Acarbose: safe and effective for lowering postprandial hyperglycaemia and improving cardiovascular outcomes

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ABSTRACT
α-Glucosidase inhibitors (AGIs) are a class of oral glucose-lowering drugs used exclusively for treatment or prevention of type 2 diabetes mellitus. AGIs act by altering the intestinal absorption of carbohydrates through inhibition of their conversion into simple sugars (monosaccharides) and thus decrease the bioavailability of carbohydrates in the body, significantly lowering blood glucose levels. The three AGIs used in clinical practice are acarbose, voglibose and miglitol. This review will focus on the cardiovascular properties of acarbose. The current available data suggest that AGIs (particularly acarbose) may be safe and effective for the treatment of prediabetes and diabetes.

MECHANISM OF ACTION
AGIs behave as pseudocarbohydrates in the intestine. They act through competitive inhibition of α-glucosidase enzymes found in the brush border of gut epithelium. These enzymes facilitate the conversion of poorly absorbable oligosaccharides and polysaccharides to monosaccharides, which are easily absorbed in the intestine.

Acarbose, a pseudo-tetrasaccharide, possesses nitrogen between the carbohydrate monomers. It competitively inhibits α-glucosidase enzymes, particularly α-glucosidase, with a high affinity. The reduced absorption of monosaccharides may lead to a decrease in postprandial hyperglycaemia. Acarbose does not inhibit β-glucosidases such as lactase.

INTRODUCTION
Currently, there are many different classes of medications to treat diabetes, such as biguanides (metformin), sulfonylureas, insulin, glucagon-like peptide 1 (GLP-1) agonists, dipeptidyl peptidase IV inhibitors, thiazolidinediones and sodium-glucose transporter 2 inhibitors (to name a few). However, α-glucosidase inhibitors (AGIs) are another class of antidiabetic medications, albeit rather neglected, in the treatment of prediabetes/diabetes. Despite this fact, acarbose has recently been recommended in certain guidelines for treating diabetes, receiving preferred status even when compared to other oral glucose lowering drugs, due to its proven ability to reduce cardiovascular events. Additionally, acarbose has minimal risk for hypoglycaemia and, when titrated slowly, is generally well tolerated despite occasional gastrointestinal side effects such as flatulence. Acarbose has also been found to improve vascular health and also likely has antiplatelet effects. Lastly, acarbose has been shown to provide euglycaemia, partially by increasing GLP-1 levels and blunting postprandial spikes of glucose and lipid levels.

SURROGATE END POINTS
Glycaemia
Foods containing starch, particularly refined carbohydrates such as white flour, generally provide a large percentage of the total daily caloric intake among cultures in the Western world. Carbohydrates, in general, differ substantially in their physiological and metabolic effects, depending on their source (eg, whole foods vs manufactured, processed and highly refined foods), and thus have varying health effects. Carbohydrates are often categorised on the basis of their glycaemic response, with low glycaemic index foods generally being considered helpful in the prevention of diabetes, coronary heart disease and obesity. The rate of carbohydrate digestion and the subsequent absorption with resultant spiking of blood glucose is the key factor affecting the glycaemic index. Low glycaemic index foods are created by different processing methods, such as adding highly viscous soluble fibre (eg, glucomannan), or amylase-inhibitory
Microvascular and macrovascular complications in type 2 diabetics are better linked with postprandial hyperglycaemia than fasting glucose. Also, postprandial hyperglycaemia is a marker of vascular risk in nondiabetics who cannot tolerate glucose. The pro-oxidative adverse effect of postprandial glycaemic excursions may be responsible for this cardiovascular risk. Moreover, glycaemic fluctuations, coupled with elevated free fatty acids, have a pro-oxidant effect on β cells of the pancreas. This can be especially dangerous in prediabetics compared to insulin-sensitive individuals, as it leads to β-cell exhaustion, which can precipitate overt clinical diabetes. Hence, the effect of acarbose to blunt postprandial hyperglycaemia may aid in preventing type 2 diabetes mellitus (T2DM) or delay its onset.

Wachters-Hagedoorn et al demonstrated that the peak glucose concentration and area under curve (AUC) from 0 to 120 min was significantly lower for corn pasta with acarbose (CPac) (6.0±0.2 mmol/L) versus CP (corn pasta alone) (6.7±0.3; p=0.007) and CPac (25.7±7.1 mmol/L/2 h) than for CP (65.3±17.3; p=0.034), respectively. Acarbose was also shown to significantly reduce the percentage of administered dose excreted as $^{14}$CO$_2$ in breath (CP 37.5±2.8 cum %/dose/6 h vs CPac 27.2±2.2; p=0.004) over the 360 min post-test meal.

A Cochrane meta-analysis found that acarbose therapy reduced glycated haemoglobin (HbA1c) levels by a mean of 0.8%. This decrease was accentuated in individuals with higher baseline HbA1c levels (baseline HbA1c of <7%, 7–9%, and >9% had decreases of 0.56% (95% CI 0.36 to 0.76), 0.78% (95% CI 0.63 to 0.93) and 0.99% (95% CI 0.53 to 1.33), respectively). A meta-regression analysis revealed regression coefficient of −0.12 (95% CI −0.26 to 0.03), showing an additional 0.12% decrease in HbA1c for every 1% increase in baseline HbA1c. Moreover, acarbose was shown to reduce fasting blood glucose by 1.09 mmol/L (28 comparisons; 95% CI 0.83 to 1.36) and 1 h postprandial glucose by 2.32 mmol/L (acarbose; 22 comparisons; 95% CI 1.92 to 2.73).

