Therapeutic Class Overview
Meglitinides

Therapeutic Class

- **Overview/Summary:** The meglitinides and the sulfonylureas are two classes of oral antidiabetic medications utilized in the management of type 2 diabetes that work by stimulating the release of insulin from pancreatic β-cells. While the meglitinide and sulfonylurea agents differ in chemical structure and act on different receptors, both medication classes act by regulating potassium channels in pancreatic β-cells, thereby increasing insulin secretion.[1] The available meglitinides, nateglinide (Starlix®) and repaglinide (Prandin®), are Food and Drug Administration (FDA)-approved as adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Nateglinide and repaglinide are both available as single-entity agents, and repaglinide is also available as a fixed-dose combination product with metformin (PrandiMet®). Metformin, a biguanide, improves glucose tolerance in type 2 diabetics by lowering both basal and postprandial plasma glucose. Specifically, the actions of metformin result in decreased hepatic glucose production, decreased intestinal absorption of glucose, and improvement in insulin sensitivity via increased peripheral glucose uptake and utilization. The repaglinide/metformin combination product is FDA-approved for patients already treated with a meglitinide and metformin or for patients who have inadequate glycemic control on a meglitinide or metformin alone. Due to their mechanism of action and pharmacokinetic profiles, the meglitinides are dosed three times daily with meals.[2-4] Currently, nateglinide is the only meglitinide that is available generically.

Table 1. Current Medications Available in the Class[2-4]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Nateglinide (Starlix®*)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Tablet: 60 mg 120 mg	✔
Repaglinide (Prandin®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Tablet: 0.5 mg 1 mg 2 mg	-
Combination Products			
Repaglinide/ metformin (PrandiMet®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with a meglitinide and metformin or who have inadequate glycemic control on a meglitinide alone or metformin alone	Tablet: 1/500 mg 2/500 mg	-

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

Evidence-based Medicine

- Available evidence suggests that the sulfonylureas may be associated with poorer outcomes following myocardial infarction in patients with diabetes.[1] Specifically, an increased mortality from cardiovascular disease in patients taking tolbutamine with diabetes was noted in the University Group Diabetes Study.[5] There are no long-term trials evaluating cardiovascular outcomes or mortality in patients receiving meglitinide therapy, and whether these agents are associated with adverse outcomes following a myocardial infarction is not known at this time.[1]
- Overall, meglitinides are effective in decreasing glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose, and postprandial glucose in patients with type 2 diabetes.
- Data from limited head-to-head clinical trials, suggest that repaglinide results in greater reductions in HbA_{1c} and fasting plasma glucose levels compared to nateglinide.[6-28]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Metformin remains the cornerstone to most antidiabetic treatment regimens.
  - 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.
  - The meglitinides are recommended as a potential second line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals.
  - Patients who are not appropriate for initial therapy with metformin, may be initiated on another oral antidiabetic agent, such as a sulfonylurea/meglitinide, pioglitazone, or a dipeptidyl peptidase-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful.
  - In addition, guidelines recognize the potential use of meglitinides when postprandial hyperglycemia is present.
  - Among all current clinical guidelines, preference of one meglitinide over another is not stated.[29-34]
- Other Key Facts:
  - Nateglinide is the only meglitinide that is available generically.

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Therapeutic Class Review
Meglitinides

Overview/Summary

The meglitinides and the sulfonylureas are two classes of oral antidiabetic medications utilized in the management of type 2 diabetes that work by stimulating the release of insulin from pancreatic β-cells. While the meglitinide and sulfonylurea agents differ in chemical structure and act on different receptors, both medication classes act by regulating adenosine triphosphate-dependent potassium channels in pancreatic β-cells, thereby increasing insulin secretion.[1]

The available meglitinides, nateglinide (Starlix®) and repaglinide (Prandin®), are Food and Drug Administration (FDA)-approved as adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Nateglinide and repaglinide are both available as single-entity agents, and repaglinide is also available as a fixed-dose combination product with metformin (PrandiMet®). Metformin, a biguanide, improves glucose tolerance in type 2 diabetics by lowering both basal and postprandial plasma glucose. Specifically, the actions of metformin result in decreased hepatic glucose production, decreased intestinal absorption of glucose, and improvement in insulin sensitivity via increased peripheral glucose uptake and utilization. The repaglinide/metformin combination product is FDA-approved for patients already treated with a meglitinide and metformin or for patients who have inadequate glycemic control on a meglitinide or metformin alone. Due to their mechanism of action and pharmacokinetic profiles, the meglitinides are required to be dosed three times daily with meals.[2-4] Currently, nateglinide is the only meglitinide that is available generically.

Available evidence suggests that the sulfonylureas may be associated with poorer outcomes following myocardial infarction in patients with diabetes.[1] Specifically, an increased mortality from cardiovascular disease in patients taking tolbutamide with diabetes was noted in the University Group Diabetes Study.[5] There are no long-term trials evaluating cardiovascular outcomes or mortality in patients receiving meglitinide therapy, and whether these agents are associated with adverse outcomes following a myocardial infarction is not known at this time. Since the meglitinides have a similar mechanism of action as sulfonylureas, a concern of poor outcomes following a myocardial infarction in patients with diabetes taking a meglitinide should be considered.[1] Overall, meglitinides are effective in decreasing glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose, and postprandial glucose in patients with type 2 diabetes. Data from limited head-to-head clinical trials, suggest that repaglinide results in greater reductions in HbA_{1c} and fasting plasma glucose levels compared to nateglinide.[6-28]

According to current clinical guidelines for the management of type 2 diabetes, 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. 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. The meglitinides are recommended as a potential second line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals. Clinical guidelines note that meglitinides are associated with a limited HbA_{1c}-lowering ability, weight gain, and a greater risk of inducing hypoglycemia compared to other available antidiabetic medications. Patients who are not appropriate for initial therapy with metformin, may be initiated on another oral antidiabetic agent, such as a sulfonylurea/meglitinide, pioglitazone, or a dipeptidyl peptidase-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful. In addition, guidelines recognize the potential use of meglitinides when postprandial hyperglycemia is present. Among all current clinical guidelines, preference of one meglitinide over another is not stated.[29-34]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single-Entity Agents		
Nateglinide (Starlix®)	Meglitinides	✔
Repaglinide (Prandin®)	Meglitinides	-
Combination Products		
Repaglinide/metformin (PrandiMet®)	Meglitinides/biguanide	-

Indications

Table 2. Food and Drug Administration-Approved Indications[2-4]

Indication(s)	Single-Entity Agents		Combination Products
	Nateglinide	Repaglinide	Repaglinide/Metformin
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	✔	✔	
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with a meglitinide and metformin or who have inadequate glycemic control on a meglitinide alone or metformin alone			✔

Pharmacokinetics

Table 3. Pharmacokinetics[35]

Generic Name	Bioavailability (%)	Renal Elimination (%)	Active Metabolites	Serum Half-Life (hours)
Single-Entity Agents				
Nateglinide	73	83	M1 (slightly active), M7 (active)	1.5
Repaglinide	56	8	None	1
Combination Products				
Repaglinide/metformin	56/50 to 60	8/90	None/None	1.0/6.2

