

# $\alpha$ -Glucosidase Inhibitors for Patients With Type 2 Diabetes

Results from a Cochrane systematic review and meta-analysis

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**OBJECTIVE** — To review the effects of monotherapy with  $\alpha$ -glucosidase inhibitors (AGIs) for patients with type 2 diabetes, with respect to mortality, morbidity, glycemic control, insulin levels, plasma lipids, body weight, and side effects.

**RESEARCH DESIGN AND METHODS** — We systematically searched the Cochrane Central register of Controlled Trials, MEDLINE, EMBASE, Current Contents, LILACS, databases of ongoing trials, and reference lists, and we contacted experts and manufacturers. Inclusion criteria were randomized controlled trials of at least 12 weeks' duration, AGI monotherapy compared with any intervention, and one of the following outcome measures: mortality, morbidity, GHb, blood glucose, lipids, insulin levels, body weight, or side effects. Two independent reviewers assessed all abstracts, extracted all data, and assessed quality. We contacted all authors for data clarification. Continuous data were expressed as weighted mean differences and analyzed with a random-effects model. Possible influences of study characteristics and quality were assessed in sensitivity and meta-regression analyses.

**RESULTS** — Forty-one studies were included in the review (30 acarbose, 7 miglitol, 1 voglibose, and 3 combined), and heterogeneity was limited. We found no evidence for an effect on mortality or morbidity. Compared with placebo, AGIs had a beneficial effect on GHb (acarbose  $-0.77\%$ ; miglitol  $-0.68\%$ ), fasting and postload blood glucose and postload insulin. With acarbose dosages higher than 50 mg t.i.d., the effect on GHb was the same, but the occurrence of side effects increased. Acarbose decreased the BMI by 0.17 kg/m<sup>2</sup> (95% CI 0.08–0.26). None of the AGIs had an effect on plasma lipids. Compared with sulfonylurea, AGIs seemed inferior with respect to glycemic control, but they reduced fasting and postload insulin levels. For comparisons with other agents, little data were available.

**CONCLUSIONS** — We found no evidence for an effect on mortality or morbidity. AGIs have clear beneficial effects on glycemic control and postload insulin levels but not on plasma lipids. There is no need for dosages higher than 50 mg acarbose t.i.d.

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Additional information for this article can be found in an online appendix at <http://care.diabetesjournals.org>.

**Abbreviations:** AGI,  $\alpha$ -glucosidase inhibitor.

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

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**A**lpha-glucosidase inhibitors (AGIs; acarbose, miglitol, voglibose) are widely used in the treatment of patients with type 2 diabetes. AGIs delay the absorption of carbohydrates from the small intestine and thus have a lowering effect on postprandial blood glucose and insulin levels.

In modern medicine, the efficacy of an intervention should be investigated in well-designed randomized trials. Results from the trials should be collected in a high-quality systematic review, if possible with a meta-analysis. And finally, the evidence should have its repercussions on practice guidelines.

How does this apply for AGIs? Recommendations on when to use AGIs and the evidence used for these recommendations appear to be different in various guidelines. For example, the guideline by the European Diabetes Policy Group (1) and a consensus statement by the American Diabetes Association (2) are not very specific. They mention the possible use of AGIs as a first-line agent or in combination with other antihyperglycemic drugs, but they don't offer a more precise judgment, and literature references are not given. The Dutch guidelines are more explicit about the use of AGIs. They advise using acarbose only when other agents are contraindicated, and references are provided with this advice (3). The guidelines of the Royal College of General Practitioners in the U.K. reach similar recommendation as the Dutch. These guidelines are based on a systematic review of the literature. For AGIs, the advice is based on 1 review article and 17 additional trials, with acarbose both as monotherapy and as additional therapy (4).

In recent years, literature reviews focused exclusively on acarbose or miglitol. Voglibose has not been subject to a literature review. It is difficult to value the results of these reviews because all have methodological weaknesses: no description of search strategy and inclusion criteria (5–7), no report of search results (5–9), and they either lack or have an unclear

quality assessment of the included studies (5–9). In general, all reviews reported beneficial effects on glycemic control. One review reported results from a meta-analysis by calculating the mean effect from 13 trials with acarbose (GHb  $-0.90\%$ ; fasting blood glucose  $-1.3$  mmol/l; postprandial blood glucose  $-3.0$  mmol/l) (7). Although generally assumed, the existence of a dose dependency of the effect could not be concluded from these reviews.

