Who Should Benefit from the Use of Alpha-Glucosidase Inhibitors?

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Although most commonly used drugs such as biguanides, sulfonylureas, and more recently, thiazolidinediones, are effective in controlling fasting hyperglycemia, a high percentage of patients have sustained elevated hemoglobin A_{1c} because of persistent elevation of postprandial plasma glucose (PPPG). α-Glucosidase inhibitors (AGIs) specifically target PPPG. AGIs have been shown in several randomized controlled trials to be effective in controlling blood glucose, whether they are used as monotherapy or in combination with other antidiabetic medications. Among the AGIs, acarbose has also been shown to decrease the risk of progressing to diabetes in subjects with impaired glucose tolerance (IGT). Studies have also suggested that acarbose could decrease the risk of cardiovascular disease, both in IGT and in diabetes. Furthermore, AGIs are very safe and are nontoxic drugs. Their only side effects are gastrointestinal, such as flatulence and diarrhea; however, these can be minimized by the "start low, go slow" approach. AGIs should be considered whenever postprandial hyperglycemia is the dominant metabolic abnormality.

Introduction

The worldwide prevalence of type 2 diabetes mellitus will double over the next 25 years, ranking the disease as an epidemic state. Type 2 diabetes is still associated with increased morbidity and excess mortality. As such, it has become a serious health problem exerting a major burden on health care costs. Intensive glycemic control has been shown to significantly decrease microvascular complications both in type 2 (UKPDS [United Kingdom Prospective Diabetes Study]) [1,2] and in type 1 diabetes (DCCT [Diabetes Control and Complications Trial]) [3]. These studies also suggested that intensive treatment of hyperglycemia could also delay macrovascular disease development [1,4].

Both the UKPDS and the DCCT have shown that the reduction of diabetic complications was proportional to the lowering of glycated hemoglobin (HbA_{1c}). HbA_{1c} represents a summation of fasting and postprandial plasma glucose (PPPG). To meet HbA_{1c} targets via glycemic management, many therapeutic strategies have been proposed. Diet and regular exercise remain the cornerstone in the prevention and treatment of type 2 diabetes. When these are insufficient to reach targeted HbA_{1c}, oral hypoglycemic agents are added including biguanides, sulfonylureas, or thiazolidinediones. If these drugs are effective in controlling fasting hyperglycemia, more than 60% of patients will remain with excessive postmeal glycemic excursions, representing one of the major causes of sustained elevated HbA_{1c} in the presence of adequate fasting blood glucose levels [5]. These postprandial excursions in plasma glucose can be minimized by including slowly absorbable carbohydrates and high-fiber food in the diet, but these regimens can be difficult to follow in the long term.

α-Glucosidase inhibitors (AGIs) offer an alternative; they are designed to specifically delay the digestion of complex carbohydrates, thus significantly reducing postprandial glycemic and insulinemic excursions. Because of the role postprandial hyperglycemia plays in the development of diabetes and its complications, it is proposed that these drugs should be used in the prediabetic state, in early type 2 diabetes, and even in long-standing diabetes if postprandial hyperglycemia remains a problem. AGIs are drugs with an excellent safety profile that can control postprandial rise in plasma glucose whether used as monotherapy or with other antidiabetic medications.

Mechanism of Action

AGIs are competitive inhibitors of pancreatic α-amylase and intestinal brush border α-glucosidases resulting in delayed hydrolysis of ingested polysaccharides, oligosaccharides, and disaccharides to monosaccharide for absorption. Normally, in a typical reaction, the ingested polymeric sugar chain is broken down into monosaccharides by the action of α-glucosidases and rapidly

