Therapeutic Class Overview
Insulins

Therapeutic Class

- **Overview/Summary:** This review will focus on the antidiabetic insulins, including human insulin products and synthetic insulin analogs.[1-17] Insulin products are Food and Drug Administration (FDA)-approved improve glycemic control in patients with diabetes mellitus (DM) type 1 and type 2. DM is a group of metabolic disorders with types 1 and 2 being the broadest categories. All categories of DM ultimately results in hyperglycemia, but the etiologies for each are distinct and may include reduced insulin secretion, decreased glucose utilization, or increased glucose production. Due to the metabolic dysregulation of DM, secondary pathophysiologic changes in multiple organ systems occur. Examples of severe complications that may occur include end-stage renal disease (ESRD), nontraumatic lower extremity amputation, and adult blindness. Additionally, it also predisposes the patient to cardiovascular disease.[18] Overall, there are a variety of oral and injectable antidiabetic agents currently available to treat diabetes. Available insulin products are summarized in Table 1. Insulin therapy is usually administered by subcutaneous injection, which allows for prolonged absorption and less pain compared to intramuscular injection.[1-17,19] Additionally, regular insulin is also formulated as an inhalation.[4] At least one formulation of all insulin products are supplied in multidose vials with only regular insulin not being formulated in a prefilled pen or syringe.[1-17] Inhaled insulin powder is formulated in disposable, single-use cartridges, known as Technosphere® which provided a more efficient inhalation device than what has been used in the past.[4] Another inhaled formulation of regular insulin, Exubera®, was previously FDA-approved; however, this agent was removed from the market in 2007 due to low patient and provider acceptance.[20] All insulin products have at least one formulation with a concentration of 100 units/mL (U-100). Two agents are also formulated with a higher concentration, regular insulin as 500 units/mL (U-500; Humulin® R U-500) and insulin glargine as 300 units/mL (U-300; Toujeo® SoloSTAR).[1-17]

Table 1. Current Medications Available in the Therapeutic Class[1-17]

Generic (Trade Name)	FDA-Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Products			
Insulin aspart (NovoLog®, NovoLog® FlexPen, NovoLog® PenFill)	To improve glycemic control in diabetes mellitus*	Cartridge: 100 units/mL Pen: 100 units/mL Vial: 100 units/mL	-
Insulin detemir (Levemir®, Levemir® FlexPen, Levemir® FlexTouch)	To improve glycemic control in diabetes mellitus*	Pen: 100 units/mL Vial: 100 units/mL	-
Insulin glargine (Lantus®, Lantus® SoloSTAR, Toujeo® SoloSTAR)	To improve glycemic control in diabetes mellitus*	Pen: 100 units/mL (Lantus® SoloSTAR) 300 units/mL (Toujeo® SoloSTAR) Vial:	-

Generic (Trade Name)	FDA-Approved Indications	Dosage Form/Strength	Generic Availability
		100 units/mL	
Insulin glulisine (Apidra®, Apidra® SoloSTAR)	To improve glycemic control in diabetes mellitus*	Pen: 100 units/mL Vial: 100 units/mL	-
Insulin lispro, human recombinant analog (Humalog®, Humalog® KwikPen)	To improve glycemic control in diabetes mellitus*	Cartridge: 100 units /mL Pen: 100 units /mL Vial: 100 units /mL	-
Insulin NPH (isophane), human recombinant (Humulin® N, Humulin® N U-100 Pen, Novolin® N, Novolin® N ReliOn)	To improve glycemic control in diabetes mellitus*	Pen: 100 units/mL Vial: 100 units/mL	-
Insulin regular, human recombinant (Afrezza®, Humulin® R, Humulin® R U-500, Novolin® R)	To improve glycemic control in diabetes mellitus* Treatment of diabetic patients with marked insulin resistance*,†	Inhalation powder (Afrezza®): 4 units/cartridge 8 units/cartridge Vial: 100 U/mL 500 U/mL(Humulin® R U-500)	-
Combination Products			
Insulin aspart/insulin aspart protamine (NovoLog® Mix 70/30, NovoLog® 70/30 Flex Pen)	To improve glycemic control in diabetes mellitus*	Pen: 70/30 units/mL Vial: 70/30 units/mL	-
Insulin lispro/insulin lispro protamine (Humalog® Mix 50/50, Humalog® Mix 75/25, Humalog® Mix 50/50 KwikPen, Humalog® Mix 75/25 KwikPen)	To improve glycemic control in diabetes mellitus*	Pen: 50/50 units/mL 75/25 units/mL Vial: 50/50 units/mL 75/25 units/mL	-
Insulin, regular/insulin, NPH, human recombinant (Humulin® 70/30, Humulin® 70/30 KwikPen, Humulin® 70/30 Pen, Novolin® 70/30, Novolin® 70/30 ReliOn)	To improve glycemic control in diabetes mellitus*	Pen: 70/30 units/mL Vial: 70/30 units/mL	-

FDA=Food and Drug Administration
*Includes diabetes mellitus type 1 and type 2. Generally, these agents have not been studied for the treatment of type 2 diabetes in pediatric patients. Additionally, some agents may carry an indication for use in pediatric patients, but have never been studied in that population.
†Humulin® R U-500 only

Evidence-based Medicine

- There are numerous clinical trials demonstrating the safety and efficacy of insulin products in the management of diabetes type 1 and 2.[21-142] Of note, only head-to-head or active-comparator trials have been included as insulin is a well-established treatment.
- The safety and efficacy of inhaled regular insulin (Afrezza®) in both diabetes type 1 and type 2. Clinical trials were 24 weeks each.[4,143,144]
    - For type 1 diabetes, inhaled regular insulin was non-inferior to insulin aspart for mean reduction in HbA_{1c}. However, it provided less HbA_{1c} reduction than insulin aspart (-0.4% vs -0.21%). On the other hand, there was a reduction in the rate of hypoglycemia (9.8 vs 14.0 events per subject month; P<0.0001) and less weight gain (−0.39 kg vs 0.93 kg; P=0.0102) with inhaled regular insulin.
    - For type 2 diabetes, mean reduction in HbA_{1c} was significantly greater in the insulin group compared to the placebo group (-0.82% vs -0.42%; 95% confidence interval [CI]: −0.57 to −0.23; P<0.0001).
- The safety and efficacy of insulin glargine U-300 (Toujeo®) was evaluated in four clinical trials. Each study compared insulin glargine U-300 to insulin glargine U-100 in an open label design over 26 weeks of therapy.
    - In all studies, insulin glargine U-300 was shown to be non-inferior to insulin glargine U-100. Additionally, the dose of basal glargine insulin required was higher in all studies for U-300 (requiring 11% to 17.5% more units). Generally, both U-100 and U-300 had similar rates of adverse events, including hypoglycemia and all three studies showed similar changes in weight.[12,71-73]
- Differences in safety and efficacy of insulin preparations are modest with slightly better improvement in in HbA_{1c} with the rapid-acting analogues compared to regular insulin.[44,45]
- Long-acting insulin analogs have been shown to be at least as effective as NPH insulin in HbA_{1c} reduction, with some studies showing a significant improvement associated with the long-acting insulin analogs compared with NPH insulin with similar rates of side effects.[64,102,103,105]
- When comparing the long-acting analogs head-to-head, several trials have demonstrated non-inferiority between the products in the same outcomes when used in the management of type 1 diabetes and as add-on therapy in type 2 diabetics.[46,47,75-77]
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Key Points within the Medication Class

- According to Current Clinical Guidelines:[145-155]
    - The goal of treatment for both type 1 and type 2 DM is to control hyperglycemia and reduce the risk of long-term complications.
    - For patients with type 1 DM, insulin therapy is required due to pathogenesis of the disease. The standard approach to therapy is a regimen that includes long-acting basal insulin and rapid-acting prandial insulin tailored to the individual.
    - For type 2 DM, there are many more options for therapy, including the insulin products, oral antidiabetic agents, and other injectable antidiabetic agents.
        - Metformin remains the cornerstone of most antidiabetic treatment regimens.
        - Patients with a high HbA_{1c} will 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.
    - For both conditions, the trend in treatment is toward a patient-centered approach focusing on patient needs, preferences and tolerances, individualized treatment, and flexibility in the

choice of drugs, the over-riding goal being to improve glycemic control while minimizing adverse effects.

- Other Key Facts:[1-17]
  - Insulin therapy is usually administered by subcutaneous injection. Regular insulin is also formulated as an inhalation. At least one formulation of all insulin products are supplied in multidose vials with only regular insulin not being formulated in a prefilled pen or syringe.[1-17]
  - All insulin products have at least one formulation with a concentration of 100 units/mL. Two agents are also formulated with a higher concentration, regular insulin as 500 units/mL (Humulin® R U-500) and insulin glargine as 300 units/mL (Toujeo® SoloSTAR).[1-17]
  - A Risk Evaluation and Mitigation Strategy (REMS) is required for this inhaled regular insulin and includes requirements for patient evaluation and testing prior to initiating therapy in order to ensure appropriate patient selection (e.g., avoiding this agent in patients with underlying chronic lung disease).
  - There are currently no generic formulations of insulin; however, there are several products available over-the-counter.

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Therapeutic Class Review
Insulins

Overview/Summary

This review will focus on the antidiabetic insulins, including human insulin products and synthetic insulin analogs.[1-17] Insulin products are Food and Drug Administration (FDA)-approved improve glycemic control in patients with diabetes mellitus (DM) type 1 and type 2. DM is a group of metabolic disorders with types 1 and 2 being the broadest categories. All categories of DM ultimately results in hyperglycemia, but the etiologies for each are distinct and may include reduced insulin secretion, decreased glucose utilization, or increased glucose production. Due to the metabolic dysregulation of DM, secondary pathophysiologic changes in multiple organ systems occur. Examples of severe complications that may occur include end-stage renal disease (ESRD), nontraumatic lower extremity amputation, and adult blindness. Additionally, it also predisposes the patient to cardiovascular disease.[18] Overall, there are a variety of oral and injectable antidiabetic agents currently available to treat diabetes.

Insulin is a natural peptide hormone that is produced in the beta cells of the pancreas. It is secreted from the pancreas along with other hormones such as C peptide and amylin in response to glucose, the key regulator of insulin section. When glucose levels in the blood reach a certain point, the pancreas is stimulated to secrete insulin so that it may exert its physiologic actions. Major physiologic actions associated with glucose homeostasis regulated by insulin include increased glucose uptake into skeletal muscle and fat and decreases glycogenolysis and gluconeogenesis. Insulin used for the treatment of DM is synthesized utilizing recombinant deoxyribonucleic acid (DNA) technology. Regular insulin is structurally identical to endogenous insulin, with various additions, deletions, or substitutions of amino acids made for the insulin analogs. Modifications made to human insulin have the greatest effect on kinetic parameters, particularly onset and duration of action. Rapid- and short-acting insulins are administered as a bolus prior to meals to control postprandial glucose excursions while intermediate- and long-acting agents act as basal insulin, which is essential for regulating glucose homeostasis.[18]

Available insulin products are summarized in Table 1. Insulin therapy is usually administered by subcutaneous injection, which allows for prolonged absorption and less pain compared to intramuscular injection. [1-17,19] Additionally, regular insulin is also formulated as an inhalation.[4] At least one formulation of all insulin products are supplied in multidose vials with only regular insulin not being formulated in a prefilled pen or syringe.[1-17] Inhaled insulin powder is formulated in disposable, single-use cartridges, known as Technosphere® which provided a more efficient inhalation device than what has been used in the past.[4] Another inhaled formulation of regular insulin, Exubera®, was previously FDA-approved; however, this agent was removed from the market in 2007 due to low patient and provider acceptance.[20] All insulin products have at least one formulation with a concentration of 100 units/mL (U-100). Two agents are also formulated with a higher concentration, regular insulin as 500 units/mL (U-500; Humulin® R U-500) and insulin glargine as 300 units/mL (U-300; Toujeo® SoloSTAR).[1-17] There are currently no generic formulations of insulin; however, there are several products available over-the-counter.

For patients with either type 1 or type 2 DM, differences in safety and efficacy of insulin preparations is modest. Generally, at best, there is a modest improvement in in glycosylated hemoglobin A_{1c} (HbA_{1c}) with the rapid-acting analogues with overall rates of hypoglycemia that were not significantly different. Long-acting insulin analogs have been shown to be at least as effective as neutral protamine Hagedorn (NPH) insulin in HbA_{1c} reduction, with some studies showing a significant improvement associated with the long-acting insulin analogs compared with NPH insulin with similar rates of side effects. When comparing the long-acting analogs head-to-head, several trials have demonstrated non-inferiority between the products in the same outcomes when used in the management of type 1 diabetes and as add-on therapy in type 2 diabetics. In terms of clinical outcomes, the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) trials have demonstrated that intensive glycemic control with insulin significantly reduces the rate of onset and progression of diabetic complications when

compared to standard therapy. Neither study identified which insulin products were utilized; however, the UKPDS noted that the risk reduction in complications was related more toward tight glycemic control rather than to one specific therapy.[21-142]

The goal of treatment for both type 1 and type 2 DM is to control hyperglycemia and reduce the risk of long-term complications. For patients with type 1 DM, insulin therapy is required due to pathogenesis of the disease. The standard approach to therapy is a regimen that includes long-acting basal insulin and rapid-acting prandial insulin tailored to the individual. For type 2 DM, there are many more options for therapy, including the insulin products, oral antidiabetic agents, and other injectable antidiabetic agents. Metformin remains the cornerstone of most antidiabetic treatment regimens of type 2 DM. Additionally, patients with a high HbA_{1c} will 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. For both conditions, the trend in treatment is toward a patient-centered approach focusing on patient needs, preferences and tolerances, individualized treatment, and flexibility in the choice of drugs, the over-riding goal being to improve glycemic control while minimizing adverse effects.[145-155]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Products		
Insulin aspart (NovoLog®, NovoLog® FlexPen, NovoLog® PenFill)	Insulins (rapid-acting)	-
Insulin detemir (Levemir®, Levemir® FlexPen, Levemir® FlexTouch)	Insulins (long-acting)	-
Insulin glargine (Lantus®, Lantus® SoloSTAR, Toujeo® SoloSTAR)	Insulins (long-acting)	-
Insulin glulisine (Apidra®, Apidra® SoloSTAR)	Insulins (rapid-acting)	-
Insulin lispro, human recombinant analog (Humalog®, Humalog® KwikPen)	Insulins (rapid-acting)	-
Insulin NPH (isophane), human recombinant (Humulin® N, Humulin® N U-100 Pen, Novolin® N, Novolin® N ReliOn)	Insulins (intermediate-acting)	-
Insulin regular, human recombinant (Afrezza®, Humulin® R, Humulin® R U-500, Novolin® R)	Insulins (short-acting)	-
Combination Products		
Insulin aspart/insulin aspart protamine (NovoLog® Mix 70/30, NovoLog® 70/30 Flex Pen)	Insulins (rapid/intermediate-acting)	-
Insulin lispro/insulin lispro protamine (Humalog® Mix 50/50, Humalog® Mix 75/25, Humalog® Mix 50/50 KwikPen, Humalog® Mix 75/25 KwikPen)	Insulins (rapid/intermediate-acting)	-
Insulin, regular/insulin, NPH, human recombinant (Humulin® 70/30, Humulin® 70/30 KwikPen, Humulin® 70/30 Pen, Novolin® 70/30, Novolin® 70/30 ReliOn)	Insulins (short/intermediate-acting	-

NPH=neutral protamine Hagedorn

Indications

Table 2. Food and Drug Administration-Approved Indications[1-17]

Generic Name	To improve glycemic control in diabetes mellitus*	Treatment of diabetic patients with marked insulin resistance*
Single Entity Products		

Generic Name	To improve glycemic control in diabetes mellitus*	Treatment of diabetic patients with marked insulin resistance*
Insulin aspart	✔	
Insulin detemir	✔	
Insulin glargine	✔	
Insulin glulisine	✔	
Insulin lispro	✔	
Insulin NPH	✔	
Insulin regular	✔	✔ (Humulin® R U-500)
Combination Products		
Insulin aspart/insulin aspart protamine	✔	
Insulin lispro/insulin lispro protamine	✔	
Insulin regular/insulin NPH	✔	

*Includes diabetes mellitus type 1 and type 2. Generally, these agents have not been studied for the treatment of type 2 diabetes in pediatric patients. Additionally, some agents may carry an indication for use in pediatric patients, but have never been studied in that population.

Insulin products may be utilized for a number of off-label uses. These include the treatment of diabetic ketoacidosis, hyperosmolar hyperglycemic state in patients with type 2 DM, gestational diabetes, treatment of hyperkalemia, and as nutritional supplementation to maintain normoglycemia in very low birthweight infants with persistent glucose intolerance. Generally, regular human insulin is recommended, but there is some evidence to support the use of insulin NPH and insulin analogs off-label.[156,157]

Pharmacokinetics

Table 3. Pharmacokinetics[1-18,157]

Generic Name(s)*	Onset (hours)	Peak (hours)	Duration (hours)	Half-Life (hours)	Mixing of Insulins
Single Entity Products					
Insulin aspart	0.0835 to 0.25	1 to 3	0.05 to 0.083	1.35	NPH
Insulin detemir	2 to 4	3 to 4‖	7.6 to >24	5 to 7	None
Insulin glargine	1 to 4#	Not Reported‖	24§	Not Reported	None
Insulin glulisine	0.2 to 0.5	Not reported	5.3	0.7	NPH
Insulin lispro	Not Reported	0.5 to 1.5	3 to 4	1	longer-acting insulin
Insulin NPH	1 to 4	Not reported	Not reported	Not reported	Insulin regular
Insulin regular	0.5	1.5 to 3.5, 0.88†	8 to 24‡, 2.66†	3.3, 0.5†	longer-acting insulin
Combination Products					
Insulin aspart/insulin aspart protamine	<15	1.5 to 4	10 to 24	Not reported	None
Insulin lispro/insulin lispro protamine	<15	1.5 to 4	10 to 24	Not reported	None
Insulin regular/ insulin NPH	30 to 60	Dual peaks¶	10 to 16	Not reported	None

*Unless otherwise noted, pharmacokinetic parameters are representative of a subcutaneous dose.
†Inhalation route (Afrezza®)
#Toujeo® listed as 4 hours; Lantus® listed as one to four hours

‡The duration of glucose-lowering activity of U-500 human regular insulin is up to 24 hours following subcutaneous administration.
§The 24-hour effect of Toujeo® is lower than Lantus®.
‖Detemir and glargine have minimal peak activity
¶Two peaks; one at two to three hours and then one several hours later.

Clinical Trials

Clinical trials demonstrating the safety and efficacy of insulin products in the management of diabetes type 1 and 2 are outlined in Table 4.[21-142] Of note, only head-to-head or active-comparator trials have been included as insulin is a well-established treatment.

The safety and efficacy of inhaled regular insulin (Afrezza®) in both diabetes type 1 and type 2. Clinical trials were 24 weeks each.[4,143,144] For type 1 DM, inhaled regular insulin was compared to mealtime insulin aspart, both in combination with basal insulin. Inhaled regular insulin was shown to be non-inferior to insulin aspart for mean reduction in HbA_{1c}. However, inhaled regular insulin provided less HbA_{1c} reduction than insulin aspart, and the difference was statistically significant (-0.4% vs -0.21%). On the other hand, there was a reduction in the rate of hypoglycemia (9.8 vs 14.0 events per subject month; P<0.0001) and less weight gain (−0.39 kg vs 0.93 kg; P=0.0102) for inhaled regular insulin compared to insulin aspart.[4,144] For type 2 diabetes, inhaled regular insulin was compared to placebo inhalation, both in combination with oral antidiabetic drugs. At week 24, mean reduction in HbA_{1c} was significantly greater in the insulin group compared to the placebo group (-0.82% vs -0.42%; 95% confidence interval [CI]: −0.57 to −0.23; P<0.0001). There was an increase in the incidence of severe hypoglycemia for Afrezza® (insulin human, regular) compared to placebo (5.1% vs 1.7%).[4,155]

The safety and efficacy of insulin glargine U-300 (Toujeo®) was evaluated in four clinical trials. Each study compared insulin glargine U-300 to insulin glargine U-100 in an open label design over 26 weeks of therapy. One unpublished study evaluated the efficacy in type 1 diabetes. In this study glargine insulin U-100 and U-300 were given once daily in a basal-bolus regimen in combination with mealtime insulin. At week 26, treatment with insulin glargine U-300 was non-inferior to insulin glargine U-100 for reduction in HbA_{1c}. Patients treated with insulin glargine U-300 used 17.5% more basal insulin than patients treated with insulin glargine U-100.[12] The EDITION studies evaluated the safety and effectiveness of insulin glargine U-300 in patients with type 2 diabetes. EDITION 1 evaluated insulin glargine U-300 in combination with mealtime insulin, while EDITION 2 and 3 evaluated combination therapy with non-insulin oral antidiabetic agents; in EDITION 3, patients were also insulin-naïve.[71-73] In all three studies, insulin glargine U-300 was shown to be non-inferior to insulin glargine U-100. Additionally, the dose of basal glargine insulin required was higher in all three studies for U-300, requiring 11, 12 and 15% more units. Generally, both U-100 and U-300 had similar rates of adverse events, including hypoglycemia and all three studies showed similar changes in weight.[71-73]

For patients with either type 1 or type 2 diabetes, differences in safety and efficacy of insulin preparations is modest. Short term trials that have compared the rapid-acting insulin analogues to regular insulin have had mixed results. Generally, at best, there is a modest improvement in in HbA_{1c} with the rapid-acting analogues with overall rates of hypoglycemia that were not significantly different.[44,45] Long-acting insulin analogs have been shown to be at least as effective as NPH insulin in HbA_{1c} reduction, with some studies showing a significant improvement associated with the long-acting insulin analogs compared with NPH insulin with similar rates of side effects.[64,102,103,105]

When comparing the long-acting analogs head-to-head, several trials have demonstrated non-inferiority between the products in the same outcomes when used in the management of type 1 diabetes and as add-on therapy in type 2 diabetics.[46,47,75-77] At this time, there is still a lack of substantial head-to-head data demonstrating the superiority of one long-acting insulin analog over another.

In terms of clinical outcomes, When comparing the long-acting analogs head-to-head, several trials have demonstrated non-inferiority between the products in the same outcomes when used in the management of type 1 diabetes and as add-on therapy in type 2 diabetics.[46,47,75-77]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Rapid-Acting and Short-Acting Insulin: Type 1 Diabetes Mellitus				
Home et al[21] Insulin aspart before meals and NPH insulin QD or BID vs regular insulin (REG) before meals and NPH insulin QD or BID Insulin doses were adjusted to achieve target FPG and bedtime glucose 5.0-8.0 mmol/L and PPG <10.0 mmol/L.	ES, MC, MN, OL, PG, RCT Patients ≥18 years of age with type 1 diabetes for at least 2 years on insulin for at least 1 year before inclusion, HbA_{1c} ≤11.0%, BMI ≤35 kg/m^2	N=753 36 months	Primary: HbA_{1c}, hypoglycemia, adverse events Secondary: Not reported	Primary: At the end of the original six month study, HbA_{1c} decreased in the insulin aspart group, with a statistically significant difference of -0.12 (95% CI, -0.22 to -0.03; P<0.02). At 30 months during the extension period, the difference of -0.16 in HbA_{1c} was maintained (95% CI, -0.32 to -0.01; P<0.035). At 30 months, mean HbA_{1c} was significantly lower in the insulin aspart group compared to the REG group after adjustment for the rate of hypoglycemic episodes and baseline HbA_{1c} (P<0.001). The RR estimate for major hypoglycemia was similar in both treatment groups at 36 months (RR, 1.0; 95% CI, 0.72 to 1.39; P value not significant). The proportion of patients reporting major hypoglycemia decreased from 16% in the first six months to 3% in the last six months in the insulin aspart group. The frequency of patients reporting major hypoglycemia also decreased in the REG group from 17 to 2%. There were no significant differences between groups in regards to major nocturnal hypoglycemia (RR, 0.89; 95% CI, 0.64 to 1.24; P value not significant). The proportion of patients experiencing adverse events during the treatment period was similar in both treatment groups (P value not reported). Secondary: Not reported
Raskin et al[22] Insulin aspart before meals and NPH insulin QD to BID vs regular insulin before meals and NPH insulin	MC, OL, RCT Type 1 diabetes patients with an HbA_{1c} ≤11.0%, baseline HbA_{1c} 7.9% in the insulin aspart group and 7.95% in the	N=882 6 months (with 6 month extension period)	Primary: Effect on eight-point blood glucose measurements and HbA_{1c} at six and 12 months Secondary: Not reported	Primary: At six and 12 months, mean PPG (90 minutes postmeal) was significantly lower with insulin aspart compared to REG (P<0.05). At six months, mean pre-prandial lunch and dinner blood glucose levels were significantly lower with insulin aspart when compared to REG (P<0.05). At 12 months, only pre-prandial dinner blood glucose levels were significantly lower with insulin aspart (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
QD to BID Doses of insulin were titrated to achieve FPG of 90-144 mg/dL, PPG ≤180 mg/dL and 2:00 AM blood glucose of 90-144 mg/dL.	REG group; patients were excluded if they had impaired hepatic, renal, or cardiac function; other exclusions included recurrent hypoglycemia, proliferative retinopathy, or total daily insulin requirement ≥1.4 units/kg			At six months, HbA_{1c} was significantly lower with insulin aspart (7.78%) when compared to REG (7.93%; P=0.005). At 12 months, HbA_{1c} was significantly lower with insulin aspart (7.78%) when compared to REG (7.91%; P=0.005). Mean NPH dose increased significantly with insulin aspart compared to REG (0.314 vs 0.296 U/kg; P=0.011). Similar rates of hypoglycemia were observed in both treatment groups. Secondary: Not reported
Mathiesen et al[23] Insulin aspart before meals and NPH insulin QD to QID vs regular insulin before meals and NPH insulin QD to QID Doses were titrated to achieve target goals FPG 4.1 to 6.1 mmol/L, PPG<7.5 mmol/L, and HbA_{1c} <6.5%.	MC, OL, PG, RCT Patients ≥18 years of age with insulin-treated type 1 diabetes for ≥12 months, either pregnant with a singleton pregnancy (gestational age ≤10 weeks) or planning to become pregnant, HbA_{1c} ≤8.0%	N=412 28 months	Primary: Major hypoglycemia during pregnancy Secondary: HbA_{1c}, self-measured eight-point plasma glucose profile, maternal adverse events, obstetric complications, diabetes complications	Primary: The rates of major maternal hypoglycemia were lower in patients taking insulin aspart than patients taking REG. There was a 28% risk reduction for major hypoglycemia (RR, 0.720; 95% CI, 0.36 to 1.46; P value not reported) and a 52% risk reduction for major nocturnal hypoglycemia (RR, 0.48; 95% CI, 0.20 to 1.14; P value not reported) for patients taking insulin aspart than patients taking REG. However, this did not reach statistical significant. Secondary: Treatment with insulin aspart was as effective as treatment with REG in regards to HbA_{1c} (mean difference, -0.04%; 95% CI, -0.18 to 0.11; P value not significant) during the second and third trimester (mean difference, -0.08%; 95% CI, -0.23 to 0.06; P value not significant). Overall eight-point plasma glucose profiles were similar between treatment groups during the second and third trimesters. PPG levels were consistently lower in the insulin aspart group following breakfast than the REG group during the first trimester (P=0.044) and the third trimester (P=0.0007). However, there was no difference in PPG after breakfast during the second trimester (P=0.153).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Both treatments were well tolerated and the adverse event profiles were similar between both groups. The frequency and profile of obstetric complications were similar between treatments with the most frequent complications being preeclampsia, threatened preterm labor, prolonged labor, and unplanned cesarean section. Treatment groups were not different in regards to changes in vital signs, physical examinations parameters, electrocardiograms, or clinical laboratory findings (P values were not reported).
Garg et al[24] Insulin glulisine before morning and evening meals and insulin glargine QD vs insulin glulisine after morning and evening meals and insulin glargine QD vs regular insulin before morning and evening meals and insulin glargine QD Prandial insulin doses were adjusted to achieve PPG of 120 to 160 mg/dL.	MC, OL, PG, RCT Patients with type 1 diabetes on insulin therapy for >1 year, baseline HbA_{1c} 7.7% for both insulin glulisine treatment groups and 7.6% for the REG group	N=860 12 weeks	Primary: Effect on HbA_{1c}, rate of hypoglycemia, and insulin dose Secondary: Not reported	Primary: HbA_{1c} reductions for insulin glulisine administered after meals (-0.11%) did not differ significantly from REG (-0.13%; P=0.6698). HbA_{1c} reductions for insulin glulisine administered before meals (-0.26%) were significantly lower than REG (-0.13%; P=0.0234). HbA_{1c} reductions for insulin glulisine administered before meals (-0.26%) were significantly lower than insulin glulisine administered after meals (-0.11%; P=0.0062). No significant differences were observed in the rates of symptomatic hypoglycemia (all and severe cases) between pre- and postmeal insulin glulisine and REG (P>0.05). Change in total insulin dose from baseline was significantly higher in the REG group (2.35 U) compared to the premeal insulin glulisine group (0.04 U; P=0.014). Secondary: Not reported
Dreyer et al[25]	MC, OL, PG,	N=672	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Insulin glulisine before meals and insulin glargine HS vs insulin lispro before meals and insulin glargine HS Insulin doses were adjusted to achieve PPG of 120 to 160 mg/dL.	RCT Patients with type 1 diabetes on insulin therapy for >1 year, baseline HbA_{1c} 7.6% for both treatment groups	26 weeks	Effect on HbA_{1c}, rate of hypoglycemia, effect on self-monitored blood glucose and insulin dose Secondary: Not reported	There was a comparable decrease in HbA_{1c} between the insulin glulisine and insulin lispro groups (-0.14% for both groups; P value NS). The incidences of all hypoglycemic events (nocturnal and severe) were similar between the two treatment groups. Self-monitored blood glucose levels were similar in both treatment groups in regards to pre- and postprandial, bedtime and nocturnal blood glucose levels. There was a significant increase in total insulin dose in the insulin lispro group (1.01 units) compared to the insulin glulisine group (-0.86 units; P=0.0123). There was no significant difference in change in rapid-acting insulin dose between treatment groups. Rates of hypoglycemia were similar in both treatment groups. Rates of adverse events were also similar among the two treatment groups. Secondary: Not reported
Philotheou et al[26] Premeal insulin glulisine vs premeal insulin lispro All patients received NPH BID or insulin glargine QD. Rapid-acting and basal insulin doses were	MC, NI, OL, PG, RCT Patients 4 to 17 years of age with type 1 diabetes for ≥1 year with HbA_{1c} between 6.0 to 11.0% who were receiving insulin therapy for ≥1 year with NPH insulin or insulin	N=570 (efficacy endpoints) N=572 (safety endpoints) 26 weeks (plus a 24-hour follow-up period)	Primary: Change in HbA_{1c} from baseline at endpoint (study did not define "endpoint") Secondary: Proportion of patients who reached target HbA_{1c}, change in HbA_{1c} from	Primary: The adjusted mean change in HbA_{1c} from baseline to endpoint was 0.10±0.08% with insulin glulisine and 0.16±0.07% with insulin lispro. The difference between the two groups was -0.06% (95% CI, -0.24 to 0.12; P value not reported), showing non-inferiority of insulin glulisine compared to insulin lispro based on the prespecified non-inferiority margin of 0.4%. Secondary: At baseline, 33.2 and 33.3% of patients had HbA_{1c} at goal in the insulin glulisine and insulin lispro groups, respectively. At endpoint, the percentage of patients with HbA_{1c} at goal was 38.4% with insulin glulisine and 32.0% with insulin lispro (P=0.039). Change in HbA_{1c} with insulin glulisine and insulin lispro was -0.01±0.07% and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
titrated to achieve age-specific FPG goal of 100 to 140 mg/dL (<8 years old) or 90 to 140 mg/dL (≥8 years old) and PPG goal of 120 to 180 mg/dL (<8 years old) or 100 to 160 mg/dL (≥8 years old) using blood-referenced blood glucose meters.	glargine as basal insulin		baseline at 12 and 26 weeks, self-monitored FPG, PPG and pre-prandial glucose, insulin doses, symptomatic hypoglycemia between 12 and 26 weeks and safety	-0.03±0.06% at 12 weeks and 0.08±0.08% and 0.17±0.08% at 26 weeks, respectively (P values not reported). At endpoint, self-monitored FPG was lower in the insulin glulisine group compared to the insulin lispro group (158.0±3.8 vs 170.5±3.7 mg/dL; P=0.014). Baseline FPG, PPG and pre-prandial glucose as well as endpoint PPG and pre-prandial glucose were comparable between the two groups. Total daily insulin doses increased by 0.01±0.01 units/kg with insulin glulisine and by 0.05±0.01 units/kg with insulin lispro (P=0.0045). The monthly rate of symptomatic hypoglycemia per patient was 3.10±4.33 and 2.91±4.35 with insulin glulisine and insulin lispro, respectively (P value not reported). No difference was seen with the two groups in severe, nocturnal or severe nocturnal symptomatic hypoglycemia. The frequency and type of treatment-emergent adverse events or serious adverse events were similar between the treatment groups.
van Bon et al[27] Insulin glulisine vs insulin aspart vs insulin lispro Insulin doses were titrated to achieve PPG <180 mg/dL and pre-prandial glucose	MC, OL, RCT, XO Patients ≥18 years of age with type 1 diabetes treated with insulin for ≥2 years and continuous SC insulin infusion for ≥6 months, requiring ≤90 units/day of insulin, with HbA_{1c} <8.5% and BMI<35	N=256 39 weeks (13 weeks of treatment period for each study medication)	Primary: Unexplained hyperglycemia (>300 mg/dL) and/or perceived infusion set occlusion Secondary: Unexplained hyperglycemia, perceived infusion set occlusion, HbA_{1c}, proportion of patients with	Statistical significant was defined as P <0.025 in this study. Primary: Percentage of patients with at least one unexplained hyperglycemia and/or perceived infusion set occlusion was comparable between insulin glulisine and insulin aspart (68.4 vs 62.1%; P=0.04) and between insulin glulisine and insulin lispro (68.4 vs 61.3%; P=0.03). Secondary: Percentage of patients reporting at least one unexplained hyperglycemia was similar when comparing insulin glulisine (61.3%) to insulin aspart (55.9%; P=0.08) and insulin lispro (56.3%; P=0.11). No significant difference was seen in the percentage of patients with at least one perceived infusion set occlusion between insulin glulisine and insulin aspart (32.8 vs 27.0%; P=0.08) and between insulin glulisine and insulin lispro (32.8 vs 27.0; P=0.06).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
between 90 to 130 mg/dL.	kg/m^2		HbA_{1c} <7.0%, seven-point plasma glucose profiles, hypoglycemic episodes, episodes of asymptomatic ketonemia and ketoacidosis, insulin doses, time to infusion set change, infusion site reactions and serious adverse reactions	HbA_{1c} remained stable from baseline at the end of treatment period with all three insulin groups, with no significant differences seen among groups. Similar percentage of patients achieved HbA_{1c} <7.0% in the insulin glulisine, insulin aspart and insulin lispro groups (28, 31 and 30%, respectively; P values not reported). The seven-point plasma glucose profiles were similar among all three groups at baseline. At the end of treatment, after-lunch glucose was higher with insulin glulisine compared to insulin aspart (166.1 vs 155.5 mg/dL; P=0.021), and midnight glucose was higher with insulin lispro compared to insulin glulisine (159.4 vs 148.1 mg/dL; P=0.018). The overall rate of symptomatic hypoglycemia per patient-year was higher with insulin glulisine (73.8) compared to insulin aspart (65.0; P=0.008) and insulin lispro (62.7; P<0.001). The monthly rate of significant hyperketonemia and/or hyperketonemia at risk for ketosis was higher with insulin glulisine (0.14) compared to insulin aspart (0.06; P=0.01) and insulin lispro (0.06; P=0.02). One patient was hospitalized for diabetic ketoacidosis while receiving insulin glulisine. Insulin doses remained stable throughout the study. No significant differences were seen among the three groups in time to infusion set change, frequency of infusion site reactions and serious adverse reactions. No death was reported.
Rave et al[28] Premeal insulin glulisine (2 minutes prior to a standardized 15-minute meal) vs	4-way XO, OL, RCT, single-dose Patients 18 to 55 years of age with type 1 diabetes on the same insulin	N=21 4 treatment periods	Primary: Blood glucose exposure and excursion at two and six hours following a meal, mean maximum blood glucose	Primary: Blood glucose exposure within two hours after the start of a meal was significantly lower with insulin glulisine than with REG (279 vs 344 mg·h/dL, respectively; P value not reported). However, at six hours following a meal, blood glucose exposure was not significantly different between both groups (708 vs 770 mg·h/dL, respectively; P value not reported). When insulin glulisine was given immediately prior to a meal and REG 30