The glycaemic effect of acarbose on HbA1c did not vary with dose, however, acarbose did decrease postprandial glucose in a dose-dependent manner. Acarbose 50, 100, 200 and 300 mg three times a day reduced HbA1c by 0.90, 0.76, 0.77 and 0.78%, respectively, and postprandial glucose by 1.63, 2.26, 2.78 and 3.62 mmol/L, respectively. This glycaemic benefit of acarbose has been more significant in Asian trials than those in the West, due to predominant consumption of a carbohydrate-rich diet among Asian populations.

The minimal efficacy of acarbose on HbA1c, as described by a UK-Prospective Diabetes Study trial with a reduction of 0.5%, could be an underestimate. In this trial, acarbose was an add-on therapy at the end of study while the patients were pretreated for 8 years with antidiabetic medications. Also, this study experienced high drop-out rates.

**Oxidative effects, endothelial dysfunction and vascular damage**

Glucose excursions can lead to the formation of reactive oxygen species (ROS) such as superoxide, which leads to oxidative stress in the body. People with diabetes have been shown to have increased plasma concentrations of superoxide anions, which also vary in direct proportion with blood glucose levels. This oxidative damage may be responsible for the development of endothelial dysfunction, reduced flow-mediated vasodilation (FMVD) and microvascular and macrovascular complications.

The four main pathways involved in hyperglycaemia-induced vascular damage include: (1) activation of protein kinase C (PKC); (2) advanced glycation end (AGE) product formation and increased flux through; (3) polyol; and (4) hexosamine pathways. The RAGE (receptor for AGE products) ligation and effects of hyperglycaemia on the electron transport chain (ETC) lead to formation of ROS. Hyperglycaemia increases the electron flow in the Kreb’s cycle, thus accumulation of nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH2), and an increased proton transport via the inner mitochondrial membrane. This inhibits the ETC and prolongs the half-life of free radicals. These free radicals interact with oxygen and cause superoxide anion overproduction.

Mariella et al demonstrated the effect of glucose excursions on plasma nitrotyrosine levels, markers of oxidative damage. Nitrotyrosine levels were unchanged in states of euglycaemia (5 mmol/L for 120 min) while hyperglycaemic states (15 mmol/L for 120 min) caused increased nitrotyrosine levels and increased blood pressure. Further research by Ceriello et al showed that oral glucose tolerance test (OGTT) in people with and without diabetes blunted antioxidant mechanisms, as assessed by total radical trapping antioxidant parameter (TRAP). TRAP levels were significantly lower in people with diabetes compared to those without diabetes (660.5+46 vs 832.6+56 μmol/L, p<0.03) and TRAP was significantly reduced in both groups following the OGTT. Similar findings were demonstrated after a meal. Nitrotyrosine levels were measured after standard meal tests in 23 people with T2DM and 15 matched controls. The former group received two standard meals—one 30 min prior to regular insulin (Actrapid) and the other with insulin aspart. This was carried out to evaluate postprandial hyperglycaemia. The results revealed a linear correlation between postprandial hyperglycaemia and nitrotyrosine levels. Insulin aspart reduced postprandial glucose excursion (p<0.03) and nitrotyrosine levels (p<0.03) as compared to regular insulin.
findings clearly depict acute hyperglycaemia as a driver of oxidative stress, particularly in type 2 diabetics. Kawano et al compared FMVD of the brachial artery in response to an OGTT in individuals with IGT (n=24) and normal individuals (n=17). FMVD at baseline was 7.53±0.40%, 6.40±0.48% and 4.77±0.37% in the controls, IGT and diabetes groups, respectively. After 1 h, the FMVD was reduced by 43.7% (p<0.05), 78.5% (p<0.005) and 71.7% (p<0.005) in the controls, IGT and diabetes groups, respectively. Furthermore, plasma levels of thiobarbituric acid, another marker of oxidative damage, correlated positively with FMVD (r=−0.58, p<0.01). 

Postprandial hyperglycaemia has also been shown to cause an adverse increase in carotid intimal medial thickness (IMT), irrespective of adjustment for associated risk factors. Benefits of acarbose on carotid IMT were evaluated in a subgroup of the Stop non-insulin dependent diabetes mellitus (STOP-NIDDM) trial, which revealed a significant reduction in the progression of IMT-mean in the acarbose versus placebo group. The acarbose cohort had an IMT-mean increase of 0.24 (0.07) mm versus 0.05 (0.06) mm in the placebo cohort, after a mean duration of 3.9 years (p=0.027). Acarbose therapy reduced the yearly IMT-mean increase by ≥50% which was further reduced to that observed in participants with normal glucose tolerance.

Further, Esposito et al showed that in individuals with both normal (n=20) and IGT (n=15) intravenous glucose pulses caused a significantly greater increase in mediators of subclinical inflammation (interleukin-6 and tumour necrosis factor-α) as compared to sustained hyperglycaemic periods. Also, oxidative stress causes upregulation of soluble adhesion molecules, facilitating leucocyte adherence to endothelium thus initiating atherogenesis. Significantly increased levels of plasma intracellular adhesion molecule-1 (ICAM-1) were observed post-OGTT in people with T2DM. This increase was blunted by supplementation of glutathione during the OGTT. A further crossover study of 10 patients with T2DM indicated that supplementation with L-arginine provided overnight euglycaemia as well as reduced plasma ICAM-1 levels. This evidence supports the hypothesis that hyperglycaemia is a key mediator in altering the homeostasis of adhesion molecules, subclinical inflammation and atherosclerosis.