Clinical Trials

Clinical trials demonstrating the safety and efficacy of the meglitinides and combination products in the management of type 2 diabetes are outlined in Table 4.[6-28] Data consistently demonstrate that meglitinides, administered either as monotherapy or in combination with other antidiabetic medications, result in a significant lowering of glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose, and postprandial glucose levels.[6-23] Results from three, relatively small head-to-head trials comparing nateglinide and repaglinide, demonstrate that treatment with repaglinide results in significantly greater reductions in HbA_{1c} and fasting plasma glucose compared to nateglinide.[14-16] As mentioned previously, clinical trial data support that as a class, the meglitinides are associated with weight gain and hypoglycemia.[6-28]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Type 2 Diabetes				
Taki et al[6] Nateglinide	OS Patients with type 2 diabetes, drug naïve, with FPG ≤150 mg/dL and had started to take nateglinide alone	N=547 12 weeks	Primary: HbA_{1c}, PPG, FPG, hypoglycemia Secondary: Not reported	Primary: In the nateglinide group, a reduction in HbA_{1c} was 0.82%, PPG was 59.4 to 158.0 mg/dL, and FPG was 11.7 to 122.4 mg/dL. Hypoglycemia was the most prevalent adverse event (2.1%). A total of nine of 11 episodes required no therapeutic intervention. Severe hypoglycemia was recognized in one case of diabetes complicated by serious renal dysfunction, for which nateglinide has been contraindicated in Japan. No patient experienced symptoms of nocturnal or prolonged hypoglycemia. Secondary: Not reported
Taki et al[7] Nateglinide	OS Japanese patients with type 2 diabetes	N=1,014 15 months	Primary: PPG, FPG, HbA_{1c}, BMI Secondary: Not reported	Primary: In patients receiving nateglinide, there were reductions in PPG of -9.3 mg/dL (from 155.1±40.0 to 145.0±35.1 mg/dL) and HbA_{1c} of 0.68% (from 7.51±1.36 to 6.83±1.09%). In patients previously treated with sulfonylurea, a decrease in HbA_{1c} was not observed. No change in BMI was noted after 15 months of nateglinide treatment. Secondary: Not reported
Ozbek et al[8] Repaglinide 4.5 mg QD vs no treatment	RCT Patients with type 2 diabetes who had been initially treated with oral antidiabetic agents without a satisfactory response (HbA_{1c}	N=50 3 months	Primary: Exogenous insulin requirements, HbA_{1c}, hypoglycemia Secondary: Not reported	Primary: A significant reduction in daily total exogenous insulin requirements was seen in the repaglinide group. The daily total insulin requirements were 57.4±14.8 and 28.8±13.8 units before and after the three month study period, respectively (P<0.01). Serum HbA_{1c} levels were 7.3±0.3 and 6.4±0.3% before and after the three month period in the repaglinide group (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients received existing insulin regimens.	<7.0%), hospitalized in a single centre for glycemic control with intensive insulin therapy involving multiple daily SC injections			None of the patients experienced symptomatic hypoglycemia episode. Secondary: Not reported
Schwarz et al[9] Nateglinide 120 mg TID before meals vs placebo	DB, PC, MC, PG, RCT Patients 65 to 90 years of age with type 2 diabetes for ≥4 weeks, oral antidiabetic agents, with FPG ≤240 mg/dL, BMI 22 to 40 mg/m^2, HbA_{1c} 7.0 to 9.5%, without history of type 1 diabetes or secondary diabetes, significant symptomatic complications of diabetes, severe cardiac dysfunction, significant cardiovascular events within 6 months prior to randomization, and severe liver disease	N=54 12 weeks	Primary: Change in baseline HbA_{1c} Secondary: FPG, PPG, proportion of patients achieved a target HbA_{1c} <7.0 or ≤6.5%, adverse events	Primary: Plasma HbA_{1c} decreased from 7.6±0.1 to 6.9±0.1% in patients receiving nateglinide (mean change, -0.7±0.1%; *P*<0.001) compared to a reduction of 7.7± 0.2 to 7.5±0.1% in patients receiving placebo (change, -0.2±0.2%; *P*=0.206). A significant difference between the two groups in HbA_{1c} change was reported (-0.5%; 95% CI, -1.0 to -0.2; *P*=0.004). Secondary: After 12 weeks of treatment, FPG decreased significantly from 164±6 to 141±7 mg/dL in patients receiving nateglinide (change, -23±7 mg/dL; *P*=0.003) compared to a reduction of 153±8 to 159±7 mg/dL in patients receiving placebo (change, 2±5 mg/dL; *P*=0.728). A significant difference between the two groups in FPG change was reported (-25 mg/dL; 95% CI, -40 to -3; *P*=0.022). Two-hour PPG decreased from 184±11 to 153±8 mg/dL in patients receiving nateglinide (change, -29±11 mg/dL; *P*=0.019) compared to a reduction of 192±14 to 188±15 mg/dL in patients receiving placebo (change, -7±17 mg/dL; *P*=0.687). A difference between two groups in Two-hour PPG change was significant (-36 mg/dL; 95% CI, -74 to -8; *P*=0.018). Sixty percent of patients in the nateglinide group achieved a target HbA_{1c} of <7.0% compared to 21% of patients in the placebo group (*P*=0.004). Significantly higher number of patients receiving nateglinide achieved a target HbA_{1c} ≤6.5% compared to placebo-treated patients (8/30 vs 1/24, respectively; *P*=0.028). Similar adverse-event profiles were reported between the two groups (15 patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				in each group reported one or more adverse events). No serious adverse events, hypoglycemic events or deaths were reported.
Marre et al[10] Nateglinide 60 to 120 mg TID before meals vs placebo All patients received existing metformin (1,000 mg BID) regimens.	DB, MC, PG, RCT Patients ≥30 years of age with type 2 diabetes for ≥6 months with HbA_{1c} 6.8 to 11.0%, BMI 20 to 35 kg/m^2, and were treated with metformin for a minimum of 3 months and stabilized at a dose of ≥1,500 mg/day for ≥4 weeks prior to study entry	N=467 24 weeks	Primary: Change in HbA_{1c} from baseline Secondary: Change in FPG, body weight, and lipid profile (TC, fasting TGs, LDL-C, HDL-C)	Primary: Mean HbA_{1c} was reduced significantly from baseline when compared to the placebo group for the nateglinide 60 mg group (-0.36%; 95% CI, -0.59 to -0.13; *P*=0.003) and for the nateglinide 120 mg group (-0.51%; 95% CI, -0.82 to -0.36; *P*<0.001) at end point. Dose-dependent reduction in HbA_{1c} was seen with nateglinide irrespective of baseline parameters, with larger mean reductions seen with nateglinide 120 mg. There was little or no change in HbA_{1c} at end point in the placebo group. Secondary: There were modest changes from baseline in FBG in the nateglinide groups and an increase was seen in the placebo group, the difference compared to baseline was significant in both the nateglinide 60 and 120 mg groups (*P*=0.044 and *P*=0.003, respectively). There were no notable changes in body weight at end point in the patients that received placebo (0.1 kg) or nateglinide 60 mg (0.4 kg). There was a significant increase (*P*<0.001) in mean weight of 0.9 kg in the nateglinide 120 mg group as compared to baseline. Fasting TGs were significantly reduced in the nateglinide 120 mg group as compared to the placebo group at end point (*P*=0.042). The mean changes in TC, LDL-C, and HDL-C remained almost unchanged throughout the study.
Horton et al[11] Nateglinide 120 mg TID before each meal plus metformin 500 mg TID immediately after the start of each meal	DB, PC, PRO, RCT Patients ≥30 years of age with type 2 diabetes for ≥3 months with a BMI 20 to 35 kg/m^2, and all patients needed to have been treated	N=701 24 weeks	Primary: Change in HbA_{1c}, FPG, glucose AUC after Sustacal challenge from baseline Secondary: Not reported	Primary: Adjusted mean change from baseline in HbA_{1c}, FPG, and glucose AUC after Sustacal challenge were significantly reduced from baseline (*P*≤0.0001) in patients receiving active treatment. HbA_{1c}, FPG, and glucose AUC were all significantly reduced compared to placebo (*P*≤0.001), except from glucose AUC with metformin monotherapy. The decrease in HbA_{1c} was greater for metformin compared to nateglinide, the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs nateglinide 120 mg TID before each meal vs metformin 500 mg TID immediately after the start of each meal vs placebo	with diet alone with an HbA_{1c} 6.8 to 11.0% and FPG level ≤15 mmol/L			between group difference was small (0.3% difference; *P*≤0.01). The decrease in FPG was greater with the metformin group compared to the nateglinide group, the between group difference was 0.9 mmol/L (*P*<0.001). The combination of nateglinide plus metformin was additive (HbA_{1c}, -1.4% and FPG, -2.4 mmol/L; *P*≤0.01 vs either monotherapy). After a Sustacal challenge, there was a greater reduction in mealtime glucose with nateglinide compared to metformin or placebo ($AUC_{0\text{-}130\ min}$, -2.1, -1.1, and 0.6 mmol/hr/L, respectively; *P*≤0.0001). A greater reduction was seen with nateglinide plus metformin ($AUC_{0\text{-}130\ min}$, -2.5 mmol/hr/L; *P*≤0.0001 vs metformin and placebo). Secondary: Not reported
Hollander et al[12] Nateglinide 120 mg TID before each meal vs glyburide 5 to 10 mg QD vs placebo	DB, MC, PC, RCT Patients 32 to 75 years of age with type 2 diabetes ≥3 months prior to entry into the trial on diet modification alone for ≥4 weeks before initial visit, mean HbA_{1c} 6.8 to 11.0%, and a BMI 20 to 35 kg/m^2	N=152 8 weeks	Primary: Change from week 0 to week eight during liquid meal challenges in FPG, fasting insulin, fasting C-peptide, and fasting proinsulin Secondary: Not reported	Primary: At week eight, FPG was reduced more with glyburide compared to nateglinide (-1.9 mmol/L; *P*<0.001). Nateglinide treatment did not have significant changes from baseline with fasting levels of C-peptide, insulin, or proinsulin. Glyburide treatment increased fasting C-peptide vs placebo and nateglinide (*P*<0.001), fasting insulin vs placebo (*P*<0.001) and nateglinide (*P*<0.05), and proinsulin vs placebo (*P*<0.001) and nateglinide (*P*<0.025). Reduction of mealtime glucose excursions from nateglinide was approximately twice that from glyburide (-4.94±0.74 vs -2.71±0.71 mmol/hr/L; *P*<0.03). The insulin secretion reflected by the C-peptide AUCs was approximately twice that in the glyburide group than in the nateglinide group (1.83±0.24 vs 0.95±0.23 nmol/hr/L, respectively; *P*=0.063 vs nateglinide). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Fonseca et al[13] Nateglinide 120 mg before each meal vs placebo All patients received existing rosiglitazone (8 mg QD) regimens.	DB, MC, PC, RCT Patients ≥21 years of age with type 2 diabetes for ≥6 months previously and treated with rosiglitazone 8 mg/day, diet, and exercise for ≥3 months, had a BMI 22 to 40 kg/m^2, FPG 6.1 to 13.3 mmol/L, and HbA_{1c} 7.0 to 11.0%	N=402 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: FPG, two-hour postprandial insulin, TC, LDL-C, HDL-C, TG, body weight, four-hour AUC for glucose, insulin during meal challenges	Primary: HbA_{1c} did not change significantly from baseline in the placebo group, but did change significantly in the nateglinide group. The change from baseline to end point was -0.8±0.1% (*P*<0.0001 vs baseline or placebo). Secondary: Change in FPG decreased significantly from a baseline of 9.8 to 9.0 mmol/L in the nateglinide group (*P*<0.001). FPG did not change significantly from the baseline (10 mmol/L) in patients receiving placebo. Two-hour postprandial insulin in the nateglinide group decreased from 14.0 to 11.4 mmol/L (*P*<0.0001). The group receiving placebo had an increase in 2-hour postprandial insulin from 14.4 to 14.8 mmol/L (*P*<0.0001 vs nateglinide). Total and incremental glucose $AUCs_{(0\text{-}4\ hours)}$ were significantly reduced in the nateglinide group (-8.6±0.8 and -6.2±0.5 mmol/L/hr, respectively; *P*<0.0001 vs baseline or placebo for both total and incremental AUCs). This represents a 16% reduction in the total and a 49% reduction in the incremental glucose AUC. Total and incremental insulin $AUCs_{(0\text{-}4\ hour)}$ were increased in the nateglinide group (425 and 395 pmol/L/hr, respectively; *P*<0.0001 vs baseline or placebo plus for both total and incremental AUCs). This represents a 46% increase in the total and 69% increase in the incremental insulin AUC. There were no significant changes in TC, LDL-C, or TG in either group. There was a small, but significant increase from baseline in HDL-C observed in patients receiving nateglinide (*P*<0.025) and in patients receiving placebo (*P*<0.005). Body weight increased in both groups. The mean change from baseline in patients receiving nateglinide (3.1±0.3 kg) was significantly greater compared to patients receiving placebo (1.1±0.3 kg; *P*<0.0001). Meal challenges were performed at week 0 and at end point. The glucose and insulin profiles were similar in the two groups at baseline, and PPG and insulin

