

Therapeutic Class Overview *α*-glucosidase Inhibitors

Therapeutic Class

- Overview/Summary:** Acarbose (Precose[®]) and miglitol (Glyset[®]) are *α*-glucosidase inhibitors Food and Drug Administration-approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.^{1,2} The *α*-glucosidase inhibitors lower blood glucose in a dose-dependent fashion by modifying the intestinal absorption of carbohydrates and fat. Specifically, the agents inhibit upper gastrointestinal enzymes (*α*-glucosidases) that are responsible for converting complex polysaccharide carbohydrates into monosaccharides. The actions of the *α*-glucosidase inhibitors ultimately result in the slowing of glucose absorption, and the resulting slower rise in postprandial blood glucose concentrations is potentially beneficial in patients with diabetes. Because these agents work in the gastrointestinal tract, gastrointestinal-related adverse events, including diarrhea and flatulence, are the primary adverse events associated with treatment, and may limit the acceptance of the *α*-glucosidase inhibitors by patients.³ Both acarbose and miglitol are available in tablet formulation, and are to be administered three times daily with the first bite of each main meal.^{1,2} Currently, acarbose is the only *α*-glucosidase inhibitor that is available generically. Overall, the *α*-glucosidase inhibitors are effective in decreasing glycosylated hemoglobin (HbA_{1c}) and postprandial glucose levels in patients with type 2 diabetes when administered as monotherapy or in combination with other antidiabetic agents. Robust head-to-head clinical trials comparing acarbose and miglitol have not been conducted.⁴⁻³¹

Table 1. Current Medications Available in the Class^{1,2}

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Acarbose (Precose [®])	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Tablet: 25 mg 50 mg 100 mg	✓
Miglitol (Glyset [®])	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Tablet: 25 mg 50 mg 100 mg	-

*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Data consistently demonstrate the *α*-glucosidase inhibitors, administered either as monotherapy or in combination with other antidiabetic medications, result in a significant lowering of glycosylated hemoglobin and postprandial glucose levels.
- Data demonstrate that the medication class reduces excessive blood glucose fluctuations and decrease hypoglycemic events, respectively.⁶⁻³⁰ Available trials include a small, pilot, crossover, head-to-head trial which demonstrates no significant difference between acarbose and miglitol in postprandial glucose variability.²⁴
- Several clinical trials have evaluated the effects of the *α*-glucosidase inhibitors on serum lipids and body weight; however, a large meta-analysis (N=8,130) found that the *α*-glucosidase inhibitors provide no clear beneficial effects for either measure.²⁶
- The effect of acarbose on cardiovascular events was evaluated in the placebo-controlled Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial (N=1,429). Results suggest that treating patients with impaired glucose tolerance with acarbose is associated with a significant reduction in the risk of cardiovascular disease and hypertension. After a mean duration of 3.3 years, there was a significant 49% reduction in the risk of cardiovascular events with acarbose compared to placebo, with the major finding being a reduction in myocardial infarction (hazard ratio, 0.09). In

addition, there was a significant 34% reduction in the risk of developing hypertension with acarbose compared to placebo in these patients.³¹

- Another analysis of the STOP-NIDDM trial suggests that acarbose could be utilized to delay the development of type 2 diabetes in patients with impaired glucose tolerance. Specifically, treatment with acarbose was associated with a significant 32% reduction in the risk of developing type 2 diabetes compared to treatment with placebo.⁴
- A large meta-analysis of five clinical trials (N=2,360) supports these findings; however, it remains unclear whether the effects of acarbose on reducing the incidence of type 2 diabetes can be interrupted as prevention, delay, or masking of diabetes.⁵

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - Metformin remains the cornerstone to most antidiabetic treatment regimens.
 - In addition, patients with a high glycosylated hemoglobin (HbA_{1c}) will most likely require combination or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered.
 - In general, the α -glucosidase inhibitors are not recommended for use in the management of patients with a high HbA_{1c} (7.6 to 9.0%), mainly due to the limited HbA_{1c}-lowering potential associated with the medication class compared to other available antidiabetic medications.
 - The α -glucosidase inhibitors may be utilized as monotherapy in the management of patients with a low HbA_{1c} (6.5 to 7.5%); however, metformin remains the most appropriate initial choice for monotherapy in all patients without contraindications.
 - In addition, clinical guidelines recognize the potential use of α -glucosidase inhibitors when postprandial hyperglycemia is present.
 - Among all current clinical guidelines, preference of one α -glucosidase inhibitor over another is not stated.³²⁻³⁷
- Other Key Facts:
 - Acarbose is the only α -glucosidase inhibitor that is available generically.

References

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Therapeutic Class Review α -glucosidase Inhibitors

Overview/Summary

Acarbose (Precose[®]) and miglitol (Glyset[®]) are α -glucosidase inhibitors Food and Drug Administration-approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.^{1,2} The α -glucosidase inhibitors lower blood glucose in a dose-dependent fashion by modifying the intestinal absorption of carbohydrates and fat. Specifically, the agents inhibit upper gastrointestinal enzymes (α -glucosidases) that are responsible for converting complex polysaccharide carbohydrates into monosaccharides. The actions of the α -glucosidase inhibitors ultimately result in the slowing of glucose absorption, and the resulting slower rise in postprandial blood glucose concentrations is potentially beneficial in patients with diabetes. Because these agents work in the gastrointestinal tract, gastrointestinal-related adverse events, including diarrhea and flatulence, are the primary adverse events associated with treatment, and may limit the acceptance of the α -glucosidase inhibitors by patients.³ Both acarbose and miglitol are available in tablet formulation, and are to be administered three times daily with the first bite of each main meal.^{1,2} Currently, acarbose is the only α -glucosidase inhibitor that is available generically.

Overall, the α -glucosidase inhibitors are effective in decreasing glycosylated hemoglobin (HbA_{1c}) and postprandial glucose levels in patients with type 2 diabetes when administered as monotherapy or in combination with other antidiabetic agents. Robust head-to-head clinical trials comparing acarbose and miglitol have not been conducted.⁴⁻³¹

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone to most antidiabetic treatment regimens. In addition, patients with a high HbA_{1c} will most likely require combination or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered. In general, the α -glucosidase inhibitors are not recommended for use in the management of patients with a high HbA_{1c} (7.6 to 9.0%), mainly due to the limited HbA_{1c}-lowering potential associated with the medication class compared to other available antidiabetic medications. The α -glucosidase inhibitors may be utilized as monotherapy in the management of patients with a low HbA_{1c} (6.5 to 7.5%); however, metformin remains the most appropriate initial choice for monotherapy in all patients without contraindications. In addition, clinical guidelines recognize the potential use of α -glucosidase inhibitors when postprandial hyperglycemia is present. Among all current clinical guidelines, preference of one α -glucosidase inhibitor over another is not stated.³²⁻³⁷

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Acarbose (Precose [®])	α -glucosidase Inhibitors	✓
Miglitol (Glyset [®])	α -glucosidase Inhibitors	-

Indications

Table 2. Food and Drug Administration-Approved Indications^{1,2}

Indication(s)	Acarbose	Miglitol
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	✓	✓

Pharmacokinetics**Table 3. Pharmacokinetics**³⁸

Generic Name	Bioavailability (%)	Renal Elimination (%)	Active Metabolites	Serum Half-Life (hours)
Acarbose	0.5 to 2.0	2	None	2
Miglitol	100	>95	None	2

Clinical Trials

Clinical trials demonstrating the safety and efficacy of the α -glucosidase inhibitors in the management of type 2 diabetes are outlined in Table 4.⁴⁻³¹ Data consistently demonstrate the α -glucosidase inhibitors, administered either as monotherapy or in combination with other antidiabetic medications, result in a significant lowering of glycosylated hemoglobin and postprandial glucose levels. The effects of α -glucosidase inhibitors on glycemic variability, or fluctuation, measured using continuous glucose monitoring have also been evaluated. Data demonstrate that the medication class reduces excessive blood glucose fluctuations and decrease hypoglycemic events, respectively.⁶⁻³⁰ Available trials include a small, pilot, crossover, head-to-head trial which demonstrates no significant difference between acarbose and miglitol in postprandial glucose variability.²⁴ Several clinical trials have evaluated the effects of the α -glucosidase inhibitors on serum lipids and body weight; however, a large meta-analysis (N=8,130) found that the α -glucosidase inhibitors provide no clear beneficial effects for either measure.²⁶

The effect of acarbose on cardiovascular events was evaluated in the placebo-controlled Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial (N=1,429). Results suggest that treating patients with impaired glucose tolerance with acarbose is associated with a significant reduction in the risk of cardiovascular disease and hypertension. After a mean duration of 3.3 years, there was a significant 49% reduction in the risk of cardiovascular events with acarbose compared to placebo, with the major finding being a reduction in myocardial infarction (hazard ratio, 0.09). In addition, there was a significant 34% reduction in the risk of developing hypertension with acarbose compared to placebo in these patients.³¹ Another analysis of the STOP-NIDDM trial suggests that acarbose could be utilized to delay the development of type 2 diabetes in patients with impaired glucose tolerance. Specifically, treatment with acarbose was associated with a significant 32% reduction in the risk of developing type 2 diabetes compared to treatment with placebo.⁴ A large meta-analysis of five clinical trials (N=2,360) supports these findings; however, it remains unclear whether the effects of acarbose on reducing the incidence of type 2 diabetes can be interrupted as prevention, delay, or masking of diabetes.⁵