A review on the effect of oral antihyperglycemic agents on serum lipids in patients with type 2 diabetes found beneficial effects of acarbose on HDL and LDL cholesterol and a decreasing effect of voglibose on triglycerides (10). However, a meta-analysis was not performed. Another study of very recent data concluded from a meta-analysis of seven trials that acarbose reduces the incidence of myocardial infarctions in patients with type 2 diabetes (11). However, this study was subject to publication bias, heterogeneity, detection bias, and confounding factors (12).

We conducted a systematic literature review and meta-analyses within the framework of the Metabolic and Endocrine Disorders Review Group of the Cochrane Collaboration. Our main research focused on the effects of AGI versus placebo (or any other intervention) with respect to 1) mortality and (diabetes-related) morbidity; 2) glycemic control, plasma lipids, insulin levels, and body weight; and 3) side effects.

## RESEARCH DESIGN AND METHODS

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Current Contents, LILACS, and reference lists of reviews on the topic, and we contacted manufacturers and experts for additional (unpublished) trials. In addition, we searched databases of ongoing trials on the Internet. The last systematic search was in December 2003 for Current Contents and in April 2003 for the other databases.

For MEDLINE, we combined the search strategies for “type 2 diabetes mellitus” and “randomized controlled trials” that we adapted from the Review Group (13) and combined these with a combination of the Medical Subject Headings key word “acarbose” and all different spellings for AGIs and their brand names.

This strategy had to be slightly adapted for EMBASE and Current Contents, making the search more sensitive. For the other databases, we searched with the words for AGIs only, because these databases already included controlled trials only (CENTRAL, databases of ongoing trials) or because its browser didn't allow complex searches (LILACS).

Studies had to meet five inclusion criteria: 1) inclusion of patients with type 2 diabetes that received no other antidiabetic medication (when both patients with and without additional antidiabetic medication were included, the results for the latter (sub)group should be well presented); 2) a duration of at least 12 weeks; 3) intervention with an AGI; 4) random allocation to the comparison groups; and 5) at least one of the following outcome measures: mortality, morbidity, quality of life, glycemic control, insulin or C-peptide levels, lipids, body weight, or adverse effects.

When a study could not be excluded on the basis of title or abstract alone, it was included and retrieved for further scrutiny. Two independent reviewers read all titles and abstracts. Interrater agreement was calculated by  $\kappa$  statistics.

## Data extraction and quality assessment

The same two independent reviewers extracted all data and assessed quality. For data extraction we used an adapted version of a form provided by the Review Group. We extracted the following aspects: general items (e.g., setting, sponsoring, ethical approval), design (parallel or cross-over, method of randomization, blinding), participants (e.g., diagnostic criteria, inclusion and exclusion criteria), interventions (e.g., dietary reinforcement, dosage schedules), baseline characteristics (e.g., age, sex, GHb), and outcomes (e.g., occurrence of mortality, changes in blood glucose and measures of variance). We attempted to contact authors in the case of missing information or uncertainties. If necessary, we also extracted data from graphical figures.

Differences in opinion between the reviewers were resolved by consensus, by referring back to the original data, or by consulting a third reviewer in case of persisting disagreement.

We assessed and scored the following quality items as being adequate or inadequate/unclear (14,15): randomization

and allocation concealment (referring to selection bias), blinding (performance bias), and handling of dropouts (attrition bias). For studies that had morbidity or quality of life as main end points, the method of blinding outcome assessment was also assessed (detection bias).

## Data analysis

Available data of sufficient quality were summarized statistically and used for meta-analyses. We first divided the data into all possible comparisons (e.g., acarbose versus placebo, voglibose versus sulfonylurea) and then subdivided them into all possible outcomes (e.g., death, GHb). Finally, within the outcomes, we made subgroups for the different dosages. Outcomes were calculated per subgroup and for all subgroups together.

Dichotomous data were expressed as odds ratios and continuous data as weighted mean differences; the overall results were calculated with the random-effects model. The measures of effect for all continuous variables were the differences from baseline to end point. When the SDs for these differences were missing, we first contacted the authors for these additional data. If these data were not provided, we calculated the SD of the difference with the following formula (14):

$$SD_{\text{paired difference}} = \sqrt{[(SD_{\text{pretreatment value}})^2 + (SD_{\text{posttreatment value}})^2 - 2 \times r \times SD_{\text{pretreatment value}} \times SD_{\text{posttreatment value}}]}$$

We used a conservative correlation coefficient ( $r$ ) of 0.4.

Heterogeneity was assessed by a visual inspection of the forest plots first. In addition, we used Z score and  $\chi^2$  statistics. We also used funnel plots to test for possible small study bias. Sensitivity analyses were performed to investigate the possible influence of the predefined quality criteria (14,15), language of publication, country, source of funding, and statistical model (random- versus fixed-effects models). Furthermore, we performed subgroup and meta-regression analyses for baseline GHb, mean age, sex, duration of diabetes, duration of intervention, use of a step-up dosage schedule, and use of a fixed dose versus an individually titrated scheme.

