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

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) HbA1c 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 HbA1c, 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 HbA1c at 3 years (P < 0.001). In patients remaining on their allocated therapy, the HbA1c difference at 3 years (309 acarbose, 470 placebo) was 0.5% lower median HbA1c (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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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

<table>
<thead>
<tr>
<th></th>
<th>Acarbose</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>n</td>
<td>973</td>
<td>973</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60 ± 9</td>
<td>60 ± 9</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>7.9 ± 2.9</td>
<td>8.0 ± 2.8</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>84 ± 17</td>
<td>84 ± 17</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.8 ± 5.6</td>
<td>29.6 ± 5.7</td>
</tr>
<tr>
<td>HbA₁c (%)⁎</td>
<td>8.7 (6.8–11.2)</td>
<td>8.7 (6.8–11.0)</td>
</tr>
<tr>
<td>FPG (mmol/l)⁎</td>
<td>7.9 (6.7–9.5)</td>
<td>8.0 (6.8–9.5)</td>
</tr>
<tr>
<td>Urine albumin (mg/l)†</td>
<td>15 (4–59)</td>
<td>15 (4–60)</td>
</tr>
<tr>
<td>β-cell function (%)β†</td>
<td>54 (25–118)</td>
<td>54 (24–123)</td>
</tr>
<tr>
<td>Insulin sensitivity (%S)†</td>
<td>46 (26–81)</td>
<td>45 (24–86)</td>
</tr>
</tbody>
</table>

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

ness, and 20 had other medical contraindi-
cations such as pregnancy or steroid ther-
apy. 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 HbA₁c, and
higher fasting plasma glucose (FPG). There
were no significant differences with regard
to the proportion of patients taking differ-
ent preexisting therapies for diabetes.

Clinic visits
Patients were seen in hospital-based
UKPDs clinics at four monthly intervals
with monitoring of HbA₁c, FPG, body
weight, side effects, and predefined clinical end points (8). Randomization was per-
formed centrally, with patients being allo-
cated to the next sequential therapy number at the time they were recruited.
Double-blind study medication was sup-
plied prepackaged (Bayer, Newbury, U.K.).
Patients were instructed to commence ther-
pay with a single 50 mg tablet (acarbose or
matching placebo) taken once a day imme-
diately 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 in-
structed to increase their study medica-
tion 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 glu-
cose 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).

HbA₁c 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 immuno-
turbidometric 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 con-
ventional 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 differ-
cence between the means for the acarbose
and placebo groups. Values between random-
ized 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 mea-
surements using homeostasis model assess-
ment (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, dur-
ation of diabetes, existing therapy for di-
betes, HbA₁c, or FPG level.

Intention-to-treat analyses
Analysis by allocated therapy showed that
the cohort of patients randomized to acar-
bose, compared with placebo, showed an ini-
tial reduction in median HbA₁c levels and
maintained a 0.2% significantly lower median HbA₁c at 1, 2, and 3 years (Fig. 1).
Although lower median HbA₁c levels were
achieved at each time point in those allocated
to acarbose, median HbA₁c values increased
progressively in both groups. At 3 years, the
mean HbA₁c differences between those allo-
cated to acarbose and placebo were similar
irrespective of preexisting therapy for dia-
betes (Table 2). At 1 year, patients random-
ized 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 allo-
cated 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 acar-
bose, compared with those allocated placebo,
Acarbose and long-term glycemic control

Figure 1—Median HbA1c 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 HbA1c between patients randomly allocated to acarbose and placebo therapy according to their preexisting therapy for diabetes

<table>
<thead>
<tr>
<th>Allocated therapy (intention to treat)</th>
<th>Acarbose (n)</th>
<th>Placebo (n)</th>
<th>Net HbA1c difference</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet alone</td>
<td>115</td>
<td>107</td>
<td>-0.20 (-0.68 to 0.27)</td>
<td>0.40</td>
</tr>
<tr>
<td>Sulphonylurea</td>
<td>193</td>
<td>185</td>
<td>-0.21 (-0.53 to 0.11)</td>
<td>0.19</td>
</tr>
<tr>
<td>Metformin</td>
<td>41</td>
<td>46</td>
<td>-0.32 (-0.98 to 0.33)</td>
<td>0.33</td>
</tr>
<tr>
<td>Basal insulin</td>
<td>114</td>
<td>125</td>
<td>-0.28 (-0.62 to 0.06)</td>
<td>0.11</td>
</tr>
<tr>
<td>Sulphonylurea plus metformin</td>
<td>154</td>
<td>142</td>
<td>-0.20 (-0.66 to 0.26)</td>
<td>0.39</td>
</tr>
<tr>
<td>Sulphonylurea plus insulin</td>
<td>42</td>
<td>49</td>
<td>-0.58 (-1.49 to 0.33)</td>
<td>0.21</td>
</tr>
<tr>
<td>Multiple insulin</td>
<td>151</td>
<td>160</td>
<td>-0.12 (-0.54 to 0.29)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Actual therapy</th>
<th>Acarbose (n)</th>
<th>Placebo (n)</th>
<th>Net HbA1c difference</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet alone</td>
<td>49</td>
<td>73</td>
<td>-0.61 (-1.31 to 0.10)</td>
<td>0.092</td>
</tr>
<tr>
<td>Sulphonylurea</td>
<td>89</td>
<td>135</td>
<td>-0.51 (-0.92 to 0.08)</td>
<td>0.019</td>
</tr>
<tr>
<td>Metformin</td>
<td>17</td>
<td>32</td>
<td>-0.70 (-1.71 to 0.32)</td>
<td>0.17</td>
</tr>
<tr>
<td>Basal insulin</td>
<td>58</td>
<td>92</td>
<td>-0.27 (-0.76 to 0.22)</td>
<td>0.28</td>
</tr>
<tr>
<td>Sulphonylurea plus metformin</td>
<td>59</td>
<td>73</td>
<td>-0.32 (-1.29 to 0.65)</td>
<td>0.51</td>
</tr>
<tr>
<td>Sulphonylurea plus insulin</td>
<td>14</td>
<td>20</td>
<td>-0.07 (-1.30 to 1.16)</td>
<td>0.90</td>
</tr>
<tr>
<td>Multiple insulin</td>
<td>33</td>
<td>51</td>
<td>-0.73 (-1.36 to -0.09)</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Data for net HbA1c differences are means (95% CIs). There were no significant differences in the net HbA1c 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 < 0.0001) 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 HbA1c and FPG over 1, 2, and 3 years, with 0.5% significantly lower median HbA1c 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 albu-min levels, β-cell function (%B), or insulin sensitivity (%) (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 HbA1c. 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 sulphonylurea, metformin, or insulin (2). The HbA1c 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 sulphonylurea, 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
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 HbA1c 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

