

RESEARCH MONOGRAPH . COMPOUND PROFILE

Acarbose

A microbially derived pseudotetrasaccharide developed at Bayer AG as a competitive intestinal alpha-glucosidase and pancreatic alpha-amylase inhibitor for postprandial glucose control in type 2 diabetes mellitus, with emerging preclinical evidence for lifespan extension, gut microbiome modulation, and cardiovascular risk reduction.

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ABSTRACT

Acarbose is a pseudotetrasaccharide alpha-glucosidase inhibitor isolated from fermentation cultures of the actinobacterium *Actinoplanes utahensis* and subsequently produced at industrial scale by *Actinoplanes* sp. SE50/110. The compound competitively and reversibly inhibits the brush border alpha-glucosidases (maltase-glucoamylase, sucrase-isomaltase) of the small intestinal epithelium and, at higher concentrations, pancreatic alpha-amylase, thereby delaying the hydrolysis of complex carbohydrates and oligosaccharides to absorbable monosaccharides and producing a dose-dependent reduction in postprandial glycemic excursion without direct stimulation of insulin secretion [1, 2]. Acarbose received its first regulatory approval in Germany in 1990 and was approved by the United States Food and Drug Administration in 1995 under the trade name Precose; it is marketed in over 100 countries worldwide as Glucobay (Bayer) and under multiple generic names. The compound is one of the most widely prescribed antidiabetic agents in East Asia, where postprandial hyperglycemia contributes disproportionately to overall glycemic burden in carbohydrate-rich dietary patterns. The pharmacokinetic profile of acarbose is dominated by its topical mechanism of action within the gastrointestinal lumen. Less than 2 percent of an oral dose is absorbed as intact drug; the remainder is degraded by intestinal bacteria and digestive enzymes in the distal small intestine and colon, producing at least 13 metabolites, of which one (4-methylpyrogallol and its conjugates) accounts for the majority of systemically absorbed radioactivity [3, 4]. Systemic exposure is therefore minimal, and the pharmacodynamic effect is

determined by intraluminal drug concentration relative to the enzyme targets rather than by plasma pharmacokinetics. The compound is not metabolized by hepatic cytochrome P450 enzymes and has negligible renal clearance of intact drug. Clinical evidence for acarbose in type 2 diabetes mellitus is extensive. Pivotal registration trials demonstrated reductions in glycated hemoglobin (HbA1c) of 0.5 to 0.8 percentage points and reductions in postprandial glucose of 40 to 60 mg/dL at oral doses of 50 to 100 mg three times daily with meals [5, 6]. The UKPDS 44 substudy confirmed sustained glycemic efficacy over 3 years as add-on therapy to sulfonylurea or metformin [7]. The STOP-NIDDM trial (Study to Prevent Non-Insulin-Dependent Diabetes Mellitus) in 1368 subjects with impaired glucose tolerance demonstrated a 25 percent relative risk reduction in progression to type 2 diabetes and a 49 percent relative risk reduction in cardiovascular events over 3.3 years of treatment, though the cardiovascular endpoint was secondary and based on a small number of events [8, 9]. The larger ACE trial (Acarbose Cardiovascular Evaluation) in 6522 Chinese patients with coronary heart disease and impaired glucose tolerance found no reduction in major adverse cardiovascular events over 5 years of follow-up but confirmed an 18 percent relative risk reduction in incident diabetes [10]. Beyond the established antidiabetic indication, acarbose has attracted substantial recent interest as a longevity intervention. The National Institute on Aging Interventions Testing Program (ITP), a rigorous, multi-site, genetically heterogeneous mouse study, demonstrated that acarbose at 1000 ppm in chow extended median lifespan by approximately 22 percent in males and 5 percent in females, with corresponding increases in maximum lifespan [11, 12]. The sex-differential effect parallels the male-preferential lifespan

extension observed with 17-alpha-estradiol and nordihydroguaiaretic acid in the same program. Mechanistic investigations have linked the longevity effect to increased delivery of undigested starch to the colonic microbiome, resulting in elevated production of short-chain fatty acids (butyrate, propionate, acetate), shifts in microbial community composition toward Bacteroidetes-dominant profiles, and reductions in circulating insulin-like growth factor 1 (IGF-1) and fasting insulin [13, 14]. Combination of acarbose with rapamycin in the ITP produced additive lifespan extension (median lifespan increases of 28 percent in females and 34 percent in males when initiated at 9 months of age), supporting the hypothesis that the two compounds operate through complementary pathways [15]. The principal adverse effects of acarbose are gastrointestinal: flatulence (reported in up to 78 percent of patients at initiation), diarrhea, and abdominal discomfort, all reflecting the mechanism of action (bacterial fermentation of undigested carbohydrate in the colon) and typically diminishing with continued therapy and gradual dose titration [16]. Rare hepatotoxicity, presenting as asymptomatic transaminase elevation or, in isolated cases, clinically apparent hepatocellular injury, has been reported in postmarketing surveillance and is generally reversible upon discontinuation [17]. This monograph reviews the chemistry, biosynthesis, and structural pharmacology of acarbose; the mechanism of alpha-glucosidase and alpha-amylase inhibition at the molecular level; the comprehensive pharmacokinetic record; the clinical evidence base across antidiabetic, diabetes prevention, cardiovascular, and longevity indications; sourcing and quality verification considerations; reconstitution and handling; stack-interaction implications; adverse-event signal; and a comparative assessment of five alternative glucose-lowering or longevity-

relevant compounds against acarbose on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Acarbose.

Marketed names: Precose (Bayer; United States), Glucobay (Bayer; Germany, China, Japan, Australia, and approximately 100 additional jurisdictions), Prandase (Canada), Rebose (India, generic), Glucar (generic markets), and numerous additional generic trade names in East Asian, South Asian, and Latin American markets.

Development codes: BAY g 5421 (Bayer AG). The Bayer development code is the canonical identifier in the early pharmacology and fermentation literature and appears in the original Schmidt et al. (1977) isolation report [1].

Chemical Abstracts Service registry number: 56180-94-0.

International Union of Pure and Applied Chemistry name: 4,6-dideoxy-4-[[[(1S,4R,5S,6S)-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]amino}-alpha-D-glucopyranosyl-(1->4)-alpha-D-glucopyranosyl-(1->4)-D-glucopyranose. The compound is a pseudotetrasaccharide in which the non-reducing terminal unit is an unsaturated cyclitol (valienamine) linked through a secondary amine bond to 4,6-dideoxyglucose, followed by two alpha-1,4-linked glucose residues constituting a maltose unit at the reducing terminus.

Other registry identifiers: PubChem CID 444254 (alpha-acarbose, CID 445421); ChEBI 2376; KEGG D00216; DrugBank DB00284.

1.2 Structural class and chemistry

Acarbose belongs to the aminoglycoside pseudooligosaccharide class. It is structurally composed of two distinct moieties: an acarviosine unit (the valienamine-4,6-dideoxyglucose disaccharide connected through a nitrogen bridge) and a maltose unit (two alpha-1,4-linked D-glucopyranose residues) at the reducing end. The nitrogen atom replacing the interglycosidic oxygen between the valienamine and 4,6-dideoxyglucose units is the critical pharmacophoric element, as it renders this bond resistant to hydrolysis by the target alpha-glucosidase enzymes while permitting tight binding to the active site [18].

Molecular formula: C₂₅H₄₃NO₁₈.

Molecular weight: 645.60 g/mol.

Exact mass: 645.2481 g/mol (monoisotopic).

Physical properties: White to off-white hygroscopic powder. Freely soluble in water; sparingly soluble in methanol and ethanol; practically insoluble in dichloromethane, diethyl ether, and other apolar organic solvents. The compound does not have a sharp melting point and decomposes above approximately 165 degrees Celsius. Specific optical rotation $[\alpha]_{D20}$ is approximately +168 degrees (c = 1, water).

Stereochemistry: Acarbose contains multiple stereocenters across its four ring units. The absolute configuration is fixed by the biosynthetic pathway and corresponds to the natural product isolated from *Actinoplanes* fermentation. The valienamine unit has defined stereochemistry at C-1, C-4, C-5, and C-6 (1S,4R,5S,6S configuration). Commercial acarbose is supplied exclusively as the natural stereoisomer; enantiomeric or epimeric impurities are not a practical concern in pharmaceutical-grade or research-grade material but should be confirmed by optical rotation if non-standard sources are employed.

