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Is acarbose equivalent to tolbutamide as first treatment for newly diagnosed type 2 diabetes in general practice? A randomised controlled trial

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Abstract

We performed a double blind randomised controlled trial in general practice to assess equivalence between tolbutamide and acarbose with respect to the effect on mean HbA_{1c} in newly diagnosed patients with type 2 diabetes. Secondary objectives were to compare the effects of both treatments on fasting and post-load blood glucose and insulin levels, lipids, and adverse events. Patients were randomised to receive acarbose, titrated step-wise to a maximum of 100 mg three times daily ($n = 48$) or tolbutamide, similarly titrated to a maximum of 2000 mg in three doses ($n = 48$). The two treatments were considered equivalent if the two-sided 90% confidence interval (CI) for the difference in mean HbA_{1c} levels was within the range −0.4 to 0.4%. Results were analysed on an intention-to-treat, per-protocol and on worst-case basis. Both agents reduced the HbA_{1c} percentage and fasting blood glucose levels. The difference in mean decrease of HbA_{1c} was 0.6% in favour of tolbutamide (90% CI 0.3, 0.9; 95% CI 0.2, 1.0). A worst-case analysis, assuming no change in HbA_{1c} for dropouts, yielded a difference in mean decrease of 0.9% (90% CI 0.6, 1.2) in favour of tolbutamide. The difference in mean decrease of fasting blood glucose was 1.0 mmol/l in favour of tolbutamide (95% CI 0.3, 1.7). There were no significant differences in post-load blood glucose, fasting and post-load insulin levels, or lipids. In the acarbose group significantly more patients (15 versus 3) discontinued therapy because of adverse effects, mostly of gastrointestinal origin. We conclude that the results of this study favour tolbutamide over acarbose as first treatment for patients with newly diagnosed type 2 diabetes.

Keywords: General practice; Sulphonylurea; α-Glucosidase inhibitor; The Netherlands

1. Introduction

Currently, sulphonylureas are the most frequently used and recommended medication for type 2 diabetes in general practice. The Dutch guidelines for general

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practitioners are the most explicit [1], recommending as first choice a sulphonylurea in non-obese patients, when diet therapy has failed. Metformin is the first choice in obese patients, and if neither is sufficient alone, the two should be combined. Acarbose is indicated if the combination of both sulphonylurea and metformin fails, or in case of contraindications to, or adverse effects from tolbutamide or metformin. In contrast to other guidelines [2], the Dutch guidelines do not recommend the use of more than two different blood glucose lowering agents.

World-wide, most experience has been gained with tolbutamide, a first-generation sulphonylurea. The results of the controversial University Group Diabetes Program, in which increased cardiovascular morbidity was associated with the use of tolbutamide, are now not considered of clinical importance [3]. Tolbutamide causes relatively few hypoglycaemic events compared to other sulphonylureas and there is no convincing evidence that second-generation sulphonylureas are to be preferred over tolbutamide [4].

Acarbose, an inhibitor of α-glucosidase of the small intestine brush border, has a beneficial effect on postprandial blood glucose and HbA_{1c} levels. It is well established in placebo-controlled trials as both first-line treatment [5] and as an adjunct to other oral agents [6,7]. An additional advantage of acarbose may be a beneficial effect on hyperinsulinemia, a risk factor for cardiovascular disease [8].

In view of its capacity to lower postprandial blood glucose and insulin levels, acarbose might be the preferred first-line agent, provided that its glucose-lowering potential equals that of the sulphonylureas.

The results of studies comparing the glucose-lowering capacities of acarbose and a sulphonylurea are contradictory. Two trials showed a 0.4% advantage for the sulphonylurea in decreasing HbA_{1c} levels ($P = 0.03$ [9] and $P = 0.068$ [10]), one showed a 0.2% ($P = 0.07$) advantage for acarbose [11], and two more showed no difference at all (*P*-value not reported) [12,13]. None of these studies were designed as equivalence trials. In addition, postprandial insulin levels were measured in three of these studies, and acarbose treatment resulted in statistically significantly lower levels compared to sulphonylurea [9–11]. None of these studies was carried out in a primary care setting or in newly diagnosed diabetic patients.

