A Randomized Double-Blind Trial of Acarbose in Type 2 Diabetes Shows Improved Glycemic Control Over 3 Years (U.K. Prospective Diabetes Study 44)

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OBJECTIVE — To determine the degree to which α-glucosidase inhibitors, with their unique mode of action primarily reducing postprandial hyperglycemia, offer an additional therapeutic approach in the long-term treatment of type 2 diabetes.

RESEARCH DESIGN AND METHODS — We studied 1,946 patients (63% men) who were previously enrolled in the U.K. Prospective Diabetes Study (UKPDS). The patients were randomized to acarbose (n = 973), titrating to a maximum dose of 100 mg three times per day, or to matching placebo (n = 973). Mean ± SD age was 59 ± 9 years, body weight 84 ± 17 kg, diabetes duration 7.6 ± 2.9 years, median (interquartile range) HbA_{1c} 7.9% (6.7–9.5), and fasting plasma glucose (FPG) 8.7 mmol/l (6.8–11.1). Fourteen percent of patients were treated with diet alone, 52% with monotherapy, and 34% with combined therapy. Patients were monitored in UKPDS clinics every 4 months for 3 years. The main outcome measures were HbA_{1c}, FPG, body weight, compliance with study medication, incidence of side effects, and frequency of major clinical events.

RESULTS — At 3 years, a lower proportion of patients were taking acarbose compared with placebo (39 vs. 58%, $P < 0.0001$), the main reasons for noncompliance being flatulence (30 vs. 12%, $P < 0.0001$) and diarrhea (16 vs. 8%, $P < 0.05$). Analysis by intention to treat showed that patients allocated to acarbose, compared with placebo, had 0.2% significantly lower median HbA_{1c} at 3 years ($P < 0.001$). In patients remaining on their allocated therapy, the HbA_{1c} difference at 3 years (309 acarbose, 470 placebo) was 0.5% lower median HbA_{1c} (8.1 vs. 8.6%, $P < 0.0001$). Acarbose appeared to be equally efficacious when given in addition to diet alone; in addition to monotherapy with a sulfonylurea, metformin, or insulin; or in combination with more complex treatment regimens. No significant differences were seen in FPG, body weight, incidence of hypoglycemia, or frequency of major clinical events.

CONCLUSIONS — Acarbose significantly improved glycemic control over 3 years in patients with established type 2 diabetes, irrespective of concomitant therapy for diabetes. Careful titration of acarbose is needed in view of the increased noncompliance rate seen secondary to the known side effects.

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Good glycemic control is essential if the risk of diabetic complications is to be minimized (1). However, treatment of type 2 diabetes—whether by diet alone or with additional monotherapy with sulfonylurea, metformin, or insulin—frequently cannot induce or maintain normal plasma glucose levels (2,3) in the face of progressive β-cell failure (4). Competitive α-glucosidase enzyme inhibitors, such as the pseudo-oligosaccharide acarbose, can diminish postprandial blood glucose excursions by delaying carbohydrate digestion in the small intestine (5), thereby offering an alternative therapeutic approach to improve blood glucose control (6,7). Because the advent of this new mode of therapy for diabetes occurred while the U.K. Prospective Diabetes Study (UKPDS) was underway, the opportunity was taken to evaluate formally its efficacy in an embedded study included in a factorial design with the existing glucose control policies (1). We present the data from this 3-year randomized controlled trial that investigated the degree to which acarbose might improve or help to maintain glycemic control in patients on established therapy for type 2 diabetes.

