Acarbose					
Plasma glucose (mg/dl)	203.7	283.0†	290.4	283.1	31,758.4
Serum insulin (μIU/ml)	14.89	36.17	39.34	43.50	3,935.8
Triglycerides*	184.9	198.3	214.9	230.4	24,343.0

Data are means. *Geometric least squares mean; †significantly different from placebo.

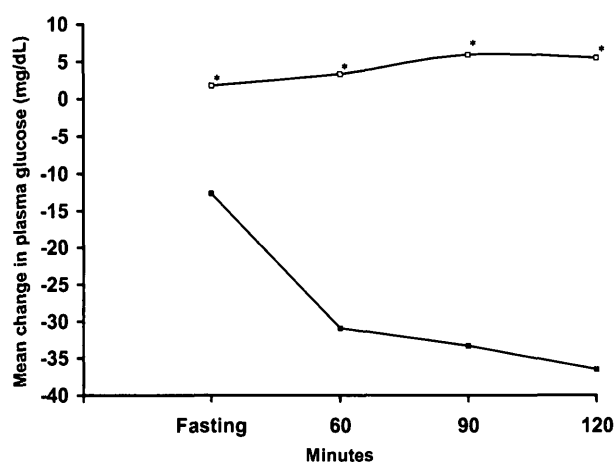


Figure 2—Mean change from baseline in fasting and postprandial plasma glucose levels in patients receiving acarbose (■) or placebo (□) at double-blind endpoint. Asterisks indicate significant difference from acarbose.

had decreased 12.7 mg/dl in the acarbose-treated patients, and this difference was statistically significant ($P = 0.0213$). After the standard meals at end point, valid patients receiving acarbose had significantly lower postprandial plasma glucose levels at 60, 90, and 120 min compared with the placebo patients ($P = 0.0001$ for each); the AUC of these glucose values was also significantly less for the acarbose-treated patients compared with the placebo patients ($P = 0.0001$) (Table 3).

For patients valid for efficacy, the mean fasting insulin level at end point had increased by 2.0 $\mu\text{IU/ml}$ in the placebo-treated patients, whereas it had decreased by 1.9 $\mu\text{IU/ml}$ in the acarbose-treated patients, and this difference was statistically significant ($P = 0.0291$). After the standard meals at end point, valid patients receiving acarbose had significantly lower serum insulin levels at 90 and 120 min ($P = 0.0167$ and $P = 0.0043$, respectively); at 60 min, the difference was marginally nonsignificant ($P = 0.0657$). At end point, the change compared with baseline in the AUC of these serum insulin values was 162 $\mu\text{IU} \cdot \text{min} \cdot \text{ml}^{-1}$ in the placebo group, but $-601 \mu\text{IU} \cdot \text{min} \cdot \text{ml}^{-1}$ in the acarbose group, and this difference was statistically significant ($P = 0.0144$).

For patients valid for efficacy, there was a trend at end point toward a significant lowering of the fasting serum triglyceride levels in the acarbose-treated patients. After the standard meals at end point, the valid patients receiving acarbose versus those receiving placebo had a slight but statistically significant blunting (compared with

the baseline meal test) of the serum triglyceride level at 120 min ($P = 0.0177$), but the differences at 60 and 90 min were not significant; the AUC of these serum triglyceride values showed no significant effect of acarbose compared with placebo.

In patients valid for efficacy, acarbose therapy had no significant effect at end point on fasting serum levels of total, HDL, or LDL cholesterol or on urinary albumin excretion. In patients valid for efficacy, acarbose therapy significantly lowered the 24-h urinary excretion of glucose by 7.57 g/day, whereas urinary glucose excretion increased by 2.80 g/day in the placebo group ($P = 0.02$).

The concomitant use of acarbose with metformin appeared to have little effect on plasma levels of metformin as shown in Table 4. Plasma levels of metformin were within an acceptable range, and any reduction in the bioavailability of metformin was

clearly clinically insignificant because the HbA_{1c} results of the acarbose-treated group were lower than those of the placebo-treated group.