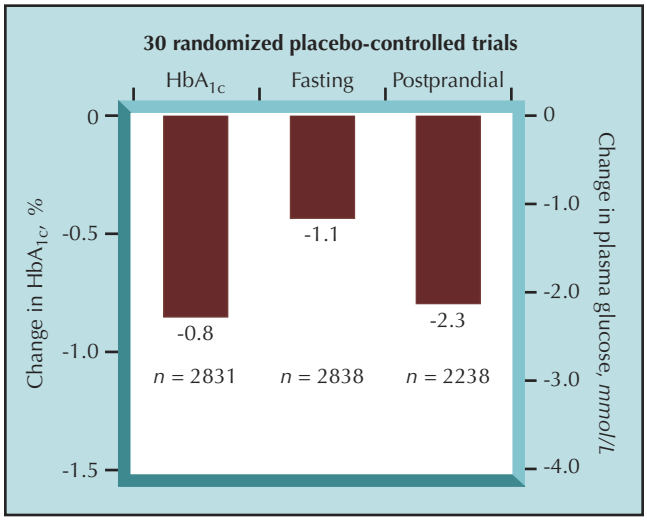

Figure 1. The efficacy of acarbose as monotherapy in type 2 diabetes. HbA_{1c}—hemoglobin A_{1c}. (*Adapted from* van de Laar et al. [8••].)

absorbed in the proximal part of the small intestine and released into the bloodstream. Having a higher affinity than natural substrates, AGIs bind to α-glucosidase enzymes, thus impeding its action. Carbohydrate absorption and digestion are slowed down and, therefore, occur throughout the length of the small intestine. Consequently, the postprandial rise in plasma glucose is blunted and prolonged [6].

Three AGIs with similar pharmacologic profiles have been developed: acarbose, miglitol, and voglibose. Acarbose is a pseudo-tetrasaccharide of microbial origin. Its chemical structure is similar to an oligosaccharide derivative after starch digestion. The molecule is a maltose unit linked to an acarviosine unit. The nitrogen linkage of the acarviosine unit confers the high affinity of the molecule for the carbohydrate-binding site of multiple α-glucosidases, with this affinity being 10- to 100,000-fold higher than that of regular oligosaccharides from nutritional carbohydrates. Moreover, this nitrogen linkage prevents acarbose from cleavage, blocking enzymatic hydrolysis and absorption of carbohydrates. However, acarbose binding to μ-glucosidases is reversible and its inhibition kinetics is competitive. Its great specificity for α-glucosidases prevents acarbose from inhibition of β-glucosidases such as lactase. Lactose's digestion and absorption is therefore unaffected by acarbose administration. Most importantly, AGIs do not compete with monosaccharide absorption such as glucose along the intestinal route. Acarbose is poorly absorbed (1% to 2%), which explains its action throughout the small intestine. Delayed digestion and absorption of carbohydrates in the small intestine can increase the amount of fermentable carbohydrates in the colon, sometimes resulting in gastrointestinal symptoms such as flatulence and diarrhea. Also, bacterial enzymes of the large intestine are able to cleave acarbose into 13 metabolites (actually identified). Even if less then 2% of acarbose is absorbed, metabolites can be found in urine, representing approximately 35% of the initial oral dose. The efficacy of acarbose resides in its ability to compete with oligo- and disaccharides. Thus, its presence at the site of enzymatic binding should coincide with the arrival of carbohydrates. Its administration should be preferentially with the first bite of each main meal, but not more then 15 minutes after the beginning of the meal.

The chemical structure of miglitol resembles a glucose molecule. It is significantly absorbed in the jejunum through the glucose transport mechanism. Its action is then possible because miglitol will then circulate and concentrate in the enterocytes of the small intestine. After absorption, miglitol is not metabolized and is excreted unchanged in the urine.

Voglibose will not be discussed in this article. This molecule is commercially available mainly in Japan and few studies have been performed with the drug.

All AGIs modulate gastrointestinal hormone secretion, such as gastric inhibitory peptide (GIP) and glucagon-like peptide 1 (GLP-1). When AGIs are taken with meals containing high carbohydrates, a decrease in GIP and an increase in GLP-1 secretion are observed, especially in the late postprandial period [7]. The exact role of AGI modulation of the GIP and GLP-1 secretion pattern is not well understood.

Efficacy of AGIs for the Treatment of Type 2 Diabetes

There is a large amount of literature on the use of AGIs in the treatment of diabetes mellitus. Many double-blind, placebo-controlled, randomized clinical trials have demonstrated the efficacy of AGIs when compared with diet alone, to metformin or to sulfonylureas, or when added to failing metformin, sulfonylureas, or glitazone, or when added to insulin regimen. Most studies have been conducted with acarbose.