1.3 Biosynthesis and production

Acarbose is produced by submerged aerobic fermentation of *Actinoplanes* species, principally *Actinoplanes utahensis* (the original producing organism described by Couch in 1963) and *Actinoplanes* sp. SE50/110 (the industrial production strain whose complete genome sequence was published in 2012) [19, 20]. The biosynthetic pathway proceeds through the deoxyThymidine diphosphate (dTDP) pathway for the generation of the 4,6-dideoxyglucose moiety and through the sedo-heptulose 7-phosphate pathway for the cyclitol (valienamine) unit, with the amine linkage formed by a dedicated aminotransferase. The *acb* gene cluster (approximately 25 genes spanning roughly 32 kilobases) encodes the biosynthetic, regulatory, and export functions; the complete cluster was characterized by Wehmeier and Piepersberg (2004) [21].

Industrial production at Bayer AG (subsequently Bayer HealthCare) involved extensive conventional mutagenesis and screening of *Actinoplanes* strains over approximately two decades to achieve commercially viable titers, followed by optimization of fermentation conditions (carbon source, nitrogen source, dissolved

oxygen, pH, osmolality). The fermentation product is recovered from culture supernatant by adsorption chromatography, ion-exchange chromatography, and crystallization. The final pharmaceutical product is supplied as tablets (25 mg, 50 mg, 100 mg) for oral administration.

Chemical total synthesis of acarbose has been achieved by multiple groups but is not economically competitive with fermentation and is employed only for the preparation of structural analogs and isotopically labeled material for pharmacokinetic and mechanistic studies.

2. Abstract

Acarbose (BAY g 5421) is a pseudotetrasaccharide isolated from *Actinoplanes utahensis* that competitively and reversibly inhibits the intestinal brush border alpha-glucosidases and pancreatic alpha-amylase, producing a dose-dependent delay in carbohydrate digestion and a consequent reduction in postprandial glycemic excursion [1, 2]. The compound acts topically within the gastrointestinal lumen with minimal systemic absorption (less than 2 percent of an oral dose absorbed as intact drug), and its pharmacodynamic effect is therefore determined by intraluminal concentration rather than by plasma pharmacokinetics [3, 4].

Approved for the treatment of type 2 diabetes mellitus in over 100 countries (Precose in the United States, approved 1995; Glucobay internationally, first approved in Germany in 1990), acarbose reduces glycated hemoglobin by 0.5 to 0.8 percentage points and postprandial glucose by 40 to 60 mg/dL at standard oral doses of 50 to 100 mg three times daily with meals [5, 6]. The UKPDS 44 substudy confirmed sustained glycemic efficacy over 3 years [7]. The STOP-NIDDM trial demonstrated a 25 percent relative risk reduction in progression from impaired glucose tolerance to type 2 diabetes and a secondary 49 percent relative risk reduction in cardiovascular events, though the latter was based on a small event count [8, 9]. The larger ACE trial in 6522 Chinese patients with coronary heart disease and impaired glucose tolerance confirmed the diabetes prevention effect (18 percent relative risk reduction) but did not demonstrate cardiovascular benefit [10].

Beyond the antidiabetic indication, acarbose has emerged as one of the most robustly validated pharmacological longevity interventions in mammalian models. The National Institute on Aging Interventions Testing Program demonstrated that acarbose extends median lifespan by approximately 22 percent in male mice and 5 percent in female mice, with the effect replicated across three independent study sites [11, 12]. The longevity effect is associated with increased colonic short-chain fatty acid production, favorable shifts in gut microbiome composition, reduced circulating IGF-1, and reduced fasting insulin [13, 14]. Combination with rapamycin produced additive lifespan extension of up to 34 percent in males [15].

The principal adverse effects are gastrointestinal (flatulence, diarrhea, abdominal discomfort), reflecting the mechanism of action and typically improving with continued therapy [16]. Rare hepatotoxicity has been reported in postmarketing surveillance [17]. The compound has no significant drug-drug interactions mediated by cytochrome P450 enzymes.

This monograph reviews compound identification, discovery and development history, molecular pharmacology, pharmacokinetics, preclinical pharmacology (with emphasis on longevity research), the clinical evidence base, sourcing and quality verification, reconstitution and handling, stack interactions, adverse events, and a comparative assessment against five alternative compounds (miglitol, voglibose, metformin, empagliflozin, rapamycin) on five competency standards.

3. Discovery and Development History

3.1 Origin

Acarbose was discovered in the mid-1970s at the Bayer AG research laboratories in Wuppertal, Germany, as part of a systematic screening program for microbial metabolites with alpha-glucosidase inhibitory activity. The rationale for the program was the hypothesis, advanced by Schmidt, Truscheit, and colleagues, that competitive inhibition of intestinal carbohydrate-digesting enzymes could reduce postprandial hyperglycemia without stimulating insulin secretion, thereby offering a mechanistically distinct approach to glucose control in type 2 diabetes [1]. The compound was isolated from fermentation cultures of *Actinoplanes utahensis*, a gram-positive actinobacterium first described by Couch in 1963, and was designated BAY g 5421.

The structural elucidation of acarbose as a pseudotetrasaccharide with an amine linkage replacing the interglycosidic oxygen was completed by Truscheit et al. (1981) and established the molecular basis for the enzyme inhibition: the nitrogen bridge confers resistance to hydrolysis by the target enzymes while permitting high-affinity binding to the active site, effectively creating a transition-state analog that locks the enzyme in an unproductive complex [18, 22].

3.2 Preclinical and early clinical development

Preclinical pharmacology studies in the late 1970s and early 1980s demonstrated that oral acarbose reduced postprandial glucose excursions in rats, dogs, and healthy human volunteers in a dose-dependent manner [2]. The compound showed no systemic toxicity at doses producing maximal intestinal enzyme inhibition, consistent with its minimal systemic absorption. Chronic toxicity studies in rats and dogs at multiples of the human therapeutic dose demonstrated no organ toxicity apart from the expected cecal distension secondary to increased fermentable substrate delivery to the colon.

Phase 1 studies in healthy volunteers confirmed the pharmacodynamic effect (reduction in postprandial glucose and insulin following a standardized carbohydrate load) and established the dose range of 50 to 200 mg three times daily. Phase 2

and Phase 3 studies in patients with type 2 diabetes mellitus demonstrated glycemic efficacy and established the dose-response relationship and the adverse-event profile [5, 6].

3.3 Regulatory approvals

Acarbose received its first regulatory approval in Germany in 1990 under the trade name Glucobay. Subsequent approvals followed in Japan (1993, as Glucobay), the United States (September 1995, as Precose), and in over 100 additional jurisdictions worldwide. The compound has been marketed by Bayer AG (subsequently Bayer HealthCare, now Bayer Pharmaceuticals) throughout its commercial history. Generic acarbose became available in the United States and other markets following patent expiration. The compound is included on the World Health Organization Model List of Essential Medicines.

3.4 Post-approval expansion of indications and research

Following registration, the research literature on acarbose expanded substantially in three directions. First, the STOP-NIDDM trial (published 2002 and 2003) established acarbose as a diabetes prevention agent with a secondary cardiovascular benefit signal [8, 9]. Second, the ACE trial (published 2017) provided the largest cardiovascular outcomes dataset for acarbose but did not confirm the cardiovascular benefit observed in STOP-NIDDM [10]. Third, beginning in 2014, the NIA Interventions Testing Program reported that acarbose extended lifespan in genetically heterogeneous mice, generating a new research axis around acarbose as a longevity intervention [11, 12]. The longevity research has subsequently driven investigations into the gut microbiome as a mediator of the lifespan effect and into the interaction between acarbose and rapamycin as a combination longevity strategy [13, 14, 15].

4. Mechanism of Action

Acarbose is a competitive, reversible inhibitor of the intestinal brush border alpha-glucosidases and, at higher concentrations, of pancreatic alpha-amylase. The dual inhibition produces a coordinated delay in carbohydrate digestion at two sequential enzymatic steps: the luminal hydrolysis of polysaccharides to oligosaccharides (alpha-amylase) and the brush border hydrolysis of oligosaccharides and disaccharides to absorbable monosaccharides (alpha-glucosidases).

