α-Glucosidase inhibitors and their use in clinical practice

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Abstract

Post-prandial hyperglycemia still remains a problem in the management of type 2 diabetes mellitus. Of all available anti-diabetic drugs, α-glucosidase inhibitors seem to be the most effective in reducing post-prandial hyperglycemia. We conducted a review analyzing the clinical efficacy and safety of α-glucosidase inhibitors, both alone and in combination with other anti-diabetic drugs, with respect to glycemic control, inflammation and atherosclerosis. α-Glucosidase inhibitors proved to be effective and safe both in monotherapy and as an add-on to other anti-diabetic drugs. Compared to miglitol and voglibose, acarbose seems to have some additive effects such as stabling carotid plaques, and reducing inflammation. Acarbose also proved to reverse impaired glucose tolerance to normal glucose tolerance.

Key words: α-glucosidase inhibitors, acarbose, voglibose, miglitol, post-prandial hyperglycemia.

Introduction

Cardiovascular disease is common in patients with diabetes mellitus and related clinical outcomes are worse compared with non-diabetics. Recent evidence suggests that advanced percutaneous coronary intervention techniques, along with best medical treatment, may be non-inferior and more cost-effective compared with coronary artery bypass graft [1, 2]. However, the golden paradigm to reduce cardiovascular (CV) complications in patients with diabetes mellitus remains a multifactorial approach based on therapeutic lifestyle management, targeting hypertension, dyslipidemia, hyperglycemia and hypercoagulability [3]. Moreover, according to the latest American Diabetes Association guidelines [4], lowering glycated hemoglobin (HbA_{1c}) to below or around 7% has been shown to reduce microvascular and neuropathic complications of diabetes and, if implemented soon after the diagnosis of diabetes, is associated with long-term reduction in macrovascular disease. Therefore, a reasonable HbA_{1c} goal for many non-pregnant adults is < 7%.

A lot of antidiabetic drugs are currently available. Usually metformin is the first line therapy. When metformin, combined with diet and lifestyle intervention, is not enough to reach the desired glycemic target, a lot of options are available, such as sulfonylureas and glinides, pioglitazone [5], α-glucosidase inhibitors, glucagon-like peptide-1 agonists [6], and DPP-4 inhibitors [7] (Table I).

However, often, even if an adequate HbA_{1c} is reached, post-prandial hyperglycemia (PPG) can occur. Post-prandial hyperglycemia significantly

Table I. Characteristics of various anti-diabetic drugs combined with metformin

Metformin	↓ HbA_{1c}	↓ PPG	Long-term efficacy	↑ Hypoglycemia	↑ Fluid retention/ heart failure	↑ Body weight	↑ Bone fractures	Long-term safety	↑ Gastrointestinal side-effects
Plus sulfonylureas	+++	+	–	+++	–	++	–	+	–
Plus repaglinide	++	++	+	++	–	++	–	+	+
Plus thiazolidinediones	++	+	++	+	++	++	+	+	–
Plus DPP-4/GLP-1	++	++	++	+	–	–	–	++	+
Plus α-glucosidase inhibitors	++	+++	+++	–	–	–	–	+++	++

contributes to the development of chronic diabetic complications, particularly cardiovascular disease, and microvascular complications of diabetes [8], even more than fasting hyperglycemia [9, 10]. In two of our previously published studies we observed that PPG, simulated using an oral glucose tolerance test (OGTT), gives a greater increase in biomarkers of systemic low-grade inflammation and endothelial dysfunction such as high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), soluble intercellular adhesion molecule 1 (sICAM-1), soluble vascular cell adhesion molecule 1 (sVCAM-1), sE-selectin, and metalloproteinases 2 and 9 in type 2 diabetic patients compared to healthy ones [11, 12]. Of all the available antidiabetic drugs, α-glucosidase inhibitors are the most effective in reducing PPG [13, 14]. This was confirmed by the International Diabetes Federation (IDF), which recently published a treatment algorithm for people with type 2 diabetes, where α-glucosidase inhibitors play an important role both as first line and second or third line therapy [15].

In this review we want to focus our attention on this class of drug, analyzing α-glucosidase inhibitors' efficacy and safety, both alone and in combination with other anti-diabetic drugs, including the most important studies conducted in the latest years.

