Hypoglycemics, Insulins

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS[1,2,3,4,5,6,7,8,9,10]

Drug	Types Available	Manufacturer	Indication(s)
human insulin (Humulin®)	R, N, 70/30	Lilly	For the treatment of patients with diabetes mellitus for the control of hyperglycemia
human insulin (Novolin®)	R, N, 70/30	Novo Nordisk	
Rapid-Acting Insulins			
insulin aspart (Novolog®)	--	Novo Nordisk	To improve glycemic control in adults and children with diabetes mellitus
insulin glulisine (Apidra™)	--	Sanofi-Aventis	To improve glycemic control in adults and children with diabetes mellitus
insulin lispro (Humalog®)	--	Lilly	For the treatment of patients with diabetes mellitus for the control of hyperglycemia
Long-Acting Insulins			
insulin detemir (Levemir®)	--	Novo Nordisk	For once or twice daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal insulin for the control of hyperglycemia
insulin glargine (Lantus®)	--	Sanofi-Aventis	To improve glycemic control in adults and children with type 1 diabetes mellitus and adults with 2 diabetes mellitus
Rapid / Intermediate-Acting Combination Insulins			
insulin aspart (Novolog® Mix)	70/30	Novo Nordisk	To improve glycemic control in patients with diabetes mellitus
insulin lispro (Humalog® Mix)	50/50, 75/25	Lilly	For the treatment of patients with diabetes mellitus for the control of hyperglycemia

insulin detemir (Levemir) is not recommended for treating diabetic ketoacidosis.

Use of insulin detemir with liraglutide (Victoza®) has been shown to be effective in clinical studies.

OVERVIEW

It is estimated that 25.8 million Americans have diabetes mellitus (DM).[11] Diabetes results in a significant economic burden to society in terms of both direct and indirect costs. Diabetes is also responsible for increased morbidity and mortality. Adequate glycemic control is crucial to minimize chronic microvascular (e.g., blindness, renal dysfunction) and macrovascular (e.g., cardiovascular disease) complications.[12]

The American Diabetes Associations (ADA) 2014 Standards of Care in Diabetes recommends the use of the HbA1c levels greater than or equal to 6.5 percent as the threshold for the diagnosis of diabetes.[13]

Exogenous insulin supplements deficient levels of endogenous insulin, and temporarily restores the ability of the body to properly utilize carbohydrates, fats, and proteins. Multiple insulin products are available and are used as replacement therapy in the management of both type 1 and of type 2 diabetes when glycemic goals are not met with oral antidiabetic agents.

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As advised by the ADA, a reasonable HbA1C goal for nonpregnant adults is less than seven percent; however more stringent HbA1c goals (< 6.5 percent) for selected individual patients (e.g. those with short duration of diabetes, long life expectancy, and no significant CVD), may be considered if this can be achieved without significant hypoglycemia.[14] Less-stringent HbA1C goals (< eight percent) 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. The 2012 ADA/European Association for the Study of Diabetes (EASD) Consensus Statement reaffirms that HbA1c goals need to be tailored to individual patient needs.[15] Antidiabetic therapy should generally start with metformin and if glycemic targets are not met, therapy modifications should be based on patient-specific factors. Insulin monotherapy or in combination with other medications may be required to maintain glycemic control. In newly diagnosed type 2 diabetic patients with markedly symptomatic and/or elevated blood glucose levels or HbA1c, consider insulin therapy, with or without additional agents, from the outset. If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the HbA1c target over three months, a second oral agent, a GLP-1 receptor agonist, or insulin should be added.

As replacement to the 2009 AACE/ACE diabetes algorithm for glycemic control, in 2013, the American Academy of Clinical Endocrinologists (AACE) released an algorithm and consensus statement for type 2 diabetes treatment with a goal HbA1c of ≤6.5% for healthy patients with low hypoglycemic risk.[16] For patients with concurrent illness and at risk of hypoglycemia goal HbA1c is >6.5% is appropriate. It suggests patients with an HbA1C <7.5% start with monotherapy; whereas patients with an HbA1C ≥7.5% begin with dual therapy. Patients with an HbA1C >9% and no symptoms may start either dual or triple antihyperglycemic therapy; patients with an HbA1C >9% with symptoms should begin insulin therapy with or without other agents. The HbA1C should be reassessed every three months and failure to improve may warrant additional complementary therapy for optimal glycemic control.

The American Association of Clinical Endocrinologists (AACE) 2011 Diabetes Care Plan Guidelines state that insulin is required in all patients with type 1 diabetes, and it should be considered for patients with type 2 diabetes, when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia.[17] When insulin therapy is indicated in patients with type 2 diabetes, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia. Short- or rapid-acting insulin may be considered if postprandial hyperglycemia is present; rapid-acting insulin analogues are preferred of the two, when control of postprandial hyperglycemia is required because they have a more rapid onset and offset of action and are associated with less hypoglycemia. Premixed insulin analogue therapy may be appropriate for patients in whom adherence to a drug regimen is problematic; although, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared with basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy.

Insulins can be administered using an insulin cartridge and/or insulin pen device to deliver multiple doses to a single patient. In March 2009, the FDA published an alert to healthcare professionals and patients to remind that insulin pens and insulin cartridges should not be used to give medication to multiple patients. Sharing insulin pens could result in the transmission of human immunodeficiency virus (HIV), the hepatitis viruses, and other blood-borne diseases. All insulin pens are approved only for single-patient use.[18]

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Pharmacology[19]

Insulin, secreted from the pancreatic beta cells, lowers blood glucose levels by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting gluconeogenesis. Insulin also inhibits lipolysis in the adipocyte, inhibits proteolysis, and enhances protein synthesis. Exogenous insulin is derived from recombinant DNA technology with *E. coli* or yeast.