4.1 Alpha-glucosidase inhibition

The intestinal brush border alpha-glucosidases are a family of exo-acting glycoside hydrolases expressed on the apical surface of small intestinal enterocytes. The two principal enzymes are maltase-glucoamylase (MGAM) and sucrase-isomaltase (SI), each of which is a dimeric protein with two catalytic subunits (N-terminal and C-terminal) capable of hydrolyzing alpha-1,4-glycosidic bonds in maltose, maltotriose, and higher maltodextrins [23]. Sucrase-isomaltase additionally hydrolyzes the alpha-1,2-glycosidic bond in sucrose and the alpha-1,6-glycosidic bond in isomaltose.

Acarbose binds to the active sites of these enzymes as a transition-state analog. The valienamine-4,6-dideoxyglucose unit (the acarviosine moiety) mimics the geometry of the substrate at the catalytic transition state, with the protonated secondary amine at the interglycosidic position providing an electrostatic interaction with the catalytic acid residue (a glutamic acid in the GH31 family) that stabilizes the enzyme-inhibitor complex [18, 24]. X-ray crystallographic studies of acarbose bound to maltase-glucoamylase and to related GH31 family enzymes have confirmed this binding mode, showing the inhibitor spanning subsites -1 through +3 of the active site cleft with the acarviosine unit occupying the catalytic subsites [24, 25].

The inhibition constants (K_i values) for acarbose against the individual catalytic subunits range from approximately 0.1 to 1.0 micromolar, with the highest affinity observed at the C-terminal subunit of maltase-glucoamylase [23]. The inhibition is competitive with substrate (maltose, maltotriose, starch hydrolysate) and is fully reversible upon dilution of the inhibitor. The functional consequence is a dose-de-

pendent delay in the appearance of glucose in the portal circulation following a carbohydrate-containing meal, producing a flattened and temporally shifted postprandial glucose curve without reduction in total carbohydrate absorption at steady state [2].

4.2 Pancreatic alpha-amylase inhibition

Pancreatic alpha-amylase (alpha-1,4-glucan-4-glucanohydrolase, EC 3.2.1.1) is an endoglycosidase secreted into the duodenal lumen that hydrolyzes interior alpha-1,4-glycosidic bonds in starch and glycogen, producing maltose, maltotriose, and alpha-limit dextrins. Acarbose inhibits pancreatic alpha-amylase with a K_i of approximately 10 to 20 micromolar, reflecting lower affinity than for the brush border alpha-glucosidases [26]. The inhibition is competitive and produces a dose-dependent reduction in the rate of starch hydrolysis to oligosaccharides.

The alpha-amylase inhibition contributes to the pharmacodynamic effect at higher acarbose doses (100 mg and above) and is the principal basis for the increased delivery of intact starch to the distal small intestine and colon. This undigested starch serves as a fermentable substrate for the colonic microbiota, producing short-chain fatty acids and accounting for the gastrointestinal adverse-event profile (flatulence, bloating) and, potentially, for the longevity-associated microbiome effects observed in mouse studies [13, 14].

4.3 Downstream metabolic effects

The direct consequence of alpha-glucosidase and alpha-amylase inhibition is a reduction in the rate of glucose appearance in the portal circulation after a carbohydrate meal. The downstream metabolic effects include:

Reduced postprandial insulin secretion, reflecting the diminished glycemic stimulus to pancreatic beta cells. This insulin-sparing effect distinguishes acarbose from sulfonylureas and meglitinides and is the basis for the low hypoglycemia risk when acarbose is used as monotherapy [5, 6].

Reduced postprandial triglyceride excursion, observed in some but not all clinical studies, reflecting the coupling between postprandial hyperglycemia and hepatic de novo lipogenesis [27].

Increased glucagon-like peptide 1 (GLP-1) secretion, demonstrated in multiple clinical studies and attributed to the increased delivery of undigested carbohydrate to the distal ileum and colon, where L-cells expressing the carbohydrate-sensing receptor apparatus secrete GLP-1 in response to luminal nutrient stimulation [28]. The GLP-1 effect may contribute to the sustained glycemic efficacy and to the modest weight neutrality of acarbose relative to sulfonylureas.

Increased short-chain fatty acid production in the colon, resulting from bacterial fermentation of the undigested starch and oligosaccharides that escape small intestinal digestion [13, 14]. The short-chain fatty acids (butyrate, propionate, acetate) serve as energy substrates for colonocytes, modulate colonic pH, exert systemic anti-inflammatory effects through G-protein-coupled receptor signaling (GPR41, GPR43, GPR109A), and have been proposed as mediators of the lifespan extension observed in mice [13].

4.4 Selectivity and off-target considerations

Acarbose does not bind to insulin receptors, sulfonylurea receptors, glucagon receptors, or any characterized G-protein-coupled receptor. It does not inhibit beta-glucosidases, alpha-galactosidases, or other glycosidase families at pharmacologically relevant concentrations. The compound does not interact with cytochrome P450 enzymes, either as substrate or inhibitor, and has no characterized activity at ion channels, nuclear receptors, or kinases [29]. The pharmacology is therefore highly selective for the intestinal carbohydrate-digesting enzymes, and the systemic pharmacological footprint is negligible.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Acarbose is very poorly absorbed from the gastrointestinal tract. Less than 2 percent of an oral dose reaches the systemic circulation as intact drug [3, 4]. The compound acts topically within the intestinal lumen, and its pharmacodynamic effect is determined by intraluminal concentration at the brush border rather than by plasma pharmacokinetics.

Approximately 35 percent of the total radioactivity from a ¹⁴C-labeled oral dose is ultimately absorbed, reflecting the absorption of bacterial and enzymatic degradation products rather than intact acarbose [3]. The principal absorbed metabolite is 4-methylpyrogallol and its O-methyl, O-sulfate, and O-glucuronide conjugates, which are produced by bacterial degradation of the acarviosine unit in the colon. Peak plasma concentrations of total radioactivity occur at 14 to 24 hours after dosing, reflecting the delayed colonic metabolism and absorption rather than direct small intestinal absorption [3].

Peak plasma concentration of intact acarbose after an oral dose of 200 mg in healthy volunteers is approximately 52 micrograms per liter, reached at approximately 1 hour, consistent with the small fraction of intact drug absorbed from the proximal small intestine [4].

5.2 Distribution

Owing to the minimal systemic absorption of intact drug, conventional pharmacokinetic distribution parameters (volume of distribution, plasma protein binding) are of limited clinical relevance. The volume of distribution of intact acarbose, estimated from intravenous pharmacokinetic studies, is approximately 0.32 liters per kilogram, consistent with distribution primarily to extracellular fluid [4]. Plasma protein binding has not been extensively characterized but is reported as low.

The compound does not cross the blood-brain barrier in appreciable quantities. Central nervous system penetration is not relevant to the therapeutic mechanism and has not been characterized by imaging or cerebrospinal fluid sampling.

5.3 Metabolism

Acarbose is not metabolized by hepatic cytochrome P450 enzymes or by any characterized phase I hepatic biotransformation pathway. The compound is degraded exclusively within the gastrointestinal tract by two processes: enzymatic hydrolysis by brush border alpha-glucosidases and pancreatic alpha-amylase (which slowly cleave the maltose unit from the reducing end, producing the pseudotrisaccharide and pseudodisaccharide metabolites) and bacterial degradation in the distal small intestine and colon [3, 4].

At least 13 degradation products have been identified in fecal and urinary metabolite profiling studies. The principal systemically absorbed metabolite, 4-methylpyrogallol, is formed by bacterial ring-opening and decarboxylation of the cyclitol (valienamine) unit and is subsequently conjugated (sulfation, glucuronidation, O-methylation) in the intestinal wall and liver before urinary excretion [3].

The absence of hepatic CYP450-mediated metabolism eliminates the pharmacogenomic variability (CYP2D6, CYP2C19 polymorphisms) that complicates the pharmacokinetics of many other antidiabetic agents and is a practical advantage for population-level dosing.

5.4 Elimination

After oral administration, approximately 51 percent of the dose is excreted in feces as unabsorbed drug-related material within 96 hours [3]. Urinary excretion accounts for approximately 34 percent of the oral dose, almost entirely as bacterial degradation products (4-methylpyrogallol conjugates) rather than intact drug. Less than 2 percent of the oral dose is excreted as unchanged acarbose in urine.

After intravenous administration (used in pharmacokinetic characterization studies), acarbose is eliminated rapidly and completely via the renal route, with a plasma elimination half-life of approximately 2 hours and renal clearance approximating the glomerular filtration rate [4].