Material and methods

A systematic search strategy was developed to identify randomized controlled trials in both MEDLINE (National Library of Medicine, Bethesda, MD; 1996 to July 2012) and the Cochrane Register of Controlled Trials (The Cochrane Collaboration, Oxford, United Kingdom). The terms "acarbose", "voglibose", "miglitol", α-glucosidase inhibitors", "type 2 diabetes", and "post-prandial hyperglycemia" were incorporated into an electronic search strategy that included the Dickersin filter for randomized controlled trials [16]. The bibliographies of all identified randomized trials and review articles were reviewed to look for additional studies of interest. We reviewed all of the citations retrieved from the electronic search to identify potentially relevant articles for this review. We subsequently reviewed the potential trials to determine their eligibility. To qualify for inclusion, clinical trials were required to meet a series of predetermined criteria regarding study design, study population, interventions evaluated, and outcome measured. Studies were required to be randomized trials comparing acarbose at any dosage with any other anti-diabetic drug in type 2 diabetic patients. Eligible trials had to present results on glycemic control or adverse events. Two different outcomes related to glycemic control decrease were of primary interest: 1) the proportion of individuals within each treatment group achieving clinically significant HbA_{1c} reduction, and 2) the mean amount decrease (in mg/dl or mmol/l) of PPG within each treatment group. Variations of fasting plasma glucose (FPG), HOMA index, lipid profile, insulin resistance and inflammatory parameters that occurred during various trials were secondary outcomes of interest, as was the frequency of patients having one or more adverse events such as meteorism. The following data were abstracted onto standardized case report forms: authors; year of publication; country of study; source of funding; study goal; means of randomization and blinding; duration of treatment; treatment characteristics; sex; number of and reasons for study withdrawals; HbA_{1c} and age characteristics of the treatment and control groups; outcomes; and adverse event data. A validated, 3-item scale was used to evaluate the overall reporting quality of the trials selected for inclusion in the present review. This scale provided scoring for randomization (0-2 points), double-blinding (0-2 points), and account for withdrawals (1 point). Scores ranged between 0 and 5, with a score of 3 indicating a study of high quality [17], and study selection was restricted to randomized controlled trials to ensure the inclusion of only high quality evidence.

Mechanism of action

Acarbose, voglibose, and miglitol are pseudo-carbohydrates that competitively inhibit α-glucosidase enzymes located in the brush border of enterocytes that hydrolyze non-absorbable oligosaccharides and polysaccharides into absorbable monosaccharides. Acarbose is the most used drug of this family. It is a pseudotetrasaccharide with a nitrogen bound between the first and second glucose unit which is obtained from fermentation processes of a microorganism, *Actinoplanes utahensis*. This modification of a natural tetrasaccharide is important for its high affinity for active centers of α-glucosidases of the brush border of the small intestine and for its stability [18]. Acarbose is most effective against glucoamylase, followed by sucrase, maltase, and dextranase [19]. It also inhibits α-amylase, but has no effect on β-glucosidases, such as lactase. Acarbose is poorly absorbed and is excreted in the feces, mostly intact, but with up to 30% undergoing metabolism predominantly via fermentation by colonic microbiota [20]. Similarly, voglibose is slowly and poorly absorbed and rapidly excreted in stools, with no metabolites identified to date [21]. In contrast, miglitol is fully absorbed in the gut and cleared unchanged by the kidneys [22]. Since α-glucosidase inhibitors prevent the digestion of complex carbohydrates, they should be taken at the start of main meals, taken with the first bite of a meal. Moreover, the amount of complex carbohydrates in the meal will determine the effectiveness of α-glucosidase inhibitors in decreasing PPG.

Clinical recommendations

α-Glucosidase inhibitors can be used as a first-line drug in newly diagnosed type 2 diabetes insufficiently treated with diet and exercise alone, as well as in combination with all oral anti-diabetics and insulin if monotherapy with these drugs fails to achieve the targets for HbA_{1c} and post-prandial blood glucose. As a first-line drug, they are particularly useful in newly diagnosed type 2 diabetes with excessive PPG, because of their unique mode of action in controlling the release of glucose from complex carbohydrates and disaccharides. α-Glucosidase inhibitors may also be used in combination with a sulfonylurea, insulin or metformin [4, 15].

α-Glucosidase inhibitors are contraindicated in patients with known hypersensitivity to the drug, in patients with diabetic ketoacidosis or inflammatory bowel disease, colonic ulceration, partial intestinal obstruction or in patients predisposed to intestinal obstruction. In addition, they are contraindicated in patients who have chronic intestinal diseases associated with marked disorders of digestion or absorption and in patients who have conditions that may deteriorate as a result of increased gas formation in the intestine.

The recommended starting dose of acarbose is 25 mg three times daily, increasing to 50 mg three times daily, until a maximum dose of 100 mg three times a day.

Voglibose should be orally administered in a single dose of 0.2 mg three times a day, just before each meal; if not sufficient, the dose can be uptitrated to 0.3 mg three times a day. Miglitol should be started at 25 mg three times daily and then increased after four to eight weeks to 50-100 mg three times daily.

Adverse events

Since α-glucosidase inhibitors prevent the degradation of complex carbohydrates into glucose, some carbohydrate will remain in the intestine and be delivered to the colon. In the colon, bacteria digest the complex carbohydrates, causing gastrointestinal side-effects such as flatulence (78% of patients) and diarrhea (14% of patients). Since these effects are dose-related, in general it is advised to start with a low dose and gradually increase the dose to the desired amount. A few cases of hepatitis have been reported with acarbose use, which regressed when the medicine was stopped [23]; therefore, liver enzymes should be checked before and during use of this medicine. As already stated above, α-glucosidase inhibitors should be started at a low dose, both to reduce gastrointestinal side effects and to permit identification of the minimum dose required for adequate glycemic control of the patient. If the prescribed diet is not observed, the intestinal side effects may be intensified.