PHARMACOKINETICS

Comparison of Insulin Products

Type of Insulin	Drug	Composition of Insulin	Onset (hrs)	Peak (hrs)	Duration (hrs)	Compatibility for Mixing
Short-acting	Human insulin regular (Humulin R, Novolin R)[20,21,22]	Crystalline regular insulin is prepared by precipitation in the presence of zinc chloride at a neutral pH.	0.5	2.5-5	8	NPH
Rapid-acting	insulin aspart (Novolog)[23,24]	Consists of human insulin aspart in a clear aqueous solution. Created when the amino acid proline is substituted with aspartic acid at position B28.	.25	0.75-1.5	3-5	NPH
	insulin glulisine (Apidra)[25, 26]	Created when the amino acid asparagine at position B3 is replaced by lysine and the lysine at position B29 is replaced by glutamic acid.	0.33	0.92	5.3	NPH
	insulin lispro (Humalog)[27, 28]	Consists of zinc-insulin lispro crystals dissolved in clear aqueous fluid. Created when the amino acids at positions 28 and 29 on the insulin B-chain are reversed.	More rapid than regular insulin	0.5-1.5	3-4	NPH
Rapid/ Intermediate-acting combination products	insulin aspart (Novolog Mix)[29]	Suspension containing insulin aspart protamine crystals and soluble insulin aspart.	0.17-0.33	1.6-3.2	Up to 24 hours	None
	insulin lispro (Humalog Mix)[30,31]	Suspension containing insulin lispro protamine suspension and insulin lispro solution.	More rapid than regular insulin	0.8-6.5	Similar to corresponding Humulin mixes	None
Intermediate-acting	human insulin NPH (Humulin N, Novolin N)[32,33,34]	Isophane (NPH) is modified, crystalline protamine zinc insulin. Its effects are comparable to a mixture of 2:1 to 3:1 regular insulin and protamine zinc insulin.	1-1.5	4-12	Up to 24	Regular, aspart, lispro, and glulisine

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Comparison of Insulin Products (continued)

Type of Insulin	Drug	Composition of Insulin	Onset (hrs)	Peak (hrs)	Duration (hrs)	Compatibility for Mixing
Long-acting	insulin detemir (Levemir)[35,36]	Created when the amino acid threonine in position B30 is omitted and a C14 fatty acid chain is added to amino acid B29	0.8-2	6-8	5.7-23.2	None
	insulin glargine (Lantus)[37]	Created when the amino acids at position 21 of human insulin are replaced by glycine and two arginines are added to the C terminus of the B chain.	1.1	5 (no actual peak as insulin glargine is released slowly over 24 hours)	Up to 24 (only studied up to 24 hrs)	None

CONTRAINDICATIONS/WARNINGS[38,39,40,41,42,43,44,45,46,47]

Insulin is contraindicated during episodes of hypoglycemia.

Changes in insulin dosages should only be made under medical supervision.

Precautions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin therapy.

Insulin aspart (Novolog), insulin detemir (Levemir), insulin glulisine (Apidra), insulin glargine (Lantus), and insulin lispro (Humalog) contain cresol that has been reported to cause localized reactions and generalized myalgias. Insulin aspart contains approximately half the amount of metacresol that insulin lispro and insulin glulisine contain.

All insulins can cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia that, if left untreated, may cause respiratory paralysis, ventricular arrhythmia, and death. Caution should be used in patients who may be at risk for hypokalemia.

Alkaline phosphatase elevations have been reported with human insulin aspart.

All insulins may require a dose adjustment for patients with renal or hepatic impairment.

DRUG INTERACTIONS[48,49,50,51,52,53,54,55,56,57]

Beta-blockers and clonidine are commonly used drugs that may mask the signs and symptoms of hypoglycemia.

Substances that may decrease insulin requirements include oral antidiabetic agents, monoamine oxidase inhibitors (MAOIs), ACE inhibitors, fibrates, fluoxetine, sulfonamide antibiotics, nonselective beta-blockers, and alpha-adrenergic blockers.

Substances that may increase insulin requirements include oral contraceptives, thiazides, glucocorticoids, growth hormone, isoniazid, niacin, sympathomimetic agents, atypical antipsychotics, and thyroid hormones.

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Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

Concurrent use of insulin with thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)- gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin.

ADVERSE EFFECTS[58,59,60,61,62,63,64,65,66,67]

The most common adverse effect of all insulin products is hypoglycemia. Glucose monitoring is recommended in all diabetic patients. Injection site reactions can occur with any type of injectable insulin. Other possible adverse effects of the injectable insulins include lipodystrophy, pruritis, and rash.

In clinical trials, insulin glargine (Lantus) had treatment-emergent injection site pain in 2.7 percent of patients versus 0.7 percent of patients on NPH insulin. Treatment discontinuation was not required. Insulin detemir (Levemir) was associated with more frequent mild injection site reactions than with insulin NPH.

Adverse effects data are obtained from prescribing information and therefore, should not be considered comparative or all-inclusive.

SPECIAL POPULATIONS[68,69,70,71,72,73,74,75,76,77]

Pediatrics

In 2013, the American Academy of Pediatrics (AAP) issued new guidance for the management of newly diagnosed type 2 diabetes mellitus in children and adolescents.[78] They advise clinicians to initiate insulin therapy in children and adolescents with type 2 diabetes who are ketotic or in diabetic ketoacidosis, in patients whom the distinction between types 1 and 2 diabetes mellitus is unclear, and for any patient with a blood glucose level ≥250 mg/dL or HbA1c >9%. The AAP suggests that clinicians monitor HbA1c concentrations every three months and intensify treatment if blood glucose and HbA1c goals are not being met.

Human insulin (Humulin, Novolin) products have been used in all age groups. Human insulin lispro (Humalog) can be used in children than three years of age and older. Human insulin aspart (Novolog) can be given to pediatric patients two years of age and older. Insulin glulisine (Apidra) is approved for use in pediatric patients with type 1 diabetes from four to 17 years of age. The safety and efficacy of insulin NPH combinations with insulin aspart and insulin lispro in children have not been evaluated by the FDA, and little data exist. Insulin glargine (Lantus) is approved for use in type 1 diabetic children from six to 15 years of age; insulin detemir (Levemir) has not been studied in children with type 1 diabetes less than two years of age. In general, intermediate and long-acting insulins can have slightly higher area-under-the-curves and maximum concentrations in children.