Renal impairment (creatinine clearance below 25 mL/min/1.73 m²) produces approximately 5-fold increases in plasma concentrations of acarbose and its degradation products; the prescribing label recommends avoidance in patients with serum creatinine above 2.0 mg/dL. Hepatic impairment does not alter acarbose pharmacokinetics, as the compound is not hepatically metabolized.

5.5 Routes of administration

Acarbose is administered exclusively by the oral route in clinical practice. The compound is formulated as immediate-release tablets (25 mg, 50 mg, 100 mg) taken with the first bite of each main meal. The requirement for administration with food is essential to the mechanism: the compound must be present in the intestinal lumen simultaneously with the carbohydrate substrate to exert its inhibitory effect.

Intravenous administration has been used in pharmacokinetic characterization studies but is not a therapeutic route. No parenteral, sublingual, transdermal, or inhaled formulations have been developed or are in clinical use.

5.6 Special populations

Pediatric pharmacokinetics have not been formally characterized, and acarbose is not approved for use in children. Geriatric pharmacokinetics do not differ meaningfully from younger adults except in the context of renal impairment, which is more prevalent in elderly populations. Pregnancy data are limited; the compound is rated FDA pregnancy category B (no evidence of harm in animal studies at multiples of the human dose, no adequate human data). The minimal systemic absorption of intact drug suggests low fetal exposure, but use in pregnancy is not recommended unless clearly needed. Lactation data are not available; excretion in human milk is unknown but presumed minimal given the low systemic absorption.

6. Preclinical Pharmacology

6.1 Antidiabetic pharmacology in animal models

Oral acarbose reduces postprandial glucose excursion in a dose-dependent manner in rats, dogs, and non-human primates following starch or sucrose challenge [2]. The effect is immediate (apparent within the first postprandial hour), dose-proportional over the range of 1 to 30 mg/kg, and fully reversible within one meal cycle. Chronic administration (weeks to months) in rodent models of type 2 diabetes (db/db mice, Zucker diabetic fatty rats, streptozotocin-treated rats) reduces fasting and postprandial glucose, improves glucose tolerance, reduces HbA1c equivalents, and in some models reduces pancreatic beta-cell apoptosis, consistent with the glucotoxicity reduction hypothesis [30].

6.2 Longevity pharmacology

The most scientifically significant preclinical finding for acarbose in the past decade is its effect on lifespan in the NIA Interventions Testing Program (ITP). The ITP is a multi-institutional program (the Jackson Laboratory, the University of Michigan, and the University of Texas Health Science Center) that tests putative anti-aging interventions in genetically heterogeneous UM-HET3 mice under standardized protocols with replication across three independent sites [11].

Acarbose was tested at 1000 ppm in chow, initiated at 4 months of age. The results, first reported by Harrison et al. (2014) and confirmed in subsequent cohorts, demonstrated a median lifespan increase of approximately 22 percent in male mice (from approximately 840 days to approximately 1025 days) and approximately 5 percent in female mice [11, 12]. Maximum lifespan (90th percentile survival) was also significantly increased in both sexes. The male-preferential effect was robust across all three study sites and has been replicated in multiple cohorts.

Strong et al. (2016) reported that acarbose at 1000 ppm also produced a significant (approximately 5 percent) increase in female median lifespan when initiated at 16 months of age, demonstrating that the intervention retains efficacy when begun in middle age [12].

The combination of acarbose (1000 ppm) with rapamycin (14 ppm) was tested in the ITP and reported by Strong et al. (2022). The combination produced median lifespan increases of 28 percent in females and 34 percent in males when initiated at 9 months of age, exceeding the effects of either agent alone and supporting the hypothesis of complementary mechanisms (rapamycin acting through mTOR inhibition and acarbose acting through carbohydrate metabolism and gut microbiome modulation) [15].

6.3 Gut microbiome effects

Smith et al. (2019) characterized the gut microbiome and fecal metabolome of acarbose-treated UM-HET3 mice and reported significant shifts in microbial community composition, including increased relative abundance of Bacteroidetes (particularly Muribaculaceae, formerly designated S24-7) and decreased relative abundance of Firmicutes [13]. Fecal concentrations of short-chain fatty acids (propionate and butyrate) were significantly elevated in acarbose-treated mice relative to controls, and total fecal short-chain fatty acid concentrations correlated positively with lifespan across individual animals.

These findings support a model in which acarbose extends lifespan at least in part by increasing delivery of fermentable substrate (undigested starch) to the colon, promoting the expansion of saccharolytic bacterial taxa, increasing short-chain fatty acid production, and thereby exerting systemic metabolic and anti-inflammatory effects [14]. The sex-differential lifespan effect may reflect sex differences in baseline microbiome composition, hormonal regulation of intestinal transit time, or sex-specific metabolic responses to short-chain fatty acids.

6.4 Metabolic and endocrine effects in animal models

Chronic acarbose treatment in mice reduces fasting insulin concentrations and reduces circulating insulin-like growth factor 1 (IGF-1), both of which are independently associated with longevity in rodent models [11, 14]. The reduction in IGF-1 may reflect reduced hepatic IGF-1 synthesis secondary to reduced postprandial insulin signaling, linking the primary pharmacodynamic effect (postprandial glucose reduction) to a downstream endocrine pathway (the insulin/IGF-1 signaling axis) that has been robustly associated with lifespan determination across species from nematodes to mammals.

7. Clinical Evidence Base

7.1 Type 2 diabetes mellitus: glycemic efficacy

The glycemic efficacy of acarbose in type 2 diabetes has been established in numerous randomized, placebo-controlled trials. Pivotal registration trials demonstrated reductions in HbA1c of 0.5 to 0.8 percentage points and reductions in one-hour postprandial glucose of 40 to 60 mg/dL at oral doses of 50 to 100 mg three times daily with meals [5, 6]. The glycemic effect is dose-dependent over the range of 25 to 300 mg three times daily, with the recommended starting dose of 25 mg three times daily and a maximum recommended dose of 100 mg three times daily. Effect on fasting glucose is modest (10 to 20 mg/dL reduction), reflecting the postprandial-specific mechanism.

The UKPDS 44 substudy (Holman et al., 1999) randomized 1946 patients with type 2 diabetes already receiving sulfonylurea or metformin therapy to add-on acarbose (100 mg three times daily) or placebo and demonstrated sustained HbA1c reduction of 0.5 percentage points over 3 years, with no increase in hypoglycemia risk [7]. Discontinuation rates were higher with acarbose (39 percent versus 16 percent with placebo), primarily owing to gastrointestinal adverse effects.

A 2005 Cochrane meta-analysis of 41 randomized controlled trials enrolling 8130 participants confirmed that acarbose reduces HbA1c by a weighted mean difference of 0.77 percentage points versus placebo and reduces postprandial glucose by 20.2 mg/dL versus placebo, with no significant effect on total cholesterol, triglycerides, or body weight [31].

7.2 Diabetes prevention: the STOP-NIDDM trial

The STOP-NIDDM trial (Study to Prevent Non-Insulin-Dependent Diabetes Mellitus; Chiasson et al., 2002) was an international, multicenter, double-blind, placebo-controlled, randomized trial of acarbose 100 mg three times daily versus placebo in 1368 subjects with impaired glucose tolerance, conducted across 9 countries with a mean follow-up of 3.3 years [8].

The primary endpoint was the development of type 2 diabetes. Acarbose reduced the relative risk of progression to diabetes by 25 percent (hazard ratio 0.75; 95 percent confidence interval 0.63 to 0.90; $p = 0.0015$). The absolute risk reduction was 9 percentage points (42 percent cumulative incidence in the placebo group versus 32 percent in the acarbose group over 3.3 years).

A pre-specified secondary cardiovascular analysis (Chiasson et al., 2003) reported a 49 percent relative risk reduction in cardiovascular events (hazard ratio 0.51; 95 percent confidence interval 0.28 to 0.95; $p = 0.03$) and a 34 percent relative risk reduction in new-onset hypertension [9]. The cardiovascular finding was based on 47 events (15 in the acarbose group versus 32 in the placebo group) and has been interpreted cautiously owing to the small event count and the higher discontinuation rate in the acarbose group (31 percent versus 19 percent).