Cost-effectiveness ratio

Piñol *et al.* [24] conducted a cost-effectiveness analysis of the addition of acarbose to existing treatment in patients with type 2 diabetes mellitus in Spain. Acarbose treatment was associated with improved life expectancy (0.23 years) and quality-adjusted life years (QALY) (0.21 years). Direct costs were on average € 468 per patient more expensive with acarbose than with placebo. The incremental cost-effectiveness ratios were € 2002 per life year gained and € 2199 per QALY gained. An acceptability curve showed that with a willingness to pay € 20 000, which is generally accepted to represent very good value for money, acarbose treatment was associated with a 93.5% probability of being cost-effective. Similar results were observed by Roze *et al.* in Germany [25]: acarbose treatment was associated with improvements in discounted life expectancy (0.21 years) and quality-adjusted life expectancy (QALE) (0.19 QALYs), but was on average marginally more expensive than treatment in

the placebo arm (€ 135 per patient). This led to incremental cost-effectiveness ratios of € 633 per life year and € 692 per quality-adjusted life year gained. For comparison, the incremental cost-effectiveness ratio for pioglitazone/metformin was € 47 636 per life year gained vs. sulfonylurea/metformin, and € 19 745 per life year gained for pioglitazone/sulfonylurea vs. metformin/sulfonylurea [26]. These studies showed that the addition of acarbose to existing treatment was associated with improvements in life expectancy and quality-adjusted life expectancy, and provided excellent value for money over patient lifetimes.

Effects of α-glucosidase inhibitors

Glycemic control in type 2 diabetes mellitus

Derosa *et al.* [27] compared acarbose and repaglinide in type 2 diabetic patients treated with a sulfonylurea-metformin combination therapy. One hundred and three patients were randomized to receive repaglinide, 2 mg three times a day or acarbose, 100 mg three times a day with forced titration for 15 weeks. The treatment was then crossed over for a further 12 weeks until the 27th week. After 15 weeks of therapy, the repaglinide-treated patients experienced a significant decrease in HbA_{1c} (–1.1%, $p < 0.05$), FPG (–9.5%, $p < 0.05$), and PPG (–14.9%, $p < 0.05$), with a significant increase in body weight (+2.3%, $p < 0.05$), BMI (+3.3%, $p < 0.05$) and fasting plasma insulin (FPI) (+22.5%, $p < 0.05$); the increase was reversed during the cross-over phase. After 15 weeks of therapy, the acarbose-treated patients experienced a significant decrease in HbA_{1c} (–1.4%, $p < 0.05$), FPG (–10.7%, $p < 0.05$), PPG (–16.2%, $p < 0.05$), body weight (–1.9%, $p < 0.05$), BMI (–4.1%, $p < 0.05$), FPI (–16.1%, $p < 0.05$), PPI (–26.9%, $p < 0.05$), and HOMA index (–30.1%, $p < 0.05$), when compared to the baseline values. All these changes were reversed during the cross-over study phase, except those relating to HbA_{1c}, FPG and PPG. The only changes that significantly differed when directly comparing acarbose and repaglinide treated patients were those relating to FPI (–16.1% vs. +22.5%, respectively, $p < 0.05$) and HOMA index (–30.1% vs. +2.7%, $p < 0.05$).

Based on the evidence that basal insulin treatment is frequently unsuccessful in controlling PPG, Kim *et al.* conducted a study where 58 type 2 diabetic patients, after FPG was optimized by insulin glargine, were randomized to take nateglinide 120 mg three times a day just before meals or acarbose 100 mg three times a day together with meals and then crossed over after the second wash-out period [28]. Both drugs effectively reduced PPG levels compared with the insulin glargine monotherapy. No significant differences were found between nateglinide and acarbose in terms of mean glucose level, standard deviation of glucose levels, mean average glucose excursion and average daily risk range. There was no episode of severe hypoglycemia, and no serious adverse events were recorded.

Kimura *et al.* [29] investigated the additive effect of α-glucosidase inhibitors in 36 type 2 diabetic patients taking lispro mix 50/50 by three times daily injection to maintain FPG < 130 mg/dl and 2-h PPG < 180 mg/dl. Twenty patients were randomly assigned to either 0.3 mg of voglibose or 50 mg of miglitol, which was administered at breakfast every other day. Another group of 16 patients was assigned to a crossover study, in which each α-glucosidase inhibitor was switched every day during the 6-day study. The addition of voglibose had no effect on PPG, but miglitol blunted the PPG rise and significantly decreased 1-h and 2-h post-prandial C-peptide levels compared with Mix50 alone. In addition, miglitol significantly decreased the 1-h post-prandial triglyceride rise and the remnant-like particle-cholesterol rise, while it increased the 1-h post-prandial high-density lipoprotein-cholesterol and apolipoprotein A-I levels in the crossover study.