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
postmeal insulin glulisine (15 minutes postmeal) vs premeal regular insulin (30 minutes premeal) vs premeal regular insulin (2 minutes premeal)	regimen for ≥2 months before enrollment, BMI 18 to 32 kg/m^2, HbA_{1c} <10.0%, serum C-peptide levels ≤0.9 ng/mL		concentration, time to reach mean maximum blood glucose concentration Secondary: Not reported	minutes prior to the meal, blood glucose control was comparable. Both two- and six-hour blood glucose exposures were well matched. However, treatment with REG resulted in time to maximum blood glucose excursion to occur 43 minutes later compared to insulin glulisine. Postmeal insulin glulisine and REG given immediately premeal produced similar effects on PPG exposure and excursion at two hours after a meal (337 vs 334 mg·h/dL, respectively) and six hours after a meal (777 vs 770 mg·h/dL, respectively; P values not reported). Insulin glulisine was absorbed more rapidly than REG and reached a mean maximum concentration that was almost twice as large as the mean maximum concentration for REG (P value was not reported). In addition, the time to reach maximum concentration for insulin glulisine was half that of REG (P value was not reported). Secondary: Not reported
Anderson et al[29] Insulin lispro before each meal and basal insulin for 3 months vs Regular insulin (REG) before each meal and basal insulin for 3 months	MC, OL, RCT, XO Patients with type 1 diabetes previously treated with REG, baseline HbA_{1c} 8.5% for both groups	N=1,008 6 months	Primary: Effect on postprandial serum glucose (one- and two-hour), HbA_{1c}, and frequency of hypoglycemia Secondary: Effect on insulin dose, frequency of premeal and basal insulin injections, and weight	Primary: One-hour postprandial serum glucose rise was significantly lower with insulin lispro compared to REG (12.9 vs 13.9 mmol/L; P<0.001). Two-hour postprandial serum glucose rise was significantly lower with insulin lispro compared to REG (11.2 vs 12.9 mmol/L; P<0.001). There was no difference in HbA_{1c} reduction between the two treatment groups. The rate of hypoglycemia was 12% less during treatment with insulin lispro when compared to REG (P<0.001). Secondary: A small but significant increase in total insulin dose was observed with insulin lispro when compared to REG (0.71 vs 0.69 U/kg; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				No significant difference was reported for frequency of premeal injections between the two treatment groups. Significantly less patients on REG required ≥2 basal insulin injections compared to insulin lispro (46.4 vs 44.0%; P<0.05). There were no significant differences in weight gain between the two treatment groups. There were no differences in type and frequency of adverse events between the two treatments.
Fairchild et al[30] Insulin lispro and NPH or Lente insulin for 3 months vs regular insulin (REG) and NPH or Lente insulin for 3 months Insulin doses were titrated to achieve HbA_{1c} 6.0 to 8.0% and preprandial blood glucose levels 4-10 mmol/L.	OL, RCT, XO Children 5 to 10 years of age with type 1 diabetes for at least 12 months, prepubertal, on BID insulin, attending the Diabetes Clinics at the New Children's Hospital, Newcastle	N=43 6 months	Primary: HbA_{1c} Secondary: Blood glucose levels before and after meals, two-hour PPG excursions, hypoglycemic events	Primary: After three months, change in HbA_{1c} was not significantly different between patients on insulin lispro and patients on REG (mean difference, -0.19±0.63%; P value not reported). Secondary: There were no significant differences in blood glucose levels before or after meals and two-hour PPG excursions. However, the 3 AM blood glucose levels were significantly lower in patients taking REG than in patients taking insulin lispro (mean difference between treatments, -2.35 mmol/L; 95% CI, -3.98 to -0.72; P=0.01). There was no significant difference in the frequency of total hypoglycemic episodes or hypoglycemic episodes with a blood glucose <3 mmol/L between patients taking REG and patients taking insulin lispro (P value was not reported).
Mortensen et al[31] Premeal biphasic insulin aspart (BIAsp) 30 plus NPH insulin at bedtime (HS)	MN, OL, PG, RCT Adolescents 10 to 17 years of age with type 1 diabetes for at	N=167 16 weeks	Primary: HbA_{1c}, change in PPG, body weight, hypoglycemia	Primary: HbA_{1c} decreased by about -0.2% in both treatment arms at endpoint. There was no significant difference in the change of HbA_{1c} between groups at study endpoint (P=0.62). At 16 weeks, both the biphasic insulin aspart group and REG group had

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs premeal REG (before lunch and dinner) plus biphasic human insulin (BHI) 30 before breakfast and NPH insulin HS Insulin doses were titrated to achieve target FPG <8 mmol/L and PPG <10 mmol/L.	least 18 months		Secondary: Not reported	reductions in average PPG (SEM, 0.37 and 0.77, respectively; P=0.47). The increase in body weight was smaller in the biphasic insulin aspart group than the REG group. The difference between groups was significant for males (P=0.007), but not for females. The rates of hypoglycemia during the day and during the night were similar between treatment groups (P value was not reported). Secondary: Not reported
Chen et al[32] Biphasic insulin aspart 30 (BIAsp30) TID, divided in a 30:30:40 ratio for 12 weeks; NPH could also be added at bedtime vs REG insulin administered TID plus NPH insulin at bedtime for 12 weeks Doses were titrated to achieve FPG 5.0 to 8.0 mmol/L and PPG 5.0 to 10.0 mmol/L.	OL, RCT, XO Patients ≥18 years of age with type 1 diabetes for ≥12 months, previously treated with soluble human insulin TID plus NPH at bedtime with a total daily dose <1.8 IU/kg, BMI <35 kg/m^2 and HbA_{1c} ≥8.0% during the last 6 months; at 12 weeks, patients were switched to the alternative	N=27 24 weeks	Primary: Change in HbA_{1c} from baseline at end of each 12 week-treatment period, daily seven-point self monitoring of blood glucose Secondary: Hypoglycemia	Primary: Eleven out of 27 patients chose to take bedtime NPH while they were being treated with insulin aspart. Both the biphasic insulin aspart and the REG groups had significant improvement in HbA_{1c} levels from baseline (P<0.01). However, the biphasic insulin aspart group had a significantly greater reduction in HbA_{1c} than that of the REG group (P<0.05). Upon further analysis it was ascertained that most of the between-group difference in HbA_{1c} was driven by the patients who administered bedtime NPH in combination with their TID biphasic insulin aspart. Both the biphasic insulin aspart and the REG groups had similar results in self monitoring of blood glucose of daytime glycemic control. However, the biphasic insulin aspart group had significantly lower blood glucose concentrations at two hours after dinner and at bedtime in comparison to the REG group (P<0.05). Secondary: The rates of hypoglycemia (events/patient-week) were similar among the biphasic insulin aspart and REG group (1.2 vs 0.7, respectively for total events and 0.2 vs 0.2, respectively for nocturnal events; P value not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	insulin regimen for another 12 weeks			reported).
Rapid-Acting and Short-Acting Insulin Administered By Continuous Subcutaneous Insulin Infusion (CSII): Type 1 Diabetes Mellitus				
Bode et al[33] Insulin aspart (IAsp) administered by CSII via external pump vs insulin lispro administered by CSII via external pump vs regular insulin (BR) administered by CSII via external pump	MC, OL, PG, RCT Patients 18 to 71 years of age with type 1 diabetes with fasting C-peptide <0.5 ng/mL who had been treated with CSII therapy continuously for the previous 3 months	N=146 16 weeks	Primary: HbA_{1c}, eight-point self monitoring blood glucose, weight, hypoglycemia Secondary: Not reported	Primary: After 16 weeks of treatment, the mean change in HbA_{1c} from baseline was not significantly different among the three groups (0.00%, 0.15%, and 0.18% for the IAsp, BR, and lispro groups, respectively). For the eight-point self monitoring blood glucose evaluation, postprandial values for subjects in the rapid-acting insulin analog groups were improved from baseline values and tended to be lower than those for subjects in the BR group. A few statistically significant differences were observed at week 16 between the treatment groups: dinner +90 minutes, the blood glucose value for the IAsp group was lower than those for BR and lispro groups (P=0.019); at 2:00 A.M., the blood glucose value for the BR group was lower than those for IAsp and lispro groups (P=0.002). Mean weight did not significantly increase or decrease during the study among the treatment groups. Similar numbers of subjects (≥90%) in each treatment group reported one or more minor hypoglycemic episodes. The rate of confirmed hypoglycemia was not significantly different between treatment groups. The rate of confirmed nocturnal hypoglycemia for the IAsp group was lower than that for the BR group and similar to that of the lispro group. No major nocturnal hypoglycemic episodes occurred during the study. Secondary: Not reported
Weinzimer et al[34] Insulin aspart administered by CSII via external pump	MC, OL, PG, RCT Patients 3 to 18 years of age with type 1 diabetes	N=298 16 weeks	Primary: HbA_{1c} at week 16 Secondary: FPG, eight-point	Primary: At study end point, the mean HbA_{1c} values were 7.9% and 8.1% (last observation carried forward) for insulin aspart and insulin lispro, respectively. The change in HbA_{1c} from baseline to week 16 was -0.15% in the insulin aspart group and -0.05% in the insulin lispro group (95% CI, -0.27 to 0.07).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs insulin lispro administered by CSII via external pump	for ≥1 year and HbA_{1c} ≤10.0% who were being treated with either insulin aspart or insulin lispro by CSII for ≥3 months		self monitoring blood glucose, weight, hypoglycemia	After 16 weeks, 59.7% of patients in the insulin aspart group and 43.8% of the patients in the insulin lispro group achieved American Diabetes Association age-specific recommendations for HbA_{1c} (P=0.040). Secondary: After 16 weeks, mean FPG were similar among the treatment groups (insulin aspart 166.5 mg/dl; lispro 180.2 mg/dl; P=0.113). The eight-point self monitoring blood glucose profiles collected before weeks 0 and 16 showed a similar pattern for both treatment groups. No significant differences between treatment groups in mean self monitoring blood glucose values were observed at any of the eight time points at week 16. Mean body weight increased from baseline for both treatment groups during the trial, but was comparable between treatment groups (insulin aspart 1.8 kg; insulin lispro 1.6 kg; P=0.387). Rates of minor and major hypoglycemic episodes were similar between the two treatment groups. A similar percentage of patients reported at least one major hypoglycemic event during the study period (9.6 and 8.0% in the insulin aspart and insulin lispro groups, respectively). Rates of nocturnal hypoglycemic events were also similar between the treatment groups.
Colquitt et al[35] Rapid-acting insulin analogs administered by CSII vs regular insulin administered by CSII	MA Analysis of 6 randomized trials that compared rapid-acting insulin analogs vs REG in the treatment of patients with diabetes using continuous	N=577 Duration varied	Primary: Effect in HbA_{1c}, insulin dose, weight change, patient preference, quality of life and adverse events Secondary: Not reported	Primary: Significant improvement in HbA_{1c} of -0.26% (95% CI, -0.47 to -0.06; P=0.01) was observed with insulin lispro compared to REG. The differences in HbA_{1c} from baseline between insulin aspart, REG, or insulin lispro were not significant. No significant difference in insulin dose was reported between treatment groups. No significant difference in weight was reported between treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	infusions; trials less than 10 weeks in duration were excluded			Two studies reported patient preference to short-acting insulin analogs. One study found no difference in satisfaction between treatment groups and one study found greater patient satisfaction towards short-acting insulin analogs. No difference in frequency of severe hypoglycemic events was reported between treatment groups. Secondary: Not reported
Rapid-Acting and Short-Acting Insulin: Type 2 Diabetes Mellitus				
McSorley et al[36] Biphasic insulin aspart (BIAsp) 30 BID for 2 weeks vs biphasic human insulin (BHI) 30 BID for 2 weeks Patients were XO to other insulin regimen after 2 weeks of initial randomized insulin regimen.	2-period, DB, RCT, XO Patients 40 to 75 years of age with type 2 diabetes for at least 1 year, had been on BID biphasic human insulin 30 for at least 6 months	N=13 4 weeks	Primary: AUC during two hours following insulin administration at dinner and breakfast Secondary: Maximum serum insulin concentration after two injections; time to reach peak serum insulin concentrations; four-hour glucose excursion following dinner, breakfast, and lunch; glucose maximum concentration	Primary: The AUC two hours following insulin administration was significantly greater for biphasic insulin aspart 30 than for biphasic human insulin 30 after dinner and breakfast (P<0.05). Secondary: Biphasic insulin aspart 30 reached a maximum concentration that was 18% higher after dinner and 35% higher after the following day's breakfast than that of biphasic human insulin 30 (P<0.05 for both values). The time taken to reach peak serum insulin concentrations was one hour earlier after breakfast and 45 minutes earlier after dinner in the biphasic insulin aspart 30 group compared to the biphasic human insulin 30 group. However, the only measure to reach statistical significance was after breakfast (P<0.05). Serum glucose excursions were significantly lower in the biphasic insulin aspart 30 group than the biphasic human insulin 30 group after dinner (P<0.05) and after breakfast (P<0.05). However, serum glucose excursion after lunch was significantly higher in the biphasic insulin aspart 30 group than the biphasic human insulin 30 group (P<0.05). Following breakfast, glucose maximum concentration was significantly lower and time to reach glucose maximum concentration was significantly earlier with biphasic insulin aspart 30 than biphasic human insulin 30 (P<0.05 for both measures).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			after dinner, breakfast, and lunch; time taken to reach glucose maximum concentration values	Both insulins were well-tolerated and had comparable adverse events. There were no major hypoglycemic episodes or serious adverse events reported.
Bretzel et al[37] Insulin aspart before meals and NPH insulin QD (if needed) vs regular insulin before meals and NPH insulin QD (if needed) vs NPH/REG insulin 70/30 mix QD to BID Insulin doses were titrated to achieve blood glucose levels of 80 to 110 mg/dL.	MC, OL, PG, RCT Adult (≥35 years old) type 2 diabetes with HbA_{1c} ≤10.0%, baseline HbA_{1c} 7.82% for insulin aspart, 7.83% for REG and 7.78% for the premixed insulin	N=231 12 weeks	Primary: Equivalence of the primary efficacy endpoint–effect on HbA_{1c} Secondary: Not reported	Primary: Insulin aspart reduced HbA_{1c} by -0.91±1.00%, while REG reduced HbA_{1c} by -0.73±0.87% and premixed insulin reduced HbA_{1c} by -0.65±1.10%. Insulin aspart was found not to be statistically equivalent to REG (P=0.025) or the premixed insulin formulation (P=0.092). Significance level for P was set at 0.0083. The proportion of patients reporting an adverse event was comparable in all three treatment groups. The proportion of patients that experienced a hypoglycemic event (41% for insulin aspart and REG and 30% for premixed insulin) was not statistically different. Secondary: Not reported
Niskanen et al[38] Insulin aspart 30% and insulin aspart protamine 70% administered via proprietary pen for 12	MC, OL, RCT, XO Patients with type 2 diabetes previously	N=137 24 weeks	Primary: Effect on HbA_{1c} and seven-point blood glucose levels	Primary: HbA_{1c} reduction was comparable between the two treatment groups. The seven-point blood glucose profile was comparable at each time point and there was no significant difference between the two treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks vs insulin lispro 25% and insulin lispro protamine 75% administered via proprietary pen for 12 weeks	treated with insulin with HbA_{1c} <12.0%, baseline HbA_{1c} for the whole sample size was 8.5%		Secondary: Patient satisfaction with the pen devices	Secondary: Significantly more patients preferred the insulin aspart pen device compared to the insulin lispro pen device (P<0.005). The incidence of reported adverse events was similar between treatment groups.
Dailey et al[39] Insulin glulisine before meals BID (AM and PM) and NPH insulin BID vs regular insulin before meals BID (AM and PM) and NPH insulin BID Insulin doses were adjusted to achieve PPG 120 to 160 mg/dL.	MC, OL, PG, RCT Patients with type 2 diabetes on continuous insulin therapy for ≥6 months, baseline HbA_{1c} 7.58% for insulin glulisine and 7.52% for REG	N=876 26 weeks	Primary: Effect on HbA_{1c}, rate of hypoglycemia, effect on self-monitored blood glucose and insulin dose Secondary: Not reported	Primary: There was a small, but significantly greater decrease in HbA_{1c} observed in the insulin glulisine group compared to the REG group (-0.46 vs -0.30%; P=0.0029). No significant differences were observed in either group in the incidence of hypoglycemia. Significantly lower two-hour PPG (breakfast and dinner) was observed in the insulin glulisine group compared to the REG group (P<0.05). There was no significant difference in total daily insulin doses between the two treatment groups throughout the study. Secondary: Not reported
Rayman et al[40] Insulin glulisine and NPH insulin BID, in addition to current oral antidiabetic agents vs	MC, MN, OL, PG, RCT Patients aged ≥18 years of age with type 2 diabetes on >6 months of continuous	N=892 26 weeks	Primary: Change in HbA_{1c}, adverse events Secondary: Difference in the change of HbA_{1c} at 12 and 26 weeks between	Primary: HbA_{1c} decreased from baseline to study endpoint in both the insulin glulisine and REG groups. HbA_{1c} in the insulin glulisine group decreased from 7.58±0.90% to 7.25±0.95% and from 7.50±0.89% to 7.19±0.90% in the REG group (P value not reported). No difference between groups was seen in the proportion of patients achieving HbA_{1c} levels ≤7.0% (P=0.8962). There was no between-treatment difference in the frequency and type of treatment emergent adverse events observed (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Regular insulin and NPH insulin BID, in addition to current oral antidiabetic agents Insulin glulisine and regular doses were adjusted to achieve target PPG 120 to 160 mg/dL. NPH insulin was titrated to achieve FPG 90 to 120 mg/dL.	insulin treatment prior to study entry, HbA_{1c} 6.0 to 11.0%, ability and willingness for self monitoring of blood glucose		insulin glulisine and REG, self-monitored seven-point blood glucose profile, symptomatic hypoglycemia, insulin dose	Secondary: There was no between-treatment difference in change in HbA_{1c} for insulin glulisine and REG at 12 weeks and study endpoint (P=0.3573 and P=0.5726, respectively). At study endpoint, glucose values were significantly lower two hours postbreakfast with insulin glulisine compared to REG (P<0.001). There were no noteworthy differences between both treatment groups in the frequencies and monthly rates of all symptomatic hypoglycemia. However, the frequencies and monthly rates of severe symptomatic hypoglycemia were lower in the insulin glulisine group than the REG group. Patients taking insulin glulisine also had fewer reports of nocturnal symptomatic hypoglycemia from month four to treatment end compared to patients taking REG (P=0.029). In terms of insulin doses, there was a larger increase in the short-acting dose with REG than with insulin glulisine (adjusted mean, 4.47 vs 2.95 U, respectively; P=0.0645). Overall, the total daily insulin dose increased slightly more with REG. However, the difference was not significant (P=0.1727).
Rosenstock et al[41] Basal bolus therapy (BBT) (premeal insulin lispro and insulin glargine HS) vs premeal premixed therapy (PPT) (lispro mix 50/50 TID)	MC, NI, OL, RCT Patients with type 2 diabetes	N=374 24 weeks	Primary: HbA_{1c}, percentage of patients achieving HbA_{1c} <7.0%, hypoglycemia Secondary: Not reported	Primary: HbA_{1c} was reduced significantly from baseline in both treatment groups (P<0.0001). At 24 weeks, HbA_{1c} was lower with basal bolus therapy compared to premeal premixed therapy (6.78 vs 6.95%, respectively; P=0.021). The difference between treatment groups was -0.22% (90% CI, -0.38 to -0.07; P value not reported). The percentage of patients achieving an HbA_{1c} <7.0% was 54 vs 69% in the premeal premixed therapy and basal bolus therapy groups, respectively (P=0.009). Rates of hypoglycemia were similar between both treatment groups. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Rapid-Acting and Short-Acting Insulin: Type 1 and Type 2 Diabetes Mellitus				
Vignati et al[42] Insulin lispro and NPH insulin BID before meals for 2 months vs regular insulin and NPH insulin BID before meals for 2 months Doses of both regimens were adjusted to achieve 2-hour postprandial serum glucose ≤160.2 mg/dL and fasting serum glucose ≤140.0 mg/dL.	MC, OL, RCT, XO Patients with type 1 diabetes and type 2 diabetes previously treated with REG and NPH, baseline HbA_{1c} 8.0% for both groups in patients with type 1 diabetes and 8.1% for both groups in patients with type 2 diabetes	N=707 4 months	Primary: Effect on HbA_{1c}, pre-prandial glucose levels, PPG levels and frequency of hypoglycemia, and insulin dose Secondary: Not reported	Primary: There was no significant difference in HbA_{1c} reduction between the two treatment groups (P>0.648). Pre-prandial glucose levels did not differ significantly between the two treatment groups for any meal (P≥0.066) or at bedtime (P>0.404). PPG was significantly lower with insulin lispro compared to REG for the morning meal (8.6 vs 9.8 mmol/L; P<0.001) and the evening meal (8.6 vs 9.6 mmol/L; P<0.005) for type 1 diabetics. No significant difference was noted in the noon meal. PPG was significantly lower with insulin lispro compared to REG in the morning meal only in type 2 diabetics (9.5 vs 10.4 mmol/L; P<0.001). There was no significant difference in hypoglycemic events between the two treatment groups (P=0.677 for type 1 diabetics and P=0.419 for type 2 diabetics). Endpoint insulin dose was significantly higher with insulin lispro compared to regular human insulin in type 1 diabetics albeit the difference was small (0.63 vs 0.60 U/kg; P=0.015). There were no significant differences in insulin doses in type 2 diabetics. Secondary: Not reported
Anderson et al[43] Insulin lispro before meals and basal insulin vs	MC, OL, RCT Patients with type 1 diabetes and type 2 diabetes previously	N=631 12 months	Primary: Effect on HbA_{1c}, postprandial rise in serum glucose, frequency of hypoglycemia,	Primary: HbA_{1c} was significantly lower with insulin lispro compared to REG in type 1 diabetics (8.1 vs 8.3%; P<0.05). There was no difference in HbA_{1c} between treatment groups for type 2 diabetics. Postprandial (two-hour) serum glucose rise was significantly reduced with insulin lispro compared to REG in type 1 diabetics (64%; P=0.007) and type 2

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
regular insulin before meals and basal insulin	treated with REG, baseline HbA_{1c} 8.2% for both groups in patients with type 1 diabetes and baseline HbA_{1c} 8.9% for REG and 8.7% for insulin aspart		and insulin dose Secondary: Not reported	diabetics (48%; P=0.004). There was no difference in rates of hypoglycemia between the two treatment groups. There was a small, but significant reduction in premeal insulin dose in the insulin lispro group (-0.03 U/kg; P=0.004) but a small and significant increase in the basal insulin dose (0.05 U/kg; P<0.001) in type 1 diabetics. There were no dose changes in the REG group. For type 2 diabetics, the daily dose increase of insulin was comparable between the treatment groups. Secondary: Not reported
Plank et al[44] Short-acting insulin analogs (insulin lispro and/or insulin aspart) vs regular insulin	MA Analysis of 42 randomized trials that compared short-acting insulin analogs vs REG in the treatment of type 1 diabetes and type 2 diabetes patients	N=7,933 Duration varied	Primary: Effect on HbA_{1c} and number of hypoglycemic episodes Secondary: Quality of life, pregnancy outcomes, and adverse events	Primary: A small but significant difference in HbA_{1c} was observed with short-acting insulin analogs compared to REG in type 1 diabetes (-0.12%; 95% CI, -0.17 to -0.07). No significant differences in HbA_{1c} were observed with short-acting insulin analogs compared to REG in patients with type 2 diabetes (-0.02%; 95% CI, -0.10 to 0.07). No significant differences in hypoglycemic rates were observed with short-acting insulin analogs compared to REG in type 1 diabetic patients (-0.05 episodes/patient/month; 95% CI, -0.22 to 0.11). No significant differences in hypoglycemic rates were observed with short-acting insulin analogs compared to REG in patients with type 2 diabetes (-0.04 episodes/patient/month; 95% CI, -0.12 to 0.04). Secondary: Quality of life reported in type 1 diabetes favored short-acting insulin analogs in four studies and found no difference in three studies. No significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				difference in quality of life was reported in studies with type 2 diabetics (two studies total). There were no significant differences in maternal or fetal outcomes between the two insulin groups. Comparable incidence and type of adverse events were reported for both insulin groups.
Siebenhofer et al[45] Rapid-acting insulin analogs (insulin lispro, insulin aspart, insulin glulisine) vs regular insulin	MA Analysis of 49 randomized trials that compared rapid-acting insulin analogs to REG in patients with type 1 diabetes and type 2 diabetes	N=8,274 Duration varied	Primary: HbA_{1c}, hypoglycemia Secondary: Adverse events	Primary: In patients with type 1 diabetes, the WMD in HbA_{1c} was estimated to be -0.1% (95% CI, -0.2 to -0.1; P=0.01) in favor of insulin analogs compared to REG. In the subgroup analyses, results were divided into patients taking continuous SC insulin injections and patients taking conventional intensified insulin therapy. In patients taking continuous SC insulin therapy compared to REG, the WMD in HbA_{1c} was -0.2 (95% CI, -0.3 to -0.1; P value not reported) and in patients taking intensified insulin therapy compared to REG, the WMD was -0.1% (95% CI, -0.1 to 0.0; P value not reported). In patients with type 2 diabetes, the WMD of HbA_{1c} was estimated to be 0.0% (95% CI, -0.1 to 0.0). None of the studies evaluating differences in HbA_{1c} between insulin analogs and REG showed significant differences (P values not reported). In children, adolescents, pregnant patients with type 1 diabetes, there were no significant reductions in HbA_{1c} (P values were not reported). The WMD in overall hypoglycemia in patients with type 1 diabetes was -0.2 (95% CI, -1.1 to 0.7; P value not reported) for insulin analogs compared to REG. In patients with type 2 diabetes, the WMD was -0.2 (95% CI, -0.5 to 0.1; P=0.8). There were also no significant differences in overall hypoglycemia in pre-pubertal children. There were no statistically significant differences in these three groups. However, in the event rate of overall hypoglycemia in adolescents per patient per 30 days was significantly reduced with insulin analogs compared to REG (P=0.02). The event rate in pregnant women was significantly higher with insulin analogs compared to REG (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Overall, frequency and type of adverse events were comparable for the two treatment groups (P values not reported).
Intermediate-Acting and Long-Acting Insulins: Type 1 Diabetes Mellitus				
Pieber et al[46] Insulin detemir BID (AM and HS) and insulin aspart before meals vs insulin glargine at bedtime and insulin aspart before meals Insulin doses were titrated to achieve a target of ≤7.3 mmol/L for pre-breakfast and pre-evening meal plasma glucose for insulin detemir and pre-breakfast plasma glucose for insulin glargine.	OL, PG, RCT Men and women 18 years of age or older with type 1 diabetes for at least 1 year who had a BMI ≤35 kg/m^2 and HbA_{1c} 7.5 to 12.0%	N=322 26 weeks	Primary: Change in HbA_{1c}, change in FPG, hypoglycemia Secondary: Not reported	Primary: At 26 weeks, both groups had comparable changes in HbA_{1c} (between-treatment difference, -0.03; 95% CI, -0.25 to 0.19; P value not reported). However, insulin glargine resulted in significantly lower home measured FPG than insulin detemir (7.0 vs 7.7 mmol/L, respectively; P<0.001). The overall risk of hypoglycemia was comparable in both treatment groups (RR, 0.96; 95% CI, 0.68 to 1.35; P=0.811). However, insulin detemir resulted in lower rates of nocturnal hypoglycemia (episodes/subject-year) than with insulin glargine (4.3 vs 6.6, respectively; P<0.05). Secondary: Not reported
Heller et al[47] Insulin detemir PM or BID (AM and PM) and insulin aspart before meals vs	MC, NI, OL, PG, RCT Patients ≥18 years of age with type 1 diabetes for ≥1 year who were receiving	N=443 52 weeks	Primary: HbA_{1c} at 52 weeks Secondary: Proportion of patients achieving HbA_{1c} ≤7.0% with	Primary: Change in HbA_{1c} from baseline at 52 weeks was -0.53 and -0.54% with insulin detemir and insulin glargine, respectively (mean difference, 0.01%; 95% CI, -0.13 to 0.16), confirming non-inferiority. Patients receiving twice-daily insulin detemir experienced greater HbA_{1c} reduction (-0.58%) compared to those receiving once-daily insulin detemir (-0.49%; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
insulin glargine PM and insulin aspart before meals Basal insulin doses were titrated to achieve PG ≤108 mg/dL. Prandial insulin doses were titrated to achieve PPG ≤162 mg/dL.	basal-bolus insulin regimen for ≥3 months with HbA_{1c} ≤11.0%		or without major hypoglycemia in the last month of treatment, FPG, within-patient variation in self-monitored pre-breakfast and pre-dinner blood glucose, 10-point self-monitored plasma glucose profiles and safety	Secondary: Similar percentage of patients achieved HbA_{1c} ≤7.0% with insulin detemir compared to insulin glargine (33.0 vs 30.4%; P value not significant). The HbA_{1c} goal was achieved without major hypoglycemia during the last month of treatment in 31.9 and 28.9% of patients in the insulin detemir and insulin glargine groups, respectively (P value NS). No significant differences were observed between the two groups with regard to changes in FPG, within-patient variation in self-monitored pre-breakfast and pre-dinner blood glucose and 10-point self-monitored plasma glucose profiles. During the study, 91.6% of patients in the insulin detemir group and 88.2% in the insulin glargine group met the criteria to switch from once- to twice-daily dosing. At the end of the study, 65.8 and 4.8% of patients in the insulin detemir and insulin glargine groups, respectively, were receiving BID dosing. The total basal insulin dose at the end of the study was 0.40 units/kg and 0.33 units/kg with insulin detemir and insulin glargine, respectively. There were no significant differences between the two groups with regard to weight gain and incidence of hypoglycemia. Adverse events were reported in 92.6 and 89.6% of patients in the insulin detemir and insulin glargine groups, respectively. Twelve and one serious adverse events were probably or possibly related to insulin detemir and insulin glargine, respectively. Injection site reactions were reported more frequently with insulin detemir compared to insulin glargine (8.0 vs 1.4%; P value not reported).
Vague et al[48] Insulin detemir BID and insulin aspart before meals vs	MC, OL, PG, RCT Adult type 1 diabetes patients on a basal-bolus insulin regimen	N=448 26 weeks	Primary: Effect on HbA_{1c}, FPG, variability in fasting self monitoring of blood glucose, weight gain, and frequency of	Primary: After six months, both insulin detemir and NPH reduced HbA_{1c} -0.55% (P value NS). After six months, FPG with insulin detemir (9.19 mmol/L) was comparable to NPH (9.94 mmol/L; P=0.097). There was significantly less day-to-day fluctuation of fasting self monitoring of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
NPH insulin BID and insulin aspart before meals Basal insulin doses were adjusted to achieve FBG 72 to 126 mg/dL and PPG <180 mg/dL.	for ≥2 months; baseline HbA_{1c} 8.18% for participants in the insulin detemir group and 8.11% for those randomized into the NPH group		hypoglycemia Secondary: Not reported	blood glucose profiles with insulin detemir when compared to NPH (P<0.001). Body weight change from baseline was significantly lower with insulin detemir (-0.2 kg) compared to NPH (0.7 kg; P<0.001). The RR of hypoglycemia was 22% lower with insulin detemir compared to NPH (P<0.05). The RR of nocturnal hypoglycemia was 34% lower with insulin detemir compared to NPH (P<0.005). Secondary: Not reported
Hermansen et al[49] Insulin detemir BID and insulin aspart before meals vs NPH insulin BID and insulin aspart before meals	OL, RCT Adult type 1 diabetes patients on a basal-bolus insulin regimen for ≥6 months, baseline HbA_{1c} 8.48% for participants in the insulin detemir group and 8.29% for those randomized into the NPH group	N=595 18 weeks	Primary: Effect on HbA_{1c}, FPG, self monitoring of blood glucose profile, weight gain, and frequency of hypoglycemia Secondary: Not reported	Primary: After 18 weeks, HbA_{1c} was significantly lower in the insulin detemir group (7.88%) compared to the NPH group (8.11%; P<0.001). After 18 weeks, there was no significant difference in FPG with insulin detemir (7.58 mmol/L) compared to NPH (8.10 mmol/L; P>0.05). There was significantly less day-to-day fluctuation of self monitoring of blood glucose profiles with insulin detemir when compared to NPH (P<0.05). Body weight change from baseline was significantly lower with insulin detemir (-0.95 kg) compared to NPH (0.07 kg; P<0.001). The risk of hypoglycemia was 21% lower with insulin detemir compared to NPH (P=0.036). The risk of nocturnal hypoglycemia was 55% lower with insulin detemir compared to NPH (P<0.001). Secondary: Not reported
Home et al[50] Insulin detemir every morning (QAM) and at	MC, OL, PG, RCT Men and women	N=409 16 weeks	Primary: Change in HbA_{1c}, change in FPG from	Primary: At 16 weeks, there was no significant difference in HbA_{1c} between all treatment groups (P=0.082). Insulin detemir every 12 hours had a reduction in HbA_{1c} of -0.85%. When dosed every morning and at bedtime, HbA_{1c} was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
bedtime plus premeal insulin aspart vs insulin detemir every 12 hours (Q12H) plus premeal insulin aspart vs NPH insulin BID plus premeal insulin aspart Doses were titrated to achieve target FPG goals 4.0 to 7.0 mmol/L and PPG goals ≤10 mmol/L.	>18 years of age with type 1 diabetes for >1 year already on mealtime plus basal insulin for >2 months, with a basal dose <100 IU/day, HbA_{1c} ≤12.0%, BMI ≤35.5 kg/m^2		baseline Secondary: 10-point self monitoring of blood glucose, frequency of hypoglycemia, weight gain	reduced by -0.82%, whereas, NPH only reduced HbA_{1c} by -0.65%. In combination, both detemir groups resulted in significantly greater reductions in HbA_{1c} than NPH (difference, -0.18%; 95% CI, -0.34 to -0.02; P=0.027). FPG levels were statistically significantly lower in both the detemir every 12 hours (P=0.004) and detemir every morning and at bedtime group (P<0.001) than the NPH group. Differences between the detemir groups did not result in statistical significance. Secondary: Overall 10-point self monitoring of blood glucose profiles were comparable between the three treatment groups (P>0.05). The overall risk of hypoglycemia was significantly lower with insulin detemir every 12 hours (25%; P=0.046) and insulin detemir every morning and at bedtime (32%; P=0.002) compared to NPH. There were no significant differences in risk of nocturnal hypoglycemia between insulin detemir every 12 hours and NPH. However, when dosed every morning and at bedtime, insulin detemir had a significantly lower risk of nocturnal hypoglycemia than NPH (53%; P<0.001). Mean weight change was significantly decreased with insulin detemir every 12 hours (-0.8 kg; P=0.006) and insulin detemir every morning and at bedtime (-0.6 kg; P=0.040) when compared to NPH. However, there was no significant difference in weight change between the insulin detemir groups (P>0.05).
Russell-Jones et al[51] Insulin detemir HS and regular insulin before meals vs NPH insulin HS and	MC, OL, PG, RCT Men and women ≥18 years of age with type 1 diabetes for ≥1 year already on basal or	N=749 6 months	Primary: Change in HbA_{1c} from baseline, change in FPG and fasting self monitoring of blood glucose, nine-point self	Primary: Mean HbA_{1c} value decreased by -0.06% with insulin detemir while HbA_{1c} increased by 0.06% with NPH. However, the baseline-adjusted mean HbA_{1c} values did not significantly differ between groups (-0.12%; 95% CI, -0.25 to 0.02; P=0.083). Both FPG and fasting self monitoring of blood glucose decreased similarly in the insulin detemir group and were slightly decreased with NPH. Both endpoints resulted in significant reductions with insulin detemir in comparison

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
regular insulin before meals Doses were titrated to achieve target FPG goal 72 to 126 mg/dL and PPG goal of 180 mg/dL.	premixed insulin QD in the evening (5 PM to 11 PM) and REG before meals for ≥2 months and HbA_{1c} ≤12.0%		monitoring of blood glucose profile, 24-hour continuous blood glucose monitoring, hypoglycemia, body weight Secondary: Not reported	to NPH (P=0.001 and P<0.001, respectively). Nine-point self monitoring of blood glucose profiles demonstrated significantly lower glucose values before breakfast with insulin detemir when compared to NPH (P<0.001). In study participants that underwent 24-hour continuous blood glucose monitoring, insulin detemir had significantly less blood glucose fluctuations for mean levels nocturnally and over 24 hours (P<0.05). Overall rates of hypoglycemia were comparable between groups. However, the RR of nocturnal hypoglycemia was 26% lower with insulin detemir compared to NPH (P=0.003). There was also a 30% risk reduction of minor hypoglycemic episodes during the night with insulin detemir (P=0.003). Body weight gain was significantly lower with insulin detemir compared to NPH (-0.54 kg; P=0.024). Secondary: Not reported
Standl et al[52] Insulin detemir BID and regular insulin before meals vs NPH insulin BID and regular insulin before meals Basal insulin doses were adjusted to achieve FPG 4.0 to 7.0	ES, MC, OL, PG, RCT Adult patients with type 1 diabetes on a basal-bolus insulin regimen for ≥2 months, baseline HbA_{1c} 7.72% for participants taking insulin detemir and 7.66% for those	N=421 (n=289 in the 6 month extension trial) 12 months (6-month treatment period and 6-month extension trial)	Primary: Effect on HbA_{1c}, FPG, nine-point self monitoring of blood glucose profile, weight gain, and frequency of hypoglycemia Secondary: Not reported	Primary: After 12 months, HbA_{1c} was comparable between the insulin detemir group (7.88%) and the NPH group (7.78%; P=0.288). After 12 months, there was no significant difference in FPG with insulin detemir (10.1 mmol/L) compared to NPH (9.84 mmol/L; P=0.665). Mean nine-point self monitoring of blood glucose profiles showed significantly lower blood glucose 90-minutes after lunch and dinner (P<0.05). There were no significant differences at other times in the profile. After 12 months, body weight change from baseline was significantly lower with insulin detemir (-1.44 kg) compared to NPH (0.3 kg; P<0.001). There was no significant difference in the overall risk of hypoglycemia