Acarbose has been demonstrated to prevent postprandial hyperglycaemia-induced acute endothelial dysfunction. Recently, Santilli et al evaluated the effects of acarbose on markers of lipid peroxidation and platelet activation (8-iso-prostaglandin (PG)F2α, 11-dehydrothromboxane (TX)B2, plasma CD40 ligand and plasma P-selectin). The acarbose group (n=25) had a significantly greater reduction in 11-dehydro-TXB2 levels (by 40% vs baseline) versus the placebo group (n=23) (mean change −0.23 vs 0.031 log pg/mg creatinine); the treatment difference was −0.26 (95% CI −0.33 to −0.18) log pg/mg creatinine (p<0.0001). Similarly, the former group had a significant reduction in P-selectin levels as opposed to the placebo group (mean change −0.19 vs 0.041 log ng/mL); the difference between treatments was −0.23 (95% CI −0.33 to −0.12) log ng/mL (p<0.0001). Also, 8-iso-PGF2α excretion rate decreased significantly more in the acarbose group (by 33% vs baseline) than in the placebo group (mean change −0.19 vs 0.013 log pg/mg creatinine); the difference between treatments was −0.20 (95% CI −0.27 to −0.13) log pg/mg creatinine (p<0.0001). The plasma CD40L also had a median decrease of 31% versus baseline after 20 weeks of acarbose therapy.

The data demonstrating beneficial effects of acarbose on endothelial dysfunction are somewhat limited. However, Shimabukuro et al observed that acarbose therapy in people with diabetes stopped the postprandial 120 and 240 min decrease in peak forearm blood flow response and total reactive hyperaemic flow, and the markers of resistance artery endothelial function on strain-gauge plethysmography were no longer seen. Also, these variables had a significant inverse correlation with peak glucose, plasma glucose excursion and ΔAUC glucose. However, this study did not compare the long-term effects of acarbose therapy on postprandial endothelial function. Kato et al evaluated these long-term effects of acarbose therapy for 12 weeks, and concluded that postprandial flow mediated dilation (FMD) of the brachial artery with acarbose therapy was significantly higher (p<0.05) than that with placebo. The percentage of postprandial decrease in FMD from baseline fasting FMD was significantly blunted in the acarbose group as opposed to the control group (−1.5±0.95 vs −5.0±2.4%, p<0.001). On extrapolating postprandial hyperglycaemia-induced pathological changes into animal models, acarbose was shown to prevent intracardiac interstitial fibrosis and cardiomyocytes hypertrophy.

This evidence, when considered in a broad perspective, suggests that postprandial hyperglycaemia is likely to cause vascular homeostatic imbalance and proatherogenic endothelial dysfunction, further increasing CV risk. Acarbose, by reducing postprandial glucotoxicity, may be an effective therapy in reducing these adverse effects.

Kidney function

Hyperglycaemic states play a key role in kidney dysfunction. This is initiated by genesis of glomerular hyperfiltration, which is later succeeded by a state that is characteristically referred to as diabetic nephropathy. This hyperglycaemic damage is known to be worse in patients with existing kidney disease (eg, those having proteinuria as compared to those with normal albumin excretion). This hyperglycaemia-induced increase in
glomerular filtration rate has a brisk onset and persists until high glucose levels return to normal. Also, glucose excursions have been demonstrated to stimulate increased collagen production by mesangial cells in vitro, which is a key characteristic of diabetic kidney disease.

Postprandial hyperglycaemia has been shown to be inversely associated with the time interval between diabetes and the development of nephropathy in people with both type 1 diabetes and T2DM. Despite this important relationship between glycaemic control and diabetes-induced kidney dysfunction, the effect of acarbose therapy remains less evaluated, especially in human beings. Most evidence is based on findings observed in animal models.

Initial research in the 1980s used the db/db mouse model to demonstrate the effects of acarbose on renal function. These models were selected as mice develop nephropathy rather quickly (ie, by 3 months of age), which is characterised by endogenous immunoglobulin deposition in the glomerular mesangium and progressive widening of the glomerular mesangial matrix. This makes them an ideal animal model to evaluate the effects on the kidneys in just a short period of time. Four groups of test animals were tested—controls (N=6), A-10 (N=6, that received acarbose 10 mg/100 g), A-20 (N=7, that received acarbose 20 mg/100 g) and A-40 (N=6, that received acarbose 40 mg/100 g). It was observed that the control and A-10 group had similar intensity and distribution of immunoglobulin staining (IgG and IgM). The A-20 group had a different pattern as opposed to controls for IgM (p=0.002) and IgA (p=0.001) staining. Interestingly, the A-40 group had significantly less immunofluorescence staining (distribution and intensity) with each immunoglobulin sample (p values, IgM=0.001, IgA=0.01, IgG=0.05) as compared to other groups. Also, unlike the animals in the control group, the animals in this group demonstrated significantly less mesangial area and no evidence of increased mesangial cellularity, and had normal glomerular and tubular basement membranes. Similarly, in 1990, a comparable research study conducted using Cohen and Rosenmann diabetic rats demonstrated significantly less incidence and severity of glomerulosclerosis in study animals as compared to controls, with 3 months (p<0.05), 5 and 7 months (p<0.01) of acarbose therapy. Further research by Cohen et al using streptozocin diabetic rats, concluded that 8 weeks of acarbose therapy reduced glomerular basement membrane (GBM) glycation and retarded the nephropathogenic process in experimentally induced diabetes mellitus. Macedo et al later made similar conclusions demonstrating that combination therapy with acarbose and insulin in alloxan-diabetic rats prevented GBM thickening, and the existing thickening was equivalent to that expected for normal rats of the same age.