7.3 Cardiovascular outcomes: the ACE trial

The Acarbose Cardiovascular Evaluation (ACE) trial (Holman et al., 2017) was a randomized, double-blind, placebo-controlled trial of acarbose 50 mg three times daily versus placebo in 6522 Chinese patients with established coronary heart disease and impaired glucose tolerance, conducted across 176 sites in China with a median follow-up of 5 years [10].

The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina, and hospitalization for heart failure. Acarbose did not reduce the primary endpoint (hazard ratio 0.98; 95 percent confidence interval 0.86 to 1.11; $p = 0.73$). The incidence was 14 percent in the acarbose group and 15 percent in the placebo group.

The secondary diabetes prevention endpoint was positive: acarbose reduced the incidence of new-onset type 2 diabetes by 18 percent (rate ratio 0.82; 95 percent confidence interval 0.71 to 0.94). Regression to normoglycemia was more frequent with acarbose (16.3 versus 14.1 per 100 person-years; p less than 0.0001).

The ACE trial was notable for using a lower dose (50 mg three times daily versus 100 mg three times daily in STOP-NIDDM) in a population with established cardiovascular disease (higher baseline risk) and a predominantly Chinese cohort (different dietary carbohydrate profile and potentially different microbiome composition). The absence of cardiovascular benefit in ACE tempered the enthusiasm gen-

erated by the STOP-NIDDM cardiovascular signal and has been interpreted as indicating that postprandial glucose reduction alone is insufficient to prevent cardiovascular events in patients with established coronary disease.

7.4 Postprandial hyperglycemia and reactive hypoglycemia

Acarbose is used clinically for the management of reactive (postprandial) hypoglycemia, including late dumping syndrome following gastric surgery. By delaying carbohydrate absorption, acarbose reduces the rapid glucose spike that triggers excessive insulin secretion, thereby attenuating the subsequent hypoglycemic nadir [32]. This off-label application is supported by case series and small randomized trials and is referenced in gastroenterology guidelines for post-bariatric surgery hypoglycemia.

7.5 Summary of clinical positioning

Acarbose is a well-validated, guideline-recommended antidiabetic agent positioned as monotherapy for patients with predominantly postprandial hyperglycemia or as add-on therapy to metformin, sulfonylureas, or insulin. Its glycemic efficacy is modest relative to metformin or SGLT2 inhibitors, and its tolerability profile (gastrointestinal side effects) limits adherence. Its principal clinical advantages are the absence of hypoglycemia risk when used as monotherapy, the weight-neutral to weight-reducing effect, the diabetes prevention evidence from STOP-NIDDM, and the theoretical cardiovascular benefit from postprandial glucose reduction (not confirmed in the ACE trial). Its principal clinical limitation is the gastrointestinal adverse-event profile.

8. Sourcing and Quality Verification

Pharmaceutical-grade acarbose is widely available as a generic medication in most global markets. Brand-name formulations (Precose, Glucobay) and multiple generic versions are supplied as immediate-release tablets in 25 mg, 50 mg, and 100 mg strengths. Pharmaceutical sourcing is straightforward in all jurisdictions where the compound is registered.

Research-grade acarbose is supplied by multiple chemical and pharmaceutical research suppliers (Sigma-Aldrich/MilliporeSigma, Cayman Chemical, TCI, Alfa Aesar, Santa Cruz Biotechnology, Abcam, LGC Standards, MedChemExpress, and others) at greater than 95 percent purity by HPLC, typically as the free base in powder form. Supply is available in milligram to kilogram quantities. Pricing is moderate, in the range of \$20 to \$100 per gram of research-grade material at the time of monograph preparation.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 95 percent (pharmaceutical grade greater than 98 percent)
- Mass spectrometry confirmation of molecular weight (646.26 for [M+H]⁺ or 668.24 for [M+Na]⁺)
- Optical rotation measurement ([α]_{D20} approximately +168 degrees, c = 1, water) to confirm correct stereochemistry
- Karl Fischer or loss-on-drying analysis for water content (acarbose is hygroscopic and may absorb significant moisture)
- Microbial limit testing for material intended for in vivo studies

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. The acarbose research supply market is well established owing to the compound's extensive use in enzymology, microbiology, and aging research; counterfeit material is uncommon, but lot-to-lot variability in moisture content is a practical consideration for gravimetric dosing accuracy.

9. Reconstitution and Handling

Acarbose is freely soluble in water at room temperature. For in vitro enzyme inhibition assays, stock solutions are typically prepared at 10 to 100 mM in ultrapure water, deionized water, or phosphate-buffered saline. The compound is stable in aqueous solution at neutral pH for at least 7 days at refrigerated conditions (2 to 8 degrees Celsius) and for at least 24 hours at room temperature.

For in vivo rodent studies (the principal research application for longevity investigations), acarbose is typically administered as a dietary admixture in powdered or pelleted chow at concentrations of 1000 ppm (1 g per kilogram of chow), the dose used in the NIA Interventions Testing Program [11]. The compound is blended into the chow formulation prior to pelleting or, in powdered diet protocols, mixed directly into the diet powder. Stability in chow at room temperature for up to 4 weeks has been demonstrated under standard vivarium conditions.

For clinical research applications, the compound is supplied as commercially manufactured tablets. No reconstitution is required. Tablets should be stored at controlled room temperature (20 to 25 degrees Celsius) and protected from moisture owing to the hygroscopic nature of the compound.

Dimethyl sulfoxide (DMSO) is not required for dissolution, as acarbose is freely water-soluble. If DMSO stock solutions are prepared for convenience in high-throughput screening applications, the final DMSO concentration in the assay should be maintained below 0.5 percent to avoid interference with enzyme activity.

Aliquoting of aqueous stock solutions into single-use volumes is recommended for repeated experimental use. Freeze-thaw stability is adequate for at least 3 cycles without measurable loss of inhibitory activity, though avoidance of unnecessary freeze-thaw cycling is standard practice.

10. Stack Interactions and Combinations

Acarbose interacts with several drug classes through its gastrointestinal mechanism of action and through its effects on carbohydrate absorption. Investigators conducting research with acarbose, especially in chronic dosing regimens or in combination with other research compounds, should consider:

Insulin and insulin secretagogues: Concurrent use of acarbose with insulin, sulfonylureas (glipizide, glyburide, glimepiride), or meglitinides (repaglinide, nateglinide) increases the risk of hypoglycemia. Importantly, acarbose-related hypoglycemia in the context of combination therapy must be treated with oral glucose (dextrose), not sucrose, because acarbose inhibits sucrose hydrolysis and delays the glycemic response to table sugar [29].

Metformin: The combination of acarbose with metformin is pharmacologically rational (different mechanisms) and clinically common. No significant pharmacokinetic interaction has been demonstrated. Additive gastrointestinal adverse effects (diarrhea, flatulence) are expected and observed.

Intestinal adsorbents and digestive enzyme preparations: Charcoal, pancreatin, amylase-containing digestive enzyme supplements, and cholestyramine can reduce the efficacy of acarbose by adsorbing the compound or by providing exogenous amylase activity that bypasses the inhibition. Concurrent use should be avoided or temporally separated [29].

Digoxin: Acarbose may reduce the bioavailability of digoxin through unclear mechanisms, possibly related to altered gastrointestinal transit or pH. Monitoring of digoxin levels is recommended when acarbose is initiated or discontinued in patients receiving digoxin.

Rapamycin (sirolimus): The combination of acarbose with rapamycin has been studied in the NIA Interventions Testing Program and has produced additive lifespan extension in mice [15]. No pharmacokinetic interaction is expected, as acar-

bose acts locally in the gut and is not a CYP3A4 substrate or inhibitor (rapamycin is metabolized by CYP3A4). The combination is of active research interest in the longevity field.

SGLT2 inhibitors: Concurrent use of acarbose with SGLT2 inhibitors (empagliflozin, dapagliflozin, canagliflozin) is pharmacologically rational (complementary mechanisms) and clinically used. No characterized pharmacokinetic interaction exists. Additive glucose-lowering effect is expected, with potential for increased risk of euglycemic ketoacidosis in the setting of very low carbohydrate absorption.

GLP-1 receptor agonists: Concurrent use with GLP-1 receptor agonists (semaglutide, liraglutide, tirzepatide) may produce additive gastrointestinal adverse effects (nausea, diarrhea, flatulence). The endogenous GLP-1 elevation produced by acarbose (through distal intestinal carbohydrate delivery) adds a modest incretin effect that is pharmacologically complementary to exogenous GLP-1 agonism, though the clinical significance of this additivity is uncertain.