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				concentrations were unchanged at end point relative to baseline in patients receiving placebo.
Rosenstock et al[14] Nateglinide 60 mg TID before each meal, titrated up to a maximum of 360 mg daily vs repaglinide 0.5 mg TID before each meal, titrated up to a maximum of 16 mg daily	MC, OL, PG, RCT Patients ≥18 years of age with type 2 diabetes for ≥3 months, BMI 24 to 42 kg/m^2, HbA_{1c} 7.0 to 12.0%, and drug naïve	N=150 16 weeks	Primary: Final HbA_{1c} and changes in HbA_{1c} from baseline Secondary: Changes in FPG from baseline	Primary: Mean baseline HbA_{1c} values were similar in both groups (8.9%). The changes in HbA_{1c} for repaglinide from baseline were -1.57 vs -1.04% for nateglinide (*P*=0.002). Final HbA_{1c} values were lower in the repaglinide group vs the nateglinide group (7.3 vs 7.9%, respectively). At the end of the study, 54% of the repaglinide-treated patients had HbA_{1c} values ≤7.0% vs 42% of nateglinide-treated patients (*P*=0.18). Secondary: The final FPG was 154.0±40.2 mg/dL for repaglinide and 188.0±62.2 mg/dL for nateglinide. The mean change from baseline in FPG was greater with repaglinide compared to nateglinide (-57 vs -18 mg/dL; *P*<0.001). There were no major hypoglycemic episodes (requiring the assistance of another person) in either treatment group. Mean weight gains from baseline to the study end point were 1.8 kg for repaglinide and 0.7 kg for nateglinide (incremental mean imputation method calculation *P*=0.04 and *P*=0.034 by last observed carried forward method calculation). The most common adverse events (3 to 10% of patients in both treatment groups) were upper respiratory tract infection, sinusitis, constipation, arthralgia, headache, and vomiting. There were no notable differences in the pattern of adverse events for the treatment groups.
Li et al[15] Nateglinide 90 mg TID before each meal vs	DB, DD, MC, RCT Chinese patients 35 to 65 years of age with type 2 diabetes, on a stable diet and exercise for 4	N=223 12 weeks	Primary: FPG, HbA_{1c}, TG, TC, BMI, HOMA-IR, β-cell function indexes, plasma insulin, C-peptide, PPG using the	Primary: Compared to baseline, FPG; 30-, 60-, and 120-minute PPG; and HbA_{1c} all decreased significantly with both repaglinide and nateglinide treatment (*P*<0.05). Effects on FPG and PPG of the two agents were not significantly different (*P*>0.05). The HbA_{1c} levels at week 12 of the repaglinide group and the nateglinide group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
repaglinide 1 mg TID before each meal	weeks, with fasting blood glucose ≥7.8 mmol/L and/or 2-hour PPG ≥11.1 mmol/L at least twice in 2 weeks, without a history of antidiabetic agents other than metformin (on stable dosage for 4 weeks)		incremental AUC ($AUC_{0\text{-}120\ min}$) after a standard 800-kcal meal (55% carbohydrate, 25% fat and 20% protein) Secondary: Not reported	were not significantly different (6.27 vs 6.59%, respectively; *P*>0.05). However, an HbA_{1c} reduction at week 12 from baseline in the repaglinide group was significantly greater than an HbA_{1c} reduction in the nateglinide group (-1.21 vs -0.68%, respectively; *P*=0.0039). AUC of glucose significantly decreased in both repaglinide and nateglinide groups at week 12 to a similar extent (20.36±4.67 vs 20.54±4.83 mmol/L/h, respectively; *P*<0.0001 vs baseline; *P*>0.05 between the groups). AUC of insulin and C-peptide in both groups were increased at week 12 to a similar extent (*P*<0.05 vs baseline; *P*>0.05 between two groups). HOMA-IR in both groups were decreased significantly, and effects of repaglinide and nateglinide on insulin sensitivity were not different (2.44 vs 2.48, at week 12 respectively; *P*<0.05 vs baseline; *P*>0.05 between the groups). β-cell function indexes were increased in both groups, but the values were not significantly different between two groups after 12 weeks of treatment (*P*<0.05 vs baseline; *P*>0.05 between the groups). After the 12 weeks of treatment with repaglinide, TG level significantly decreased from baseline (no values reported; *P*<0.05). In both groups, TC level was decreased from baseline at week 12 (no values reported; *P*<0.05), and BMI was reduced slightly (*P*>0.05). Effects of both agents on TG, TC and BMI were not different (no values reported; *P*>0.05). Adverse events between the groups were reported to be similar (*P*>0.05). However, the rate of adverse reaction was reported to be 4.5% (hypoglycemic event, thrombocytopenia, elevation of liver enzymes) in the repaglinide group and 0.87% (thrombocytopenia) in the nateglinide group. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Raskin et al[16] Nateglinide 120 mg TID before meals vs repaglinide 1 to 4 mg TID before meals All patients received existing metformin (1,000 mg BID) regimens.	MC, OL, PG, RCT Patients ≥18 years of age with type 2 diabetes for ≥3 months, BMI 24 to 42 kg/m^2, HbA_{1c} 7.0 to 12.0% on previous monotherapy with a sulfonylurea, metformin, or low dose glyburide plus metformin	N=192 16 weeks	Primary: Final HbA_{1c} values and changes in HbA_{1c} from baseline Secondary: Changes in FPG and assessment of glucose area under the time concentration curves from 0 to 240 minutes ($AUC_{0\text{-}240\ min}$), insulin $AUC_{0\text{-}240\ min}$, and glucagon $AUC_{0\text{-}240\ min}$ after a liquid test meal at baseline and at study end point	Primary: Mean HbA_{1c} changes from baseline were significantly greater in the repaglinide group compared to the nateglinide group (-1.28 vs -0.67%; *P*<0.001). The final HbA_{1c} at 16 weeks was 7.1±1.1% for the repaglinide group and 7.5±1.4% for the nateglinide group. The percent of patients who achieved final HbA_{1c} values ≤7.0% was 59% for the repaglinide group and 47% for the nateglinide group (*P* value not reported). Secondary: FPG values were significantly different between the two treatment groups with one week of therapy. Mean changes in FPG values from baseline were significantly greater for the repaglinide group (-39 vs -21 mg/dL for nateglinide group; *P*=0.002). The final FPG at 16 weeks was 150.0±45.1 mg/dL for the repaglinide group and 170±52 mg/dL for the nateglinide group. At the end of the 16 week maintenance study, 48% of the repaglinide group had reductions of FPG values >40 mg/dL and 26% of the nateglinide group had a response of this magnitude. Mean end point reductions in PPG levels from baseline were not significantly different between the groups (glucose $AUC_{0\text{-}240\ min}$). The treatments were also similar for changes in insulin $AUC_{0\text{-}240\ min}$ and glucagon $AUC_{0\text{-}240\ min}$ during the study (*P* values not reported). There were no patients in either group who experienced major hypoglycemic episodes (requiring the assistance of another person). The most frequent adverse event in both groups was upper respiratory infection (12 vs 21%). Adverse events that occurred from 3 to 8% included nausea, viral infection, accidental injury, sinusitis, diarrhea, and headache. The repaglinide group had 5% incidence of chest pain and arthralgia, as compared to 1% for each in the nateglinide groups. Mean changes from baseline in weight were small for both groups, 0.6 kg gain for repaglinide compared to 0.5 kg loss with nateglinide.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Wang et al (abstract)[17] Repaglinide 1 mg TID, titrated up to 4 mg TID vs repaglinide 1 mg TID plus metformin 500 mg TID, titrated up to 4 mg TID and 500 mg TID	AC, OL, PG, RCT Patients 18 to 75 years of age with type 2 diabetes, HbA_{1c} >8.5%, BMI ≤35 kg/m^2, and who were naïve to oral antidiabetic agents,	N=432 16 weeks	Primary: Change in baseline HbA_{1c} Secondary: FPG, two-hour PPG, seven-point plasma glucose, safety	Primary: Mean HbA_{1c} reduction was 4.51±1.64% with combination therapy and 4.05±1.59% with repaglinide. Estimated mean treatment difference for combination therapy vs repaglinide was -0.30% (95% CI, -0.49 to -0.11; *P*< 0.01). Secondary: Combination therapy demonstrated significant improvements compared to repaglinide in FPG, seven-point plasma glucose, and lunchtime and dinnertime two-hour PPG (*P*<0.05 for all). Hypoglycemia rates were 2.04 events/patient-year with combination therapy compared to 1.35 events/patient-year with repaglinide (*P*=0.058). Adverse events were comparable between the two treatments.
