Acarbose Improves Glycemic Control in Overweight Type 2 Diabetic Patients Insufficiently Treated With Metformin

PATRICK PHILLIPS, MA, FRACP[1]
JEFF KARRASCH, FRACP[2]
RUSSELL SCOTT, MD[3]
DENNIS WILSON, MD, FRACP[4]
ROBERT MOSES, MD[5]

OBJECTIVE — To investigate the efficacy and safety of acarbose as add-on therapy in overweight type 2 patients with diabetes inadequately controlled by metformin.

RESEARCH DESIGN AND METHODS — This study adopted a multicenter, randomized, double-blind, placebo-controlled, parallel group design. After a 4-week placebo run-in period, subjects were randomized to either acarbose (titrated up to 100 mg b.i.d.) or placebo. The primary efficacy variable was the change in HbA_{1c} from baseline to the end of the 24-week treatment period. Change in fasting blood glucose was assessed as a secondary efficacy parameter.

RESULTS — The intention-to-treat analysis from baseline to week 24 (81 patients for HbA_{1c} and 82 for fasting blood glucose) showed statistically significant differences between acarbose and placebo treatment in HbA_{1c} (1.02%; 95% CI 0.543–1.497; $P = 0.0001$) and fasting blood glucose (1.132 mmol/l; 95% CI 0.056–2.208; $P = 0.0395$) (adjusted least square means). In all, 18 patients (47%) in the acarbose group were classified as responders with a ≥5% reduction in HbA_{1c} (relative to baseline) at the end point compared to 6 (14%) in the placebo group ($P = 0.001$). The safety profiles were similar for both treatment groups except for the higher incidence of gastrointestinal side effects during acarbose therapy.

CONCLUSIONS — The addition of acarbose to metformin monotherapy provides an efficacious and safe alternative for glycemic improvement in overweight type 2 patients inadequately controlled by metformin alone.

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Management of type 2 diabetes strives to achieve near-normal glycemic control to reduce the risk of diabetic complications. When dietary measures fail, oral antidiabetic agents are the first treatment choice. In the treatment of obese type 2 patients, metformin is often used as first-line therapy because it lowers blood glucose concentrations without causing hypoglycemia or weight gain (1). Its glucose-lowering effect results from reduced hepatic glucose production and increased glucose utilization.

Monotherapy using any oral antidiabetic agent is unfortunately limited as a long-term strategy. The U.K. Prospective Diabetes Study found that ~50% of patients needed more than one pharmacological agent after 3 years of treatment because monotherapy did not achieve HbA_{1c} target values (2). Several studies have investigated metformin as adjunctive therapy to sulfonylureas (3–5); one study compared metformin and sulfonylurea (glyburide) efficacy as monotherapy and in various combinations (6), and several recent studies have described the effect of add-on therapy to metformin using the insulin secretagogue repaglinide (7), the insulin sensitizers rosiglitazone (8) and pioglitazone hydrochloride (9), and the sulfonylurea glimepiride (10).

Chiasson et al. (11) were the first to examine the use of acarbose as adjunctive therapy to metformin. The α-glucosidase inhibitor acarbose delays glucose absorption and thus attenuates postprandial rises in blood glucose and insulin. It has proven efficacious as first-line therapy (12–14) and in combination with sulfonylureas or insulin (15–17). In combination with metformin, acarbose has been shown to improve long-term glycemic control (HbA_{1c} measurement) by 0.8% (12), 0.65% (18), and 0.9% (19). Acarbose and metformin are both associated with beneficial effects on hyperglycemia, hyperinsulinemia, body weight, and, in some studies, triglyceride levels (20). Because these factors are part of a cluster of risk factors for cardiovascular disease (21), combining the two drugs may be useful. In long-term clinical studies, acarbose has shown a favorable safety profile (22,23).

This study was conducted as a further investigation into the efficacy and safety of concurrent use of acarbose and metformin in type 2 diabetes overweight patients.

RESEARCH DESIGN AND METHODS

— The study was designed as a multicenter, randomized, double-blind, placebo-controlled parallel group comparison between the two treatment arms, acarbose and placebo. Patients whose type 2 diabetes was insufficiently controlled by metformin and who were on a stable twice-daily dose for at least 3 months before the start of the study were recruited by five centers, four in Australia and one in New Zealand. The

From the [1]Department of Endocrinology, The Queen Elizabeth Hospital, Woodville, Australia; the [2]Peninsula Specialist Centre, Kippa Ring, Australia; the [3]Lipid and Diabetes Research Group, Christchurch Hospital, Christchurch, New Zealand; the [4]Department of Endocrinology, The Canberra Hospital, Garran, Australia; and the [5]Diabetes Centre Wollongong, Wollongong, Australia.