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Diabetes Prevention				
Chiasson et al ⁴ STOP-NIDDM Acarbose 100 mg TID vs placebo	DB, MC, PC, RCT Patients 40 to 70 years of age, with a BMI 25 to 40 kg/m ² , and impaired glucose tolerance test according to the WHO criteria, and a FPG 100 to 140 mg/dL	N=1,429 3.3 years (mean duration)	Primary: The development of diabetes on the basis of a yearly oral glucose tolerance test Secondary: Not reported	Primary: One hundred seventeen (17%) patients developed diabetes in the acarbose group compared to 178 (26%) patients in the placebo group (HR, 0.68; 95% CI, 0.54 to 0.85; <i>P</i> =0.0010), resulting in an absolute reduction of 8.7% and a relative reduction of 32.4% when a FPG of 7.0 mmol/L or greater was reported on two consecutive visits as the criterion for the development of diabetes. When any two positive oral glucose tolerance tests with a two-hour plasma glucose of 11.1 mmol/L or greater, 105 (15%) patients converted to diabetes in the acarbose group compared to 165 (24%) patients in the placebo group (HR, 0.64; 95% CI, 0.4981 to 0.8129; <i>P</i> =0.003) for an absolute reduction of 8.7% and a relative reduction of 36.4%. Based on one abnormal plasma glucose concentration, cumulative incidence of diabetes was 221 (32%) patients in the acarbose group and 285 (42%) patients in the placebo group (relative hazard, 0.75; 95% CI, 0.63 to 0.90; <i>P</i> =0.0015). Probability of reverting to normal glucose tolerance over time was significantly higher in patients on acarbose than in those on placebo (<i>P</i> <0.001). Secondary: Not reported
van de Laar et al ⁵ Acarbose vs placebo, metformin, diet and exercise, or both	MA (5 trials) Patients with impaired glucose tolerance or impaired fasting blood glucose	N=2,360 1 to 6 years	Primary: Occurrence of type 2 diabetes Secondary: Cardiovascular morbidity and mortality, glycemic control, lipids, BP, body weight	Primary: In the comparison of acarbose to placebo, the incidence of or conversion to type 2 diabetes was reduced (RR, 0.78; 95% CI, 0.68 to 0.90). Neither acarbose nor metformin had significant effects on the incidence of type 2 diabetes when compared to one another. However, when compared to diet and exercise, acarbose had beneficial effects on the incidence of type 2 diabetes (RR, 0.40; 95% CI, 0.17 to 0.96). Secondary: There were no significant effects on total mortality or mortality due to cardiovascular causes in trials comparing acarbose to placebo. In one trial (STOP-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>NIDDM), a decreasing effect on the incidence of cardiovascular disease as a combined end point (MI, angina, revascularization procedures, cardiovascular death, congestive heart failure, cerebrovascular events, and peripheral vascular disease) was reported (RR, 0.47; 95% CI, 0.26 to 0.86).</p> <p>Acarbose decreased PPG by 0.61 mmol/L (95% CI, 0.27 to 0.95) compared to placebo. In the EDIT study, acarbose significantly decreased FPG and PPG in comparison to placebo ($P=0.0043$ and $P=0.0075$, respectively). In comparison to metformin, acarbose showed a decreasing effect on PPG (1.40 mmol/L; 95% CI, 0.55 to 2.25). Similarly, acarbose vs diet and exercise also showed significant reductions in FPG and PPG (-1.37 [95% CI, -0.50 to -2.24] and -2.79 mmol/L [95% CI, -1.79 to -3.79]).</p> <p>There were no significant effects on DBP and SBP in trials comparing acarbose to placebo. However, metformin showed significant decreases in both TC and DBP in comparison to acarbose (0.90 mmol/L [95% CI, 0.19 to 1.61] and 6 mm Hg [95% CI, 2.81 to 9.19], respectively).</p> <p>Acarbose decreased body weight by 1.2 kg (95% CI, 0.5 to 1.8) and BMI by 0.3 kg/m² (95% CI, 0.1 to 0.5) compared to placebo.</p>
Type 2 Diabetes				
<p>Buse et al⁶ PROTECT</p> <p>Acarbose 25 to 50 mg TID</p> <p>The dose remained at 50 mg TID, or the dose was increased to 100 mg TID, or a sulfonylurea was added, or the dose of the sulfonylurea was increased.</p>	<p>MC, OL, PRO</p> <p>Patients ≥ 21 years of age with type 2 diabetes who were inadequately controlled with either diet alone or diet and a sulfonylurea</p>	<p>N=6,142</p> <p>28 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline PPG</p>	<p>Primary: Mean HbA_{1c} after 28 weeks was 8.41%. The mean change from baseline in HbA_{1c} at trial end was -0.66% ($P<0.001$).</p> <p>Secondary: Mean PPG level was 208.1 mg/dL after 28 weeks of therapy. The mean PPG level decreased by 41 mg/dL at trial end ($P<0.001$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Mori et al⁷</p> <p>Acarbose 300 mg/day, administered on 2 of 4 days</p> <p>vs</p> <p>no treatment</p>	<p>SA</p> <p>Adults with type 2 diabetes</p>	<p>N=10</p> <p>4 days</p>	<p>Primary: Glucose fluctuations</p> <p>Secondary: Not reported</p>	<p>Primary: During treatment, significant decreases in median of 24-hour mean blood glucose (22.48 vs 32.78 mg/dL; $P=0.004$), 24-hour mean blood glucose fluctuations (453.27 vs 677.05 mg/dL; $P=0.002$), and mean amplitude of glycemic excursions (65.00 vs 97.09; $P=0.010$) were achieved with acarbose compared to no treatment.</p> <p>Secondary: Not reported</p>
<p>Jian-bin et al⁸</p> <p>Acarbose 50 mg TID</p> <p>vs</p> <p>no treatment</p> <p>All patients received existing insulin regimens.</p> <p>After an initial 3 day continuous glucose monitoring test, patients with mean amplitude of glycemic excursions >3.4 mmol/L received acarbose for 2 weeks (high group); patients with values <3.4 mmol/L did not receive additional treatment (low group).</p>	<p>PRO</p> <p>Type 2 diabetics receiving premixed insulin BID for >3 consecutive months and HbA_{1c} <6.5%</p>	<p>N=106 (includes 20 control subjects who had normal glucose regulation)</p> <p>3 days</p>	<p>Primary: Glycemic variability, hypoglycemia</p> <p>Secondary: Not reported</p>	<p>Primary: Among the 86 patients, the mean amplitude of glycemic excursions and mean of daily differences of type 2 diabetes groups were all higher compared to control patients ($P<0.01$).</p> <p>Twenty-four percent of patients in the high group (n=11) had a total of 13 hypoglycemic events, and 10 of the 13 events occurred at night. Five percent of patients in the low group (n=2) had a total of two hypoglycemic events, and both occurred at night (24 vs 5%; $P<0.01$). Mean amplitude of glycemic excursion value was correlated with hypoglycemia value and two-hour PPG value ($P<0.05$).</p> <p>After further treatment with acarbose and second continuous glucose monitoring, mean amplitude of glycemic excursions and mean of daily differences values in the high group were all significantly decreased (40%; $P<0.01$, and 15%; $P<0.05$, respectively), but remained higher compared to control patients ($P<0.05$). Two percent of patients (n=1) had a total of one hypoglycemic event.</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>de Luis Roman et al (abstract)⁹</p> <p>Miglitol 50 mg BID for 1 week, followed by 50 mg TID</p>	<p>OL</p> <p>Patients with type 2 diabetes inadequately controlled (HbA_{1c} >7.5%) on sulfonylureas and insulin</p>	<p>N=33</p> <p>3 months</p>	<p>Primary: Change in weight, height, BMI, SBP, DBP, HbA_{1c}, number of episodes of peripheral hypoglycemia, basal glucose, albuminuria, TC, LDL-C, HDL-C, TG, and transaminases</p> <p>Secondary: Not reported</p>	<p>Primary: Blood glucose and HbA_{1c} decreased 4.8 and 5.8%, respectively.</p> <p>There was a decrease in the number of hypoglycemia episodes (39.4% previous quarter vs 3% during the miglitol quarter).</p> <p>The required dose of sulfonylureas decreased (86.2±24.3 vs 64.6 ±21.9 mg/day; <i>P</i><0.05).</p> <p>TC, HDL-C, and LDL-C were not modified. There was a reduction in TG from 145.2 ±111.0 to 133.1±79.0 mg/dL (<i>P</i><0.05).</p> <p>Fifteen percent of patients experienced digestive discomfort, which disappeared two or three weeks after beginning the treatment.</p> <p>Secondary: Not reported</p>
<p>Hwu et al¹⁰</p> <p>Asian Acarbose Study Group</p> <p>Acarbose 50 mg TID for 6 weeks, titrated up to 100 mg TID for 12 weeks</p> <p>vs placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Asian patients 35 to 70 years of age with type 2 diabetes receiving insulin with inadequate control, an HbA_{1c} 8.0 to 11.0%, requiring ≥2 injections of intermediate insulin per day, and a BMI ≤35 kg/m²</p>	<p>N=117</p> <p>18 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Changes in baseline FPG, PPG, and lipids</p>	<p>Primary: HbA_{1c} improved with acarbose (-0.5±1.3%) and worsened with placebo (0.2±1.2%). The comparison between the two treatments showed a difference of -0.69% (95% CI, -1.18 to -0.20; <i>P</i>=0.008) in favor of acarbose.</p> <p>Secondary: FPG decreased with acarbose by trial end, but there was not a significant difference between placebo (0.04 mmol/L; 95% CI, -1.28 to 1.66; <i>P</i>=0.094).</p> <p>Differences between the two treatments were significant for the PPG data (-1.89 mmol/L; 95% CI, -3.50 to -0.28; <i>P</i>=0.029), but was not significant for the two-hour post-prandial data (-1.83 mmol/L; 95% CI, -3.67 to 0.00; <i>P</i>=0.051).</p> <p>There were no differences between the two treatments, from baseline to trial end, for TG, TC, and LDL-C (<i>P</i>=0.378, <i>P</i>=0.935, <i>P</i>=0.294, respectively). There was a small decrease in HDL-C with acarbose (<i>P</i>=0.049).</p>
<p>Josse et al¹¹</p> <p>Acarbose 50 to 100 mg</p>	<p>DB, PC, RCT</p> <p>Patients >65 years</p>	<p>N=192</p> <p>1 year</p>	<p>Primary: Change in HbA_{1c}, FPG, fasting</p>	<p>Primary: Differences in the change from baseline in HbA_{1c} between acarbose and placebo was -0.6% (<i>P</i><0.05). Acarbose 100 mg TID resulted in a greater HbA_{1c} treatment</p>

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TID vs placebo	of age with type 2 diabetes treated with diet alone		insulin, relative insulin sensitivity, and glucose; insulin incremental AUC Secondary: Not reported	effect compared to acarbose 50 TID (-0.9 vs -0.2%; <i>P</i> value not reported). Change in FPG level was greater with acarbose compared to placebo (-0.7 mmol/L; <i>P</i> <0.05). Change in fasting insulin was -9±4 and -9 pmol/L with acarbose and placebo; the difference was not significant (<i>P</i> value not reported). Acarbose showed a significant reduction in glucose and insulin incremental AUC compared to placebo (glucose, -2.1 mmol/h l [<i>P</i> <0.05] and insulin, -45 pmol/h l; [<i>P</i> <0.05]). Acarbose showed a significant reduction in relative insulin resistance compared to placebo (-0.8; <i>P</i> <0.05). Secondary: Not reported
Lam et al ¹² Acarbose 50 mg TID for 4 weeks, titrated up to 100 mg TID for 20 weeks vs placebo	DB, MC, RCT Patients with type 2 diabetes, BMI <30 kg/m ² , HbA _{1c} 8.4 to 10.8%, and on maximal doses of glibenclamide* or gliclazide† and metformin for ≥6 months	N=90 24 weeks	Primary: Change in baseline HbA _{1c} , FPG, PPG, insulin levels, and fasting lipid levels Secondary: Not reported	Primary: Acarbose was associated with greater reductions in HbA _{1c} (-0.5±0.2 vs 0.1±0.2%; <i>P</i> =0.038), one-hour PPG (-2.3 ±0.4 vs 0.7±0.4 mmol/L; <i>P</i> <0.001) and body weight (-0.54±0.32 vs 0.42±0.29 kg; <i>P</i> <0.05). No significant differences between the two treatments with regards to FPG, lipids, or fasting and postprandial insulin levels (<i>P</i> values not reported). Gastrointestinal symptoms were the most common side effects with flatulence occurring the most compared to placebo (<i>P</i> <0.05). Secondary: Not reported
Lin et al ¹³ Acarbose 100 mg TID vs	DB, MC, PC, RCT Asian patients 35 to 70 years of age with type 2 diabetes for ≥3 months, HbA _{1c}	N=69 24 weeks	Primary: Change in baseline HbA _{1c} Secondary: Change in baseline	Primary: Acarbose was associated with significantly greater reductions in HbA _{1c} (-0.91 vs 0.13%; <i>P</i> =0.0018) and PPG levels (-2.84 vs 0.28 mmol/L; <i>P</i> =0.002). Secondary: There were no significant differences between the treatment groups regarding