In one multicenter, open-label, randomized, six-month study, 349 type 1 diabetes mellitus patients aged five to 16 years received insulin glargine once daily or NPH insulin either once or twice daily.[79] There was no difference between insulin glargine and NPH insulin in the primary efficacy measure of change in HbA1c from baseline to end point. Fasting blood glucose (FBG) levels decreased significantly more in the insulin glargine group (-1.29 mmol/L) than in the NPH insulin group (-0.68 mmol/L,

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p=0.02). The percentage of patients that reported at least one symptomatic hypoglycemic episode was similar between groups; however, fewer patients in the insulin glargine group reported severe hypoglycemia (23 versus 29 percent, respectively) and severe nocturnal hypoglycemia (13 versus 18 percent, respectively), although these differences were not statistically significant. Fewer serious adverse events occurred in the insulin glargine group than in the NPH insulin group (p<0.02).

The clinical efficacy and safety of two treatment regimens (biphasic insulin aspart at all three meals plus NPH insulin at bedtime versus premixed human insulin at breakfast and regular insulin at lunch and dinner, with NPH at bedtime) were compared in 167 adolescents with type 1 diabetes.[80] The multinational, randomized, open-label, parallel-group trial was four months in duration. HbA1c after four months on biphasic insulin aspart (9.39 percent) was not significantly different from that with human insulin (9.30 percent). The body mass index increased in both groups, but significantly (p=0.005) less in the biphasic insulin aspart group. No significant group differences were found for the rate of hypoglycemic episodes.

In a 26-week, open-label, randomized, parallel-group study, 347 children with type 1 diabetes, aged six to 17 years, received insulin detemir or NPH insulin once or twice daily plus insulin aspart before meals.[81] The mean HbA1c decreased by approximately 0.8 percent with both treatments. Within-subject variation in self-measured fasting plasma glucose was significantly lower with insulin detemir than with NPH insulin (p<0.001), as was mean fasting plasma glucose (8.4 versus 9.6 mmol/L, p=0.022). The risk of nocturnal hypoglycemia was 26 percent lower with insulin detemir (p=0.041).

A one-year open-labeled, parallel group trial compared insulin detemir with NPH insulin, in combination with mealtime insulin aspart in 347 patients aged two to 16 years with type 1 diabetes mellitus.[82,83] Randomization was stratified by age (two to five years, n=82; six to 16 years, n=265). Mean HbA1c was similar between groups at baseline (8.2 versus 8.1 percent), and changed little over one year (8.1 versus 8.3 percent). Fasting plasma glucose (FPG) was similar at baseline (8.44 versus 8.56 mmol/L) and decreased during the study (-1.0 versus -0.45 mmol/L). A lower rate of hypoglycemia was observed with Insulin detemir compared with NPH (24-h; 50.6 versus 78.3 episodes per patient-year; nocturnal hypoglycemia, eight versus 17.4 episodes per patient-year). No severe hypoglycemic episodes occurred with insulin detemir, while three subjects reported six episodes with NPH.

In an effort to compare the safety and efficacy of insulin glulisine to that of insulin lispro in children and adolescents with type 1 diabetes, 572 patients aged four years and older were randomized to receive either insulin glulisine or insulin lispro, administered subcutaneously within 15 minutes before a meal, in an open-label, active-controlled, non-inferiority trial.[84] During this 26-week study, patients also received insulin glargine (administered once daily in the evening) or NPH insulin (administered once in the morning and once in the evening). There were no significant differences observed between the two treatment groups with respect to glycemic control.

In May 2011 the FDA approved insulin lispro (Humalog) use in a continuous insulin infusion pump in the pediatric population.

Pregnancy

The human insulins, insulin aspart, insulin detemir, and insulin lispro are Pregnancy Category B., Insulin glargine, and insulin glulisine are Pregnancy Category C.

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According to AACE, the preferred treatment for postprandial hyperglycemia in pregnant women is regular or rapid-acting insulin analogues.[85] Basal insulin can be controlled with the use of rapid-acting insulin via infusion pump therapy or long-acting insulin.

In 322 pregnant women with type 1 diabetes, meal-time regular insulin (given 30 minutes before meal) or insulin aspart (given immediately before meal) was administered in an open-label, parallel-group, multicenter study.[86] Patients had HbA1c equal to 8 percent or less at confirmation of pregnancy, and insulin doses were titrated toward predefined glucose targets and HbA1c less than 6.5 percent. Major hypoglycemia occurred at a rate of 1.4 versus 2.1 episodes per year-exposure with insulin aspart and regular insulin, respectively (relative risk 0.72 [95% CI, 0.36 to 1.46]). The risk of major nocturnal hypoglycemia was 52 percent (RR 0.48 [0.20 to -1.143]) lower with insulin aspart compared with regular insulin. The HbA1c for insulin aspart patients was comparable with human insulin in second and third trimesters, and a total of 80 percent of subjects achieved HbA1c of 6.5 percent or less. Maternal safety profiles and pregnancy outcomes were similar between treatments.

In 2012, the pregnancy category for insulin detemir was modified from C to B. In an open-label study 310 women with type 1 diabetes who were pregnant or intended to become pregnant were randomized to insulin detemir (once or twice daily) or NPH insulin (one to three times daily). Insulin aspart was administered before each meal. Mean HbA1c was < seven percent at 10, 12, and 24 weeks of gestation in both arms. In the intent-to-treat population, the adjusted mean HbA1c at gestational week 36 was similar in each arm. There were no differences in pregnancy outcomes or the health of the fetus and newborn between the groups.

Renal impairment

Renally impaired patients are subject to increased levels of circulating insulin. Dose adjustments may be warranted in this patient population.

Hepatic impairment

Dose adjustments may be needed in patients with hepatic impairment.

Other

For categories as age, gender, and obesity, there are no significant data that suggest a difference in drug effect in these patients.