RESEARCH DESIGN AND METHODS

Patients

Of 3,309 patients attending UKPDS clinics (8) between May and September 1994, 1,946 (59%) agreed to take part in a 3-year, double-blind, placebo-controlled trial of acarbose given in addition to their preexisting therapy for diabetes. Local research ethics committee approval and written informed patient consent were obtained in all 23 participating clinical centers. Baseline characteristics of the patients recruited are shown in Table 1. Pre-existing therapies for diabetes were diet alone in 14%, monotherapy in 52% (sulfonylurea 26%, metformin 6%, insulin 20%), and combination therapy in 34% (sulfonylurea plus metformin 16%, sulfonylurea plus insulin 4%, multiple insulin 14%). Of the 1,353 patients who did not enter the study, 944 (28%) declined and 419 (13%) were excluded—213 were thought to be unsuitable for the study by their physicians, 112 had gastrointestinal problems, 74 had a severe or immediately life-threatening ill-

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Abbreviations: FPG, fasting plasma glucose; UKPDS, U.K. Prospective Diabetes Study.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline characteristics of patients randomly allocated to acarbose or placebo*

	Acarbose	Placebo
n	973	973
Age (years)	60 ± 9	60 ± 9
Duration of diabetes (years)	7.9 ± 2.9	8.0 ± 2.8
Body weight (kg)	84 ± 17	84 ± 17
BMI (kg/m^2)	29.8 ± 5.6	29.6 ± 5.7
HbA_{1c} (%)*	8.7 (6.8–11.2)	8.7 (6.8–11.0)
FPG (mmol/l)*	7.9 (6.7–9.5)	8.0 (6.8–9.5)
Urine albumin (mg/l)†	15 (4–59)	15 (4–60)
β-cell function (%β)†	54 (25–118)	54 (24–123)
Insulin sensitivity (%S)†	46 (26–81)	45 (24–86)

Data are means ± SD, *medians (interquartile range), or †geometric means (1 SD interval).

ness, and 20 had other medical contraindications such as pregnancy or steroid therapy. Patients not entering the study showed small but statistically significant differences from those recruited, being slightly older with a longer duration of diabetes, lower mean body weight, higher HbA_{1c}, and higher fasting plasma glucose (FPG). There were no significant differences with regard to the proportion of patients taking different preexisting therapies for diabetes.

Clinic visits

Patients were seen in hospital-based UKPDS clinics at four monthly intervals with monitoring of HbA_{1c}, FPG, body weight, side effects, and predefined clinical end points (8). Randomization was performed centrally, with patients being allocated to the next sequential therapy number at the time they were recruited. Double-blind study medication was supplied prepackaged (Bayer, Newbury, U.K.). Patients were instructed to commence therapy with a single 50 mg tablet (acarbose or matching placebo) taken once a day immediately before their main meal for 1 week. They were then asked to increase the dose after 1 week, in the absence of side effects, by taking a second tablet with another meal (100 mg per day), and after 2 weeks, to take one tablet with each of three meals (150 mg per day), if tolerated. At 4 months, when they attended for their next routine UKPDS follow-up visit, patients were instructed to increase their study medication in a similar fashion, over a 3-week period, to the scheduled maximum of two tablets three times a day (300 mg per day). In the event of side effects, patients were asked to reduce the dose to the maximum tolerable number of tablets. Compliance with study medication was assessed by direct questioning and by counting the number of tablets returned. Preexisting therapies for diabetes were adjusted only if required according to the UKPDS protocol.

Biochemistry

Clinical center plasma glucose analyzers were monitored monthly by a central glucose quality assurance scheme; the mean interlaboratory imprecision was 4%, and values were within 0.1 mmol/l of those obtained by the U.K. External Quality Assessment Scheme. Blood and urine samples were transported overnight at 4°C to the central biochemistry laboratory and assayed as previously described (9). HbA_{1c} was measured by high-performance liquid chromatography (Biorad Diamat Automated Haemoglobin Analyser, Hemel Hempstead, U.K.) with a reference range for nondiabetic subjects of 4.5–6.2%, urine albumin by an immunoturbidometric method (reference range 1.4–36.5 mg/l), and plasma insulin by a double-antibody radioimmunoassay (Pharmacia RIA 100; Pharmacia and Upjohn, Milton Keynes, U.K.) with 100% cross-reaction to intact proinsulin and 25% to 32/33 split proinsulin.