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placebo	7.0 to 10.0%, stable body weight (≤ 35 kg), and uncontrolled by diet and sulfonylureas		blood glucose (FPG and PPG), serum insulin (fasting and one-hour postprandial), urinary glucose, safety	<p>changes in FPG ($P=0.1941$), fasting insulin ($P=0.5003$), insulin PPG ($P=0.2799$), urinary glucose (P value not reported), and body weight (P value not reported).</p> <p>Change in blood glucose (FPG and PPG) was significant for acarbose compared to placebo ($P=0.0020$).</p> <p>Adverse events occurred with similar frequency with both treatments except for drug-related gastrointestinal side effects with acarbose (48.5 vs 12.5%; P value not reported).</p>
<p>Halimi et al¹⁴</p> <p>Acarbose 50 to 100 mg TID</p> <p>vs</p> <p>placebo</p> <p>All patients received existing metformin (850 mg BID to TID) regimens.</p>	<p>DB, PC, PG, RCT</p> <p>Patients 30 to 70 years of age with type 2 diabetes, BMI 25 to 35 kg/m², having poor glycemic control despite receiving metformin ≥ 2 months before the study start</p>	<p>N=152</p> <p>6 months</p>	<p>Primary: HbA_{1c} at trial end</p> <p>Secondary: Blood glucose, insulin profiles, TG</p>	<p>Primary: Mean difference in HbA_{1c} from baseline to trial end was $-0.7 \pm 1.2\%$ with acarbose compared to $0.2 \pm 1.3\%$ with placebo ($P=0.0001$).</p> <p>Patients were classified as responders if their HbA_{1c} values at trial end were $< 7.0\%$ or had decreased by $< 15\%$ relative to baseline. The total numbers of responders were 25 of 49 (42%) patients receiving acarbose and 12 of 70 (17%) patients receiving placebo ($P=0.002$).</p> <p>Secondary: Mean difference in the fasting blood glucose level from baseline to trial end was -1.0 ± 2.8 mmol/L with acarbose compared to 1.3 ± 2.8 mmol/L with placebo ($P=0.0001$).</p> <p>Mean difference in two-hour PPG level from baseline to trial end was -1.4 ± 3.8 mmol/L with acarbose compared to 1.1 ± 3.5 mmol/L with placebo ($P=0.0001$).</p> <p>Mean changes between acarbose compared to placebo for TG, fasting and postprandial serum insulin were not significant (P value not significant).</p>
<p>Phillips et al¹⁵</p> <p>Acarbose 50 to 100 mg BID</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients ≥ 40 years of age with type 2 diabetes for ≥ 6 months, BMI 25 to 35 kg/m², HbA_{1c} 7.0</p>	<p>N=83</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG</p>	<p>Primary: Mean HbA_{1c} increased with placebo from $7.82 \pm 0.83\%$ at baseline to $8.10 \pm 1.06\%$ at week 12 and $8.50 \pm 1.44\%$ at trial end. The mean increase after 24 weeks was $0.68 \pm 1.17\%$, with a significant overall time effect ($P=0.0001$).</p> <p>With acarbose, mean HbA_{1c} decreased from $8.02 \pm 0.85\%$ at baseline to $7.78 \pm 1.00\%$ at week 12 ($P=0.0261$). At the trial end, mean HbA_{1c} increased to $7.97 \pm 1.10\%$. There was no significant overall time effect for acarbose (P value not</p>

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All patients received existing metformin regimens.	to 10.0% at screening week and 6.8 to 10.2% at baseline, and inadequately controlled by metformin			<p>reported).</p> <p>Adjusted least square means for the change in HbA_{1c} from baseline to trial end showed a decrease of 0.16±0.18% with acarbose compared to an increase of 0.86±0.16% with placebo. There was a significant difference between the treatment groups of 1.02% (95% CI, 0.543 to 1.497; <i>P</i>=0.0001).</p> <p>Secondary: Mean FPG levels increased with placebo from baseline (9.41 ±1.99 mmol/L) to week 4 (10.06 ±2.43 mmol/L) to trial end (10.77 ±3.39 mmol/L). The levels only changed slightly with acarbose.</p> <p>Mean FPG increases were 1.36±2.88 mmol/L with placebo and 0.08±1.98 mmol/L with acarbose. The adjusted least square means showed increase at trial end with both treatments of 0.34±0.42 mmol/L with acarbose vs 1.48±0.39 mmol/L with placebo, with a significance of 1.132 mmol/L between the two treatments (95% CI, 0.056 to 2.208; <i>P</i>=0.0395).</p>
<p>Wagner et al¹⁶</p> <p>Acarbose 100 mg TID</p> <p>vs</p> <p>aerobic/anaerobic exercise group training for 50 minutes 3 times weekly</p> <p>vs</p> <p>acarbose 100 mg TID plus exercise</p>	<p>RCT</p> <p>Patients 45 to 60 years of age with type 2 diabetes for ≥3 months, HbA_{1c} <7.5%, and BMI 25 to 30 kg/m²</p>	<p>N=62</p> <p>12 weeks</p>	<p>Primary: Change in baseline HbA_{1c}, insulin sensitivity (M value), regional fat distribution, Vo_{2max} (a measure of physical fitness)</p> <p>Secondary: Not reported</p>	<p>Primary: At trial end, acarbose resulted in no effects on HbA_{1c}, FPG, M value, BMI, body composition, or Vo_{2max}. However, fasting plasma proinsulin level was significantly reduced (<i>P</i>=0.009).</p> <p>With exercise there were significant reductions in BMI, waist circumference, total and truncal fat, and total and intra-abdominal fat area. Although Vo_{2max} was unchanged, there was an increase in maximal workload (<i>P</i>=0.005) and in the M value (<i>P</i>=0.017). HbA_{1c} was unchanged.</p> <p>Acarbose plus exercise resulted in significant decreases in BMI, waist circumference, total and truncal fat, and total and intra-abdominal fat. Maximal workload, Vo_{2max}, and M values were all increased (<i>P</i>=0.028, <i>P</i>=0.046, and <i>P</i>=0.002, respectively). Additionally, fasting plasma proinsulin levels were significantly reduced (<i>P</i>=0.013), as well as HbA_{1c} (<i>P</i> value not reported).</p> <p>Secondary: Not reported</p>

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<p>Aoki et al¹⁷</p> <p>Miglitol, administered prior to breakfast</p> <p>vs</p> <p>miglitol, administered 15 minutes after the start of breakfast</p> <p>vs</p> <p>miglitol, administered 30 minutes after the start of breakfast</p> <p>vs</p> <p>placebo</p>	<p>XO</p> <p>Adult patients with type 2 diabetes, BMI 26.7 kg/m² (mean), HbA_{1c} 9.3% (mean), and an average duration of diabetes of 7.4 years</p>	<p>N=13</p> <p>180 minutes</p>	<p>Primary: Effect of plasma glucose at 0, 30, 60, 120, and 180 minutes after breakfast; effect on serum insulin</p> <p>Secondary: Not reported</p>	<p>Primary: At 30 and 60 minutes, plasma glucose levels were significantly decreased in those who took miglitol just before breakfast compared to control ($P<0.05$).</p> <p>At 60 and 120 minutes, plasma glucose levels were significantly decreased in those taking miglitol 15 minutes after breakfast ($P<0.05$) while those taking miglitol 30 minutes after breakfast had significant reductions at 120 and 180 minutes ($P<0.05$) compared to control.</p> <p>There were no significant differences between groups.</p> <p>The AUC of serum insulin was lower with all three groups compared to control.</p> <p>Secondary: Not reported</p>
<p>Johnston et al¹⁸</p> <p>Miglitol 25 to 50 mg TID</p> <p>vs</p> <p>glyburide 1.25 to 20 mg QD</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients ≥ 60 years of age with type 2 diabetes treated with diet alone for ≥ 12 weeks, HbA_{1c} 6.5 to 10.0%, and FPG >140 mg/dL</p>	<p>N=411</p> <p>1 year</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline plasma glucose, serum insulin, and TG</p>	<p>Primary: Mean placebo-subtracted HbA_{1c} reduction from baseline was -0.50% with miglitol 25 mg TID ($P<0.05$ vs glyburide), -0.41% with miglitol 50 mg TID ($P<0.05$ vs glyburide), -0.93% for glyburide QD, and -0.01% for placebo ($P<0.05$ vs all active treatments).</p> <p>Secondary: Changes in mean plasma glucose (AUC) were +716 mg·min/dL with placebo ($P<0.05$ vs all active treatments), -3,361 mg·min/dL with miglitol 25 mg TID, -5,462 mg·min/dL with miglitol 50 mg TID, and -3,615 mg·min/dL with glyburide ($P=0.0001$ for miglitol 50 mg TID vs placebo).</p> <p>Postprandial insulin levels were significantly greater with glyburide compared to placebo and miglitol ($P<0.01$).</p> <p>Mean changes from baseline to end point for fasting TG were 1.01 with placebo</p>