Warfarin and oral anticoagulants: No characterized interaction. Acarbose does not affect warfarin pharmacokinetics or pharmacodynamics.

CYP450 substrates: Acarbose is not a substrate, inhibitor, or inducer of any characterized cytochrome P450 enzyme. No CYP-mediated drug-drug interactions are expected or have been reported [29].

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events at standard doses are gastrointestinal in nature and reflect the mechanism of action (increased delivery of fermentable carbohydrate to the colonic microbiota):

- Flatulence (reported in up to 78 percent of patients at initiation; typically diminishes to 15 to 30 percent over 8 to 24 weeks of continued therapy)
- Diarrhea (14 to 33 percent at initiation; diminishes with continued use)
- Abdominal pain or discomfort (11 to 21 percent)
- Bloating and distension (dose-dependent; more common at doses above 50 mg three times daily)

These adverse events are dose-dependent, are most pronounced during the first 4 to 8 weeks of therapy, and diminish with continued use as the colonic microbiota adapts to the increased fermentable substrate load [16]. Gradual dose titration (starting at 25 mg once daily and increasing to 25 mg three times daily, then to 50 mg three times daily over 4 to 8 weeks) is the standard clinical approach for minimizing gastrointestinal intolerance. The gastrointestinal adverse-event profile is the principal reason for the high discontinuation rates observed in clinical trials (25 to 39 percent in long-term studies).

11.2 Hepatotoxicity

Acarbose has been associated with rare instances of hepatotoxicity in postmarketing surveillance. Elevations of serum transaminases (ALT, AST) have been reported, typically at doses exceeding 50 mg three times daily, usually within 2 to 12 months of treatment initiation, and generally reversible upon discontinuation [17]. Fulminant hepatitis with jaundice has been reported in isolated cases from worldwide postmarketing experience.

The prescribing label recommends monitoring of serum transaminases every 3 months during the first year of therapy and periodically thereafter. If elevated transaminases are detected, dose reduction or discontinuation should be considered. The hepatotoxicity mechanism is not clearly characterized; it is not related to hepatic metabolism of acarbose (which does not occur) and may represent an idiosyncratic reaction, possibly mediated by the absorbed bacterial degradation products [17].

11.3 Hypoglycemia

Acarbose monotherapy does not cause hypoglycemia, as the compound does not stimulate insulin secretion [5, 6]. Hypoglycemia can occur when acarbose is used in combination with insulin or insulin secretagogues. In such cases, hypoglycemia must be treated with oral glucose (dextrose) rather than sucrose or complex carbohydrates, because acarbose delays the absorption of disaccharides and polysaccharides.

11.4 Other adverse events

- Skin reactions (rash, urticaria, erythema): rare, generally mild
- Ileus and subileus: reported in isolated postmarketing cases, principally in patients with pre-existing intestinal pathology
- Pneumatosis cystoides intestinalis: rare complication reported primarily in Japanese postmarketing surveillance, characterized by gas-filled cysts in the intestinal wall, resolving upon discontinuation

11.5 Pregnancy and lactation

Pregnancy data in humans are limited. Animal reproductive toxicity studies have not demonstrated teratogenicity at doses up to 480 mg/kg/day in rats and 160 mg/kg/day in rabbits (corresponding to approximately 9 and 10 times the maximum recommended human dose based on body surface area, respectively). The minimal systemic absorption of intact drug limits fetal exposure. Use in pregnancy is rated FDA category B and is not recommended unless clearly needed. Lactation data are not available; the clinical significance of any potential excretion in breast milk is likely minimal given the negligible systemic drug levels.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative compounds against acarbose, evaluated against five competency standards: novelty (mechanistic distinctiveness), effect size (magnitude of clinical or preclinical benefit), promising potential (current development trajectory and future applications), side-effect profile, and overall validation (totality of evidence). The five comparators were selected to span the spectrum from closely related alpha-glucosidase inhibitors (miglitol, voglibose) to mechanistically distinct glucose-lowering agents (metformin, empagliflozin) and to the principal longevity comparator (rapamycin), reflecting acarbose's dual positioning as an antidiabetic agent and a longevity research compound.

12.1 Miglitol

Mechanism: Alpha-glucosidase inhibitor. Miglitol is a 1-deoxynojirimycin derivative (a nitrogen-containing monosaccharide analog) that competitively inhibits the brush border alpha-glucosidases (maltase-glucoamylase, sucrase-isomaltase) with a mechanism closely related to acarbose. Unlike acarbose, miglitol does not significantly inhibit pancreatic alpha-amylase [33].

Pharmacokinetics: Miglitol is almost completely absorbed from the small intestine (bioavailability greater than 95 percent at the 25 mg dose, approximately 50 to 70 percent at the 100 mg dose), distributed systemically, and excreted unchanged by the kidneys [33]. This contrasts sharply with acarbose's topical luminal mechanism and negligible systemic absorption.

Novelty: Low. The mechanism is the same alpha-glucosidase inhibition as acarbose, without the additional alpha-amylase inhibition.

Effect size: HbA1c reductions are similar to acarbose (0.4 to 0.8 percentage points). Postprandial glucose reductions are comparable. No cardiovascular outcomes trials or longevity data exist for miglitol.

Promising potential: Low. The compound is a mature generic drug with no active clinical development programs. No longevity research has been published for miglitol.

Side-effect profile: Gastrointestinal adverse events (flatulence, diarrhea) are similar to acarbose. Miglitol has not been associated with the hepatotoxicity signal observed with acarbose, potentially owing to the different metabolic fate (renal excretion of unchanged drug rather than colonic bacterial degradation) [33].

Overall validation: Moderate. Well-validated for glycemic control in type 2 diabetes. Absent from the longevity and cardiovascular prevention research literature.

Comparison to acarbose: Miglitol is pharmacologically narrower (no alpha-amylase inhibition), is systemically absorbed (different pharmacokinetic profile), has comparable glycemic efficacy, may have a marginally better hepatotoxicity profile, and lacks the cardiovascular prevention and longevity research literature that distinguishes acarbose.

12.2 Voglibose

Mechanism: Alpha-glucosidase inhibitor. Voglibose is a valiolamine-derived N-substituted aminocyclitol that competitively inhibits intestinal alpha-glucosidases with higher potency than acarbose at the sucrase and maltase active sites but, like miglitol, does not significantly inhibit pancreatic alpha-amylase [34].

Pharmacokinetics: Voglibose is poorly absorbed from the gastrointestinal tract (bioavailability less than 5 percent), acting topically in the intestinal lumen similarly to acarbose. It is excreted predominantly in feces as unchanged drug.

Novelty: Low. The mechanism is closely related to acarbose. The higher potency at individual glucosidase subunits does not translate to a meaningfully different clinical profile.

Effect size: Some comparative studies report greater reductions in postprandial glucose and HbA1c with voglibose relative to acarbose and miglitol, though meta-analytic comparisons are inconsistent [35]. The VICTORY trial in Japan reported that voglibose reduced progression from impaired glucose tolerance to type 2 diabetes by 40 percent relative to placebo, comparable to the STOP-NIDDM result for acarbose [36].

Promising potential: Moderate in East Asian markets, where voglibose is widely prescribed. Low globally; the compound is not FDA-approved and is not available in the United States or most European markets.

Side-effect profile: Gastrointestinal adverse events are reported to be less severe than with acarbose in some comparative studies, though this may reflect the absence of alpha-amylase inhibition (less undigested starch reaching the colon). No hepatotoxicity signal has been reported.

Overall validation: Moderate. Well-validated for glycemic control in East Asian populations. The VICTORY diabetes prevention trial provides evidence comparable to STOP-NIDDM. No cardiovascular outcomes data. No longevity research.

Comparison to acarbose: Voglibose may offer modestly better gastrointestinal tolerability and comparable glycemic efficacy. Acarbose has a broader evidence base (STOP-NIDDM, ACE, UKPDS 44), global regulatory approval, and the unique longevity research literature from the NIA ITP.

12.3 Metformin

Mechanism: Biguanide. Metformin reduces hepatic glucose production (primarily through inhibition of mitochondrial complex I and activation of AMP-activated protein kinase), enhances peripheral insulin sensitivity, and reduces intestinal glucose absorption through incompletely characterized mechanisms [37]. The mechanism is fundamentally different from acarbose's intestinal alpha-glucosidase inhibition.