Advancing this research, Cohen et al demonstrated that a similar 8-week course of acarbose therapy after induction of diabetes in streptozocin diabetic rats reduced the increase in urinary albumin excretion (UAE) in untreated diabetic rats with respect to controls. Another investigation from Japan, by Sato et al, revealed that Wistar diabetic rats had a significantly elevated UAE versus non-diabetic controls (829.0+478.6 vs 199.1+60.6 pg/day, p<0.001), while rats on 8 weeks of acarbose therapy demonstrated UAE suppression versus diabetic rats (411.7+309.7 pg/day, p<0.05). Also, diabetic rats had elevated, while acarbose treated rats had a significant suppression, of hyperglycaemia-induced increase in creatinine clearance as opposed to non-diabetic controls (p=0.05 for both comparisons). Lastly, acarbose was also shown to normalise the density and number of anionic sites on GBM, which were normally depleted in diabetic rats.

Macedo et al evaluated the effects of long-term treatment with insulin and/or acarbose on GBM thickening in alloxan-diabetic rats. They found that untreated diabetic rats had a significantly thicker GBM as opposed to normal rats. Beginning at 6 months after diabetes induction, the GBM of untreated diabetic rats was significantly (p<0.05) thicker (4.446 +/- 0.45 mm) than that of normal rats (2.977 +/- 0.63 mm). Both insulin and acarbose prevented GBM thickening and their combination induced thickening similar to the age-dependent thickening observed for normal rats of the same age.

The possible beneficial effects of acarbose treatment in patients of chronic kidney disease (CKD) were evaluated by Evenepoel et al. Patients with CKD and on haemodialysis (n=107), have been shown to possess high concentrations of p-cresol (0.10 (0.30-64.45) mg/L) and other protein fermentation metabolites. Also, numerous in-vitro data suggest possible implication of p-cresol in immunodeficiency and endothelial dysfunction, which characterise the uraemic syndrome. The ability of acarbose to increase colonic carbohydrate availability and lower pH by increasing colonic production of short-chain fatty acid butyrate, helps bacteria to use carbohydrates for energy instead of fermenting amino-acids. This process is referred to as ‘catabolite-repression’. This decreases the ammonia and nitrogen load to be filtered by the kidneys, and protects kidney function. Per-protocol analysis by Wilcoxon signed rank test for paired data revealed significant differences between baseline and acarbose treatment, serum p-cresol (mg/L) -1.14 (CI 0.93 to 3.03) versus 1.11 (CI 0.31 to 1.82), p=0.047, urinary p-cresol (mg/day) -29.93 (CI 6.79 to 75.19) versus 10.54 (CI 1.08 to 30.85), p=0.031, urinary p-cresol/urea nitrogen ratio (mg/g) -1.65 (CI 0.46 to 6.33) versus 0.62 (CI 0.05 to 2.38), p=0.031 and faecal nitrogen (g/day) -1.04 (CI 0.47 to 2.29) versus 1.14 (CI 0.76 to 3.08), p=0.047, respectively. Additionally, in contrast to other AGIs, acarbose is not absorbed from the intestinal lumen, making it an ideal candidate in patients with CKD. Considering the above evidence, acarbose likely has renoprotective effects, particularly in those with, or at
risk of diabetes. Further research is warranted to evaluate the use of acarbose on renal function.

**Lipaemia**

The beneficial effects of acarbose therapy on serum lipids have been well described. Initial research by Hillebrand et al., from a double-blind crossover study, showed that acarbose has a dose–dependent effect for reducing postprandial total triglycerides, with a 200 mg dose being the most effective.

Baron et al., showed that, with acarbose treatment, the mean fasting cholesterol level fell from 214±19 to 187 ±15 mg/dL, p<0.03, the mean high-density lipoprotein (HDL) cholesterol level rose from 41±4 to 44±7 mg/dL, p>0.05, and the HDL to total cholesterol (TC) ratio increased from 0.20±0.02 to 0.24±0.03, p<0.05. The tri-glyceride levels in patients on acarbose were lower throughout the day and the integrated area under the triglyceride concentration curve was 16 211 ±2875 mg/dL/h pretreatment compared to 11 127 ±1827 mg/dL/h post-treatment (p<0.05).

In 1989, Walter-Sack et al., concluded that, in patients fed with a fibre-free formula diet, acarbose reduced total cholesterol, LDL cholesterol and fasting triglyceride concentration. Reaven et al., showed that acarbose lowered plasma triglyceride concentrations (2.4±0.1 to 2.1 ±0.1 mM, p<0.01) in individuals with poorly controlled T2DM (n=12).

Hanefeld et al., demonstrated, in a randomised, double-blind, placebo-controlled trial, that acarbose (100 mg three times daily) for 24 weeks as a first line therapy in patients with T2DM (n=94) reduced 1 h post-prandial triglyceride levels. Another description by Leonhardt et al., showed that acarbose reduced total serum cholesterol and total-to-HDL-cholesterol ratio. Also, after a test meal on day 0 and on week 24 of acarbose treatment, there was a significantly lower postpran-dial rise in serum triglycerides.