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mmol/L (72 to 126 mg/dL) and PPG <10 mmol/L (180 mg/dL).	randomized into the NPH group			between insulin detemir and NPH (P=0.139). There was no significant difference in the risk of nocturnal hypoglycemia between insulin detemir and NPH (P=0.067). Secondary: Not reported
De Leeuw et al[53] Insulin detemir BID and insulin aspart before meals vs NPH insulin BID and insulin aspart before meals Basal insulin doses were adjusted to achieve FBG 72 to 126 mg/dL and PPG <180 mg/dL.	ES, MC, OL, PG, RCT Adult type 1 diabetes patients on a basal-bolus insulin regimen for ≥2 months, baseline HbA_{1c} 8.18% for participants in the insulin detemir group and 8.03% for those randomized into the NPH group	N=316 12 months (6-month treatment period and 6-month extension period)	Primary: Effect on HbA_{1c}, FPG, nine-point self monitoring of blood glucose, frequency of hypoglycemia, and weight gain Secondary: Not reported	Primary: Similar reductions in mean HbA_{1c} values were observed in both treatment groups. After 12 months, insulin detemir reduced HbA_{1c} -0.64% and NPH reduced HbA_{1c} -0.56% (P value was not reported). After 12 months, FPG with insulin detemir (10.7 mmol/L) was comparable to NPH (10.8 mmol/L; P value not reported). Nine-point self monitoring of blood glucose profiles were comparable between insulin detemir when compared to NPH (value not reported; P<0.24). There were no significant differences in overall rates of hypoglycemia between treatment groups. The RR of nocturnal hypoglycemia was 32% lower with insulin detemir when compared to NPH (P=0.016). After 12 months, body weight gain was significantly lower with insulin detemir compared to NPH (-1.34 kg; P<0.001). Secondary: Not reported
Pieber et al[54] Insulin detemir BID (AM and PM) and insulin aspart before meals vs	MC, OL, PG, RCT Adult type 1 diabetes patients on a basal-bolus insulin regimen	N=400 16 weeks	Primary: Effect on HbA_{1c} and FPG Secondary: Variability in fasting self monitoring of	Primary: HbA_{1c} was significantly reduced in all three groups. Insulin detemir dosed in the morning and at dinner reduced HbA_{1c} -0.43%. When dosed in the morning and at bedtime, HbA_{1c} was reduced -0.49%. NPH reduced HbA_{1c} -0.39%. There was no significant difference between the groups (P=0.64). FPG reductions were significantly greater with insulin detemir dosed in the morning and dinner (-0.17 mmol/L; P<0.001) and insulin detemir dosed in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
insulin detemir BID (AM and HS) and insulin aspart before meals vs NPH insulin BID (AM and HS) and insulin aspart before meals Basal insulin doses were adjusted to achieve FBG 72 to 126 mg/dL and PPG <180 mg/dL.	for ≥2 months; baseline HbA_{1c} 8.01% for participants taking insulin detemir every morning and at dinner, 8.13% for those taking insulin detemir every morning and at bedtime, and 8.08% for those randomized into the NPH group		blood glucose, 10-point self monitoring of blood glucose, 24-hour glucose profile, frequency of hypoglycemia, and weight gain	morning and bedtime (-1.48 mmol/L; P<0.006) when compared to NPH (0.49 mmol/L). There was no significant difference in FPG between the insulin detemir groups (P=0.15). Secondary: Within-person variation in fasting self monitoring of blood glucose was significantly lower with either insulin detemir treatments compared to NPH (P<0.001). There was no significant difference in fasting self monitoring of blood glucose between the insulin detemir groups (P=0.48). Overall 10-point self monitoring of blood glucose profiles were comparable between the three groups (P=0.103). Twenty four-hour glucose profiles demonstrated lower glucose fluctuations with both insulin detemir treatments compared to NPH (P=0.049). Overall and nocturnal rates of hypoglycemia were comparable between all groups. Mean weight changes were significantly different with detemir dosed in the morning and dinner (-0.6 kg; P<0.001) and insulin detemir dosed in the morning and bedtime (0.1 kg; P=0.050) when compared to NPH (0.7 kg).
Kølendorf et al[55] Insulin detemir BID and insulin aspart before meals for 16 weeks vs NPH insulin BID and insulin aspart before meals for 16 weeks	OL, RCT, XO Adult type 1 diabetes patients on a basal-bolus insulin regimen for >4 months, baseline HbA_{1c} 7.9% for participants receiving insulin detemir first and	N=130 32 weeks	Primary: Incidence of self-recorded hypoglycemia Secondary: Incidence of severe hypoglycemic episodes, effect on HbA_{1c} and self monitoring plasma glucose	Primary: The RR of hypoglycemia was 18% lower with insulin detemir compared to NPH (P=0.001). The RR of nocturnal hypoglycemia was 50% lower with insulin detemir compared to NPH (P<0.0001). Secondary: There were 19 severe hypoglycemic episodes with insulin detemir and 33 episodes with NPH; however, due to the low number of episodes an analysis could not be conducted. HbA_{1c} was reduced by approximately -0.3% in both treatment arms (P value was not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	7.9% for those receiving NPH first			There was significantly less day-to-day fluctuation of self-monitored plasma glucose profiles with insulin detemir when compared to NPH (P<0.001).
Robertson et al[56] Insulin detemir HS or BID (AM and HS) and insulin aspart before meals vs NPH insulin QD or BID and insulin aspart before meals Insulin aspart doses were titrated to achieve PPG 121 to 182 mg/dL.	OL, PG, RCT Children 6 to 17 years of age with type 1 diabetes, treated with insulin for at least 12 months (total daily dose ≤2 U/kg), and HbA_{1c} ≤12.0%	N=347 26 weeks	Primary: HbA_{1c} and eight-point plasma glucose profiles assessed at 18 and 26 weeks, self-measured FPG on four days after 18 and 26 weeks Secondary: Hypoglycemia	Primary: HbA_{1c} at 26 weeks decreased by approximately -0.8% in both the insulin detemir and NPH groups (8.0 vs 7.9%, respectively; 95% CI, -0.1 to 0.3; P value not reported). The mean eight-point plasma glucose profiles after 26 weeks were assumed parallel and did not have a statistically significant difference between insulin detemir and NPH (P=0.302). Plasma glucose levels were lower with insulin detemir than NPH at all time points except at 03.00 hour. However, the analysis of self-measured nocturnal plasma glucose at 03.00 hour did not show a statistical difference between treatments (P=0.194). Mean self-measured FPG after 26 weeks was lower with insulin detemir than with NPH (P=0.022). Within-subject FPG variation also showed lower FPG levels with insulin detemir than NPH (P<0.001). Secondary: The study determined that the risk of having nocturnal hypoglycemia was 26% lower with insulin detemir (P=0.041). However, the risks of 24-hour and diurnal hypoglycemia were similar in both groups (P=0.351 and P=0.492, respectively). Also, the risks of having severe episodes, confirmed episodes or symptoms of hypoglycemia were similar in both groups (P=0.799, P=0.275, and P=0.425, respectively).
Bartley et al[57] Insulin detemir PM or BID and insulin aspart before meals vs	OL, PG, RCT Patients ≥18 years of age with type 1 diabetes, HbA_{1c} ≤11.0%, BMI ≤35.0 kg/m^2, and receiving a	N=497 24 months	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, proportion of	Primary: Insulin detemir resulted in significantly greater decreases in HbA_{1c} compared to NPH (final HbA_{1c}, 7.36 vs 7.50%; decrease, -0.94 vs -0.72%; difference, -0.22%; 95% CI, -0.41 to -0.03). Secondary: Insulin detemir significantly decreased FPG compared to NPH (final FPG, 8.35 vs 9.43 mmol/L; P=0.019).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
NPH insulin PM or BID and insulin aspart before meals Insulin doses were titrated to achieve plasma glucose target ≤6.0 mmol/l before breakfast and dinner.	basal-bolus insulin regimen ≥3 months		patients achieving HbA_{1c} ≤7.0% without hypoglycemia, incidence in hypoglycemia, change in baseline body weight, safety	Significantly more patients receiving insulin detemir achieved HbA_{1c} ≤7.0% without hypoglycemia compared to patients receiving NPH (22 vs 13%; P=0.019). The risk of major and nocturnal hypoglycemia was significantly lower with insulin detemir (P<0.001). Specifically, insulin detemir was associated with a 69 and 49% lower risk of major and nocturnal hypoglycemia. Insulin detemir resulted in significantly less weight gain compared to NPH (1.7 vs 2.7 kg; P=0.024). The overall safety prolife was similar between the two treatments. Four deaths were reported with insulin detemir (cardiorespiratory arrest in relation to status epilepticus, sudden death, bronchopneumonia, and MI following surgery). All events were judged to not be related to insulin detemir. Withdrawals due to adverse events were more common with insulin detemir.
Ratner et al[58] Insulin glargine HS vs NPH insulin HS or BID (AM and HS) Doses of both insulins were titrated to achieve preprandial blood glucose 4.4 to 6.7 mmol/L.	PG, RCT Type 1 diabetes patients, baseline HbA_{1c} 7.7% in both groups	N=534 28 weeks	Primary: Effect on HbA_{1c}, FPG, and incidence of hypoglycemia Secondary: Not reported	Primary: Reduction in HbA_{1c} was similar with NPH (-0.21%) and insulin glargine (-0.16%; P=0.4408). Reduction in FPG was similar with NPH (-0.94 mmol/L) and insulin glargine (-1.12 mmol/L; P=0.3546). After the one month titration phase, significantly less patients on insulin glargine reported symptomatic hypoglycemia (39.9 vs 49.2%; P=0.0219) or nocturnal hypoglycemia (18.2 vs 27.1%; P=0.0116). Overall incidence of all symptomatic hypoglycemia was similar between treatment groups throughout the study. Secondary: Not reported
Tan et al[59]	RETRO	N=71	Primary: Change in HbA_{1c},	Primary: There was no difference in HbA_{1c} between baseline and six months after

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Analysis was on data 6 months prior to initiating insulin glargine therapy and data 6 months after initiating insulin glargine therapy. Patients were divided into those taking insulin glargine only and those taking insulin glargine plus NPH insulin in the AM.	Patients ≤18 years of age with type 1 diabetes when initiating insulin glargine therapy between June 1, 2001 and June 30, 2002, not using continuous SC insulin infusion or inhaled insulin before starting insulin glargine therapy	12 months	blood glucose concentrations, hypoglycemia (number of self-reported symptomatic hypoglycemia and number of blood glucose readings <50 mg/dL) Secondary: Not reported	initiating insulin glargine therapy (8.9±1.6% and 8.9±1.5%, respectively). In the divided groups, there was no statistical difference in the change in HbA_{1c} between patients taking insulin glargine only vs patients taking insulin glargine plus NPH (P value not reported). Mean blood glucose concentrations decreased slightly after initiating insulin glargine in all subjects. Patients taking insulin glargine plus NPH had slight improvements in average blood glucose levels, whereas patients taking insulin glargine only had a slight deterioration and a slight rise in average blood glucose levels. All changes were not statistically significant (P values not reported). There was a decrease in self-reported episodes of symptomatic hypoglycemia after initiating insulin glargine therapy. However, there was no difference between baseline and after starting insulin glargine therapy in the frequency of blood glucose values <50 mg/dL (P value not reported). Secondary: Not reported
Ashwell et al[60] Insulin glargine HS and insulin lispro before meals for 16 weeks vs NPH insulin QD or BID and regular insulin before meals for 16 weeks Doses were adjusted to achieve target pre-breakfast, preprandial, and postprandial levels of	MC, RCT, 2-way, XO Patients aged 18 to 65 years of age with type 1 diabetes, no previous experience with insulin glargine, previously on a multiple insulin injection regimen for at least 1 year, random C-peptide ≤0.10 nmol/L,	N=56 32 weeks	Primary: HbA_{1c} at treatment endpoints Secondary: Prebreakfast self monitoring of blood glucose concentration, 24-hour eight-point self monitoring of blood glucose levels, 24-hour inpatient plasma glucose levels,	Primary: At 16 weeks, HbA_{1c} was lower with insulin glargine compared to NPH (between treatment difference, -0.5; 95% CI, -0.7 to -0.3; P<0.001). Secondary: Prebreakfast self monitoring of blood glucose concentration was lower in the insulin glargine group than the NPH group (between treatment difference, -1.5; 95% CI, -2.6 to -0.5; P<0.005). Self monitoring of blood glucose concentrations were lower before and after breakfast with insulin glargine compared to NPH. The 24-hour eight-point self monitoring of blood glucose concentrations was also lower with insulin glargine (between treatment difference, -1.9; 95% CI, -3.1 to -0.8; P=0.001). During the inpatient assessment, 24-hour eight-point self monitoring of blood glucose levels were lower at all points with insulin glargine compared to NPH

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
4.0 to 6.5 mmol/L, in the absence of hypoglycemia.	HbA_{1c} 7.0 to 9.5%		monthly rate of hypoglycemia	(P=0.037 for plasma glucose AUC; P=0.002 for PPG AUC; P=0.038 for plasma glucose before breakfast). Seventy-two percent of patients taking insulin glargine reported nocturnal hypoglycemia compared to 83% of patients taking NPH. This resulted in a -44% reduction in the monthly rate of nocturnal hypoglycemia with insulin glargine compared to NPH (P<0.001).
Herwig et al[61] Insulin glargine QD and regular insulin or insulin lispro before meals vs NPH insulin QD to TID and regular insulin or insulin lispro before meals Doses of insulin glargine were titrated to achieve target FBG 4.4 to 7.8 mmol/L and doses of NPH insulin were titrated to achieve target FBG 4.4 to 8.9 mmol/L.	OL Pediatric patients with type 1 diabetes for >1 year duration	N=142 20±10 months	Primary: HbA_{1c}, hypoglycemia Secondary: Not reported	Primary: HbA_{1c} significantly increased from 7.3±1.0% to 7.6±1.1% (P=0.003) and from 7.7±1.6% to 8.3±1.5% (P=0.0001) in both the insulin glargine and NPH groups. The incidence of symptomatic hypoglycemia was comparable between both groups; however, the overall incidence of severe hypoglycemia was significantly lower in the insulin glargine group (P=0.002). Secondary: Not reported
Kudva et al[62] Insulin glargine and insulin aspart before meals vs	RCT, XO Patients with median age of 43 years with type 1 diabetes	N=22 16 weeks	Primary: Hypoglycemia Secondary: Not reported	Primary: Measures of glycemic variation did not differ significantly between insulin glargine and ultralente insulin. In the insulin glargine group, the standard deviation of blood glucose showed a tendency to be lower and the standard deviation of nocturnal blood glucose concentrations was significantly lower. However, glucose concentrations were significantly lower during the one hour before and three hours after lunch with ultralente insulin.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ultralente insulin and insulin aspart before meals				Secondary: Not reported
Chatterjee et al[63] Insulin glargine QD and insulin aspart before meals for 16 weeks vs NPH insulin BID and insulin aspart before meals for 16 weeks	OL, RCT, XO Patients 18 to 75 years of age with type 1 diabetes for at least 6 months on either BID or multiple dose insulin injections, BMI <45 kg/m^2, HbA_{1c} 6.0 to 11.0%	N=60 36 weeks	Primary: Change in HbA_{1c} Secondary: Frequency of overall hypoglycemic episodes, change in FPG, body weight, lipid profile	Primary: At 36 weeks, treatment with insulin glargine resulted in lower HbA_{1c} levels compared to NPH (between-treatment difference, -0.19±0.09; 95% CI, -0.36 to 0.01; P=0.04). At the end of the second treatment period, those patients switching from glargine to NPH experienced an increase in HbA_{1c} of 0.16%, whereas those who switched from NPH to glargine experienced a reduction of -0.1%. Secondary: Both groups had similar mean incidences of overall hypoglycemic episodes (between-treatment difference, 1.21; 95% CI, 0.56 to 2.64; P=0.63). The OR for the incidence of hypoglycemia compared in both groups was 1.2 (95% CI, 0.55 to 2.59; P value not reported). FPG was also lower with insulin glargine vs NPH (between-treatment difference, -3.00; 95% CI, -4.80 to -1.20; P<0.01). There was no significant difference in change in body weight between both groups (mean difference, -0.24; 95% CI, -0.87 to 0.39; P=0.45). Similarly, there was no difference in TC or TG levels between groups (P value not reported).
Manini et al[64] Insulin glargine vs intensive insulin treatment (NPH)	RCT Patients with a mean age of 46 years with type 1 diabetes for at least 1 year duration and suboptimal glucose control	N=47 8 months	Primary: Change in HbA_{1c}, health-related quality of life Secondary: Not reported	Primary: Insulin glargine resulted in a mean HbA_{1c} decrease of -0.7% from baseline (P<0.0001). Insulin glargine also resulted in improved health-related quality of life scores using a Well-being Enquiry for Diabetics questionnaire. The results showed improvements in discomfort (P=0.020), impact (P=0.0002), and total score (P=0.0005). The questionnaire score changes were also associated with a lower perceived risk of hypoglycemia and fewer daily-life associated issues with insulin glargine.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	under intensive insulin treatment			Secondary: Not reported
Rosenstock et al[65] Insulin glargine HS (containing 30 µg/mL zinc chloride) vs insulin glargine HS (containing 80 µg/mL zinc chloride) vs NPH insulin HS or BID	DB, MC, PG, RCT Patients with type 1 diabetes on basal-bolus multiple daily insulin regimen for at least 2 months, 18 to 70 years of age, had BMI 18 to 28 kg/m^2, HbA_{1c} <10.0%, postprandial serum C-peptide <0.2 pmol/mL	N=256 4 weeks	Primary: FPG at study end point calculated as the mean of three FPG values on days 27, 28 and 29 Secondary: Change from baseline in overnight plasma glucose, mean FPG, blood glucose profile, nocturnal blood glucose, stability of FPG, $HbA_{1c,}$, safety and adverse events	Primary: Adjusted mean FPG at end point was 9.2 mmol/L for the pooled insulin glargine groups and 11.3 mmol/L for the NPH group (P=0.001). Secondary: The adjusted mean overnight plasma glucose levels after 5 AM were 7.8 mmol/L for insulin glargine 30, 7.3 mmol/L for insulin glargine 80, and 10.7 mmol/L for NPH (P values not reported). At the end of the study, the mean standard deviations for FPG were 7.6±2.3 and 7.5±1.9 mmol/L for the insulin glargine 30 and insulin glargine 80 groups, respectively, and 9.0±2.4 mmol/L for the NPH group (P<0.001). Blood glucose profile determined from seven self monitoring of blood glucose values during the day was not different among the treatment group (P value not reported). Nocturnal blood glucose measured by self monitoring of blood glucose at 3 AM was higher in the insulin glargine group than in the NPH group (P value not reported). Stability of FPG was significantly lower in patients receiving insulin glargine 30 compared to patients receiving NPH (P<0.05). The mean standard deviation for HbA_{1c} levels were -0.40±0.48 and -0.40±-0.49 in the insulin glargine 30 and insulin glargine 80 groups, respectively, and -0.40±0.48 in the NPH group (P value not reported). Fewer patients receiving NPH (93.2%) reported a hypoglycemic episode than patients receiving insulin glargine (97.6 and 100% for insulin glargine 30 and insulin glargine 80, respectively; P=0.03). All events were considered mild and none resulted in discontinuation from study treatment.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Insulin glargine was as safe as NPH with no differences between treatments with regard to the incidence of adverse effects, including the most frequent event, injection site reactions.
Rossetti et al[66] Insulin glargine PM and insulin lispro before meals vs insulin glargine HS and insulin lispro before meals vs NPH insulin QD and insulin lispro before meals Glycemic targets were blood glucose 6.4 to 7.2 mmol/L in the fasting state, before meals, and at bedtime and blood glucose at 8.0 to 9.2 mmol/L 90 minutes after meals.	RCT Patients with type 1 diabetes and fasting plasma C-peptide ≤0.15 nmol/L on intensified treatment with multiple daily combinations of lispro and NPH at each meal and NPH at bedtime	N=51 12 weeks	Primary: HbA_{1c} level Secondary: Blood glucose profile from home blood glucose monitoring, hypoglycemia	Primary: In patients taking NPH, HbA_{1c} increased slightly from baseline, but was not statistically significant. However, HbA_{1c} decreased both with the dinnertime as well as the bedtime dose of insulin glargine (P<0.04). There was no significant difference in the change of HbA_{1c} in both insulin glargine groups (P value NS). Secondary: Patients taking insulin glargine had lower blood glucose concentrations in the fasting state, after breakfast, before lunch, and after lunch (P<0.05). The before-dinner blood glucose with NPH and insulin glargine at dinnertime was similar (P value NS), but was lower with insulin glargine at bedtime (P<0.05). The after-dinner blood glucose was lower with insulin glargine at dinner-time and bedtime than with NPH (P<0.05). However, the bedtime blood glucose was not different with all three treatment groups (P value NS). The frequency of mild hypoglycemia was lower in patients taking insulin glargine than in patients taking NPH (P<0.005). There was no difference between the insulin glargine at dinnertime and insulin glargine at bedtime groups (P value NS). Patients taking insulin glargine had a lower frequency of nocturnal hypoglycemic episodes than patients taking NPH (P<0.05). There were no differences between both insulin glargine groups (P value NS).
Pesić et al[67] Insulin glargine QD and insulin aspart before meals	RCT Patients with type 1 diabetes on long-term	N=48 12 weeks	Primary: Change in FPG, change in HbA_{1c} Secondary:	Primary: FPG was lower in the glargine group in comparison to the NPH BID group (7.30 vs 7.47 mmol/L, respectively), but this difference was not significant. FPG levels for the NPH-at-bedtime group were reported as significantly higher compared to either of the other two groups (8.44 mmol/L; P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs NPH insulin HS and insulin aspart before meals vs NPH insulin BID and insulin aspart before meals	conventional insulin therapy		Frequency of hypoglycemia	At 12 weeks, HbA_{1c} decreased in both the NPH BID (from 7.80±0.83% to 7.01±0.63%) and insulin glargine groups (from 7.72±0.86% to 6.87±0.50%). However, there was no change in HbA_{1c} in the NPH-at-bedtime group. Secondary: A lower frequency of mild hypoglycemic episodes was observed in the insulin glargine group compared to both NPH groups (P<0.05).
Dundar et al[68] NPH QD vs insulin detemir QD vs insulin glargine QD All patients received NPH insulin for ≥6 months before transitioning to either insulin detemir or insulin glargine at a dose that was 40 to 45% of total daily NPH insulin dose, in addition to insulin aspart TID at the same	RETRO, XO Pediatric and adolescent patients with a mean age of 12.7±3.4 years, with type 1 diabetes for 5.4±3.0 years who were receiving NPH insulin daily and insulin aspart three times daily for ≥6 months	N=34 12 months (6 months of NPH, followed by 6 months of insulin detemir or insulin glargine)	Primary: Mean total daily insulin dose, mean FPG, numbers of severe and nocturnal hypoglycemia, mean HbA_{1c}, BMI SDS and safety Secondary: Not reported	Primary: Total daily insulin doses were similar among all three insulin groups (P>0.05 for all comparisons). No significant difference was seen in mean FPG between NPH and both long-acting insulins combined (P>0.05). Incidence of severe hypoglycemia with NPH was similar compared to insulin detemir and insulin glargine (P>0.05). Eight episodes of nocturnal hypoglycemia was reported in four patients during NPH treatment compared to three episodes reported in three patients in both long-acting insulin groups combined (P>0.05). Mean HbA_{1c} was significantly lower with insulin glargine and insulin detemir compared to NPH (P<0.05 for both). No significant difference was seen between insulin glargine and insulin detemir. The increase in BMI SDS was significantly lower with insulin detemir compared to the increase seen with NPH and insulin glargine (P<0.05 for both). No difference was noted between NPH and insulin glargine. No adverse events were reported during treatment with insulin glargine and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
doses.				insulin detemir. Secondary: Not reported
Chase et al[69] Insulin glargine AM and insulin lispro before meals vs NPH or Lente insulin BID (AM and PM) and insulin lispro before meals Basal insulin doses were titrated to achieve FPG 70 to 100 mg/dL.	AC, OL, PG, RCT Patients 9 to 17 years of age with type 1 diabetes with HbA_{1c} ≥7.0 to ≤9.5%, and receiving any daily insulin regimen consisting of ≥2 injections or a continuous infusion	N=175 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Incidence of hypoglycemia, safety	Primary: There was no difference in the decrease in HbA_{1c} with insulin glargine (-0.25%) and NHP (0.05%; P=0.1725). However, it was reported that the decrease in HbA_{1c} was significantly greater with insulin glargine in patients with higher baseline HbA_{1c}. Secondary: The incidence of hypoglycemia was significantly higher with insulin glargine (P=0.0298). There was no difference in the incidence of severe hypoglycemia between the two treatments. Both treatments were well tolerated and there was no difference in the rate of overall adverse events between them (P=0.1944). Metabolism and nutrition disorders (e.g., hypoglycemia, hyperglycemia, etc) were the most commonly reported treatment-emergent adverse events, and these occurred with comparable frequency between the two treatments (11.8 vs 5.6%; P=0.1803). Significantly more serious adverse events were reported with insulin glargine (P=0.0164).
Ahern et al[70] Insulin pump therapy containing basal insulin The total patient population was stratified based on age: 1 to 6 years, 7 to 11 years, and 12 to 18 years. Patients were started on daily dose of insulin	PRO Patients ≤18 years of age with type 1 diabetes, followed in children's diabetes clinic for at least 1 year prior to start of pump therapy,	N=161 Average of 32±9 months	Primary: HbA_{1c}, diabetes-related adverse events Secondary: Not reported	Primary: Patients in all three groups had good diabetes control prior to study start. However, HbA_{1c} levels fell by 0.6 to 0.7% in all three groups by 12 months. These levels were significantly lower than prepump levels (P≤0.02). Within each age group, the incidence of severe hypoglycemic events during pump therapy was lower than during prior injection therapy. The differences did not achieve statistical significant. When all three groups were combined, there was a significantly lower incidence of severe hypoglycemic events during the first 12 months of pump therapy than during the 12 months prior to pump therapy (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
therapy prior to study start. The total daily dose was divided as 50% premeal bolus doses and 50% as basal replacement, given as a single hourly rate over the first 24 hours.	previously on a 2 to 3 injection/day regimen			Secondary: Not reported
Intermediate-Acting and Long-Acting Insulins: Type 2 Diabetes Mellitus				
Riddle et al[71] EDITION 1 Insulin glargine U-300 via modified SoloSTAR® pen QPM vs insulin glargine U-100 via SoloSTAR® pen QPM Dose adjustment weekly, but no more often than every three days. Metformin was continued at prior dosage throughout the study.	MC, OL, PG Patients ≥18 years of age with a diagnosis of T2DM, HbA_{1c} 7.0 to 10.0%, and use of basal insulin therapy (≥42 units/day) with or without metformin for at least one year	N=804 6 months	Primary: HbA_{1c} change from baseline at month six Secondary: FPG change from baseline, percentage of participants attaining HbA_{1c} <7.0% and ≤6.5% or FPG ≤6.7 and <5.6 mmol/L, changes of basal and total daily insulin doses and of body weight, changes in SMPG profiles, hypoglycemic events, including percentage of participants with	Primary: Mean HbA_{1c} decreased similarly in the two treatment groups with a final HbA_{1c} of 7.25% (SD 0.85) in the U-300 group compared to 7.28% (0.92) in the U-100 group. The LS mean change was 0.83% for both groups; difference 0.00% (95% CI, 0.11 to 0.11). Because the upper CI limit was below the 0.4% threshold, U-300 met the non-inferiority criterion. Secondary: Similar reductions to HbA_{1c} were observed for FPG in both treatment groups (from 8.72 mmol/L [SD 2.83] to 7.24 mmol/L [2.57] with U-300 and 8.90 mmol/L [2.94] to 7.21 mmol/L [2.40] with U-100). The percentages of participants attaining target HbA_{1c} levels were similar with U-300 and U-100 (39.6 and 40.9% for HbA_{1c} <7.0%, 21.0 and 21.6% for HbA_{1c} ≤6.5%, 46.3 and 44.9% for FPG ≤6.7, and 26.5 and 23.2% for FPG <5.6 mmol/L, respectively). Daily basal insulin dosage increased for both U-300 and U-100 at the end of the six month study. The dose increase was higher with U-300 than with U-100; LS mean difference was 0.09 units/kg/day (95% CI, 0.062 to 0.124). Mealtime insulin doses increased slightly in the first two weeks but were unchanged from baseline and alike in the two groups thereafter. Body weight increased by 0.9 kg in both treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			one or more confirmed or nocturnal hypoglycemic event from week nine to month six, and other adverse events	The SMPG profiles declined in both treatment groups. No significant differences between changes in means at individual time points were demonstrated. The reduction of preinjection SMPG (combination of pre- and post-dinner measurements) from baseline to month six was similar between treatments. There was also no between-treatment difference in the change of day-to-day variability of preinjection SMPG during treatment. The proportion of participants with one or more confirmed or severe nocturnal hypoglycemic events between the start of week nine and month six was 36% (146/404) on U-300, compared with 46% (184/400) on U-100. Analysis of this prespecified main measure of hypoglycemia demonstrated superiority of U-300 over U-100 with a significantly lower relative risk (RR 0.79; 95% CI, 0.67 to 0.93; P=0.0045). The percentage of participants reporting severe hypoglycemia at any time was similar for the two groups with 5.0% for U-300 compared with 5.7% for U-100 (RR 0.87; 95% CI, 0.48 to 1.55). The most common adverse events were infections, gastrointestinal events, or musculoskeletal complaints; these were equally distributed between the groups.
Yki-Järvinen et al[72] EDITION 2 Insulin glargine U-300 via modified SoloSTAR® pen QPM vs insulin glargine U-100 via SoloSTAR® pen QPM Insulin dose adjustment weekly. Other oral antidiabetic agents were	MC, OL, PG, RCT Patients ≥18 years of age with a diagnosis of T2DM, HbA_{1c} 7.0 to 10.0%, use of basal insulin therapy (≥42 units/day)	N=808 6 months	Primary: HbA_{1c} change from baseline at month six or last visit on treatment without rescue therapy Secondary: FPG change from baseline, percentage of participants attaining HbA_{1c} <7.0% and ≤6.5%	Primary: Mean HbA_{1c} decreased similarly in the two treatment groups with a final HbA_{1c} at six months of 7.57% for U-300 and 7.56% for U-100, representing a mean treatment difference of -0.01% (95% CI, -0.14 to 0.12). Because the upper CI limit was below the 0.4% threshold, U-300 met the non-inferiority criterion. Secondary: Similar reductions in FPG from baseline (-1.14 and -1.06), percentage of participants attaining HbA_{1c} <7.0% (30.6% and 30.4%) and ≤6.5% (14.5% and 14.8%), were observed in the U-300 and U-100 groups respectively. Numerically, percentage of participants attaining a FPG ≤6.7 mmol/L (48.7% and 54.1%) and <5.6 mmol/L (29.4% and 33.6%) were higher for the U-300 group than U-100 group, the difference was not statistically significant. Overall, glucose measurements of the 8-point profile showed a comparable

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
continued.			or FPG ≤6.7 and <5.6 mmol/L, changes of basal and total daily insulin doses and of body weight, changes in SMPG profiles, hypoglycemic events, including percentage of participants with one or more confirmed or nocturnal hypoglycemic event from week nine to month six, and other adverse events	decrease in SMPG for both the U-300 and U-100 groups. However, the mean prebreakfast SMPG was lower with U-100 than with U-300 during the first eight weeks, and a more gradual decrease in prebreakfast SMPG was observed with U-300 than with U-100. At month six, a similar average prebreakfast SMPG was reached in both groups (119 mg/dL for U-300 and 113 mg/dL for U-100). Comparable results were observed between U-300 and U-100 for change in preinjection SMPG and variability in preinjection SMPG. The daily basal insulin dose increased from baseline to month six in both groups, mainly during the first 12 weeks. There was a significant difference in insulin dose between treatment groups at month six, with a LS mean difference of 11 units/day (95% CI, 8 to 14), with those in the U-300 group requiring 10% more basal insulin (units/kg/day) than those receiving U-100. Overall, 123 participants (30.5%) in the U-300 group experienced 379 nocturnal hypoglycemic events, and 169 participants (41.6%) in the U-100 group experienced 766 nocturnal hypoglycemic events. A significantly lower percentage of participants reported at least one nocturnal or severe hypoglycemic event from week nine to month six with U-300 (21.6%) compared with U-100 (27.9%). Analysis of this prespecified main secondary end point demonstrated superiority of U-300 over U-100 (RR 0.77; 95% CI, 0.61 to 0.99, P=0.038). . The risk of nocturnal confirmed or severe hypoglycemia was also reduced with U-300 compared with U-100 during the six-month study period (RR 0.71, 95% CI, 0.58 to 0.86). During the six-month treatment period, 288 participants (71.5%) treated with U-300 and 322 participants (79.3%) treated with U-100 reported one or more hypoglycemic events. In total, 2,750 hypoglycemic events were reported in the U-300 group and 3,675 in the U-100 group. The most common adverse events in the U-300 and U-100 groups were infections, nervous system disorders, gastrointestinal events and musculoskeletal complaints. These were equally distributed between the treatment groups.
Bolli et al[73]	MC, OL, PG, RCT	N=873	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
EDITION 3 Insulin glargine U-300 via TactiPen® injector QPM vs insulin glargine U-100 via SoloSTAR® pen QPM Insulin dose adjustment weekly.	Patients ≥18 years of age with a diagnosis of T2DM for at least one year, use of oral glucose-lowering drugs in the last six months, and insulin naïve	6 months	HbA_{1c} change from baseline at month six Secondary: FPG change from baseline, percentage of participants attaining HbA_{1c} <7.0% and ≤6.5% or FPG ≤6.7 and <5.6 mmol/L, changes of basal and total daily insulin doses and of body weight, changes in SMPG profiles, hypoglycemic events, including percentage of participants with one or more confirmed or nocturnal hypoglycemic event from week nine to month six, and other adverse events	The mean decrease in HbA_{1c} was equivalent in the two treatment groups. At month six, the LS mean difference in change of HbA_{1c} was 0.04% (95% CI, −0.09 to 0.17) meeting the non-inferiority criterion. Secondary: The proportion of participants reaching target HbA_{1c} or laboratory-measured FPG at month six was much the same in the two treatment groups. Similar results in both the U-300 and U-100 groups were observed for change in pre-injection SMPG and variability in pre-injection SMPG. FPG from baseline to month six was somewhat greater in the U-100 group than in the U-300 group (LS mean difference, 0.39; 95% CI, 0.10 to 0.68). Over the 24-hour period, the eight-point SMPG profiles showed a similar decrease from baseline to month six with both U-300 and U-100 (LS mean difference 0.18; 95% CI, −0.07 to 0.42). The pre-breakfast SMPG decreased more gradually with U-300 than with U-100. The basal insulin dose increased throughout the six-month treatment period in both treatment groups, but more so with U-300; mean increase was 0.62 (0.29) U/kg/day U-300, and to 0.53 (0.24) U/kg/day with U-100 (no P value reported). Between the start of week nine and month six, the percentage of participants experiencing at least one nocturnal confirmed or severe hypoglycemic event was 16% with U-300 and 17% with U-100 (RR 0.89; 95% CI, 0.66 to 1.20). The percentage of participants who experienced ≥1 confirmed or severe hypoglycemic event was lower with U-300 (201/435, 46%) than with U-100 (230/438, 53%) over the six-month study period (RR 0.88; 95% CI, 0.77 to 1.01). Weight gain during the treatment period was lower with U-300 (LS mean increase 0.49 [95% CI, 0.14 to 0.83] kg) than with U-100 (LS mean increase 0.71; 95% CI, 0.36 to 1.06 kg; P value was non-significant).
Meneghini et al[74]	OL, OS	N=1,832	Primary: Incidence of	Primary: No severe adverse drug reactions were reported during the 12 week follow-up.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Insulin detemir±oral antidiabetic drug transferred from 3 groups of patients: oral antidiabetic drug only, NPH±oral antidiabetic drug, insulin glargine±oral antidiabetic drug	Subgroup of patients with type 2 diabetes from the German cohort of PREDICTIVE study	12 weeks	severe adverse drug reactions (severe adverse drug reactions) (major hypoglycemic events) Secondary: Hypoglycemic events, weight changes, HbA_{1c}, FPG	Reports of adverse drug reactions occurred in 0.3% of patients, including one report of drug intolerance, two diabetes-related reports, one report of headache, and one report of skin allergy (P values were not reported). Secondary: The percentage of patients experiencing hypoglycemia and the frequency of hypoglycemic episodes were lower in the insulin detemir group during the four weeks preceding the follow-up visit compared to baseline. The total, daytime, and nocturnal hypoglycemic events at baseline decreased from 3.3, 2.0, and 1.3 events/patient-year, respectively, to -2.7, -1.6, and -1.2, respectively (P<0.0001). The percentage of patients experiencing these events decreased from 7.2, 5.5, and 3.7%, respectively, to 2.0, 1.6, and 0.5% at follow-up (P values not reported). There were overall reductions in body weight following the transition to insulin detemir (P<0.0001). All three groups of patients had weight reduction after initiating insulin detemir (P<0.0001 in the oral antidiabetic drug only group, P<0.0099 in the NPH±oral antidiabetic drug group, and P<0.0001 in the insulin glargine±oral antidiabetic drug group). A reduction of -1.1±0.03% in mean HbA_{1c} was observed at study endpoint (P<0.0001). Patients that were in the oral antidiabetic drug only group had a reduction of -1.29±0.03% (P<0.0001) from baseline, which was a slightly greater reduction than in the NPH±oral antidiabetic drug and insulin glargine±oral antidiabetic drug groups (-0.60±0.09% and -0.59±0.06%, respectively; P<0.0001 for both). There was a significant reduction in mean FPG overall (P<0.0001). However, patients transitioning from the oral antidiabetic drug only group tended to have a greater reduction in FPG from baseline than those transitioning from the other two treatment regimens (P<0.0001).
Hollander et al[75] Insulin detemir PM or BID (AM and PM) and insulin	MC, NI, OL, PG, RCT Patients ≥18	N=319 52 weeks	Primary: HbA_{1c} at 52 weeks	Primary: Mean HbA_{1c} at 52 weeks was 7.19% with insulin detemir and 7.03% with insulin glargine (mean difference, 0.17; 95% CI, -0.07 to 0.40), meeting the prespecified non-inferiority margin.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
aspart before meals vs insulin glargine PM and insulin aspart before meals Basal insulin doses were titrated to achieve pre-breakfast and pre-dinner PG ≤108 mg/dL. Prandial insulin doses were titrated to achieve PPG ≤162 mg/dL. Insulin secretagogues and α-glucosidase inhibitors were discontinued. United States patients on TZDs were allowed to continue treatment.	years of age with type 2 diabetes for ≥1 year who were receiving oral diabetic medications or insulin with or without oral diabetes medications for >4 months with HbA_{1c} 7.0 to 11.0% and BMI ≤40 kg/m^2		Secondary: Change in body weight, proportion of patients achieving HbA_{1c} ≤7.0% with or without major hypoglycemia in the last three months of treatment, FPG, within-patient variation in self-monitored pre-breakfast and pre-dinner blood glucose, 10-point self-monitored plasma glucose profiles and safety	Secondary: Patients receiving insulin detemir experienced significantly less weight gain compared to those receiving insulin glargine (2.8 vs 3.8 kg; P<0.05). Similar percentage of patients achieved HbA_{1c} ≤7.0% with insulin detemir compared to insulin glargine (36.2 vs 36.7%; P value NS). The HbA_{1c} goal was achieved without symptomatic hypoglycemia in 17.1 and 21.4% of patients in the insulin detemir and insulin glargine groups, respectively (P value NS). No significant differences were observed between the two groups with regard to FPG at the end of study, changes in FPG, within-patient variation in self-monitored pre-breakfast and pre-dinner blood glucose and 10-point self-monitored plasma glucose profiles. Episodes of major hypoglycemia were reported in 4.7 and 5.7% of patients in the insulin detemir and insulin glargine groups, respectively (P=0.588). Incidence of nocturnal and symptomatic hypoglycemia was also comparable between the two groups (P>0.05 for both). Severe treatment-emergent adverse events were reported in 13.6 and 19.0% of patients in the insulin detemir and insulin glargine groups.
Raskin et al[76] Insulin detemir PM or BID (AM and PM) and insulin aspart before meals (IDet) vs insulin glargine PM and	MC, NI, OL, PG, RCT Patients ≥18 years of age with type 2 diabetes who previously received any oral diabetes medication or	N=385 26 weeks	Primary: HbA_{1c} at 26 weeks Secondary: FPG, body weight, safety	Primary: The least squared mean change in HbA_{1c} from baseline at 26 weeks was -1.08% with insulin detemir and -1.28% with insulin glargine (difference, 0.207; 95% CI, 0.0149 to 0.3995; P=0.035), showing non-inferiority. When last observation carried forward analysis was used, the least squared mean change in HbA_{1c} was -0.94 and -1.25% with insulin detemir and insulin glargine, respectively. The difference between the two groups (0.307; 95% CI, 0.1023 to 0.5109; P=0.004) was inconclusive regarding possible inferiority of insulin detemir since the 95% CI included 0.4, the prespecified inferiority