Efficacy of AGIs as monotherapy in drug-naive patients with type 2 diabetes

The efficacy of acarbose is illustrated in Figure 1 from a meta-analysis by the Cochrane group in over 2000 patients with type 2 diabetes on diet alone [8••]. Compared with placebo, acarbose treatment resulted in a reduction in PPPG (in mmol/L) (-2.3 [95% CI, -2.73 to -1.92]) and in fasting plasma glucose (FPG) (-1.1 [95% CI, -1.36 to -0.83]); this was associated with a decrease in HbA_{1c} of 0.8% (95% CI, -0.90 to -0.64). Miglitol was also compared with placebo in over 1000 patients. It also reduced PPPG by 2.7 mmol/L (95% CI, -5.54 to +0.14) and FPG by 0.52 mmol/L (95% CI, -0.88 to -0.16) and was associated with a decrease in HbA_{1c} of 0.68% (95% CI, -0.93 to -0.44). Two studies have tested AGIs in elderly patients with type 2 diabetes: one with acarbose [9] and one with miglitol [10]. In the

acarbose study ($n = 192$), HbA_{1c} was reduced by 0.6% ($P < 0.05$) compared with placebo after 1 year. Miglitol ($n = 411$) was also associated with a significant reduction in HbA_{1c} (-0.49% and 0.40%) compared with placebo ($P < 0.05$). The medication was well tolerated in the populations studied.

Efficacy of AGIs compared or added to metformin or sulfonylureas

Only two studies have compared AGIs to metformin in patients with type 2 diabetes suboptimally controlled with diet alone: one with acarbose and one with miglitol. Hoffmann and Spengler [11] showed that acarbose, 100 mg, three times a day (TID) with meals had similar efficacy as metformin, 850 mg, twice a day, resulting in a mean reduction in HbA_{1c} of 1% after 6 months of treatment. Miglitol at 100 mg TID with meals was less effective than metformin at 500 mg TID (HbA_{1c} = -0.4% vs -1.2%) after 1 year of treatment [12]. However, when the drug was combined with metformin, a synergy was observed between the two treatments, resulting in a mean reduction of 1.8% in HbA_{1c} [12].

At least three studies have compared acarbose to sulfonylureas in patients with type 2 diabetes [13]. Overall, acarbose treatment was associated with an absolute reduction in HbA_{1c} of 0.66% compared with 0.88% for sulfonylureas.

AGIs have been tested in patients with type 2 diabetes failing on metformin and sulfonylureas. Four studies have been published where acarbose was compared with placebo in patients with type 2 diabetes ($n = 466$) who were suboptimally controlled with metformin. The overall net effect compared with placebo was a reduction in HbA_{1c} of 0.79% plus or minus 0.05% [13]. Similarly, at least three studies have compared acarbose with placebo in patients with type 2 diabetes ($n = 227$) who were not adequately controlled with sulfonylureas. Overall, the mean reduction in HbA_{1c} was 1.03%. This is an interesting feature of AGIs. Patients who have failed on the two most commonly prescribed oral antidiabetic medications, metformin and sulfonylureas, still respond to AGIs because their mechanism of action is not dependent on the availability of insulin.

Efficacy of AGIs compared or added to insulin

In type 2 diabetic subjects failing on oral agents, bedtime neutral protamine Hagedorn was more effective in reducing HbA_{1c} than the addition of acarbose with meals [14]. However, a clear metabolic benefit was observed in six studies ($n = 426$) after acarbose treatment was introduced in type 2 diabetic patients on insulin therapy, resulting in a mean reduction in HbA_{1c} of 0.71% [15–19]. A decrease in insulin requirement was also noted after the introduction of acarbose [18,20], but the clinical significance is questionable. However, adding acarbose to insulin therapy is associated with less weight gain [19]. This is an interesting additional benefit of the AGIs.