We used Revman 4.2.3 (Cochrane Collaboration, Oxford, U.K.) for all analy-

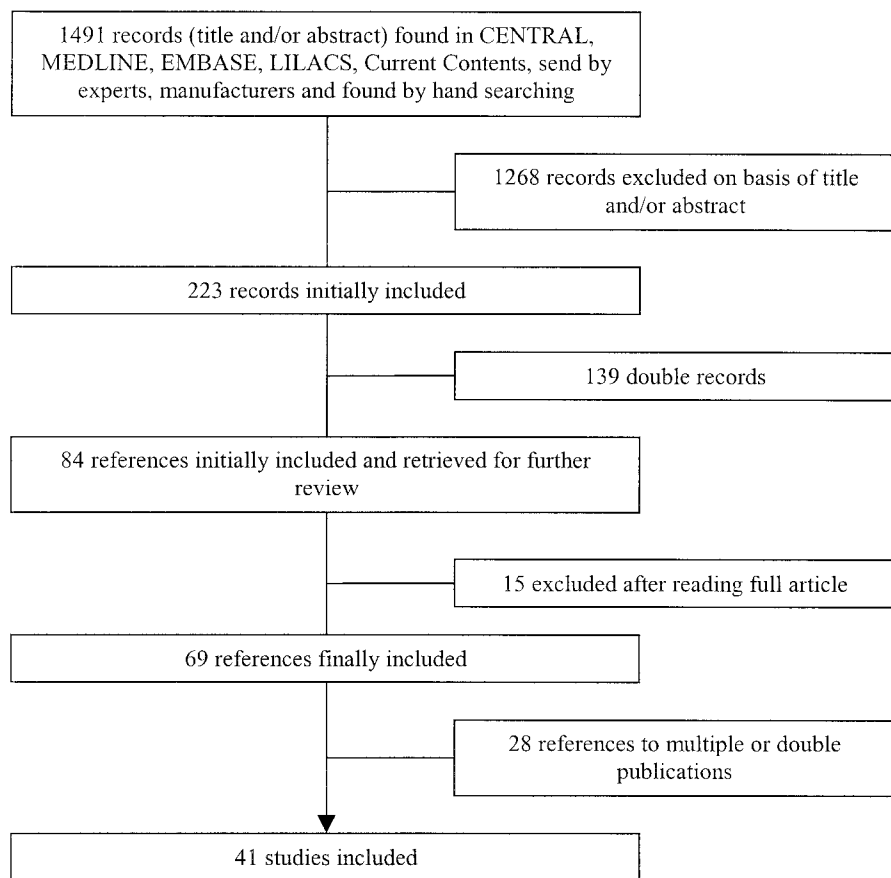


Figure 1—Study flow diagram.

ses, except for meta-regression analyses, which were done with SAS Proc Mixed (version 8.0).

**RESULTS**— Interrater  $\kappa$  for agreement on inclusion read by the two reviewers was 0.74 (95% CI 0.67–0.81). All differences in opinion were resolved by consensus. We included 41 studies in the systematic review (Fig. 1) (16–56). Fifteen studies were excluded after reading the full article. Eleven studies investigated the use of AGIs in addition to other antidiabetic therapy, and there was no clear report of a diet-only subgroup (57–67). Two studies had a duration less than 12 weeks (68,69), one study was not randomized (70), and one study included patients with impaired glucose tolerance (71). In addition, we found three trials in registers of ongoing trials (72–74), but we were not able to obtain published or unpublished reports.

The main study characteristics are listed in Table 1. All but three studies (33,36,38) showed one or more defi-

ciency or insufficient reporting of the main quality criteria. Pharmaceutical companies sponsored 33 studies, 2 studies were sponsored by another fund, 1 study was not sponsored, and possible sponsoring was unclear for 5 studies. We attempted to contact all authors for data clarification, which led to additional data for 22 studies.

#### Effects on mortality and morbidity

Three studies reported mortality and found no differences between treatment groups (24,37,40). The trial performed within the United Kingdom Prospective Diabetes Study (UKPDS) reported prospectively collected data concerning “any diabetes-related endpoint” and microvascular disease. The relative risks for acarbose compared with placebo were 1.00 (95% CI 0.81–1.23) and 0.91 (95% CI 0.61–1.35), respectively. Another study with miglitol found statistically significant less cardiovascular events in the miglitol-treated patients than in patients treated with glyburide (17 vs. 29%), but

these outcomes were derived from the safety data and not collected in a well-defined and prospective way (40).