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
insulin aspart before meals (IGla) Basal insulin doses were titrated to achieve pre-breakfast PG ≤108 mg/dL. Treatment with insulin secretagogues and α-glucosidase inhibitors were discontinued. Treatment with TZDs and metformin was continued.	insulin with or without oral diabetes medications with HbA_{1c} 7.0 to 11.0% and BMI ≤40 kg/m^2			margin. Secondary: No significant differences were seen in change in FPG from baseline at 26 weeks between the two treatment groups. Patients in the insulin detemir group experienced less weight gain compared to those in the insulin glargine group (1.20±3.96 vs 2.70±3.94 kg; P=0.001). Rates of overall, nocturnal and major hypoglycemic events were comparable between the two groups. Sixty-six percent of patients in the insulin detemir group and 71% in the insulin glargine group reported treatment-emergent adverse events.
Rosenstock et al[77] Insulin detemir PM or BID (AM and HS) vs insulin glargine HS Basal insulin doses were titrated to achieve FPG ≤6 mmol/L. Existing oral antidiabetic drug therapy was continued.	MC, NI, OL, PG, RCT Insulin-naïve type 2 diabetics ≥18 years of age, receiving oral antidiabetic agents, with HbA_{1c} 7.5 to 10.0%, and BMI ≤40.0 kg/m^2	N=582 52 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline plasma glucose and body weight, proportion of patients achieving HbA_{1c} ≤7.0% without hypoglycemia, incidence of hypoglycemia, safety	Primary: Decreases in HbA_{1c} were -1.5% with both treatments and were comparable after 52 weeks at 7.2 and 7.1% (difference, 0.05%; 95% CI, -0.11 to 0.21), thereby meeting the criteria for non-inferiority for insulin detemir vs insulin glargine. Secondary: Within-patient variation of self-monitored plasma glucose pre-breakfast and -dinner did not differ significantly between the two treatments. The overall shape of the 10-point self-monitored plasma glucose profile during the last week of treatment was similar between the two treatments (P value NS). Weight gain was significantly less with insulin detemir compared to insulin glargine (3.0 vs 3.9 kg; P=0.01). With both treatments, 52% of patients achieved HbA_{1c} ≤7.0%, with 33 and 35% of patients receiving insulin detemir and insulin glargine doing so without hypoglycemia (P value not reported). The risk of hypoglycemia of any type was comparable between the two

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				treatments. The overall rate was low at 5.8 vs 6.2 episodes per patient-year with insulin detemir vs insulin glargine (RR, 0.94; 95% CI, 0.71 to 1.25), while the rate of nocturnal hypoglycemia was 1.3 episodes per patient-year with both treatments. Serious adverse events were less frequent with insulin detemir (42 patients with 47 events vs 53 patients with 73 events; P value not reported). One death was reported with insulin detemir (cause and/or reason unknown). Adverse events recorded as serious tended to be of a wide-ranging disparate nature, with no clear pattern of between-treatment differences. The only differences in adverse events were injection-site disorders (4.5 vs 1.4%), allergic reactions (3 vs 1 patients), and skin disorders including pruritus and rash (6 vs 1 patients).
King et al[78] Insulin detemir SC QD vs insulin glargine SC QD Once the patient achieved 2 consecutive days at goal, the insulin treatment was switched to the other agent.	DB, RCT, XO Type 2 diabetics receiving oral antidiabetic agents	N=36 24 hours	Primary: 24-hour glycemic control, time to basal glycemic control, insulin dose Secondary: Not reported	Primary: Glucose profiles for each hour were similar between the two treatments. Glucose values for each five minute interval for insulin detemir during the basal period, the period 12 hours after injection, and overall 24-hour period were similar to insulin glargine. The AUC for the self-monitored glucose levels over 24 hours was 293.2 and 3,114.5 mg.h/dL (point ratio, 0.941; 90% CI, 0.885 to 1.001); therefore, the two treatments were considered bioequivalent for 24-hour glucose. Target basal glycemic control was achieved in all patients in 3.8 and 3.5 days with insulin detemir and insulin glargine (*P*=0.360). The dose of insulin detemir was similar to that of insulin glargine (26.3 and 22.6 units/day; *P*=0.837). Approximately one percent of all glucose values during the basal period were <70 mg/dL. Secondary: Not reported
Meneghini et al[79] Insulin detemir	OL, RCT Insulin-naïve adults with type	N=457 26 weeks	Primary: Change in HbA_{1c} from baseline	Primary: The observed mean HbA_{1c} reductions with detemir and glargine from baseline were 0.48% and 0.74% to end-of-study values of 7.48% and 7.13%, respectively. The estimated between-treatment difference (detemir–glargine)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs insulin glargine Treat-to-target with weekly titrations	2 diabetes on a stable dose of metformin ≥1500 mg with an HbA_{1c} of 7 to 9%		Secondary: Proportion of subjects achieving HbA_{1c} levels ≤7 or ≤6.5% at 26 weeks, and the proportions achieving this without symptomatic hypoglycemia during the last month of treatment; safety	was 0.30% (95% CI, 0.14 to 0.46%) in the full analysis set and 0.35% (95% CI, 0.19 to 0.51%) in the per protocol analysis set. As the upper 95% CI values exceeded 0.4%, non-inferiority for detemir could not be confirmed. Secondary: The proportions of patients reaching HbA_{1c} ≤ 7% at 26 weeks were 38% (80/209) and 53% (107/204) (P=0.026) in the detemir and glargine groups, respectively; whereas for patients reaching HbA_{1c} ≤ 7% without hypoglycemia in the last four weeks, there was no significant difference between the treatments (32 and 38%, respectively; P=0.438). HbA_{1c} ≤ 6.5% was attained by 11 and 21% in the detemir and glargine groups, respectively (P=0.011), 8.6% and 15.2% without hypoglycemia (P=0.073). The overall rate of hypoglycemia was low, with fewer than five episodes per subject-year in either treatment arm; the only two major events reported occurred with glargine. There was a significantly lower (27%) rate of all hypoglycemic episodes with detemir versus glargine, with no difference in the rate of nocturnal hypoglycemia Weight decreased slightly with detemir and increased slightly with glargine. Observed mean weight change was −0.49 kg with detemir and +1.0 kg with glargine, with a statistically significant estimated treatment difference of −1.5 kg (95% CI, −2.17 to −0.89 kg) in favor of detemir.
Liebl et al[80] Insulin detemir PM and insulin aspart before meals vs biphasic insulin aspart 30 (consisting of 30% insulin aspart and 70% protamine-	MC, RCT Adult type 2 diabetics ≥6 months, BMI ≤40 kg/m^2, currently receiving 1 or 2 oral antidiabetic agents, with or without concomitant QD intermediate- or	N=719 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} ≤7.0%; change in baseline FPG and body weight, self-monitored glucose	Primary: Insulin detemir plus insulin aspart significantly decreased HbA_{1c} compared to biphasic aspart 30 (-1.56 vs -1.23%; treatment difference, 0.234%; 95% CI, 0.398 to -0.070; P=0.0052). Final HbA_{1c} values were 6.96 and 7.17%. Secondary: After 26 weeks, 60 and 50% of patients achieved HbA_{1c} ≤7.0% with insulin detemir plus insulin aspart and biphasic aspart 30 (P value not reported). Patients previously receiving basal insulin had significantly greater decrease with insulin detemir plus insulin aspart (-1.21 vs -0.75%; P=0.0129), whereas insulin-naïve patients had similar decreases (-1.69 vs -1.42%; P=0.106).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
crystallized insulin aspart) BID Insulin detemir doses were titrated to achieve pre-breakfast PG 72 to 126 mg/dL and insulin aspart doses were titrated to achieve PPG ≤180 mg/dL. Biphasic insulin aspart doses were titrated to achieve pre-breakfast and pre-dinner plasma glucose 72 to 126 mg/dL. All oral antidiabetic drugs were discontinued to compare two insulin regimens.	long-acting insulin, and HbA_{1c} ≥7.0 to ≤12.0%		prolife, incidence of hypoglycemia	There was no difference in the decrease of FPG between the two treatments (-52.3 vs -51.8 mg/dL; P=0.345). There was no difference in the amount of weight gain between the two treatments (4.1 vs 4.0 kg; P value not reported). Daily glucose profiles indicate that both treatments decrease glucose levels throughout the day. PPG was significantly lower with insulin detemir plus insulin aspart compared to biphasic aspart 30 (after breakfast; P=0.012, after lunch; P<0.001, and after dinner; P<0.001). A total of five and zero patients experienced major hypoglycemia with insulin detemir plus insulin aspart compared to biphasic aspart 30 (P value not reported). The rate of minor hypoglycemia was 31 vs 28%; P=0.837). The rate of nocturnal minor hypoglycemia was similar between the two treatments (7.4 vs 7.3%; P=0.666).
Haak et al[81] Insulin detemir HS and insulin aspart before meals vs NPH insulin HS and insulin aspart before meals Insulin doses were adjusted to achieve an	MC, OL, PG, RCT Patients aged ≥35 years of age with type 2 diabetes for ≥12 months, HbA_{1c} ≤12.0% and who had received insulin treatment for ≥2 months	N=505 26 weeks	Primary: Change in HbA_{1c} and FPG from baseline, nine-point self monitoring of blood glucose profile, hypoglycemia, weight gain Secondary: Not reported	Primary: At 26 weeks, significant HbA_{1c} reductions were observed with both the insulin detemir group (-0.2%; P=0.004) and the NPH group (-0.4%; P=0.0001). There was no significant difference in HbA_{1c} reduction between the two groups (P value not reported). At 26 weeks, both the insulin detemir group and NPH group had significant reductions in FPG from baseline (P=0.027 and P=0.026, respectively). However, differences between groups were NS (P=0.66). There were no significant differences in mean nine-point self monitoring of blood glucose profiles between the two groups (P=0.58). There was no significant difference in both nocturnal and total hypoglycemia

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
FBG goal 4.0 to 7.0 mmol/L, PPG goal <10 mmol/L, and nocturnal goal of 4 to 7 mmol/L.				between insulin detemir and NPH (P=0.95 and P=0.48, respectively). At 26 weeks, body weight changes from baseline were significantly lower with insulin detemir compared to NPH (1.0 vs 1.8 kg, respectively; P=0.017). Secondary: Not reported
Fajardo Montañana et al[82] Insulin detemir HS and insulin aspart before meals vs NPH insulin HS and insulin aspart before meals Basal insulin doses were titrated to achieve pre-breakfast PG ≤6.1 mmol/L. Insulin aspart doses were titrated to achieve PPG ≤10.0 mmol/L. Metformin therapy could be continued.	RCT, OL, PG, MC Patients ≥18 years of age with type 2 diabetes, HbA_{1c} 7.5 to 11.0%, BMI 25 to 40 kg/m^2, who were receiving two daily doses of insulin (at least one of them a premix) for ≥3 months; patients could also be receiving treatment with metformin; patients on other oral antidiabetic drugs were excluded	N=277 26 weeks	Primary: Weight changes after 26 weeks Secondary: HbA_{1c} and FPG, proportion of patients achieving HbA_{1c} ≤7.0% without hypoglycemia during the last four weeks of treatment, intra-subject variability in FPG, hypoglycemia	Primary: Mean weight gain at week 26 in the ITT population was significantly lower with insulin detemir (0.4 kg) than with NPH insulin (1.9 kg; P≤0.0001). In the PP analysis, there were similar changes in weight (0.4 kg with insulin detemir and 2.0 kg with NPH insulin; P≤0.0001). BMI increased less with insulin detemir (0.2 kg/m^2) than with NPH insulin (0.8 kg/m^2; P≤0.0001). Overall, 46.4% of insulin detemir patients showed no change or weight loss compared with 22.6% of NPH insulin patients. Secondary: At week 26, HbA_{1c} decreased from 8.9 to 7.8% in the insulin detemir group and from 8.8 to 7.8% in the NPH group (P=NS). FPG decreased from 10.8 to 8.8 mmol/L in the insulin detemir group and from 10.1 to 8.9 mmol/L in the NPH insulin group (P=NS). The proportion of patients achieving an HbA_{1c} ≤7.0% without hypoglycemia during the last four weeks of treatment was 27% in both treatment groups (P=NS). Intra-subject variability of self-measured FPG at 26 weeks was lower with insulin detemir than with NPH insulin (P<0.0001). Patients in the insulin detemir group experienced significantly less hypoglycemia than patients in the NPH insulin group. Hypoglycemia was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				reported by 34.7% of patients treated with insulin detemir and by 65.3% of patients receiving NPH insulin. Nocturnal hypoglycemia was reported in 30.1% of insulin detemir patients and 69.9% of NPH insulin patients (RR 0.62 for all hypoglycemic events and 0.43 for nocturnal events; P<0.0001 for both).
Philis-Tsimikas et al[83] Insulin detemir PM vs insulin detemir AM vs NPH insulin PM Insulin doses titrated to achieve a pre-breakfast and pre-dinner FPG ≤108 mg/dL. Existing oral antidiabetic drug therapy was continued.	MC, OL, PG, RCT Men and women ≥18 years of age, had a BMI ≤40 kg/m^2, type 2 diabetes for ≥12 months, insulin naïve, HbA_{1c} 7.5 to 11.0% following at least 3 months of treatment with ≥1 oral antidiabetic drug	N=498 20 weeks	Primary: Change in HbA_{1c} from baseline Secondary: Change in FPG, nine-point self monitoring of blood glucose profile, hypoglycemia	Primary: Both insulin detemir groups had similar reductions in HbA_{1c} compared to that of the NPH group. At 20 weeks, both evening and morning insulin detemir was found to be as effective as evening NPH (mean difference, 0.10%; 95% CI, -0.08 to 0.29 and 0.13%; 95% CI, -0.07 to 0.32, respectively). Equivalence was found between both insulin detemir groups (estimated difference, -0.03%; 95% CI, -0.21 to 0.15; P value not reported). Secondary: At 20 weeks, evening insulin detemir had changes in FPG similar to those with evening NPH (mean difference, -0.46 mmol/L; 95% CI, -1.05 to 0.13). However, morning insulin detemir had significantly higher FPG than both evening NPH and evening insulin detemir (mean difference, 0.88 mmol/L; 95% CI, 0.31 to 1.5; P=0.003 and 1.33 mmol/L; 95% CI, 0.85 to 1.80; P<0.001, respectively). Prebreakfast self monitoring of blood glucose was higher in the morning insulin detemir group in comparison to both evening groups (P<0.001). However, predinner self monitoring of blood glucose was lower in the morning insulin detemir group than that of the evening detemir and evening NPH groups (P=0.005 and P<0.001, respectively). Both evening groups resulted in similar self monitoring of blood glucose profiles. When compared to evening NPH, evening insulin detemir resulted in a significant risk reduction in the rate of hypoglycemic episodes over 24 hours and confirmed nocturnal episodes (P=0.0019 and P=0.031, respectively). On the other hand, when comparing morning and evening detemir, the rates of hypoglycemia were statistically similar. In comparison to evening NPH, morning insulin detemir did have a significant risk reduction of 87% for confirmed nocturnal hypoglycemia (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Montanana et al[84] Insulin detemir SC QD vs NPH SC BID All patients received insulin aspart at main meals. Concomitant treatment with metformin was allowed.	PG, RCT Type 2 diabetics ≥18 years of age with HbA_{1c} 7.5 to 11.0%, BMI 25 to 40 kg/m^2, and receiving 2 daily doses of insulin (≥1 premix) ≥3 months	N=271 26 weeks	Primary: Change in baseline body weight Secondary: Change in baseline HbA_{1c} and FPG; proportion of patients achieving HbA_{1c} ≤7.0% without hypoglycemia, incidence of hypoglycemia, safety	Primary: Insulin detemir (0.4kg) resulted in significantly less weight gain compared to NPH (1.9 kg; difference, 1.5 kg; *P*<0.0001). Increases in BMI were significantly less with insulin detemir compared to NPH (difference, 0.6 kg/m^2; *P*<0.0001). Secondary: There was no difference in the decrease in HbA_{1c} between the insulin detemir (8.9 to 7.8%) and NPH (8.8 to 7.8%) (*P* value not reported). There was no difference in the decrease in FPG between insulin detemir (10.0 to 8.8 mmol/L) and NPH (10.1 to 8.9 mmol/L) (*P* value not reported). The proportion of patients achieving HbA_{1c} ≤7.0% without hypoglycemia during the last four weeks of treatment was 27% with both treatments. The incidence of hypoglycemia was significantly lower with insulin detemir compared to NPH (RR, 0.62 (all events) and 0.43 (nocturnal); *P*<0.0001 for both). Both treatments were well tolerated with no major safety concerns noted and a similar incidence of adverse events with both treatments.
Hermansen et al[85] Insulin detemir BID vs NPH insulin BID Basal insulin doses were adjusted to achieve pre-breakfast FBG of 108 mg/dL.	MC, OL, PG, RCT Adult type 2 diabetes patients with no history of insulin use, baseline HbA_{1c} 8.61% for participants taking insulin detemir and 8.51% for those	N=476 26 weeks	Primary: Effect on HbA_{1c} Secondary: FPG, proportion of participants achieving an HbA_{1c} ≤7.0%, proportion of participants achieving an HbA_{1c} ≤7.0%	Primary: After 26 weeks, HbA_{1c} reductions in the insulin detemir group (-1.8%; P=0.004) did not differ significantly from reductions observed in the NPH group (-1.9%; P=NS). Secondary: After 26 weeks, the difference in mean FPG reductions between insulin detemir and NPH was not significant (0.32 mmol/L; P>0.05). The proportion of patients achieving an HbA_{1c} ≤7.0% was 70% in those taking insulin detemir and 74% with those taking NPH. The difference between treatment groups was not significant.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Existing oral antidiabetic drug therapy was continued.	randomized into the NPH group		without hypoglycemia, 10-point self monitoring of blood glucose, frequency of hypoglycemia, and weight gain	The proportion of patients achieving an HbA_{1c} ≤7.0% without hypoglycemia was significantly higher in those taking insulin detemir (26%) compared to those taking NPH (16%; P=0.008). There was significantly less day-to-day fluctuation of fasting self monitoring of blood glucose profiles with insulin detemir when compared to NPH (P=0.021). There were no significant differences in mean 10-point self monitoring of blood glucose profiles between the two treatment groups (P=0.19). There was a 47% lower risk of overall hypoglycemia with insulin detemir compared to NPH (P<0.001). There was a 55% lower risk of nocturnal hypoglycemia with insulin detemir compared to NPH (P<0.001). After 26 weeks, body weight change from baseline was significantly lower with insulin detemir (1.2 kg) compared to NPH (2.8 kg; P<0.001).
Strojek et al[86] Insulin glargine QD vs biphasic aspart 30 QD Insulin doses were titrated to achieve a FPG of 5.0 to 6.1 m mol/L. All patients also received metformin and glimepiride.	MC, NI, OL, PG, RCT Patients ≥18 years of age with type 2 diabetes who were insulin-naïve and receiving oral diabetes medications for ≥6 months, with HbA_{1c} >7.0 and ≤11.0%, BMI ≤40 kg/m^2	N=433 26 weeks	Primary: HbA_{1c} at 26 weeks Secondary: Proportion of patients achieving HbA_{1c} ≤6.5 and <7.0% without hypoglycemia after 26 weeks, HbA_{1c} reduction by >1% from baseline, nine-point self-measured plasma glucose profiles, PPG	Primary: HbA_{1c} at 26 weeks was 7.1 and 7.3% with biphasic aspart and insulin glargine, respectively (difference, -0.16%, 95% CI, -0.30 to -0.02; *P*=0.029), demonstrating non-inferiority. Secondary: In both treatment groups, 25% of patients achieved HbA_{1c} ≤6.5%. In the biphasic aspart group, 44.9% of patients achieved HbA_{1c} <7.0%, and 19.4% of patients achieved this value without hypoglycemia. The corresponding results with insulin glargine were 44.9 and 20.0%, respectively (*P* values not reported). In the biphasic aspart and insulin glargine groups, 60 and 57% of patients, respectively, achieved HbA_{1c} reduction by >1% (*P* value not reported). Biphasic aspart was associated with lower post-dinner and bedtime plasma glucose compared to insulin glargine on the nine-point self-measured plasma glucose profiles (*P*<0.05). No significant differences were observed at other

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			increments, Diab-MedSat and safety	time points. PPG increments were comparable between the two groups. No significant difference was seen between biphasic aspart and insulin glargine in treatment satisfaction as measured by Diab-MedSat questionnaire (score difference, -0.11; 95% CI, -2.36 to 2.14; *P* value not reported). Fifty-eight and 51% of patients in the biphasic aspart and insulin glargine groups, respectively, reported at least one hypoglycemic event (RR, 1.41; 95% CI, 1.03 to 1.93; *P*=0.034). The risk of nocturnal hypoglycemia was also higher with biphasic aspart compared to insulin glargine (RR, 2.41; 95% CI, 1.34 to 4.34; *P*=0.003). No significant differences were seen in daytime hypoglycemia. Treatment-emergent adverse events were reported in 51 and 48% of patients in the biphasic aspart and insulin glargine groups, respectively. Less than 1% of patients reported serious adverse events that are possibly or probably related to study medications. One treatment-emergent death was reported in the insulin glargine group and was considered not related to the study medication. No significant differences were seen in cardiovascular risk markers, waist circumference or body weight.
Bretzel et al[87] APOLLO Insulin glargine QD vs pre meal insulin lispro Insulin glargine doses were titrated to achieve FPG <5.5 mmol/L.	MC, NI, OL, PG, RCT Patients 18 to 75 years of age with type 2 diabetes for ≥1 year, HbA_{1c} 7.5 to 10.5%, BMI ≤35 kg/m^2, FPG ≥6.7 mmol/L and receiving oral diabetes	N=418 (intent-to-treat) N=377 (per-protocol) 44 weeks	Primary: Change in HbA_{1c} from baseline at 44 weeks Secondary: Proportion of patients with HbA_{1c} ≤6.5 or ≤7.0%, change in FPG, proportion of	Per-protocol population was used in all efficacy endpoint analyses for non-inferiority testing. Intent-to-treat population was used subsequently for superiority testing. Primary: The adjusted mean change in HbA_{1c} was -1.71 and -1.87% with insulin glargine and insulin lispro, respectively, which met the predefined 0.4% limit for non-inferiority between the two groups. Intent-to-treat analysis failed to show superiority (-1.69 vs -1.82%; *P*=0.0908). Secondary: Thirty percent and 38% of patients reached HbA_{1c} ≤6.5% and 57 and 69% of patients reached HbA_{1c} ≤7.0% in the insulin glargine and insulin lispro

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Insulin lispro doses were titrated to achieve pre-prandial glucose <5.5 mmol/L and PPG <7.5 mmol/L. The dose of oral diabetes medications remained stable throughout the entire study. Patients who were treated with a sulfonylurea were converted to equivalent dose of glimepiride during the screening phase.	medications for ≥6 months with no dose change in the past 3 months		patients with FPG ≤5.5 mmol/L, changes in nocturnal blood glucose and eight-point blood glucose profiles, percentage of patients with nocturnal, severe and symptomatic hypoglycemia	groups, respectively (*P* values not reported). Change in FPG from baseline at 44 weeks was -4.3±2.3 and -1.8±2.3 mmol/L with insulin glargine and insulin lispro (*P*<0.0001). Significantly more patients in the glargine group achieved FPG ≤5.5 mmol/L compared to the insulin lispro group (38 vs 6%; *P* value not reported [per-protocol]; 35 vs 5%; *P*<0.001 [intent-to-treat]). Decrease in nocturnal glucose was significantly greater with insulin glargine compared to insulin lispro (-3.3 vs -2.6 mmol/L; *P*=0.0041 [per-protocol]; -3.3 vs -2.7 mmol/L; *P*=0.0017 [intent-to-treat]). A greater reduction was seen with insulin lispro compared to insulin glargine in PPG after breakfast, lunch, dinner and bedtime (*P*<0.05 for all). The rate of nocturnal hypoglycemia per patient was similar between insulin glargine and insulin lispro (0.42 vs 0.27; *P*=0.0709). The rates of severe and symptomatic hypoglycemia are significantly lower with insulin glargine compared to insulin lispro (0.02 vs 0.06; *P*=0.0989; 3.46 vs 11.02; *P*<0.0001, respectively).
Buse et al[88] DURABLE Insulin glargine SC QD vs biphasic lispro 25 SC BID	MC, OL, PG, RCT Type 2 diabetics 30 to 80 years of age with HbA_{1c} >7.0%, receiving ≥2 oral antidiabetic agents for 90 days, and BMI <45 kg/m^2	N=1,045 24 weeks	Primary: HbA_{1c} at trial end Secondary: Change in baseline HbA_{1c}, body weight, and insulin dose; proportion of patients achieving HbA_{1c}	Primary: Biphasic lispro 25 achieved a significantly lower final HbA_{1c} compared to insulin glargine (7.3 vs 7.2%; P=0.005). Secondary: Biphasic lispro 25 had significantly greater decreases in HbA_{1c} compared to insulin glargine (-1.7 vs -1.8%; P=0.005). Biphasic lispro 25 was associated with significantly more weight gain compared to insulin glargine (2.5 vs 3.6 kg; P<0.0001). After 24 weeks, the total daily insulin dose was significantly higher with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			<7.0 and ≤6.5%; seven-point self-monitored glucose profiles; incidence of hypoglycemia; safety	biphasic lispro 25 compared to insulin glargine (0.40 vs 0.47 units/kg; P<0.001). The proportion of patients achieving HbA_{1c} <7.0% was significantly greater with biphasic lispro 25 compared to insulin glargine (40.3 vs 47.5%; P<0.001). There was no difference between the two treatments in the proportions of patients achieving HbA_{1c} ≤6.5% (22.2 vs 24.6%; P=0.174). Biphasic lispro 25 had a significantly higher rate of overall hypoglycemia (23.1 vs 28.0 episodes per patient-year; P=0.007), but a significantly lower rate of nocturnal hypoglycemia compared to insulin glargine (11.4 vs 8.9 episodes per patient year P=0.009). The rate of severe hypoglycemia was similar between the two treatments (0.03 vs 0.10 episodes per patient year; P=0.167). Overall, 4.3 and 6.2% of patients receiving insulin glargine and biphasic lispro 25 experienced at least one serious adverse event (P=0.051); the rate of cardiovascular-related serious adverse events was similar between the two treatments (26 vs 29%; P=0.716). There were six and 15 adverse events leading to discontinuation with insulin glargine and biphasic lispro 25 (P=0.077). One and five deaths occurred with insulin glargine and biphasic lispro 25 (P=0.218).
Yki-Järvinen et al[89] Insulin glargine HS vs NPH insulin HS Initial doses were titrated to achieve FPG target ≤120 mg/dL. Existing oral antidiabetic	RCT Patients 40 to 80 years of age with type 2 diabetes for at least 3 years, BMI <40 kg/m^2, HbA_{1c} 7.5 to 12.0%, previous oral therapy with either sulfonylureas alone or	N=426 52 weeks	Primary: HbA_{1c} Secondary: FPG, 24-hour blood glucose profile, incidence of hypoglycemia, and serum C-peptide concentrations	Primary: The HbA_{1c} in the insulin glargine group decreased to 8.34±0.09% at end point from baseline (P<0.001) and 8.24±0.09% in the NPH group (P<0.001). Secondary: In the group of patients that achieved target FPG ≤120 mg/dL, HbA_{1c} decreased to 7.75±0.14% and 7.60±0.12% in the insulin glargine and NPH groups, respectively. However, there was no difference between groups (P values not reported). At study end point, blood glucose concentrations were significantly lower in the insulin glargine group than the NPH group before and after dinner. However, in the group of patients that achieved target FPG, blood glucose at 3 AM was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
drug therapy was continued.	combined with acarbose, metformin, or metformin alone for at least 1 year, negative history of ketoacidosis, women of childbearing potential were required to be on contraceptive protection, willingness to perform self monitoring of blood glucose			significantly lower in patients taking NPH than those taking insulin glargine (P=0.0012). In the entire group of patients, the percentage of patients experiencing at least one symptomatic hypoglycemic episode was lower in the insulin glargine group than the NPH group. In the group of patients achieving target FPG, the percentage of patients experiencing symptomatic hypoglycemia was 33.0% and 50.7% in the insulin glargine and NPH groups, respectively (P=0.027). Serum C-peptide concentrations decreased similarly from baseline in both treatment groups (P<0.001).
Riddle et al[90] Insulin glargine HS vs NPH insulin HS Insulin doses were titrated to achieve target FPG ≤100 mg/dL. Existing oral antidiabetic drug therapy was continued.	CS, MC, OL, PG, RCT Patients 30 to 70 years of age with type 2 diabetes for ≥2 years, treated with stable doses of 1 or 2 oral antidiabetic drug for ≥3 months, BMI 26 to 40 kg/m^2, HbA_{1c} 7.5 to 10.0%, FPG ≥140 mg/dL at screening	N=764 24 weeks	Primary: Percentage of patients achieving an HbA_{1c} ≤7.0% without a single instance of symptomatic nocturnal hypoglycemia confirmed by plasma-referenced glucose ≤72 mg/dL Secondary: Changes from baseline in	Primary: The percentage of patients reaching a target HbA_{1c} ≤7.0% without a single instance of symptomatic nocturnal hypoglycemia was achieved by more patients taking insulin glargine than patients taking NPH (32.2 vs 26.7%, respectively; P<0.05). Secondary: Mean HbA_{1c} at end point was 6.96% with insulin glargine and 6.97% with NPH (between-treatment difference, -0.03%; 95% CI, -0.13 to 0.08; P=NS). Both groups also achieved comparable decreases in FPG at end point (between-treatment difference, -3.6 mg/dL; 95% CI, -8.82 to 1.62; P=NS). Weight increased similarly from baseline to end point in both groups (between-treatment difference, 0.2 kg; 95% CI, -0.24 to 0.68; P=NS). The HbA_{1c} ≤7.0% target was reached by 58.0% of patients on insulin glargine and 57.3% of patients in the NPH group. The goal FPG ≤100 mg/dL was achieved by 36.2% of patients on insulin

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			HbA_{1c}, FPG, and weight; percentage of patients achieving an HbA_{1c} ≤7.0% or FPG ≤100 mg/dL independent of the occurrence of hypoglycemia; percentage of patients achieving FPG ≤100 mg/dL without confirmed hypoglycemia; overall rates of symptomatic hypoglycemia	glargine and 34.4% of patients on NPH. This target was achieved without hypoglycemia more often by patients taking insulin glargine. FPG ≤100 mg/dL without documented nocturnal hypoglycemia was achieved by 22.1% of patients taking insulin glargine compared to 15.9% of patients taking NPH (P<0.03). The rates of hypoglycemia (events/patient-year) with insulin glargine vs NPH were 13.9 vs 17.7, respectively for all symptomatic events (P<0.02) and 9.2 vs 12.9, respectively, for all confirmed events (P<0.005).
Rosenstock et al[91] Insulin glargine HS vs NPH insulin BID Insulin doses were titrated to achieve FPG ≤120 mg/dL during the first 3 years of the study, then FPG ≤100 mg/dL	MC, OL, PG, RCT Patients 30 to 70 years of age with type 2 diabetes with HbA_{1c} 6.0 to 12.0% who were treated with oral antidiabetic drugs or insulin (alone or in combination) for ≥1 year	N=1,017 5 years	Primary: Percentage of patients with three or more step progression in Early Treatment Diabetic Retinopathy Study score after five years of treatment with either insulin glargine or NPH insulin	Primary: In the ITT analysis, 12.5% of patients in the insulin glargine group experienced a ≥3 step progression in Early Treatment Diabetic Retinopathy Study score after five years compared to 14.6% of patients receiving NPH insulin (difference, −2.10%; 95% CI, −6.29 to 2.09). In the PP analysis, 14.2 and 15.7% of patients experienced a ≥3 step progression in Early Treatment Diabetic Retinopathy Study score after five years, respectively (difference, -1.98%; 95% CI, -7.02 to 3.06). Secondary: After five years, the mean FPG in the insulin glargine group was 7.8 and 7.7 mmol/L in the NPH insulin group (ITT population).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
during the last 2 years of the study. Oral antidiabetic drug and/or prandial insulin could be continued or modified during the trial, and regular insulin could be added with meals at the investigator's discretion.			Secondary: HbA_{1c}, FPG, and hypoglycemia	The proportion of patients achieving FPG ≤5.6 mmol/L was 28.5% with insulin glargine and 24.3% with NPH insulin. After five years, the mean HbA_{1c} (last observation carried forward) improved from a baseline of 8.4 and 8.3 to 7.8 and 7.6% for patients in the insulin glargine and NPH insulin groups, respectively (difference, 0.21%; P=0.0053). Weight gain was 3.7 kg with insulin glargine compared to 4.8 kg with NPH insulin (ITT; P=0.0505). The use of NPH insulin was associated with a greater incidence of severe hypoglycemia than insulin glargine (11.1 vs 7.6%, respectively; P=0.0439). However, there was no significant difference in symptomatic hypoglycemia (P=0.1366) or nocturnal hypoglycemia (P=0.2248) between the treatment groups.
Fritsche et al[92] Insulin glargine AM and glimepiride 3 mg QD vs insulin glargine HS and glimepiride 3 mg QD vs NPH insulin HS and glimepiride 3 mg QD	MC, OL, PG, RCT Patients with type 2 diabetes <75 years of age, previously on oral therapy with any sulfonylurea as monotherapy or in combination with metformin or acarbose, BMI <35 kg/m^2, FPG ≥120 mg/dL, HbA_{1c} 7.5 to 10.5%	N=700 28 weeks	Primary: Change in HbA_{1c} from baseline to end point, frequency of patients who experienced hypoglycemic episodes during the study Secondary: HbA_{1c} ≤7.5%, FBG ≤100 mg/dL, response rates, mean 24-hour blood glucose values, hypoglycemic events and	Primary: Over the 24-week treatment period, HbA_{1c} levels improved by -1.24% (two-sided 90% CI, -1.10 to -1.38) with morning insulin glargine, -0.96% (90% CI, -0.81 to -1.10) with bedtime insulin glargine and -0.84% (90% CI, -0.69 to -0.98) with bedtime NPH (P values not reported). Improvement in HbA_{1c} was significant in patients receiving morning insulin glargine than in patients receiving NPH (-0.40%; 90% CI, -0.23 to -0.58; P<0.001) and bedtime insulin glargine (-0.28%; 90% CI, -0.11 to -0.46; P=0.008). Secondary: More patients in the morning insulin glargine group achieved HbA_{1c} level of <7.5% (43%) than patients in the bedtime NPH (32%) and bedtime insulin glargine groups (33%; P=0.021). FPG levels improved in all three groups. The average reduction in FPG level achieved over the 24-week treatment did not differ among the groups (P>0.2). The morning insulin glargine group showed a greater decrease in mean daily