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				<p>and miglitol 25 mg TID, 0.98 with miglitol 50 mg TID, and one with glyburide ($P=0.573$ for miglitol 50 mg vs placebo).</p> <p>Mean changes from baseline to end point for TG (AUC) were 1.01 with placebo, 1.03 with miglitol 25 mg TID, 1.00 with miglitol 50 mg TID, and 1.06 with glyburide ($P=0.8559$ miglitol 50 mg TID vs placebo).</p> <p>Hypoglycemia, weight gain, and routine and serious cardiovascular events were more frequent in the glyburide group ($P<0.05$ vs placebo and miglitol).</p>
<p>Nemoto et al¹⁹</p> <p>Miglitol 50 mg TID</p> <p>vs</p> <p>placebo</p> <p>All patients received existing insulin regimens.</p>	<p>DB, PC, RCT</p> <p>Patients ≥ 20 years of age with type 2 diabetes receiving insulin therapy, plasma glucose level at either 1 or 2 hours after a meal was ≥ 180 mg/dL, and HbA_{1c} $\geq 6.5\%$</p>	<p>N=107</p> <p>12 weeks (plus an additional 4 to 10 week observation period)</p>	<p>Primary: Change in baseline PPG and HbA_{1c}</p> <p>Secondary: Safety</p>	<p>Primary: The mean decrease in PPG with miglitol was significantly larger compared to placebo (-60.3 ± 70.1 vs 5.1 ± 68.2 mg/dL; $P<0.001$). The decrease in plasma glucose AUC was significantly larger with miglitol compared to placebo (-102.8 ± 122.2 vs 8.7 ± 121.1 mgh/dL; $P<0.001$).</p> <p>Miglitol exhibited a significantly lower HbA_{1c} compared to placebo from week eight to trial end. The decrease from baseline in HbA_{1c} at week 12 was significantly greater with miglitol compared to placebo (-0.37 ± 0.68 vs $0.04 \pm 0.56\%$; $P<0.001$).</p> <p>Secondary: The total incidence of adverse events was 78.5 and 76.0% with miglitol and placebo. Adverse events with high incidence included flatulence (20.6 vs 12.0%), abdominal distension (15.0 vs 4.0%), diarrhea (14.0 vs 4.0%), and hypoglycemia (39.3 vs 35.0%). The incidences of abdominal distention and diarrhea were significantly higher with miglitol ($P<0.05$ for both). All hypoglycemic events were mild and improved without treatment, by ingestion of glucose, supplements, or meals.</p>
<p>Van Gaal et al²⁰</p> <p>Miglitol 25 to 100 mg TID</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 30 to 75 years of age with type 2 diabetes for ≥ 1 year, HbA_{1c} ≥ 7.5 to $\leq 10.5\%$, BMI 23 to 40 kg/m², stable</p>	<p>N=152</p> <p>32 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in FPG, PPG, serum insulin, fasting and one-hour</p>	<p>Primary: There was a significant decrease in HbA_{1c} with miglitol compared to placebo (-0.21 vs 0.22%; $P=0.011$).</p> <p>Secondary: PPG decreased with both treatments, but the reduction was more significant with miglitol (from 16.5 ± 3.8 mmol/L at baseline to 13.8 ± 5.0 mmol/L at trial end) compared to placebo (from 16.3 ± 3.4 mmol/L at baseline to 15.7 ± 3.8 mmol/L at trial end). The baseline adjusted means were 13.8 mmol/L with miglitol vs 15.8 mmol/L</p>

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All patients received existing metformin (500 TID or 850 mg BID or TID) regimens.	body weight over the previous 3 months, and whose diabetes was inadequately controlled by diet and metformin		postprandial TG levels	<p>with placebo ($P=0.0007$).</p> <p>Fasting insulin levels decreased more with miglitol compared to placebo, the difference was not significant (P value not reported).</p> <p>FPG, fasting and postprandial TG levels showed a descriptive advantage for miglitol, but did not reach a statistical difference. Mean FPG levels fell more with miglitol (baseline, 11.5 ± 2.7 mmol/L; end of treatment, 10.8 ± 3.6 mmol/L) compared to placebo (baseline, 11.6 ± 3.1 mmol/L; end of treatment, 11.5 ± 3.4 mmol/L; difference of adjusted means; $P=0.15$). Fasting TG levels fell with miglitol (treatment effect, -16.3 mg/dL) compared to placebo (treatment effect, 3.77 mg/dL; $P=0.26$). Similar results were seen for postprandial TG.</p>
<p>Chiasson et al²¹</p> <p>Miglitol 100 mg TID</p> <p>vs</p> <p>metformin 500 mg TID</p> <p>vs</p> <p>miglitol 100 mg TID plus metformin 500 mg TID</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Patients >40 years of age with type 2 diabetes inadequately controlled by diet alone, HbA_{1c} 7.2 to 9.5%</p>	<p>N=324</p> <p>36 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG and PPG, insulin levels, and TG</p>	<p>Primary: Mean change in HbA_{1c} from baseline was $0.38\pm 0.12\%$ with placebo, $0.02\pm 0.10\%$ with miglitol, $-0.85\pm 0.12\%$ with metformin, and $-1.39\pm 0.11\%$ with combination therapy. A reduction in mean placebo-subtracted HbA_{1c} of -1.78% was seen with combination therapy, and this was significantly different from metformin (-1.25%; $P=0.002$).</p> <p>Mean reductions in HbA_{1c} compared to placebo were -0.37% with miglitol, -1.25% with metformin, and -1.78% with combination therapy. The end of treatment mean HbA_{1c} was 8.5% with placebo, 8.2% with miglitol, 7.3% with metformin, and 6.9% with combination therapy. Significantly more patients ($P=0.0014$) receiving combination therapy (70.6%) were classified as responders (i.e., showed $\geq 15\%$ reduction from baseline in HbA_{1c} or achieved an HbA_{1c} $< 7.0\%$) compared to metformin (45.5%).</p> <p>Secondary: Combination therapy resulted in better metabolic control compared to metformin for FPG ($P=0.0025$) and two-hour PPG AUC ($P=0.0001$).</p> <p>Changes in TG levels from baseline to trial end did not differ significantly between combination therapy compared to metformin, and showed no consistent trend (P value not reported).</p>

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<p>Hsieh et al²²</p> <p>Miglitol 50 mg TID, titrated up to 100 mg TID</p> <p>vs</p> <p>placebo</p> <p>Patients received existing sulfonylurea regimens.</p>	<p>DB, MC, PC, RCT</p> <p>Chinese patients >20 years of age with type 2 diabetes, FPG 100 to 240 mg/dL, HbA_{1c} 6.5 to 10.0%, history of uncontrolled type 2 diabetes despite prior nutrition therapy; and stable dosing with a sulfonylurea for ≥ 8 weeks</p>	<p>N=105</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG, PPG, and post-prandial serum insulin; safety</p>	<p>Primary: Mean change in HbA_{1c} with miglitol was $-0.85 \pm 0.12\%$ compared to $-0.19 \pm 0.11\%$ with placebo ($P < 0.001$).</p> <p>Secondary: No significant differences in the changes in FPG and post-prandial serum insulin were observed ($P = 0.052$ and $P = 0.364$).</p> <p>There was a significant difference in the change in PPG between the two treatments ($P < 0.001$).</p> <p>Among the population, 49 (94.2%) patients receiving miglitol and 42 (79.3%) patients receiving placebo experienced at least one adverse event during the trial. A total of 59 and 39 adverse events occurred with miglitol and placebo, respectively. The most frequently reported adverse events were abdominal discomfort, diarrhea, hypoglycemia, and other; and there were no differences in the incidences of these events between the two treatments.</p>
<p>Standl et al²³</p> <p>Miglitol 25 to 100 mg TID</p> <p>vs</p> <p>placebo</p> <p>All patients received existing regimens of glibenclamide* (3.5 to 5 mg BID to QID) and metformin (500 to 850 mg/day)</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 30 to 70 years of age with type 2 diabetes for ≥ 3 years; HbA_{1c} ≥ 7.5 to $\leq 10.5\%$; BMI ≤ 35 kg/m²; stable body weight over the previous 3 months; and inadequately controlled on combination therapy of diet, glibenclamide* and metformin</p>	<p>N=154</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: FPG, PPG, fasting and postprandial serum insulin, TG, urinary glucose</p>	<p>Primary: Miglitol produced a significant reduction in HbA_{1c} (-0.55%; $P = 0.04$) and PPG (-2.6 mmol/L; $P = 0.0009$) compared to placebo.</p> <p>Secondary: FPG decreased with miglitol and was almost unchanged with placebo; the difference was not significant ($P = 0.10$).</p> <p>Fasting insulin levels were unchanged with both treatments throughout the trial, with no significant difference between them ($P = 0.79$).</p> <p>Postprandial insulin decreased from baseline to trial end, but the difference between the groups was not significant ($P = 0.26$).</p> <p>Postprandial TG decreased slightly with miglitol and remained unchanged with placebo, and the difference was not significant ($P = 0.47$).</p>