#### Meta-analyses

Most data for meta-analyses were available from studies with acarbose. The main overall results are summarized in Table 2.

#### Glycemic control

Compared with placebo, acarbose decreased GHb by 0.77% (95% CI 0.64–0.90) (online appendix A [available at <http://care.diabetesjournals.org>]) and miglitol by 0.68% (95% CI 0.44–0.93), respectively. For voglibose, only one study was available, which yielded a difference of 0.47% in favor of voglibose (95% CI 0.31–0.63) (43). With respect to GHb, we found no evidence for a dose dependency for acarbose in the range from 50 to 300 mg t.i.d.. The subgroup analyses for acarbose 50, 100, 200, and 300 mg t.i.d. showed a decrease in GHb of 0.90, 0.76, 0.77, and 0.78%, respectively (online appendix A). In contrast, for miglitol, such a dose dependency seemed to be present; miglitol 25, 50, 100, and 200 mg t.i.d. decreased GHb by 0.46, 0.58, 0.79, and 1.26%, respectively. However, the results from this meta-analysis are based on seven comparisons, of which four were derived from one (multiarm) trial (28).

In the subgroup analysis and meta-regression analyses, we found a tendency toward a larger effect on GHb of acarbose at higher baseline levels for GHb. The subgroup analyses for studies with baseline GHb <7%, 7–9%, and >9% yielded a decrease in GHb of 0.56% (95% CI 0.36–0.76), 0.78% (95% CI 0.63–0.93), and 0.93% (95% CI 0.53–1.33), respectively. In the meta-regression analysis with the effect on GHb as dependent and baseline GHb as an independent variable, we found a regression coefficient of  $-0.12$  (95% CI  $-0.26$  to  $0.03$ ), indicating an extra 0.12% GHb decrease for every 1% higher baseline GHb.

The subgroup analysis for study duration indicated that long-term studies (more than 24 weeks) showed less effect on GHb. The decrease in GHb for studies with a duration of less than 24 weeks, equal to 24 weeks, and more than 24 weeks was 0.77% (95% CI 0.61–0.93), 0.82% (95% CI 0.63–1.01), and 0.53% (95% CI 0.20–0.87), respectively. This was mostly due to the data from the

Table 1—Characteristics of 41 randomized controlled trials of at least 12 weeks' duration, comparing AGIs with any other intervention

Ref.	Design,* location, setting	Duration (weeks)	Random- ization†	Allocation conceal- ment†	Blind- ing†	Handling of dropouts†	Patients random- ized (n)	Mean age (years)	Female (%)	Mean duration diabetes (months)	Interventions
16	Germany, GP	24	B	B	A	B	152	60.5‡	41.9‡	16.5‡	ACA 100 mg t.i.d., PLA
17	Scotland, OP	16	B	B	B	B	28	58.7‡	30.0‡	48.0‡	ACA max. 200–100– 200 mg (decreased with intolerance), PLA
18	Spain, OP	16	B	B	A	B	40	ND	ND	ND	ACA 100 mg t.i.d., PLA
19	United King- dom, GP	156	A	B	A	B	789	62.0‡	34.9‡	38.1‡	ACA 50 mg t.i.d., ACA 100 mg t.i.d., PLA
20	Asia, OP	24	B	B	A	A	126	53.4	49.2	28.8	ACA 100 mg t.i.d., PLA
21	Canada, OP	52	B	B	B	B	77§	57.2	37.7	62.4	ACA max 200 mg t.i.d. (titrated), PLA
22	Canada, OP	36	B	B	A	A	324	58.1	25.9	55.0	MIG 100 mg t.i.d., met- formin 500 mg t.i.d., PLA (combination of MIG and metformin)
23	U.S., OP	24	A	A	A	A	212	55.8‡	50‡	65.5‡	ACA max 300 mg t.i.d. (titrated), PLA
24	U.S., OP	24	A	A	A	A	290	56.5	51‡	70.9	ACA 200 mg t.i.d., tol- butamide max 1,000 mg t.i.d. (titrated), PLA (combination ACA and tolbutamide)
25	U.S., OP	16	A	A	A	B	290	55.4	43	66	ACA 100 mg t.i.d., ACA 200 mg t.i.d., ACA 300 mg t.i.d., PLA
26	Russia, OP	24	B	B	B	B	180	51.0‡	62.1‡	ND	ACA 100 mg t.i.d., PLA
27	Switzerland, OP	16	B	B	B	B	17	ND	30.0	26	ACA 50 mg b.i.d., PLA
28	The Nether- lands, GP/ “study centres”	24	B	A	A	B	599	63.4‡	45.1‡	40.0‡	MIG 25 mg t.i.d., MIG 50 mg t.i.d., MIG 100 mg t.i.d., PLA
29	Europe, OP	24	A	A	A	B	495	56.6‡	47.1‡	21.7‡	ACA 25 mg t.i.d., ACA 50 mg t.i.d., ACA 100 mg t.i.d., ACA 200 mg t.i.d., PLA
30	No blinding, Germany, OP	24	A	B	—	A	96	61.5	58.9	26.5	ACA 100 mg t.i.d., glib- enclamide max 3.5 mg t.i.d. (titrated)
31	Crossover, Italy, OP	12	B	B	B	B	76	ND	76.7	110.4	ACA 100 mg t.i.d., PLA
32	Germany, OP	16	B	B	B	B	77	58.7	48.1	80.0	ACA 100 mg t.i.d., glib- enclamide 1 mg t.i.d., PLA
33	Germany, OP	24	A	A	A	A	100	59.5‡	48.9‡	59.5‡	ACA 100 mg t.i.d., PLA
34	Crossover, Ger- many, OP	12	B	B	B	B	18	ND	ND	ND	ACA 200 mg b.i.d., MIG 200 mg b.i.d., gliben- clamide 7 mg q.d.
35	Single blind (for gliben- clamide), Germany, OP	24	A	A	A	B	96	58.5‡	55.3‡	14.0‡	ACA 100 mg t.i.d., glib- enclamide max 3.5 mg t.i.d. (titrated)
36	Single blind (for metformin), Germany, OP	24	A	A	A	A	96	58.4‡	66.0‡	35.1‡	ACA 100 mg t.i.d., met- formin 850 mg b.i.d., PLA

