

Therapeutic Class Overview

Alpha-Glucosidase Inhibitors

INTRODUCTION

- Diabetes mellitus affects more than 30.3 million people in the US. A total of 84.1 million American adults have prediabetes, with 88.4% of this population unaware that they have the disease (*Centers for Disease Control and Prevention [CDC] 2017*).
- Type 2 diabetes mellitus (T2DM), the most common form of diabetes, is characterized by elevated fasting and postprandial glucose concentrations (*American Diabetes Association [ADA] 2018[a]*). It is a chronic illness that requires continuing medical care and self-management to prevent acute complications and reduce the risk of long-term complications (*ADA 2018[b]*).
- Complications of T2DM include heart disease, stroke, vision loss, kidney disease, and amputations of toes, feet, or legs. It is the leading cause of kidney failure, lower-limb amputations, and adult-onset blindness and the seventh leading cause of death in the US (*CDC 2017*).
- In addition to dietary and lifestyle management, T2DM can be treated with a variety of oral and injectable antidiabetic medications. Many patients with T2DM will require combination therapy (*Garber et al 2018*).
- Classes of oral medications for the management of blood glucose levels in patients with T2DM may work by increasing insulin secretion, increasing sensitivity to insulin, decreasing the rate of carbohydrate absorption, and blocking glucose reabsorption by the kidney (*Inzucchi et al 2015*).
- Pharmacologic options for T2DM include sulfonylureas, biguanides, thiazolidinediones (TZDs), meglitinides, alpha-glucosidase inhibitors (AGIs), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogs, amylin mimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, and insulin (*ADA 2018[b]*).
- AGIs delay the absorption of ingested carbohydrates, resulting in a smaller rise in postprandial glucose (PPG) levels. The effect of AGIs is typically additive when used in combination with medications from other pharmacological classes due to its different mechanism of action (*Glyset Prescribing information 2016, Precose Prescribing information 2015*).
- Medispan Class: Alpha-Glucosidase Inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Glyset (miglitol)	✓
Precose (acarbose)	✓

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. Food and Drug Administration (FDA)-Approved Indications

Indication	Glyset (miglitol)	Precose (acarbose)
As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	✓	✓

(*Prescribing information: Glyset, 2016, Precose, 2015*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- AGIs have demonstrated efficacy in the management of T2DM when used as monotherapy and in combination with other antidiabetic agents. Most trials evaluated the addition of an AGI to one or more classes of antidiabetic agents.
- Both acarbose and miglitol have consistently shown beneficial effects on hemoglobin A1c (HbA1c) and PPG when added to the following therapies:
 - Metformin (*Halimi et al 2000, Van Gaal et al 2001, Wang et al 2013*)
 - Sulfonylureas (*Bayraktar et al 1996, Hsieh et al 2011, Lin et al 2003*)