Glycemic excursions

Mori *et al.* [30] conducted a study using continuous glucose monitoring (CGM) to assess mean amplitude of glycemic excursions (MAGE) with acarbose. Five of the patients were randomized to acarbose at 300 mg/day on days 1 and 2, but not on days 3 and 4; the remaining five patients were not administered acarbose on days 1 and 2, but were given 300 mg/day on days 3 and 4. During CGM, insulin was administered at the same time and the same dose. When acarbose was administered, the average CGM profile was decreased in almost all patients regardless of the current insulin regimen. The 24-h mean blood glucose level when acarbose was not administered was 158.03 ±32.78 mg/dl, the 24-h blood glucose fluctuation was 677.05 mgh/dl, and MAGE was 97.09. The 24-h mean blood glucose level when acarbose was administered was 131.19 ±22.48 mg/dl ($p = 0.004$), the 24-h blood glucose fluctuation was 453.27 mg/dl ($p = 0.002$), and MAGE was 65.00 ($p = 0.010$). The mean proportion of time spent in the hyperglycemic range (defined as ≥ 180 mg/dl) during CGM was 29.5 ±24.4% when acarbose was not administered and 16.2 ±25.4% when it was administered. The mean proportion of time spent in the hyperglycemic range (defined as ≥ 140 mg/dl) during CGM was 58.7 ±29.4% and 40.4 ±36.3%, respectively. The mean proportion of time spent in the hypoglycemic range (defined as < 70 mg/dl) during CGM was 0.31 ±0.63% when acarbose was not administered and 0.02 ±0.5% when it was administered. These data show that hypoglycemia was not increased by concomitant treatment targeting PPG.

A similar study conducted by Wang *et al.* [31, 32] evaluated the effects of acarbose versus glibenclamide on MAGE and oxidative stress in type 2 diabetic patients not well controlled by metformin. Patients treated with metformin monotherapy (1500 mg daily) were randomized to either acarbose (50 mg three times a day for the first month, then 100 mg three times a day), or glibenclamide (2.5 mg three times a day for the first month, then 5 mg three times a day) for 16 weeks. Continuous glucose monitoring for 72 h and a meal tolerance test (MTT) after a 10-hour overnight fast were conducted before randomization and at the end of the study. HbA_{1c} significantly decreased in both treatment groups (from 8.2 ±0.8% to 7.5 ±0.8%, $p < 0.001$ with acarbose, and from 8.6 ±1.6% to 7.4 ±1.2%, $p < 0.001$ with glibenclamide). The MAGE did not change significantly with glibenclamide, whereas oxidized low-density lipoprotein (ox-LDL) increased significantly (from 242.4 ±180.9 ng/ml to 470.7 ±247.3 ng/ml, $p < 0.004$). Acarbose decreased MAGE (5.6 ±1.5 mmol/l to 4.0 ±1.4 mmol/l, $p < 0.001$) without significant change in ox-LDL levels (from 254.4 ±269.1 ng/ml to 298.5 ±249.8 ng/ml, $p < 0.62$). Body weight and serum triglycerides decreased (all $p < 0.01$) and serum adiponectin increased ($p < 0.05$) after treatment with acarbose, whereas HDL-C decreased ($p < 0.01$) after treatment with glibenclamide. β-cell response to PPG increments was negatively correlated with MAGE ($r = 0.570$, $p < 0.001$) and improved significantly with acarbose (35.6 ±32.2 pmol/mmol to 56.4 ±43.7 pmol/mmol, $p < 0.001$), but not with glibenclamide (27.9 ±17.6 pmol/mol to 36.5 ±24.2 pmol/mmol, $p < 0.12$).

Inflammation

Derosa *et al.* [33, 34] evaluated effects of acarbose 100 mg three times a day compared to placebo on glycemic control, lipid profile, insulin resistance, and inflammatory parameters in diabetic patients before and after a standardized oral fat load (OFL). As expected, acarbose better reduced HbA_{1c} ($p < 0.01$), FPG ($p < 0.05$), PPG ($p < 0.05$), and HOMA-IR ($p < 0.05$) compared to placebo after 7 months. Regarding lipid profile, acarbose significantly reduced total cholesterol (TC), triglycerides (Tg), and low-density lipoprotein cholesterol (LDL-C) after 7 months compared with the control group ($p < 0.05$ for all). Acarbose also improved adiponectin (ADN) and retinol binding protein-4 compared to placebo ($p < 0.05$) in a fasting condition. After the OFL, acarbose was more effective in reducing the post-OFL peaks of all the various parameters including the insulin resistance and the inflammatory markers, after 7 months of therapy.