Statistical analyses

Statistical analyses were performed using SAS (10) according to allocated therapy on an intention-to-treat basis. Analyses by actual therapy include only those patients who were continuing to take their allocated therapy at the time in question. There was no imbalance in the proportions of patients randomized to acarbose or placebo with respect to their original allocation to conventional or intensive treatment policies in the UKPDS. Data are given as mean ± 1 SD, median (interquartile range), or geometric mean (1 SD interval) except for changes over time, which are given as mean (95% CI). Net differences were calculated as the difference between the means for the acarbose and placebo groups. Values between randomized groups were compared by analysis of variance or the Mann-Whitney *U* test after testing for normality. Changes over time were tested using a paired sample *t* test or Wilcoxon sign test. β-Cell function (%β) and insulin sensitivity (%S) were calculated annually, for patients not taking exogenous insulin, from paired FPG and insulin measurements using homeostasis model assessment (HOMA) (11). Although this 3-year study was not designed to assess differences in clinical outcome rates, the opportunity was taken to examine the clinical end point data collected as required by the UKPDS protocol (1). A Kaplan-Meier analysis was used, with a log-rank test and a hazard ratio (used to estimate the relative risk) obtained from a Cox proportional-hazards model.

RESULTS

Patients

At 3 years, 322 (17%) patients were no longer attending routine UKPDS clinics or had died. These patients did not differ, at entry, from those remaining in the study with respect to age, sex, ethnic group, duration of diabetes, existing therapy for diabetes, HbA_{1c}, or FPG level.

Intention-to-treat analyses

Analysis by allocated therapy showed that the cohort of patients randomized to acarbose, compared with placebo, showed an initial reduction in median HbA_{1c} levels and maintained a 0.2% significantly lower median HbA_{1c} at 1, 2, and 3 years (Fig. 1). Although lower median HbA_{1c} levels were achieved at each time point in those allocated to acarbose, median HbA_{1c} values increased progressively in both groups. At 3 years, the mean HbA_{1c} differences between those allocated to acarbose and placebo were similar irrespective of preexisting therapy for diabetes (Table 2). At 1 year, patients randomized to acarbose, compared with placebo, had a significantly lower median FPG ($P < 0.0036$) but not thereafter (Fig. 1). Mean body weight was significantly less at 1 year in those allocated to acarbose (0.4 kg, $P = 0.015$), but no significant differences were seen at 2 or 3 years (Table 3). Urine albumin, β-cell function (%β), and insulin sensitivity (%S) were not significantly different at any time (Table 3). No significant differences were seen in the proportion of patients in each group with any of the predefined UKPDS end points (8). For patients allocated to acarbose, the relative risk, compared with placebo, for "any diabetes-related end point" was 1.00 (95% CI 0.81–1.23), and for microvascular disease, 0.91 (0.61–1.35).

Therapy compliance

Significantly fewer patients allocated acarbose, compared with those allocated placebo,