Address correspondence and reprint requests to Dr. Patrick Phillips, Department of Endocrinology, The Queen Elizabeth Hospital, Woodville SA 5011, Australia. E-mail: patrick.phillips@nwahs.sa.gov.au.

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Abbreviations: FBG, fasting blood glucose; ITT, intention to treat; PP, per protocol.

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

study period consisted of a 4-week placebo run-in phase and a 24-week treatment phase. Patients aged ≥40 years with a BMI of 25–35 kg/m^2 were included in the study if they had an HbA_{1c} level of 7–10% at screening (week −4) and 6.8–10.2% at baseline (week 0). Further inclusion criteria were a history of type 2 diabetes for 6 months or longer and an 80–120% compliance record during the run-in period. Patients were excluded from the study if any of the following conditions applied at the screening or baseline visits: having taken an antidiabetic medication other than metformin during the last 3 months; presence of significant diseases or conditions, including emotional disorders and substance abuse, likely to alter the course of diabetes or the patient's ability to complete the study; presence of gastrointestinal diseases likely to be associated with abnormal gut mobility or altered absorption of nutrients; medication causing a significant change in gastrointestinal mobility and/or absorption, such as cholestyramine; administration of oral neomycin; treatment with preparations containing digestive enzymes, such as amylase or pancreatin; conditions that might be aggravated by abnormally large amounts of gas in the intestine, including gastrocardiac syndrome, significant hernias, intestinal stenoses, and active ulcers; chronic pancreatitis; or concomitant medication affecting glucose homeostasis, such as glucocorticoids within 8 weeks before screening (β-blockers, ACE-inhibitors, or thiazide diuretics could be continued if unchanged during the study and stable for 8 weeks before the study). Patients were excluded if they had a currently uncontrolled thyroid function, transaminases elevated three times the upper limit of normal, or serum creatinine ≥2 mg/dl or if they had any infections likely to affect glucose metabolism. Neither pregnant or lactating women nor patients receiving any other investigational drug or participating in any other clinical study within 8 weeks before screening were allowed to participate. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. The protocol and subsequent amendments were approved by the ethics committee of each participating center. Written informed consent was obtained from all participating patients.

A total of 89 patients were enrolled into the study (visit 1, week −4) and continued their usual metformin dose throughout the study period. During the first visit, a physical examination and assessment of demographic data, medical history and concomitant medication, body weight, height, vital signs, and diet were carried out. Samples for HbA_{1c}, fasting blood glucose (FBG), thyroid stimulating hormone/free T4, and routine laboratory analysis were taken. Patients were then provided with placebo tablets identical to the active tablets to be taken twice daily for the next 4 weeks in a single-blind placebo run-in phase. At visit 2 (week 0) patients fulfilling inclusion criteria were randomly assigned to either 50 mg acarbose b.i.d. or matching placebo for 2 weeks followed by a 22-week period on 100 mg acarbose b.i.d. or matching placebo. If this regimen was not well tolerated, the dosage could be reduced to 50 mg b.i.d. Patients were instructed to take one tablet with the first mouthful of their morning and evening meals. Drug compliance was determined at each visit by tablet count. Patients were assessed at 0, 2, 4, 12, and 24 weeks for weight and vital signs, diet, concomitant medication, routine laboratory parameters, and adverse events. Efficacy variables were measured at weeks 0, 12, and 24, with an additional recording taken for FBG at week 4. A second physical examination was conducted at the end of the study (week 24).