Kado et al., evaluated the effect of acarbose on post-meal lipaemia, in a crossover, placebo controlled trial involving patients with T2DM treated solely with medical nutrition therapy and/or sulfonylureas. They observed significantly lower serum triglycerides on post-meal tests with and without acarbose at 60, 90 and 120 min (p<0.01, p<0.01 and p<0.05, respectively). On measuring serum remnant-like particle (RLP) cholesterol postpran-dially, with and without acarbose, there were significant differences in favour of acarbose at 60 and 120 min (p<0.05 for both). Plasma RLP cholesterol is known to be involved in pathogenesis of atherosclerosis. Additionally, the serum apoC-II level at fasting level was significantly lesser than at 30, 60, 90, 120 and 180 min postprandial.

In a randomised placebo controlled study by Ogawa et al., using a single dose of 100 mg of acarbose and long-term treatment with 300 mg/day for 8 weeks, it was revealed that both therapies reduced one or more of the following: free fatty acids (FFAs) (postprandial or fasting), postprandial total triglycerides, and very low-density lipoprotein and chylomicron (CM) levels. Furthermore, two studies by Derosa et al., concluded that 7 months of acarbose therapy decreased TC, triglycerides and LDL cholesterol levels as opposed to the control group (both, p<0.05). Recently, in another year long prospective, randomised, parallel-group study by Koyasu et al., patients on acarbose had a significant decrease from baseline in mean 2 h fasting TC (from 178.0 (28.3) mg/dL to 165.5 (22.9) mg/dL; mean change, −11.26 (26.1) mg/dL; p=0.009 and triglyceride concentrations (from 146.8 (79.5) mg/dL to 112.8 (55.7) mg/dL; mean change, −30.4 (62.7) mg/dL; p=0.003).

The landmark STOP-NIDDM trial came to similar conclusions on the triglyceride-lowering efficacy of acar-bose therapy. The mean change in triglycerides from baseline to 3 years was favourable (placebo, −0.04 vs acarbose, −0.18 mg/dL), and the effect of acarbose evaluated using a repeated measures analysis of variance in reducing triglyceride levels was significant (p<0.01). The evaluation of relationship, according to the Cox Proportional Hazards Model Analysis, between treatment allocation and total triglyceride on the development of cardiovascular events, led to a HR of 1.236 (CI 1.001 to 1.526, p<0.05). The HRs for total, HDL and LDL cholesterol were 1.146 (CI 0.850 to 1.545), 0.382 (CI 0.125 to 1.707) and 1.185 (CI 0.838 to 1.677), respectively, but were not significant.

The Essen II study (n=96) in patients with uncontrolled T2DM treated at baseline solely with medical nutrition, compared the therapeutic effects of 24 weeks of acarbose with metformin on the serum lipid profile. There was a 26.8% decrease in mean triglycerides among the acarbose group, compared to 9.2% in the metformin group, and an 8.8% reduction in the placebo group. The LDL-C level increased by 5% in the placebo group, but was reduced by 21.8% with acarbose treatment, and remained unchanged with metformin treatment (p=0.0065 for acarbose vs placebo; p=0.0134 for acarbose vs metformin). HDL cholesterol improved by 16.2% with acarbose treatment, was lowered by 9.7% in the placebo group and was unaffected by metformin (p=0.0162 for acarbose vs placebo). The LDL-C to HDL-C ratio decreased 26.7% with acarbose, was unaltered by metformin, and by 14.4% in the placebo group (p=0.0013 for acarbose vs placebo; p=0.0311 for acarbose vs metformin). Another study by Willms and Ruge showed that acarbose and metformin therapy had similar outcomes regarding TC concentration (−0.23 mM for both), but acarbose was superior in triglyceride reduction (−0.41 mM for acarbose, −0.27 mM for metformin, and −0.3 mM for placebo).

A recent meta-analysis evaluating the effects of acar-bose, pioglitazone, DPP-4 inhibitors and sulfonylureas showed that triglycerides were reduced significantly with acarbose (MD −0.19 (−0.24 to −0.15) mmol/L; 95% CI −16.81 (−21.23 to −13.27) mg/dL), pioglitazone (MD
Acarbose has also been shown to be beneficial in other states of hypertriglyceridaemia unrelated to T2DM. In a study involving participants with isolated familial hypertriglyceridaemia, progressive reduction of mean baseline triglyceride levels was demonstrated for 4 months (p<0.05). There was also an increase in HDL-C with acarbose (p<0.008). Another case report describes use of acarbose for the treatment of severe hypertriglyceridaemia after 10 days of l-asparaginase therapy, along with dexamethasone use, in a patient with acute lymphoblastic leukaemia. Acarbose halved the levels of serum triglycerides in just a few days, and then reduced these levels to less than 10 mmol/L.\textsuperscript{96}

A preliminary report by Nakano \textit{et al}, which evaluated the mechanism behind the lipid lowering effects of acarbose, used Caco-2 cells, a common in vitro model of enterocytes. On treatment of Caco-2 cells with acarbose (10 mmol/L), oleic acid absorption decreased by 30\%, the amount of secreted triglyceride-rich lipoprotein decreased by around 10\% and apo B-48 secretion reduced by 50\%. Apo A-I secretion remained unaffected.\textsuperscript{99} Thus these authors proposed that acarbose could reduce CM synthesis or secretion by intestinal cells, thus decreasing serum lipids. Also, acarbose was shown to reduce apo B-48 secretion,\textsuperscript{99} and thus decrease RLP cholesterol particles,\textsuperscript{87} which is known to be proatherogenic.\textsuperscript{88}