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DOSAGES[87,88,89,90,91,92,93,94,95,96]

Drug	Dosing	Time of administration related to mealtime	Availability
human insulin (Humulin, Novolin)	Dosing should be titrated to glycemic control in combination with an intermediate or long acting insulin (and/or with oral antidiabetic agents for type 2 diabetics)	30-60 minutes prior to meal	10 mL vials, Humulin 500 units/mL 20 mL vials 3 mL prefilled pen (Humulin N, 70/30) 3 mL prefilled Kwikpen (Humulin 70/30, Humulin N 100)
insulin aspart (Novolog)		5-10 minutes before eating	10 mL vial, 3 mL prefilled FlexPen 3 mL cartridge (Novolog 100)
insulin glulisine (Apidra)		Within 15 minutes before a meal or within 20 minutes after starting a meal	10 mL vial, 3 mL cartridge for Opticlik, 3 mL prefilled SoloStar pen
insulin lispro (Humalog)		No more than 15 minutes before a meal or immediately after a meal	10 mL vial, 3 mL vial, 3 mL cartridge, 3 mL prefilled KwikPen
insulin aspart/ protamine aspart (Novolog Mix 70/30)	Dosing should be titrated to glycemic control	Typically dosed on a twice-daily basis (breakfast and dinner) Type 1 diabetes: within 15 minutes before meal initiation Type 2 diabetes: within 15 minutes before or after meal initiation	10 mL vial, 3 mL prefilled FlexPen
insulin lispro/ protamine lispro (Humalog Mix 75/25, Humalog Mix 50/50)		Within 15 minutes before meal initiation or immediately after a meal	10 mL vial, 3 mL prefilled KwikPen
insulin detemir (Levemir)	0.1-0.2 units/kg once daily or 10 units once or twice daily	Once daily (with the evening meal or at bedtime) or twice daily (with the evening meal, at bedtime, or 12 hours after the morning dose)	10 mL vial, 3 mL prefilled FlexPen
insulin glargine (Lantus)	Dosing should be individualized based on the type of diabetes and whether the patient is insulin-naïve. Initial dose in patients with Type 1 diabetes is one-third of the total daily insulin requirements. Short-acting, pre-meal insulin should be used to satisfy the remainder of the daily insulin requirement.	Once daily at anytime during the day, at the same time every day	10 mL vial, 3 mL prefilled SoloStar pen

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Humulin N and Humulin 70/30 original prefilled pens will be phased out by the manufacturer in first quarter of 2014.

Regular insulin, insulin glulisine (Apidra), insulin lispro (Humalog), and insulin aspart (Novolog) can be administered intravenously. Insulin aspart/protamine aspart (Novolog Mix), insulin lispro/ protamine lispro (Humalog Mix), insulin detemir (Levemir), and insulin glargine (Lantus) should not be given intravenously or used in insulin infusion pumps.

Doses of insulin should be individualized. Generally, for both children and adults, an initial dose is 0.5 to 1 unit/kg/day. Insulin requirements may be altered during major illness, emotional disturbances, stress, or changes in exercise, meal patterns, or coadministered drugs. The duration of action of all insulins will vary according to the dose, injection site, blood flow, temperature, and level of physical activity.

All of the insulin products are available in vials, cartridge and/or pen delivery systems. The FlexPen® delivery system was redesigned and launched in a prefilled pen for insulin detemir (Levemir), insulin aspart (Novolog), and insulin aspart/protamine aspart (Novolog Mix).[97] The new design requires 30 percent less injection force than the original pen device, and does not allow patients to dial a dose of insulin larger than the amount of insulin remaining in the pen. The new design also has enhanced color branding with color-coded cartridge holders for easy identification and differentiation of rapid- and long-acting insulin products. The FlexPen is able to dial up to 60 units of insulin in one-unit increments.

The KwikPen™ prefilled pen device for insulin lispro (Humalog) and insulin lispro/ protamine lispro (Humalog Mix) is able to provide up to 60 units of insulin in one-unit increments utilizing a dial mechanism.

For patients that may require smaller doses of insulin (e.g., children), there are two reusable pen devices currently available. The HumaPen® Luxura™ HD allows patients to dial insulin in half-unit increments (from one to 30 units), and should only be used with insulin lispro (Humalog) cartridges.[98] The NovoPen® Junior can dial half-unit increments (from one to 35 units), and should only be used with the Novo Nordisk product line of insulin cartridges.[99]

The SoloStar® prefilled pen devices for insulin glargine (Lantus) and insulin glulisine (Apidra) are useful for patients that require larger doses of insulin.[100,101] This pen system is able to dial up to 80 units of insulin in one-unit increments.

As of November 2011, the HumaPen® Memoir digital insulin pen device is no longer available in the US. However, the prefilled cartridge for use in the HumaPen Memoir will still continue to be available for those patients still using the device.[102]

Most cartridges and pens are refrigerated before use. Following the first use, these formulations should be stored at room temperature. Expiration dates are typically 10-14 days for regular insulin and insulin NPH, as well as mixes of regular insulin, insulin aspart, or insulin lispro with insulin NPH. The rapid-acting insulins and insulin glargine cartridges and pens expire in 28 days, while those for insulin detemir last 42 days.

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CLINICAL TRIALS

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all brand names in this class. Randomized, comparative, controlled trials comparing agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Numerous studies were found meeting standard criteria. The data included here were further evaluated to remove studies that were found to be unacceptable for the following reasons: small treatment group, post hoc analysis, use of insulin pumps, studies relying on outcomes from self-reported data, inappropriate treatment duration, and unapproved formulation, dosage regimen, or route of administration.

The method of administration and associated monitoring makes it difficult to perform properly blinded studies with these drugs. Due to the lack of double-blind studies, open-label studies have been included; while these large studies may produce accurate results, the study design should be taken into consideration.

In countries outside of the US, blood glucose values are typically reported in mmol/L. For those studies reporting blood glucose values in mmol/L, the value in mg/dL can be estimated by multiplying the mmol/L value by 18.

insulin aspart (Novolog) and regular human insulin

A prospective, multicenter, randomized, parallel-group, open-label study was performed in 423 basal-bolus treated patients with type 1 diabetes.[103] Main outcome measures included blood glucose control assessed by HbA1c, nine-point self-monitored blood glucose profiles, insulin dose, quality of life, hypoglycemia, and adverse events. An algorithm-driven increase occurred in the dose and number of daily injections of basal insulin, particularly in the insulin aspart group. After 12 weeks of treatment, HbA1c was significantly lower in the insulin aspart group compared to regular human insulin subjects by 0.17 percent (95% CI, 0.30 to 0.04, $p<0.05$). Comparison of the blood glucose profiles showed lower blood glucose levels with insulin aspart after breakfast ($p<0.0001$) and dinner ($p<0.01$). There were no differences between treatments in the incidence of hypoglycemic episodes or in the adverse event profiles. The WHO Diabetes Treatment Satisfaction Questionnaire score for perceived hyperglycemia was lower with insulin aspart ($p=0.005$).