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Table 1—Continued

Ref.	Design,* location, setting	Duration (weeks)	Random- ization†	Allocation conceal- ment†	Blind- ing†	Handling of dropouts†	Patients random- ized (n)	Mean age (years)	Female (%)	Mean duration diabetes (months)	Interventions
37	England, OP	156	A	A	A	B	256 <sup>§</sup>	60.5	28.9	87.2	ACA 100 mg t.i.d. (de- creased in case of intolerance), PLA
38	Germany/ France/ Spain, OP	24	A	A	A	A	179	62.4	35.2	58.5	ACA 100 mg t.i.d. (de- creased in case of intolerance), nateglin- ide 120 mg t.i.d.
39	Japan, OP	24	B	A	A	B	40	48.9‡	24.3‡	56.4‡	ACA 100 mg t.i.d., PLA
40	U.S., OP	56	B	B	A	A	411	67.8‡	32.4‡	64.4‡	MIG 25 mg t.i.d., MIG 50 mg t.i.d., gly- buride max 20 mg q.d. (titrated), PLA
41	U.S., OP	52	B	B	B	B	69 <sup>§</sup>	ND	ND	ND	MIG max. 200 mg t.i.d. (decreased in case of intolerance), PLA
42	U.S., OP	28	B	B	B	A	45 <sup>§</sup>	56.6‡	42.2‡	49.6‡	MIG 100 mg t.i.d. (de- creased in case of intolerance), PLA
43	Japan, setting unclear	12	B	B	B	B	445	ND	ND	ND	MIG 50 mg t.i.d., VOG 0.2 mg t.i.d., PLA
44	Single blind (for gliben- clamide), OP	24	B	A	A	A	102	57.8	53.9	54	ACA 100 mg t.i.d., glib- enclamide max. 3.5 mg t.i.d. (titrated), PLA
45	Canada, OP	52	B	B	B	A	192	70.0	34.9	63.4	ACA max. 100 mg t.i.d. (titrated), PLA
46	Canada, OP	24	B	A	A	A	100	58.0‡	40.6‡	71.8‡	MIG 100 mg t.i.d., glib- enclamide mg b.i.d. (+1 PLA)
47	No blinding, Germany, GP	24	A	B	—	B	76	57.5	ND	27.7	ACA 100 mg t.i.d., glib- enclamide max. 10.5 mg in two doses (ti- trated)
48	Europe, setting unclear	24	B	B	B	B	603	ND	ND	ND	ACA 100 mg t.i.d., MIG 50 mg t.i.d., MIG 100 mg t.i.d., PLA
49	No blinding, Turkey, OP	24	A	A	—	B	72	54.4‡	42.1‡	53.6‡	ACA max. 100 mg t.i.d. (may be reduced), gliclazide 80 mg b.i.d. (in general, max. dose not recommended)
50	Italy, OP	16	A	B	B	B	84	55.8‡	35.9‡	51.5‡	ACA 50 mg t.i.d., ACA 100 mg t.i.d., PLA
51	New Zealand/ Australia, OP	16	B	A	A	B	105	56.5	36	23.5	ACA 100 mg t.i.d. (de- creased in case of intolerance), PLA
52	Europe, OP	24	B	B	A	B	201	58.7‡	42‡	ND	MIG 100 mg t.i.d., glib- enclamide 3.5 mg q.d. (or b.i.d. when hypoglycemia was unacceptable)
53	No blinding, Germany, OP	24	A	B	—	B	72	59.5‡	60‡	ND	ACA 100 mg t.i.d., glib- enclamide max. 3.5 mg (titrated)