Because of these contradictory results, we conducted a study in newly diagnosed type 2 diabetic patients in primary care to asses equivalence in the capacity of lowering HbA_{1c} levels between acarbose and tolbutamide. Secondary objectives were to compare the effects of both treatments on fasting and post-load blood glucose and insulin levels, plasma lipids, and tolerability.

2. Materials and methods

2.1. Patient selection

The study took place from April 1995 to July 1998. Forty-six general practitioners working in general practices spread throughout The Netherlands recruited patients. Not all physicians participated for the entire period of 3 years. The physicians were asked to select patients either with symptoms suggestive of diabetes mellitus and a capillary fasting blood glucose (FBG) $\geq$ 6.7 mmol/l or patients in whom a raised blood glucose level was found coincidentally. For patients without symptoms more than one abnormal fasting blood glucose was needed [14].

Patients were eligible for the trial if their FBG levels were between 6.7 and 20.0 mmol/l after an 8-week dietary treatment period (see below), and they met the following criteria: age between 40 and 70 years; and sufficient understanding of spoken Dutch to follow instructions.

Exclusion criteria were: any significant disease or condition likely to prevent patients from completing the study; uncorrected endocrine disturbances; pregnancy or breast-feeding; women of childbearing age not using contraceptives; diseases with abnormal gut motility or altered absorption of nutrients, or use of medications for such conditions; use of systemic glucocorticoids; hypersensitivity or other contraindications to acarbose or tolbutamide; habitual use of drugs or an alcohol intake > 10 units daily; lactose intolerance; participation in another experimental study; serum cholesterol > 10 mmol/l or a serum triglyceride > 4 mmol/l; use of lipid lowering agents containing ionic-substitution resins (e.g. colestipol); aspartate aminotransferase (AST)> 50 U/l, alanine aminotransferase (ALT)> 50 U/l, Gamma GT> 150 U/l;

creatinine> 150 μmol/l; myocardial infarction within the last 6 months.

All patients gave their written informed consent and the study protocol was approved by a central review board on medical ethics and was conducted in accordance with the Declaration of Helsinki.

2.2. Study design

All selected patients entered an 8-week dietary treatment period. Dietary advice tailored to individual food habits and to levels of HbA_{1c} and lipids was given by a registered dietician. This was given at two visits and followed current recommendations for type 2 diabetes mellitus. All patients who still had a FBG between 6.7 and 20 mmol/l at the end of the diet phase were randomised into the tolbutamide or the acarbose group. During the 30 weeks trial period patients visited their general practitioner seven times. At each visit the FBG was measured, and compliance, concomitant diseases or medication, and adverse events were checked. Post-load glucose, fasting and post-load insulin, lipids, and liver and kidney functions were measured 1 week before randomisation and in week 29. HbA_{1c} was measured before randomisation and in weeks 22 and 29.

In the first 6 weeks after randomisation patients received an individually titrated step-up dose of tolbutamide or acarbose. As long as the FBG exceeded 6.7 mmol/l the physician increased the dosage of the double-blind medication at 2, 4 and/or 6 weeks. The maximum dosage schedule at weeks 0, 2, 4 and 6 was for acarbose (milligrams, morning–afternoon–evening): 50–0–0, 50–0–50, 50–50–50 and 100–100–100, respectively. Similarly, for tolbutamide the scheme was 500–0–0, 500–0–500, 500–500–500 and 1000–500–500, respectively. Otherwise medication dosage was continued to the end of the trial. If FBG was > 20 mmol/l at the end of the sixth trial week patients were excluded from the study.

2.3. Randomisation and blinding

Patients entering the trial received a code provided by a computer program generating random numbers at the trial centre. Each code corresponded to one of the treatments. The clinical quality assurance manager kept the allocation schedule in a central study file not accessible to the participating general practitioners. The code was sent to the general practitioner in a sealed radio-opaque envelope that was only to be broken in case of a medical emergency. At the end of the study the envelope had to be returned unopened.

Because of the different sizes of the actual tablets it was necessary to use the so-called ‘double dummy’ technique to ensure blinding. All patients received two sets of pills, apparently acarbose and tolbutamide, but only one set contained an active substance.