Both intention-to-treat (ITT) and per-protocol (PP) analyses were performed as efficacy analyses. Patients included in the ITT analysis had received at least one dose of study medication, had efficacy data at baseline, and had at least one postbaseline measurement of the respective variable. To be included in the PP analysis, patients also had to meet all protocol criteria and comply with the study medication regimen. Because the first postbaseline measurement of FBG was carried out in week 4 and the first measurement of HbA_{1c}, in week 12, some patients were included in the efficacy analysis for FBG but not HbA_{1c}. The ITT analysis was regarded as the primary efficacy analysis. The primary efficacy parameter was the change in HbA_{1c} from baseline to the end of the study at week 24. HbA_{1c} values were determined using a DCA 2000 clinical analyzer (Bayer Diagnostics, Tarrytown, NY). The change in fasting blood glucose levels from baseline to end point was assessed as a secondary variable. The proportion of patients who were treatment responders was also determined. The definition considered a patient a responder if HbA_{1c} levels showed a ≥5% relative reduction from baseline at the end of the study.

All randomized patients were included in the safety analysis. Safety was evaluated by examining vital signs, routine laboratory parameters, and reports of adverse events.

Data analysis was performed using the SAS program system (Version 6.12; SAS Institute, Cary, NC). End point determination of the efficacy variables used the "last observation carried forward" approach for missing data. ANCOVA with treatment and center as factors and baseline as covariate was used, and treatment by center interaction was included in the model for HbA_{1c} data. Model-adequate least square means and 95% CIs for mean differences between the two treatment groups were calculated. A repeated-measure ANOVA was used to assess efficacy parameters over the course of the study. The difference between treatment arms in the proportion of responders was determined using χ^2 tests or Fisher's exact test. These tests were also used to assess treatment differences regarding the incidence of adverse events.

RESULTS — A total of 83 patients were randomized to the two treatment arms. Of those, 2 patients were excluded from the ITT analysis for HbA_{1c} (acarbose $n = 38$, placebo $n = 43$) and 1 patient had no baseline fasting blood glucose data and was thus excluded from the ITT analysis for FBG (acarbose $n = 39$, placebo $n = 43$). In the PP population, 71 patients were included for HbA_{1c} analysis (acarbose $n = 33$, placebo $n = 38$) and 74 for FBG analysis (acarbose $n = 35$, placebo $n = 39$). All randomized patients were included in the safety analysis (acarbose $n = 40$, placebo $n = 43$). Baseline demographic data and efficacy variables of all randomized subjects compared well between the treatment groups (Table 1). Both treatment groups received the same median dosage of metformin (1,700 mg/day).

Figure 1*A* shows the change in mean HbA_{1c} levels during the study course (ITT analysis). Significant differences between the treatment groups compared to baseline were seen for weeks 12 and 24 ($P = 0.0009$ and $P = 0.0023$, respectively). Mean HbA_{1c} levels increased in the pla-

Table 1—*Baseline demographic characteristics and efficacy variables of patients valid for safety analysis*

Characteristics	Acarbose	Placebo	*P*
n	40	43	
Age (years)	58.37 ± 10.7	62.39 ± 8.02	0.127*
Sex (%)			0.259†
Female	35.0	23.3	
Male	65.0	76.7	
Ethnicity (%)			
White	80.0	97.7	
Asian	5.0	0.0	
Others	15.0	2.3	
Weight (kg)	89.77 ± 12.73	87.88 ± 11.7	0.632*
BMI (kg/m^2)	30.75 ± 2.96	30.09 ± 2.85	0.086*
Duration of diabetes (years)	5.32 ± 4.55	6.06 ± 5.32	0.757‡
Daily metformin dosage (mg)	1,700 (500–4,000)	1,700 (500–3,000)	0.490‡
HbA_{1c} (%)	8.05 ± 0.89	7.82 ± 0.83	0.498*
FBG (mmol/l)	9.97 ± 2.47	9.41 ± 1.99	0.719*

Data are *n*, means ± SD, or median (min–max). *ANOVA with center and center by treatment interaction; †Cochran-Mantel-Haenszel test adjusting for center effect; ‡Wilcoxon's rank-sum test.

cebo group from 7.82 ± 0.83% at baseline to 8.1 ± 1.06% at week 12 and 8.5 ± 1.44% at study end. The mean increase after 24 weeks was 0.68 ± 1.17%, with a significant overall time effect (P = 0.0001). In the acarbose group, levels decreased from 8.02 ± 0.85% at baseline to 7.78 ± 1.0% at week 12 (P = 0.0261). Levels then increased to 7.97 ± 1.1% at study end (mean change after 24 weeks was −0.05 ± 0.8%). There was no significant overall time effect for acarbose. The adjusted least square means for the change in HbA_{1c} from baseline to week 24 showed a reduction of 0.16 ± 0.18% in the acarbose arm compared to an increase of 0.86 ± 0.16% in the placebo group, with a statistically significant difference between the treatment arms of 1.02% (95% CI 0.543–1.497, P = 0.0001). There was a significantly greater proportion of responders in the acarbose group (n = 18; 47%) than in the placebo group (n = 6; 14%) (P = 0.001) at the end of the study.