Shimazu *et al.* [35] investigated the effect of acarbose on circulating levels of platelet-derived microparticles (PDMP), selectins, and ADN in patients with type 2 diabetes. Expression of cell adhesion molecules is increased in diabetes, and these molecules have been suggested to have a role in the microvascular complication of this disease. Patients were instructed to take acarbose 300 mg/day for 3 months. Acarbose therapy significantly decreased the plasma PDMP level relative to baseline (0 vs. 3 months, 53.3 ±56.7 U/ml vs. 32.5 ±30.1 U/ml, $p < 0.05$). Acarbose also caused a significant decrease of sP-selectin (0 vs. 3 months, 235 ±70 U/ml vs. 174 ±39 U/ml, $p < 0.05$) and sL-selectin (0 vs. 3 months, 805 ±146 U/ml vs. 710 ±107 U/ml, $p < 0.05$). On the other hand, acarbose therapy led to a significant increase of ADN levels after 3 months compared with baseline (0 vs. 3 months, 3.61 ±1.23 µg/ml vs. 4.36 ±1.35 µg/ml, $p < 0.05$). The authors also investigated the effect of acarbose in diabetic patients with or without thrombosis, since 12 of the 30 diabetic patients had a history of thrombotic complications. The decrease of PDMP and selectin levels during acarbose therapy was significantly greater in the thrombotic group than in the non-thrombotic group ($p < 0.05$). On the other hand, ADN did not show such a difference. These data suggest that acarbose may be beneficial for primary prevention of atherothrombosis in patients with type 2 diabetes.

Osonoi *et al.* [36] examined the effects of switching from acarbose or voglibose to miglitol in type 2 diabetes mellitus patients for 3 months on gene expression of inflammatory cytokines/cytokine-like factors in peripheral leukocytes and on glucose fluctuations. Forty-seven Japanese patients with HbA_{1c} levels of 6.5-7.9% were treated with acarbose (100 mg three times a day) or voglibose (0.3 mg three times a day) in combination with insulin or sulfonylurea. The current α-glucosidase inhibitors were switched to miglitol (50 mg three time a day), and the new treatments were maintained for 3 months. The switch to miglitol for 3 months did not affect hemoglobin HbA_{1c}, FPG, or lipid profile. On the other hand, hypoglycemia symptoms and glucose fluctuations were significantly improved by the switch. The expression of interleukin-1β, TNF-α, and inflammatory cytokines that are predominantly expressed in monocytes and neutrophils were suppressed by switching to miglitol.

Emoto *et al.* [37] studied the effect of 3-month repeated administration of miglitol on endothelial dysfunction: 50 patients with type 2 diabetes and coronary artery disease were randomly assigned to miglitol 150 mg/day or voglibose 0.6 mg/day for 3 months. At the end of the trial, HbA_{1c} decreased in the two groups, but the improvements in 1,5-anhydroglucitol, a marker of frequent short-term elevations in glucose, in the miglitol group were significantly higher than in the voglibose group. Insulin resistance index, C-reactive protein, and

percentage flow-mediated dilatation were also improved in the miglitol group, but not in the voglibose group.

Fujitaka *et al.* [38] compared the effect of early intervention with pioglitazone versus voglibose on physical and metabolic profiles and serum ADN level in type 2 diabetic patients associated with metabolic syndrome. Sixty patients were analyzed for insulin sensitivity, lipid profile, serum ADN and systemic inflammation. Those patients were randomly assigned to pioglitazone or voglibose in addition to conventional diet and exercise training. Body mass index and waist circumference did not change in the pioglitazone group, whereas these physical parameters significantly decreased in the voglibose group during a 6-month follow-up period. However, HbA_{1c}, FPG, and HOMA-IR more significantly decreased in the pioglitazone group; the level of serum ADN, especially high-molecular weight ADN, markedly increased in the pioglitazone group, and hs-CRP significantly decreased only in the pioglitazone group.

Carotid plaque

A recently published study [39] evaluated whether acarbose may rapidly stabilize unstable atherosclerotic plaques in patients with acute coronary syndrome and type 2 diabetes mellitus. Patients were randomly assigned to acarbose (150 mg/day or 300 mg/day) or to placebo. Acarbose treatment was initiated within 5 days after the onset of ACS. Unstable carotid plaques were assessed by measuring plaque echolucency using carotid ultrasound with integrated backscatter (IBS) before, and at 2 weeks and 1 and 6 months after the initiation of treatment. An increase in the IBS value reflected an increase in carotid plaque echogenicity. In the results, the IBS value of echolucent carotid plaques showed a significant increase at 1 month and a further increase at 6 months after treatment in the acarbose group, but there was minimal change in the control group. The increase in IBS values was significantly correlated with a decrease in C-reactive protein levels, showing that acarbose rapidly improved carotid plaque echolucency.

A similar study was conducted by Koyasu *et al.* [40] where patients with established coronary artery disease (~50% stenosis on quantitative coronary angiography), recently diagnosed with impaired glucose tolerance (IGT) or mild type 2 diabetes, were randomly randomized to receive acarbose 150 mg/day or placebo to evaluate the absolute change from baseline to 12 months in the largest measured intima-media thickness (IMT) value in the right and left common carotid arteries. After 12 months in the acarbose group, IMT increased from a mean of 1.28 ±0.53 mm to 1.30 ±0.52 mm (mean change 0.02 ±0.29 mm, p not significant), whereas in the control group, it increased from a mean of 1.15 ±0.37 mm to 1.32 ±0.046 mm (mean change: 0.17 ±0.25 mm; $p < 0.001$). The difference between the acarbose and control groups was statistically significant ($p = 0.01$).