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<p>Tsujino et al²⁴</p> <p>Acarbose 50 mg, administered before each meal on day 2</p> <p>vs</p> <p>miglitol 100 mg, administered before each meal on day 2</p> <p>Alternative treatments were administered on day 3 in a XO design.</p>	<p>RCT, XO</p> <p>Patients 20 to 79 years of age with type 2 diabetes, taking α-glucosidase inhibitors without any other antidiabetic medications</p>	<p>N=10</p> <p>4 days</p>	<p>Primary: Glucose variability</p> <p>Secondary: Not reported</p>	<p>Primary: No significant differences in regard to the range of increase in glucose levels from baseline to peak, time to peak PPG levels from the preprandial period, and AUC for glycemic variability from the preprandial period to three hours after each meal between the two treatments were observed. The range of increase in glucose levels at 30 minutes (0.4 vs 30.7 mg/dL; $P<0.0001$) and 60 minutes (32.8 vs 67.5 mg/dL; $P<0.0001$) after lunch and 30, 60, and 90 minutes after dinner (3.3 vs 22.2 mg/dL; $P=0.0249$, 36.6 vs 67.5 mg/dL; $P<0.0001$, and 60.5 vs 81.6 mg/day; $P=0.0073$, respectively) were significantly smaller with miglitol compared to acarbose.</p> <p>Secondary: Not reported</p>
<p>Bao et al²⁵</p> <p>Glipizide XL</p> <p>vs</p> <p>glipizide XL plus acarbose</p>	<p>AC, OL, RCT</p> <p>Newly diagnosed type 2 diabetes, 30 to 70 years of age, with HbA_{1c} 7.0 to 9.8%, and no prior use of antidiabetic medications</p>	<p>N=40</p> <p>8 weeks</p>	<p>Primary: Glycemic control, improvements in insulin secretion and sensitivity, glycemic variability, hypoglycemia</p> <p>Secondary: Not reported</p>	<p>Primary: After eight weeks, FPG, two-hour post-oral glucose tolerance test plasma glucose, mean blood glucose, HbA_{1c}, glycated albumin, and HOMA-IR were significantly decreased with both treatments. HOMA-B increased significantly compared to baseline ($P<0.01$ for both). Compared to glipizide XL, combination therapy had significantly lower mean blood glucose and HOMA-IR values after eight weeks ($P<0.05$ for both). Mean changes in mean blood glucose, HbA_{1c}, and glycated albumin were all greater with combination therapy compared to monotherapy, with only differences in mean blood glucose reaching significant. The overall glucose-lowering and -stabilizing effects were more pronounced with combination therapy.</p> <p>Over the duration of the trial, the decreases in mean amplitude of glycemic excursions and AUC_{postprandial incremental} were significant with both treatments ($P<0.01$). There was also a significant decrease in mean of daily differences with combination therapy compared to baseline ($P<0.01$). Patients receiving combination therapy had significantly lower mean of daily differences, mean amplitude of glycemic outcomes, and AUC_{postprandial incremental} values compared to patients receiving monotherapy after eight weeks ($P<0.05$ for all).</p> <p>There were no significant between-group differences in either the frequency or the duration of hypoglycemia. The mean duration of hypoglycemia was 88.8±84.7</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>minute per event with monotherapy and 176.3±123.5 minute per event with combination therapy ($P=0.114$). Patients receiving monotherapy had 0.7±0.4 events per day compared to 0.8±0.4 events per day in patients receiving combination therapy ($P=0.612$). There was no difference in total instances of severe hypoglycemia reported.</p> <p>Secondary: Not reported</p>
<p>van de Laar et al²⁶</p> <p>α-glucosidase inhibitor monotherapy</p>	<p>MA (41 trials)</p> <p>Patients with type 2 diabetes who received no other antidiabetic medication</p>	<p>N=8,130</p> <p>≥12 weeks</p>	<p>Primary: Mortality, morbidity, quality of life, glycemic control, insulin, or C-peptide levels, lipids, body weight, safety</p> <p>Secondary: Not reported</p>	<p>Primary: There was only limited data on mortality, morbidity, and quality of life. Three trials reported mortality outcomes and found no differences between treatments.</p> <p>Acarbose demonstrated an effect on glycemic control compared to placebo: HbA_{1c}, -0.8% (95% CI, -0.9 to -0.7); FPG, -2.3 mmol/L (95% CI, -2.7 to -1.9); and post-load glucose, -2.3 mmol/L (95% CI, -2.7 to -1.9). The effect on HbA_{1c} from acarbose 50 to 300 mg TID was not dose-dependent. There seemed to be a dose dependency with miglitol in regards to HbA_{1c}: miglitol 25, 50, 100, and 200 mg TID decreased HbA_{1c} by 0.46, 0.58, 0.79, and 1.26%, respectively.</p> <p>A decreasing effect on post-load insulin was found.</p> <p>There were no clinically relevant effects on lipids or body weight found.</p> <p>Adverse events were generally of gastrointestinal origin and dose dependent.</p> <p>Secondary: Not reported</p>
<p>Saenz et al²⁷ (2005)</p> <p>Metformin monotherapy</p> <p>vs</p> <p>placebo, sulfonylureas,</p>	<p>MA (29 RCTs)</p> <p>Adult patients with type 2 diabetes</p>	<p>N=5,259</p> <p>≥3 months</p>	<p>Primary: Incidence of any diabetes-related outcomes (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart</p>	<p>Primary: Obese patients receiving metformin showed a greater benefit than chlorpropamide, glibenclamide*, or insulin for any diabetes-related outcomes ($P=0.009$) and for all-cause mortality ($P=0.03$).</p> <p>Obese patients receiving metformin showed a greater benefit than overweight patients on conventional treatment (diet) for any diabetes-related outcomes ($P=0.004$), diabetes-related death ($P=0.03$), all cause mortality ($P=0.01$), and MI ($P=0.02$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
TZDs, meglitinides, α -glucosidase inhibitors, diet, any other oral antidiabetic intervention, insulin			<p>failure, stroke, renal failure, amputation [of at least one digit], vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from MI, stroke, peripheral vascular disease, renal disease, hypoglycemia or hyperglycemia, and sudden death); all-cause mortality</p> <p>Secondary: Changes in HbA_{1c}, FPG, quality of life, weight, BMI, lipids, insulin, C-peptide, BP, micro-albuminuria, glomerular filtration rate, renal plasma flow</p>	<p>Secondary: Patients receiving metformin monotherapy showed a significant benefit for glycemic control, weight, dyslipidemia, and DBP. Metformin presents a strong benefit for HbA_{1c} when compared to diet and placebo. Additionally, metformin showed a moderate benefit for glycemic control, LDL-C, and BMI or weight when compared to sulfonylureas.</p>
Richter et al ²⁸ Pioglitazone	MA of DB (15) or OL (4) RCTs (last search conducted in	22 trials N=6,200	Primary: Patient-oriented outcomes including	Primary: Only one trial (PROactive Study) evaluated mortality and morbidity as an end point. The primary composite end point (time from randomization to all-cause

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>monotherapy (16 trials) vs acarbose (1 trial), metformin (4 trials), placebo (4 trials), repaglinide (1 trial), rosiglitazone (1 trial), or a sulfonylurea (8 trials)</p> <p>or</p> <p>pioglitazone combination therapy vs a similar combination with another compound (9 trials including 2 trials vs rosiglitazone)</p> <p>Some studies had more than one treatment arm.</p>	<p>August 2006, included PROactive Study), PG</p> <p>Adults with type 2 diabetes, trial duration of at least 24 weeks</p>	<p>randomized to pioglitazone treatment (total N not reported)</p> <p>24 weeks to 34.5 months</p>	<p>mortality, morbidity and adverse effects</p> <p>Secondary: Health-related quality of life and HbA_{1c}</p>	<p>mortality, nonfatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle) did not show statistically significant differences between the pioglitazone and placebo group (HR, 0.90; 95% CI, 0.80 to 1.02; <i>P</i>=0.095).</p> <p>Time to the first event of the composite end point of death from any cause, MI and stroke indicated a statistically significant difference between pioglitazone and placebo (HR, 0.84; 95% CI, 0.72 to 0.98; <i>P</i>=0.027). The individual components of the primary composite end point did not disclose statistically significant differences between the intervention and control groups. Significantly more patients developed heart failure requiring hospitalization following administration of pioglitazone (6 vs 4% on placebo; <i>P</i>=0.007).</p> <p>The percentage of overall and serious adverse events was comparable between the intervention and control groups. Six trials reported a more pronounced (sometimes dose-related) decrease of hemoglobin after pioglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between -0.50 and -0.75 g/dL. Fifteen trials evaluated body weight and observed an increase up to 3.9 kg after pioglitazone treatment; seven trials described a rise in body mass index up to 1.5 kg/m². Eleven of the 22 included trials showed data on hypoglycemic episodes: compared to the active monotherapy control, pioglitazone treatment resulted in somewhat lower rates of hypoglycemia (<i>P</i> value not reported). The RR for development of edema with pioglitazone compared to the control was 2.86 (95% CI, 2.14 to 3.18; <i>P</i><0.00001) when results from 18 trials were pooled.</p> <p>Secondary: No study investigated health-related quality of life.</p> <p>Active glucose-lowering compounds like metformin, glibenclamide‡, gliclazide* or glimepiride resulted in similar reductions of HbA_{1c} compared to pioglitazone treatment (<i>P</i> values not reported).</p>
<p>Monami et al²⁹ (2008)</p> <p>Metformin</p>	<p>MA</p> <p>Patients with type 2 diabetes mellitus</p>	<p>N=7,890 (27 RCT)</p> <p>Variable</p>	<p>Primary: Reduction in HbA_{1c} at 16 to 36 months</p>	<p>Primary: Combining the results of different placebo-controlled trials, sulfonylurea, α-glucosidase inhibitors, and TZDs led to a reduction in HbA_{1c} by -0.85% (95% CI, 0.78 to 0.94], -0.61% (95% CI, 0.55 to 0.67), and -0.42% (95% CI, 0.40 to 0.44),</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs sulfonylureas, α -glucosidase inhibitors, TZDs, glinides, GLP-1 agonists		duration	Secondary: Not reported	respectively when combined with metformin. In direct comparisons, sulfonylureas led to a greater reduction in HbA _{1c} (0.17%; 95% CI, 0.16 to 0.18; <i>P</i> <0.05) than TZDs. Differences between sulfonylureas and α -glucosidase inhibitors, and between α -glucosidase inhibitors and TZDs, were not statistically significant. Secondary: Not reported
Bolen et al ³⁰ Biguanides vs meglitinides vs TZDs vs α -glucosidase inhibitors vs second-generation sulfonylureas	MA (Analysis of 216 controlled trials and cohort studies, and 2 systemic reviews) Patients with type 2 diabetes	N=136 (articles on intermediate outcomes) N=167 (articles on adverse events) N=68 (articles on micro-vascular outcomes and mortality) Duration varied	Primary: Intermediate outcomes: HbA _{1c} , body weight, BP, lipid panels, all-cause mortality, cardiovascular morbidity and mortality, microvascular outcomes Secondary: Adverse events: hypoglycemia, gastrointestinal problems, congestive heart failure, edema or hypervolemia, lactic acidosis, elevated liver enzymes, allergic reactions requiring hospitalization, other serious adverse events	Primary: Results from clinical trials showed that most oral agents including TZDs, metformin, and repaglinide improved glycemic control to the same degree as sulfonylureas (absolute decrease in HbA _{1c} level of about 1%). Nateglinide and α -glucosidase inhibitors have slightly weaker effects, on the basis of indirect comparisons of placebo-controlled trials. TZDs were the only class with beneficial effect on HDL-C (mean relative increase, 3 to 5 mg/dL) but a harmful effect on LDL-C (mean relative increase, 10 mg/dL) compared to other oral agents. Metformin decreased LDL-C levels by about 10 mg/dL, whereas other oral agents had no effects on LDL-C. TZDs, second-generation sulfonylureas, and metformin had similarly minimal effects on SBP. Most agents except metformin increased body weight by 1 to 5 kg. In the ADOPT (A Diabetes Outcome Progression Trial), the incidence of cardiovascular events was lower with glyburide compared to rosiglitazone or metformin (1.8, 3.4, and 3.2%, respectively; <i>P</i> <0.05). In the RECORD study (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes), rosiglitazone plus metformin or a sulfonylurea compared to metformin plus a sulfonylurea had a HR of 1.08 (95% CI, 0.89 to 1.31) for the primary end point of hospitalization or death from cardiovascular disease. The HR was driven by more congestive heart failure in the rosiglitazone plus metformin group compared to the control group of metformin plus sulfonylurea