Increased levels of non-fasting triglycerides are of even more concern regarding their effect on metabolic health. They lead to increased levels of RLP cholesterol and also predispose to an increased risk of myocardial infarction, ischaemic heart disease and death, in men as well as in women. These conclusions were based on a prospective study by Nordestgaard \textit{et al} during a mean follow-up of 26 years; 1793 participants (691 women and 1102 men) developed myocardial infarction (MI), 3479 (1567 women and 1912 men) developed IHD and 7818 (3731 women and 4087 men) died. HRs were calculated for four categories of baseline non-fasting triglycerides (TGs) (1–1.99 mmol/L, 1.99 to 2.99 mmol/L, 2.99 to 4.99 mmol/L, 4.99 to 9.99 mmol/L) and more (>9.99 mmol/L) versus TGs of less than 1 mmol/L (<0.85 mg/dL). The age-adjusted HRs and multifactorially adjusted HRs (aHRs) for MI in each category were 2.2 (aHR, 1.7), 4.4 (aHR, 2.5), 3.9 (aHR, 2.1), 5.1 (aHR, 2.4) and 16.8 (aHR, 5.4), respectively (for both, p for trend <0.001), in women, and 1.6 (aHR, 1.4), 2.3 (aHR, 1.6), 3.6 (aHR, 2.3), 3.3 (aHR, 1.9) and 4.6 (aHR, 2.4), respectively (for both, p for trend <0.001), in men. The HR values for IHD were 1.7 (aHR, 1.4), 2.8 (aHR, 1.8), 3.0 (aHR, 1.8), 2.1 (aHR, 1.2) and 5.9 (aHR, 2.6), respectively (for both, p for trend <0.001), in women, and 1.3 (aHR, 1.1), 1.7 (aHR, 1.3), 2.1 (aHR, 1.3), 2.0 (aHR, 1.2) and 2.9 (aHR, 1.5), respectively (p for trend <0.001 for HR and p for trend =0.05 aHR), in men. Lastly, the ratios for total death, among women, were 1.3 (aHR, 1.3), 1.7 (aHR, 1.6), 2.2 (aHR, 2.2), 2.2 (aHR, 1.9) and 4.3 (aHR, 3.3), respectively (for both, p for trend <0.001), and 1.5 (aHR, 1.2), 1.4 (aHR, 1.4), 1.7 (aHR, 1.5), 1.8 (aHR, 1.6) and 2.0 (aHR, 1.8), respectively (for both, p for trend <0.001), in men.\textsuperscript{100} Thus acarbose, by its advantageous effect on postprandial lipid metabolism may be a useful drug to improve morbidity and mortality outcomes of diabetes (further discussed below).
this synergistic effect was removed with concurrent administration of inhibitors of mitochondrial ATP-sensitive K channels (mKATP). Conversely, ischaemic preconditioning involves upregulation of mKATP channels, thus preventing ischaemic-reperfusion injury. The channels open during ischaemic injury and reduce the potential gradient, thus decreasing mitochondrial calcium influx, and, in turn, preserving mitochondrial function. This suggests that acarbose may exert a protective effect on the heart mechanistically similar to ischaemic preconditioning and may reduce infarct size. Acarbose has also been shown to be beneficial in patients with Roux-en-Y Gastric Bypass operations as it ameliorates reactive hypoglycaemia.

**PATIENT-RELATED OUTCOMES**

**Weight loss**

Consistent data demonstrate that acarbose induces weight loss in animals. The data in humans are more ambiguous; some reports indicate that acarbose is weight-neutral, while others report significant weight loss. The studies reporting weight loss are mostly from Asia, and some of them report weight loss of more than 1 kg. The explanation for the weight-loss effect of acarbose has been attributed to its ability to increase secretion of GLP-1.

A recent ethno-specific meta-analysis by Li et al evaluated the effects of acarbose monotherapy on weight in Eastern and Western populations. Overall, acarbose was shown to provide significantly more weight-loss by an average of 0.52 kg (95% CI −0.78 to −0.25) as opposed to placebo (p=0.0001), and, in the Eastern population, acarbose caused significant weight loss of 1.20 kg (95% CI −1.73 to −0.68) compared with placebo (p<0.05), whereas in the Western group, it produced minimal, insignificant weight loss of 0.28 kg (95% CI −0.59 to 0.03) versus placebo (p=0.08). Also, it was found that acarbose was more effective for weight reduction in the Eastern compared to Western population (by 0.92 kg, 95% CI 0.20 to 1.64, p<0.0001; I²=88.8%). Additionally, acarbose caused significantly more weight-loss by an average of 0.67 kg (95% CI −1.36 to −0.47), with a significant trend towards the former (difference: −1.35 kg; χ²=17.55, df=1, p=0.05; I²=94.3%). Also, reduction in absolute BMI with acarbose therapy was 1.68 kg/m² (−3.37 to 0.02) and 0.45 kg/m² (−0.82 to −0.08) for Eastern populations and Western populations, respectively; however, the inter-group difference was non-significant.

It has been reported that each 1 kg of weight reduction improves life expectancy by 3–4 months in individuals with diabetes. Also, Wing et al have concluded that modest weight loss of 5–10% leads to a significant improvement in CVD risk factors at 1 year. These benefits were increased with larger weight reduction. Thus, acarbose may be useful as an adjunct to diet and exercise for reducing cardiovascular risk and improving longevity in hyperglycaemic individuals.