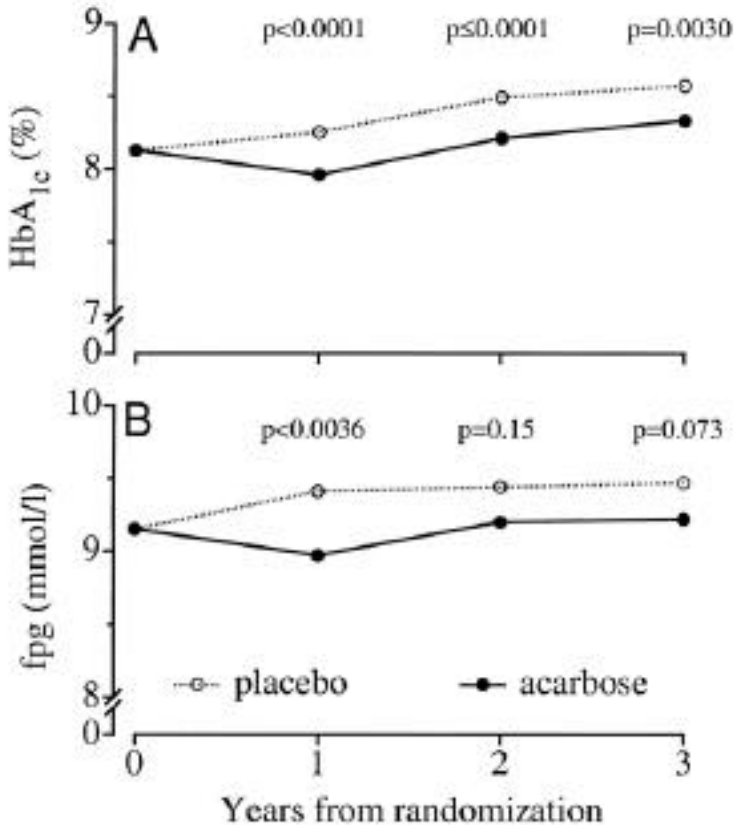

Figure 1—*Median HbA_{1c} levels (A) and FPG levels (B), analyzed according to allocated therapy (intention to treat) at baseline and 1, 2, and 3 years after randomization.*

Table 2—***Analysis at 3 years, by allocated therapy (intention to treat) and by actual therapy, of the net difference in HbA_{1c} between patients randomly allocated to acarbose and placebo therapy according to their preexisting therapy for diabetes***

	Acarbose (*n*)	Placebo (*n*)	Net HbA_{1c} difference	*P*
Allocated therapy (intention to treat)				
Diet alone	115	107	−0.20 (−0.68 to 0.27)	0.40
Sulphonylurea	193	185	−0.21 (−0.53 to 0.11)	0.19
Metformin	41	46	−0.32 (−0.98 to 0.33)	0.33
Basal insulin	114	125	−0.28 (−0.62 to 0.06)	0.11
Sulphonylurea plus metformin	154	142	−0.20 (−0.66 to 0.26)	0.39
Sulphonylurea plus insulin	42	49	−0.58 (−1.49 to 0.33)	0.21
Multiple insulin	151	160	−0.12 (−0.54 to 0.29)	0.57
Actual therapy				
Diet alone	49	73	−0.61 (−1.31 to 0.10)	0.092
Sulphonylurea	89	135	−0.51 (−0.92 to −0.08)	0.019
Metformin	17	32	−0.70 (−1.71 to 0.32)	0.17
Basal insulin	58	92	−0.27 (−0.76 to 0.22)	0.28
Sulphonylurea plus metformin	59	73	−0.32 (−1.29 to 0.65)	0.51
Sulphonylurea plus insulin	14	20	−0.07 (−1.30 to 1.16)	0.90
Multiple insulin	33	51	−0.73 (−1.36 to −0.09)	0.025

Data for net HbA_{1c} differences are means (95% CIs). There were no significant differences in the net HbA_{1c} differences between the established therapy groups (analysis of variance [ANOVA]). Interaction for allocated therapy group, $P = 0.43$, and for actual therapy group, $P = 0.89$ (ANOVA).

continued to take study medication at 1 (49 vs. 70%), 2 (43 vs. 60%), and 3 (39 vs. 58%) years ($P < 0.0001$). At 3 years, the lower compliance rate for acarbose, compared with placebo, related primarily to the increased proportion of patients reporting flatulence (30 vs. 12%, $P < 0.00001$) and diarrhea (16 vs. 8%, $P < 0.0001$). Otherwise, there were no significant differences between the two groups with respect to specific side effects.

Actual therapy analyses

In view of the significant acarbose and placebo noncompliance rates, an analysis by actual therapy was performed to estimate potential glycemic differences. Figure 2 shows the mean changes in HbA_{1c} and FPG over 1, 2, and 3 years, with 0.5% significantly lower median HbA_{1c} values in the group taking acarbose at each time point. Median FPG values were significantly lower by 0.5 mmol/l at 1 year in the group taking acarbose, with similar, but not statistically significant, reductions at 2 and 3 years. Mean body weight was significantly less in those taking acarbose at 1 year (0.7 kg, $P = 0.0018$) and at 3 years (0.8 kg, $P = 0.040$) (Table 3). No significant differences were seen in urinary albumin levels, β-cell function (%β), or insulin sensitivity (%S) (Table 3). The frequency of self-reported minor or major hypoglycemic episodes did not differ between groups at any time point (data not shown).