Mean levels of the secondary efficacy variable FBG increased in the placebo arm from baseline (9.41 ± 1.99 mmol/l) to week 4 (10.06 ± 2.43 mmol/l) and continued to increase to the end of study (10.77 ± 3.39 mmol/l), whereas levels in the acarbose arm varied only slightly from baseline (Fig. 1*B*). The mean increase was 1.36 ± 2.88 mmol/l for the placebo and 0.08 ± 1.98 mmol/l for the acarbose group. The adjusted least square means showed an increase at end point in both groups: 0.34 ± 0.42 mmol/l for acarbose compared to 1.48 ± 0.39 mmol/l for placebo patients, with a statistically significant difference of 1.132 mmol/l between the two groups (95% CI 0.056–2.208, P = 0.0395). PP analyses for both variables showed similar results, but were not statistically significant for treatment differences concerning FBG.

Of the 83 patients valid for safety analysis, 76 completed the study. Mean study duration was 169 days for both acarbose (29–184 days) and placebo (39–176 days). Overall compliance (80–120% compliance) was 100% for acarbose and 95.3% for placebo patients. In all, five patients reduced the medication dose to 50 mg b.i.d. because of adverse events (acarbose, n = 3; placebo, n = 2); three of these patients later reverted back to the original dosage. Patients in both treatment groups experienced a small mean weight reduction over the study period (1.32 ± 2.37 kg for acarbose vs. 0.43 ± 2.9 kg for placebo patients), which was not significantly different (P = 0.13). There were also no significant changes in vital signs. Changes in routine laboratory parameters were similar in both treatment groups, except for one patient (acarbose group) with elevated liver function enzymes who was withdrawn from the study. In total, seven patients were prematurely withdrawn from the study during the 24-week treatment period: four because of treatment-emergent adverse events, one patient on placebo because of constipation and depression, and three patients on acarbose with flatulence, flatulence accompanied by abdominal pain, and the aforementioned elevated liver enzymes. A serious adverse event with remote or no relation to the study medication was experienced by two acarbose patients and one placebo patient; no fatalities occurred. Treatment-emergent adverse events with a relation to the study medication rated as "possible" or "probable" were reported by 75% of

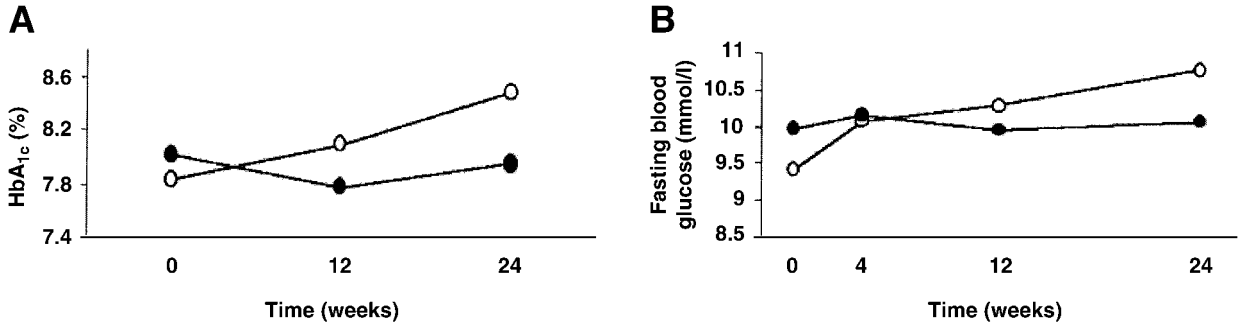

Figure 1—*Change in mean HbA_{1c} (A) and mean FBG (B) during a 24-week treatment period with acarbose (●) or placebo (○) adjunctive therapy in the ITT population.*

Table 2—*Most frequently reported treatment-emergent adverse events*

Adverse event	Acarbose	Placebo
n	40	43
Flatulence	57.5*	27.9
Diarrhea	15.0	14.0
Abdominal pain	10.0	7.0
Enlarged abdomen	7.5	4.7
Nausea	5.0	2.3
Chest pain	5.0	2.3
Dyspnea	5.0	0.0
Constipation	2.5	7.0
Any	75.0	55.8

Data are %. Possible or probable relation to study medication given. *$P = 0.0064$ vs. placebo.

acarbose and 55.8% of placebo patients. The main difference between the treatment groups was the higher frequency of gastrointestinal complaints in the acarbose group (Table 2).