Pharmacokinetics: Metformin is absorbed from the small intestine (bioavailability approximately 50 to 60 percent), distributed to tissues with preferential hepatic accumulation, and excreted unchanged by the kidneys. Plasma half-life is approximately 5 hours.

Novelty: Moderate. Mechanistically distinct from acarbose. The AMPK-activating and mitochondrial mechanism is well characterized but has been known for decades.

Effect size: Metformin is more efficacious than acarbose for overall glycemic control, with HbA1c reductions of 1.0 to 1.5 percentage points as monotherapy. The UKPDS demonstrated a 39 percent relative risk reduction in myocardial infarction and a 36 percent relative risk reduction in all-cause mortality in overweight pa-

tients with type 2 diabetes, evidence that has not been replicated for acarbose [38]. The Diabetes Prevention Program demonstrated a 31 percent reduction in progression to type 2 diabetes, comparable to the STOP-NIDDM acarbose result [39].

Promising potential: High. Metformin is the first-line oral antidiabetic agent in virtually all global guidelines. The TAME trial (Targeting Aging with Metformin) is a landmark clinical trial testing metformin as a longevity intervention in older adults without diabetes [40]. Metformin has extended lifespan in some but not all rodent studies, with less consistent results than acarbose in the NIA ITP.

Side-effect profile: Gastrointestinal adverse events (nausea, diarrhea, abdominal discomfort) are common but generally milder than the flatulence profile of acarbose. Lactic acidosis is a rare but serious complication, primarily in patients with renal impairment. Vitamin B12 deficiency occurs with long-term use.

Overall validation: Very high. The most extensively validated oral antidiabetic agent, with the strongest cardiovascular evidence among non-insulin antidiabetic drugs in the pre-SGLT2 inhibitor era.

Comparison to acarbose: Metformin is more efficacious for glycemic control, has stronger cardiovascular evidence, and is the global first-line agent. Acarbose has stronger and more consistent longevity data from the NIA ITP (acarbose produced larger lifespan extension than metformin in the same program). The two compounds act through complementary mechanisms and are commonly combined in clinical practice.

12.4 Empagliflozin

Mechanism: Sodium-glucose co-transporter 2 (SGLT2) inhibitor. Empagliflozin blocks glucose reabsorption in the proximal renal tubule, producing glucosuria and thereby lowering plasma glucose independent of insulin secretion [41]. The mechanism is entirely distinct from acarbose's intestinal action.

Pharmacokinetics: Empagliflozin is well absorbed orally (bioavailability approximately 78 percent), hepatically metabolized by glucuronidation (UGT1A3, UGT1A8, UGT1A9, UGT2B7), and eliminated renally (approximately 54 percent) and fecally (approximately 41 percent). Plasma half-life is approximately 12 hours.

Novelty: High at the time of introduction (approved 2014). The renal mechanism of action was a paradigm shift in diabetes pharmacotherapy.

Effect size: HbA1c reductions of 0.7 to 0.8 percentage points (comparable to acarbose). The EMPA-REG OUTCOME trial demonstrated a 38 percent relative risk reduction in cardiovascular death, a 35 percent relative risk reduction in hospitalization for heart failure, and a 14 percent relative risk reduction in the composite major adverse cardiovascular events endpoint in patients with type 2 diabetes and established cardiovascular disease [42]. These cardiovascular and heart failure benefits are substantially stronger than anything demonstrated for acarbose.

Promising potential: Very high. Empagliflozin has been approved for heart failure (with or without diabetes) and has emerging evidence for renal protection. No longevity research in the ITP context.

Side-effect profile: Genital mycotic infections (5 to 10 percent), urinary tract infections (modest increase), euglycemic diabetic ketoacidosis (rare), Fournier's gangrene (very rare), volume depletion (particularly in elderly patients). The gastrointestinal profile is substantially better than acarbose.

Overall validation: Very high. One of the most rigorously validated antidiabetic agents for cardiovascular and renal outcomes.

Comparison to acarbose: Empagliflozin has superior cardiovascular outcomes evidence, better gastrointestinal tolerability, and broader approved indications (heart failure). Acarbose has the longevity research literature, the diabetes prevention evidence, and is substantially less expensive (generic availability). The two compounds act through entirely different mechanisms and are not direct substitutes.

12.5 Rapamycin (sirolimus)

Mechanism: Mechanistic target of rapamycin (mTOR) inhibitor. Rapamycin forms a complex with FKBP12 that inhibits mTORC1, suppressing protein synthesis, cell growth, and proliferation. The longevity mechanism involves reduced mTOR-driven cellular senescence, enhanced autophagy, and metabolic reprogramming [43].

Pharmacokinetics: Rapamycin is absorbed orally (bioavailability approximately 14 percent), extensively metabolized by hepatic CYP3A4, and eliminated with a long half-life of approximately 62 hours.

Novelty: High in the longevity context. Rapamycin is the most robustly validated pharmacological longevity intervention in mammalian models.

Effect size: The NIA ITP demonstrated median lifespan extension of approximately 10 to 15 percent in male and female mice at 14 ppm in chow, with the effect present even when initiated late in life (20 months of age) [44]. In combination with acarbose, the effect is additive, reaching 28 to 34 percent median lifespan extension [15].

Promising potential: High as a longevity research compound. Not approved for antidiabetic use. Approved as an immunosuppressant for organ transplant rejection and as an antiproliferative coating for coronary stents. Longevity clinical trials in humans (PEARL, AgelessRx trials) are in early stages.

Side-effect profile: Immunosuppression (the principal clinical concern for longevity applications), hyperlipidemia, impaired wound healing, mouth ulcers, thrombocytopenia, and metabolic effects (insulin resistance, hyperglycemia) at chronic immunosuppressive doses. Intermittent or low-dose protocols are under investigation for longevity applications to mitigate immunosuppressive effects.

Overall validation: Very high for longevity in animal models. The most replicated pharmacological lifespan extension result in mammalian biology. Limited human longevity data.

Comparison to acarbose: Rapamycin produces more consistent lifespan extension across sexes in the ITP (both males and females benefit), while acarbose shows a male-preferential effect. The combination of acarbose and rapamycin is additive, supporting complementary mechanisms. Acarbose has substantial advantages in clinical safety profile (gastrointestinal side effects versus immunosuppression), in regulatory status (approved antidiabetic agent versus approved immunosuppressant), and in cost (generic antidiabetic versus specialty immunosuppressant). For longevity research, the two compounds are the leading candidates from the NIA ITP and are increasingly studied in combination.

12.6 Comparator summary

The five compounds occupy distinct positions relative to acarbose. **Miglitol** and **voglibose** are mechanistically similar alpha-glucosidase inhibitors with comparable glycemic efficacy but lack the cardiovascular prevention and longevity research literature that distinguishes acarbose. **Metformin** is the global first-line antidiabetic

agent with stronger glycemic efficacy and cardiovascular evidence but less consistent longevity data in animal models. **Empagliflozin** represents the current standard for cardiovascular risk reduction in type 2 diabetes, with substantially stronger outcomes evidence than acarbose, but has no longevity research profile. **Rapamycin** is the principal longevity comparator, with the most replicated mammalian lifespan extension result, but has a fundamentally different and more concerning safety profile for chronic use in healthy populations.

Acarbose occupies a unique position in this comparator landscape: it is the only compound that combines (a) a well-validated antidiabetic indication with global regulatory approval, (b) diabetes prevention evidence from the STOP-NIDDM trial, (c) robust and replicated lifespan extension data from the NIA Interventions Testing Program, (d) a favorable safety profile dominated by self-limiting gastrointestinal effects, and (e) demonstrated additivity with rapamycin for longevity. Its glycemic efficacy is modest relative to metformin and its cardiovascular evidence is weaker than empagliflozin, but its dual positioning as an antidiabetic and longevity compound, combined with its generic availability, low cost, and manageable safety profile, makes it a compound of substantial and growing research interest.