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			adverse events	blood glucose levels compared to both the bedtime NPH group (P<0.001) and the bedtime insulin glargine group (P=0.002). Hypoglycemic events were similar among the three groups. The number of patients experiencing nocturnal hypoglycemia was lower in both the morning and bedtime insulin glargine groups than with the bedtime NPH group (P<0.001). Fewer patients experienced symptomatic hypoglycemia with bedtime insulin glargine (43%) than with bedtime NPH (58%; P=0.001) and morning insulin glargine (56%; P=0.004). Adverse event rates were similar in all three groups (P values not reported).
Pan et al[93] Insulin glargine HS and glimepiride 3 mg QD vs NPH insulin HS and glimepiride 3 mg QD	MN, NI, OL, PG, RCT Insulin-naïve Asian patients 40 to 80 years of age with type 2 diabetes and random venous plasma glucose concentration ≥11.1 mmol/L, FPG ≥7 mmol/L, or PPG ≥11.1 mmol/L 2 hours after oral glucose tolerance test, poorly controlled on oral antidiabetic drug for ≥3 months prior to study entry, BMI 20 to	N=448 24 weeks	Primary: Change in HbA_{1c} from baseline to endpoint Secondary: Mean FPG level, eight-point blood glucose profiles, proportion of patients with HbA_{1c} <7.5%, proportion of combined responders (defined as HbA_{1c} <7.5% and FPG ≤120 mg/dL), change in BMI, hypoglycemia	Primary: The insulin glargine group had a decrease of -1.10% in HbA_{1c} vs -0.92% in the NPH group. There was not a statistically significant difference between both groups (P=0.0631). The results were confirmed in a full analysis set, the difference between adjusted mean changes in the two groups was 0.22 (95% CI, 0.02 to 0.42; P=0.0319). Secondary: FPG decreased to a similar extent in both the insulin glargine and NPH groups (-106 and -104 mg/dL, respectively; P value not reported). At study end, the eight-point blood glucose profiles were similar in both the insulin glargine and NPH groups, except at postdinner time, when the use of insulin glargine resulted in lower glucose concentrations (P=0.0436). The insulin glargine group had greater decreases in daily blood glucose levels than the NPH group (-94 vs -80 mg/dL, respectively; P=0.018). The proportion of patients achieving HbA_{1c} <7.5% at the end of the study was greater for the insulin glargine group than the NPH group (38.1 vs 30.3%, respectively). This was also consistent with the proportion of patients achieving target FPG (62.3 vs 58.7%, respectively). In the insulin glargine group, a greater proportion of patients achieved HbA_{1c} <7.5% without experiencing nocturnal symptomatic hypoglycemia (P=0.0174).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	35 kg/m^2, HbA_{1c} 7.5 to 10.5%, and FPG >120 mg/dL			Both groups had similar changes in BMI from baseline (1.40 and 1.29 kg/m^2 in the insulin glargine and NPH groups, respectively). The number of hypoglycemic episodes was significantly lower with insulin glargine than with NPH (P<0.004). These differences were seen in particular with symptomatic hypoglycemia (P<0.0003), severe hypoglycemia (P<0.03), and nocturnal hypoglycemia (P<0.001).
Eliaschewitz et al[95] Insulin glargine HS and glimepiride 4 mg QD vs NPH insulin HS and glimepiride 4 mg QD Insulin doses were titrated to achieve target FPG ≤100 mg/dL.	MC, OL, RCT Men and women ≤75 years of age with type 2 diabetes, who had not achieved good metabolic control on oral antidiabetic drugs for at least 6 months, with HbA_{1c} levels 7.5 to 10.5%, FPG ≥100 mg/dL, and BMI ≤35 kg/m^2	N=528 24 weeks	Primary: Change in HbA_{1c} from baseline to end of study Secondary: Percentage of patients who responded to treatment (defined as those who achieved HbA_{1c} ≤7.5% and FPG ≤100 mg/dL by end of study), change in FPG from baseline, hypoglycemia	Primary: At 24 weeks, both groups demonstrated equivalence in change in HbA_{1c} (adjusted mean difference, -0.047; 90% CI, -0.232 to 0.138). Based on equivalence result, an analysis was conducted and also revealed no significant difference between groups (adjusted mean difference, -0.029; 90% CI, -0.210 to 0.153; P=0.795). Secondary: The percentages of responders were similar in both the insulin glargine group and NPH group for HbA_{1c} ≤7.5% (50.4 vs 48.0%, respectively; P=0.529) and FPG ≤100 mg/dL (42.1 vs 39.8%, respectively; P=0.752). There was no significant difference between groups in changes in FPG (P=0.298). The insulin glargine group had a lower RR of hypoglycemia than the NPH group (RR, 1.27; 95% CI, 1.03 to 1.57). There was also a greater reduction in the risk of nocturnal hypoglycemia (RR, 1.2; 95% CI, 1.09 to 1.37) and confirmed nocturnal events (RR, 1.19; 95% CI, 1.07 to 1.31) in the insulin glargine group than the NPH group (P value not reported).
Yki-Järvinen et al[95] Insulin glargine HS and metformin (G+MET) vs NPH insulin HS and	MC, OL, PG, RCT Men and women 35 to 75 years of age with type 2 diabetes previously	N=110 36 weeks	Primary: Change in HbA_{1c} from baseline Secondary: Diurnal glucose concentrations,	Primary: At 36 weeks, HbA_{1c} decreased from 9.13±0.15% to 7.14±0.12% and from 9.26±0.15% to 7.16±0.14% in the G+MET and NPH+MET groups, respectively. The changes in HbA_{1c} were determined to be not significant between groups (P value not reported). Secondary: The diurnal profiles were consistently lower in the G+MET group compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
metformin (NPH+MET) Insulin doses were titrated to achieve an FPG 72 to 100 mg/dL in both groups.	treated with a stable dose of sulfonylurea and metformin (>1.5 g) or metformin alone for at least 3 months prior to screening, with a BMI 20 to 40 kg/m^2, HbA_{1c} ≥8.0%, FPG ≥7 mmol/L measured during self monitoring of blood glucose between 4 and 2 weeks prior to study start, and fasting C-peptide ≥0.33 nmol/L		symptomatic hypoglycemia	the NPH+MET group (8.6±0.3 vs 10.1±0.3 mmol/L, respectively; P=0.002). During the first 12 weeks, the G+MET group had significantly lower number of episodes of symptomatic hypoglycemia than the NPH+MET group, but the rates became similar thereafter. The frequency of hypoglycemia averaged 5.4 and 8.0 episodes/patient-year for the G+MET and NPH+MET groups, respectively (P=0.12).
Holman et al[96] Biphasic insulin aspart 30 BID vs insulin aspart TID before meals vs insulin detemir HS to BID	MC, OL, RCT Patients ≥18 years of age with type 2 diabetes who had not been previously treated with insulin, HbA_{1c} 7.0 to 10.0%, on maximum tolerated doses of metformin and a sulfonylurea for	N=708 1 year	Primary: HbA_{1c} at one year Secondary: Proportion of patients with HbA_{1c} ≤6.5%, proportion of patients with ≤ 6.5% but without hypoglycemia during weeks 48	Primary: At 52 weeks, the reduction in HbA_{1c} from baseline was 1.3% in the biphasic group, 1.4% in the prandial group, and 0.8% in the basal group. The difference between the HbA_{1c} levels in the biphasic group (7.3%) and the prandial group (7.2%) were not significant (P=0.08); however, the HbA_{1c} level was higher in the basal group (7.6%; P<0.001 for both comparisons with the basal group). Secondary: The proportion of patients with an HbA_{1c} ≤6.5% was 17% in the biphasic group and 23.9% in the prandial group (P=0.08). The proportion of patients in the basal group was 8.1%, which was lower than the other groups (P=0.001 for the comparison with the biphasic group and P<0.001 for the comparison with the prandial group).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(AM and HS) Insulin doses were titrated to achieve pre-meal capillary blood glucose 72 to 99 mg/dL or PPG 90 to 126 mg/dL. Existing oral antidiabetic drug regimens were continued.	≥4 months, and BMI ≤40 kg/m^2		to 52, rate of hypoglycemia, weight gain, eight-point self monitoring blood glucose	The proportion of patients with an HbA_{1c} ≤6.5% without hypoglycemia during weeks 48 to 52 were 52.5, 43.9, and 78.9% in the biphasic, prandial, and basal groups, respectively (P=0.001). The proportion of patients with an HbA_{1c} level of ≤7.0% was significantly different between the basal group (27.8%) and each of the two other groups (biphasic group, 41.7%; prandial group, 48.7%; P<0.001 for both comparisons). Patients gained weight on all regimens, with a greater increase in the prandial group (5.7 kg; P<0.001 vs basal) than in the biphasic group (4.7 kg; P=0.005 vs prandial and P<0.001 vs basal) or the basal group (1.9 kg). There were no significant differences in overall mean self monitoring blood glucose among the treatment groups. Overall rates of hypoglycemia were 91.9% in the biphasic group (P=0.08 vs prandial), 96.2% in the prandial group (P<0.001 vs basal), and 73.9% in the basal group (P<0.001 vs biphasic). The mean numbers of hypoglycemic events per patient per year were 5.7 in the biphasic group, 12.0 in the prandial group, and 2.3 in the basal group.
Holman et al[97] Biphasic insulin aspart 30 BID vs insulin aspart TID before meals vs insulin detemir HS to BID	MC, OL, RCT Patients ≥18 years of age with type 2 diabetes who had not been previously treated with insulin, HbA_{1c} 7.0 to 10.0%, on maximum tolerated doses of metformin and a sulfonylurea for	N=708 3 years	Primary: HbA_{1c} at three years Secondary: Proportion of patients with HbA_{1c} ≤6.5%, rate of hypoglycemia, weight gain, self monitoring blood glucose	Primary: The mean reduction in HbA_{1c} from baseline to year three was 1.3% in the biphasic group, 1.4% in the prandial group, and 1.2% in the basal group. Secondary: The proportion of patients with an HbA_{1c} ≤6.5% was 31.9% in the biphasic group and 44.7%% in the prandial group (P=0.006). The proportion of patients in the basal group was 43.2% (P=0.03 vs biphasic). The proportion of patients with an HbA_{1c} ≤7.0%was 49.4% in the biphasic group, 67.4% in the prandial group (P<0.001 vs biphasic) and 63.2% in the basal group (P=0.02 vs biphasic).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(AM and HS) Insulin doses were titrated to achieve pre-meal capillary blood glucose 72 to 99 mg/dL or PPG 90 to 126 mg/dL. Existing oral antidiabetic drug regimens were continued.	≥4 months, and BMI ≤40 kg/m^2			Self monitoring blood glucose values were significantly lower in the prandial group than in the biphasic group (P=0.001), but were not significantly different than in the basal group (P=0.06). No significant differences were seen in fasting glucose values in the three groups. A greater mean reduction in postprandial glucose values was seen in the prandial group than in either the biphasic group (P<0.001) or the basal group (P=0.007), with a greater reduction in the basal group than in the biphasic group (P=0.04). The reduction in 3 a.m. glucose values was significantly greater in the basal group than in the prandial group (P=0.02) Patients gained weight on all regimens, with a greater increase in the prandial group (6.4 kg; P<0.001 vs basal) than in the biphasic group (5.7 kg; P=0.20 vs prandial and P=0.005 vs basal) or the basal group (3.6 kg). Overall rates of hypoglycemia were 49.4% in the biphasic group (P=0.68 vs prandial), 51.0% in the prandial group (P=0.14 vs basal), and 44.0% in the basal group (P=0.29 vs biphasic). The median number of hypoglycemic events per patient per year during the trial was 3.0 in the biphasic group, 5.5 in the prandial group, and 1.7 in the basal group. At 3 years, no differences were seen in changes from baseline in either systolic or diastolic blood pressure, high-density lipoprotein or low-density lipoprotein cholesterol, triglycerides, or the ratio of urinary albumin to creatinine, although the differences in high-density lipoprotein cholesterol were significant (P=0.03).
Garber et al[98] Insulin detemir QD or BID and prandial insulin (insulin aspart or regular insulin) or oral antidiabetic drug treatment vs	MC, OL, PG, pooled analysis, RCT Patients ≥18 years of age with type 2 diabetes for at least 1 year treated with insulin, insulin	N=1,374 22 to 26 weeks	Primary: Difference in HbA_{1c} at study endpoint between younger and older patients Secondary: Glucose variability, FPG, insulin doses,	Primary: HbA_{1c} with insulin detemir was as effective as NPH after 22 to 26 weeks (mean treatment difference, 0.035%; 95% CI, -0.114 to 0.183 for older persons and 0.100%; 95% CI, -0.017 to 0.217 for younger persons; P value not reported). Secondary: After 22 to 26 weeks, within-person variation was significantly lower with insulin detemir than with NPH for older persons (24.3 vs 27.2 mg/dL for insulin detemir and NPH, respectively; P<0.05) and for younger persons (22.6 vs 25.8 mg/dL for insulin detemir and NPH, respectively; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
NPH insulin QD or BID and prandial insulin (insulin aspart or regular insulin) or oral antidiabetic drug treatment Insulin doses were adjusted to achieve target FBG 72 to 126 mg/dL, FPG <108 mg/dL, PPG <180 mg/dL or <162 mg/dL.	analogs, or oral antidiabetic drugs for at least 2 months, HbA_{1c} ≤12.0% (in study 3, patients with HbA_{1c} 7.5 to 10% were enrolled); patients were stratified to older (aged ≥65 years) and younger (18 to 64 years of age) subgroups		body weight, hypoglycemia	FPG with insulin detemir was similar to that with NPH after 24 or 26 weeks for both older and younger patients (mean treatment difference, 0.97 mg/dL; 95% CI, -8.01 to 9.95 for older persons and 4.69 mg/dL; 95% CI, -2.30 to 11.67 for younger persons; P value not reported). The mean daily insulin dose was 0.63±0.45 IU/kg for insulin detemir and 0.48±0.28 IU/kg for NPH in younger patients. Older patients had similar doses to younger patients (0.59±0.44 IU/kg for insulin detemir and 0.46±0.26 IU/kg for NPH; P value not reported). The RR for overall hypoglycemia was statistically lower with insulin detemir than with NPH in both older and younger patients (0.59; P=0.002 and 0.75; P=0.022, respectively). The RR for all nocturnal episodes was significantly lower with insulin detemir (P<0.001) in younger patients, but was not significant in older patients.
Raslová et al[99] Insulin detemir QD or BID and prandial insulin (insulin aspart or regular insulin) vs NPH insulin QD or BID and prandial insulin (insulin aspart or regular insulin)	PG, pooled analysis, RCT Patients with insulin-treated type 2 diabetes	N=900 22 to 24 weeks	Primary: Weight gain, HbA_{1c} Secondary: Not reported	Primary: Patients taking insulin detemir had little weight gain, regardless of BMI at study entry. However, patients taking NPH had increased weight gain as baseline BMI increased (P=0.025). Glycemic control was similar with both treatment groups (P value not reported). Secondary: Not reported
Siegmund et al[100] Insulin glargine plus premeal rapid-acting insulin analogs	OS, PRO Patients with type 2 diabetes	N=119 18 months	Primary: Change in HbA_{1c} from baseline Secondary:	Primary: For the insulin glargine group, results showed statistically significant reductions in HbA_{1c} compared to baseline (-0.49%; 95% CI, -0.26 to -0.71; P<0.001). However, the reduction from baseline in HbA_{1c} for the NPH group was determined to be not significant (-0.12%; 95% CI, -0.31 to 0.06; P=0.189). After 18 months, the difference between the two treatment groups

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs NPH plus premeal rapid-acting insulin analogs			Weight gain, incidence of hypoglycemia	was 0.37% (P<0.015). Secondary: Average weight gain was significantly higher in the NPH group than in the glargine group (2.10 vs 0.25 kg, respectively; P=0.025). Although there was a lower risk of hypoglycemia in the insulin glargine group than in the NPH group (0.50 vs 0.71 episodes/patient/month, respectively), the results did not reach statistical significance (P=0.081).
Rosenstock et al[101] Insulin glargine HS vs NPH insulin QD or BID	MA MA of 4 randomized trials in type 2 diabetics comparing insulin glargine to NPH, baseline HbA_{1c} 8.8% in the insulin glargine group and 8.7% in the NPH group	N=2,304 20 to 24 weeks	Primary: Incidence of hypoglycemia Secondary: Effect on HbA_{1c}, percentage of patients reaching target HbA_{1c} (≤7.0%), effect on FPG, and insulin dose	Primary: Significant reductions in symptomatic hypoglycemic risk (-11%; P=0.0006) and nocturnal hypoglycemic risk (-26%; P<0.0001) were reported with insulin glargine compared to NPH. Secondary: No significant difference was noted between groups in HbA_{1c} reduction or percentage of patients reaching target HbA_{1c} ≤7.0%. FPG was significantly lower with insulin glargine (155 mg/dL) compared to NPH (161 mg/dL; P=0.0233). Both groups had similar mean basal and total insulin doses at all study endpoints.
Horvath et al[102] Insulin analogs (insulin glargine or insulin detemir) vs NPH insulin	MA Analysis of 8 studies comparing long-acting insulin analogs to NPH in patients with type 2 diabetes	N=2,293 24 to 52 weeks	Primary: Change in HbA_{1c} from baseline to endpoint Secondary: Number of overall, severe, and nocturnal	Primary: In a MA of studies with relevant data available comparing insulin glargine vs NPH when both agents were administered in the evening, the WMD of change of HbA_{1c} from baseline was estimated to be 0.1% (95% CI, -0.1 to 0.2; P=0.49) in favor of NPH. In all studies comparing evening insulin glargine to NPH, the WMD of change of HbA_{1c} was estimated to be 0.00% (95% CI, -0.1 to 0.1; P=0.93) which confirmed the previous result. In both analyses that compared change in HbA_{1c} with insulin detemir to NPH, NPH was favored (WMD, 0.1%; 95% CI, 0.01 to 0.20; P=0.03 when standard

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			hypoglycemia	deviations were calculated and 0.2%; 95% CI, 0.02 to 0.30; P=0.08 using pooled standard deviations). Even though this result indicated a statistically significant difference in change of HbA_{1c} between insulin detemir and NPH, the difference was within the "non-inferiority" margin of 0.4% for both studies. Secondary: In both comparisons of insulin glargine vs NPH and insulin detemir vs NPH, both long-acting agents had statistically lower rates of severe hypoglycemia (OR, 0.70; 95% CI, 0.40 to 1.23; P value not reported and 0.50; 95% CI, 0.18 to 1.38; P=0.18, respectively). Insulin glargine was found to have a lower frequency of symptomatic hypoglycemia than NPH (RR, 0.84; 95% CI, 0.75 to 0.95; P=0.005). In terms of overall hypoglycemia, there was no difference in the rates of at least one hypoglycemic episode between insulin glargine in the morning, insulin glargine in the evening, and NPH at bedtime (74, 68 and 75%, respectively; P=NS). When comparing insulin detemir to NPH, insulin detemir had significantly lower rates of symptomatic and overall hypoglycemia (RR, 0.56; 95% CI, 0.42 to 0.74; P<0.001 and 0.82; 95% CI, 0.74 to 0.90; P<0.0001, respectively). Both insulin glargine and insulin detemir resulted in significantly lower rates of nocturnal hypoglycemia in comparison to NPH (RR, 0.66; 95% CI, 0.55 to 0.80; P<0.0001 and 0.63; 95% CI, 0.52 to 0.76; P<0.00001, respectively).
Bazzano et al[103] Insulin glargine vs NPH insulin	MA, SR (12 RCTs) Patients with type 2 diabetes with or without oral antidiabetic agents, and not receiving insulin	N=4,385 ≥4 weeks	Primary: Change in baseline HbA_{1c}, FPG, and body weight Secondary: Incidence of hypoglycemia	Primary: Changes in HbA_{1c}, FPG, and body weight demonstrate positive values favoring insulin glargine and negative values favoring NPH. The pooled net change for FPG was 0.21 mmol/L (95% CI, -0.02 to 0.45). Final HbA_{1c} was 7.9 and 7.7% with insulin glargine and insulin NPH, respectively. Pooled net change in body weight was -0.33 kg (95% CI, -0.61 to -0.06). Secondary: The proportions of patients reporting any (59.0 vs 53.0%; P<0.001),

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				symptomatic (51.4 vs 42.9%; P<0.001) and nocturnal hypoglycemia (33.3 vs 19.1%; P<0.001) were significantly greater with insulin NPH. The rates of confirmed (10.0 vs 6.3%; P=0.11) and severe hypoglycemia (2.5 vs 1.4%; P=0.07) were not different between the two treatments.
Davidson et al[104] Biphasic insulin aspart 30 (BIAsp 30) vs biphasic human insulin 30 (BHI 30)	MA Patients with type 2 diabetes who received treatment with biphasic insulin aspart 30 or biphasic human insulin 30	N=1,674 (9 trials) 12 to 48 weeks	Primary: Overall rate of nocturnal hypoglycemia (all major, minor, and symptoms-only) Secondary: Major hypoglycemia, minor hypoglycemia, daytime hypoglycemia, overall hypoglycemia (the sum of all major, minor, and symptoms-only episodes), change in weight from baseline to 12 to 16 weeks of treatment	Primary: No significant difference was found between treatments with respect to the rate of overall hypoglycemia (RR, 1.08; 95% CI, 0.94 to 1.24; P=NS). Secondary: BIAsp 30 had a significantly lower rate of nocturnal hypoglycemia than BHI 30 (RR, 0.50; 95% CI, 0.38 to 0.67; P<0.01). BHI 30 was associated with a significantly lower rate of daytime hypoglycemia (RR, 1.24; 95% CI, 1.08 to 1.43; P<0.01). Significantly fewer patients experienced a major hypoglycemic episode with BIAsp 30 compared with BHI 30 (P<0.05). Rates of minor hypoglycemia were not significantly different between treatments. BIAsp 30 treatment was associated with a larger reduction in PPG than BHI 30 (P<0.01). BHI 30 treatment was associated with a significantly larger reduction in FPG than BIAsp 30 (P<0.01). There were no significant differences in HbA_{1c} among the treatment groups. Both BIAsp 30 and BHI 30 were associated with an increase in weight from base line (0.2 and 0.7 kg, respectively; P=NS).
Fakhoury et al[105] NPH QD	MA (5 OL, PG, RCTs) Patients between	N=2,092 5 to 12 months	Primary: Weight gain, hypoglycemia, HbA_{1c}	Primary: Patients receiving insulin detemir experienced significantly less weight gain compared to those receiving insulin glargine (WMD, -1.22 kg; 95% CI, -2.15 to -0.29; P=0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs insulin detemir in the evening vs insulin glargine in the evening All patients remained on oral diabetes medications.	55.5 and 61.0 years of age with type 2 diabetes who were insulin-naïve and currently receiving oral diabetes medications, with HbA_{1c} 8.6 to 9.6% and BMI of 28.5 to 32.0 kg/m^2		Secondary: Not reported	Fewer episodes of hypoglycemia was reported with insulin detemir compared to insulin glargine (OR, 0.52; 95% CI, 0.28 to 0.98; P=0.044). No significant difference was seen in the mean HbA_{1c} between insulin detemir and insulin glargine (standardized mean difference, 0.09; 95% CI, -0.16 to 0.33; P=0.48). No significant differences were seen in weight gain, incidence of hypoglycemia and mean HbA_{1c} between NPH and insulin glargine. Secondary: Not reported
Singh et al[106] Insulin analogs vs conventional insulin	MA Adult and pediatric patients with type 1 diabetes and type 2 diabetes, and women with gestational diabetes	117 Trials 4 to 30 weeks	Primary: HbA_{1c} and hypoglycemia Secondary: Not reported	Primary: *Adults – Type 1 Diabetes Mellitus* The use of insulin lispro resulted in a lower HbA_{1c} (difference, –0.09%, 95% CI, –0.16 to –0.02), a lower risk of severe hypoglycemia (RR, 0.80; 95% CI, 0.67 to 0.96) and a lower rate of nocturnal hypoglycemia (RR, 0.51; 95% CI, 0.42 to 0.62) compared to regular insulin. For overall hypoglycemia, the rate was similar between the groups receiving insulin lispro and those receiving regular human insulin. For insulin aspart, the mean HbA_{1c} was lower than with regular insulin (difference, –0.13%; 95% CI, –0.20 to –0.07). There were no significant differences between treatments in the risk of severe hypoglycemia or the rate of overall hypoglycemia. The rate of nocturnal hypoglycemia (reported in one study) in patients receiving insulin aspart (CSII) was significantly lower than in patients receiving regular insulin (RR, 0.55; 95% CI, 0.43 to 0.70). There was no significant difference in HbA_{1c} (reported in one study) with insulin lispro or insulin aspart administered through CSII (difference, 0.25%; 95% CI, –0.20 to 0.71). There was also no significant difference in the rates of nocturnal hypoglycemia among the two treatment groups (RR, 1.20; 95% CI, 0.89 to 1.68). The rate of overall hypoglycemia was higher with insulin lispro than with insulin aspart (RR, 1.49; 95% CI, 1.37 to 1.63).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Insulin glargine led to greater reductions in HbA_{1c} compared to NPH insulin (difference, –0.11%; 95% CI, –0.21 to –0.02). There were no significant differences for any type of hypoglycemia when the same bolus insulin was used in each treatment arm. There was no significant difference in HbA_{1c} with insulin detemir and NPH insulin (difference, –0.06%; 95% CI, –0.13 to 0.02). There was a lower risk of severe hypoglycemia (RR, 0.74; 95% CI, 0.58 to 0.96) and nocturnal hypoglycemia (RR, 0.92; 95% CI, 0.85 to 0.98) with insulin detemir compared to NPH; however, there was no difference in overall hypoglycemia. There was no significant difference in HbA_{1c} (reported in one study) between insulin detemir and insulin glargine (difference, –0.03%; 95% CI, –0.26 to 0.20). The risk of severe hypoglycemia (RR, 0.25; 95% CI, 0.07 to 0.86), as well as the risk for severe and nocturnal hypoglycemia were significantly lower with insulin detemir. *Children and Adolescents – Type 1 Diabetes Mellitus* Only one trial compared insulin lispro with regular insulin in adolescents with type 1 diabetes. This study found no difference in HbA_{1c} (difference, –0.01%; 95% CI, –0.21 to 0.19) or the risk of severe hypoglycemia (RR, 1.00; 95% CI, 0.29 to 3.43) among the two treatment groups. The risk of nocturnal hypoglycemia (RR, 0.61; 95% CI, 0.57 to 0.64) and overall hypoglycemia favored insulin lispro. There was no significant difference between insulin lispro and regular insulin in preadolescent patients for the following outcomes: HbA_{1c} (difference, 0.14%; 95% CI, –0.18 to 0.46), risk of severe hypoglycemia (RR, 0.69; 95% CI, 0.24 to 2.01), rates of nocturnal hypoglycemia (RR, 0.96; 95% CI, 0.74 to 1.26), and overall hypoglycemia. Only one trial compared insulin aspart and regular insulin in preadolescent patients with type 1 diabetes. This study found no difference in HbA_{1c} or risk of overall hypoglycemia among the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was no significant difference between insulin glargine and intermediate-acting insulins (mostly NPH insulin) in children and adolescents with type 1 diabetes in HbA_{1c} (difference, –0.25%; 95% CI, –0.55 to 0.05) or any type of hypoglycemia. Only one trial compared insulin detemir with NPH insulin in children and adolescents with type 1 diabetes. This study showed no significant differences between treatments in HbA_{1c} (difference, 0.10%; 95% CI, –0.10 to 0.30) or severe hypoglycemia (RR, 0.80; 95% CI, 0.50 to 1.28). The risk of nocturnal hypoglycemia (RR, 0.85; 95% CI, 0.77 to 0.94), as well as for nocturnal and overall hypoglycemia demonstrated small, statistically significant benefits in favor of insulin detemir. *Adults – Type 2 Diabetes Mellitus* There was no significant difference in HbA_{1c} (difference, –0.03%; 95% CI, –0.12 to 0.06) or risk of severe hypoglycemia (RR, 0.43; 95% CI, 0.08 to 2.37), nocturnal hypoglycemia (RR, 1.63; 95% CI, 0.71 to 3.73) or overall hypoglycemia with insulin lispro and regular insulin. There was no significant difference in HbA_{1c} (difference, –0.09%; 95% CI, –0.21 to 0.04) or risk of any type of hypoglycemia with insulin aspart and regular insulin. Only one trial compared biphasic insulin lispro and biphasic insulin aspart. This study showed no significant difference in HbA_{1c} (difference, 0.14%; 95% CI, –0.02 to 0.30) or overall hypoglycemia in adults with type 2 diabetes. Most of the studies with insulin glargine and NPH insulin have allowed the use of oral antidiabetic drugs. Only one study compared insulin glargine and NPH insulin in combination with a prandial insulin without the use of oral antidiabetic drugs. Glycemic control was no better in the insulin glargine group regardless of the type of combined therapy (difference in $HbA_{1c,}$ –0.05%; 95% CI, –0.13 to 0.04, for insulin glargine with oral antidiabetic therapy; 0.28%, 95% CI, 0.07 to 0.49, for insulin glargine with prandial insulin). There was no significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				difference in the risk of severe hypoglycemia in the studies that used oral antidiabetic therapy (RR, 0.66; 95% CI, 0.29 to 1.48). The relative risk for nocturnal hypoglycemia significantly favored insulin glargine in both the prandial insulin study (RR, 0.78; 95% CI, 0.62 to 0.98) and the studies that allowed oral antidiabetic drugs (RR, 0.56; 95% CI, 0.47 to 0.68). There was a significant reduction in risk of overall hypoglycemia in favor of insulin glargine in the studies allowing oral antidiabetic therapy but not in the bolus insulin study. Most of the studies with insulin detemir and NPH insulin have been conducted in patients receiving oral antidiabetic drugs. One study used prandial insulin (insulin aspart) before meals. There was a significant reduction in HbA_{1c} with NPH insulin compared to insulin detemir in studies that allowed the use of oral antidiabetic drugs (difference, 0.13%; 95% CI, 0.03 to 0.22). The risk for severe hypoglycemia was not statistically significant. The risk for nocturnal hypoglycemia (RR, 0.53; 95% CI, 0.31 to 0.91) and overall hypoglycemia significantly favored insulin detemir. There was no significant difference between treatment groups in terms of HbA_{1c} (difference, 0.10%; 95% CI, –0.18 to 0.38) or risk of overall hypoglycemia in the study that used prandial insulin. The risk of nocturnal hypoglycemia was lower in the insulin detemir group (RR, 0.66; 95% CI, 0.45 to 0.96). Two studies compared insulin detemir with insulin glargine in patients with type 2 diabetes. One of the studies allowed the use of oral antidiabetic therapy and showed no significant difference in HbA_{1c} (difference, 0.10%; 95% CI, –0.06 to 0.26) or nocturnal hypoglycemia. The other study used prandial insulin (insulin aspart) and reported a higher HbA_{1c} with insulin detemir (difference, 0.20%; 95% CI, 0.10 to 0.30). There was no difference in risk of overall hypoglycemia. *Pregnant Women With Diabetes* There were no significant differences in HbA_{1c} with insulin lispro or regular insulin (difference, 0.20%; 95% CI, –1.03 to 1.43) or the risk of severe hypoglycemia (RR, 0.21; 95% CI, 0.01 to 4.10) among pregnant women with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				type 1 diabetes. There was no significant difference in HbA_{1c} with insulin lispro or regular insulin (difference, 0.06%; 95% CI, –0.11 to 0.23) among women with gestational diabetes. Results from a single trial comparing insulin aspart with regular insulin in pregnant women with type 1 diabetes were similar to those for insulin lispro in terms of HbA_{1c} (difference, –0.08%; 95% CI, –0.28 to 0.12), risk of severe hypoglycemia (RR, 1.14; 95% CI, 0.76 to 1.71) and risk of overall hypoglycemia (RR, 1.04; 95% CI, 0.98 to 1.11). Secondary: Not reported
Intermediate-Acting and Long-acting Insulins: Type 1 and 2 Diabetes				
Yenigun et al[107] Insulin detemir QD Patients were originally receiving insulin glargine (QD or BID), and then were switched to insulin detemir.	Subgroup analysis of PREDICTIVE study (MC, OL, OS, PRO) Patients with type 1 or 2 diabetes, with or without concomitant oral antidiabetic agents	N=1,285 12 weeks	Primary: Change in baseline HbA_{1c} Secondary: Changes in baseline FPG, insulin dose, and body weight; incidence of hypoglycemia; safety	Primary: Switching to insulin detemir significantly decreased HbA_{1c} (insulin glargine QD and type 1 diabetes, -0.47; P<0.0001, insulin glargine QD and type 2 diabetes, -0.51%; P<0.0001, insulin glargine BID and type 1 diabetes; -0.31%; P<0.05, insulin glargine BID and type 2 diabetes; -0.89%; P<0.05). Secondary: Significant decreases in self-monitored FPG and within-patient FPG variability were reported in patients who switched from insulin glargine QD to insulin detemir (P<0.000 for all). Results were not significant in patients who switched from insulin glargine BID because of a small sample size. Except for type 2 diabetics who switched from insulin glargine BID, total daily insulin dose increased by 1 to 5% in patients transferring to insulin detemir. There was a significant decrease in body weight in patients who switched from insulin glargine QD (P<0.05). Body weight decreased in patients who switched from insulin glargine BID; however, it did not reach significance. On case of serious hypoglycemia was reported in a patient who switched from

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				insulin glargine QD. No serious adverse events were reported in type 2 diabetes, although three patients experienced major hypoglycemia that were not reported as a severe adverse event. The number of hypoglycemic episodes was significantly reduced in patients with type 1 and 2 diabetes who switched from insulin glargine QD, as well as type 2 diabetes who switched from insulin glargine BID (P<0.0001). There was also a significant decrease in the number of major and nocturnal hypoglycemic events in patients who switched from insulin glargine QD (P<0.0001).
Trials Comparing Insulin Devices				
Ignaut et al[108] Insulin lispro administered via KwikPen® device vs insulin lispro administered via vial/syringe vs insulin aspart administered via FlexPen® device	OL, RCT, XO Patients 40 to 75 years of age with type 1 or type 2 diabetes who had been preparing and self-injecting insulin using vial and syringe for at least the previous 3 months, and who were pen device-naïve	N=232 1 day	Primary: Preference (responses to Question 13 of the insulin device preference battery post-assessment and the final preference question) Secondary: Characteristics of different insulin pen devices (overall ease of use, ease of handling, ease of pressing injection button while injecting)	Primary: The KwikPen® was significantly preferred to vial and syringe, with 89% of patients preferring KwikPen® (95% CI, 0.8437-0.9284). KwikPen® was significantly preferred to FlexPen®, with 67% of patients preferring KwikPen® (95% exact CI, 0.6063-0.7312). FlexPen® was significantly preferred to vial and syringe (81%; 95% CI, 0.7529-0.8581). Secondary: For the ease of use assessment, 94% of KwikPen® users and 84% of FlexPen® users either strongly agreed or agreed that the device was easy to use (P=0.006). For the ease of handling assessment, 87% of KwikPen® users and 73% of FlexPen® users either strongly agreed or agreed that the pen was easy to hold in their hand when they injected insulin (P=0.002). For the ease of injection assessment, 85% of KwikPen® users and 66% of FlexPen® users either strongly agreed or agreed that the injection buttons on their respective pens were easy to press when injecting their dose (P<0.001). When comparing preference with the KwikPen® to vial/syringe, all comparison were statistically significant favoring KwikPen® in terms of appearance, quality of the device, discretion, convenience, use in public, easy to learn, easy to use, reliability, dose confidence, ability to follow an insulin regimen, overall satisfaction, and recommendation to others.
Korytkowski et al[109]	OL, RCT, XO	N=121	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Insulin aspart protamine and insulin aspart 70/30 mix vial/syringe for 4 weeks vs biphasic insulin aspart protamine and insulin aspart 70/30 mix prefilled pen for 4 weeks	Patients with type 1 diabetes and type 2 diabetes were stabilized on 70% insulin aspart and 30% insulin aspart protamine then randomized to use vial/syringe or a prefilled pen for 4 weeks; after 4 weeks, patients were XO to the other administration method; baseline HbA_{1c} 8.7%	12 weeks	Patient preference Secondary: Effect on glycemic control (HbA_{1c}, FPG, fructosamine, and four-point glucose profile)	Seventy-four percent indicated preference for prefilled pen over the vial/syringe (95% CI, 71 to 87) compared to 20% who indicated a preference for the vial/syringe. Secondary: Overall, a significant reduction in HbA_{1c} (-3%; $P<0.05$) was observed during the entire study (no comparison between treatment groups made). There was no significant difference in FPG, fructosamine or four-point glucose profile between treatment groups. There was no difference in safety profile between treatment groups.
Insulin Therapy Compared to Other Antidiabetic Medications: Type 2 Diabetes				
Mu et al[110] Insulin glargine vs no additional treatment All patients received oral antidiabetic medications. Active treatments were stopped after normoglycemia was maintained for 3 months.	RCT Patients 35 to 50 years of age with newly diagnosed type 2 diabetes, FPG ≥9.0 mmol/L, and HbA_{1c} ≥9.0%	N=129 1 year	Primary: Effects on β-cell function, diabetes remission rate Secondary: Not reported	Primary: Both treatment groups improved HOMA-B and HOMA-IR significantly. They had similar effects on insulin resistance (0.50±0.09 vs 0.48±0.09; P=0.23). However, the addition of insulin therapy could recover β-cell function much more than no additional treatment (2.17±0.14 vs 2.11±0.13; P=0.03). More patients achieved target glycemic control with the addition of insulin therapy (98.3% [58 of 59]) in less time (10.4±2.5 days) compared to no additional treatment (95.7% [67 of 70] and 12.4±3.4 days). At one year follow-up, more patients maintained target glycemia without any drugs in patients who received additional insulin therapy compared to patients who received no additional treatment (37.9 vs 20.9%). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Patients were then followed-up with diet and physical exercise at 1 year.				
Okerson et al[111] Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs placebo or insulin All patients also received existing antidiabetic treatment regimens.	Post-hoc analysis (6 RCTs) Type 2 diabetics ≥18 years of age with HbA_{1c} ≥6.5 to ≤11.0%, BMI ≥25 to ≤45 kg/m^2, and stable body weight	N=2,171 24 to 52 weeks	Primary: Change in baseline BP and pulse pressure Secondary: Not reported	Primary: In the overall study population, by the end of the six month trial period, exenatide was associated with a significantly greater decrease in SBP compared to placebo (-2.20±0.56 vs 0.60±0.56 mm Hg; treatment difference, -2.80±0.75 mm Hg; P=0.002) and insulin (-4.5±0.6 vs -0.9±0.6 mm Hg; treatment difference, -3.7±0.85 mm Hg; P<0.0001). In contrast, DBP was minimally decreased and not different between exenatide and placebo (-0.70±0.33 vs -0.20±0.33 mm Hg; P=0.21) or insulin (-1.60±0.35 vs -0.80±0.36 mm Hg; P=0.16). No differences in the proportions of patients altering the number, type, or intensity of ongoing antihypertensive regimens were observed between treatments (data not reported). Patients with abnormal SBP at baseline achieved the greatest decreases with exenatide (exenatide vs placebo, -8.3 vs -4.5 mm Hg; treatment difference, -3.8 mm Hg; P=0.0004 and exenatide vs insulin, -8.3 vs -4.2 mm Hg; treatment difference, -4.0 mm Hg; P<0.0001). In patients with normal BP at baseline, no differences in the decreases in SBP or DBP were observed between any of the treatments (P values not reported). Pulse pressure effects trended similarly to SBP effects, with the most pronounced decrease occurring in exenatide-treated patients with baseline pulse pressures ≥40 mm Hg. In this subgroup, the reduction in pulse pressure was significantly greater with exenatide compared to placebo (-3.5 vs -0.5 mm Hg; treatment difference, -2.9 mm Hg; P<0.0001) and insulin (-4.0 vs -0.9 mm Hg; treatment difference, -3.0 mm Hg; P<0.0001). By the end of the six month treatment period, a significantly greater proportion of exenatide-treated patients with elevated baseline SBP (26%) achieved the SBP goal for type 2 diabetics compared to insulin (treatment difference, 19%; P=0.03); however, no treatment effect on DBP was observed. In contrast, although no significant exenatide-related shifts were observed in SBP classifications, a significantly greater proportion of exenatide-treated patients