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- Insulin (*Hwu et al 2003, Nemeto et al 2011, Schnell et al 2007*)
- Combination sulfonylurea and metformin (*Lam et al 1998, Standl et al 2001*)
- However, clinical trial results have demonstrated inconsistent effects on fasting plasma glucose (FPG) (*Halimi et al 2000, Hsieh et al 2011, Hwu et al 2003, Lam et al 1998, Lin et al 2003, Standl et al 2001, Van Gaal et al 2001*).
- In addition, acarbose has been compared to other classes of antidiabetics in a number of trials. Bayraktar et al performed a small crossover study (N = 18) comparing acarbose 100 mg 3 times daily to metformin 500 mg 3 times daily in patients with T2DM inadequately controlled on maximal doses of a sulfonylurea. Results demonstrated that both treatments improved FPG, PPG, and HbA1c; acarbose lowered PPG to a greater extent than metformin ($p < 0.05$) (*Bayraktar et al 1996*). Two studies compared acarbose to a sulfonylurea in patients with T2DM without previous pharmacologic treatment. In these studies, acarbose was associated with smaller reductions in HbA1c and FPG compared to tolbutamide (*van de Laar et al 2004*) and glimepiride (*Feinbock et al 2003*). Acarbose 100 mg 3 times daily was compared to bedtime NPH insulin in a small crossover study of patients inadequately controlled with combination sulfonylurea and metformin. In this study, acarbose demonstrated reductions in FPG and PPG, but overall results were superior in the insulin-treated group (*Lopez-Alvarenga 1999*). When compared to vildagliptin (*Pan et al 2008*) and to repaglinide (*Derosa et al 2009*), acarbose demonstrated comparable effects on PPG and HbA1c, and superior effects on weight loss. A comparison of acarbose and saxagliptin in 488 Chinese patients uncontrolled on metformin alone found that saxagliptin was non-inferior to acarbose in glycemic control, but was associated with fewer gastrointestinal adverse events (*Du et al 2017*).
- Miglitol has also been compared to other classes of diabetes treatments in a small number of trials. Johnston et al compared two doses of miglitol to glyburide for the treatment of drug-naïve patients greater than 60 years of age with T2DM. In this study, glyburide had greater beneficial effects on HbA1c, but miglitol had greater beneficial effects on body weight and one-hour PPG levels (in the miglitol 50 mg group). The glyburide group also had a higher incidence of hypoglycemia (*Johnston et al 1998*). Another study compared miglitol to metformin and the combination of both for the treatment of patients with T2DM inadequately treated with diet. In this trial, improvement in HbA1c, FPG, and PPG were numerically greater with metformin compared to miglitol, and with combination treatment compared to metformin. P-values were not provided for comparison between the monotherapy arms, because the primary comparison for efficacy was between the metformin monotherapy and the combination therapy group (*Chiasson et al 2001*).
- The effects of acarbose on cardiovascular outcomes in patients with coronary heart disease and impaired glucose tolerance was evaluated in the ACE trial (*Holman et al 2017*). The primary endpoint for the trial was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospital admission for unstable angina, and hospital admission for heart failure. The incidence of new onset diabetes was evaluated as a secondary endpoint. A total of 6522 Chinese patients were randomized 1:1 to acarbose or placebo. After a median follow up period of 5 years, there was no significant difference in the incidence of the primary endpoint (14% with acarbose vs 15% with placebo; hazard ratio [HR], 0.98; 95% confidence interval [CI], 0.86 to 1.11; $p = 0.73$). Fewer patients in the acarbose group developed diabetes (rate ratio [RR], 0.82; 95% CI, 0.71 to 0.94).
- A 2005 Cochrane review reported that acarbose has clear beneficial effects on glycemic control compared to placebo, but no clinically relevant effects on body weight or lipids. Authors noted that few data are available on the effects of AGIs on morbidity, mortality, or quality of life (*van de Laar et al 2005*). Acarbose has been compared to placebo for major cardiovascular events in 1,429 obese patients with impaired glucose tolerance tests over 3 years (*Chiasson et al 2003*). Acarbose was associated with a 2.5% absolute risk reduction and 49% relative risk reduction (HR, 0.51; 95% CI, 0.25 to 0.95; $p = 0.03$) in the development of any cardiovascular event. Fewer patients treated with acarbose (17%) developed diabetes compared to the placebo group (26%) (HR, 0.68; 95% CI, 0.54 to 0.85; $p = 0.001$) (*Chiasson et al 2002*).
- A systematic review of 136 trials showed that most oral agents including TZDs, metformin, and repaglinide improved glycemic control to the same degree as sulfonylureas, with an absolute decrease in HbA1c level of about 1% (moderate-to-high strength of evidence) (*Bolen et al 2007*). Nateglinide and AGIs have slightly weaker effects, on the basis of indirect comparisons of placebo-controlled trials (low strength of evidence).
- A network meta-analysis evaluating the efficacy of 12 oral agents calculated surface under the cumulative ranking curves (SUCRA) based on direct and indirect evidence from 15 trials (*Wang et al 2017*). The analysis concluded that the HbA1c and FPG SUCRA values were highest for liraglutide and lowest for acarbose, suggesting that acarbose is the least effective for glycemic control.

CLINICAL GUIDELINES

- **American Diabetes Association (ADA):** Standards of Medical Care in Diabetes (2018)