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In a six-month, similarly designed trial in 1,070 adults with type 1 diabetes, HbA1c was significantly lower in the insulin aspart group (0.12 percent reduction in HbA1c) after six months.[104] The insulin aspart group had lower post-prandial blood glucose levels, but had higher preprandial glucose levels before breakfast and dinner (p<0.01). Major hypoglycemia episodes overall were similar in both treatment groups, but major hypoglycemia episodes occurring at night that required parenteral treatment occurred more often in the regular insulin group.

Another similarly designed study was performed over six months with a six-month extension period. In 882 men and women with type 1 diabetes, HbA1c values were significantly lower with insulin aspart than with regular insulin (7.78 versus 7.93 percent; p=0.005) at six months.[105] In the extension period (n=714), the difference in HbA1c continued to remain significant at 12 months. The mean basal NPH dose at 12 months was significantly higher for the insulin aspart group than that for the regular insulin group (0.314 versus 0.296 units/kg; p=0.011). A similar percentage of patients in each treatment group had a major hypoglycemic episode by six months. Fewer subjects in the insulin aspart group than in the regular insulin group (four versus eight percent) experienced a major hypoglycemic episode during the night.

A trial was conducted in patients with type 1 diabetes who were randomized to mealtime insulin aspart with up to four daily NPH doses and a 25 percent increase in bedtime NPH dose (n=187) or to mealtime human unmodified insulin with once or twice daily basal NPH insulin (n=181).[106] Efficacy and safety were evaluated at 12 weeks (primary evaluation period) and 64 weeks. At 12 and 64 weeks, there was no statistically significant difference in HbA1c reduction between the insulin aspart and regular insulin groups (-0.09 and -0.14 percent, respectively). Post-prandial glucose values were lower with insulin aspart, and no significant differences were found in mild or severe hypoglycemia or adverse event rates. At 64 weeks, treatment satisfaction was higher in the insulin aspart group while quality of life was not different.

To compare quality of life (QOL) and treatment satisfaction, 424 patients were randomized to basal-bolus treatment with either insulin aspart (n=283) or regular human insulin (n=141) in the six-month, multinational, randomized, open-label trial.[107] After six months, insulin aspart was associated with significantly greater improvement in treatment satisfaction than human insulin in two different scales (p<0.01), and in QOL with respect to diet restrictions (p<0.01). Improved satisfaction was mainly due to increased dietary and leisure time flexibility (p<0.0001).

In the multinational, double-blind, crossover trial, 155 patients with type 1 diabetes were randomized to two 16-week treatment periods on either insulin aspart or human insulin.[108] NPH insulin was given as basal insulin once or twice daily as needed. Treatment periods were separated by a four-week washout. The rate of major nocturnal hypoglycemic episodes was 72 percent lower with insulin aspart than with human insulin (0.067 versus 0.225 events/month; p=0.001). The total rate of major hypoglycemia did not differ significantly between treatments (insulin aspart/human insulin relative risk 0.72; 95% CI, 0.47 to 1.09, p=0.12). Mean HbA1c remained constant, slightly below 7.7 percent on both treatments.

A total of 231 type 2 diabetic patients were randomized to insulin aspart (n=75), regular insulin (n=80), or insulin 70/30 (n=76) for three months with or without bedtime NPH insulin.[109] A total of 204 patients completed the trial according to protocol. The primary endpoint was change in HbA1c from baseline. HbA1c decreased 0.91 ± 1 percent for insulin aspart, 0.73 ± 0.87 percent for regular insulin, and 0.65 ± 1.10 percent for insulin 70/30. Postprandial blood glucose decreased more in the insulin

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aspart group compared with regular insulin and insulin 70/30. Hypoglycemic events per month were 0.56 with regular insulin, 0.40 with insulin aspart, and 0.19 with insulin 70/30.

biphasic insulin aspart (Novolog Mix 70/30) and human insulin 70/30

In a randomized, open-label, parallel trial, 177 patients with type 2 diabetes were assigned to meal-related injection of biphasic insulin aspart three times a day or biphasic human insulin twice a day over a study period of 24 weeks.[110] The mean difference between treatment groups in HbA1c after 24 weeks of treatment was 0.08 percent (p=0.6419). Significant differences in blood glucose levels were observed after lunch (156 versus 176 mg/dL, p=0.0289), before dinner (142 versus 166 mg/dL p=0.006), and after dinner (154 versus 182 mg/dL p=0.002) in favor of biphasic insulin aspart. No differences were found regarding safety parameters in the two treatment groups.

biphasic insulin aspart (Novolog Mix 70/30) and NPH human insulin

In the double-blind study of 403 patients with type 2 diabetes not controlled on oral hypoglycemic agents, patients were randomized to receive either biphasic insulin aspart or NPH insulin immediately before breakfast and dinner for 16 weeks.[111] Oral hypoglycemic agents were discontinued. In both groups, HbA1c decreased by greater than 0.6 percent (p<0.0001 versus baseline). The biphasic insulin aspart group had a decreased daily postprandial glycemic exposure (mean difference 0.69 mmol/L; p<0.0001). Overall safety profile of both groups was similar.

biphasic insulin aspart (Novolog Mix 70/30) and biphasic insulin lispro (Humalog Mix 75/25)

Patients (n=137) with type 2 diabetes mellitus currently receiving insulin treatment were randomized to a multicenter, open-label, crossover comparison of biphasic insulin aspart and biphasic insulin lispro.[112] Efficacy and safety profiles were assessed after 12 weeks of treatment. Treatment with biphasic insulin aspart was not inferior to treatment with biphasic insulin lispro. Adverse event profiles were similar between treatments, as was the incidence of hypoglycemic episodes (0.69 episodes/month with biphasic insulin aspart and 0.62 episodes/month with biphasic insulin lispro, p=NS). For all device features assessed, the biphasic insulin aspart FlexPen consistently received higher scores (all p<0.005). Furthermore, 74.6 percent of patients preferred to continue using the FlexPen, whereas 14.3 percent preferred the biphasic insulin lispro pen (p<0.001).