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				were favorably shifted from a baseline classification of “abnormal DBP” to “normal DBP” compared to placebo (treatment difference, 41.4 vs 32.4%; P=0.02). Secondary: Not reported
Diamant et al[112] DURATION-3 Exenatide ER 2 mg SC once weekly vs insulin glargine SC QD All patients received existing background oral glucose-lowering regimens.	OL, PG, RCT Type 2 diabetics ≥18 years of age with suboptimum glycemic control despite maximum tolerated doses of metformin (stable dose of ≥1,500 mg for ≥8 months) or combined metformin and sulfonylurea treatment ≥3 months, HbA_{1c} 7.1 to 11.0%, BMI 25 to 45 kg/m^2, and a stable body weight ≥3 months	N=456 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} <7.0 or <6.5%, fasting serum glucose, self-monitored blood glucose concentrations, body weight, fasting lipid profile, BP, markers of cardiovascular risk, β cell function, insulin profile, patient-reported quality of life, safety	Primary: Decreases in HbA_{1c} were significantly greater with exenatide ER (-1.5±0.05%) compared to insulin glargine (-1.3±0.06%; treatment difference, -0.16±0.07%; 95% CI, -0.29 to -0.03; P=0.017). In patients receiving exenatide ER or insulin glargine plus metformin only, HbA_{1c} was decreased by -1.5±0.06 and -1.4±0.07% (treatment difference, -1.8±0.08%; 95% CI, -0.34 to -0.02; P=0.031). Secondary: Significantly greater proportions of exenatide ER-treated patients achieved HbA_{1c} <7.0 (60 vs 48%; P=0.010) and <6.5% (35 vs 23%; P=0.004) compared to insulin glargine treated patients. Fasting serum glucose decreased with both treatments (-2.1±0.2 vs -2.8±0.2 mmol/L); however, insulin glargine significantly decreased values compared to exenatide ER (treatment difference, -0.6 mmol/L; 95% CI, 0.2 to 1.0; P=0.001). With regards to self-monitored blood glucose concentrations, both treatments significantly decreased FPG and PPG at all eight time points (P<0.0001 for all). Significantly lower concentrations with insulin glargine compared to exenatide ER were observed at 0300 hour (P=0.022) and before breakfast (P<0.0001), and significantly lower concentrations with exenatide ER were observed after dinner (P=0.004). Exenatide ER resulted in significantly greater reductions in post-prandial glucose excursions compared to insulin glargine after morning (P=0.001) and evening meals (P=0.033). Seventy nine percent of patients receiving exenatide ER experienced both a decrease in HbA_{1c} and body weight compared to 63% of patients receiving insulin glargine who experienced a decrease in HbA_{1c} and increase in body

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				weight. Only exenatide ER resulted in a significant decrease in TC (-0.12 mmol/L; P<0.05). There were no differences between the two treatments in the decreases in TC (treatment difference, -0.07 mmol/L; 95% CI, -0.21 to 0.06) and LDL-C (treatment difference, -0.09 mmol/L; 95% CI, -0.21 to 0.03), and the increase in HDL-C (treatment difference, -0.02; 95% CI, -0.05 to 0.02) observed. Only exenatide ER resulted in a significant decrease in SBP (-3 mm Hg; P<0.05). There were no differences between the two treatments in the decreases in SBP (treatment difference, -2 mm Hg; 95% CI, -4 to 1) and DBP (treatment difference, 0 mm Hg; 95% CI, -2 to 1) observed. Only exenatide ER resulted in a significant decrease in high-sensitivity CRP (-2.0 mg/dL; P<0.05). There were no differences between the two treatments in the decreases in high-sensitivity CRP (-1.2 mg/dL; 95% CI, -2.8 to 0.3) and urinary albumin:creatinine ratio (0.06 mg/mmoL; 95% CI, -1.70 to 1.80) observed. Both treatments resulted in improvements in IWQOL-Lite, binge eating scale, and DTSQ total scores, with only patients receiving exenatide ER achieving significant improvements on the EQ-5D index. Significant improvements with exenatide ER compared to insulin glargine were observed for one of the IWQOL-Lite domains (self-esteem) and one EQ-5D dimension (usual activities) (data not reported). Gastrointestinal events including nausea and diarrhea were among the most common reported adverse events with exenatide ER, with nasopharyngitis and headache being the most commonly reported with insulin glargine. Gastrointestinal events were all mild or moderate and no serious adverse events were reported by more than one patient, except chest pain (two patients).
Diamant et al[113] DURATION-3 Exenatide ER 2 mg SC	ES Type 2 diabetics ≥18 years of age	N=390 84 weeks	Primary: Change in baseline HbA_{1c}	Primary: At 84 weeks, HbA_{1c} decreased from baseline by -1.2% with exenatide ER compared to -1.0% with insulin glargine (P=0.029).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
once weekly vs insulin glargine SC QD All patients received existing background oral glucose-lowering regimens.	with suboptimum glycemic control despite maximum tolerated doses of metformin (stable dose of ≥1,500 mg for ≥8 months) or combined metformin and sulfonylurea treatment ≥3 months, HbA_{1c} 7.1 to 11.0%, BMI 25 to 45 kg/m^2, and a stable body weight ≥3 months		Secondary: Proportions of patients achieving HbA_{1c} <7.0 and ≤6.5%, body weight, incidence of hypoglycemia, safety	Secondary: The proportions of patients who achieved end point HbA_{1c} targets <7.0 and ≤6.5% were 44.6 and 36.8% with exenatide ER and insulin glargine (P=0.084) and 31.3 and 20.2% with exenatide ER and insulin glargine (P=0.009), respectively. Patients receiving exenatide ER lost 2.1 kg of body weight compared to patients receiving insulin glargine who gained 2.4 kg (P<0.001). Among patients receiving metformin plus a sulfonylurea, the incidence of minor hypoglycemia was 24 and 54% with exenatide ER and insulin glargine (P<0.001). Among adverse events occurring in ≥5% of all patients, diarrhea (12 vs 6%) and nausea (15 vs 1%) occurred more frequently (P<0.05) with exenatide ER compared to insulin glargine.
Bergenstal et al[114] Exenatide 5 µg BID for 4 weeks, then 10 µg BID vs insulin aspart 12 units QD before dinner (BIAsp 30 QD) vs insulin aspart 12 units	OL, PG, RCT Patients 18 to 80 years of age with type 2 diabetes mellitus and HbA_{1c} ≥8.0%, insulin-naïve, and receiving treatment with metformin and a sulfonylurea for at least 3 months prior to enrolling	N=372 24 Weeks	Primary: Change in HbA_{1c} from baseline Secondary: FPG, eight-point plasma glucose profiles, changes in body weight	Primary: At 24 weeks, HbA_{1c} values were 7.61, 7.75, 8.46% for BIAsp 30 BID, BIAsp 30 QD, and exenatide, respectively (both P<0.0001 compared to exenatide). At the end of the study, 37% of patients in the BIAsp 30 BID group achieved an HbA_{1c} <7.0% compared to 20% of patients in the exenatide group (P=0.0060). Additionally, 25% of patients in the BIAsp 30 BID group achieved an HbA_{1c} ≤6.5% compared with 8% in the exenatide group (P=0.0004). At the end of the study, 26% of patients in the BIAsp 30 QD group achieved an HbA_{1c} <7.0% compared to 20% of patients in the exenatide group (P=0.3488). Additionally, 12% of patients in the BIAsp 30 QD group achieved an HbA_{1c} ≤6.5% compared with 8% in the exenatide group (P=0.3802).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
divided equally before breakfast and dinner (BIAsp 30 BID) All patients were receiving metformin with or without a sulfonylurea. Insulin dose was titrated as necessary.	in the study			The percentage of patients who achieved HbA_{1c} ≤6.5% was higher with BIAsp 30 BID compared to BIAsp 30 QD (25 vs 12%; P=0.0122). Secondary: There were significant changes in FPG with BIAsp 30 BID (-62.7 mg/dL; P<0.0001 vs exenatide) and BIAsp 30 QD (-52.4 mg/dL; P=0.0002 vs exenatide) compared to exenatide (-21.4 mg/dL). At the end of the study, the eight-point plasma glucose profiles were significantly lower with BIAsp 30 BID and BIAsp 30 QD than exenatide. At 24 weeks, hypoglycemia was reported in 56% of patients in the BIAsp 30 QD group, 61% of patients in the BIAsp 30 BID group, and 29% in the exenatide group. Weight loss was reported in the exenatide group (-1.9 kg) compared with weight gain in the BIAsp 30 QD (+2.8 kg) and BIAsp 30 BID (4.1 kg). There were more reports of nausea and vomiting with exenatide than in the insulin groups.
Heine et al[115] Exenatide 5 µg BID for 4 weeks, then 10 µg BID vs insulin glargine QD at bedtime All patients were receiving existing metformin and/or sulfonylurea regimens.	OL, RCT Patients 30 to 75 years of age with type 2 diabetes not adequately controlled (defined as HbA_{1c} 7.0 to 10.0%) with combination metformin and sulfonylurea therapy at maximally effective doses,	N=551 26 weeks	Primary: Change in HbA_{1c} Secondary: Change in FPG, fasting glucose <100 mg/dL and body weight loss	Primary: At 26 weeks, similar reductions in HbA_{1c} were noted between exenatide and insulin glargine (–1.11%; CI, –0.123 to 0.157). Secondary: A significantly reduction in fasting plasma glucose from baseline was observed in the insulin glargine group (–51.5 mg/dL; P<0.001). The reduction from baseline in the exenatide group was not significant (–25.7 mg/dL). A significant reduction was observed in the insulin group when compared to the exenatide group (95% CI, 20 to 34 mg/dL). A significantly greater proportion of patients taking insulin glargine (21.6%) achieved fasting glucose of <100 mg/dL than those taking exenatide (8.6%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	BMI between 25 to 45 kg/m^2 and a history of stable body weight (≤10% variation for ≥3 months before screening)			A significant weight loss was experienced in the exenatide group (–2.3 kg) compared to a gain of +1.8 kg in the insulin group (CI, –4.6 to –3.5; P<0.001). Similar rates of hypoglycemia were reported with both agents (CI, –1.3 to 3.4 events/patient-year). Exenatide patients had a higher incidence of daytime hypoglycemia (CI, 0.4 to 4.9 events/patient-year), and a lower rate of nocturnal hypoglycemia than insulin glargine patients (CI, –2.3 to –0.9 events/patient-year). A significantly higher incidence of gastrointestinal side effects, including nausea (57.1 vs 8.6%; P<0.001), vomiting (17.4 vs 3.7%; P<0.001) and diarrhea (8.5 vs 3%; P=0.006), upper abdominal pain (P=0.012), constipation (P=0.011), dyspepsia (P=0.011), decreased appetite (P=0.021), and anorexia (P=0.002) were reported in the exenatide group vs the insulin group. Withdrawals due to adverse events occurred in 9.5% of exenatide patients vs 0.7% of insulin patients.
Secnik Boye et al[116] Exenatide 5 µg BID for 4 weeks, then 10 µg BID vs insulin glargine QD at bedtime All patients were receiving existing metformin and/or sulfonylurea regimens.	MC, OL, RCT Secondary analysis on patients with type 2 diabetes inadequately controlled (defined as an HbA_{1c} between 7.0 and 10.0%) with sulfonylurea and metformin therapy at maximally effective doses, enrolled in a previous 26 week	N=455 26 weeks	Primary: Patient-reported health outcome measures: Diabetes Symptom Checklist-revised, DTSQ, EQ-5D, Medical Outcomes Study 36-Item Short-Form Health Survey, Diabetes Medical Outcomes Study 36-Item Short-Form Health Survey	Primary: Both exenatide and insulin glargine groups experienced a significant improvement from baseline in patient-reported health outcome measures as demonstrated by Diabetes Symptom Checklist-revised overall scores, DTSQ, EQ-5D and Medical Outcomes Study 36-Item Short-Form Health Survey scores (P<0.05 for all measures). There was not a statistical difference between treatment groups in any of the outcome measures (P>0.05 for all measures). Neither the exenatide nor the insulin glargine group experienced a significant improvement in Medical Outcomes Study 36-Item Short-Form Health Survey scores (P=0.93 for both groups). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	study		Secondary: Not reported	
Nauck et al[117] Exenatide 5 µg BID for 4 weeks, then 10 µg BID vs insulin aspart BID All patients were receiving existing metformin and/or sulfonylurea regimens.	MC, OL, RCT Patients 30 and 75 years of age who had suboptimal glycemic control despite receiving optimally effective metformin and sulfonylurea therapy for ≥3 months, HbA_{1c} ≥7.0 and ≤11.0%, a BMI ≥25 and ≤40 kg/m^2, and a history of stable body weight (≤10% variation for ≥3 months)	N=501 52 weeks	Primary: Mean change in HbA_{1c} levels, weight, fasting serum glucose levels, postprandial glucose levels, adverse events Secondary: Not reported	Primary: There was not a significantly different change from baseline in mean HbA_{1c} levels between the exenatide (–1.04%) and insulin aspart groups (–0.89%, 95% CI, −0.32% to 0.01%; P=0.067). Patients in the exenatide group experienced a gradual weight loss of –2.5 kg, compared to a gradual weight gain of 2.9 kg in the insulin aspart group, (95% CI, −5.9 to −5.0; P<0.001) at the end of 52 weeks. Patients in both exenatide (–1.8 mmol/L) and insulin aspart (–1.7 mmol/L) groups had a significant decrease in fasting serum glucose compared to baseline (P<0.001 for both groups). There was not a significant difference between groups (CI, −0.6 to 0.4; P=0.689). Patients in the insulin aspart group had significantly lower mean glucose values at pre-breakfast (P=0.037), pre-lunch (P=0.004) and 03.00 hours (P=0.002). Patients in the exenatide group had a greater reduction in postprandial glucose excursions following morning (P<0.001), midday (P=0.002) and evening meals (P<0.001). The withdrawal rate was 21.3% in the exenatide group and 10.1% in the insulin aspart group. Adverse events that were more commonly reported in the exenatide vs insulin aspart group included: nausea (33.2 vs 0.4%), vomiting (15.0 vs 3.2%), diarrhea (9.5 vs 2%) and other clinically relevant adverse events (13.4 vs 6.4%). Secondary: Not reported
Kabadi et al[118] Tolazamide 1 gram daily plus premixed 70% NPH	PC, RCT Patients with type 2 diabetes	N=40 7 months	Primary: Changes in body weight, HbA_{1c}, and fasting C-	Primary: Changes in body weight were 2.5±0.8 kg for the tolazamide group, 2.6±1.0 kg for the glyburide group, 2.4±0.9 kg for the glipizide XL group, and 2.2±0.7 kg for the glimepiride group, all were significant compared to placebo (P<0.01)

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and 30% regular insulin daily vs glyburide 20 mg daily plus premixed 70% NPH and 30% regular insulin daily vs glipizide XL plus premixed 70% NPH and 30% regular insulin daily vs glimepiride 8 mg daily plus premixed 70% NPH and 30% regular insulin daily vs placebo plus premixed 70% NPH and 30% regular insulin daily	mellitus with a lapse of glycemic control, established by documentation of HbA_{1c} >7.4% on ≥2 occasions at an interval of ≥3 months in each patient while taking oral sulfonylureas consisting of one of these drugs in the maximum recommended daily dose: tolazamide 1 g daily, glyburide 20 mg daily, glipizide XL 20 mg daily, or glimepiride 8 mg daily		peptide concentrations Secondary: Changes in daily insulin dose and the number of hypoglycemic episodes confirmed by finger stick blood glucose <60 mg/dL	after the addition of insulin. All groups achieved optimal glycemic control as expressed by HbA_{1c} <7.4%, 1% above the highest normal level of 6.4% in our laboratory as recommended by the American Diabetes Association after the addition of insulin. HbA_{1c} was 6.8±0.4% for tolazamide, 6.9±0.4% for glyburide, 6.7±0.4% for glipizide XL, 6.7±0.3% for glimepiride, and 7.0±0.3% for placebo. C-peptide levels decreased in all groups. The reduction in the C-peptide level was significantly greater (P<0.05) in the placebo group compared to the sulfonylurea groups. There were no significant differences among the sulfonylurea groups. Secondary: Patients receiving sulfonylureas required a significantly lower (P<0.01) daily insulin dose, as well as dose per kilogram of body weight in comparison to patients receiving placebo (P<0.01). The daily insulin dose and units per kilogram of body weight was significantly lower (P<0.05) in patients receiving glimepiride in comparison to those receiving tolazamide, glyburide, or glipizide XL. The number of hypoglycemic episodes during the last four weeks of the study were significantly lower in the sulfonylurea groups as compared to the placebo group (P<0.01). The differences among the individual sulfonylurea groups were not significantly different.
Russell-Jones et al[119] LEAD-5 Liraglutide 1.8 mg SC QD vs	PC, PG, RCT Type 2 diabetic patients 18 to 80 years of age with oral glucose lowering agents	N=581 26 weeks	Primary: Change in baseline in HbA_{1c} Secondary: Change in baseline body	Primary: Decreases in HbA_{1c} were -1.33, -0.24, and -1.09% with liraglutide, placebo, and insulin. Decreases achieved with liraglutide were significantly greater compared to placebo and insulin (differences for liraglutide vs placebo, -1.09%; 95% CI, -1.28 to -0.90; P<0.0001 and differences for liraglutide vs glargine, -0.24%; 95% CI, -0.39 to -0.08; P=0.0015).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo vs insulin glargine (OL) All patients also received metformin 2,000 mg/day and glimepiride 4 mg/day.	≥3 months before screening, HbA_{1c} 7.5 to 10.0% (previous oral glucose lowering agent monotherapy) or 7.0 to 10.0% (previous oral glucose lowering agent combination therapy), and BMI ≤45 kg/m^2		weight, waist circumference, FPG, eight-point self-monitored glucose concentrations, β cell function, and BP	Secondary: The decrease in body weight with liraglutide (-1.8 kg) was significantly greater compared to placebo (0.42 kg; treatment difference, -1.39 kg; 95% CI, -2.10 to -0.69; P=0.0001). Additionally, patients gained weight with insulin (1.6 kg; treatment difference, -3.43 kg; 95% CI, -4.00 to -2.86; P<0.0001). The decrease in waist circumference with liraglutide (-1.50 cm) was significantly greater compared to insulin (0.89 cm; treatment difference, -2.40 cm; 95% CI, -3.14 to -1.65; P<0.0001), but not compared to placebo (-0.62 cm; treatment difference, -0.88 cm; 95% CI, -1.81 to 0.04; P=0.0608). Final decreases in FPG were -1.55, -1.79, and -0.53 mmol/L with liraglutide, insulin, and placebo. The decrease with liraglutide, and the likelihood of achieving American Diabetes Association targets (FPG 5.0 to 7.2 mmol/L) was significantly greater compared to placebo (treatment difference, -2.08 mmol/L; 95% CI, 2.53 to -1.64; P<0.0001; OR, 4.99; 95% CI, 2.65 to 9.39), but not compared to insulin (data not reported). Decreases in PPG were achieved with liraglutide (-1.81 mmol/L) and insulin (-1.61 mmol/L), with liraglutide being significantly greater compared to placebo (0.03 mmol/L; treatment difference, -1.84 mmol/L; 95% CI, -2.63 to -1.33; P<0.0001), but not compared to insulin (data not reported). Significant improvements in β cell function as demonstrated by the proinsulin:C-peptide ratio compared to insulin (treatment difference, -0.00366; 95% CI, -0.00597 to -0.00136; P=0.0019) and placebo (treatment difference, -0.00671; 95% CI, -0.00964 to -0.00377; P<0.0001) were achieved with liraglutide. A significant decrease in SBP was achieved with liraglutide (-4.00 mm Hg) compared to insulin (-0.54 mm Hg; treatment difference, -4.51 mm Hg; 95% CI, -6.82 to -2.20; P=0.001), but not compared to placebo (-1.4 mm Hg; treatment difference, -2.53 mm Hg; 95% CI, -5.36 to 0.29; P=0.0791). No significant decreases in DBP were achieved with liraglutide relative to either placebo or insulin.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Civera et al[120] Repaglinide 2 mg TID before meals plus metformin 850mg BID plus NPH insulin before dinner vs metformin 850mg BID plus NPH insulin before dinner vs NPH insulin BID	OL, PG Patients with poorly controlled type 2 diabetes despite being on two or more oral antidiabetic drugs	N=37 24 weeks	Primary: HbA_{1c}, hypoglycemia, body weight Secondary: Not reported	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 (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
Cesur et al[121] Repaglinide up to 4 mg QD vs glimepiride up to 8 mg QD vs insulin glargine up to 36 U QD	MC, OL, OS, PRO Patient 33 to 67 years of age with type 2 diabetes, HbA_{1c} 6.0 to 8.0% taking oral diabetes agents, who were willing to fast throughout Ramadan month	N=65 Duration not specified	Primary: FBG, PPG, HbA_{1c}, fructosamine, BMI, lipid metabolism and hypoglycemia in pre-Ramadan and post-Ramadan fasting Secondary: Not reported	Primary: In the fasting group, both FPG and PPG levels showed no significant changes at post-Ramadan and one-month post-Ramadan compared to pre-Ramadan. In the nonfasting group, FPG levels did not change significantly throughout the study, whereas PPG levels increased at post-Ramadan (P<0.05 and P<0.01, respectively). At post-Ramadan and one-month post-Ramadan, changes in PPG values in the fasting group were lower compared to the nonfasting group (P<0.01 for both time periods). There was no significant change in HbA_{1c} levels between the nonfasting and fasting groups. There was a significant increase in fructosamine levels in both fasting group and non-fasting group at one-month post-Ramadan (P<0.01 for both). BMI did not change during the study in fasting group but a gradual increase in BMI was seen in the nonfasting group (P<0.05 between pre-Ramadan and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				post-Ramadan in nonfasting group). TC, LDL-C and TG did not change throughout the study period but HDL-C levels significantly increased at post-Ramadan in the fasting group (P<0.01). In nonfasting group, LDL-C and TG levels significantly increased at post-Ramadan (P<0.05 for both). At least one hypoglycemia episode was reported in 12.2% of patients in the fasting group and 12.5% of patients in the nonfasting group. Hypoglycemia was seen in 14.3% of patients in the glimepiride group, 11.1% in the repaglinide group and 10% in the insulin group. There was no significant difference between three drug groups regarding the rate of hypoglycemia. Secondary: Not reported
Chisalita et al[122] Repaglinide 4mg TID before meals for 10 weeks vs insulin aspart 13 to 46 units/day (4 to 20 units at breakfast, 5 to 15 units at lunch and 4 to 15 units at dinner) for 10 weeks	XO Patients ≥60 years of age with type 2 diabetes	N=5 20 weeks	Primary: HbA_{1c}, blood glucose, C-peptide, free human insulin, free total (human and analogue) insulin, proinsulin, islet amyloid polypeptide, growth hormone binding protein, and plasma lipoprotein concentrations were measured Secondary: Not reported	Primary: The HbA_{1c} was 6.1% at the end of repaglinide therapy and 5.9% at the end of insulin aspart therapy (P=NS). C-peptide concentrations were significantly higher during repaglinide treatment compared to insulin aspart treatment (AUC 2,453 vs 1,153; P=0.02). Free human insulin levels were significantly higher on repaglinide than on insulin aspart therapy (AUC 215 vs128; P<0.05). Proinsulin levels were higher when measured during repaglinide treatment than during treatment with insulin aspart. Islet amyloid polypeptide levels tended to be higher during repaglinide compared to insulin aspart treatment (P=NS). Fasting plasma insulin like growth factor-I concentration was 220 ng/mL during treatment with insulin aspart and 226 ng/mL during treatment with repaglinide (P=NS).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Compared to fasting levels, the insulin like growth factor binding protein-1 levels were lower during repaglinide (P<0.05), but not during insulin aspart treatment (P=NS). Repaglinide treatment increased plasma growth hormone binding protein concentration compared with insulin aspart (1,094 vs 942 pmol/L; P=0.02). Repaglinide treatment resulted in higher postprandial plasma TC, TG and apolipoprotein B concentrations compared with insulin aspart. There was no significant difference in LDL-C or HDL-C Secondary: Not reported
Meneghini et al[123] (abstract) Insulin glargine vs pioglitazone	MC, OL, PG Adults with poorly controlled type 2 diabetes (HbA_{1c} 8.0 to 12.0%), despite ≥3 months of sulfonylurea or metformin monotherapy	N=389 48 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, BMI, body weight, safety	Primary: At trial end, insulin glargine resulted in a significantly greater reduction in HbA_{1c} compared to pioglitazone (-2.48 vs -1.86%; 95% CI, -0.93 to -0.31; P=0.001). Secondary: Insulin glargine resulted in significantly greater reductions in FPG at all time points (trial end difference, -34.9 mg/dL; 95% CI, -47.6 to -22.2; P<0.0001). Changes in weight and BMI were similar between the two treatments. Compared to pioglitazone, insulin glargine resulted in a lower overall incidence of possibly treatment-emergent adverse events (12.0 vs 20.7%) and fewer study discontinuations (2.2 vs 9.1%), but a higher rate (per patient-year) of confirmed clinically relevant hypoglycemic episodes (4.97 vs 1.04; P<0.0001) and severe hypoglycemia (0.07 vs 0.01; P=0.0309).
Dorkhan et al[124] Pioglitazone 30 to 45 mg QD and existing oral hypoglycemic therapy	RCT, OL Patients with type 2 diabetes and inadequate glycemic	N=36 26 weeks	Primary: Change in HbA_{1c}, β-cell function, insulin sensitivity, degree of patient satisfaction	Primary: After 26 weeks, the change in HbA_{1c} from baseline was -1.3% (P<0.01) for pioglitazone and -2.2% (P<0.01) for insulin glargine. There was no significant difference between the treatment groups (P=0.050). There was no difference in insulin, β-cell function, or insulin sensitivity among

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs insulin glargine 6-10 IU/day administered in the morning (titrated as necessary) and existing oral hypoglycemic therapy	control (defined as treatment with metformin and sulfonylurea/ meglitinide in doses ≥50% of maximum recommended doses and HbA_{1c} >6.2%		Secondary: Not reported	the two treatment groups (P value not significant). Insulin glargine resulted in a greater reduction in proinsulin concentrations than pioglitazone (-55 vs -25%; P<0.01). Pioglitazone increased HDL-C (0.14 mmol/L) compared to a slight decrease in the insulin glargine group (-0.04 mmol/L; P<0.01 between groups). There were no significant differences between the treatment groups with regards to other lipid parameters (P value not significant). The degree of satisfaction with treatment was similar in the pioglitazone and insulin glargine treatment groups. There was a doubling of serum adiponectin levels in the pioglitazone group (7.5 to 15; P<0.01) compared to a significant decrease in the insulin glargine group (8.7 to 7.6; P=0.04; P<0.01 between groups). Secondary: Not reported
Aljabri et al[125] Pioglitazone 30 to 45 mg QD vs NPH insulin 0.3 unit/kg QD All patients were receiving existing sulfonylurea or metformin therapy	OL, RCT Patients with poorly controlled type 2 diabetes (HbA_{1c} >8%) with insulin secretagogues and metformin monotherapy	N=62 16 weeks	Primary: Effect on HbA_{1c}, FPG, incidence of hypoglycemia (< 68 mg/dL), effect on lipoproteins, quality of life (assessed using the DTSQ) Secondary: Not reported	Primary: Similar reductions in HbA_{1c} were observed in pioglitazone-treated (–1.9%) and NPH insulin-treated patients (–2.3%; P=0.32). Nonsignificant differences in reduction in FPG were observed with NPH insulin (–77 mg/dL) and pioglitazone (–52 mg/dL; P=0.07). Significantly more patients reported hypoglycemia with NPH insulin (19) than with pioglitazone (11; P=0.02). Significant increases in HDL-C were observed with pioglitazone (4 mg/dL) compared to NPH insulin (0 mg/dL; P=0.02). No significant differences in total cholesterol, LDL cholesterol and triglycerides were reported between the two treatment groups. No significant differences were noted for the DTSQ scores between the two

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				treatment groups. Secondary: Not reported
Ligvay et al[126] Pioglitazone 15 to 45 mg QD plus glyburide 1.25 mg BID vs insulin aspart protamine and insulin aspart (NovoLog Mix 70/30) 0.2 units/kg divided twice daily All patients were receiving metformin 1,000 mg BID Doses of medications could be titrated at the investigator's discretion.	RCT, OL Patients 21 to 70 years of age with type 2 diabetes who were treatment naïve	N=58 36 months	Primary: HbA_{1c}, rate of treatment failures (defined as HbA_{1c} >8.0%), hypoglycemia, weight gain, compliance, QOL, and patient satisfaction Secondary: Not reported	Primary: After 36 months, HbA_{1c} was 6.1 % in the insulin-treated group compared to 6.0% in the triple oral group (P=0.26). The percentage of patients achieving HbA_{1c} <7.0% was 100% in both groups at baseline; 92% of patients in the insulin group and 76% of patients in the triple oral group met the HbA_{1c} goal at the end of 36 months. Three patients in each group reached the "treatment failure" end point. The insulin group had 0.51 mild hypoglycemia events/person month and the triple oral group had 0.68 event/person-month (P=0.18). The insulin group averaged 0.04 severe hypoglycemic event/person-year, and the triple oral group averaged 0.09 event/ person-year (P=0.53). In the completer analysis, the triple oral group experienced more weight gain than the insulin group: 10.10 kg (95% CI, 4.46 to 15.74) versus 3.36 kg (-0.47 to 7.20; P=0.04). Compliance was high throughout the trial: 93% in the insulin-treated group and 90% in the triple oral group. There were differences between the groups for any of the 12 QoL domains evaluated. All patients receiving insulin reported satisfaction with insulin treatment and willingness to continue insulin at 18 months after randomization. Secondary: Not reported
Ibrahim et al[127]	NI, RCT	N=90	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Group I: oral metformin (500 mg TID) without increasing the insulin dose vs group II: increased insulin dose	Pregnant women with gestational or pre-existing DM at gestations between 20 and 34 weeks who showed insulin resistance (defined as poor glycemic control at a daily dose of ≥1.12 units/kg)	Variable duration	Maternal glycemic control Secondary: Maternal hypoglycemia, hospital admissions, neonatal outcomes	Glycemic control was achieved in 76.1% of patients in group I and 100% of patients in group II (P=0.001). Secondary: Readmission for poor glycemic control was not significantly different between groups (P=0.471). Bouts of maternal hypoglycemia occurred in 6.5% of patients in group I and 22.7% in group II (P=0.029). Only two neonatal/delivery outcomes showed a statistical difference: Neonatal hypoglycemia occurred in 7.0% of cases in group I vs 38.5% in group II (P=0.001). Neonatal Intensive Care Unit admission occurred in 18.6% of group I neonates and 41% of group II neonates (P=0.026).
Spaulonci et al[128] Metformin vs insulin	PRO, RCT Women with gestational diabetes with singleton pregnancy, use of diet and exercise for a minimum period of 1 week without satisfactory glycemic control, absence of risk factors for lactic acidosis, and absence of anatomic and/or chromosome anomalies of the conceptus detected by	N=92 Variable duration	Primary: Maternal glycemic control Secondary: Neonatal outcomes	Primary: Higher mean glucose levels were observed in the insulin group (P=0.020), mainly because of higher levels observed after dinner (P=0.042). Twenty-one percent of women using insulin and 27% of women using metformin achieved adequate glycemic control in the first week of treatment (P=0.11). Twelve (26.08%) of the 46 women in the metformin group required supplemental insulin for adequate glycemic control. Secondary: No significant differences between the two groups were observed regarding the following neonatal outcomes: gestational age at birth, 1-minute Apgar score, 5-minute Apgar score, umbilical artery pH at birth, or newborn weight. There were no fetuses with macrosomia in the group metformin vs three (6.5%) cases in the insulin group (P=0.242). A higher frequency of neonatal hypoglycemia was observed in cases treated with insulin (22.2%) compared with newborns from the metformin group (6.5%) (P=0.032).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	ultrasonography.			
Niromanesh et al[129] Metformin vs insulin	RCT, SB Gestational diabetes mellitus women with singleton pregnancy and gestational age between 20 and 34 weeks who did not achieve glycemic control on diet	N=160 Variable duration	Primary: Maternal glycemic control, birth weight Secondary: Neonatal and obstetric complications	Primary: The two groups were comparable with respect to mean fasting blood sugar and postprandial measurements throughout pregnancy after randomization until delivery. The mean fasting blood sugar was <95 mg/dL in 74% and 79% of women in the metformin and insulin groups, respectively (P=0.457). Neonates from the metformin group had a significantly lower circumference of head, arm and chest (P<0.05) and had lower birth weight (P=0.005) and height (P=0.033). The frequency rate of SGA (small for gestational age; birth weight < 10th percentile) was 3.8% in the metformin group and 2.5% in the insulin group. The relative risk of LGA (large for gestational age; birth weight > 90th percentile) in the metformin group was half that of the insulin group (RR, 0.5; 95% CI, 0.3 to 0.9, P=0.012). Secondary: The relative risk of emergency cesarean and preterm delivery was 1.6 and 2.2 times higher, respectively, in the metformin group; however, this was not statistically significant. The two groups were not statistically different in terms of need for phototherapy, incidence of hypoglycemia, and birth defects. The two groups were comparable with respect to umbilical artery pH, Apgar score at 5 min, and hospitalization days. Neonatal Intensive Care Unit admission and respiratory distress syndrome was nonsignificantly more frequent in the metformin group (RR, 2.5; 95% CI, 0.5 to 12.5, P=0.443).
Poolsup et al[130] Pool A: metformin vs insulin Pool B: glyburide vs insulin	MA Women with gestational diabetes mellitus	N=2,151 (13 RCTs) Variable duration	Primary: Safety and efficacy of oral antidiabetic agents compared to insulin Secondary: Not reported	Primary: <u>Pool A</u> There was a nonsignificant difference in the risk of macrosomia (RR, 0.93; 95% CI, 0.61 to 1.41) and large for gestational age (LGA) births (RR, 0.88; 95% CI, 0.70 to 1.12) between the two study groups. A significant increase in the risk of preterm births occurred in the metformin group as compared to insulin (RR, 1.51; 95% CI, 1.04 to 2.19; P=0.03). Rate of neonatal/perinatal mortality was very low in both groups and results remained statistically non-significant. Risk of shoulder dystocia, neonatal hypoglycemia, congenital abnormality, and small for gestational age (SGA) births tended to be lower with metformin but statistical significance was not achieved. A non-significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				decrease in risk of caesarean section, pre-eclampsia, and labor induction was noticed with metformin compared to insulin. A significant decrease in the risk of gestational hypertension was observed in the metformin arm (RR, 0.54; 95% CI, 0.31 to 0.91; P=0.02). A significant decrease in PPG levels occurred (mean difference, -2.47 mg/dL; 95% CI, -4.00 to -0.94, P=0.002) in metformin group compared to insulin, while results were statistically nonsignificant between the two groups for FPG levels (mean difference, 0.74 mg/dL; 95% CI, -0.52 to -2.01). Pool B Glyburide significantly increased the risk of macrosomia (RR, 3.07; 95% CI, 1.14 to 8.23; P=0.03) and neonatal hypoglycemia (RR, 2.30; 95% CI, 1.28 to 4.11; P=0.005) compared to insulin. There was no difference between glyburide and insulin with regard to risk for LGA births; statistically significant heterogeneity was detected for this outcome. There were no significant differences in the risk of preterm births, neonatal mortality, congenital abnormality, or SGA births for glyburide versus insulin. None of the maternal outcomes (caesarean section, pre-eclampsia, maternal hypoglycemia, glycemic levels) displayed a significant difference between glyburide and insulin. The effect estimate for fasting glucose levels (mean difference, 1.90 mg/dL; 95% CI, -0.38 to 4.18) and postprandial glucose levels (mean difference, 3.42 mg/dL; 95% CI, -1.17 to 8.02) favored the insulin group, but results remained nonsignificant. Secondary: Not reported
Nichols et al[131] Metformin vs sulfonylurea vs	MC, OS, RETRO Patients who initiated metformin, sulfonylurea, insulin or TZDs between 1996 and 2002 and	N=9,546 ≥12 months	Primary: Weight changes Secondary: Not reported	Primary: Patients treated with metformin lost an average of 2.4 kg, sulfonylurea-treated patients gained 1.8 kg, insulin-treated patients gained 3.3 kg, and thiazolidinedione-treated patients gained 5.0 kg. All comparisons with metformin were statistically significant. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
insulin vs TZDs	continued use of that drug for at least 12 months without adding other therapies			
Black et al[132] 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 effects, 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 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				using a variety of validated diseases specific and nonspecific tools. Treatment satisfaction using the World Health Organization DTSQ improved significantly in patients receiving repaglinide compared to patients receiving placebo.
Saenz et al[133] 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 photo-coagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from MI, stroke, peripheral vascular disease, renal disease, hypoglycemia or hyperglycemia, and sudden death); all-cause	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
			mortality Secondary: Changes in HbA_{1c}, FPG, quality of life, weight, BMI, lipids, insulin, C-peptide, BP, microalbuminuria, glomerular filtration rate, renal plasma flow	
Monami et al[134] DPP-4 inhibitors (linagliptin, alogliptin, sitagliptin, saxagliptin, vildagliptin*) vs placebo or active comparator (oral hypoglycemic agents and/or insulin)	MA (53 trials) Patients with type 2 diabetes who were receiving a DPP-4 inhibitor	N=33,881 ≥24 weeks	Primary: Incidence of cancer Secondary: Incidence of pancreatitis, all-cause and cardiovascular mortality, incidence of major cardiovascular events	Primary: There were 176 cases of cancer (107 and 69 in patients receiving DPP-4 inhibitors and comparators, respectively); 12.5% were gastrointestinal, 5.7% were pancreatic, 6.2% were pulmonary, 14.7% were mammary gland/female genital tract, 11.3% were male urogenital tract, 3.4% were thyroid, and 26.1% were of another origin. There was no difference in the proportion of cases between patients receiving DPP-4 inhibitors or a comparator (P=0.90). Secondary: The risk of pancreatitis with DPP-4 inhibitors was 0.786 (P=0.55). The number of reported deaths was 28 and 31 with DPP-4 inhibitors and comparators, respectively. Cardiovascular deaths occurred in 10 patients receiving DPP-4 inhibitors and 20 patients receiving comparators. The risk for all-cause death and cardiovascular death in patients receiving DPP-4 inhibitors was 0.668 (P=0.149 and P=0.054, respectively). There were 137 and 120 major cardiovascular events reported with DPP-4 inhibitors and comparators, respectively. DPP-4 inhibitors were associated with a significantly lower risk of major cardiovascular events (OR, 0.689; P=0.006).
Shyangdan et al[135]	MA (RCTs)	N=not reported	Primary: Change in	Primary: Change in baseline HbA_{1c}