2.4. Measurements

Post-load blood samples for glucose and insulin were taken 1 h after ingestion of 75 g glucose in 300 ml water. Patients were instructed to take the morning study medication after the test was completed. We chose the option of the post-load glucose test, using it as a measure of severity of the insulin-resistance syndrome. Insulin was measured by a radioimmunoassay technique (Pharmacia, Uppsala, Sweden). HbA_{1c} measurements were done by HPLC (Perkin-Elmer, series 4, reference range 4.5–6.0%, assay DCCT aligned). For cholesterol and HDL-cholesterol estimation the CHOD-PAP method on Hitachi 717 (Boehringer Mannheim, Almere, The Netherlands) was used, and for triglycerides the Peridochrom triglycerid GPO-PAP method on the same machine. Fasting and 1 h post-load glucose measurements were performed on the spot using a calibrated glucometer for capillary samples. Reference ranges for the safety parameters were: AST 8–32 U/l, ALT 8–32 U/l, Gamma GT 8–28 U/l and creatinine 56–125 μmol/l (females) and 39–103 μmol/l (males). Drug compliance was checked by pill counting, and adverse effects were assessed by history taking and, if necessary, physical examination.

2.5. Statistical analysis

The number of participants was calculated by the formula for the power of the two-sample *t*-test for equivalence [15]. Given a beta value of 20%, the formula yielded a sample size of 70 patients per treatment group.

The efficacy analysis was performed on an intention-to-treat (ITT) basis and as a per-protocol analysis

(PP). ITT analysis included all randomised patients, including those who were included in the trial in error, those with low compliance, and patients whose data were missing. Missing data were handled according to the last-observation-carried-forward principle. Patients without baseline or without both post-baseline HbA_{1c} measurements were excluded from ITT analysis. In the event of significant differences in drop-out rates, a worst-case-analysis was carried out assuming that HbA_{1c} values for drop-outs did not change from baseline values. The PP analysis included all patients who completed the protocol without any violation.

Analysis for safety was carried out for all patients who received at least one dose of the study medication.

The primary efficacy measure was defined as the decrease in HbA_{1c} levels at the end of treatment, analysed by means of co-variance (ANCOVA) with the baseline values as covariates. Therapeutic equivalence was assumed if the two-sided 90% confidence interval for the difference in mean HbA_{1c} levels between the two treatments was entirely within the range from −0.4 to 0.4%. In addition a second analysis was performed assessing the difference in proportion of patients with a reduction of $HbA_{1c} \geq 0.8\%$, taking this difference as a cut-off level for successful treatment. The decrease of 0.8% was based on expected effects of both agents as described in a recent literature overview [16].

Secondary efficacy measures were the fasting and 1 h post-load blood glucose levels; fasting and 1 h post-load insulin levels; total cholesterol, triglycerides, and HDL-cholesterol; and adverse events. Glucose, insulin, and lipid levels in the two treatment groups were also compared, by means of analysis of covariance, with baseline values as covariates. For each measure the 95% confidence interval for the difference in mean level was computed.

Differences in the occurrence of adverse events were assessed by the Cochrane–Mantel–Haenszel χ^2 test.

In the case of withdrawals before week 22, no post-baseline HbA_{1c} measurements were available. Therefore, to estimate the possible influence of withdrawal on trial results, we analysed fasting blood glucose levels in all randomised patients. Missing values were handled according to the last-observation-carried-forward principle.