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- When lifestyle efforts alone do not achieve or maintain glycemic goals, metformin (if not contraindicated and if tolerated) is the preferred initial pharmacological agent for T2DM.
- Initiation of insulin therapy (with or without additional agents) should be considered in patients with newly diagnosed T2DM who are markedly symptomatic and/or have blood glucose levels ≥ 300 mg/dL or HbA1c $\geq 10\%$.
- If noninsulin monotherapy at the maximum tolerated dose does not achieve or maintain the HbA1c target after 3 months, a second oral agent (eg, sulfonylurea, TZD, DPP-4 inhibitor, SGLT-2 inhibitor), a GLP-1 receptor agonist, or basal insulin should be added. **For patients with atherosclerotic cardiovascular disease, a second agent with evidence of cardiovascular risk reduction should be considered instead.**
- A patient-centered approach should be used to guide the choice of pharmacological agents. Considerations include efficacy, cost, potential adverse events, weight, comorbidities, hypoglycemia risk, and patient preferences.
- Advantages of AGIs include low risk for hypoglycemia and decreased postprandial glucose excursions, while disadvantages include modest efficacy, gastrointestinal side effects, and frequent dosing schedule. The guidelines do not recommend AGIs in their general recommendation treatment algorithm (*ADA 2018[b]*).
- **American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE): Type 2 Diabetes Management Algorithm – Executive Summary (2018)**
 - For patients with recent onset T2DM or mild hyperglycemia (HbA1c $< 7.5\%$), monotherapy with metformin is preferred. Alternatives include GLP-1 receptor agonists, SGLT-2 inhibitors, DPP-4 inhibitors, **and AGIs. Sulfonylureas, TZDs, and glinides may be used with caution.**
 - For patients with a HbA1c $\geq 7.5\%$, metformin or another first-line agent with a second agent (eg, GLP-1 receptor agonist, SGLT2 inhibitor, DPP-4 inhibitor, colesevelam, bromocriptine quick release, or an AGI) should be initiated. **TZD, basal insulin, or sulfonylurea/glinide should be used with caution.**
 - AGIs have modest HbA1c-lowering effects and low risk for hypoglycemia. While clinical trials have suggested cardiovascular benefit in patients with impaired glucose tolerance and diabetes, side effects (eg, bloating, flatulence, diarrhea) have limited their use in the US. AGIs should be used with caution in patients with chronic kidney disease (*Garber et al 2018*).

SAFETY SUMMARY

- **Contraindications:**
 - Hypersensitivity to the drugs or any of their components
 - Diabetic ketoacidosis
 - Cirrhosis (acarbose only)
 - Chronic intestinal diseases associated with marked disorders of digestion or absorption, or with conditions that may deteriorate as a result of increased gas formation in the intestine
 - Inflammatory bowel disease, colonic ulceration, partial intestinal obstruction, or patients predisposed to intestinal obstruction
- **Adverse Events:**
 - The most common adverse events are gastrointestinal in nature, including flatulence, diarrhea, and abdominal pain/distention.
 - Acarbose has been associated with elevated serum transaminase levels.
 - Miglitol has been associated with skin rash.
- **Drug Interactions:**
 - Intestinal adsorbents (eg, charcoal) and digestive enzyme preparations containing carbohydrate-splitting enzymes (eg, amylase, pancreatin) may reduce the effect of AGIs and should not be taken concomitantly.
 - Miglitol reduces the bioavailability of ranitidine and propranolol.
 - Acarbose may reduce the bioavailability of digoxin; dose adjustment of digoxin may be necessary.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Glyset (miglitol)	Tablets	Oral	Three times daily at the start of each meal	Avoid use in CrCl < 25 mL/min Not recommended in nursing women

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Precose (acarbose)	Tablets	Oral	Three times daily at the start of each meal	Avoid use in SCr > 2 mg/dL Not recommended in nursing women

Abbreviations: CrCl = creatinine clearance; SCr = serum creatinine

See the current prescribing information for full details

CONCLUSION

- AGIs are one of several oral drug classes used for the treatment of T2DM. Both acarbose and miglitol have demonstrated benefits for reducing glucose parameters, particularly HbA1c and PPG levels. Effects on FPG were inconsistent across studies.
- Effects on HbA1c, in the range of 0.7 to 0.8%, are modest compared to other classes of antidiabetics.
- While AGIs are not associated with hypoglycemia when given as monotherapy, they can contribute to hypoglycemia when administered in combination with other agents used to treat T2DM.
- Both acarbose and miglitol are poorly tolerated due to GI effects such as abdominal pain, flatulence, and diarrhea.
- Available clinical guidelines are consistent in their recommendation to use metformin as first-line therapy for T2DM unless contraindicated (*ADA 2018[b]*, *Garber et al 2018*, *Inzucchi et al 2015*, *Qaseem et al 2017*). AGIs are listed as one of several potential alternatives or add-on therapies; however, AGIs are not among the agents preferentially recommended in combination with metformin as dual or triple combination therapy for patients with T2DM.
- Both available AGIs require a frequent dosing schedule of 3 times daily at the start of each main meal.
- Acarbose and miglitol have not been directly compared to one another in a randomized trial, and few distinctions can be made between them. Acarbose has been studied in a larger number of clinical trials and is not significantly absorbed. In contrast, miglitol has been studied in a smaller number of trials, is absorbed systemically, and is eliminated renally.

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