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
GLP-1 receptor agonist based therapies (albiglutide*, exenatide ER, liraglutide, lixisenatide*, semaglutide*, and taspoglutide*) vs non-GLP-1 receptor based therapies (placebo, TZDs, DPP-4 inhibitors, insulin glargine, and sulfonylureas)	Type 2 diabetics ≥18 years of age	8 to 26 weeks	baseline HbA_{1c}, incidence of hypoglycemia, weight change Secondary: Health-related quality of life, safety, mortality, morbidity, BP, FPG, PPG, lipid profile, β cell function	Exenatide ER significantly decreased HbA_{1c} compared to TZDs (-1.5 vs -1.2%; P=0.02), DPP-4 inhibitors (-1.5 vs -0.9%; P<0.0001), and insulin glargine (-1.5 vs -1.3%; treatment difference, -0.2%; 95% CI, -0.35 to -0.05; P=0.03). There was no difference in the proportion of patients achieving an HbA_{1c} <7.0% between exenatide ER and TZDs (60 vs 52%; P=0.15). A significantly greater proportion of patients receiving exenatide ER achieved an HbA_{1c} <7.0% compared to patients receiving DPP-4 inhibitors (60 vs 35%; P<0.0001) and patients receiving insulin glargine (60 vs 48%; P=0.03). Compared to placebo, treatment with liraglutide 1.2 mg significantly decreased HbA_{1c} (-1.15%; 95% CI, -1.33 to -0.96; P<0.00001). Patients receiving liraglutide 1.2 mg were more likely to achieve an HbA_{1c} <7.0% compared to patients receiving placebo (OR, 2.91; 95% CI, 1.74 to 4.87; P<0.05). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.64%; 95% CI -0.83 to -0.45; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to TZDs (OR, 1.60; 95% CI, 1.18 to 2.15; P value not reported). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.34%; 95% CI -0.53 to -0.15; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to DPP-4 inhibitors (OR, 2.56; 95% CI, 1.94 to 3.37; P value not reported). Liraglutide 1.2 mg was not associated with a decrease in HbA_{1c} compared to sulfonylureas (-0.01%; 95% CI, -0.27 to 0.29; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.2 mg compared to sulfonylureas (OR, 0.98; 95% CI, 0.84 to 1.14; P=0.78). Compared to placebo, liraglutide 1.8 mg significantly decreased an HbA_{1c} (-1.15%; 95% CI, -1.31 to -0.99; P<0.05). Patients receiving liraglutide 1.8 mg were more likely to achieve HbA_{1c} <7.0% compared to patients receiving placebo (OR, 3.25; 95% CI, 1.97 to 5.36; P<0.05). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.69%; 95% CI -0.88 to -0.50%; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.8 mg compared to TZDs (OR, 1.91; 95% CI, 1.43 to 2.53; P value not reported). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.60%; 95% CI -0.78 to -0.42; P value

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				not reported). The likelihood of achieving HbA_{1c} <7.0% was greater with liraglutide 1.8 compared to DPP-4 inhibitors (OR, 1.99; 95% CI, 1.48 to 2.66; P value not reported). Liraglutide 1.8 mg was not associated with a reduction in HbA_{1c} compared to sulfonylureas (-0.02%; 95% CI -0.30 to 0.26; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.8 mg compared to sulfonylureas (OR, 1.09; 95% CI, 0.94 to 1.26; P=0.27). Liraglutide decreased HbA_{1c} to a greater extent compared to insulin glargine (-0.24%; 95% CI, -0.49 to 0.01; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not different between insulin glargine and liraglutide (OR, 1.16; 95% CI, 0.96 to 1.40; P value not reported). Liraglutide 1.2 mg was associated with a non-significant increase in HbA_{1c} compared to 1.8 mg (0.10%; 95% CI, -0.03 to 0.23; P=0.13). Patients receiving liraglutide 1.2 mg were not more likely to achieve an HbA_{1c} <7.0% compared to the 1.8 mg dose (P=0.92). Incidence of hypoglycemia The incidence of minor hypoglycemia was similar between exenatide ER and TZDs. The incidence of minor hypoglycemia was higher with DPP-4 inhibitors (five vs two patients) and insulin glargine (26 vs 8%) compared to exenatide ER. The incidence of major hypoglycemia was higher with insulin glargine compared to exenatide ER (two vs one patients). Overall, there was no difference in the incidence of minor hypoglycemia between liraglutide 1.2 mg and placebo (P=0.42), and there was significantly more hypoglycemia with liraglutide 1.8 mg (OR, 1.66; 95% CI, 1.15 to 2.40; P=0.007). The incidence of minor hypoglycemia was higher with insulin glargine compared to liraglutide (29 vs 27%). Liraglutide was associated with a significantly higher rate of minor hypoglycemia compared to TZDs (P=0.048), and similar rates compared to DPP-4 inhibitors (P values not reported). Liraglutide was associated with a significantly lower incidence of hypoglycemia compared to sulfonylureas (P<0.00001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Weight loss Exenatide ER significantly decreased weight compared to TZDs (-2.3 vs 2.8 kg; P<0.00001), DPP-4 inhibitors (-2.3 vs -0.8 kg; P=0.0009), and insulin glargine (-2.6 vs 1.4 kg; P<0.00001). Patients receiving liraglutide 1.2 mg experienced an average weight loss of -0.75 kg (95% CI, -1.95 to 0.45; P=0.22). Liraglutide 1.2 mg was associated with a greater decrease in weight compared to insulin glargine (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), TZDs (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), DPP-4 inhibitors (-1.90 kg; 95% CI, -2.65 to -1.15; P value not reported), and sulfonylureas (-3.60 kg; 95% CI, -4.15 to -3.05; P value not reported). Patients receiving liraglutide 1.8 mg experienced a significant weight loss compared to placebo (-1.33 kg; 95% CI, -2.38 to 0.27; P=0.0014). Liraglutide 1.8 mg was associated with a greater decrease in weight compared to TZDs (-2.30 kg; 95% CI, -2.85 to -1.75; P value not reported), DPP-4 inhibitors (-2.42 kg; 95% CI, -3.17 to -1.67; P value not reported), and (-3.80 kg; 95% CI, -4.35 to -3.25; P value not reported). Patients were more likely to experience weight gain with liraglutide 1.2 mg compared to 1.8 mg (0.48 kg; 95% CI, 0.16 to 0.80; P value not reported). Secondary: Data on mortality and morbidity were not reported for any treatment. Quality of life Exenatide ER significantly improved weight-related QOL and IWQOL total scores compared to TZDs (IWQOL treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). Both exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and DPP-4 inhibitors (4.56; 95% CI, 2.56 to 6.57) resulted in significant improvements in weight-related QOL and IWQOL total scores. Treatment satisfaction was significantly greater with exenatide ER compared to DPP-4 inhibitors (treatment difference, 1.61; 95% CI, 0.07 to 3.16; P=0.0406). Exenatide ER significantly improved the self-esteem IWQOL domain and one

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				EQ-5D dimensions compared to insulin glargine. Data for liraglutide were not reported. Safety Withdrawals due to adverse events were greater with exenatide ER compared to TZDs (6.9 vs 3.6%), DPP-4 inhibitors (6.9 vs 3.0%), and insulin glargine (4.7 vs 0.9%). More serious adverse events occurred with TZDs (6 vs 3%) compared to exenatide ER. The incidence of serious adverse events was similar between exenatide ER and DPP-4 inhibitors (3 vs 3%) and insulin glargine (5 vs 4%). Compared to placebo, withdrawals due to adverse events were between 5 and 10% with liraglutide 1.2 mg and between 4 and 15% with liraglutide 1.8 mg. Withdrawals were also higher with liraglutide compared to sulfonylureas (9.4 to 12.9 vs 1.3 to 3.0%). Liraglutide was associated with more gastrointestinal adverse events (nausea, vomiting, and diarrhea) compared to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas. BP There was no difference in the decreases in SBP and DBP between exenatide ER and TZDs. Exenatide ER significantly decreased SBP compared to DPP-4 inhibitors (treatment difference, -4 mm Hg; 95% CI, -6 to -1; P=0.0055). There was no difference in the decrease in DBP between treatments. Data comparing exenatide ER and insulin glargine were not reported. Liraglutide 1.2 mg did not significantly decrease SBP (P=0.15) compared to placebo (P=0.15) and DPP-4 inhibitors (P=0.76). Liraglutide 1.8 mg significantly decreased SBP (P=0.05) compared to placebo, but not DPP-4 inhibitors (P=0.86). Liraglutide also significantly decreased SBP compared to insulin glargine (P=0.0001) and sulfonylureas (P value not reported). No difference in SBP was observed between liraglutide and DPP-4 inhibitors. There was no difference between liraglutide in the decrease in DBP compared to placebo, insulin glargine, or sulfonylureas. DPP-4 inhibitors significantly decreased DBP compared to liraglutide 1.8 mg (P value not reported). Data

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				comparing liraglutide and TZDs were not reported. FPG There was no difference in the decrease in FPG between exenatide ER and TZDs (-1.8 vs -1.5 mmol/L; P=0.33). Exenatide ER significantly decreased FPG compared to DPP-4 inhibitors (-0.90 mmol/L; 95% CI, -1.50 to -0.30; P=0.0038), and insulin glargine significantly decreased FPG compared to exenatide ER (-0.70 mmol/L; 95% CI, 0.14 to 1.26; P=0.01). Liraglutide significantly decreased FPG compared to placebo (1.2 mg; P<0.0001 and 1.8 mg; P<0.00001), TZDs (P≤0.006), and DPP-4 inhibitors (P<0.00001). There was no difference between liraglutide and insulin glargine or sulfonylureas in decreases in FPG (P value not reported). PPG There was no difference in the decrease in PPG between exenatide ER and TZDs. Exenatide ER significantly decreased PPG at all measurements on a 6-point self-monitored glucose concentrations profile compared to DPP-4 inhibitors (P<0.05). Both exenatide ER and insulin glargine decreased PPG at all eight time points, with significant difference in favor of exenatide ER after dinner (P=0.004) and insulin glargine at 03000 hour (P=0.022) and before breakfast (P<0.0001). Liraglutide significantly decreased PPG compared to placebo (P value not reported), TZDs (P<0.05), and sulfonylureas (liraglutide 1.8 mg; P<0.0001). There was no difference between liraglutide and insulin glargine in decreases in PPG (P value not reported). It was reported that PPG recorded in trials comparing liraglutide and DPP-4 inhibitors was highly variable. Lipid profile TZDs significantly decreased TG compared to exenatide ER. Exenatide ER decreased TC and LDL-C, while TZDs and DPP-4 inhibitors increased these measures. All treatments increased HDL-C. Data comparing exenatide ER and insulin glargine were not reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Compared to placebo, liraglutide 1.2 decreased TG (P<0.05) and LDL-C (P<0.05), and no difference was observed with liraglutide 1.8 mg. Data comparing liraglutide to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas were not reported. β cell function Data for exenatide ER are not reported. Liraglutide significantly improved HOMA-B compared to placebo (P value not reported), TZDs (P<0.05), and DPP-4 inhibitors (P value not reported); and proinsulin:insulin ratio compared to placebo (P value not reported), insulin glargine (P=0.0019), and TZDs (P≤0.02). There was no difference between liraglutide and sulfonylureas in the improvements in HOMA-B and proinsulin:insulin ratio.
Gangji et al[136] 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
Lincoff et al[137] Pioglitazone monotherapy vs metformin (1 trial), placebo (4 trials), sulfonylureas (6 trials) or rosiglitazone (1 trial) or	DB, MA, RCT with placebo or active comparator Adult patients with type 2 diabetes and inadequate glycemic control	N=16,390 (19 trials) 4 months to 3.5 years	Primary: Composite of death from any cause, MI or stroke Secondary: Incidence of serious heart failure	Primary: Death, MI, or stroke occurred in 375 of 8,554 patients (4.4%) receiving pioglitazone and 450 of 7,836 patients (5.7%) receiving control therapy (HR, 0.82; 95% CI, 0.72 to 0.94; P=0.005). Individual components of the primary end point were reduced with pioglitazone treatment with varying degrees of statistical significance (death: HR, 0.92; P=0.38, MI: HR, 0.81; P=0.08, death and MI: HR, 0.85; P=0.04, and stroke: HR, 0.80; P=0.09). Progressive separation of time-to-event curves became apparent after

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
pioglitazone combination therapy (7 trials) with insulin, metformin, or sulfonylureas vs active comparator or placebo				approximately one year of therapy. Secondary: Serious heart failure was reported in 2.3% of the pioglitazone-treated patients and 1.8% of the control treated patients (HR, 1.41; 95% CI, 1.14 to 1.76; P=0.002). The composite of serious heart failure and death was not significantly increased among patients receiving pioglitazone (HR, 1.11; 95% CI, 0.96 to 1.29; P=0.17).
Karter et al[138] Patients initiated pioglitazone (15.2%), sulfonylureas (25.3%), metformin (50.9%), and insulin (8.6%) alone, or in addition to pre-existing therapies	Cohort study of all patients in the Kaiser Permanente Medical Care Program with type 2 diabetes (Kaiser Permanente Northern California Diabetes Registry) who initiated any new diabetes pharmacotherapy between October 1999 and November 2001	N=23,440 10.2 months (mean)	Primary: Time-to-incident admission to hospital for congestive heart failure Secondary: Not reported	Primary: Three hundred and twenty admissions for congestive heart failure were observed during the follow-up (mean, 10.2 months) after drug initiation. Relative to patients initiating sulfonylureas, there were no significant increases in the incidence of hospitalization for congestive heart failure in those initiating pioglitazone (HR, 1.28; 95% CI, 0.85 to 1.92). There was a significantly higher incidence among those initiating insulin (HR, 1.56; 95% CI, 1.00 to 2.45) and lower incidence among those initiating metformin (HR, 0.70; 95% CI, 0.49 to 0.99). Secondary: Not reported
Nissen et al[139] Rosiglitazone monotherapy or combination therapy vs	MA of RCTs of more than 24 weeks that had outcome data for MI and death from cardiovascular causes (included ADOPT and	42 trials n=15,560 for rosiglitazone; n=12,283 for comparator 24 to 208	Primary: MI and death from cardiovascular causes Secondary: Not reported	Primary: Rosiglitazone was associated with a significant increase in the risk of MI compared to the control agent (OR, 1.43; 95% CI, 1.03 to 1.98; P=0.03). Compared to the control agent, rosiglitazone was associated with a trend toward increased cardiovascular death (OR, 1.64; 95% CI, 0.98 to 2.74; P=0.06).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo or active comparators (including gliclazide*, glimepiride, glipizide, glyburide, insulin, and metformin)	DREAM trials) Mean age of participants was 56 years, mean baseline HbA_{1c} 8.2%	weeks		Although not a prespecified end point, the OR for death from any cause with rosiglitazone was 1.18 (95% CI, 0.89 to 1.55; P=0.24). Secondary: Not reported
Kheirbek et al[140] Hypoglycemic medications (metformin, glyburide, glipizide, rosiglitazone, acarbose, chlorpropamide, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, insulin, and DPP-4 inhibitors) *Defined as any use of the medication independent of dose or days of use	OS, RETRO Veterans with diabetes cared for at a Veterans Administration Capital area medical center	N=17,773 Variable duration	Primary: All-cause mortality Secondary: Not reported	Primary: After adjustments were made for severity of illness and patient demographics, the remaining variance in mortality was explained by exposure to five medications, listed in order of impact on risk-adjusted mortality: glipizide (OR=1.566), glyburide (OR=1.804), rosiglitazone (OR=1.805), insulin (OR=2.382), and chlorpropamide (OR=3.026). None of the other medications (metformin, acarbose, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, and DPP-4 inhibitors) were associated with excess mortality beyond what could be expected from the patients' severity of illness or demographic characteristics. Insulin, glyburide, glipizide, and rosiglitazone continued to be associated with statistically significant increased mortality after controlling for possible drug interactions. Secondary: Not reported
Long-Term Outcomes Trials				
DCCT Research Group[141] Insulin administered QD or BID vs insulin administered TID or via external pump	RCT Insulin-dependent patients with type 1 diabetes with mild retinopathy (secondary prevention cohort) or	N=1,441 6.5 years (mean)	Primary: Effect on retinopathy development (primary prevention cohort) or progression (secondary prevention cohort)	Primary: Intensive insulin therapy significantly reduced the risk of retinopathy onset (primary prevention cohort) by 76% compared to standard therapy (P<0.001). Intensive insulin therapy significantly reduced the risk of retinopathy progression (secondary prevention cohort) by 54% compared to standard therapy (P<0.001). Secondary: Intensive insulin therapy significantly reduced the risk of microalbuminuria by 34% in the primary prevention cohort (P=0.04) and by 43% in the secondary

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	without retinopathy (primary prevention cohort), baseline HbA_{1c} 9.1% in both treatment groups		Secondary: Effect on renal function (micro-albuminuria and albuminuria), neuropathy development, and macrovascular disease	prevention cohort (P=0.001) compared to standard therapy. Intensive insulin therapy significantly reduced the risk of albuminuria by 56% in the secondary prevention cohort (P=0.01) compared to standard therapy. Intensive insulin therapy significantly reduced the risk of neuropathy appearance by 69% in the primary prevention cohort (P=0.006) and by 57% in the secondary prevention cohort (P<0.001) compared to standard therapy. Nonsignificant reduction of risk of macrovascular disease was observed with intensive insulin therapy (44%; 95% CI, -10 to 68) compared to standard therapy. Intensive insulin therapy had a threefold higher incidence of hypoglycemic events (P<0.001) compared to standard therapy.
UKPDS Group[142] Intensive therapy with sulfonylurea (chlorpropamide, glyburide, or glipizide) or insulin vs dietary therapy	RCT Patients newly diagnosed with type 2 diabetes, baseline HbA_{1c} 7.05% in the dietary treatment group and 7.09% in the intensive therapy group	N=3,867 10 years	Primary: Time to the first occurrence of any diabetes-related endpoint, time to diabetes-related death, all-cause mortality Secondary: MI, sudden death, stroke, amputation or death due to peripheral vascular disease, microvascular complications,	Primary: There was a 12% risk reduction (95% CI, 1 to 21; P=0.029) for any diabetes-related end point, 10% risk reduction (95% CI, -11 to 27; P=0.34) for any diabetes-related death, and a 6% risk reduction (95% CI, -10 to 20; P=0.44) for all-cause mortality when intensive therapy (sulfonylurea or insulin) was compared to conventional therapy with diet. Patients receiving an intensive treatment (sulfonylurea or insulin) had a 25% risk reduction (95% CI, 7 to 40; P=0.0099) in microvascular end points compared with conventional therapy with diet. Most of this reduction was due to fewer cases of retinal photocoagulation. There were no differences between the intensive and conventional treatment groups or between the three intensive treatment groups in the number of patients who had a silent MI, cardiomegaly, evidence of peripheral vascular disease, or absent peripheral pulses. Secondary: There was no significant difference between chlorpropamide, insulin, and glibenclamide in macrovascular events.[†]

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			retinopathy, vitreous hemorrhage, and/or fatal or nonfatal renal failure	There was no significant difference between the three intensive treatments in microvascular end points or in the risk reduction for retinal photocoagulation.

*Agent is not available in the United States.
†Glibenclamide is a synonym for glyburide.
Drug regimen abbreviations: BID=twice daily, ER=extended-release, QAM=once every morning, QD=once daily, QID=four times daily, QPM=once every evening, SC=subcutaneous, TID=three times daily,
Study abbreviations: AC=active-comparator, CS=comparator study, ES=extension study, MA=meta-analysis, MC=multicenter, MN=multinational, NI=noninferiority, OL=open-label, OS=observational, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized-controlled trial, RETRO=retrospective, SR=systematic review, XO=cross-over
Miscellaneous abbreviations: AUC=area under the curve, BMI=body mass index, BP=blood pressure, CI=confidence interval, CRP=C-reactive protein, CSII=continuous subcutaneous insulin infusion, DBP=diastolic blood pressure, DPP-4 inhibitor=dipeptidyl peptidase-4 inhibitor, DTSQ=Diabetes Treatment Satisfaction Questionnaire, EQ-5D=EuroQol Quality of Life, FPG=fasting plasma glucose, GLP-1=glucagon-like peptide 1, HbA1c=glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, HOMA-B=homeostasis model assessment-beta, HOMA-IR=homeostasis model assessment-insulin resistance, HR=hazard ratio, ITT=intention-to-treat, IWQOL=Impact of Weight on Quality of life Questionnaire, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, NPH=human insulin isophane (neutral protamine Hagedorn), OR=odds ratio, PP=per protocol, PPG=post-prandial glucose, REG=regular human insulin, RR=relative risk, SBP=systolic blood pressure, SDS=standard deviation score, SEM=standard error of mean, SMPG=self-monitoring plasma glucose, T2DM=type 2 diabetes mellitus, TC=total cholesterol, TG=triglycerides, TZD=thiazolidinedione, WMD=weighted mean difference

Special Populations

Table 5. Special Populations[1-17]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Entity Products					
Insulin aspart	Use caution in elderly; initial and changes in dosing may cause hypoglycemia. Safety and efficacy in children <2 years of age with T1DM have not been established. Safety and efficacy in children with T2DM have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	B	Not expected; use with caution.
Insulin detemir	Use caution in elderly; initial and changes in dosing may cause hypoglycemia. Safety and efficacy in children <2 years of age with T1DM have not been established. Safety and efficacy in children with T2DM have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	C	Not expected; use with caution.
Insulin glargine	Use caution in elderly; initial and changes in dosing may cause hypoglycemia. Lantus®: Safety and efficacy in children <6 years of age with T1DM have not been established. Safety and efficacy in children with T2DM have not been established. Toujeo®: Safety and efficacy in children have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	C	Not expected; use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Insulin glulisine	Use caution in elderly; initial and changes in dosing may cause hypoglycemia. Safety and efficacy in children <4 years of age with T1DM has have been established. Safety and efficacy in children with T2DM have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	C	Not expected; use with caution.
Insulin lispro	Use caution in elderly; initial and changes in dosing may cause hypoglycemia. Safety and efficacy in children <3 years of age with T1DM have not been established. Safety and efficacy in children with T2DM have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	B	Not expected; use with caution.
Insulin NPH	Use caution in elderly; initial and changes in dosing may cause hypoglycemia. Information regarding use in children is not reported.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	C	Not expected; use with caution.
Insulin regular	Use caution in elderly; initial and changes in dosing may cause hypoglycemia. Humulin® R, Novolin® R: Approved for use in children (age not reported). Humulin® R U-500: Approved for use in children (age not reported; there are no well-controlled trials of use in children). Afrezza®: Safety and efficacy in children have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	B	Not expected; use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Combination Products					
Insulin aspart/ insulin aspart protamine	Use caution in elderly; initial and changes in dosing may cause hypoglycemia. Safety and efficacy in children have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	B	Not expected; use with caution.
Insulin lispro/ insulin lispro protamine	Use caution in elderly; initial and changes in dosing may cause hypoglycemia. Safety and efficacy in children have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	B	Not expected; use with caution.
Insulin regular/ insulin NPH	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported

T1DM=type 1 diabetes mellitus, T2DM=type 2 diabetes mellitus

Adverse Drug Events

Adverse events with the insulin products are rare and are similar among the various products, with the exception of inhaled regular insulin (Afrezza®) having several additional adverse reactions due to its route of administration.[1-17]

Hypoglycemia is the most common adverse event reported with insulin therapy and may be severe enough to cause seizure or death. Due to differences in formulation between insulin products, the timing of hypoglycemia can vary. Risk factors for hypoglycemia include receiving an excessive dose, decreased caloric intake, increase physical activity, illnesses, or when receiving medications that increase the hypoglycemic effects of insulin.[1-17]

Injection site reactions are common among the injectable insulin products. Redness, swelling, and itching may result if administration is not done properly, if the skin is sensitive to cleansing solution, or if the patient is allergic to insulin or components of the insulin formulation.[1-3,5-17]

Generalized insulin allergies are rare but may present as a skin rash over the body, shortness of breath, fast pulse, sweating, a drop in blood pressure, bronchospasm, shock, anaphylaxis, or angioedema.[1-3,5-17]

Inhaled regular insulin (Afrezza®) has a rate of hypoglycemia similar to other insulin preparations. Unlike the injectable products, inhaled regular insulin has several respiratory adverse events which include cough (27%), throat pain/irritation (5%) and bronchitis (2.5%). Additionally, patients treated with inhaled regular insulin had a greater decrease in forced expiratory volume in one second (FEV_1) by 40 mL (95% CI, -80 to -1) compared to patients treated with other antidiabetic treatments in a clinical trial. The decline occurred during the first three months of therapy and persisted over two years. A ≥15% decline in FEV_1 occurred in 6% of patients treated with inhaled regular insulin compared to 3% of comparator-treated subjects.[4]

Contraindications

Table 6. Contraindications[1-17]

Drug	Contraindication		
	Use during acute episodes of hypoglycemia	Hypersensitivity to the drug or any excipient	Chronic lung disease, (e.g. asthma/COPD)
Single Entity Products			
Insulin aspart	✔	✔	-
Insulin detemir	-	✔	-
Insulin glargine	✔ †	✔	-
Insulin glulisine	✔	✔	-
Insulin lispro	✔	✔	-
Insulin NPH	✔ *	✔	-
Insulin regular	✔	✔	✔ ‡
Combination Products			
Insulin aspart/insulin aspart protamine	✔	✔	-
Insulin lispro/insulin lispro protamine	✔	✔	-
Insulin regular/insulin NPH	✔ *	✔	-

COPD= chronic obstructive pulmonary disease
*Not reported for Novolin N or Novolin 70/30
†Toujeo® only
‡Afrezza® only

Black Box Warning for Afrezza® (Insulin, regular)[4]

WARNING
Risk of Acute Bronchospasm in Patients with Chronic Lung Disease Acute bronchospasm has been observed in patients with asthma and COPD using Afrezza® (Insulin, regular). Afrezza® (Insulin, regular) is contraindicated in patients with chronic lung disease such as asthma or COPD. Before initiating Afrezza® (Insulin, regular), perform a detailed medical history, physical examination, and spirometry (FEV1) to identify potential lung disease in all patients.

Warnings and Precautions

Table 7. Warnings and Precautions[1-17]

Warning/Precaution	Single Entity Products							Combination Products		
	aspart	detemir	glargine	glulisine	lispro	NPH‖	regular	aspart/ aspart protamine	lispro/ lispro protamine	regular/ NPH‖
Administration; eat a meal five to ten minutes after administration	✔	-	-	-	-	-	-	-	-	-
Administration; inject within 15 minutes of meal initiation	-		-	-	-	-	-	✔	✔	-
Administration; for SQ use only	-	✔	-	-	-	-	-	✔	✔	✔
Antibody production to insulin product has been reported	✔	-	-	-	-	-	✔ §	✔	✔	✔
Bronchospasm, acute; increased risk	-	-	-	-	-	-	✔ ‡	-	-	-
Concurrent use of thiazolidinediones can cause dose-related fluid retention especially in combination with insulin; use caution in heart failure	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Device sharing is not recommended even when the needle is changed; risk of blood-borne pathogens.*	✔	✔	✔	✔	✔	✔	-	✔	✔	✔
Diabetic ketoacidosis risk increased	-	-	-	-	-	-	✔	-	-	-
Dose adjustment and monitoring of blood glucose is essential for insulin therapy	-	✔	✔	✔	✔	✔	✔	✔	✔	✔
External pump use (continuous subcutaneous insulin infusion); don't mix with other insulins or dilute, change vials as appropriate	✔	-	-	✔	✔	-	-	-	-	-
Hepatic dose adjustment may be required	✔	✔	-	✔	✔	-	✔	✔	✔	-
Hypersensitivity and allergic reactions	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Hypoglycemia	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Hypokalemia	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Intravenous infusions; monitor blood glucose and potassium carefully, don't mix insulins for intravenous infusions	-	-	-	✔	-	-	-	-	-	-
Medication errors have been reported; instruct patients to check insulin before each injection	-	-	✔	-	-	-	-	-	-	-
Lung cancer was observed in two patients during clinical trials; there were	-	-	-	-	-	-	✔ ‡	-	-	-

Warning/Precaution	Single Entity Products							Combination Products		
	aspart	detemir	glargine	glulisine	lispro	NPH‖	regular	aspart/ aspart protamine	lispro/ lispro protamine	regular/ NPH‖
zero cases in the control group										
Mix only insulin products that compatible with each other†	✔	-	-	✔	✔	-	-	-	-	-
Pulmonary function declines with use	-	-	-	-	-	-	✔ ‡	-	-	-
Renal dose adjustment may be required	✔	✔	✔	✔	✔	-	✔	✔	✔	-

SQ=subcutaneous
*Formulations in prefilled pens or syringes only.
†Refer to Table 3 for insulins that may be mixed with specific products.
‡Inhalation formulation only (Afrezza®)
§Novolin R only;
‖Only reported for Humulin N and Humulin 70/30; no warnings and precautions listed for Novolin N or Novolin 70/30

Drug Interactions

Table 8. Drug Interactions[1-17,157]

Generic Name	Interacting Medication or Disease	Potential Result
Insulin	β-blockers, nonselective	β-blockers may blunt the sympathetic mediated response to hypoglycemia and may mask hypoglycemic symptoms. Discontinue nonselective β-blocker therapy or switch to a β-blocker with selective activity if possible.
Insulin	Ethanol	The glucose-lowering action of insulin may be potentiated by ethanol-induced release of insulin following a glucose load and inhibition of gluconeogenesis. Ethanol consumption in moderation with a meal should be done to prevent this interaction. Monitor for signs of hypoglycemia.
Insulin	Fenfluramine	Fenfluramine may potentiate the hypoglycemic effects of insulin. Monitor blood glucose concentrations and adjust dose of insulin as needed to avoid hypoglycemia.
Insulin	Monoamine oxidase inhibitors	MAOIs may potentiate the hypoglycemic effects of insulin by stimulating insulin secretion and inhibiting gluconeogenesis. Monitor blood glucose concentrations and adjust the dose of insulin as needed.
Insulin	Salicylates	Salicylates increase basal insulin secretion and acute insulin response to a glucose load. The hypoglycemic effects of insulin may be potentiated. Monitor blood glucose concentrations and adjust the dose of insulin as needed.

Dosage and Administration

Table 9. Dosing and Administration[1-17]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Entity Products			
Insulin aspart	To improve glycemic control in diabetes mellitus: Dosage must be individualized. May be administered via SC injection, CSII by external pump, and intravenously. SC injection: inject immediately (within 5 to 10 minutes) before a meal CSII: approximately 50% of the total dose is usually given as meal-related boluses and the remainder is given as a basal infusion. Pre-meal boluses of should be infused immediately (within 5 to 10 minutes) before a meal IV: infuse at a concentration of 0.05 to 1.0 units/mL	To improve glycemic control in diabetes mellitus (DMT1, age ≥2 years): See adult dosing Safety and efficacy have not been established for pediatric patients with DMT2.	Cartridge: 100 units/mL Pen: 100 units/mL Vial: 100 units/mL
Insulin detemir	To improve glycemic control in diabetes mellitus: Dosage must be individualized. May be administered via SC injection. SC injection (type 1 diabetes): administer once daily or twice daily SC injection (type 2 diabetes): 10 units once daily in the evening or divided into a twice daily regimen	To improve glycemic control in diabetes mellitus (DMT1, age ≥2 years): See adult dosing Safety and efficacy have not been established for pediatric patients with DMT2.	Pen: 100 units/mL Vial: 100 units/mL
Insulin glargine	To improve glycemic control in diabetes mellitus: Dosage must be individualized. May be administered via SC injection. SC injection: administer QD at the same time every day; maintenance, 2 to 100 units/day (Lantus®); higher daily doses will be needed for Toujeo®	To improve glycemic control in diabetes mellitus (DMT1, age ≥6 years): Lantus®:See adult dosing Safety and efficacy have not been established for pediatric patients with DMT2. Toujeo®:	Pen: 100 units/mL (Lantus® SoloSTAR) 300 units/mL (Toujeo® SoloSTAR) Vial: 100 units/mL

Generic Name	Adult Dose	Pediatric Dose	Availability
		Safety and efficacy have not been established for pediatric patients with DMT1 or DMT2.	
Insulin glulisine	To improve glycemic control in diabetes mellitus: Dosage must be individualized. May be administered via SC injection, CSII by external pump, and intravenously. SC injection: inject 15 minutes before a meal or within 20 minutes of starting a meal CSII: dosage must be individualized IV: infuse at a concentration of 0.05 to 1.0 units/mL	To improve glycemic control in diabetes mellitus (DMT1, age ≥4 years): See adult dosing Safety and efficacy have not been established for pediatric patients with DMT2.	Pen: 100 units/mL Vial: 100 units/mL
Insulin lispro	To improve glycemic control in diabetes mellitus: Dosage must be individualized. May be administered via SC injection and CSII by external pump. SC injection, CSII by external pump: 0.5 to 1 unit/kg/day; inject within 15 minutes before or immediately after a meal	To improve glycemic control in diabetes mellitus (DMT1, age ≥3 years): See adult dosing Safety and efficacy have not been established for pediatric patients with DMT2.	Cartridge: 100 units /mL Pen: 100 units /mL Vial: 100 units /mL
Insulin NPH	To improve glycemic control in diabetes mellitus: Dosage must be individualized. May be administered via SC injection. SC injection: 0.5 to 1 units/kg/day; administer in 2 divided daily doses and within 60 minutes of a meal	To improve glycemic control in diabetes mellitus (DMT1 or DMT2, age ≥12 years): See adult dosing	Pen: 100 units/mL Vial: 100 units/mL
Insulin regular	To improve glycemic control in diabetes mellitus and treatment of diabetic patients with marked insulin resistance*: Dosage must be individualized. May be administered via SC injection and intravenously. Inhalation: Initial (insulin-naïve), 4 units with each meal; dose must be	To improve glycemic control in diabetes mellitus (DMT1, age ≥2 years): SC injection, intravenous: See adult dosing	Inhalation powder (Afrezza®): 4 units/cartridge 8 units/cartridge Vial: 100 U/mL 500 U/mL(Humulin® R U-500)

Generic Name	Adult Dose	Pediatric Dose	Availability
	individualized based on response or conversion from other formulations; for doses greater than 8 units, multiple cartridges will be needed	Safety and efficacy have not been established for pediatric patients with DMT2. Inhalation: Safety and efficacy have not been established in pediatric patients with DMT1 or DMT2.	
Combination Products			
Insulin aspart/ insulin aspart protamine	To improve glycemic control in diabetes mellitus: Dosage must be individualized. May be administered via SC injection. SC injection: fixed ratio insulins are typically dosed on a BID basis (i.e., before breakfast and supper) with each dose intended to cover two meals or a meal and snack. May be injected within 15 minutes of meal initiation.	Safety and efficacy have not been established in pediatric patients.	Pen: 70/30 units/mL Vial: 70/30 units/mL
Insulin lispro/ insulin lispro protamine	To improve glycemic control in diabetes mellitus: Dosage must be individualized. May be administered via SC injection. May be injected within 15 minutes of meal initiation.	Safety and efficacy have not been established in pediatric patients.	Pen: 50/50 units/mL 75/25 units/mL Vial: 50/50 units/mL 75/25 units/mL
Insulin regular/ insulin NPH	To improve glycemic control in diabetes mellitus: Dosage must be individualized. May be administered via SC injection.	To improve glycemic control in diabetes mellitus (age ≥12 years): See adult dosing	Pen: 70/30 units/mL Vial: 70/30 units/mL

BID=twice daily, DMT1=diabetes mellitus type 1, DMT2=diabetes mellitus type 2, CSII=Continuous Subcutaneous Insulin Infusion, IV=intravenous
*Only U-500 insulin indicated for the treatment of diabetic patients with marked insulin resistance

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
American Diabetes Association: **Standards of Medical Care in**	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

Clinical Guideline	Recommendations
Diabetes (2014)[145]	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 6.4%, 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 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable HbA_{1c} goal for many nonpregnant adults is <7.0%. • It may be reasonable for providers to suggest more stringent HbA_{1c} goals (<6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease. • Conversely, less stringent HbA_{1c} goals (<8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. 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 pre-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 to reduce hypoglycemic risk. Pharmacologic and overall approaches to treatment-type 2 diabetes • At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated. • 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.