On the other hand, voglibose was evaluated in the DIANA (DIAbetes and diffuse coronary NArrowing) study [41]: in this trial 302 patients with coronary artery disease (CAD), impaired glucose tolerance/diabetes mellitus pattern according to 75-g oral glucose tolerance test and $HbA_{1c} < 6.9\%$ were randomly assigned to life-style intervention, voglibose (0.9 mg/day) or nateglinide treatment (180 mg/day). One year coronary atherosclerotic changes were evaluated by quantitative coronary arteriography. Although voglibose significantly increased the number of patients with normal glucose tolerance at 1 year, there were no significant differences in coronary atherosclerotic changes at 1 year. However, overall, less atheroma progression was observed in patients in whom glycemic status was improved at 1 year (% change in total lesion length: 3.5% vs. 26.2%, $p < 0.01$, % change in average lesion length: 0.7% vs. 18.6%, $p = 0.02$).

Impaired glucose tolerance

Kawamori *et al.* [42] conducted a study to assess whether voglibose could prevent type 2 diabetes developing in high-risk Japanese subjects with IGT. Voglibose was administered in 897 patients, while 883 received placebo; the study was planned for treatment to be continued until participants developed type 2 diabetes or for a minimum of 3 years. An interim analysis significantly favored voglibose; subjects treated with voglibose had a significantly lower risk for progression to type 2 diabetes than placebo (50/897 vs. 106/881: hazard ratio 0.595). Also, significantly more subjects in the voglibose group achieved normoglycemia compared with those in the placebo group (599/897 vs. 454/881: hazard ratio 1.539).

Also acarbose proved to be safe and effective in patients with IGT; in the STOP-NIDDM (Study To Prevent Non-Insulin Dependent Diabetes Mellitus) trial [43], 714 patients with IGT were randomized to acarbose 100 mg three times daily and 715 to placebo. Acarbose significantly increased reversion of IGT to normal glucose tolerance ($p < 0.0001$); the risk of progression to diabetes over 3.3 years was reduced by 25%. At the end of the study, treatment with placebo was associated with an increase in conversion of IGT to diabetes. The same study also showed that decreasing PPG with acarbose was associated with a 49% relative risk reduction in the development of cardiovascular events ($p = 0.03$) and a 2.5% absolute risk reduction [44]. Among cardiovascular events, the major reduction was in the risk of myocardial infarction ($p = 0.02$). Acar-

bose was also associated with a 34% relative risk reduction in the incidence of new cases of hypertension (p = 0.006) and a 5.3% absolute risk reduction. Even after adjusting for major risk factors, the reduction in the risk of cardiovascular events (p = 0.02) and hypertension (p = 0.004) associated with acarbose treatment was still statistically significant.

Discussion

Of all α-glucosidase inhibitors, acarbose remains the most widely studied drug of the class. From the studies reported above, it emerged that α-glucosidase inhibitors were superior to placebo in reducing HbA_{1c}, FPG, and PPG. There is also evidence that α-glucosidase inhibitors more effectively reduced intraday and interday glucose variability compared to other anti-diabetic drugs [33]. Regarding the effects on inflammatory markers, miglitol seemed more effective than voglibose or acarbose in suppressing glucose fluctuations and the gene expression of inflammatory cytokines/cytokine-like factors in peripheral leukocytes, with fewer adverse effects [36]. However, acarbose showed some additive action compared to voglibose and miglitol: acarbose improved echolucency in carotid plaque after 1 month of treatment, continuing during the next 5 months [39]. These results suggest that early treatment of hyperglycemia with acarbose may potentially stabilize vulnerable carotid plaques in acute coronary syndrome type 2 diabetic patients. The mechanism of that can be sought in PPG: hyperglycemia induces oxidative stress, endothelial dysfunction and proinflammatory cytokines through oxidative stress-induced activation of nuclear factor κB [45]. Reducing hyperglycemia, acarbose also reduced proinflammatory cytokines and stabilized carotid plaque. This positive action on carotid plaque was not confirmed by voglibose, suggesting that this effect was peculiar to acarbose [41].

Finally, both voglibose and acarbose proved to significantly increase reversion of IGT to normal glucose tolerance [42-44], and to give a 49% relative risk reduction in the development of cardiovascular events in patients with IGT [44]. Also from the cost-effectiveness ratio point of view, acarbose improved life expectancy and quality-adjusted life expectancy, and provided excellent value for money over patient lifetimes [24, 25].

From all the considerations reported above, we can safely conclude that α-glucosidase inhibitors proved to be safe and effective in improving glycemic control and PPG, and in particular acarbose proved to have a lot of additive effects that can help in reducing the macro- and microvascular complications related to type 2 diabetes.