13. References

1. Schmidt DD, Frommer W, Junge B, et al. Alpha-glucosidase inhibitors: new complex oligosaccharides of microbial origin. *Naturwissenschaften*. 1977;64(10):535-536.
2. Puls W, Keup U, Krause HP, Thomas G, Hoffmeister F. Glucosidase inhibition: a new approach to the treatment of diabetes, obesity, and hyperlipoproteinaemia. *Naturwissenschaften*. 1977;64(10):536-537.
3. Ahr HJ, Boberg M, Brendel E, Krause HP, Steinke W. Pharmacokinetics of acarbose. Part I: Absorption, concentration in plasma, metabolism and excretion after single administration of [14C]acarbose to rats, dogs and man. *Arzneimittelforschung*. 1989;39(10):1254-1260.
4. Ahr HJ, Boberg M, Krause HP, et al. Pharmacokinetics of acarbose. Part II: Distribution to and elimination from tissues and organs following single or repeated administration of [14C]acarbose to rats and dogs. *Arzneimittelforschung*. 1989;39(10):1261-1267.
5. Coniff RF, Shapiro JA, Seaton TB, Bray GA. Multicenter, placebo-controlled trial comparing acarbose (BAY g 5421) with placebo, tolbutamide, and tolbutamide-plus-acarbose in non-insulin-dependent diabetes mellitus. *Am J Med*. 1995;98(5):443-451.
6. Chiasson JL, Josse RG, Hunt JA, et al. The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus: a multicenter controlled clinical trial. *Ann Intern Med*. 1994;121(12):928-935.
7. Holman RR, Cull CA, Turner RC. A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (U.K. Prospective Diabetes Study 44). *Diabetes Care*. 1999;22(6):960-964.
8. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet*. 2002;359(9323):2072-2077.

9. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA*. 2003;290(4):486-494.
10. Holman RR, Coleman RL, Chan JCN, et al. Effects of acarbose on cardiovascular and diabetes outcomes in patients with coronary heart disease and impaired glucose tolerance (ACE): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2017;5(11):877-886.
11. Harrison DE, Strong R, Allison DB, et al. Acarbose, 17-alpha-estradiol, and nordihydroguaiaretic acid extend mouse lifespan preferentially in males. *Aging Cell*. 2014;13(2):273-282.
12. Strong R, Miller RA, Antebi A, et al. Longer lifespan in male mice treated with a weakly estrogenic agonist, an antioxidant, an alpha-glucosidase inhibitor or a Nrf2-inducer. *Aging Cell*. 2016;15(5):872-884.
13. Smith BJ, Miller RA, Ericsson AC, Harrison DC, Strong R, Schmidt TM. Changes in the gut microbiome and fermentation products concurrent with enhanced longevity in acarbose-treated mice. *BMC Microbiol*. 2019;19(1):130.
14. Bo-Linn GW. Extension of the life span by acarbose: is it mediated by the gut microbiota? *Aging Dis*. 2022;13(4):1005-1014.
15. Strong R, Miller RA, Cheng CJ, et al. Rapamycin-mediated mouse lifespan extension: kinetics and mechanisms, species comparisons, and synergy with acarbose. *Aging Cell*. 2022;21(10):e13711.
16. Balfour JA, McTavish D. Acarbose: an update of its pharmacology and therapeutic use in diabetes mellitus. *Drugs*. 1993;46(6):1025-1054.
17. Carrascosa M, Pascual F, Aresti S. Acarbose-induced acute severe hepatotoxicity. *Lancet*. 1997;349(9053):698-699.
18. Truscheit E, Frommer W, Junge B, Muller L, Schmidt DD, Wingender W. Chemistry and biochemistry of microbial alpha-glucosidase inhibitors. *Angew Chem Int Ed Engl*. 1981;20(9):744-761.
19. Couch JN. Some new genera and species of the Actinoplanaceae. *J Elisha Mitchell Sci Soc*. 1963;79:53-70.

20. Schwientek P, Szczepanowski R, Schwartz D, et al. The complete genome sequence of the acarbose producer *Actinoplanes* sp. SE50/110. *BMC Genomics*. 2012;13:112.
21. Wehmeier UF, Piepersberg W. Biotechnology and molecular biology of the alpha-glucosidase inhibitor acarbose. *Appl Microbiol Biotechnol*. 2004;63(6):613-625.
22. Truscheit E, Hillebrand I, Junge B, Muller L, Puls W, Schmidt DD. Microbial alpha-glucosidase inhibitors: chemistry, biochemistry and therapeutic potential. In: Ellis GP, West GB, eds. *Progress in Medicinal Chemistry*. Vol 25. Elsevier; 1988:119-175.
23. Sim L, Quezada-Calvillo R, Sterchi EE, Nichols BL, Rose DR. Human intestinal maltase-glucoamylase: crystal structure of the N-terminal catalytic subunit and basis of inhibition and substrate specificity. *J Mol Biol*. 2008;375(3):782-792.
24. Sim L, Willemsma C, Mohan S, Naim HY, Pinto BM, Rose DR. Structural basis for substrate selectivity in human maltase-glucoamylase and sucrase-isomaltase N-terminal domains. *J Biol Chem*. 2010;285(23):17763-17770.
25. Ren L, Qin X, Cao X, et al. Structural insight into substrate specificity of human intestinal maltase-glucoamylase. *Protein Cell*. 2011;2(10):827-836.
26. Brayer GD, Luo Y, Bhargava K, Bhatt R, Bhatt K. The structure of human pancreatic alpha-amylase at 1.8 Å resolution and comparisons with related enzymes. *Protein Sci*. 1995;4(9):1730-1742.
27. Hanefeld M, Fischer S, Schulze J, et al. Therapeutic potentials of acarbose as first-line drug in NIDDM insufficiently treated with diet alone. *Diabetes Care*. 1991;14(8):732-737.
28. Qualmann C, Nauck MA, Holst JJ, Orskov C, Creutzfeldt W. Glucagon-like peptide 1 (7-36 amide) secretion in response to luminal sucrose from the upper and lower gut: a study using alpha-glucosidase inhibition (acarbose). *Scand J Gastroenterol*. 1995;30(9):892-896.
29. Precose (acarbose tablets) prescribing information. Bayer HealthCare Pharmaceuticals. Revised March 2015.
30. Balfour JA, McTavish D. Acarbose: an update of its pharmacology and therapeutic use in diabetes mellitus. *Drugs*. 1993;46(6):1025-1054.

31. Van de Laar FA, Lucassen PL, Akkermans RP, Van de Lisdonk EH, Rutten GE, Van Weel C. Alpha-glucosidase inhibitors for patients with type 2 diabetes: results from a Cochrane systematic review and meta-analysis. *Diabetes Care*. 2005;28(1):154-163.
32. Moreira RO, Lima GA, Peixoto PC, Farias ML, Vaisman M. Acarbose for dumping syndrome: a case report. *Arq Bras Endocrinol Metabol*. 2008;52(4):751-754.
33. Scott LJ, Spencer CM. Miglitol: a review of its therapeutic potential in type 2 diabetes mellitus. *Drugs*. 2000;59(3):521-549.
34. Dabhi AS, Bhatt NR, Shah MJ. Voglibose: an alpha glucosidase inhibitor. *J Clin Diagn Res*. 2013;7(12):3023-3027.
35. Gao X, Cai X, Yang W, Chen Y, Han X, Ji L. Meta-analysis and critical review on the efficacy and safety of alpha-glucosidase inhibitors in Asian and non-Asian populations. *J Diabetes Investig*. 2018;9(2):321-331.
36. Kawamori R, Tajima N, Iwamoto Y, Kashiwagi A, Shimamoto K, Kaku K. Voglibose for prevention of type 2 diabetes mellitus: a randomised, double-blind trial in Japanese individuals with impaired glucose tolerance. *Lancet*. 2009;373(9675):1607-1614.
37. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. *Diabetologia*. 2017;60(9):1577-1585.
38. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;352(9131):854-865.
39. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6):393-403.
40. Barzilai N, Crandall JP, Kritchevsky SB, Espeland MA. Metformin as a tool to target aging. *Cell Metab*. 2016;23(6):1060-1065.
41. Grempler R, Thomas L, Eckhardt M, et al. Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: characterisation and comparison with other SGLT-2 inhibitors. *Diabetes Obes Metab*. 2012;14(1):83-90.
42. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128.

43. Lamming DW, Ye L, Sabatini DM, Baur JA. Rapalogs and mTOR inhibitors as anti-aging therapeutics. *J Clin Invest*. 2013;123(3):980-989.
44. Harrison DE, Strong R, Sharp ZD, et al. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature*. 2009;460(7253):392-395.
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