*Continued on facing page*

Table 1—Continued

Ref.	Design,* location, setting	Duration (weeks)	Random- ization†	Allocation conceal- ment†	Blind- ing†	Handling of dropouts†	Patients random- ized (n)	Mean age (years)	Female (%)	Mean duration diabetes (months)	Interventions
54	No blinding, Japan, OP	12	B	B	—	B	36	50.5	28‡	0	VOG 0.3 mg t.i.d., gly- buride 1.25 mg q.d., diet therapy
55	The Nether- lands, GP	30	A	A	A	B	96	58.6	48	0	ACA max. 100 mg t.i.d. (titrated), tolbutamide max. 2,000 mg in 3 doses (titrated)
56	China, OP	24	B	B	B	A	77	49.3	48	49.8	ACA 100 mg t.i.d., PLA

\*Except when indicated, all studies were parallel and double blind. †A, adequate; B, inadequate, unclear. ‡All values except these are based on all randomized patients. §Subgroup of patients treated with diet only. ||Based on proportion of patients in analysis; number of patients randomized in diet-only group not reported. ACA, acarbose; GP, general practice; MIG, miglitol; ND, no available data; OP, outpatient; PLA, placebo; VOG, voglibose.

UKPDS (duration 156 weeks), in which a decrease of only 0.19% on GHb was found (95% CI  $-0.29-0.67$ ) (37).

In the subgroup and meta-regression analyses, we also found that the application of a fixed dosage scheme and the absence of a step-up dosage scheme increased the effect on glycemic control but also increased the occurrence of side effects (data not shown).

For acarbose, fasting blood glucose decreased by 1.09 mmol/l (28 comparisons; 95% CI 0.83–1.36), for miglitol by 0.52 mmol/l (2 comparisons; 95% CI 0.16–0.88), and for voglibose by 0.60 mmol/l (1 comparison; 95% CI 0.23–0.97). One-hour postload glucose decreased by 2.32 mmol/l (acarbose; 22 comparisons; 95% CI 1.92–2.73), 2.70 mmol/l (miglitol; 2 comparisons; 95% CI  $-0.14$  to 5.54), and 2.40 mmol/l (voglibose; 1 comparison; 95% CI 1.83–2.97). In contrast to the outcome for GHb, acarbose showed a dose-dependent decrease of postload glucose. Acarbose 50, 100, 200, and 300 mg t.i.d. reduced postload glucose by 1.63, 2.26, 2.78, and 3.62 mmol/l, respectively (online appendix B).

Data from studies that compared AGI with other blood glucose lowering interventions were scarce. Pooling of results was only possible for the comparison of acarbose with sulfonylurea. The overall comparison of acarbose with sulfonylurea yielded a nonsignificant advantage for sulfonylurea with respect to overall GHb of 0.38% (data not shown; online appendix C). However, seven of the studies in the meta-analyses used unequal comparators, because they compared a fixed dose of acarbose with individually adjusted

dosages of sulfonylurea (24,30,35, 44,47,49) or a usual dose of acarbose with a very low dose of glibenclamide (32). The results for the subgroup “acarbose 100 mg versus glibenclamide 3.5 mg” were not consistent with the other comparisons. This discrepancy remained unexplained. Leaving this subgroup out of the meta-analysis yielded an overall effect of 0.63% (95% CI 0.26–1.00) in favor of sulfonylurea. In the same comparison, outcomes for the meta-analyses for fasting and 1-h postload blood glucose were 0.69 mmol/l in favor of sulfonylurea (95% CI 0.16–1.23) and 0.10 mmol/l in favor of acarbose (95% CI  $-0.43$  to 0.22) (37).

#### Insulin levels

Compared with placebo, acarbose had no effect on fasting insulin levels and a lowering effect on 1-h postload insulin levels of 40.8 pmol/l (95% CI 21.0–50.6). For miglitol and voglibose, only a limited number of comparisons were available, and no statistically significant effects were found (Table 2).

Compared with sulfonylurea, acarbose had a statistically significant decreasing effect on fasting insulin of 24.8 pmol/l (7 comparisons; 486 participants; 95% CI 6.3–43.3) and 1-h postload insulin of 133.2 pmol/l (7 comparisons; 483 participants; 95% CI 81.8–184.5) (Table 2).