Adverse events that occurred significantly more often in the acarbose-treated patients compared with the placebo-treated patients were gastrointestinal complaints. A digestive complaint of any type was reported by 24 (29%) of the patients taking placebo and by 47 (56%) of the patients taking acarbose, and this difference was significant. Flatulence was reported by 4 (5%) of the patients taking placebo and by 26 (31%) of the patients taking acarbose; this difference was significant (Table 5). There was a nonsignificant trend toward more complaints of diarrhea in the acarbose-treated patients than in the placebo-treated patients (17 vs. 11%). There was also a nonsignificant trend toward more complaints of abdominal pain in the acarbose-treated patients than in the placebo-treated patients (8 vs. 6%).

Of the patients taking placebo, 3 (4%) discontinued from the study prematurely because of adverse events, as did 10 (12%) of the patients taking acarbose. The most common adverse events leading to discontinuation in the acarbose group were diarrhea (four patients) and, to a lesser extent, flatulence (two patients) and abdominal pain (two patients). Hypoglycemic events were rare, occurring in only one acarbose-treated patient and two placebo-treated patients.

No acarbose- or placebo-treated patients developed serum glutamic-oxaloacetic transaminase (SGOT) levels >1.8 times the upper limit of normal. One acarbose-treated patient (1%) developed a level of serum glutamic-pyruvic transaminase (SGPT) >1.8 times the upper limit of normal (in fact, sur-

Table 3—Changes from baseline in secondary efficacy variables for all valid patients

	Fasting	Postprandial (min)			AUC
		60	90	120	
Placebo					
Plasma glucose (mg/dl)	1.83	1.83	3.33	5.90	5.52
Serum insulin ($\mu\text{IU/ml}$)	482.0	2.03	0.84	2.80	-0.28
Triglycerides*	1.02	0.97	1.00	1.00	1.00
Acarbose					
Plasma glucose (mg/dl)	-12.70†	-30.99†	-33.30†	-36.50†	-3,259.9†
Serum insulin ($\mu\text{IU/ml}$)	-1.93†	-5.59	-5.78†	-10.35†	-601.6†
Triglycerides*	0.94	0.97	0.94	0.90†	0.95

Data are means. *Geometric adjusted mean of the ratio of the end-point value to the baseline value; †significantly different from placebo.

Table 4—Geometric adjusted mean plasma metformin levels (ng/ml) at weeks 4, 12, and 24

Evaluation	Placebo	Acarbose	Ratio	90% CI
Week 4				
Predose	461.3	477.6	1.04	0.84–1.28
2-h postdose	1,668.9	1,655.1	0.99	0.92–1.07
Week 12				
Predose	4,74.5	458.5	0.97	0.76–1.22
2-h postdose	1,737.3	1,638.7	0.94	0.87–1.02
Week 24				
Predose	458.8	453.9	0.99	0.81–1.20
2-h postdose	1,643.0	1,467.6	0.89	0.81–0.98

passing three times the upper limit of normal and then returning to normal during continuation of treatment), but this patient had a positive serology test for hepatitis A. Three placebo-treated patients (4%) developed SGPT levels >1.8 times the upper limit of normal. The difference between the groups was not statistically significant ($P = 0.364$). No placebo-treated patient developed a serum level of SGPT >3 times the upper limit of normal.

There were no significant differences between treatment groups with respect to the mean changes in fasting weight, vital signs, or diet variables. At end point, the placebo group had a mean reduction in weight of 0.88 kg compared with a mean reduction of 0.98 kg in the acarbose group ($P = 0.8108$).