3. Results

3.1. Patient flow

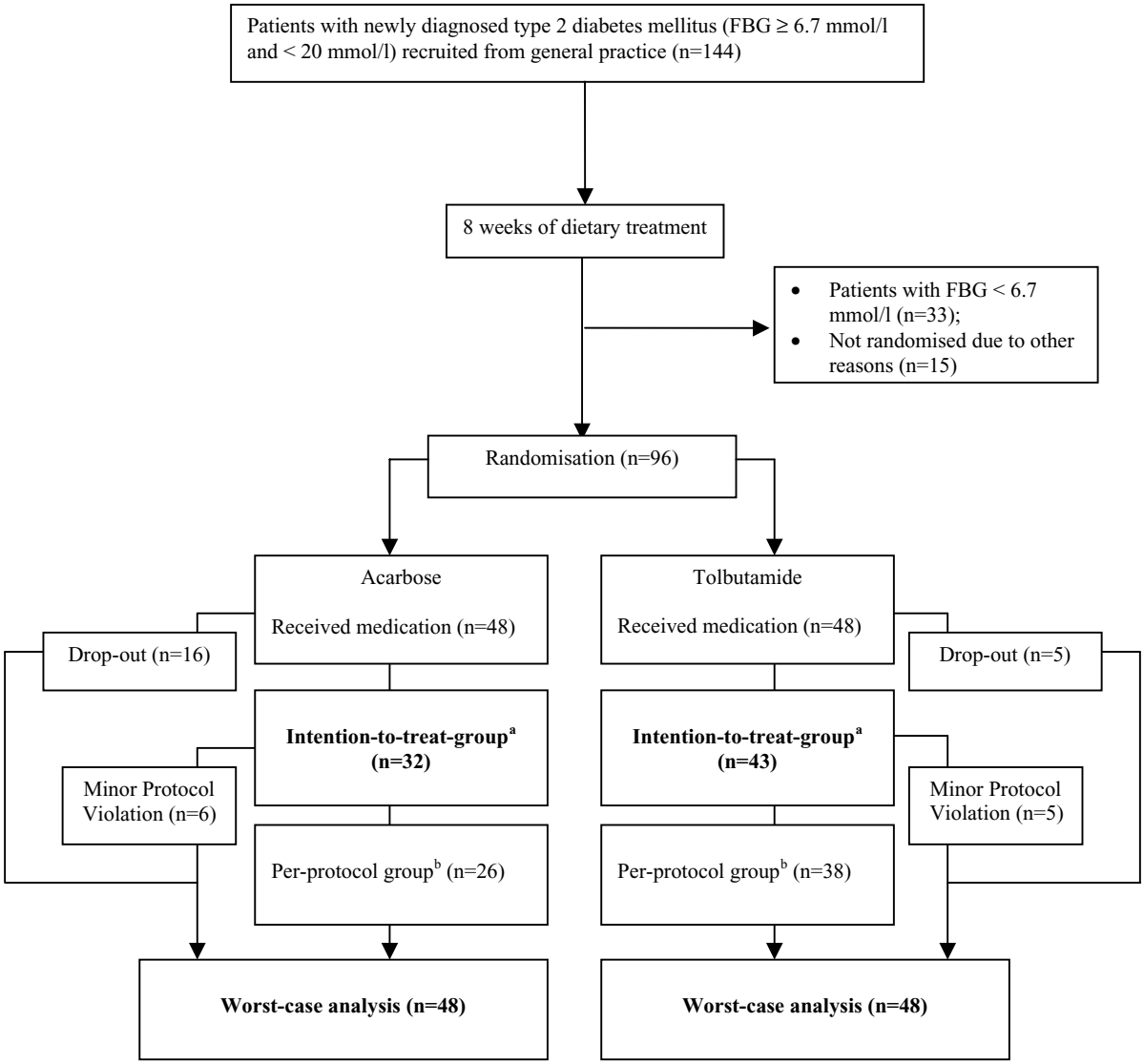
We recruited 144 subjects with newly diagnosed type 2 diabetes. Forty-eight patients did not enter randomisation because of the following reasons: FBG < 6.7 mmol/l ($n = 33$), high liver enzymes ($n = 5$), consent withdrawn ($n = 6$), FBG> 20 mmol/l ($n = 1$), protocol violation ($n = 1$), falsely included ($n = 2$). Of 96 patients that were eligible for randomisation, 48 were randomised to acarbose and 48 to tolbutamide (Fig. 1). In the acarbose group, 15 patients discontinued the study due to side effects: gastrointestinal adverse events such as flatulence, diarrhoea, abdominal pain or nausea ($n = 13$), headache ($n = 1$), not reported ($n = 1$). One patient discontinued for other, unknown, reasons. In the tolbutamide group five patients discontinued, three because of eructation, nausea and flatulence. For two patients the reason was not known. The difference between the two groups was statistically significant ($P = 0.007$).