**CARDIOVASCULAR RISK**

Glucose excursions are known to be key mediators of macrovascular and microvascular complications, not only in diabetic individuals but also in people with impaired glucose tolerance (IGT). Persons with IGT are almost three-times more likely to develop coronary heart disease and other major cardiovascular events than people with normal glucose tolerance (NGT). Acarbose, by beneficiary the surrogate markers of CVD (as described above), may be a useful drug for reducing CVD risk (box 1).

The landmark Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial evaluated the utility of acarbose therapy over 3 years versus placebo for the prevention of diabetes among 1429 patients with IGT. In the patients randomised to acarbose therapy, 32% developed overt diabetes compared to 42% on placebo (relative hazard 0.75 (95% CI 0.63 to 0.90); p=0.0015). Additionally, acarbose significantly reversed IGT to NGT; an effect that was highly significant when compared to the placebo group (p<0.0001). Importantly, acarbose also led to a 49%
relative risk reduction (2.5% absolute risk reduction) in cardiovascular (CV) events (HR: 0.51; 95% CI 0.28 to 0.95; p=0.03) with a 91% relative risk reduction in the risk of MI (HR, 0.09; 95% CI 0.01 to 0.72; p=0.02) and a 34% relative risk reduction (a 5.3% absolute risk reduction) in the incidence of newly diagnosed hypertension (HR, 0.66; 95% CI 0.49 to 0.89; p=0.006). The cardiovascular event risk reduction (HR, 0.47; 95% CI 0.24 to 0.90; p=0.02) and hypertension risk reduction (HR, 0.62; 95% CI 0.45 to 0.86; p=0.004) linked with acarbose treatment remained statistically significant even after adjusting for major risk factors.95 138

MeRia (MeTa-analysis of Risk Improvement under Acarbose), a meta-analysis of seven randomised trials testing acarbose in 2180 patients with T2DM and a follow-up of 1 year or longer, revealed a significant 64% decrease of relative risk of myocardial infarction (9 vs 19, HR=0.36 (95% CI 0.16 to 0.80), p=0.0120) and a 35% relative risk reduction for any CV event (76 vs 88, HR=0.65 (95% CI 0.48 to 0.88), p=0.0061) with acarbose therapy versus placebo.139 Box 2 summarises the CV benefits of acarbose.

Though it is reasonable to hypothesise that acarbose is beneficial at reducing CV events, the number of CV events reported in these studies was small and the dates were obtained from post hoc analyses. Thus, a definitive large, prospective, randomised, placebo controlled trial is warranted to effectively prove the above hypothesis.95 139 140 To fulfil this requirement, the Acarbose Cardiovascular Evaluation (ACE) Trial was started in 2009, and was designed to assess the usefulness of acarbose in reducing CV complications in a secondary prevention population with IGT.140 141

The ACE trial is a randomised, placebo-controlled, double-blind, secondary prevention trial enrolling 7500 patients with IGT and coronary heart disease (a MI in the past, unstable angina or current stable angina) in China and Hong Kong. The patients are randomised into two groups, one receiving acarbose 50 mg three times a day and the other receiving matching placebo in a 1:1 fashion. All the patients will receive effective guideline-based CV care with a minimum of 3 months out from a previous MI. The time to first occurrence of CV death, non-fatal MI or stroke is the primary CV outcome, with the prevention of diabetes as well as all-cause mortality as secondary outcomes.140 141

**Longevity**

With increasing data demonstrating benefits of acarbose therapy in hyperglycaemic individuals, it is reasonable to hypothesise a broader potential of acarbose in health promotion. In a study involving mice spanning their entire lives, it was revealed that an add-on of 0.1% acarbose to standard diet (65% carbohydrates and 22% protein for total caloric intake), starting at the age of 4 months, caused a significant increase in median and maximal lifespan in both sexes, more so in males than females (22%, p<0.0001 vs 5%, p=0.01). The levels of HbA1c remained unaffected because of minimal impact on fasting hyperglycaemia, whereas acarbose mainly impacted the postprandial glucose rise.142 However, despite these findings, it is difficult to explain the increase in longevity as these mice were not diabetic and were not at risk of developing diabetes.

It was discovered that acarbose therapy in mice led to a significant rise in the levels of serum FGF21 and a significant decline in serum insulin-like growth factor-1 (IGF-1) levels.142 It has been established that systemic IGF-1 activity mediates the ageing process and influences longevity in mice.143 Also, FGF 21 by decreasing IGF-1 activity and thus increases longevity.143 Moreover, genetically altered mice with constitutive FGF21 secretion have been reported to have increase in both mean and maximal lifespan, thought to be mediated by IGF-1 downregulation.147 148

Though there is no evidence of acarbose-induced hepatic FGF21 production, long-term therapy with acarbose diverts surplus glucose to distal parts of the intestine and stimulates GLP-1 production101–103 149; moreover, long-acting GLP-1 agonists have been reported to stimulate hepatic FGF21 production.146 150 The transcription of FGF21 is stimulated after a key interaction between Sirt1 deacetylated peroxisome proliferator-activated receptor (PPAR)α with the FGF21 promoter.151–155 GLP-1 agonists, by the virtue of increasing PPARα and Sirt1 expression in hepatocytes, mediate FGF21 upregulation.109 114 156 Hence, the above statements suggest that acarbose therapy-induced GLP-1 upregulation may promote hepatic FGF21 production, which suppresses IGF-1 activity and thus increases longevity.

**SIDE EFFECTS**

Based on more than 20 years of clinical use of acarbose, numerous controlled trials and postmarketing
surveillance studies have not demonstrated any significant toxicity or possible relation with subsequent comorbidities; however, nuisance-like gastrointestinal side effects can limit its use.