CONCLUSIONS — This study shows that acarbose therapy can significantly improve glycemic control in patients with type 2 diabetes over a period of 3 years. The glycemic difference seen throughout the study in those patients who continued to take acarbose was a 0.5% reduction in HbA_{1c}. This degree of glycemic improvement is not dissimilar to that achieved in patients newly diagnosed with type 2 diabetes and randomly allocated to monotherapy with sulfonylurea, metformin, or insulin (2). The HbA_{1c} reductions were achieved irrespective of the type of preexisting therapy for diabetes, suggesting that acarbose can usefully be given to patients treated with diet alone, in combination with sulfonylurea, metformin, or insulin, or as part of a more complex regimen. The UKPDS has shown conclusively that minimizing hyperglycemia is essential if the risk of diabetes-related complications is to be reduced (1), confirming the need for all patients with type 2 diabetes to aim for the best achievable blood

Table 3—*Analysis over 1, 2, and 3 years, by allocated therapy (intention to treat) and by actual therapy, of the mean change in body weight, urine albumin, β-cell function (%β), and insulin sensitivity (%S) between patients randomly allocated to acarbose and placebo therapy*

	Allocated therapy				Actual therapy			
	Acarbose (*n*)	Placebo (*n*)	Net difference	*P* value	Acarbose (*n*)	Placebo (*n*)	Net difference	*P* value
Change in weight (kg)								
0–1 year	683	692	−0.4 (−0.7 to −0.1)	0.015	346	514	−0.7 (−1.1 to −0.3)	0.0018
0–2 years	674	694	−0.3 (−0.7 to 0.1)	0.18	312	451	−0.5 (−1.0 to 0.1)	0.12
0–3 years	686	699	−0.3 (−0.8 to 0.2)	0.24	284	433	−0.8 (−1.5 to 0.0)	0.04
Change in urinary albumin (mg/l)								
0–1 year	563	597	−5.4 (−10.8 to 0.1)	0.054	284	436	−0.9 (−6.6 to 4.9)	0.76
0–2 years	532	568	−25.9 (−57.3 to 5.6)	0.11	249	370	−27.4 (−75.0 to 20.2)	0.26
0–3 years	529	560	−11.6 (−37.5 to 14.3)	0.38	220	350	−14.6 (−62.5 to 33.3)	0.55
Change in β-cell function (%)								
0–1 year	264	237	−2.4 (−23.1 to 18.4)	0.82	140	195	−8.3 (−38.2 to 21.7)	0.59
0–2 years	247	239	−4.7 (−21.1 to 11.7)	0.57	122	163	−4.2 (−26.9 to 18.5)	0.72
0–3 years	286	269	−13.7 (−29.5 to 2.2)	0.091	113	159	−12.7 (−37.7 to 13.4)	0.32
Change in insulin sensitivity (%)								
0–1 year	264	237	−5.2 (−17.4 to 7.0)	0.40	140	195	−6.5 (−20.8 to 7.8)	0.37
0–2 years	247	239	−0.2 (−4.2 to 3.8)	0.92	122	163	−0.8 (−6.4 to −4.8)	0.78
0–3 years	286	269	−0.3 (−3.9 to 3.4)	0.90	113	159	−0.5 (−6.1 to −5.2)	0.87

Data for net differences are means (95% CIs).