insulin detemir (Levemir) and insulin NPH (Novolin N)

A six-month, prospective, randomized, open-label, controlled, parallel-group trial conducted at 92 sites included 749 men and women with type 1 diabetes with HbA1c < 12 percent who were already taking daily intermediate- or long-acting insulin and a fast-acting human insulin or insulin analogue as bolus insulin.[113] Patients were randomized to insulin detemir or NPH at bedtime in combination with human insulin with main meals. Main outcome measures included HbA1c, FPG, and hypoglycemia. After six months, FPG was lower with insulin detemir than with NPH (-1.16 mmol/L difference; p=0.001), whereas HbA1c did not differ significantly between treatments (-0.12 percent; p=NS). Day-to-day variability in self-measured fasting blood glucose was lower with insulin detemir (2.82 versus 3.60 mmol/L; p<0.001). Lower glucose levels were seen before breakfast with insulin detemir compared to NPH (p<0.001). There was a 26 percent reduction in the relative risk of nocturnal hypoglycemia with

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insulin detemir compared with NPH (p=0.003). The adverse effect profiles were similar between treatment groups.

In the 20-week, multicenter, randomized, open-label, parallel-group trial, 504 (intent-to-treat group [ITT] n=498) type 2 diabetic patients, poorly controlled on oral antidiabetic therapy, were randomly assigned to receive an evening SC injection of insulin detemir, a pre-breakfast injection of insulin detemir, or an evening injection of NPH insulin, in addition to their existing oral antidiabetic regimen.[114] Morning and evening detemir were associated with reductions in HbA1c similar to those receiving evening NPH (-1.58, -1.48, and -1.74 percent, respectively). Compared with evening NPH, 24-hour and nocturnal hypoglycemia were reduced by 53 percent (p=0.019) and 65 percent (p=0.031), respectively, with evening insulin detemir. Incidences of hypoglycemia did not differ significantly between groups that received morning and evening insulin detemir, but nocturnal hypoglycemia was reduced further, by 87 percent, with morning insulin detemir compared with evening NPH (p<0.001). Weight gain was 1.2, 0.7, and 1.6 kg with morning insulin detemir, evening insulin detemir, and NPH, respectively (p=0.005 for evening detemir versus NPH).

Patients with type 2 diabetes (n=476) with HbA1c 7.5-10 percent were randomized to the addition of insulin detemir or NPH insulin twice daily to existing oral antidiabetic agent therapy in a parallel-group, open-label, multicenter trial.[115] At 24 weeks, HbA1c had decreased by 1.8 and 1.9 percent for insulin detemir and NPH insulin, respectively (p=NS). In both groups, 70 percent of participants achieved an HbA1c<7, but the proportion achieving this without hypoglycemia was higher with insulin detemir than with NPH insulin (26 versus 16 percent, p=0.008). Compared with NPH insulin, the risk for all hypoglycemia with insulin detemir was reduced by 47 percent (p<0.001) and nocturnal hypoglycemia by 55 percent (p<0.001). The mean weight gain was 1.2 kg with insulin detemir and 2.8 kg with NPH insulin (p<0.001).

insulin detemir (Levemir), insulin aspart (Novolog), and biphasic insulin aspart (Novolog Mix 70/30)

In an open-label, controlled, multicenter trial, 708 patients who were receiving maximally tolerated doses of metformin and sulfonylurea were randomly assigned to receive biphasic insulin aspart twice daily, insulin aspart three times daily, or insulin detemir once daily (twice if necessary).[116] Outcome measures at one year were HbA1c, the proportion of patients with a HbA1c of 6.5 percent or less, the rate of hypoglycemia, and weight gain. At one year, HbA1c was similar in the biphasic group and the insulin aspart group (7.3 versus 7.2 percent, respectively; p=0.08), but higher in the basal group (7.6 percent, p<0.001 for both comparisons). The respective proportions of patients with a HbA1c<6.5 percent were 17, 23.9, and 8.1 percent; respective mean numbers of hypoglycemic events per patient per year were 5.7, 12, and 2.3 percent; and respective mean weight gains were 4.7 kg, 5.7 kg, and 1.9 kg. Rates of adverse events were similar among the three groups.

insulin detemir (Levemir), insulin NPH (Novolin N), and insulin aspart (Novolog)

The study was an open-label, parallel-group comparison conducted at 46 centers in five countries and included 448 patients (n=447 ITT) with type 1 diabetes. Patients were randomized to insulin detemir or NPH insulin before breakfast and at bedtime. Insulin aspart was given to both groups at meals.[117] After six months, comparable HbA1c levels were found between the two treatment groups. FPG was lower in patients treated with insulin detemir (-0.76 mmol/L), but this difference was not statistically significant (p=0.097). Within-subject variation oft self-measured FPG was lower with insulin detemir

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than with NPH insulin (3.37 versus 3.78 mmol/L, p<0.001). Risk of hypoglycemia was 22 percent lower with insulin detemir than with NPH insulin (p<0.05) and 34 percent lower for nocturnal hypoglycemia (p<0.005). Nightly plasma glucose profiles were smoother and more stable with insulin detemir (p=0.05). Body weight was significantly lower with insulin detemir at the end of the trial (p<0.001).

Patients with type 1 diabetes (n=408) were randomized in a 16-week, open-label, parallel-group trial to insulin detemir administered twice daily either before breakfast and at bedtime or at a 12-hour interval or NPH insulin administered before breakfast and at bedtime.[118] Insulin aspart was the mealtime insulin. Although HbA1c for each insulin detemir group was not different from the NPH group at endpoint, HbA1c for the pooled insulin detemir groups was significantly lower than the NPH group (mean difference -0.18 percent; p=0.027). With both insulin detemir groups, before breakfast and at bedtime or at a 12-hour interval, clinician measured FPG was lower than with NPH insulin (-1.5 mmol/L, p=0.004; -2.3 mmol/L, p<0.001, respectively), as was self-measured pre-breakfast plasma glucose (p=0.006 and p=0.004, respectively). Within-person between-day variation of self-measured pre-breakfast plasma glucose was lower for both detemir groups (both p<0.001). The risk of minor hypoglycemia was lower in both insulin detemir groups (25 percent, p=0.046; 32 percent, p=0.002; respectively) compared with NPH insulin in the last 12 weeks of treatment, mainly attributable to a reduction in nocturnal hypoglycemia in the insulin detemir breakfast/bedtime group (p<0.001). Few severe hypoglycemic episodes were recorded, with no statistical differences between the groups. The NPH group gained weight during the study, but there was no clinically significant change in weight in either of the insulin detemir groups (-0.8 kg, p=0.006; -0.6 kg, p=0.04, respectively).