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>(absolute risk, 1.7 vs 0.8%, respectively).</p> <p>Too few comparisons were made to draw firm comparative conclusions on microvascular outcomes.</p> <p>Secondary: According to several RCTs and some OS trials, sulfonylureas and repaglinide were associated with greater risk for hypoglycemia. In many RCTs, TZDs were associated with a higher risk for edema than sulfonylureas or metformin (absolute risk difference, 2 to 21%).</p> <p>In cohort studies, TZDs were associated with higher risk for congestive heart failure although absolute risks were small (1 to 3%) and higher risk for mild anemia yet produced similarly low rates of elevated aminotransferase levels (<1%) compared to sulfonylureas and metformin.</p> <p>In many trials and a few OS trials, metformin was associated with greater risk for gastrointestinal problems compared to other oral diabetes agents.</p> <p>According to a SR of 176 comparative trials, lactic acidosis events were similar between metformin and other oral diabetes agents.</p>
Cardiovascular Outcomes Trials				
<p>Chiasson et al³¹ STOP-NIDDM</p> <p>Acarbose 100 mg TID</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Patients 40 to 70 years of age, with a BMI 25 to 40 kg/m² with impaired glucose tolerance test and a FPG 100 to 140 mg/dL</p>	<p>N=1,429</p> <p>3.3 years (mean duration)</p>	<p>Primary: Number of patients who developed major cardiovascular events</p> <p>Secondary: New cases of hypertension</p>	<p>Primary: Fifteen patients receiving acarbose and 32 patients receiving placebo experienced any cardiovascular event. Acarbose was associated with a 49% RR reduction in the development of any cardiovascular event (HR, 0.51; 95% CI, 0.25 to 0.95; <i>P</i>=0.03) and a 2.5% absolute risk reduction.</p> <p>There was a significant reduction in the risk of MI associated with acarbose treatment; one patient experienced a MI with acarbose and 12 patients with placebo (HR, 0.09; 95% CI, 0.01 to 0.72; <i>P</i>=0.02).</p> <p>Five patients receiving acarbose experienced angina compared to 12 patients receiving placebo (<i>P</i>=0.13). Eleven patients receiving acarbose experienced revascularization procedures and 20 patients receiving placebo (<i>P</i>=0.18). One patient receiving acarbose experienced cardiovascular death compared to two</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>patients receiving placebo ($P=0.63$). No patient receiving acarbose and two patients receiving placebo experienced congestive heart failure. Two patients receiving acarbose and four patients receiving placebo experienced a cerebrovascular event or stroke ($P=0.51$). One patient in each group experienced peripheral vascular disease ($P=0.93$).</p> <p>Secondary: Seventy eight (11%) of the 682 patients receiving acarbose developed hypertension compared to 115 (17%) of the 686 patients receiving placebo. There was a 34% RR decrease in the incidence of new hypertension cases associated with acarbose (HR, 0.66; 95% CI, 0.49 to 0.89; $P=0.006$) and a 5.3% absolute risk reduction.</p> <p>Reduction in the risk of cardiovascular events (HR, 0.47; 95% CI, 0.24 to 0.90; $P=0.02$) and hypertension (HR, 0.62; 95% CI, 0.45 to 0.86; $P=0.004$) associated with acarbose was significant after adjusting for the major risk factors.</p>

*Synonym for glyburide.

†Agent not available in the United States.

Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times a day, TID=three times daily, XL=extended-release

Study abbreviations: AC=active comparator, CI=confidence interval, DB=double-blind, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=risk ratio, SA=single arm, XO=crossover

Miscellaneous abbreviations: AUC=area under the curve, BMI=body mass index, BP=blood pressure, DBP=diastolic blood pressure, FPG=fasting plasma glucose, GLP-1=glucagon-like peptide=1, HbA_{1c}= glycosylated hemoglobin, HOMA-B=homeostasis model assessment-beta cell function, HOMA-IR=homeostasis model assessment-estimated insulin resistance, HDL-C=high density lipoprotein cholesterol, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, M value=insulin sensitivity, PPG=postprandial plasma glucose, SBP=systolic blood pressure, TC=total cholesterol, TG=triglyceride, TZD=thiazolidinedione, V_{O2MAX}=regional fat distribution, WHO=World Health Organization

Special Populations**Table 5. Special Populations**^{1,2}

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Acarbose	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Not studied in significant renal dysfunction; therefore, treatment is not recommended.	Dosage adjustment not required.	B	Yes; do not administer to nursing women.
Miglitol	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Not recommended for use in patients with a creatinine clearance <25 mL/minute.	Dosage adjustment not required.	B	Yes; do not administer to nursing women.

Adverse Drug Events**Table 6. Adverse Drug Events (%)**^{1,2}

Adverse Event	Acarbose	Miglitol
Dermatologic		
Skin rash	-	4.3
Gastrointestinal		
Abdominal pain	19	11.7
Diarrhea	31	28.7
Flatulence	74	41.5
Laboratory Findings		
Low serum iron	-	9.2

-Event not reported.

Contraindications/Precautions**Table 7. Contraindications**^{1,2}

Contraindication(s)	Acarbose	Miglitol
Chronic intestinal diseases associated with marked disorders of digestion or absorption and in patients who have conditions that may deteriorate as a result of increased gas formation in the intestine	✓	✓
Cirrhosis	✓	-
Diabetic ketoacidosis	✓	✓
Hypersensitivity	✓	✓
Inflammatory bowel disease, colonic ulceration, or partial intestinal obstruction, and in patients predisposed to intestinal obstruction	✓	✓
Partial intestinal obstruction or in patients predisposed to intestinal obstruction	✓	-

Table 8. Warnings and Precautions^{1,2}

Warning(s)/Precaution(s)	Acarbose	Miglitol
Elevated serum transaminase levels; have been observed in long-term trials conducted in the United States	✓	-
Hypoglycemia; when therapy is administered in combination with a sulfonylurea or insulin will cause a further lowering of blood glucose, it may increase the potential for hypoglycemia	✓	✓
Loss of control of blood glucose; when diabetic patients are exposed to stress, a temporary loss of control of blood glucose may occur	✓	✓
Macrovascular outcomes; there have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with therapy or any other antidiabetic drug	✓	✓

Drug Interactions**Table 9. Drug Interactions³⁹**

Generic Name	Interacting Medication or Disease	Potential Result
α -glucosidase inhibitors (acarbose)	Digoxin	Serum digoxin concentrations may be reduced, decreasing the therapeutic effects.

Dosage and Administration**Table 10. Dosing and Administration^{1,2}**

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Acarbose	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:</u> Tablet: initial, 25 mg TID with meals; maintenance, 25 to 50 mg TID; maximum, 50 mg TID (≤ 60 kg) or 100 mg TID (>60 kg)	Safety and efficacy in children have not been established.	Tablet: 25 mg 50 mg 100 mg
Miglitol	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:</u> Tablet: initial, 25 mg TID with meals; maintenance, 50 mg TID; maximum, 100 mg TID	Safety and efficacy in children have not been established.	Tablet: 25 mg 50 mg 100 mg

TID=three times daily

Clinical Guidelines

Current clinical guidelines are summarized in Table 11. Please note that guidelines addressing the treatment of type 1 and 2 diabetes are presented globally, addressing the role of various medication classes.

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
American Diabetes Association: Standards of Medical Care in Diabetes (2013) ³²	<p><u>Current criteria for the diagnosis of diabetes</u></p> <ul style="list-style-type: none"> The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) $\geq 6.5\%$, or a fasting plasma glucose (FPG) ≥ 126 mg/dL, or a two-hour plasma glucose ≥ 200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥ 200 mg/dL). <p><u>Prevention/delay of type 2 diabetes</u></p>

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥ 150 minutes/week of moderate activity, should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%. • Metformin therapy for prevention of type 2 diabetes may be considered in patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.7%, especially for those with a body mass index >35 kg/m², age <60 years, and women with prior gestational diabetes mellitus. <p><u>Glycemic goals in adults</u></p> <ul style="list-style-type: none"> • Lowering HbA_{1c} to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable HbA_{1c} goal for many nonpregnant adults is $<7.0\%$. • It may be reasonable for providers to suggest more stringent HbA_{1c} goals ($<6.5\%$) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease. • Conversely, less stringent HbA_{1c} goals ($<8.0\%$) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. <p><u>Pharmacologic and overall approaches to treatment-type 1 diabetes</u></p> <ul style="list-style-type: none"> • Recommended therapy consists of the following components: <ul style="list-style-type: none"> ○ Use of multiple dose insulin injections (three to four injections per day of basal and prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. ○ Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. ○ For many patients, use of insulin analogs. <p><u>Pharmacologic and overall approaches to treatment-type 2 diabetes</u></p> <ul style="list-style-type: none"> • Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacological agent. • In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA_{1c}, consider insulin therapy, with or without additional agents, from the onset. • If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the HbA_{1c} target over three to six months, add a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin. • Due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients.
<p>American Diabetes Association/ European Association for the Study of Diabetes:</p>	<p><u>Key points</u></p> <ul style="list-style-type: none"> • Glycemic targets and glucose-lowering therapies must be individualized. • Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program.

Clinical Guideline	Recommendations
Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach (2012) ³³	<ul style="list-style-type: none"> • Unless there are prevalent contraindications, metformin is the optimal first line drug. • After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize adverse events where possible. • Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. • All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values. • Comprehensive cardiovascular risk reduction must be a major focus of therapy. <p><u>Initial drug therapy</u></p> <ul style="list-style-type: none"> • It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent. • Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, HbA_{1c} goals. • Patients with high baseline HbA_{1c} (e.g., $\geq 9.0\%$) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance. • If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c} (e.g., ≥ 10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency. • If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase-4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a GLP-1 receptor agonist might be useful. • Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and adverse event profiles make them less attractive candidates. • Specific patient preferences, characteristics, susceptibilities to adverse event, potential for weight gain, and hypoglycemia should play a major role in drug selection. <p><u>Advancing to dual combination therapy</u></p> <ul style="list-style-type: none"> • If monotherapy alone does not achieve/maintain HbA_{1c} target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the HbA_{1c}, the more likely insulin will be required. • On average, any second agent is typically associated with an approximate further reduction in HbA_{1c} of approximately 1.0%. • If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a difference mechanism of action substituted. • Uniform recommendations on the best agent to be combined with