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References

1. Athyros VG, Gossios TD, Tziomalos K, Florentin M, Karagiannis A, Mikhailidis DP. Is there an additional benefit from coronary revascularization in diabetic patients with acute coronary syndromes or stable angina who are already on optimal medical treatment? Arch Med Sci 2011; 7: 1067-75.
2. Aronow WS. Editorial on management of diabetes mellitus with coronary artery disease. Arch Med Sci 2011; 7: 928-30.
3. Rydén L, Standl E, Bartnik M, et al; Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC); European Association for the Study of Diabetes (EASD). Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J 2007; 28: 88-136.
4. American Diabetes Association. Standards of medical care in diabetes: 2012. Diabetes Care 2012; 35 (Suppl 1): S11-63.
5. Derosa G, Tinelli C, Maffioli P. Effects of pioglitazone and rosiglitazone combined with metformin on body weight in people with diabetes. Diabetes Obes Metab 2009; 11: 1091-9.
6. Derosa G, Maffioli P. GLP-1 agonists exenatide and liraglutide: a review about their safety and efficacy. Curr Clin Pharmacol 2012; 7: 214-28.
7. Derosa G, Maffioli P. Dipeptidyl peptidase-4 inhibitors: 3 years of experience. Diabetes Technol Ther 2012; 14: 350-64.
8. Shiraiwa T, Kaneto H, Miyatsuka T, et al. Postprandial hyperglycemia is a better predictor of the progression of diabetic retinopathy than HbA1c in Japanese type 2 diabetic patients. Diabetes Care 2005; 28: 2806-7.
9. DECODE Study Group, the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med 2001; 161: 397-405.
10. Bell DS, O'Keefe JH, Jellinger P. Postprandial dysmetabolism: the missing link between diabetes and cardiovascular events? Endocr Pract 2008; 14: 112-24.
11. Derosa G, D'Angelo A, Salvadeo SA, et al. Modification of vascular and inflammation biomarkers after OGTT in overweight healthy and diabetic subjects. Microvasc Res 2010; 79: 144-9.
12. Derosa G, D'Angelo A, Salvadeo SA, et al. Oral glucose tolerance test effects on endothelial inflammation markers in healthy subjects and diabetic patients. Horm Metab Res 2010; 42: 8-13.
13. Derosa G, Mereu R, D'Angelo A, et al. Effect of pioglitazone and acarbose on endothelial inflammation biomarkers during oral glucose tolerance test in diabetic patients