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

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

<table>
<thead>
<tr>
<th>Change in weight (kg)</th>
<th>Allocated therapy</th>
<th></th>
<th></th>
<th></th>
<th>Actual therapy</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acarbose (n)</td>
<td>Placebo (n)</td>
<td>Net difference</td>
<td>P value</td>
<td>Acarbose (n)</td>
<td>Placebo (n)</td>
<td>Net difference</td>
<td>P value</td>
</tr>
<tr>
<td>0–1 year</td>
<td>683</td>
<td>692</td>
<td>−0.4 (−0.7 to −0.1)</td>
<td>0.015</td>
<td>346</td>
<td>514</td>
<td>−0.7 (−1.1 to −0.3)</td>
<td>0.0018</td>
</tr>
<tr>
<td>0–2 years</td>
<td>674</td>
<td>694</td>
<td>−0.3 (−0.7 to −0.1)</td>
<td>0.18</td>
<td>312</td>
<td>451</td>
<td>−0.5 (−1.0 to −0.1)</td>
<td>0.12</td>
</tr>
<tr>
<td>0–3 years</td>
<td>686</td>
<td>699</td>
<td>−0.3 (−0.8 to −0.2)</td>
<td>0.24</td>
<td>284</td>
<td>433</td>
<td>−0.8 (−1.5 to −0.0)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change in urinary albumin (mg/l)</th>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>0–1 year</td>
<td>563</td>
<td>597</td>
<td>−5.4 (−10.8 to 0.1)</td>
<td>0.054</td>
<td>284</td>
<td>436</td>
<td>−0.9 (−6.6 to 4.9)</td>
<td>0.76</td>
</tr>
<tr>
<td>0–2 years</td>
<td>532</td>
<td>568</td>
<td>−25.9 (−57.3 to 5.6)</td>
<td>0.11</td>
<td>249</td>
<td>370</td>
<td>−27.4 (−75.0 to 20.2)</td>
<td>0.26</td>
</tr>
<tr>
<td>0–3 years</td>
<td>529</td>
<td>560</td>
<td>−11.6 (−37.5 to 14.3)</td>
<td>0.38</td>
<td>220</td>
<td>350</td>
<td>−14.6 (−62.5 to 33.3)</td>
<td>0.55</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Change in β-cell function (%)</th>
<th></th>
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<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1 year</td>
<td>264</td>
<td>237</td>
<td>−2.4 (−23.1 to 18.4)</td>
<td>0.82</td>
<td>140</td>
<td>195</td>
<td>−8.3 (−38.2 to 21.7)</td>
<td>0.59</td>
</tr>
<tr>
<td>0–2 years</td>
<td>247</td>
<td>239</td>
<td>−4.7 (−21.1 to 11.7)</td>
<td>0.57</td>
<td>122</td>
<td>163</td>
<td>−4.2 (−26.9 to 18.5)</td>
<td>0.72</td>
</tr>
<tr>
<td>0–3 years</td>
<td>286</td>
<td>269</td>
<td>−13.7 (−29.5 to 2.2)</td>
<td>0.091</td>
<td>113</td>
<td>159</td>
<td>−12.7 (−37.7 to 13.4)</td>
<td>0.32</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Change in insulin sensitivity (%)</th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1 year</td>
<td>264</td>
<td>237</td>
<td>−5.2 (−17.4 to 7.0)</td>
<td>0.40</td>
<td>140</td>
<td>195</td>
<td>−6.5 (−20.8 to 7.8)</td>
<td>0.37</td>
</tr>
<tr>
<td>0–2 years</td>
<td>247</td>
<td>239</td>
<td>−0.2 (−4.2 to 3.8)</td>
<td>0.92</td>
<td>122</td>
<td>163</td>
<td>−0.8 (−4.4 to −4.8)</td>
<td>0.78</td>
</tr>
<tr>
<td>0–3 years</td>
<td>286</td>
<td>269</td>
<td>−0.3 (−3.9 to 3.4)</td>
<td>0.90</td>
<td>113</td>
<td>159</td>
<td>−0.5 (−6.1 to −5.2)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Figure 2—Mean change from baseline in HbA1c and FPG levels, analyzed according to actual therapy at 1, 2, and 3 years after randomization.
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 medication. 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.

Acknowledgments — We thank Bayer U.K. for their support. The cooperation of the patients and the many National Health Service (NHS) and non-NHS staff members at the centers is much appreciated.

References