Clinical Guideline	Recommendations																																																																																									
	<p>metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered.</p> <ul style="list-style-type: none"> It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration. For all medications, consideration should also be given to overall tolerability. <p><u>Advancing to triple combination therapy</u></p> <ul style="list-style-type: none"> Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin. Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., HbA_{1c} \geq8.5%) makes it unlikely that another drug will be of sufficient benefit. In using triple combinations the essential consideration is to use agents with complementary mechanisms of action. Increasing the number of drugs heightens the potential for adverse event and drug-drug interactions which can negatively impact patient adherence. <p>Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations</p> <table border="1"> <tr> <td>Initial drug monotherapy</td> <td colspan="5">Metformin</td> </tr> <tr> <td>Efficacy (\downarrowHbA_{1c})</td> <td colspan="5">High</td> </tr> <tr> <td>Hypoglycemia</td> <td colspan="5">Low risk</td> </tr> <tr> <td>Weight</td> <td colspan="5">Neutral/loss</td> </tr> <tr> <td>Adverse events</td> <td colspan="5">Gastrointestinal/lactic acidosis</td> </tr> <tr> <td colspan="6">If needed to reach individualized HbA_{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference).</td> </tr> <tr> <td>Two drug combinations</td> <td>Metformin + sulfonylurea</td> <td>Metformin + thiazolidinedione (TZD)</td> <td>Metformin + DPP-4 inhibitor</td> <td>Metformin + GLP-1 receptor agonist</td> <td>Metformin + insulin (usually basal)</td> </tr> <tr> <td>Efficacy (\downarrowHbA_{1c})</td> <td>High</td> <td>High</td> <td>Intermediate</td> <td>High</td> <td>Highest</td> </tr> <tr> <td>Hypoglycemia</td> <td>Moderate risk</td> <td>Low risk</td> <td>Low risk</td> <td>Low risk</td> <td>High risk</td> </tr> <tr> <td>Weight</td> <td>Gain</td> <td>Gain</td> <td>Neutral</td> <td>Loss</td> <td>Gain</td> </tr> <tr> <td>Major adverse events</td> <td>Hypoglycemia</td> <td>Oedema, heart failure, bone fracture</td> <td>Rare</td> <td>Gastrointestinal</td> <td>Hypoglycemia</td> </tr> <tr> <td colspan="6">If needed to reach individualized HbA_{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)</td> </tr> <tr> <td>Three drug combinations</td> <td>Metformin + sulfonylurea +</td> <td>Metformin + TZD +</td> <td>Metformin + DPP-4 inhibitor +</td> <td>Metformin + GLP-1 receptor agonist +</td> <td>Metformin + Insulin therapy +</td> </tr> <tr> <td></td> <td>TZD, DPP-4 inhibitor, GLP-1 receptor</td> <td>Sulfonylurea, or DPP-4 inhibitor, GLP-1 receptor</td> <td>Sulfonylurea, TZD, or insulin</td> <td>Sulfonylurea, TZD, or Insulin</td> <td>TZD, DPP-4 inhibitor, or GLP-1</td> </tr> </table>						Initial drug monotherapy	Metformin					Efficacy (\downarrow HbA _{1c})	High					Hypoglycemia	Low risk					Weight	Neutral/loss					Adverse events	Gastrointestinal/lactic acidosis					If needed to reach individualized HbA _{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference).						Two drug combinations	Metformin + sulfonylurea	Metformin + thiazolidinedione (TZD)	Metformin + DPP-4 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + insulin (usually basal)	Efficacy (\downarrow HbA _{1c})	High	High	Intermediate	High	Highest	Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	High risk	Weight	Gain	Gain	Neutral	Loss	Gain	Major adverse events	Hypoglycemia	Oedema, heart failure, bone fracture	Rare	Gastrointestinal	Hypoglycemia	If needed to reach individualized HbA _{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)						Three drug combinations	Metformin + sulfonylurea +	Metformin + TZD +	Metformin + DPP-4 inhibitor +	Metformin + GLP-1 receptor agonist +	Metformin + Insulin therapy +		TZD, DPP-4 inhibitor, GLP-1 receptor	Sulfonylurea, or DPP-4 inhibitor, GLP-1 receptor	Sulfonylurea, TZD, or insulin	Sulfonylurea, TZD, or Insulin	TZD, DPP-4 inhibitor, or GLP-1
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Adverse events	Gastrointestinal/lactic acidosis																																																																																									
If needed to reach individualized HbA _{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference).																																																																																										
Two drug combinations	Metformin + sulfonylurea	Metformin + thiazolidinedione (TZD)	Metformin + DPP-4 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + insulin (usually basal)																																																																																					
Efficacy (\downarrow HbA _{1c})	High	High	Intermediate	High	Highest																																																																																					
Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	High risk																																																																																					
Weight	Gain	Gain	Neutral	Loss	Gain																																																																																					
Major adverse events	Hypoglycemia	Oedema, heart failure, bone fracture	Rare	Gastrointestinal	Hypoglycemia																																																																																					
If needed to reach individualized HbA _{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)																																																																																										
Three drug combinations	Metformin + sulfonylurea +	Metformin + TZD +	Metformin + DPP-4 inhibitor +	Metformin + GLP-1 receptor agonist +	Metformin + Insulin therapy +																																																																																					
	TZD, DPP-4 inhibitor, GLP-1 receptor	Sulfonylurea, or DPP-4 inhibitor, GLP-1 receptor	Sulfonylurea, TZD, or insulin	Sulfonylurea, TZD, or Insulin	TZD, DPP-4 inhibitor, or GLP-1																																																																																					

Clinical Guideline	Recommendations					
		agonist, or insulin	agonist, or insulin			receptor agonist
	If combination therapy that includes basal insulin has failed to achieve HbA _{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents:					
	More complex insulin strategies	Insulin (multiple daily doses)				
American College of Physicians: Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus (2012) ³⁴	<ul style="list-style-type: none"> Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia. Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes. It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia. 					
American Association of Clinical Endocrinologists: Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan (2011) ³⁵	<p><u>Antihyperglycemic pharmacotherapy</u></p> <ul style="list-style-type: none"> The choice of therapeutic agents should be based on their differing metabolic actions and adverse event profiles as described in the 2009 American Association of Clinical Endocrinologists/ American College of Endocrinology Diabetes Algorithm for Glycemic Control.³⁶ Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia. Antihyperglycemic agents may be broadly categorized by whether they predominantly target FPG or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making. TZDs and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG. When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia. The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose. When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia. When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia. Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, HbA_{1c}, and weight. Premixed insulin analogue therapy may be considered for patients in 					

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	<p>whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy.</p> <ul style="list-style-type: none"> • Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained. • Most patients with an initial HbA_{1c} level >7.5% will require combination therapy using agents with complementary mechanisms of action.
<p>American Association of Clinical Endocrinologists/ American College of Endocrinology: Statement by an American Association of Clinical Endocrinologists/ American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: An Algorithm for Glycemic Control (2009)³⁶</p>	<p><u>Principles underlying the algorithm</u></p> <ul style="list-style-type: none"> • Lifestyle (dietary and exercise) modifications are essential for all patients with diabetes. • Achieving an HbA_{1c} 6.5% is recommended as the primary goal; however, the goal must be customized for individual patients. • If glycemic goals are not achieved, dosages of medications can be titrated, regimens can be changed (add or discontinue medications), or, in certain instances, glycemic goals can be reconsidered and revised. • When using combination therapy it is important to have medications that have complementary mechanisms of action. • Effectiveness of therapy must be re-evaluated frequently, typically every two to three months. <p><u>Stratification by current HbA_{1c}</u></p> <ul style="list-style-type: none"> • Patients with an HbA_{1c} \leq7.5% may be able to achieve a goal of 6.5% with monotherapy; however, if monotherapy fails to achieve this goal, the usual progression is to combination therapy, and then to triple therapy. Insulin therapy, with or without additional agents, should be initiated if goals still fail to be achieved. • Patients with an HbA_{1c} 7.6 to 9.0% should be initiated on combination therapy as monotherapy in these patients is likely not to achieve glycemic goals. If combination therapy fails, triple therapy and then insulin therapy, with or without additional oral agents, should be administered. • Patients with an HbA_{1c} >9.0% have a small possibility of achieving glycemic goals, even with combination therapy. In these patients, if they are asymptomatic triple therapy based on a combination of metformin and an incretin mimetic or a DPP-4 inhibitor combined with either a sulfonylurea or a TZD should be initiated. If patients are symptomatic or if they have failed therapy with similar agents, insulin therapy with or without additional oral agents should be initiated. <p><u>Management of patients with a HbA_{1c} 6.5 to 7.5%</u></p> <ul style="list-style-type: none"> • In these patients monotherapy with metformin, an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD are recommended. Because of the established safety and efficacy of metformin, it is the cornerstone of monotherapy and is usually the most appropriate initial choice for monotherapy. • If monotherapy, even after appropriate dosage titration, is unsuccessful in achieving glycemic goals combination therapy should be initiated. • Because of the established safety and efficacy of metformin, it is considered the cornerstone of combination therapy for most patients. When contraindicated, a TZD may be used as the foundation for combination therapy options.

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	<ul style="list-style-type: none"> • Due to the mechanism of action (insulin sensitizer) of metformin and TZDs, it is recommended that the second agent in combination therapy be an incretin mimetic, DPP-4 inhibitor, or a secretagogue (glinide or sulfonylurea). • The GLP-1 receptor agonists (incretin mimetics) and DPP-4 inhibitors are associated with less hypoglycemia compared to the secretagogues. • Despite the gastrointestinal adverse events, dosing frequency and injection-based therapy, the GLP-1 receptor agonists are preferred due to its greater effectiveness in reducing postprandial glucose excursions (relative to the DPP-4 inhibitors) and the potential for weight loss. • Combination metformin and TZD therapy is efficacious but carries risks of adverse events associated with both agents. The combination is recommended with a higher priority than a secretagogue because of a lower risk of hypoglycemia and greater flexibility in timing of administration. • The combination therapies of metformin and an α-glucosidase inhibitor and metformin and colesevelam are also included in the algorithm because of their safety and the ability of colesevelam to lower lipid profiles. • If combination therapy fails after each medication has been titrated to its maximally effective dose then triple therapy should be initiated. • The following triple therapy regimens are considered: <ul style="list-style-type: none"> ○ Metformin + GLP-1 receptor agonist + TZD. ○ Metformin + GLP-1 receptor agonist + glinide. ○ Metformin + GLP-1 receptor agonist + sulfonylurea. ○ Metformin + DPP-4 inhibitor + TZD. ○ Metformin + DPP-4 inhibitor + glinide. ○ Metformin + DPP-4 inhibitor + sulfonylurea. • Because of the established safety and efficacy of metformin, it is considered the cornerstone for triple therapy. • The GLP-1 receptor agonist, exenatide, is the second preferred component of triple therapy because of its safety (low risk of hypoglycemia) and its potential for inducing weight loss. It also inhibits glucagon secretion in a glucose-dependent manner after consumption of meals resulting in increased satiety and delayed gastric emptying. • The third component of triple therapy is recommended in order to minimize the risk of hypoglycemia. • The combination with metformin, especially when combined with an incretin mimetic, may counteract the weight gain often associated with glinides, sulfonylureas, and TZDs. • When triple therapy fails to achieve glycemic goals, insulin therapy is needed. <p><u>Management of patients with a HbA_{1c} 7.6 to 9.0%</u></p> <ul style="list-style-type: none"> • The management of these patients is similar to that just described except patients can proceed directly to combination therapy because monotherapy is unlikely to be successful in these patients. • The following combination therapy regimens are considered: <ul style="list-style-type: none"> ○ Metformin + GLP-1 receptor agonist. ○ Metformin + DPP-4 inhibitor. ○ Metformin + TZD. ○ Metformin + sulfonylurea. ○ Metformin + glinide. • Metformin is again considered the cornerstone of combination therapy.