Moses et al[18] Repaglinide 0.5 to 4 mg TID before each meal plus metformin 1,000 to 3,000 mg/day vs repaglinide 0.5 to 4 mg TID before each meal vs metformin 1,000 to 3,000 mg/day	DB, MC, PG, RCT Patients 40 to 75 years of age with type 2 diabetes treated with metformin alone (1 to 3 g/day) for >6 months and had not achieved optimal glycemic control (HbA_{1c} >7.0%) and BMI ≥21 kg/m^2	N=83 3 months	Primary: Change in baseline HbA_{1c} and FPG Secondary: Change in fasting insulin, C-peptide levels, fasting TG, TC, HDL-C, LDL, free fatty acids, body weight	Primary: Patients in the metformin plus repaglinide group had a significant decrease in HbA_{1c} from 8.3 to 6.9% (*P*=0.0016) and FPG from 10.2 to 8.0 mmol/L (*P*=0.0003) compared to baseline. There were no significant changes in HbA_{1c} or FPG for patients receiving metformin alone and repaglinide alone. The HbA_{1c} and FPG changes from baseline for metformin plus repaglinide vs metformin alone and metformin plus repaglinide vs repaglinide were significant (*P*<0.05 for all). Secondary: Fasting insulin and C-peptide levels increased significantly from baseline in both groups receiving repaglinide (*P*<0.05 for both). Lipid levels (TC, HDL-C, LDL-C, TG, FFA) did not change significantly from baseline in the metformin plus repaglinide group. No significant differences were found between the metformin plus repaglinide group and the monotherapy groups. In both groups receiving repaglinide there was an increase in body weight which was significant compared to baseline (*P*<0.05 for both).
Civera et al[19] Repaglinide 2 mg TID	OL, PG Patients with poorly	N=37 24 weeks	Primary: HbA_{1c}, hypoglycemia, body	Primary: The HbA_{1c} was lower in the repaglinide triple therapy group (7.2%) compared to the metformin plus NPH insulin group (8.8%; *P*=0.02) and the NPH insulin group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
before meals plus metformin 850mg BID plus NPH insulin before dinner vs metformin 850mg BID plus NPH insulin before dinner vs NPH insulin BID	controlled type 2 diabetes despite being on two or more oral antidiabetic drugs		weight Secondary: Not reported	(8.4%; *P*=0.02). The absolute reduction in HbA_{1c} was -2.4% in the repaglinide triple therapy group compared to -0.7% (*P*=0.01) in the metformin plus NPH insulin group and -1.4% in the insulin NPH group. Lower PPG values were seen with the repaglinide triple therapy group compared to the other two treatment groups (*P*<0.01). Significant differences in weight gain and hypoglycemia were not seen. Secondary: Not reported
Raskin et al[20] Repaglinide 0.5 to 4 mg TID plus rosiglitazone 2 to 4 mg BID vs repaglinide 0.5 to 4 mg TID vs rosiglitazone 2 to 4 mg BID	MC, OL, PG, RCT Patients ≥18 years old with type 2 diabetes for ≥12 months with an HbA_{1c} >7.0 to ≤12.0% during previous monotherapy with sulfonylurea or metformin for ≥3 months with a BMI ≤45 kg/m^2	N=252 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG	Primary: Mean change in HbA_{1c} from baseline with repaglinide was -0.17% and -0.56% with rosiglitazone. The mean change in HbA_{1c} from baseline with combination therapy was -1.43 (*P*≤0.001 vs either monotherapy). The reduction in HbA_{1c} from baseline was greater with combination therapy compared to the sum of the responses for monotherapy (*P*<0.01). Secondary: Mean FPG change from baseline with repaglinide was -3 mmol/L and -3.7 mmol/L with rosiglitazone. Mean FPG change from baseline with combination therapy was -5.2 mmol/L (*P*≤0.001 vs either monotherapy).
Swinnen et al[21] Continuation of secretagogues (sulfonylureas or	PRO Patients 40 to 75 years of age with type 2 diabetes,	N=865 24 weeks	Primary: Change in HbA_{1c} Secondary: Hypoglycemia, body	Primary: In patients continuing secretagogue treatment, HbA_{1c} decreased to 7.0±0.8% at week 12 compared to 7.4±0.9% in patients discontinuing their secretagogues. Endpoint HbA_{1c} level was 7.2±0.9% in both treatment groups. The difference in mean HbA_{1c} reduction during the trial was not significant (-1.59±1.08% for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
meglitinides) vs discontinuation of secretagogues (sulfonylureas or meglitinides) All patients received existing metformin regimens and initiated insulin therapy.	HbA_{1c} 7.0 to 10.5% receiving oral glucose-lowering drugs		weight, insulin dose	patients continuing secretagogues and -1.30±1.14% for patients discontinuing secretagogues; *P*=0.382). Secondary: Compared to patients who discontinued secretagogues, patients who continued secretagogues experienced significantly more hypoglycemia (40.0 vs 24.5%; *P*<0.001) and gained significantly more weight (1.44±3.04 vs 0.43±3.00 kg; *P*<0.001). End of trial insulin doses, were significantly lower in patients who continued secretagogues compared to patients who discontinued secretagogues (*P*<0.001).
Black et al[22] Meglitinide vs meglitinide plus metformin vs meglitinide plus insulin vs metformin vs placebo	MA (15 trials) Patients with type 2 diabetes	N=3,781 Duration varied	Primary: Mortality and morbidity Secondary: Change in HbA_{1c}, weight or BMI, hypoglycemia, adverse events, quality of life	Primary: No trials reported the effect of meglitinides on mortality and morbidity. Secondary: In the 11 trials comparing meglitinides to placebo, both repaglinide and nateglinide resulted in reductions in HbA_{1c} (0.1 to 2.1% and 0.2 to 0.6%, respectively). In two trials comparing repaglinide to nateglinide, reduction in HbA_{1c} was similar. When compared to metformin, both repaglinide and nateglinide showed similar or slightly smaller reduction in HbA_{1c} compared to metformin. The combination therapy of metformin plus a meglitinide showed a clinically significant reduction in HbA_{1c} compared to metformin. Weight gain was generally greater in patients receiving meglitinides compared to patients receiving metformin. Evidence from the meglitinide trials with metformin suggests that both repaglinide and nateglinide had fewer gastrointestinal adverse events including diarrhea. There was no evidence of serious adverse events associated with meglitinides. There were more reports of hypoglycemia episodes in patients receiving meglitinides compared to patients receiving placebo. In the two head-to-head trials of repaglinide and nateglinide, fewer patients receiving nateglinide reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				hypoglycemia symptoms (2 vs 7%). When compared to metformin, patients receiving meglitinides reported more hypoglycemia episodes. There were two trials that assessed quality of life in patients receiving repaglinide vs placebo and in patients receiving repaglinide plus insulin vs metformin plus insulin. There were no substantial changes in quality of life using a variety of validated diseases specific and nonspecific tools. Treatment satisfaction using the World Health Organization Diabetes Treatment Satisfaction Questionnaire improved significantly in patients receiving repaglinide compared to patients receiving placebo.
Gangji et al[23] Glyburide vs sulfonylureas, meglitinides, insulin	MA (21 trials) Patients with type 2 diabetes	N=not reported Duration varied	Primary: Hypoglycemia, glycemic control, cardiovascular events, body weight, death Secondary: Not reported	Primary: Glyburide was associated with a 52% higher risk of experiencing at least one episode of hypoglycemia compared to other secretagogues (RR, 1.52; 95% CI, 1.21 to 1.92) and with an 83% higher risk compared to other sulfonylureas (RR, 1.83; 95% CI, 1.35 to 2.49). Glyburide was not associated with a higher risk of cardiovascular events (RR, 0.84; 95% CI, 0.56 to 1.26), death (RR, 0.87; 95% CI, 0.70 to 1.07), or end-of-trial weight (95% CI, -0.4 to 3.80) compared to other secretagogues. Secondary: Not reported
Monami et al[24] (2008) Metformin vs sulfonylureas, α-glucosidase inhibitors, TZDs, glinides, GLP-1 agonists	MA Patients with type 2 diabetes mellitus	N=7,890 (27 RCT) Variable duration	Primary: Reduction in HbA_{1c} at 16 to 36 months Secondary: Not reported	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), 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; $P<0.05$) than TZDs. Differences between sulfonylureas and α-glucosidase inhibitors, and between α-glucosidase inhibitors and TZDs, were not statistically significant. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Cardiovascular Outcomes Trials				
Bolen et al[25] 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; *P*<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 (absolute risk, 1.7 vs 0.8%, respectively). Too few comparisons were made to draw firm comparative conclusions on microvascular outcomes. Secondary: According to several RCTs and some OS trials, sulfonylureas and repaglinide