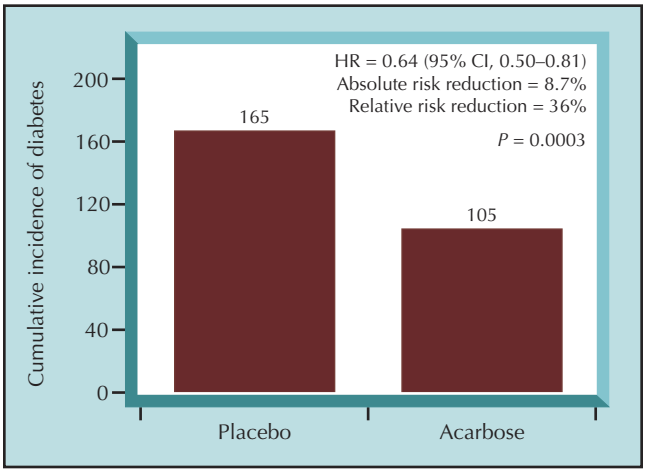

Figure 2. The efficacy of acarbose in the prevention of diabetes in subjects with impaired glucose tolerance. HR—hazard ratio. (*Adapted from* Chiasson et al. [22].)

Efficacy of AGIs in the Prevention of Type 2 Diabetes

It is generally believed that all subjects developing type 2 diabetes must pass through a prediabetic phase called impaired glucose tolerance (IGT). This category of glucose intolerance is characterized by postprandial or postchallenge (75 g of glucose) hyperglycemia resulting from insulin resistance and insulin secretion defect. A number of observational studies have clearly shown that in subjects with IGT, the risk of progressing to diabetes is directly proportional to the 2-hour plasma glucose after a 75-g oral glucose tolerance test (OGTT) [21]. It was therefore hypothesized that reducing postprandial hyperglycemia with acarbose in subjects with IGT should result in a reduction in the risk of progressing to diabetes. This hypothesis was tested in the STOP-NIDDM (Study to Prevent Non-Insulin-Dependent Diabetes Mellitus) trial [22].

A total of 1429 subjects were randomized in a double-blind fashion to acarbose (up to a dose of 100 mg TID with meals) or placebo. The patients were followed up for a mean period of 3.3 years. Acarbose treatment was associated with a relative risk reduction of 25% if a single positive OGTT was used for the diagnosis of diabetes. However, on the basis of two positive OGTTs as recommended by the World Health Organization and the American Diabetes Association, the relative risk reduction was 35.6% (Fig. 2) [23,24]. This beneficial effect of acarbose was independent of age, sex, and body mass index. Furthermore, the STOP-NIDDM trial also demonstrated an increase in conversion of IGT to normal glucose tolerance in the group treated with acarbose (hazard ratio = 1.42 [95% CI, 1.24–1.62]; $P < 0.0001$). The number needed to treat was 11 over a period of 3.3 years to prevent one new case of diabetes mellitus. The Chinese study also showed a reduction in the incidence of diabetes in 321 subjects with IGT randomized to either no treatment, diet and exercise, acarbose, or metformin for a period of 3 years

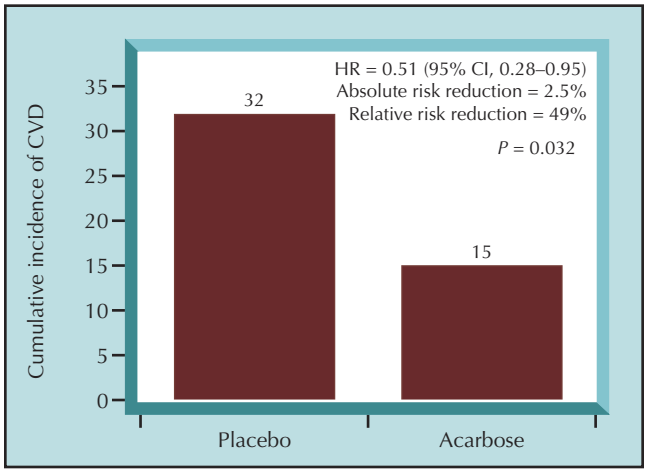

Figure 3. The effect of acarbose treatment on cardiovascular events. CVD—cardiovascular disease; HR—hazard ratio. (*Adapted from* Chiasson et al. [37].)