Due to protocol deviations we excluded for the PP analysis six patients in the acarbose group (insufficient data on compliance $n = 2$, myocardial infarction $n = 1$, single FBG < 6.7 mmol/l before randomisation $n = 1$, low compliance and duodenal ulcer $n = 1$, breast carcinoma $n = 1$), and five patients in the tolbutamide group (insufficient data on compliance $n = 1$, myocardial infarction $n = 1$, cholecystitis and pancreatitis $n = 1$, randomisation code broken $n = 2$). There were no significant differences in baseline characteristics between the groups (Table 1).

In the acarbose group, 5, 4, 7, and 17 patients used 50, 100, 150 and 300 mg of acarbose respectively in the tolbutamide group, 8, 8, 7, and 20 patients used 500, 1000, 1500, and 2000 mg respectively.

3.2. Efficacy

In both groups the primary efficacy measure, HbA_{1c} percentage, decreased significantly. The decrease of HbA_{1c} levels was more pronounced with tolbutamide than with acarbose. The calculated difference in mean decrease was 0.6% (90% CI 0.3, 0.9, 95% CI 0.2, 1.0) (Table 2). By definition, equivalence would have been established if the confidence interval of the dif-



[a] Patients with at least one post-baseline HbA_{1c} measurement
[b] Patients who completed the protocol without deviations

Fig. 1. Study design and patient flow.

ference in mean decrease in HbA_{1c} concentration was between −0.4 and 0.4%. Thus, these results do not demonstrate equivalence between acarbose and tolbutamide. However, equivalence cannot be ruled out on the basis of these results, as 0.4%, the predefined lower limit of equivalence, lies within the confidence interval.

The worst-case-analysis, assuming no change in HbA_{1c} for dropouts, yielded a difference of 0.9% (90% CI 0.6, 1.2) between acarbose and tolbutamide in favour of tolbutamide. The proportion of patients with a reduction of $HbA_{1c} \geq 0.8\%$ was 17/48 (35.4%) in the acarbose group and 35/48 (72.9%) in the tolbutamide group. Drop-outs were considered to have a

Table 1
Baseline characteristics in all randomised patients, intention-to-treat and per-protocol analysis groups

	Acarbose			Tolbutamide		
	Randomised	ITT	PP	Randomised	ITT	PP
Sex (male/female)	25/23	16/16	14/12	25/23	23/20	21/17
Mean age (years)	59.3 (7.5)	58.6 (7.7)	59.0 (7.9)	57.8 (7.3)	58.6 (7.1)	58.8 (7.2)
BMI (kg/m^2)	29.1 (4.6)	29.1 (5.0)	29.0 (4.8)	28.8 (5.5)	28.7 (5.6)	28.1 (5.0)
HbA_{1c} (%)	8.1 (1.8)	7.9 (1.8)	8.0 (1.5)	8.1 (1.6)	8.2 (1.7)	8.2 (1.7)
Fasting blood glucose (mmol/l)	10.0 (2.7)	9.8 (2.5)	9.9 (1.9)	10.2 (2.7)	10.3 (2.8)	10.3 (2.8)
Glucose 1 h post-load (mmol/l)	18.8 (4.3)	18.5 (4.4)	18.8 (3.6)	18.8 (3.7)	18.8 (3.9)	18.7 (4.0)
Fasting insulin (pmol/l)	138 (64)	138 (72)	137 (65)	147 (99)	152 (103)	142 (74)
Insulin 1 h post-load (pmol/l)	405 (219)	390 (230)	379 (198)	507 (313)	515 (324)	491 (303)
Triglyceride (mmol/l)	2.4 (2.0)	2.4 (2.4)	2.5 (2.6)	2.6 (2.2)	2.7 (2.3)	2.7 (2.5)
Total cholesterol (mmol/l)	5.8 (1.0)	5.7 (1.1)	5.7 (1.2)	5.9 (1.1)	5.9 (1.7)	6.0 (1.2)
LDL cholesterol (mmol/l)	3.7 (0.8)	3.6 (0.9)	3.7 (0.9)	3.7 (0.9)	3.7 (1.0)	3.8 (0.9)
HDL cholesterol (mmol/l)	1.0 (0.2)	1.0 (0.3)	1.0 (0.3)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)