A multinational, open-label, parallel-group trial studied 505 patients with type 2 diabetes.[119] Patients were randomized to insulin detemir or NPH, receiving basal insulin either once or twice daily, according to their pretrial insulin treatment, and insulin aspart at mealtimes. After 26 weeks of treatment, significant reductions in HbA1c were observed for insulin detemir (p=0.004) and NPH (p=0.0001), resulting in comparable levels at study end (insulin detemir, 7.6 percent; NPH insulin, 7.5 percent). The number of basal insulin injections administered per day had no effect on HbA1c levels (p=0.50). At study end, FPG concentrations were similar for the two treatment groups (p=0.66), as were reductions in FPG (insulin detemir, 0.5 mmol/L; NPH insulin, 0.6 mmol/L). However, within-subject day-to-day variation in fasting FPG was significantly lower with insulin detemir (p=0.021). The frequency of adverse events and the risk of hypoglycemia were comparable for the two treatment groups.

The multinational, 16-week, open-label, parallel-group trial included 400 people with type 1 diabetes randomized to insulin detemir in the morning and before dinner or morning and bedtime, or to NPH morning and bedtime, all in combination with mealtime insulin aspart.[120] HbA1c was comparable among the three groups after 16 weeks, with reductions of 0.39-0.49 percent (p=0.64). Lower FPG was observed with insulin detemir morning/dinner and insulin detemir morning/bedtime compared with NPH groups (9.8 and 9.1 versus 11.1 mmol/L, p=0.006), but the insulin detemir groups did not differ significantly (p=0.15). Within-person variation in self-measured FPG was significantly lower for both insulin detemir regimens than for NPH (SD: insulin detemir morning/dinner 2.5, insulin detemir morning/bedtime 2.6, NPH 3.1 mmol/L, p<0.001) but was comparable between the two insulin detemir groups (p=0.48). Ten-point plasma glucose profiles were lower between dinner and breakfast in the insulin detemir morning/dinner group (p=0.043) compared with the two other groups. Risk of overall and nocturnal hypoglycemia was similar for the three groups.

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insulin detemir (Levemir) + insulin aspart (Novolog) and insulin NPH (Novolin N) + regular insulin (Novolin R)

In the 18-week, randomized, open-label, parallel trial, 595 patients with type 1 diabetes received insulin detemir or NPH insulin in the morning and at bedtime in combination with mealtime insulin aspart or regular human insulin, respectively.[121] Glycemic control with insulin detemir/insulin aspart was improved in comparison with NPH insulin/regular human insulin (HbA1c: 7.88 versus 8.11 percent; p<0.001). Lower postprandial plasma glucose levels were seen in the insulin detemir/insulin aspart group (p<0.001), as well as lower within-person day-to-day variation in plasma glucose (SD: 2.88 versus 3.12 mmol/L; p<0.001). Risk of overall and nocturnal hypoglycemia was 21 percent (p=0.036) and 55 percent (p<0.001) lower in the insulin detemir/insulin aspart group than in the NPH insulin/regular human insulin group, respectively.

A 22-week, multinational, open-label, randomized, parallel-group trial enrolled 395 patients with type 2 diabetes. Patients were randomized to treatment with either basal insulin detemir in combination with insulin aspart at meals or basal insulin NPH in combination with regular human insulin at meals.[122] At 22 weeks, HbA1c was comparable between treatments (insulin detemir group: 7.46 percent, NPH group: 7.52 percent, p=0.515) with decreases from baseline of 0.65 and 0.58 percent, respectively. The insulin detemir group was associated with a significantly lower within-person variation in self-measured FPG (SD: 1.20 versus 1.54 mmol/L, p<0.001), as well as a lower body weight gain (0.51 versus 1.13 kg, p=0.038) than with the NPH group. The risk of nocturnal hypoglycemia was 38 percent lower with the insulin detemir group compared to the NPH group (p=0.14). The overall safety profile was similar between the two treatments.

insulin glargine (Lantus) and NPH human insulin

In an open-label study to determine the safety and efficacy of insulin glargine in type 1 diabetics, patients were randomized to receive insulin glargine once daily (n=310) or NPH insulin (n=309) over 16 weeks.[123] NPH insulin patients maintained their regimen of either once daily or twice daily injections whereas insulin glargine patients received once daily injections at bedtime. All patients continued to administer individually titrated insulin lispro before meals. Insulin glargine patients had lower self-reported fasting blood glucose concentrations. More patients achieved a fasting blood glucose concentration of less than 119 mg/dL in the insulin glargine group (29.6 percent) than in the NPH insulin group (16.8 percent). No differences were noted in the HbA1c or hypoglycemic episodes between the groups. Less variability of blood glucose concentrations was noted in the insulin glargine group. More injection site pain was reported in the insulin glargine group (6.1 percent) than in the NPH group (0.3 percent).

In a multicenter, randomized, open-label, parallel-group study, 534 type 1 diabetics were randomized to receive premeal regular insulin and either daily insulin glargine or NPH insulin (once or twice daily) for up to 28 weeks.[124] A small decrease in HbA1c levels was noted with both insulin glargine (-0.16 percent) and NPH insulin (-0.21 percent; p>0.05). Significant reductions in median FPG levels from baseline (-1.67 versus -0.33 mmol/L with NPH insulin, p=0.0145) were achieved with insulin glargine compared to NPH insulin. After the one-month titration phase, significantly fewer subjects receiving insulin glargine experienced symptomatic hypoglycemia (39.9 versus 49.2 percent, p=0.0219) or nocturnal hypoglycemia (18.2 versus 27.1 percent, p=0.0116) compared with subjects receiving NPH insulin.