CONCLUSIONS— This study documents that the addition of acarbose therapy in patients with type 2 diabetes who are treated with metformin and diet is safe and generally well tolerated and that it effectively lowers HbA_{1c}. Acarbose was significantly superior ($P = 0.0001$) to placebo as judged according to the primary criterion of change in HbA_{1c} from baseline to double-blind end point. A positive clinical response, which was defined as an HbA_{1c} value $\leq 7\%$ associated with a reduction from baseline in HbA_{1c} of at least 0.5%, or a reduction from baseline in HbA_{1c} of at least 1.0%, was seen in 36% of patients treated with acarbose, compared with a 16% response rate in the placebo-treated patients.

The results of the present study are consistent with a prior study in which acarbose was combined with metformin therapy in patients with type 2 diabetes. That eight-center double-blind randomized placebo-controlled Canadian study consisted of a 6-week pretreatment period, followed by 52 weeks of double-blind treatment with

acarbose or placebo added to baseline therapy for diabetes (diet only, metformin, sulfonylurea, or insulin) (7). A total of 354 patients were entered into the trial. Of relevance to the present discussion are the 83 patients in the diet and metformin stratum who were randomized to acarbose (41 patients) or placebo (42 patients). In this stratum, 35 acarbose-treated patients and 39 placebo-treated patients were valid for the analysis of efficacy. For the patients valid for efficacy, the diet- and metformin-treated patients who received acarbose had a mean decrease in HbA_{1c} at end point of 0.5%, and the diet- and metformin-treated patients who received placebo had a mean increase in HbA_{1c} at end point of 0.3%. Thus, the placebo-subtracted difference in HbA_{1c} was -0.8% , which was statistically significant ($P = 0.0106$). Patients who received acarbose in addition to metformin therapy also had significantly reduced postprandial glucose levels, and this effect was maintained for the duration of the 12-month treatment period. It should be noted that a higher dose of acarbose was used in that study than in the current study.

In the present study, postprandial plasma glucose levels were markedly improved by acarbose, and fasting plasma glucose values were also lowered, compared with placebo. The clinical relevance of the effect of acarbose on postprandial hyperglycemia is highlighted by the significant decrease in HbA_{1c} levels observed in patients treated with acarbose and metformin and by the slight increase in HbA_{1c} observed in the placebo and metformin treatment group. Since postprandial glucose excursions were less extreme in the acarbose-treated patients after test meals, the release of insulin levels from β -cells during these postprandial periods should also have been less in these patients. In fact, acarbose did have a favorable effect on post-

Table 5—Incidence of selected adverse events

Adverse event	Placebo	Acarbose
Flatulence	4/84 (5)	26/84 (31)*
Diarrhea	9/84 (11)	14/83 (17)
Abdominal pain	5/84 (6)	7/84 (8)

Data are proportions (%). *Significantly different from placebo.

prandial insulin levels. Acarbose also significantly lowered the mean fasting serum insulin levels compared with placebo. The lower fasting serum insulin levels achieved after treatment with acarbose therapy may reflect the overall improvement in glucose control of the patients. Of note, the weight remained stable in the metformin-acarbose group despite the improved glycemic control that often causes weight gain with other combination therapies.

Although acarbose-treated patients reported more adverse events than did placebo patients, most patients completed the study. Gastrointestinal complaints, particularly flatulence, were the major obstacles to therapy with acarbose. Hypoglycemic events were not significantly increased when acarbose was added to metformin therapy. Acarbose did not cause elevation of serum levels of hepatic transaminases when compared with placebo.

This study confirms the beneficial role of acarbose in improving glycemic control in patients with type 2 diabetes that is inadequately controlled with diet and metformin at daily doses of 2,000 or 2,500 mg. The complementary modes of action of acarbose and metformin allow a combination therapy that improves glycemic control without weight gain after secondary failure with metformin occurs. The secondary failure rate of metformin is estimated to be 5–10% each year (12). In addition, the 6-year results of the U.K. Prospective Diabetes Study have shown that the majority of newly diagnosed obese patients treated with metformin as monotherapy required additional antidiabetic therapy at 6 years (13). The present results demonstrate that acarbose is a safe and effective adjunct to metformin and diet therapy.

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