[25]. Relative risk reduction in the development of diabetes was 83% for acarbose ($P < 0.001$), compared with 65% for metformin ($P < 0.001$) and 29% for diet and exercise (not significant). Thus, acarbose is effective in preventing type 2 diabetes in patients with IGT.

Significant risk reduction of diabetes in patients with IGT has also been demonstrated with intensive lifestyle modification program or through other pharmacologic therapy (eg, metformin, glitazones). Metformin showed similar efficacy as acarbose in preventing or delaying development of diabetes (31%) [26]. However, in the DPP (Diabetes Prevention Program) study, metformin was not effective in older patients (> 65 years) and in less obese patients (body mass index < 35 kg/m^2). Lifestyle intervention and rosiglitazone showed the highest efficacy (~ 60%) [26–28].

Efficacy of AGIs in the Prevention of Vascular Complications

The current criteria for the diagnosis of diabetes are based on the appearance of diabetes-specific microvascular complications. Although prediabetes such as IGT is not associated with microvascular complications, it is associated with an increased risk of macrovascular complications [29].

Intensive glycemic control resulting in reduced HbA_{1c} is associated with a significant reduction in microvascular complications in both type 1 and type 2 diabetes [1,3]. Monnier et al. [30] have shown that HbA_{1c} level is the product of both PPPG as well as FPG. In fact, they have shown that at HbA_{1c} levels between 7.3% to 8.4%, the contribution between PPPG and FPG is 50:50. In their diabetic population, below 7.3%, PPPG contributed 70% of the HbA_{1c}, thus suggesting that PPPG contributes significantly to the development of diabetes-specific complications. However, no studies have looked specifically at the effect of treatment of PPPG on microvascular complications. Shiraiwa et al. [31] have followed 151 newly diagnosed type 2 diabetic patients over a 5-year period under different treatment and have looked at the predictors for microvascular complications. The 2-hour PPPG was a stronger predictor of retinopathy than HbA_{1c}. It is therefore suggested that the importance of PPPG in the development of diabetes-specific complications is understated.

More data support an important role of PPPG in the development of macrovascular disease [29,32,33]. In the Paris Prospective study, Eschwege et al. [34] have shown that in subjects with IGT, incidence of cardiovascular disease (CVD) was twice as high as subjects with normal glucose tolerance test and similar to those with newly diagnosed type 2 diabetes. This was also supported by Hu et al. [35], who showed that cardiovascular events started many years before the development of diabetes. This has now been confirmed by a number of observational studies in populations with various degrees of glucose intolerance; hyperglycemia, particularly postprandial hyperglycemia, was always a strong and independent risk factor for CVD [36].

In the DECODE (Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe) study, FPG was not a risk factor after adjusting for the 2-hour plasma glucose [29]. It was therefore postulated that decreasing PPPG should result in a reduction in the risk of CVD. This was tested in subjects with IGT in the STOP-NIDDM trial as a secondary objective [37]. Acarbose treatment in subjects with IGT was associated with a significant reduction in cardiovascular events (hazard ratio 0.51 [95% CI, 0.28–0.95]; P = 0.032) (Fig. 3). Furthermore, in a subpopulation of the STOP-NIDDM trial population ($n = 115$), Hanefeld et al. [38] showed that acarbose treatment was associated with a 50% reduction in the progression of the intima-media thickness of the carotid arteries ($P = 0.027$), an accepted surrogate for atherosclerosis. Furthermore, Hanefeld et al. [39] did a meta-analysis of long-term randomized controlled studies with acarbose in patients with type 2 diabetes looking at cardiovascular events. A total of 2180 patients were included: 1248 on acarbose and 932 on placebo. Using the Cox proportional analysis, acarbose treatment was associated with a risk reduction of 35% ($P = 0.006$) for any cardiovascular events and 64% ($P = 0.012$) for myocardial infarction. This was similar to the observation made in subjects with IGT in the STOP-NIDDM trial.