treated with sulphonylureas and metformin. J Clin Pharm Ther 2010; 35: 565-79.
14. Derosa G, D'Angelo A, Salvadeo SA, et al. Modulation of adipokines and vascular remodelling markers during OGTT with acarbose or pioglitazone treatment. Biomed Pharmacother 2009; 63: 723-33.
15. http://www.idf.org/treatment-algorithm-people-type-2-diabetes
16. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. BMJ 1994; 309: 1286-91.
17. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of randomized controlled trials: is blinding necessary? Control Clin Trials 1996; 17: 1-12.
18. Puls W. Pharmacology of glucosidase inhibitors. Oral Antidiabetics. Springer, Berlin 1996; 119: 497-525.
19. Krause HP, Ahr HJ. Pharmacokinetics and metabolism of glucosidase inhibitors. In: Handbook of experimental pharmacology. Oral Antidiabetics. Kuhlmann J, Puls W (eds). Springer, Berlin 1996; 541-5.
20. Bischoff H. Pharmacology of alpha-glucosidase-inhibitors. In: Drugs in development: alpha-glucosidase inhibition: potential use in diabetes. Vasselli J, Maggio C, Scriabine A (eds). Neva Press, Branford 1993; 3-13.
21. Göke B, Fuder H, Wieckhorst G, et al. Voglibose (AO-128) is an efficient alpha-glucosidase inhibitor and mobilizes the endogenous GLP-1 reserve. Digestion 1995; 56: 493-501.
22. Standl E, Schernthaner G, Rybka J, Hanefeld M, Raptis SA, Naditch L. Improved glycaemic control with miglitol in inadequately-controlled type 2 diabetics. Diabetes Res Clin Pract 2001; 51: 205-13.
23. WHO Pharmaceuticals Newsletter 1999, No. 01&02. Available at: http://apps.who.int/medicinedocs/en/d/Js2268e/2.html#Js2268e.2.1 [accessed 1999].
24. Piñol C, Roze S, Valentine W, Evers T. Cost-effectiveness of the addition of acarbose to the treatment of patients with type-2 diabetes in Spain. Gac Sanit 2007; 21: 97-104.
25. Roze S, Valentine WJ, Evers T, Palmer AJ. Acarbose in addition to existing treatments in patients with type 2 diabetes: health economic analysis in a German setting. Curr Med Res Opin 2006; 22: 1415-24.
26. Neeser K, Lübben G, Siebert U, Schramm W. Cost effectiveness of combination therapy with pioglitazone for type 2 diabetes mellitus from a german statutory healthcare perspective. Pharmacoeconomics 2004; 22: 321-41.
27. Derosa G, Salvadeo SA, D'Angelo A, et al. Metabolic effect of repaglinide or acarbose when added to a double oral antidiabetic treatment with sulphonylureas and metformin: a double-blind, cross-over, clinical trial. Curr Med Res Opin 2009; 25: 607-15.
28. Kim MK, Suk JH, Kwon MJ, et al. Nateglinide and acarbose for postprandial glucose control after optimizing fasting glucose with insulin glargine in patients with type 2 diabetes. Diabetes Res Clin Pract 2011; 92: 322-8.
29. Kimura T, Suzuki J, Ichikawa M, et al. Differential effects of alpha-glucosidase inhibitors on postprandial plasma glucose and lipid profile in patients with type 2 diabetes under control with Insulin Lispro Mix 50/50. Diabetes Technol Ther 2012; 14: 545-51.
30. Mori Y, Shiozaki M, Matsuura K, Tanaka T, Yokoyama J, Utsunomiya K. Evaluation of efficacy of acarbose on glucose fluctuation and postprandial glucose using continuous glucose monitoring in type 2 diabetes mellitus. Diabetes Technol Ther 2011; 13: 467-70.
31. Wang JS, Lin SD, Lee WJ, et al. Effects of acarbose versus glibenclamide on glycemic excursion and oxidative stress in type 2 diabetic patients inadequately controlled by metformin: a 24-week, randomized, open-label, parallel-group comparison. Clin Ther 2011; 33: 1932-42.
32. Lin SD, Wang JS, Hsu SR, et al. The beneficial effect of alpha-glucosidase inhibitor on glucose variability compared with sulfonylurea in Taiwanese type 2 diabetic patients inadequately controlled with metformin: preliminary data. J Diabetes Complications 2011; 25: 332-8.
33. Derosa G, Maffioli P, D'Angelo A, Fogari E, Bianchi L, Cicero AF. Acarbose on insulin resistance after an oral fat load: a double-blind, placebo controlled study. J Diabetes Complications 2011; 25: 258-66.
34. Derosa G, Maffioli P, Ferrari I, et al. Acarbose actions on insulin resistance and inflammatory parameters during an oral fat load. Eur J Pharmacol 2011; 651: 240-50.
35. Shimazu T, Inami N, Satoh D, et al. Effect of acarbose on platelet-derived microparticles, soluble selectins, and adiponectin in diabetic patients. J Thromb Thrombolysis 2009; 28: 429-35.
36. Osonoi T, Saito M, Mochizuki K, et al. The alpha-glucosidase inhibitor miglitol decreases glucose fluctuations and inflammatory cytokine gene expression in peripheral leukocytes of Japanese patients with type 2 diabetes mellitus. Metabolism 2010; 59: 1816-22.
37. Emoto T, Sawada T, Hashimoto M, et al. Effect of 3-month repeated administration of miglitol on vascular endothelial function in patients with diabetes mellitus and coronary artery disease. Am J Cardiol 2012; 109: 42-6.
38. Fujitaka K, Otani H, Jo F, et al. Comparison of metabolic profile and adiponectin level with pioglitazone versus voglibose in patients with type-2 diabetes mellitus associated with metabolic syndrome. Endocr J 2011; 58: 425-32.
39. Hirano M, Nakamura T, Obata JE, et al. Early improvement in carotid plaque echogenicity by acarbose in patients with acute coronary syndromes. Circ J 2012; 76: 1452-60.
40. Koyasu M, Ishii H, Watarai M, et al. Impact of acarbose on carotid intima-media thickness in patients with newly diagnosed impaired glucose tolerance or mild type 2 diabetes mellitus: a one-year, prospective, randomized, open-label, parallel-group study in Japanese adults with established coronary artery disease. Clin Ther 2010; 32: 1610-7.
41. Kataoka Y, Yasuda S, Miyamoto Y, et al; DIANA study investigators. Effects of voglibose and nateglinide on glycemic status and coronary atherosclerosis in early-stage diabetic patients. Circ J 2012; 76: 712-20.
42. Kawamori R, Tajima N, Iwamoto Y, Kashiwagi A, Shimamoto K, Kaku K. Alpha-glucosidase inhibitor for the prevention of type 2 diabetes mellitus: a randomised, double-blind trial in Japanese subjects with impaired glucose tolerance. Nihon Rinsho 2009; 67: 1821-5.
43. Chiasson JL, Josse RG, Gomis R, et al; STOP-NIDDM Trail Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. Lancet 2002; 359: 2072-7.
44. Chiasson JL, Josse RG, Gomis R; STOP-NIDDM Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA 2003; 290: 486-94.
45. Zarich SW, Nesto RW. Implications and treatment of acute hyperglycemia in the setting of acute myocardial infarction. Circulation 2007; 115: e436-9.