The predominant gastrointestinal symptom associated with acarbose is flatulence; though loose stools and/or abdominal discomfort have also been reported. These result from undigested carbohydrates entering from the small intestine directly into the colon, mimicking malabsorption. The end result is fermentation of this undigested carbohydrate by colonic bacteria leading to intestinal gas production. The incidence of such side effects varies widely over the existing literature. Flatulence and/or meteorism ranges between less than 10% to more than 50% of patients on acarbose therapy in controlled trials. Trials in the US report a higher incidence of these symptoms (about 40%) than in trials from Germany (about 25%) and Asian trials (about 17%).

Surveillance studies evaluating individualised monotherapy, with a better patient-centric approach, form a reliable basis for assessing the intestinal side effects of acarbose. The PROTECT (Precose Resolution of Optimal Titration to Enhance Current Therapies) surveillance study of 6142 patients from the US population, reported the incidence of flatulence to be 37%. Another surveillance study, involving 27,803 patients from Germany treated with fixed increasing dosages of acarbose, demonstrated a 13.7% incidence of flatulence. The reported incidence in German population was even lower (3.9%) in a 5-year postmarketing surveillance study (n=1996) with no fixed acarbose dosing. Such studies in Chinese and Asian populations showed an incidence of 0.6% (n=2550) and 2% (n=14 418), respectively.

This inter-regional variability may be due to several reasons. Though these side effects were labelled dose-dependent by dose-ranging studies, they failed to demonstrate significant efficacy differences between 100 and 50 mg acarbose administered three times daily. Interestingly, most patients in the German and Asian studies were treated with 50 mg three times daily. However, an early study effectively showed 50 mg acarbose to have less malabsorptive side effects as opposed to a 100 mg dose (6% vs 30%). Another study, by May et al., assessed the tolerability with a step-by-step increase beginning with a 100 mg dose three times daily, and concluded that gastrointestinal symptoms were reduced from 70% to 31% over an 8 week period. Even though controlled studies demonstrate 200 mg three times daily to be more effective, usually, acarbose is prescribed at a maximum of 100 mg three times daily, as the former is known to have a higher incidence of malabsorptive adverse effects.

Another key reason for variance in gastrointestinal symptoms is variability in α-glucosidase enzyme activity among populations, due to dietary habits. A study by Creutzfeldt et al evaluating sucrose and maltase (the key α-glucosidase enzymes) content in proximal and distal portions of the intestine, revealed that the latter had poor enzyme activity with a fibre-free diet as opposed to with a fibre-rich diet, moving unabsorbed carbohydrates into the colon. It was also observed that the addition of acarbose in participants on a fibre-free diet gradually increased distal intestinal enzyme activity and normalised carbohydrate digestion. However, in the fibre-rich group, the already increased enzyme activity remained unchanged with addition of acarbose. These data might be a plausible explanation for the population-based side effect heterogeneity, as the conventional Asian and Chinese diet contains much more fibre as compared to the conventional Western diet. Also, it explains the increased incidence of gastrointestinal symptoms when acarbose therapy is initiated, which eventually dissipate.

Another study emphasising the importance of dietary habits with acarbose use, reported 200 times higher malabsorption with sucrose consumption as opposed to starch, measured by breath hydrogen. Additionally, it suggested increased incidence of gastrointestinal symptoms with sugar rich soft drink consumption. Thus, rational use, slow titration from low to medium dose, focused patient education and good dietary advice may help ameliorate the gastrointestinal adverse effects associated with acarbose.

Apart from its gastrointestinal effects, acarbose is an extremely safe drug, which is consistent with its site of action and its very low systemic availability. A prospective 5-year postmarketing surveillance study (n=1996) reported no severe or fatal adverse events associated with acarbose. Additionally, the data from STOP-NIDDM trial revealed that incidence of adverse effects with acarbose was similar to that with placebo and no serious adverse events were reported.

Some rare reports, immediately after approval of acarbose, documented elevated liver transaminases with acarbose use; however, no differences were observed in clinical studies as opposed to placebo, and only 19 cases were reported of 500,000 participants. Such transaminasaemia has not been observed during treatment in patients with IGT; moreover, several studies involving acarbose use in diabetic participants demonstrated a beneficial effect on the progression of chronic liver disease.

Some labelled contraindications of acarbose include inflammatory bowel disease, colonic ulceration, predisposition or partial intestinal obstruction and chronic malabsorptive disorders. Hypoglycaemia should not occur with acarbose monotherapy in either fasting or postprandial conditions; however, in combination therapy with sulfonylureas or insulin, acarbose may contribute to hypoglycaemia.

Hence, acarbose, when carefully prescribed in combination with adequate dietary advice, seems to be one of the safest antidiabetic agents available, used either alone or in combination with other glucose-lowering
strategies. However, further randomised controlled trials are required to better understand the safety and efficacy of the AGIs.

CONCLUSION

Acarbose, an oral AGI, appears to reduce risk of cardiovascular events with a minimal risk for hypoglycaemia. If started at a low dose and titrated slowly, acarbose tends to cause occasional nuisance gastrointestinal side effects that are generally tolerable. Acarbose, as with metformin, should be considered a first-line antidiabetic agent, and is an effective pharmacological option for preventing diabetes in the prediabetic patient. Larger, long-term trials testing acarbose in diabetic patients as well as in other patient populations would be useful to confirm its cardiovascular benefits and safety profile.

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