Overall, these observations do support a role for acarbose in the prevention of macrovascular disease. This is also supported by mechanistic studies showing that in subjects with IGT, acarbose, through a lowering of PPPG, resulted in a lowering of PPPG-associated rise in oxidative stress markers [40], in inflammatory markers (Lu, Personal communication), in procoagulation markers [41], and in endothelial dysfunction [42]. However, definite proof has to come from a prospective well-powered study whose objective will be the effect of acarbose on cardiovascular events in subjects with IGT. This is now being done in the ACE (Acarbose Cardiovascular Evaluation) trial.

Table 1. General features of acarbose in the treatment of type 2 diabetes

Acarbose is effective in all patients with postprandial hyperglycemia, no matter the treatment in place
Patients with recent-onset diabetes or drug-naive subjects seem to benefit more from acarbose introduction
Glucose-lowering effect is noted within the first week of treatment and persists even after 3 years of treatment
Efficacy is independent of sex or racial origin
Acarbose is not associated with weight gain. Most studies show a small but consistent weight loss
Acarbose is not associated with hypoglycemia when used as monotherapy
The efficacy of acarbose is dose-dependent, with a plateau effect between 100 and 200 mg three times a day

Indications for AGIs

The indications for the prescription of AGIs have to be based on their unique mechanism of action, affecting primarily postprandial hyperglycemia. Therefore, AGIs should be considered in every subject in whom postprandial hyperglycemia is the dominant metabolic abnormality (Table 1).

- AGIs should be considered for monotherapy in all patients with postprandial hyperglycemia and normal or slightly elevated FPG (< 10 mmol/L), particularly in elderly patients with type 2 diabetes
- AGIs should be considered for combination with other oral hypoglycemia agents or basal insulin in the presence of inadequate glycemic control, particularly postprandial
- AGIs should be considered as an alternative when other oral hypoglycemic agents are contraindicated
- AGIs should also be considered in patients poorly controlled with a combination of oral hypoglycemic agents refusing insulin
- AGIs are recognized as safe and nontoxic drugs. Their only side effects are gastrointestinal symptoms, mainly flatulence and diarrhea, and are related to their mechanism of action. These can be minimized by a "start low, go slow" approach. For acarbose, it is suggested to start with 25 mg every day and increase by 25 mg per day once a week till a dose of 50 mg TID with meals is achieved by the 6th week
- The recommended doses for the AGIs are 25 to 100 mg TID with meals for both acarbose and miglitol. It has to be administered after the first bite of each meal or no later than 15 minutes after the beginning of the meal
- There are no absolute contraindications to AGIs. However, it is not recommended to use acarbose therapy in patients presenting with intestinal malabsorption syndromes, inflammatory bowel disease, intestinal obstruction, and hepatic diseases. It should be noted that trials in diabetic cirrhotic patients have demonstrated improved glycemic control with acarbose, without adverse effects on liver function [43]. Thus, restrictions related to hepatic function can be re-questioned. Also, because of lack of data in certain groups of patients, AGIs should be avoided in cases of severe renal impairment (creatinine clearance < 25 mL/min), in pregnant or lactating women, and in children below 12 years of age.

Conclusions

The role of postprandial hyperglycemia has been underestimated in the development of diabetes and its vascular complications. AGIs are drugs that specifically target PPPG. Of this family of drugs, acarbose has to be the best studied among all oral antidiabetic agents. It has been shown to be effective in preventing diabetes in subjects with IGT. It also has proven to be effective in improving glycemic control and HbA_{1c} in patients with diabetes. One can extrapolate that such reduction in HbA_{1c} should be associated with a decreased risk of microvascular complications. There are data both in IGT and in type 2 diabetes suggesting that acarbose can also reduce the risk of macrovascular disease. Furthermore, it is a safe and nontoxic drug. Its only side effects are moderate gastrointestinal symptoms that can be avoided or minimized by the "start low, go slow" approach. In type 2 diabetes, controlling postprandial hyperglycemia is essential for achieving recommended HbA_{1c} goals [5].

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