CONCLUSIONS — Oral antidiabetic drugs such as acarbose or metformin that do not induce hyperinsulinemia are useful treatments for type 2 diabetes (24). The present study demonstrated the beneficial effect on overall glycemic control of additional acarbose therapy in overweight patients insufficiently controlled by metformin alone. HbA_{1c} levels showed a clinically significant difference of 1.02% (least square means) in acarbose patients after 24 weeks of treatment compared to placebo patients ($P = 0.0001$). The results also indicated that the lower than usual dosage of acarbose in the present study (200 mg/day compared to 300 mg/day in long-term studies) (listed in 14) is sufficient in many patients for efficacious glycemic control. The U.K. Prospective Diabetes Study found that each 1% reduction in updated mean HbA_{1c} was associated with a 37% decrease in risk for microvascular complications and a 21% decrease in the risk of any end point or death related to diabetes (25). Acarbose in combination with metformin thus has the potential to delay diabetes complications through improvement of metabolic control. There was also a favorable effect on fasting blood glucose levels. Reduced glucose toxicity through decreasing postprandial blood glucose elevations and a beneficial effect of the increased late rise in glucagon-like peptide 1 on reducing fasting blood glucose are possible mechanisms for this effect (26).

The proportion of patients with a ≥5% relative reduction from baseline in HbA_{1c} ("responders") was significantly higher in the acarbose group (47%) than in the placebo group (14%). This outcome differed from other metformin/acarbose combination studies in which the number of patients classified as responders according to protocol definition (an absolute HbA_{1c} value <7% or a decrease of at least 15% of baseline value) was 40% (11) and 42% (19). Higher dosages of acarbose in those studies might account for the difference: patients in the Canadian study received up to 600 mg/day acarbose (11) and patients in the French study were given up to 300 mg/day (19).

Major side effects included gastrointestinal with flatulence, similar to findings in other acarbose/metformin combination studies (11,18,19). Incidences of diarrhea and abdominal pain were similar in both treatment groups and were probably attributable to metformin (27). No hypoglycemic episodes occurred during treatment, and body weight decreased more in acarbose patients.

Several other studies have described the use of add-on therapy of antidiabetic drugs to metformin. In one study, treatment with the postprandial glucose regulator repaglinide significantly decreased HbA_{1c} levels by 1.4% and FBG by 2.2 mmol/l from baseline to study end point in overweight type 2 patients, but increased fasting insulin levels and body weight (7). In the combination group, 33% of patients reported hypoglycemic incidences that were mild to moderate. The addition of the sulfonylurea glimepiride to metformin monotherapy in overweight type 2 patients resulted in a significant reduction of HbA_{1c} of 0.74% as well as significant reductions in FBG and postprandial blood glucose (10). Body weight increased slightly, and the incidence of hypoglycemia was significantly higher (22%; $P = 0.039$) compared to monotherapy. Treatment with the insulin sensitizers rosiglitazone or pioglitazone hydrochloride both resulted in a significant reduction in HbA_{1c} in overweight type 2 patients (8,9). Body weight increased in both studies.

Our study confirmed the significant improvement in metabolic control using acarbose therapy, which has also been demonstrated in the studies by Rosenstock et al. (18) and Halimi et al. (19). Taking into account the repaglinide and glimepiride treatment results (7,10), acarbose showed a better safety profile owing to the clinical advantage associated with the lack of hypoglycemic episodes. The unchanged or slightly reduced weight experienced during acarbose treatment is also a contributing factor, suggesting that acarbose is an appropriate drug for the treatment of overweight patients. The frequency of gastrointestinal complaints resulting from acarbose's mode of action might be minimized in clinical practice where the physician can lower the dosage to the individual requirement of the patient (22).

This study has demonstrated that acarbose represents a good treatment approach in combination therapy, especially in overweight patients whose diabetes is inadequately controlled by metformin monotherapy.

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