Randomised ($n = 96$): All randomised patients who took study medication. Intention-to-treat group ($n = 75$): All randomised patients with at least one post-baseline HbA_{1c} measurement. Per-protocol group ($n = 64$): All randomised patients who completed the protocol without any violations. Values are mean (standard deviation).

reduction <0.8%. This difference was statistically significant ($P < 0.001$).

Except for fasting blood glucose, all secondary measures of efficacy, including post-load insulin levels, did not differ significantly. The results from analysis on a PP basis did not differ from the results of the ITT analysis (data not displayed).

To estimate the effect of premature withdrawals, the mean difference in FBG levels in all randomised patients was calculated. The point estimate (acarbose–tolbutamide) was 1.01 mmol/l (0.29, 1.73). This result was similar to that of the ITT and PP analysis.

3.3. Safety and adverse drug reactions

Of the 96 patients who received at least one dose of the study medication, 22 (46%) patients in the acarbose treatment group and 12 (25%) patients in the tolbutamide treatment group reported 39 and 27 drug-related adverse events, respectively. The most frequently occurring drug-related adverse events were flatulence, diarrhoea, and abdominal pain or nausea. Except for the expected higher rate of flatulence in the acarbose treatment group (acarbose 27%; tolbutamide 2%), the two treatment groups had similar profiles of drug-related adverse events. There were no hypoglycaemic events reported in either treatment group.

No patients had to be excluded due to FBG> 20 mmol/l during the treatment period.

4. Discussion

Equivalence between acarbose and tolbutamide could not be established in this trial. Rather, this trial provides evidence that, when taking all aspects of treatment and side effects into account, the effects of acarbose are inferior. The result of the worst-case analysis and the more pronounced reduction of FBG values among tolbutamide users underpin this.

Further, this study shows no difference in post-load insulin levels and a statistically and clinically significant difference in adverse effects in favour of tolbutamide.

With respect to the primary efficacy measure the results of this study are in line with the results of Coniff [9] and Salman [10]. Statistical significance, however, was only established in the study of Coniff et al., which was also the only trial with tolbutamide as the sulphonylurea. The studies that report no differences or an advantage for acarbose were performed earlier and all conducted by the same group [11–13].

We found no differences in post-load insulin levels. This was surprising because such evidence as is available indicates an advantage for acarbose [9–11]. This conflicting result might be because we did not conduct full meal tolerance tests, but instead we measured post-load insulin after ingestion of 75 g glucose, without previous ingestion of the study medication. Because acarbose does not affect the absorption of