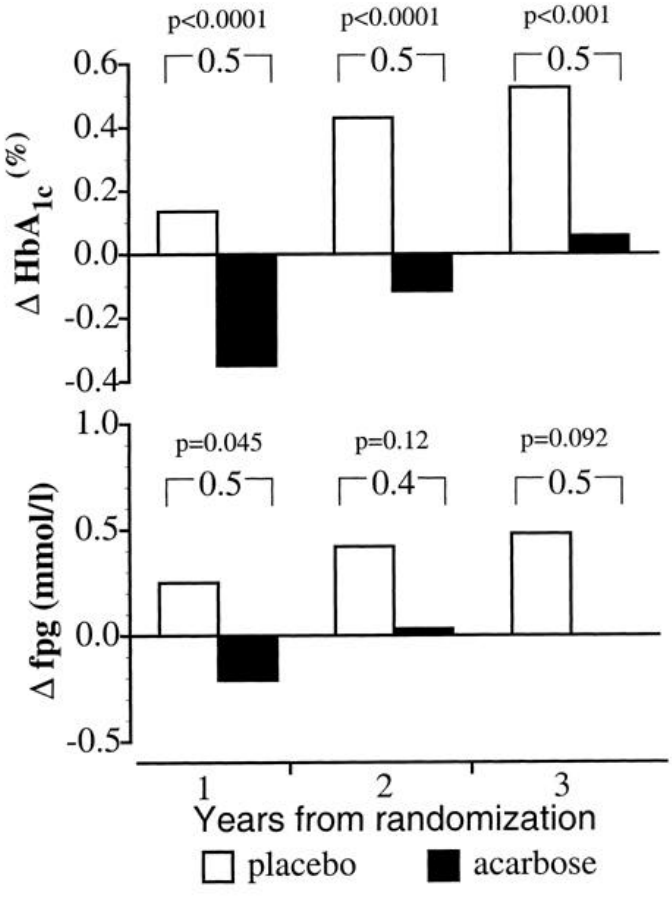

Figure 2—*Mean change from baseline in HbA_{1c} and FPG levels, analyzed according to actual therapy at 1, 2, and 3 years after randomization.*

glucose control. Because type 2 diabetes is a progressive disease (3), it is inevitable that, with time, therapies for diabetes that have complementary actions will need to be given in combination.

Acarbose, like metformin (3), is weight neutral and does not appear to promote hypoglycemia. No significant differences were seen in relation to acarbose therapy for the clinical outcomes monitored as part of the UKPDS, although this trial was not designed, and was not large enough, to address this question. Although improved glucose control has been shown, in the longer term, to reduce urinary albumin (1), levels were not significantly different in this 3-year trial. Acarbose has been reported to improve insulin sensitivity in subjects with impaired glucose tolerance (12), but in this study no significant effects were seen on insulin sensitivity or β-cell function. This lack of effect is reflected in the HbA_{1c} and FPG increase following an initial reduction in the acarbose group, parallel to those in the placebo group.

Many of the patients enrolled in the study were already taking a number of medications including preexisting therapy for diabetes, antihypertensive therapy, or other therapies such as for arthritis. Many patients found it difficult to add yet another tablet that needed to be taken three times a day. Of those allocated to placebo tablets, 70% continued to take

their double-blind study medication at 1 year and 58% at 3 years. The greater noncompliance rate seen in those patients allocated acarbose (49% at 1 year and 39% at 3 years) related primarily to side effects, 30% of patients citing flatulence and 16% loose motions as the main reason for discontinuing study medi-cation. Most of the patients who discontinued acarbose therapy did so during the 1st year, suggesting that once tolerance is established, compliance is easier to maintain.

Acarbose, with its novel mechanism of action providing an alternative therapeutic approach, is of potential benefit, since none of the currently available pharmacologic treatments for type 2 diabetes, as monotherapy, can control blood glucose levels satisfactorily in the long term. Acarbose may be particularly useful as an alternative first-line treatment for type 2 diabetes, when diet alone is insufficient, as it is an antihyperglycemic that targets postprandial hyperglycemia rather than a hypoglycemic agent. This specific mode of action also means that acarbose can be combined successfully with other agents, such as sulfonylurea or metformin, which primarily reduce fasting hyperglycemia. The lack of any deleterious effects with respect to clinical outcomes, the minimal risk of hypoglycemia, and the absence of effect on body weight are desirable features for a drug that may be taken for many years.

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