#### Plasma lipids

Meta-analyses were only possible for studies with acarbose. We found a small effect of  $-0.09$  mmol/l for acarbose on triglycerides that was borderline statistically significant (95% CI  $-0.18$  to 0.00;  $P = 0.06$ ). The effect on triglycerides be-

came smaller and lost statistical significance in the sensitivity analysis excluding studies with inadequate randomization and the analyses excluding studies with high total and selective drop-out rates. No other effects on other lipids were found.

#### Body weight

We found that acarbose had a statistically significant decreasing effect on BMI of 0.17, but the effect on the outcome “body weight” was not statistically significant (Table 2). We found no beneficial effects on body weight for acarbose compared with sulfonylurea.

#### Adverse events

We used the total number of patients that experienced at least one adverse event. Most studies reported that gastrointestinal events occurred most frequently. But for most reports, the definitions were insufficiently similar to be used for meta-analysis.

Compared with placebo, patients treated with acarbose had significantly more side effects (OR 3.37; RR 1.43) (Table 2). There was a dose-dependent increase in adverse events in the 25- to 200-mg t.i.d. range. This relationship was even more clear when the subgroup of studies that applied a fixed dose (in contrast to an individually titrated dose) was analyzed (ORs of 1.95, 4.12, 6.97, and 8.31 for 50, 100, 200, and 300 mg acarbose t.i.d., respectively). Results for miglitol were similar (OR 4.01) (Table 2).

Sensitivity analyses were performed for the comparison of acarbose versus placebo only. As for the other comparisons, the number of included studies was too

Table 2—Results of overall meta-analysis for the comparison of acarbose and miglitol versus placebo and sulfonylurea

Outcome	Placebo-controlled studies						Sulfonylurea-controlled studies					
	Acarbose			Miglitol			Acarbose			Miglitol		
	Comp, part*	Effect size†	95% CI	Comp, part*	Effect size†	95% CI	Comp, part*	Effect size†	95% CI	Comp, part*	Effect size†	95% CI
GHb (%)	28, 2,831	-0.77	-0.90-0.64	7, 1,088	-0.68	-0.93-0.44	8, 596	0.38	-0.02-0.77	1, 90	0.40	-0.16-0.96
Fasting blood glucose (mmol/l)	28, 2,838	-1.09	-1.36-0.83	2, 398	-0.52	-0.88-0.16	8, 596	0.69	0.16-1.23	1, 90	0.27	-0.74-1.28
1-h postload blood glucose (mmol/l)	22, 2,238	-2.32	-2.73-1.92	2, 398	-2.70	-5.54-0.14	8, 591	-0.10	-0.43-0.22	1, 88	-0.60	-3.43-2.23
Fasting insulin (pmol/l)	15, 1,264	-0.5	-7.9-6.9	1, 162	-18.2	-57.0-20.6	7, 486	-24.8	-43.3-6.3	1, 90	-44.8	-53.7-35.8
1-h postload insulin (pmol/l)	13, 1,050	-40.8	-60.6-21.0	2, 398	-16.6	-39.2-6.0	7, 483	-133.2	-184.5-81.8	ND	ND	ND
Total cholesterol (mmol/l)	23, 2,133	0.00	-0.10-0.09	ND	ND	ND	7, 499	-0.09	-0.23-0.05	1, 88	0.08	-0.29-0.45
HDL cholesterol (mmol/l)	14, 924	0.00	-0.04-0.04	ND	ND	ND	7, 485	0.02	-0.02-0.06	1, 86	-0.01	-0.26-0.24
LDL cholesterol (mmol/l)	4, 402	-0.08	-0.41-0.25	ND	ND	ND	4, 312	0.10	-0.07-0.27	ND	ND	ND
Triglycerides (mmol/l)	21, 1,969	-0.09	-0.18-0.00	ND	ND	ND	8, 591	0.01	-0.18-0.20	1, 89	-0.04	-0.40-0.32
Body weight (kg)	16, 1,451	-0.13	-0.46-0.20	1, 162	0.27	-0.50-1.04	5, 397	-1.90	-4.01-0.21	1, 90	0.46	-0.48-1.40
BMI (kg/m <sup>2</sup> )	14, 1,430	-0.17	-0.25-0.08	ND	ND	ND	4, 230	-0.39	-0.83-0.05	ND	ND	ND
Occurrence of any side effect	23, 3,819	3.37	2.60-4.36	7, 1,304	4.01	1.69-9.52	7, 607	3.95	2.00-7.80	2, 232	1.29	0.69-2.41