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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%). 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. In many trials and a few OS trials, metformin was associated with greater risk for gastrointestinal problems compared to other oral diabetes agents. According to a SR of 176 comparative trials, lactic acidosis events were similar between metformin and other oral diabetes agents.
Saenz et al[26] Metformin monotherapy vs placebo, sulfonylureas, TZDs, meglitinides, α-glucosidase inhibitors, diet, any other oral antidiabetic intervention, insulin	MA (29 RCTs) Adult patients with type 2 diabetes	N=5,259 ≥3 months	Primary: Incidence of any diabetes-related outcomes (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart 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	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). 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). 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			MI, stroke, peripheral vascular disease, renal disease, hypo-glycemia or hyperglycemia, and sudden death); all-cause mortality Secondary: Changes in HbA_{1c}, FPG, quality of life, weight, BMI, lipids, insulin, C-peptide, BP, micro-albuminuria, glomerular filtration rate, renal plasma flow	
Richter et al[27] Rosiglitazone monotherapy (10 trials) vs glyburide (2 trials), metformin (3 trials), pioglitazone (1 trial), placebo (5 trials), or repaglinide (1 trial) or rosiglitazone combination therapy vs a similar	MA of DB (11) or OL (5) RCTs (last search conducted in April 2007, included the ADOPT trial), PG Adults with type 2 diabetes, trial duration of at least 24 weeks	18 trials N=3,888 randomized to rosiglitazone treatment (total N not reported) 24 weeks to 4 years (median 26 weeks)	Primary: Patient-oriented outcomes including mortality, morbidity, adverse events Secondary: Health-related quality of life, metabolic control (HbA_{1c})	Primary: No study included mortality as a primary or secondary end point. While not an initial primary or secondary study end point, the ADOPT trial reported that the all-cause mortality was 2.3% in the rosiglitazone group, 2.1% in the metformin group and 2.2% in the glyburide group (*P* values not reported in this reference). The ADOPT trial also reported comparable hospitalization rates for any cause between rosiglitazone (11.6%), metformin (11.8%), and glyburide (10.4%) groups (*P* values were not reported in this reference). Cardiovascular disease was increased in the rosiglitazone group compared to the glyburide group but not the metformin group with serious/total events reported in 3.4/4.3% and 1.8/2.8% of patients receiving rosiglitazone and glyburide, respectively (events were 3.2/4.0% with metformin; *P* values were not reported in this reference). Congestive heart failure was observed more frequently in patients receiving rosiglitazone (1.5%) than patients receiving glyburide (0.6%) but not metformin (1.3%; *P* values were not reported in this reference).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
combination with another compound (8 trials) Some studies had more than 1 treatment arm.				The percentage of overall adverse events was comparable between the intervention and control groups (which included placebo arms); serious adverse events appeared to happen more often after rosiglitazone treatment (median of 6 vs 4% in the control groups; *P* value not reported). Median discontinuation rate following rosiglitazone administration was also higher than after control therapy (median of 7 vs 4%; *P* value not reported). Three studies reported a more pronounced (apparently dose-related) decrease of hemoglobin after rosiglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between 0.5 and 1.0 g/dL. Eleven studies evaluated body weight and observed an increase up to 5.0 kg after rosiglitazone treatment; four studies described a rise in body mass index up to 1.5 kg/m^2. Seven of the 18 included studies showed data on hypoglycemic episodes: compared to active monotherapy control, rosiglitazone treatment resulted in somewhat lower rates of hypoglycemia, especially when compared to sulfonylureas. Occurrence of edema was significantly raised when results of nine studies were pooled (OR, 2.27; 95% CI, 1.83 to 2.81; *P*<0.00001). The ADOPT trial reported a higher incidence of fractures in women receiving rosiglitazone (9.30%) than metformin (5.08%; *P*<0.01) or glyburide (3.47%; *P*<0.01). Secondary: No study investigated health-related quality of life. Active glucose-lowering compounds like metformin, glibenclamide* or glimepiride resulted in similar reductions of HbA_{1c} compared to rosiglitazone treatment.
Richter et al[28] Pioglitazone monotherapy (16 trials) vs acarbose (1 trial), metformin (4 trials), placebo (4 trials), repaglinide (1 trial), rosiglitazone (1 trial), or a sulfonylurea	MA of DB (15) or OL (4) RCTs (last search conducted in August 2006, included PROactive Study), PG Adults with type 2 diabetes, trial duration of at least	22 trials N=6,200 randomized to pioglitazone treatment (total N not reported)	Primary: Patient-oriented outcomes including mortality, morbidity, adverse events Secondary: Health-related QOL, HbA_{1c}	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 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; *P*=0.095). 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(8 trials) or pioglitazone combination therapy vs a similar combination with another compound (9 trials including 2 trials vs rosiglitazone) Some studies had more than 1 treatment arm.	24 weeks	24 weeks to 34.5 months		placebo (HR, 0.84; 95% CI, 0.72 to 0.98; *P*=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; *P*=0.007). 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/m^2. 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 (*P* 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; *P*<0.00001) when results from 18 trials were pooled. Secondary: No study investigated health-related quality of life. Active glucose-lowering compounds like metformin, glibenclamide*, gliclazide† or glimepiride resulted in similar reductions of HbA_{1c} compared to pioglitazone treatment (*P* values not reported).