Table 2
Secondary efficacy measures

	Acarbose			Tolbutamide			Point estimate[a]	95% CI
	Baseline (S.D.)	Endpoint (S.D.)	Change (*n*; S.D.; 95% CI)	Baseline (S.D.)	Endpoint (S.D.)	Change (*n*; S.D.; 95% CI)		
HbA_{1c} (%)	7.9 (1.7)	6.8 (1.3)	−1.1 (32; 1.0; −1.4, −0.7)	8.2 (1.7)	6.4 (1.0)	−1.8 (43; 1.3; −2.2, −1.4)	0.57	0.3, 0.9[b]
FBG (mmol/l)	9.8 (2.5)	8.3 (2.5)	−1.5 (32; 2.1; −2.2, −0.7)	10.3 (2.8)	7.4 (1.7)	−2.9 (43; 2.6; −3.7, −2.1)	1.15	0.3, 2.0
BG 1 h post-load (mmol/l)	18.1 (4.1)	16.9 (3.7)	−1.2 (29; 3.9; −2.7, 0.3)	18.8 (3.9)	16.4 (3.4)	−2.2 (41; 2.8; −3.0, −1.3)	0.7	−0.6, 2.1
Fasting insulin (pmol/l)	139.5 (59.3)	134.8 (56.8)	−4.7 (28; 56.0; −26.4, 17.0)	154.9 (107.8)	151.7 (123.2)	−3.2 (35; 96.1; −36.2, 29.9)	−6.0	−45.3, 33.3
Insulin 1 h post-load (pmol/l)	385.4 (192.3)	392.9 (208.7)	7.5 (25; 136.5; −48.9, 63.8)	494.3 (324.1)	520.7 (301.2)	26.4 (35; 282.2; −70.5, 123.4)	−61.5	−172.8, 49.9
Triglycerides (mmol/l)	2.5 (2.5)	2.2 (1.2)	−0.3 (28; 1.6; −0.9, 0.3)	2.7 (2.4)	2.4 (1.9)	−0.4 (39; 2.1; −1.0, 0.3)	−0.1	−0.7, 0.6
Total cholesterol (mmol/l)	5.5 (0.9)	5.7 (1.0)	0.1 (28; 0.5; −0.1, 0.3)	6.0 (1.1)	6.0 (1.2)	0.0 (39; 0.7; −0.2, 0.2)	0.1	−0.2, 0.4
LDL-cholesterol (mmol/l)	3.5 (0.6)	3.6 (0.8)	0.1 (27; 0.4; −0.1, 0.3)	3.8 (1.0)	3.7 (0.8)	−0.1 (38; 0.7; −0.3, 0.2)	0.1	−0.2, 0.4
HDL-cholesterol (mmol/l)	1.0 (0.2)	1.1 (0.3)	0.1 (28; 0.2; 0.0, 0.2)	1.1 (3.1)	1.2 (0.3)	0.1 (38; 0.4; 0.0, 0.2)	−0.1	−0.2, 0.1

ITT analysis $n = 75$. Values are mean (standard deviation).

[a] Calculated by analysis of covariance (ANCOVA) with baseline values as covariates.

[b] 90% CI, 95% CI 0.2, 1.0.

simple carbohydrates like glucose, ingestion of acarbose prior to a glucose tolerance test would not have influenced the normal insulin rise. We also found no evidence that treatment with acarbose offers advantages over tolbutamide with respect to glucose tolerance, fasting insulin levels, and insulin response.

In contrast to previous studies, adverse effects were a major cause for discontinuation, especially in the acarbose group. One of the reasons for this remarkable discrepancy might be the increase in dosage from 150 to 300 mg, which could be too rapid. Also, the setting of the study may have been contributed to the large number of dropouts. Comparable studies were performed in hospitals or specialised diabetes centres with more opportunities to monitor and motivate participating patients. The general practitioners who treated patients in our study probably had only limited time to motivate patients who experienced adverse gastrointestinal effects. Although the high number of withdrawals is disappointing for the investigators, it demonstrates everyday practice and is therefore a valuable outcome, which hampers the long-term treatment of at least one in every three patients. By calculating the outcome for fasting blood glucose in all randomised patients we showed that it is unlikely that these withdrawals affected the primary endpoint.

We could not achieve the number of patients required by the power calculation. To estimate the influence of insufficient power, we recalculated the difference in mean HbA1c using 70 patients per treatment group, assuming the same statistical distribution. This resulted in a 90% confidence interval of 0.3, 0.8. Thus, even if the patient numbers called for by the power calculation had been met, a statistically significant outcome was not sure. This was also true for the secondary efficacy measures.

Because about 75% of all type 2 diabetic patients in The Netherlands are treated by general practitioners, our findings represent the main patient population treated for diabetes mellitus. To our knowledge there is no previous study conducted in a similar setting: this makes comparison with other reports insecure. The literature does not provide unequivocal results that allow drawing unambiguous conclusions. Nevertheless, this study may be a guide to judging the usefulness of acarbose in general practice by its true merits.

To conclude, we found no evidence to challenge the current policy of giving a sulphonylurea as the first treatment of choice for type 2 diabetes in general practice. The relatively low cost of sulphonylureas compared to acarbose together with a favourable safety profile, underlines this policy. Acarbose remains a rational alternative, however, when a sulphonylurea fails, or as an addition to other drug therapy.

For a definite answer to our primary question, we strongly recommend a meta-analysis of our results together with those of previous studies.

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