Continuous data are expressed as weighted mean differences; occurrence of side effects is expressed as odds ratio. Results are calculated with a random-effects model. \*Number of comparisons (comp), participants (part). †A negative value indicates an advantage for acarbose or miglitol. ND, no available data.

low. In the sensitivity analyses, we found very few statistically significant results. Studies with inadequate or unclear randomization showed, in contrast to studies with adequate randomization, a statistically significant beneficial effect on total cholesterol: -0.25 (95% CI -0.47 to -0.03) vs. 0.04 (95% CI -0.06 to 0.14). Studies with a high drop-out rate showed no statistically significant effect on post-load insulin levels. Non-European studies showed a more profound effect on post-load glucose levels. Repeating the analyses with a fixed-effects model yielded a statistically significant decrease in fasting insulin and body weight.

**CONCLUSIONS**— In this systematic review of 41 randomized studies on the efficacy of AGIs, we have found no evidence for a beneficial effect on morbidity or mortality. In meta-analyses we found statistically significant effects on GHb and fasting blood glucose (acarbose and miglitol), postload glucose and insulin levels, and BMI (acarbose). The effect on GHb was more profound in studies with higher baseline values for GHb, and we found evidence that this effect was less in studies that lasted longer than 6 months. We found no effects on fasting insulin levels and lipids and only minor effects on body weight. There was no increase in effect on GHb for acarbose dosages higher than 50 mg t.i.d. In general, most evidence and the best results were found for acarbose. Comparisons with other drugs were limited and mostly hampered by unequal comparators.

With respect to the effect on glycemic control, the results from our review are roughly in line with previous reviews. But there are significant differences and additional findings. First, we found evidence for a dose-dependent effect on fasting and postload blood glucose but not for GHb. This remarkable finding might be explained by a lower compliance of patients that received higher dosages. After all, occurrence of side effects increased with higher dosages, and the effect of a lower compliance will probably hardly affect fasting and postload blood glucose because patients will not “forget” their medication before a study visit. Secondly, we could not find an effect on plasma lipids in a meta-analysis. However, the conclusions from previous reviews were not based on a meta-analysis but on the results from single studies. Third, we could

not confirm the optimistic view on side effects in the previous reviews. Although due to differences in reporting, we were only able to perform a meta-analysis for the occurrence of "all adverse events," it was obvious from all reports that gastrointestinal events (flatulence, diarrhea, stomachache) were the most frequent occurring. Finally, we could not affirm the optimistic view about the efficacy of AGIs compared with other agents. Sufficient data were available only for the comparison of acarbose versus sulfonylurea, and these comparisons point in the direction of inferior effects on glycemic control and side effects but a clear superior effect on fasting and postload insulin levels.

This systematic review included a high number of trials. Because of the strict inclusion criteria, studies were similar with respect to key items: all were randomized, included patients with type 2 diabetes, and applied AGI monotherapy. Heterogeneity by other crucial factors such as comparison drug and different dosages was addressed by using different (sub)groups for the meta-analyses. The residual heterogeneity seemed to be limited in this review, because visual inspection of the forest plots of the main outcomes showed consistent outcomes. Further sensitivity, subgroup, and meta-regression analyses for a number of possible confounders, including quality items, only yielded a few significant results. AGIs given as a fixed dose and without a step-up scheme have the largest positive effect on GHb but also have a worsening effect on side effects.

One of the main limitations of our study was that not all data in the original studies were available in a way appropriate for a meta-analysis. This was especially striking for one study of long duration and with a high number of participants; data from this trial could not be used because the main outcome measure was the time until patients with good control on diet alone needed additional medication (19). A pharmaceutical company sponsored at least 33 studies. Research funded by pharmaceutical companies is more likely to produce results favoring the tested drug, which is mostly due to publication bias or inappropriate comparators (75). The risk for publication bias is limited because we have made every possible effort to find published and unpublished studies. However, inappropriate comparators were obvious

in the studies comparing acarbose with sulfonylurea.

### Clinical applicability and implications for research

The place of AGIs in the treatment of patients with type 2 diabetes cannot be determined from the results of this review alone. Developers of guidelines should weigh the best available evidence, preferably from high quality systematic reviews, evaluating other drugs in the first line treatment of diabetes. The exact place for AGIs also depends on the priorities in diabetes treatment. For example, how important is a reduction of (postload) insulin levels?

Studies with AGI monotherapy investigating surrogate end points such as GHb or insulin levels are redundant. Therefore, future research should aim at assessing effects on end points that are directly relevant to patients, such as mortality or morbidity, instead of focusing on surrogate parameters. At least such end points should be included in all trials with patients with chronic diseases. Even if the study is underpowered for such an end point, such data might be useful for a meta-analysis.

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