*Synonym for glyburide.
†Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, QD=once daily, SC=subcutaneous, TID=three times daily
Study abbreviations: AC=active-comparator, CI=confidence interval, DB=double-blind, DD=double-blind, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, OS=observational, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk
Miscellaneous abbreviations: AUC=area under the curve, BMI=body mass index, BP=blood pressure, DBP=diastolic blood pressure, FFA=free fatty acid, FPG=fasting plasma glucose, HbA_{1c}=glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, HOMA-IR=homeostasis model assessment-estimated insulin resistance, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, NPH=neutral protamine Hagedorn, PPG=postprandial plasma glucose, TC=total cholesterol, TG=triglyceride, TZD=thiazolidinedione

Special Populations

Table 5. Special Populations[2-4]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single-Entity Agents					
Nateglinide	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.	No dosage adjustment required.	No dosage adjustment required in mild hepatic dysfunction. Not studied in moderate to severe hepatic dysfunction; therefore, use with caution.	C	Unknown; do not use.
Repaglinide	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.	Renal dosage adjustment required; in patients with severe renal dysfunction, an initial dose of 0.5 mg is recommended; subsequently, patients should be carefully titrated.	No dosage adjustment required. Use with caution in hepatic dysfunction.	C	Unknown; do not use.
Combination Products					
Repaglinide/ metformin	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.	Do not use in renal dysfunction.	Avoid in hepatic dysfunction.	C	Unknown; do not use.