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	• Because of the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes.
American Diabetes Association/ European Association for the Study of Diabetes: **Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach (2012)**[146]	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 side effects 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 side effect profiles make them less attractive candidates. • Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major 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.

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- 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 different 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 side effects 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				
Side Effects	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 Combin-ations	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 risk	Low risk	Low risk	Low risk	High risk
Weight	Gain	Gain	Neutral	Loss	Gain
Major Side Effects	Hypo-glycemia	Edema, heart failure, bone fracture	Rare	Gastro-intestinal	Hypo-glycemia
If needed to reach individualized HbA_{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)					
Three Drug Combin-ations	Metformin + sulfonylurea +	Metformin + TZD +	Metformin + DPP-4 inhibitor +	Metformin + GLP-1 receptor agonist +	Metformin + insulin therapy +

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
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<table>
<tr><td></td><td>TZD, DPP-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>Complex Insulin Strategies</td><td colspan="5">Insulin (multiple daily doses)</td></tr>
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<tr><td>American Association of Clinical Endocrinologists: Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan (2011)[147]</td><td>
<u>Antihyperglycemic pharmacotherapy</u>

The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2009 American Association of Clinical Endocrinologists/ American College of Endocrinology Diabetes Algorithm for Glycemic Control.[59]
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 because they are associated with less hypoglycemia.
The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose.
When postprandial hyperglycemia is present, glinides and/or alpha-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

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	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 Association of Clinical Endocrinologists: **Comprehensive Diabetes Management Algorithm 2013 Consensus Statement (2013)**[148]	Principles underlying the algorithm • Lifestyle optimization is essential for all patients with diabetes; however, should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on patient response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it. • Achieving an HbA_{1c} ≤6.5% is recommended as the primary goal if it can be achieved in a safe and affordable manner; however, higher targets may be appropriate for certain individuals and may change for a given individual over time. • Minimizing risk of hypoglycemia and weight gain is a priority. It is a matter of safety, adherence, and cost. • For optimal glycemic control, therapies with complementary mechanisms of action must typically be used in combination. • Therapeutic effectiveness must be evaluated frequently until stable (e.g., every three months). • Safety and efficacy should be given higher priority than the initial acquisition cost of medications, as medication cost is only a small part of the total cost of diabetes care. In assessing the cost of a medication, consideration should be given to monitoring requirements and risks of hypoglycemia and weight gain. • Rapid-acting insulin analogs are superior to regular insulin because they are more predictable. • Long-acting insulin analogs are superior to neutral protamine Hagedorn insulin because they provide a fairly flat response for approximately 24 hours and provide better reproducibility and consistency, both between and within patients, with a corresponding reduction in hypoglycemia risk. Monotherapy • Patients with recent-onset diabetes and those with mild hyperglycemia (HbA_{1c} ≤7.5%), initial monotherapy with metformin (at doses of 1,500 to 2,000 mg/day) and life-style modifications will achieve their glycemic goals in a majority of patients. • In patients with intolerance or contraindications to metformin, acceptable therapeutic alternatives that reduce glucose without weight gain or hypoglycemia (in order based on suggested hierarchy of usage) include: o GLP-1 receptor agonists. o DPP-4 inhibitors. o Alpha-glucosidase inhibitors. o Sodium glucose cotransporter 2 (SGLT-2) inhibitors. • TZD, sulfonylurea, and glinides (in order based on suggested hierarchy of usage) may be used but with caution due to possible weight gain and hypoglycemia. Combination therapy • Patients who present with an initial HbA_{1c} ≥7.5% or who do not reach their target HbA_{1c} with metformin in three months should be started on a second agent to be used in combination with metformin.

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	• Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • In metformin-intolerant patients, two drugs from other classes with complimentary mechanisms of action should be used. • Combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent) plus: o GLP-1 receptor agonists. o DPP-4 inhibitors. o TZD. o SGLT-2 inhibitors. o Basal insulin. o Colesevelam. o Bromocriptine quick release. o Alpha-glucosidase inhibitors. o Sulfonylureas and glinides. <u>Three-drug combination therapy</u> • Generally, the efficacy of a third antidiabetic agent added to dual therapy is reduced compared to the efficacy of the same drug used as monotherapy or combination therapy with one other agent. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • Patients who present with an HbA_{1c} <8.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs after 3 months has a high likelihood of reaching target with a third agent. • Patients who present with an HbA_{1c} >9.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs has are less likely of reaching target with a third agent or fourth agent and insulin should be considered. • Continuation with noninsulin therapies while starting basal insulin is common and does not increase cardiovascular risk, but may increase risk of hypoglycemia when sulfourea are used in conjunction with insulin. • Three-drug combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent), a second-line agent plus: o GLP-1 receptor agonists. o TZD. o SGLT-2 inhibitors. o Basal insulin. o DPP-4 inhibitors. o Colesevelam. o Bromocriptine quick release. o Alpha-glucosidase inhibitors. o Sulfonylureas and glinides <u>Insulin therapy algorithm</u> • Patients who present with an initial HbA_{1c} >9.0% and are symptomatic, should initiate therapy with insulin with or without other antidiabetic agents. • Start insulin if a patient has marked hyperglycemia despite treatment with several oral antidiabetic agents and is symptomatic with polyuria and weight loss. • Patients who are not at target HbA_{1c} despite the use of oral antidiabetic agents or GLP-1 therapy should be considered for insulin therapy. • Patients with an HbA_{1c} level >8.0% while receiving ≥2 antidiabetic agents,

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	particularly individuals with long duration of diabetes, have significant impairment of beta cell insulin secretory capacity and are unlikely to reach the recommended target by the addition of further oral antidiabetic drugs. Basal insulin • Patients with an HbA_{1c} level >8.0% while receiving ≥2 oral antidiabetic agents or GLP-1 therapy can be started on single daily dose of basal insulin as an add-on to the patient's existing regimen. • Titrate insulin dose every two to three days to reach glycemic goals. • Basal insulin analogues (glargine and detemir) are preferred over protamine Hagedorn insulin because they have been shown to provide a relatively flat serum insulin concentration for up to 24 hours from a single daily injection. • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations can also be considered for basal intensification with a DPP-4 inhibitor or GLP-1 receptor agonist if the glucose level is not markedly elevated, because this approach tends to not cause weight gain or additional hypoglycemia. Basal-bolus insulin regimens • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations and those with symptomatic hyperglycemia and HbA_{1c} >10% often respond better to combined basal and mealtime bolus insulin. • A full basal-bolus program with an insulin basal analogue once or twice daily and a rapid-acting analogue at each meal is most effective and provides flexibility for patients with variable mealtimes and meal carbohydrate content. • Doses of insulin may be titrated every two to three days to reach glycemic goals. Basal insulin and incretin therapy regimens • Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in patients with type 2 diabetes. • The incretin therapies (GLP-1 receptor agonists and DPP-4 inhibitors) have similar properties, and also increase endogenous insulin secretion. Therefore, the combination of basal insulin and incretin therapy decreases basal and postprandial glucose and may minimize the weight gain and hypoglycemia risk observed with basal-bolus insulin replacement.
American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus (2007)**[149]	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%. 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. Glycemic management-patients with type 2 diabetes • Aggressively implement all appropriate components of care at the time of diagnosis.

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	• 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 has 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 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

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	and to perform a ketone test each time a measured glucose concentration is >250 mg/dL. Clinical support-clinical considerations in patients with type 1 diabetes • Instruct patients to administer pre-prandial rapid-acting analog insulin 20 to 30 minutes before the meal when the pre-meal blood glucose levels is high and after the meal has begun when the pre-meal blood glucose level is below the reference range. • Measure 2:00 to 3:00 AM blood glucose periodically in all patients with diabetes to asses for nocturnal hypoglycemia, especially when the morning blood glucose level is elevated. • Consider using regular insulin instead of rapid-acting insulin analogs to obtain better control of post-prandial and pre-meal glucose levels in patients with gastroparesis. Insulin pump therapy may also be advantageous in these patients. • Some type 1 diabetics treated with basal insulin may require two daily injections of basal insulin for greater stability. • Carefully assess PPG levels when the HbA_{1c} level is elevated and pre-meal 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. • Arrange for continuous glucose monitoring for patients with unstable glucose control and for patients unable to achieve an acceptable HbA_{1c} level. Continuous glucose monitoring is particularly valuable in detecting both unrecognized nocturnal hypoglycemia and post-prandial hyperglycemia. • Some patients using pramlintide may achieve better post-prandial and pre-meal glucose control by combining it with regular insulin rather than rapid-acting analogs. • Individualize insulin regimens to accommodate patient exercise patterns. • Treat hypoglycemic reactions with simple carbohydrates. Clinical support-clinical considerations in patients with type 2 diabetes • 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.

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	• Administer basal insulin in the evening if fasting glucose is elevated. • Long-acting insulin analogs are associated with less hypoglycemia than protamine Hagedorn insulin.
National Institute for Health and Care Excellence: **The Management of Type 2 Diabetes (2014)**[150]	Metformin • Start metformin in overweight or obese patients and whose blood glucose is inadequately controlled by lifestyle interventions alone. • Consider metformin as an option for first-line glucose-lowering therapy for patients who are not overweight. • Continue metformin if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication (usually a sulfonylurea) is added. • Step up metformin therapy gradually over weeks to minimize risk of gastrointestinal (GI) side effects. Consider a trial of extended release metformin if GI tolerability prevents continuation of therapy. Insulin secretagogues • Consider a sulfonylurea as an option for first-line glucose-lowering therapy if the patient is not overweight, the patient does not tolerate metformin (or it is contraindicated), or a rapid response to therapy is required because of hyperglycemic symptoms. • Add a sulfonylurea as second-line therapy when blood glucose control remains or becomes inadequate with metformin. • Continue sulfonylurea therapy if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication is added. • When adherence is a problem, offer a once-daily, long-acting sulfonylurea. Rapid-acting insulin secretagogues • Consider offering a rapid-acting insulin secretagogue to a patient with an erratic lifestyle. Acarbose • Consider acarbose for a patient unable to use other oral glucose-lowering medications. DPP-4 inhibitors • Consider adding a DPP-4 inhibitor to metformin (as second-line therapy) instead of a sulfonylurea when blood glucose control is inadequate (HbA1c ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated. • Consider adding a DPP-4 inhibitor to sulfonylurea (as second-line therapy) when control of blood glucose is inadequate (HbA1c ≥6.5%) if the person does not tolerate metformin or if metformin is contraindicated. • Consider adding a DPP-4 inhibitor as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c ≥7.5%) and insulin is unacceptable or inappropriate. • Only continue DPP-4 inhibitor therapy if the person has had a beneficial metabolic response (≥0.5% reduction in HbA1c in 6 months). • A DPP-4 inhibitor may be preferable to a thiazolidinedione (TZD) if: o Further weight gain would cause or exacerbate significant problems associated with a high body weight. o A thiazolidinedione is contraindicated.

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	o The person has previously had a poor response to, or did not tolerate, a thiazolidinedione. o There may be some individuals for whom either a DPP-4 inhibitor or a TZD may be suitable. The choice of treatment should be based on patient preference. TZDs • Consider adding a TZD to metformin (as second-line therapy) instead of a sulfonylurea when blood glucose control is inadequate (HbA1c ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated. • Consider adding a TZD to sulfonylurea (as second-line therapy) when control of blood glucose is inadequate (HbA1c ≥6.5%) if the person does not tolerate metformin or if metformin is contraindicated. • Consider adding a TZD as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c ≥7.5%) and insulin is unacceptable or inappropriate. • Do not use a TZD is people who have heart failure, or who are at higher risk of fracture. • Only continue TZD therapy if the person has had a beneficial metabolic response (≥0.5% reduction in HbA1c in 6 months). • Consider combining TZD with insulin therapy for a person who previously had a marked glucose-lowering response to TZD therapy or who is on high-dose insulin therapy and whose blood glucose is inadequately controlled. • A TZD may be preferable to a DPP-4 inhibitor if: o The person has marked insulin insensitivity. o A DPP-4 inhibitor is contraindicated. o The person has previously had a poor response to, or did not tolerate, a DPP-4 inhibitor. o There may be some individuals for whom either a DPP-4 inhibitor or a TZD may be suitable. The choice of treatment should be based on patient preference. Gliptins: GLP-1 enhancers • No recommendations are made on the use of gliptins as these drugs are not covered in this guideline. GLP-1 mimetics • Consider adding a GLP-1 mimetic as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose is inadequate (HbA1c ≥7.5%) and the person has: o A body mass index ≥35 kg/m2 in those of European descent (with appropriate adjustment for other ethnic groups). o A BMI <35 kg/m2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. • Only continue GLP-1 mimetic therapy if the person has had a beneficial metabolic response (≥1% reduction in HbA1c and weight loss ≥3% of initial body weight at six months). Insulin therapy

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	• May be offered to patients with inadequate blood glucose control on optimized oral glucose-lowering agents. • When starting basal insulin therapy: o Continue with metformin and the sulfonylurea (and acarbose, if used). o Review the use of the sulfonylurea if hypoglycemia occurs. • When starting pre-mixed insulin therapy (or mealtime plus basal insulin regimens): o Continue with metformin. o Continue the sulfonylurea initially and discontinue if hypoglycemia occurs. • Begin with human NPH insulin injected at bedtime or twice daily according to need. • Consider using a long-acting insulin analogue if: o The person needs assistance from a caregiver or healthcare professional to inject insulin, and use of a long-acting insulin analogue would reduce the frequency of injections from twice to once daily. o The person's lifestyle is restricted by recurrent symptomatic hypoglycemic episodes. o The person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs. o The person cannot use the device to inject NPH insulin. • Consider twice-daily pre-mixed (biphasic) human insulin (particularly if HbA1c ≥9.0%). A once-daily regimen may be an option. • Consider pre-mixed preparations that include short-acting insulin analogs, rather than pre-mixed preparations that include short-acting human insulin preparations, if: o A person prefers injecting insulin immediately before a meal. o Hypoglycemia is a problem. o Blood glucose levels rise markedly after meals. • Consider switching to a long-acting insulin analogue from NPH insulin in people: o Who do not reach their target HbA1c because of significant hypoglycemia. o Who experience significant hypoglycemia on NPH insulin irrespective of the level of HbA1c reached. o Who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to a long-acting insulin analogue were made. o Who need help from a caregiver or healthcare professional to administer insulin injections and for whom switching to a long-acting insulin analogue would reduce the number of daily injections. o Monitor a person on a basal insulin regimen (NPH insulin or a long-acting insulin analogue) for the need for short-acting insulin before meals (or a pre-mixed insulin preparation).
Institute for Clinical Systems Improvement: **Diagnosis and Management of Type 2 Diabetes**	• Personalize goals to achieve glycemic control with a hemoglobin HbA1c in the range of <7 or 8% based on the risks and benefits of each patient. A goal of <8% may be more appropriate when: o Known cardiovascular disease or high cardiovascular risk, may be determined by the Framingham or ACC/AHA Cardiovascular Risk Calculator, or alternatively as having two or more cardiovascular

Clinical Guideline	Recommendations
Mellitus in Adults (2014)[151]	risks (BMI >30, hypertension, dyslipidemia, smoking, and microalbuminuria). o Inability to recognize and treat hypoglycemia, including a history of severe hypoglycemia requiring assistance. o Inability to comply with standard goals, such as polypharmacy issues. o Limited life expectancy or estimated survival of less than 10 years. o Cognitive impairment. o Extensive comorbid conditions such as renal failure, liver failure, and end-stage disease complications. • A multifactorial approach to diabetes care that includes emphasis on blood pressure, lipids, glucose, aspirin use, and non-use of tobacco will maximize health outcomes far more than a strategy that is limited to just one or two of these clinical domains. • Recommend education and self-management, as appropriate. • Initiate metformin as first-line pharmacotherapy for patients with type 2 diabetes, unless medically inappropriate. o Metformin may reduce HbA1c by 1 to 1.5%, rarely causes hypoglycemia when used as monotherapy and does not cause weight gain. o Metformin can also be used in combination with all other glucose-lowering agents. • Improved microvascular and macrovascular outcomes have been demonstrated in large clinical trials.
International Diabetes Federation Clinical Guidelines Task Force: **Global Guideline for Type 2 Diabetes (2012)**[152]	<u>Lifestyle management</u> • Changing patterns of eating and physical activity can be effective in controlling many of the adverse risk factors found in type 2 diabetes. • Match the timing of medication (including insulin) and meals. • Reduce energy intake and control of foods with high amounts of added sugars, fats, or alcohol. • Introduce physical activity gradually, based on the individual's willingness and ability, and setting individualized and specific goals. • Encourage increased duration and frequency of physical activity (where needed), up to 30 to 45 minutes on three to five days per week, or an accumulation of 150 minutes per week of moderate-intensity aerobic activity (50 to 70% of maximum heart rate). In the absence of contraindications, encourage resistance training three times per week. • Provide guidance for adjusting medications (insulin) and/or adding carbohydrate for physical activity. <u>Glucose control levels</u> • Maintaining HbA1c below 7% minimizes the risk of developing complications. • A lower HbA1c target may be considered if it is easily and safely achieved. • A higher HbA1c target may be considered for people with comorbidities or when previous attempts to optimize control have been associated with unacceptable hypoglycemia. <u>Oral therapy</u> • Begin oral glucose lowering medications when lifestyle interventions alone are unable to maintain blood glucose control at target levels. Maintain support for lifestyle measures throughout the use of these medications.

Clinical Guideline	Recommendations
	• Consider each initiation or dose increase of an oral glucose lowering medication as a trial, monitoring response in three months. • First-line therapy o Begin with metformin unless there is evidence of renal impairment or other contraindication. o Titrate the dose over early weeks to minimize discontinuation due to gastrointestinal intolerance. Monitor renal function and use metformin with caution if estimated glomerular filtration rate <45 mL/min/1.73m2. o Other options include a sulfonylurea (or glinide) for rapid response where glucose levels are high, or α-glucosidase inhibitors in some populations; these agents can also be used initially where metformin cannot. o In some circumstances dual therapy may be indicated initially if it is considered unlikely that single agent therapy will achieve glucose targets. • Second-line therapy o When glucose control targets are not achieved, add a sulfonylurea. o Other options include adding metformin if not used first-line, an α-glucosidase inhibitor, a dipeptidyl peptidase 4 (DPP-4) inhibitor, or a thiazolidinedione (TZD). A rapid-acting insulin secretagogue is an alternative option to sulfonylureas. • Third-line therapy o When glucose control targets are no longer being achieved, start insulin or add a third oral agent. o If starting insulin, add basal insulin or use premix insulin. o If adding a third oral agent options include an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD. o Another option is to add a glucagon-like peptide-1 (GLP-1) agonist. • Fourth-line therapy o Begin insulin therapy when optimized oral blood glucose lowering mediations (and/or GLP-1 agonist) and lifestyle interventions are unable to maintain target glucose control. Insulin therapy • Do not unduly delay the commencement of insulin. Maintain lifestyle measures. Consider every initiation or dose increase of insulin as a trial, monitoring the response. • Provide education and appropriate self-monitoring. • Explain that starting doses of insulin are low, for safety reasons, but that eventual dose requirement is expected to be 30 to 100 units/day. • Continue metformin. Other oral agents may also be continued. • Begin with a basal insulin once daily such as neutral protamine Hagedorn (NPH) insulin, insulin glargine, or insulin detemir, or once or twice daily premix insulin (biphasic insulin). • Initiate insulin using a self-titration regimen (dose increases of two units every three days) or with biweekly or more frequent contact with a health-care professional. • Aim for pre-meal glucose levels of <6.5 mmol/L (<115 mg/dL). • Monitor glucose control for deterioration and increase dose to maintain target levels or consider transfer to a basal plus mealtime insulin regimen.
American Diabetes	• Insulin type, mixture of insulins, site of injection, and individual patient

Clinical Guideline	Recommendations
Association: **Care of Children and Adolescents with Type 1 Diabetes (2005)**[152]	response differences can all affect the onset, peak, and duration of insulin activity. • Children with diabetes often require multiple daily injections of insulin, using combinations of rapid-, short-, intermediate-, or long-acting insulin before meals and at bedtime to maintain optimal blood glucose control. • The basal/bolus insulin regimen uses a long-acting insulin analog combined with a rapid-acting insulin analog given before meals and snacks. This regimen has been shown to result in stable glycemic control and less hypoglycemia compared with regimens using intermediate and short insulin regimens. • Many young children and teenagers consume multiple snacks throughout the day. An ideal basal/bolus regimen may consist of as many as six to seven insulin injections per day. A combination of rapid-acting insulin with small amounts of intermediate-acting insulin to allow coverage for snacks may be an appropriate alternative to the basal/bolus plan. However, two or three doses of mixed rapid-acting or short-acting insulin with intermediate-acting insulin generally cannot maintain HbA1c levels within the target range. Recommendations now support moving toward a basal/bolus insulin regimen for most patients. • The combination of rapid-acting insulin analogs and a long-acting insulin offers an excellent option for basal and bolus insulin administration. • Basal/bolus regimens have been shown to result in lower fasting blood glucose levels with less nocturnal hypoglycemia than regimens that use NPH insulin in children/adolescents, as well as in adults.
American Academy of Pediatrics: **Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents (2013)**[153]	• Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between types 1 and 2 diabetes mellitus is unclear and, in usual cases, should initiate insulin therapy for patients o Who have random venous or plasma blood glucose (BG) concentrations ≥250 mg/dL. o Whose HbA1c is >9%. • In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM. • Monitoring of HbA1c concentrations is recommended every three months and intensifying treatment is recommended if treatment goals for finger-stick BG and HbA1c concentrations are not being met. • Advise patients to monitor finger-stick BG concentrations in patients who: o Are taking insulin or other medications with a risk of hypoglycemia; or o Are initiating or changing their diabetes treatment regimen; or o Have not met treatment goals; or o Have intercurrent illnesses. • Incorporate the Academy of Nutrition and Dietetics' Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines in dietary or nutrition counseling of patients with T2DM at the time of diagnosis and as part of ongoing management. • Encourage children and adolescents with T2DM to engage in moderate-to-vigorous exercise for at least 60 minutes daily and to limit nonacademic "screen time" to less than two hours a day.
National Institute for	Children (aged younger than 11 years) and young people (aged 11 to <18

Clinical Guideline	Recommendations
Health and Care Excellence: **Diagnosis and Management of Type 1 Diabetes in Children, Young People, and Adults (2014)**[154]	years) • Children and young people with type 1 diabetes should be offered an ongoing integrated package of care by a multidisciplinary pediatric diabetes care team. • Insulin regimens o One, two, or three insulin injections per day: these are usually injections of short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting insulin. The insulin preparations may be mixed by the patient at the time of injection. o Multiple daily injection regimen: the person has injections of short-acting insulin or rapid-acting insulin analogue before meals, together with one or more separate daily injections of intermediate-acting insulin or long-acting insulin analogue. o Continuous subcutaneous insulin infusion (insulin pump therapy): a programmable pump and insulin storage reservoir that gives a regular or continuous amount of insulin (usually in the form of a rapid-acting insulin analogue or short-acting insulin) by a subcutaneous needle or cannula. • Pre-school and primary school children should be offered the most appropriate individualized regimens to optimize glycemic control. • Young people should be offered multiple daily injection regimens to help optimize glycemia control. • As it improves glycemic control, multiple daily injection regimens should be offered only as part of a package of care that involves continuing education; dietary management; instruction on the use of insulin delivery systems and blood glucose monitoring; emotional and behavioral support; and medical, nursing, and dietetic expertise in pediatric diabetes. • Children and young people using multiple daily injection regimens should be informed that they may experience an initial increase in the risk of hypoglycemia and short-term weight gain. • Children and young people and their families should be informed about strategies for the avoidance and management of hypoglycemia. • Young people who do not achieve satisfactory glycemic control with multiple daily injection regimens should be offered additional support and, if appropriate, alternative insulin therapy (once, twice, or three times daily mixed insulin regimens or continuous SC insulin infusion using an insulin pump). • Young people who have difficulty adhering to the multiple daily injection regimens should be offered twice-daily injection regimens. • Continuous SC insulin infusion is recommended as an option for patients provided that: o Multiple-dose insulin therapy (including, where appropriate, the use of insulin glargine) has failed, and; o Patients receiving the treatment have the commitment and competence to use the therapy effectively. • Continuous SC insulin infusion therapy should be initiated only by a trained specialist team. • All individuals beginning continuous SC insulin infusion therapy should be provided with specific training in its use. • Established users of continuous SC insulin infusion therapy should have their insulin management reviewed by their specialist team so that a decision can be made about whether a trial or a switch to multiple-dose

Clinical Guideline	Recommendations
	insulin incorporating insulin glargine would be appropriate. • Insulin preparations: o Children and young people should be offered the most appropriate insulin preparations according to their individual needs with the aim of obtaining an HbA1c <7.5% without frequent disabling hypoglycemia and maximizing quality of life. o Children and young people using multiple daily insulin regimens should be informed that injection of rapid-acting insulin analogs before eating (rather than after eating) reduces PPG levels thus helps to optimize blood glucose control. o For pre-school children it may be appropriate to use rapid-acting insulin analogs shortly after eating (rather than before eating) because food intake can be unpredictable. o Children and young people who use insulin preparations containing intermediate-acting insulin should be informed that these preparations should be mixed before use according to instructions provided in patient information leaflets. • Insulin delivery: o Children and young people should be offered a choice of insulin delivery systems that takes account of their insulin requirements and personal preferences. o Children and young people using insulin injection regimens should be offered needles that are of an appropriate length for their body fat. • Non-insulin agents (oral antidiabetic agents): o Children and young people should not be offered acarbose or sulfonylureas in combination with insulin because they may increase the risk of hypoglycemia without improving glycemic control. o Metformin in combination with insulin is suitable for use only within research trials because the effectiveness of this combination therapy in providing glycemic control is uncertain. <u>Adults (aged 18 years or older): Insulin regimens</u> • Patients should have access to the types (preparation and species) of insulin they find allow them optimal well-being. • Cultural preferences need to be discussed and respected in agreeing on the insulin regimen for a patient. • Multiple insulin injection regimens, in patients who prefer them, should be used as part of an integrated package of which education, food, and skills training should be integral parts. • Appropriate self-monitoring and education should be used as part of an integrated package to help achieve optimal diabetes outcomes. • Mealtime insulin injections should be provided by injection unmodified ('soluble') insulin or rapid-acting insulin analogs before main meals. • Rapid-acting insulin analogs should be used as an alternative to mealtime unmodified insulin where nocturnal or late inter-prandial hypoglycemia is a problem, and in those in whom they allow equivalent blood glucose control without use of snacks between meals and this is needed or desired. • Basal insulin therapy (including nocturnal insulin supply) should be provided by the use of isophane (NPH) insulin or long-acting insulin analogs (insulin glargine). Isophane (NPH) insulin should be given at bedtime. If rapid-

Clinical Guideline	Recommendations
	acting insulin analogs are given at mealtimes or the midday insulin dose is small or lacking, the need to give isophane (NPH) insulin twice-daily (or more often) should be considered. • Long-acting insulin analogs (insulin glargine) should be used when: o Nocturnal hypoglycemia is a problem on isophane (NPH) insulin. o Morning hypoglycemia on isophane (NPH) insulin results in difficult daytime blood glucose control. o Rapid-acting insulin analogues are used for mealtime blood glucose control. • Twice-daily insulin regimens should be used by those adults who consider number of daily injections an important issue in quality of life: o Biphasic insulin preparations (pre-mixes) are often the preparations of choice in this circumstance. o Biphasic rapid-acting insulin analog pre-mixes may give an advantage to those prone to hypoglycemia at night. o Such twice-daily regimens may also help those who find adherence to their agreed lunchtime insulin injection difficult and those with learning difficulties who may require assistance from others. • Adults whose nutritional and physical activity patterns vary considerably from day-to-day, for vocational or recreational reasons, may need careful and detailed review of their self-monitoring and insulin injection regimen(s). This should include all the appropriate preparations and consideration of unusual patterns and combinations. • For adults undergoing periods of fasting or sleep following eating (e.g., during religious feasts and fasts, after night-shift work), a rapid-acting insulin analog before the meal (provided the meal is not prolonged) should be considered. • For adults with erratic and unpredictable blood glucose control, rather than a change in a previously optimized insulin regimen, the following should be considered: o Re-suspension of insulin and injection technique. o Injection sites. o Self-monitoring skills. o Knowledge and self-management skills. o Nature of lifestyle. o Psychological and psychosocial difficulties. o Possible organic causes (e.g., gastroparesis). • Continuous SC insulin infusion is recommended as an option provided that: o Multiple-dose insulin therapy (including, where appropriate, the use of insulin glargine) has failed, and o Patients receiving the treatment have the commitment and competence to use the therapy effectively. • Partial insulin replacement to achieve blood glucose control targets (basal insulin only, or just some mealtime insulin) should be considered for patients initiating insulin therapy, until such time as islet β-cell deficiency progresses further. • Clear guidelines and protocols should be given to all patients to assist them in adjusting insulin doses appropriate during intercurrent illness. • Oral glucose-lowering drugs should generally not be used in the management of type 1 diabetics. Adults (aged 18 years or older): Insulin delivery

Clinical Guideline	Recommendations
	• Adults who inject insulin should have access to the insulin injection delivery device they find allows them optimal well-being, often using one or more types of insulin injection pen. • Adults who have special visual or psychological needs should be provided with injection devices or needle-free systems that they can use independently for accurate dosing. • Insulin injection should be made into the deep SC fat. To achieve this, needles of a length appropriate to the individual should be made available. • Adults should be informed that the abdominal wall is the therapeutic choice for mealtime insulin injections. • Adults should be informed that extended-acting suspension insulin (e.g., isophane [NPH] insulin) may give a longer profile of action when injected into the SC tissue of the thigh rather than the arm or abdominal wall. • Adults should be recommended to use one anatomical area for the injections given at the same time of day, but to move the precise injection site around in the whole of the available skin within that area. • Patients should be provided with suitable containers for the collection of used needles. Arrangements should be available for the suitable disposal of these containers. • Injection site condition should be checked annually, and if new problems with blood glucose control occur.
American Diabetes Association: **Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association (2014)**[155]	Nutritional therapy • Individualized medical nutrition therapy is recommended for all people with type 1 diabetes as an effective component of the overall treatment plan. • Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, remains a key strategy in achieving glycemic control. • If adults with type 1 diabetes choose to drink alcohol, they should be advised to do so in moderation (one drink per day or less for adult women and two drinks per day or less for adult men). Discussion with a health care provider is advised to explore potential interactions with medications. Adults should be advised that alcohol can lower blood glucose levels and that driving after drinking alcohol is contraindicated. Physical activity and exercise • Exercise should be a standard recommendation as it is for individuals without diabetes; however, recommendations may need modifications due to the presence of macro- and microvascular diabetes complications. • Patients of all ages (or caregivers of children) should be educated about the prevention and management of hypoglycemia that may occur during or after exercise. • Patients should be advised about safe preexercise blood glucose levels (typically 100 mg/dL or higher depending on the individual and type of physical activity). • Reducing the prandial insulin dose for the meal/snack preceding exercise and/or increasing food intake can be used to help raise the preexercise blood glucose level and reduce hypoglycemia. • A reduction in overnight basal insulin the night following exercise may reduce the risk for delayed exercise-induced hypoglycemia. • Self-monitoring of blood glucose should be performed as frequently as needed, and sources of simple carbohydrate should be readily available to prevent and treat hypoglycemia.

Clinical Guideline	Recommendations
	Glycemic control goals • The American Diabetes Association strongly believes that blood glucose and HbA1c targets should be individualized with the goal of achieving the best possible control while minimizing the risk of severe hyperglycemia and hypoglycemia and maintaining normal growth and development. • An HbA1c goal of <7.5% is recommended across all pediatric age-groups. • A reasonable HbA1c goal for many nonpregnant adults with type 1 diabetes is <7%. • Providers might reasonably suggest more stringent HbA1c goals (such as <6.5%) for select individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. • Less stringent HbA1c goals (such as <8.5%) may be appropriate for patients with a history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced microvascular/ macrovascular complications, or extensive comorbid conditions. Insulin therapy • Most individuals with type 1 diabetes should be treated with multiple daily insulin injections (three or more injections per day of prandial insulin and one to two injections of basal insulin) or continuous subcutaneous insulin infusion. • Most individuals should be educated in how to match prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity. • Most individuals should use insulin analogs to reduce hypoglycemia risk. • All individuals with type 1 diabetes should be taught how to manage blood glucose levels under varying circumstances, such as when ill or receiving glucocorticoids or for those on pumps, when pump problems arise. • Child caregivers and school personnel should be taught how to administer insulin based on provider orders when a child cannot self-manage and is out of the care and control of his or her parent/guardian. Adjunctive therapies • Pramlintide may be considered for use as adjunctive therapy to prandial insulin in adults with type 1 diabetes failing to achieve glycemic goals. • Evidence suggests that adding metformin to insulin therapy may reduce insulin requirements and improve metabolic control in overweight/ obese patients and poorly controlled adolescents with type 1 diabetes, but evidence from larger longitudinal studies is required. • Current type 2 diabetes medications (GLP-1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors) may be potential therapies for type 1 diabetic patients, but require large clinical trials before use in type 1 diabetic patients.

Conclusions

Insulin products are Food and Drug Administration (FDA)-approved improve glycemic control in patients with diabetes mellitus (DM) type 1 and type 2.[1-17] Additionally, insulin products may be utilized for a number of off-label uses. These include the treatment of diabetic ketoacidosis, hyperosmolar hyperglycemic state in patients with type 2 DM, gestational diabetes, treatment of hyperkalemia, and as nutritional supplementation to maintain normoglycemia in very low birthweight infants with persistent glucose intolerance.[156,157] Regular insulin is structurally identical to endogenous insulin, with various additions, deletions, or substitutions of amino acids made for the insulin analogs. Modifications made to human insulin have the greatest effect on kinetic parameters, particularly onset and duration of action. Rapid- and short-acting insulins are administered as a bolus prior to meals to control postprandial glucose excursions while intermediate- and long-acting agents act as basal insulin, which is essential for regulating glucose homeostasis.[18]

For patients with either type 1 or type 2 DM, differences in safety and efficacy of insulin preparations is modest. Generally, at best, there is a modest improvement in in HbA_{1c} with the rapid-acting analogues with overall rates of hypoglycemia that were not significantly different. Long-acting insulin analogs have been shown to be at least as effective as NPH insulin in HbA_{1c} reduction, with some studies showing a significant improvement associated with the long-acting insulin analogs compared with NPH insulin with similar rates of side effects. When comparing the long-acting analogs head-to-head, several trials have demonstrated non-inferiority between the products in the same outcomes when used in the management of type 1 diabetes and as add-on therapy in type 2 diabetics. In terms of clinical outcomes, the DCCT and UKPDS trials have demonstrated that intensive glycemic control with insulin significantly reduces the rate of onset and progression of diabetic complications when compared to standard therapy. Neither study identified which insulin products were utilized, however, the UKPDS noted that the risk reduction in complications was related more toward tight glycemic control rather than to one specific therapy.[21-142]

The goal of treatment for both type 1 and type 2 DM is to control hyperglycemia and reduce the risk of long-term complications. For patients with type 1 DM, insulin is the standard of therapy due to pathogenesis of the disease. For type 2 DM, the oral antidiabetic agents are generally considered before insulin therapy, with metformin being the cornerstone of most regimens. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific agents for each patient should be considered.[145-155]

Insulin therapy is usually administered by subcutaneous injection; however, regular insulin is also formulated as an inhalation. All insulin products have at least one formulation with a concentration of 100 units/mL (U-100). Two agents are also formulated with a higher concentration, regular insulin as 500 units/mL (U-500; Humulin® R U-500) and insulin glargine as 300 units/mL (U-300; Toujeo® SoloSTAR). There are currently no generic formulations of insulin; however, there are several products available over-the-counter.[1-17]

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