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	<ul style="list-style-type: none"> • A GLP-1 receptor agonist or DPP-4 inhibitor is the preferred second component in view of the safety and efficacy of these agents in combination with metformin. Additionally, a GLP-1 receptor agonist is given higher priority in view of its somewhat greater effect on reducing PPG excursions and its potential for inducing substantial weight loss. • TZDs are positioned lower due to the risks of weight gain, fluid retention, congestive heart failure, and fractures associated with their use. • Glinides and sulfonylureas are relegated to the lowest position because the greater risk of inducing hypoglycemia. • When combination therapy fails to achieve glycemic goals, triple therapy should be started. • The following triple therapy regimens are considered: <ul style="list-style-type: none"> ○ Metformin + GLP-1 receptor agonist + TZD. ○ Metformin + DPP-4 inhibitor + TZD. ○ Metformin + GLP-1 receptor agonist + sulfonylurea. ○ Metformin + DPP-4 inhibitor + sulfonylurea. ○ Metformin + TZD + sulfonylurea. • Metformin is the foundation to which either a TZD or sulfonylurea is added, followed by incretin-based therapy with either a GLP-1 receptor agonist or a DPP-4 inhibitor. • The preference for metformin and the GLP-1 receptor agonist or DPP-4 inhibitor is based on the safety of these agents and minimal associated risks of hypoglycemia. • TZDs are assigned a higher priority than a sulfonylurea because of their lower risk of hypoglycemia. • A GLP-1 receptor agonist is assigned a higher priority than a DPP-4 inhibitor because of its somewhat greater effect on reducing PPG excursions and the possibility that it might induce considerable weight loss. • Metformin + TZD + sulfonylurea is relegated to the lowest priority due to an increased risk of weight gain and hypoglycemia. • α-glucosidase inhibitors, colesevelam, and glinides are not considered as options in these patients due to their limited HbA_{1c}-lowering potential. • The considerations for insulin therapy in these patients are similar to those used in patients with an HbA_{1c} 6.5 to 7.5%. <p>Management of patients with a HbA_{1c} >9.0%</p> <ul style="list-style-type: none"> • Patients who are drug-naïve with an HbA_{1c} >9.0% are unlikely to achieve glycemic goals with the use of one, two, or even three agents (other than insulin). • For patients who are asymptomatic, particularly with a relatively recent onset of diabetes, there is a good chance that some endogenous β-cell function exists; implying that combination or triple therapy may be sufficient. • The following combination and triple therapy regimens are considered: <ul style="list-style-type: none"> ○ Metformin + GLP-1 receptor agonist. ○ Metformin + GLP-1 receptor agonist + sulfonylurea. ○ Metformin + DPP-4 inhibitor. ○ Metformin + DPP-4 inhibitor + sulfonylurea. ○ Metformin + TZD. ○ Metformin + TZD + sulfonylurea. ○ Metformin + GLP-1 receptor agonist + TZD.

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	<ul style="list-style-type: none"> ○ Metformin + DPP-4 inhibitor + TZD. • Metformin again provides the foundation of treatment in these patients. • An incretin-based therapy can be added with a GLP-1 receptor agonist being preferred due to its greater effectiveness at controlling post-prandial glycemia and its potential for inducing weight loss. However the DPP-4 inhibitors in combination with metformin have also demonstrated a robust benefit for drug-naïve patients in this HbA_{1c} range. • A sulfonylurea or a TZD can also be added, with a sulfonylurea being preferred because of its somewhat greater efficacy and more rapid onset of action. • If patients are symptomatic (polydipsia, polyuria, weight loss) or if they have already failed the aforementioned treatment regimens, insulin therapy should be initiated without delay. • Insulin therapy for these patients follows the same principals as outlined previously for patients with different HbA_{1c} levels. • This algorithm favors the use of GLP-1 receptor agonists (at the time of publication only exenatide had Food and Drug Administration-approval) and DPP-4 inhibitors with higher priority due to their effectiveness and overall safety profiles. Additionally, due to the increasing amount of literature indicating the serious risks of hypoglycemia, these agents are becoming preferred in most patients in place of secretagogues. • The algorithm moves sulfonylureas to a lower priority due to the risks of hypoglycemia and weight gain associated with their use, as well as the failure of these agents to provide improved glycemic control after use for a relatively short period. • A TZD is considered a “well-validated” effective agent due to demonstrated extended durability of action, but these agents have a lower priority for many patients in light of their potential adverse events. • The three classes of medications; α-glucosidase inhibitors, colesevelam, and glinides, are considered in relatively narrow, well-defined clinical situations, due to their limited efficacy.
<p>American Association of Clinical Endocrinologists: Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus (2007)³⁷</p>	<p><u>Glycemic management-all patients with diabetes</u></p> <ul style="list-style-type: none"> • Encourage patients to achieve glycemic levels as near normal as possible without inducing clinically significant hypoglycemia. Glycemic targets include the following: <ul style="list-style-type: none"> ○ HbA_{1c} \leq6.5%. ○ FPG <100 mg/dL. ○ Two-hour PPG <140 mg/dL. • Refer patients for comprehensive, ongoing education in diabetes self-management skills and nutrition therapy. • Initiate self-monitoring blood glucose levels. <p><u>Glycemic management-patients with type 2 diabetes</u></p> <ul style="list-style-type: none"> • Aggressively implement all appropriate components of care at the time of diagnosis. • Persistently monitor and titrate pharmacologic therapy until all glycemic goals are achieved. <ul style="list-style-type: none"> ○ First assess current HbA_{1c} level, fasting/pre-prandial glycemic profile, and two-hour PPG profile to evaluate the level of control and identify patterns. ○ After initiating pharmacologic therapy based on the patterns identified in the profile, persistently monitor and titrate therapy over

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	<p>the next two to three months until all glycemic goals are achieved.</p> <ul style="list-style-type: none"> ○ If glycemic goals are not achieved at the end of two to three months, initiate a more intensive regimen and persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved. ○ Recognize that patients currently treated with monotherapy or combination therapy who have not achieved glycemic goals will require either increased dosages of current medications or the addition of a second or third medication. ○ Consider insulin therapy in patients with HbA_{1c} >8.0% and symptomatic hyperglycemic, and in patients with elevated fasting blood glucose levels or exaggerated PPG excursions regardless of HbA_{1c} levels. ○ Initiate insulin therapy to control hyperglycemia and to reverse glucose toxicity when HbA_{1c} >10.0%. Insulin therapy can then be modified or discontinued once glucose toxicity is reversed. ○ Consider a continuous SC insulin infusion in insulin-treated patients. <ul style="list-style-type: none"> ● Instruct patients whose glycemic levels are at or above target while receiving multiple daily injections or using an insulin pump to monitor glucose levels at least three times daily. Although monitoring glucose levels at least three times daily is recommended, there is no supporting evidence regarding optimal frequency of glucose monitoring with or without insulin pump therapy. ● Instruct insulin-treated patients to always check glucose levels before administering a dose of insulin by injection or changing the rate of insulin infusion delivered by an insulin pump. ● Instruct patients whose glycemic levels are above target while being treated with oral agents alone, oral agents plus once-daily insulin, or once-daily insulin alone to monitor glucose levels at least two times daily. There is no supporting evidence regarding optimal frequency of glucose monitoring in these patients. ● Instruct patients who are meeting target glycemic levels, including those treated non-pharmacologically, to monitor glucose levels at least once daily. ● Instruct patients whose glycemic levels are above target or who experience frequent hypoglycemia to monitor glucose levels more frequently. Monitoring should include both pre-prandial and two-hour PPG levels and occasional 2:00 to 3:00 AM glucose levels. ● Instruct patients to obtain comprehensive pre-prandial and two-hour PPG measurements to create a weekly profile periodically and before clinician visits to guide nutrition and physical activity, to detect post-prandial hyperglycemia, and to prevent hypoglycemia. ● Instruct patients to monitor glucose levels anytime there is a suspected (or risk of) low glucose level and/or before driving. ● Instruct patients to monitor glucose levels more frequently during illness and to perform a ketone test each time a measured glucose concentration is >250 mg/dL. <p><u>Clinical support-clinical considerations in patients with type 2 diabetes</u></p> <ul style="list-style-type: none"> ● Combining therapeutic agents with different modes of action may be advantageous. ● Use insulin sensitizers, such as metformin or TZDs, as part of the

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	<p>therapeutic regimen in most patients unless contraindicated or intolerance has been demonstrated.</p> <ul style="list-style-type: none"> • Insulin is the therapy of choice in patients with advanced chronic kidney disease. • Metformin, TZDs, and incretin mimetics do not cause hypoglycemia. However, when used in combination with secretagogues or insulin, these medications may need to be adjusted as blood glucose levels decline. • The weight gain associated with TZDs in some patients may be partly offset by combination therapy with metformin. • Carefully assess PPG levels if the HbA_{1c} level is elevated and pre-prandial glucose measurements are at target levels. • Instruct patients to assess PPG levels periodically to detect unrecognized exaggerated PPG excursions even when the HbA_{1c} level is at or near target. • Individualize treatment regimens to accommodate patient exercise patterns. • Administer basal insulin in the evening if fasting glucose is elevated. • Long-acting insulin analogs are associated with less hypoglycemia than neutral protamine Hagedorn (NPH) insulin.

Conclusions

There are two α -glucosidase inhibitors currently available, acarbose (Precose[®]) and miglitol (Glyset[®]), which are Food and Drug Administration-approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.^{1,2} This medication class works in the management of type 2 diabetes by modifying the intestinal absorption of carbohydrates and fat, and ultimately results in a slower rise in postprandial blood glucose concentrations. Both acarbose and miglitol are to be administered three times daily with the first bite of each main meal. Because these agents work in the gastrointestinal tract, the primary adverse events associated with the α -glucosidase inhibitors are gastrointestinal-related.³ Currently, acarbose is the only α -glucosidase inhibitor that is available generically.

Overall, the α -glucosidase inhibitors, when administered as monotherapy or in combination with other antidiabetic medications, are effective in decreasing glycosylated hemoglobin (HbA_{1c}) and postprandial glucose levels in patients with type 2 diabetes. There is insufficient evidence to suggest that one α -glucosidase inhibitor is more efficacious than another. Treatment with acarbose has demonstrated to be associated with a significant reduction in the risk of cardiovascular disease and hypertension when administered in patients with impaired glucose tolerance. In addition, the agent has been shown to significantly reduce the risk of the development of type 2 diabetes in this patient population; however, the true clinical significance of this finding remains unclear.⁴⁻³¹⁰

According to current clinical guidelines, metformin remains the cornerstone to most antidiabetic treatment regimens. Additionally, patients with a high HbA_{1c} will most likely require combination or triple therapy in order to achieve glycemic goals, and at this time, there are no uniform recommendations on the best agent to be combined with metformin. Due to the limited HbA_{1c}-lowering ability of the α -glucosidase inhibitors in comparison to other available antidiabetic medications, these agents are generally not recommended for use in the management of patients with a high HbA_{1c} (7.6 to 9.0%). The α -glucosidase inhibitors may be utilized as monotherapy in the management of patients with a low HbA_{1c} (6.5 to 7.5%); however, metformin remains the most appropriate initial choice for monotherapy in all patients. Clinical guidelines do recognize the potential use of α -glucosidase inhibitors when postprandial hyperglycemia is present. Among all current clinical guidelines,³²⁻³⁷ no one α -glucosidase inhibitor is recommended or preferred over another.

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