Adverse Drug Events

Table 6. Adverse Drug Events (%)[2-4,34,36]

Adverse Events	Single-Entity Agents		Combination Products
	Nateglinide	Repaglinide	Repaglinide/Metformin
Cardiovascular			
Arrhythmia	-	≤1	≤1
Chest pain	-	<2	<2
Electroencephalography abnormal	-	≤1	≤1

Adverse Events	Single-Entity Agents		Combination Products
	Nateglinide	Repaglinide	Repaglinide/Metformin
Hypertension	-	≤1	≤1
Myocardial infarction	-	≤1	≤1
Palpitations	-	≤1	≤1
Central Nervous System			
Dizziness	4	-	-
Headache	-	9 to 11	22
Dermatologic			
Pruritus	✔	-	-
Rash	✔	-	-
Urticaria	✔	-	-
Endocrine/Metabolic			
Hypoglycemia	2	16 to 31	33
Gastrointestinal			
Constipation	-	2 to 3	-
Diarrhea	3.2	4 to 5	19
Dyspepsia	-	2 to 4	-
Nausea	-	3 to 5	15
Vomiting	-	2 to 3	>5
Hepatic			
Hepatic dysfunction	-	✔	✔
Hepatitis	✔	✔	✔
Jaundice	✔	✔	✔
Laboratory Test Abnormalities			
Hemolytic anemia	-	✔	✔
Liver enzymes increased	✔	✔	✔
Thrombocytopenia	-	✔	✔
Musculoskeletal			
Arthralgia	3	3 to 6	-
Back pain	4	5 to 6	-
Paresthesia	-	2 to 3	-
Respiratory			
Bronchitis	2.7	2 to 6	-
Coughing	2.4	-	-
Rhinitis	-	3 to 7	-
Sinusitis	-	3 to 6	-
Upper respiratory infection	10	10 to 16	11
Other			
Accidental trauma	2.9	-	-
Allergy	-	1 to 2	-
Alopecia	-	✔	✔
Anaphylactic reaction	-	✔	✔
Blurred vision	-	✔	✔
Flu symptoms	4	-	-
Pancreatitis	-	✔	✔
Stevens-Johnson Syndrome	-	✔	✔
Tooth disorder	-	2	-
Urinary tract infection	-	2 to 3	-
Weight gain	✔	-	-

✔ Percent not specified.
- Event not reported.

Contraindications/Precautions

Table 7. Contraindications[2-4]

Contraindication(s)	Single-Entity Agents		Combination Products
	Nateglinide	Repaglinide	Repaglinide/Metformin
Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma	✔	✔	✔
Coadministration of gemfibrozil	-	✔	✔
Hypersensitivity	✔	✔	✔
Renal impairment	-	-	✔
Type 1 diabetes	✔	✔	-

Table 8. Warnings and Precautions[2-4]

Warning(s)/Precaution(s)	Single-Entity Agents		Combination Products
	Nateglinide	Repaglinide	Repaglinide/Metformin
Alcohol intake; alcohol is known to potentiate the effect of metformin on lactate metabolism	-	-	✔
Change in clinical status of patients with previously controlled type 2 diabetes; a patient with type 2 diabetes previously well controlled on therapy who develops laboratory abnormalities or clinical illness should be evaluated promptly for evidence of ketoacidosis or lactic acidosis	-	-	✔
Concomitant medications affecting renal function or metformin; concomitant medications that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion, should be used with caution	-	-	✔
General; therapy is not indicated for use in combination with neutral protamine Hagedorn-insulin	-	✔	✔
Hypoglycemia; all oral blood glucose-lowering drugs are capable of producing hypoglycemia, proper patients selection, dosage, and instructions to the patients are important to avoid hypoglycemic episodes	✔	✔	✔
Hypoxic states; cardiovascular collapse from whatever cause have been associated with lactic acidosis and may also cause prerenal azotemia, and if such events occur, therapy should be promptly discontinued	-	-	✔

Warning(s)/Precaution(s)	Single-Entity Agents		Combination Products
	Nateglinide	Repaglinide	Repaglinide/Metformin
Lactic acidosis; lactic acidosis is a serious, metabolic complication that can occur due to metformin accumulation during therapy	-	-	✔
Loss of control of blood glucose; when a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur, and at such times it may be necessary to temporarily withhold therapy	✔	✔	✔
Macrovascular outcomes; there have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with therapy or any other antidiabetic drug	✔	-	✔
Radiologic studies with intravascular iodinated contrast materials; intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin, and therapy should be temporarily discontinued in patients undergoing such studies	-	-	✔
Surgical procedures; use of therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal	-	-	✔
Vitamin B_{12} levels; the risk of a decrease to subnormal levels of previously normal serum vitamin B_{12} levels may be relevant in patients receiving long term metformin therapy, and adverse hematologic and neurologic reactions have been reported postmarketing	-	-	✔

Black Box Warning for PrandiMet® (repaglinide/metformin)[4]

WARNING
Lactic acidosis is a rare but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure. The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing

WARNING
somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. If acidosis is suspected, PrandiMet® should be discontinued and the patient hospitalized immediately.

Drug Interactions

Table 9. Drug Interactions[36]

Generic Name	Interacting Medication or Disease	Potential Result
Meglitinides (all)	Cyclosporine	Meglitinide plasma concentrations and pharmacologic effects may be increased.
Meglitinides (all)	Rifamycins	Meglitinide plasma concentrations and pharmacologic effects may be decreased.
Meglitinides (repaglinide)	Gemfibrozil	Repaglinide plasma concentrations may be greatly increased and prolonged, increasing the risk of severe and protracted hypoglycemia.
Meglitinides (repaglinide)	Macrolide and related antibiotics	Certain macrolide and related antibiotics may elevate repaglinide plasma levels, increasing the pharmacologic effects and adverse reactions.
Biguanides (metformin)	Iodinated contrast materials, parenteral	Increased risk of metformin-induced lactic acidosis.

Dosage and Administration

Table 10. Dosing and Administration[2-4]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Single-Entity Agents			
Nateglinide	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Tablet: initial, 60 to 120 mg TID before meals; maintenance, 120 mg TID before meals	Safety and efficacy in children have not been established.	Tablet: 60 mg 120 mg
Repaglinide	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Tablet: initial, 0.5 to 2 mg with meals; maintenance, 0.5 to 4 mg with meals; maximum, 16 mg/day	Safety and efficacy in children have not been established.	Tablet: 0.5 mg 1 mg 2 mg
Combination Products			
Repaglinide/ metformin	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with a meglitinide and metformin or who have inadequate glycemic control on a meglitinide alone or metformin alone: Tablet: initial, 1/500 mg BID to TID with meals, unless the patient is already taking higher coadministered doses of repaglinide and metformin; maximum, 4/1,000 mg/day	Safety and efficacy in children have not been established.	Tablet: 1/500 mg 2/500 mg

BID=twice-daily, TID=three times daily

Clinical Guidelines

Current clinical guidelines are summarized in Table 11. Please note that guidelines addressing the treatment of type 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)**[29]	Current criteria for the diagnosis of diabetes • The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥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). Prevention/delay of type 2 diabetes • 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/m^2, age <60 years, and women with prior gestational diabetes mellitus. Glycemic goals in adults • Lowering HbA_{1c} to below or around 7% 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 events 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. Pharmacologic and overall approaches to treatment-type 1 diabetes • Recommended therapy consists of the following components: o Use of multiple dose insulin injections (three to four injections per day of basal and prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. o Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. o For many patients, use of insulin analogs. Pharmacologic and overall approaches to treatment-type 2 diabetes • Metformin, if not contraindicated and if tolerated, is the preferred initial

Clinical Guideline	Recommendations
	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.
American Diabetes Association/European Association for the Study of Diabetes: **Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach (2012)**[30]	Key points • Glycemic targets and glucose-lowering therapies must be individualized. • Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program. • 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. Initial drug therapy • 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., ≥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 events, potential for weight gain, and hypoglycemia should play a major

Clinical Guideline	Recommendations

role in drug selection.

Advancing to dual combination therapy

- 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 metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered.
- 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.

Advancing to triple combination therapy

- 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} ≥8.5%) 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 events and drug-drug interactions which can negatively impact patient adherence.

Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations

Initial drug monotherapy	Metformin				
Efficacy (↓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 + thia-zolidinedione (TZD)	Metformin + DPP-4 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + insulin (usually basal)
Efficacy (↓HbA_{1c})	High	High	Inter-mediate	High	Highest
Hypoglycemia	Moderate	Low risk	Low risk	Low risk	High risk

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>risk</td><td></td><td></td><td></td><td></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>Hypo-glycemia</td><td>Oedema, heart failure, bone fracture</td><td>Rare</td><td>Gastro-intestinal</td><td>Hypo-glycemia</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, DDP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonylurea, or DPP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>Sulfonyl-urea, TZD, or Insulin</td><td>TZD, DPP-4 inhibitor, or GLP-1 receptor agonist</td></tr>
<tr><td colspan="6">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:</td></tr>
<tr><td>More complex insulin strategies</td><td colspan="5">Insulin (multiple daily doses)</td></tr>
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<tr><td>American College of Physicians: Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus (2012)[31]</td><td>
• 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.
</td></tr>
<tr><td>American Association of Clinical Endocrinologists: Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan (2011)[32]</td><td>
<u>Antihyperglycemic pharmacotherapy</u>
• 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.[32]
• 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
</td></tr>
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Clinical Guideline	Recommendations
	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 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. • 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.
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)**[33]	<u>Principles underlying the algorithm</u> • 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. <u>Stratification by current HbA_{1c}</u> • Patients with an HbA_{1c} ≤7.5% 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

Clinical Guideline	Recommendations
	without additional oral agents should be initiated. Management of patients with a HbA_{1c} 6.5 to 7.5% • 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. • 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: o Metformin + GLP-1 receptor agonist + TZD. o Metformin + GLP-1 receptor agonist + glinide. o Metformin + GLP-1 receptor agonist + sulfonylurea. o Metformin + DPP-4 inhibitor + TZD. o Metformin + DPP-4 inhibitor + glinide. o 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 means 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

Clinical Guideline	Recommendations
	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. Management of patients with a HbA_{1c} 7.6 to 9.0% • 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: o Metformin + GLP-1 receptor agonist. o Metformin + DPP-4 inhibitor. o Metformin + TZD. o Metformin + sulfonylurea. o Metformin + glinide. • Metformin is again considered the cornerstone of combination therapy. • 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: o Metformin + GLP-1 receptor agonist + TZD. o Metformin + DPP-4 inhibitor + TZD. o Metformin + GLP-1 receptor agonist + sulfonylurea. o Metformin + DPP-4 inhibitor + sulfonylurea. o 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%.

Clinical Guideline	Recommendations
	Management of patients with a HbA_{1c} >9.0% • 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: o Metformin + GLP-1 receptor agonist. o Metformin + GLP-1 receptor agonist + sulfonylurea. o Metformin + DPP-4 inhibitor. o Metformin + DPP-4 inhibitor + sulfonylurea. o Metformin + TZD. o Metformin + TZD + sulfonylurea. o Metformin + GLP-1 receptor agonist + TZD. o 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.
American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice**	Glycemic management-all patients with diabetes • Encourage patients to achieve glycemic levels as near normal as possible without inducing clinically significant hypoglycemia. Glycemic targets include the following: o HbA_{1c} ≤6.5%.

Clinical Guideline	Recommendations
for the Management of Diabetes Mellitus (2007)[34]	o FPG <100 mg/dL. o 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. <u>Glycemic management-patients with type 2 diabetes</u> • Aggressively implement all appropriate components of care at the time of diagnosis. • Persistently monitor and titrate pharmacologic therapy until all glycemic goals are achieved. o 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. o After initiating pharmacologic therapy based on the patterns identified in the profile, persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved. o 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. o 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. o 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. o 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. o Consider a continuous SC insulin infusion in insulin-treated patients. • 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

Clinical Guideline	Recommendations
	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. <u>Clinical support-clinical considerations in patients with type 2 diabetes</u> • Combining therapeutic agents with different modes of action may be advantageous. • Use insulin sensitizers, such as metformin or TZDs, as part of the therapeutic regimen in most patients unless contraindicated or intolerance has been demonstrated. • 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

Nateglinide (Starlix®) and repaglinide (Prandin®) are the available meglitinides, which are Food and Drug Administration-approved as adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Repaglinide is also available as a fixed-dose combination product with metformin (PrandiMet®) and is approved for patients who are already treated with a meglitinide and metformin or for patients who have inadequate glycemic control on a meglitinide or metformin alone. Due to their mechanism of action and pharmacokinetic profiles, the meglitinides are required to be dosed three times daily with meals.[2-4] Currently, nateglinide is the only meglitinide that is available generically.

The meglitinides share a similar mechanism of action to the sulfonylureas, another class of medications utilized in the management of type 2 diabetes. Evidence is available to suggest that the sulfonylureas may be associated with poorer outcomes after a myocardial infarction in patients with diabetes. While it is not known if the meglitinides are associated with this risk, due to the similarities in mechanisms of action between meglitinides and sulfonylureas, the same consideration should be held for meglitinides.[1,5]

Meglitinides are effective in decreasing glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose, and postprandial glucose in patients with type 2 diabetes.[6-28] Data from limited head-to-head clinical trials, suggests that repaglinide results in greater reductions in HbA_{1c} and fasting plasma glucose levels compared to nateglinide.[14-16] Overall, there is insufficient evidence to suggest that one meglitinide is more efficacious than another.[6-28]

According to current clinical guidelines, metformin remains the cornerstone to most antidiabetic treatment regimens. In addition, patients with a high HbA_{1c} will likely require combination or triple therapy to achieve glycemic goals. At this time, there are no uniform recommendations on the best agent to be combined with metformin. The meglitinides are recommended as a potential second line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals. Clinical guidelines note that meglitinides are associated with a limited HbA_{1c}-lowering ability, weight gain, and a greater risk of inducing hypoglycemia compared to other available antidiabetic medications. Meglitinides may also be useful as initial therapy in patients who cannot receive metformin. Among all current clinical guidelines, no one meglitinide is recommended or preferred over another.[29-34]

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