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Patients with type 1 diabetes were treated for up to 28 weeks with once-daily insulin glargine (n=199) or twice-daily NPH insulin (n=195) in addition to preprandial regular insulin in a randomized, parallel-group study.[125] A greater mean decrease in FBG was achieved at endpoint with insulin glargine compared with NPH insulin (-21 versus -10 mg/dL; p=0.015), and a greater percentage of patients treated with insulin glargine reached the target FBG (32.6 versus 21.3 percent; p=0.015). Similar percentages of patients in both treatment groups achieved HbA1c values of 7 percent or less at endpoint. After the one-month titration phase, the percentage of patients who reported at least one symptomatic hypoglycemic event confirmed by a blood glucose value of less than 50 mg/dL was significantly lower with insulin glargine than with NPH insulin (73.3 versus 81.7 percent; p=0.021). Severe hypoglycemia was also significantly reduced in insulin glargine patients.

One hundred and twenty-one patients with type 1 diabetes mellitus on four times a day NPH and lispro insulin at each meal were randomized to either continuation of NPH four times a day (n=60) or once daily insulin glargine at dinnertime (n=61) for one year.[126] Lispro insulin at meal-time was continued in both groups. Mean daily blood glucose was lower with insulin glargine (p<0.05). HbA1c at four months did not change with NPH but decreased with insulin glargine from 7.1 to 6.7 percent, and remained lower than NPH at 12 months (6.6 percent, p<0.05 versus NPH). The frequency of mild hypoglycemia was lower with insulin glargine versus NPH (7.2 versus 13.2 episodes/patient-month, p<0.05). After one year, NPH treatment resulted in no change of responses to hypoglycemia, while plasma glucose, thresholds and maximal responses of plasma adrenaline and symptoms to hypoglycemia improved with insulin glargine (p<0.05).

In an open-label, 24-week, multicenter trial, 765 patients with type 2 diabetes on one or two oral medications with inadequate glycemic control (HbA1c > 7.5 percent) were randomized to either bedtime insulin glargine or NPH insulin once daily and also continued their prestudy medications.[127] Mean FPG at end point was similar with insulin glargine and NPH (117 versus 120 mg/dL), as was HbA1c (6.96 versus 6.97 percent). A majority of patients (approximately 60 percent) attained HbA1c less than 7 percent with each insulin type. However, nearly 25 percent more patients attained this without documented nocturnal hypoglycemia (≤ 72 mg/dL) with insulin glargine (33.2 versus 26.7 percent, p<0.05). Rates of other categories of symptomatic hypoglycemia were 21 to 48 percent lower with insulin glargine.

A total of 518 type 2 diabetics who were receiving NPH insulin with or without regular insulin for postprandial control were randomized to receive insulin glargine once daily (n=259) or NPH insulin once or twice daily (n=259) for 28 weeks in an open-label, multicenter trial.[128] The treatment groups showed similar improvements in HbA1c from baseline to end point on intent-to-treat analysis. The mean change in HbA1c from baseline to endpoint was similar in the insulin glargine group (-0.41 ± 0.1 percent) and the NPH group (-0.59 ± 0.1 percent). The treatments were associated with similar reductions in fasting glucose levels. Overall, mild symptomatic hypoglycemia was similar in insulin glargine subjects (61.4 percent) and NPH insulin subjects (66 percent). However, nocturnal hypoglycemia in the insulin glargine group was reduced by 25 percent more than the NPH group during the treatment period after the dose-titration phase (26.5 versus 35.5 percent, p=0.0136). Patients in the insulin glargine group experienced less weight gain than those in the NPH group (0.4 versus 1.4 kg, p<0.0007).

In an open-label, randomized, controlled trial, 695 patients with type 2 diabetes mellitus previously treated with oral antidiabetic agents were randomized to treatment with morning insulin glargine, bedtime NPH insulin, or bedtime insulin glargine for 24 weeks in addition to 3 mg of glimepiride.[129]

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HbA1c levels improved by -1.24 percent with morning insulin glargine, -0.96 percent with bedtime insulin glargine, and -0.84 percent with bedtime NPH insulin. HbA1c improvement was more pronounced with morning insulin glargine than with NPH insulin (p=0.001) or bedtime insulin glargine (p=0.008). Baseline to endpoint fasting blood glucose levels improved similarly in all three groups. Nocturnal hypoglycemia was less frequent with morning (17 percent) and bedtime insulin glargine (23 percent) than with bedtime NPH insulin (38 percent, p<0.001).

In a multicenter, open-label, randomized study, 570 patients with type 2 diabetes were treated with insulin glargine or NPH insulin given once daily at bedtime.[130] Previous oral antidiabetic therapy was continued throughout the study. At 52 weeks, there was a trend toward a decrease in HbA1c values from baseline to endpoint with both drugs (insulin glargine: -0.46 percent; NPH insulin: -0.38 percent; p=0.415). Over the entire treatment period, NPH insulin-treated patients (41 percent) and insulin glargine-treated patients (35 percent) experienced a similar level of symptomatic hypoglycemia, but there was a statistically significant difference in the percentage of patients that experienced nocturnal hypoglycemia in NPH patients compared with those treated with insulin glargine in the overall population (24 versus 12 percent, p=0.002). The incidence of adverse events was similar for the two treatments.

Glycemic control and symptomatic hypoglycemia rates with insulin glargine versus NPH were studied in 125 poorly controlled type 1 diabetes patients.[131] Patients received preprandial insulin lispro and either insulin glargine or NPH at bedtime for 30 weeks in a randomized, single-blinded fashion. Basal insulin dosage was titrated to achieve FBG values under 5.5 mmol/L. At endpoint, mean HbA1c was 8.3 versus 9.1 percent for the insulin glargine versus NPH groups, but HbA1c was lower in the insulin glargine versus NPH group at study initiation (9.2 versus 9.7 percent). Adjusted least-squares mean change from baseline was -1.04 versus -0.51 percent, a significant treatment benefit in favor of insulin glargine (p<0.01). The mean values for end-point FBG were 7.9 versus 9 mmol/L in favor of insulin glargine (p<0.05). Significantly fewer moderate or severe nocturnal hypoglycemic episodes were observed in the insulin glargine group (p=0.04 and p=0.02).

An open-label, 24-week, randomized study compared the efficacy and safety of insulin glargine and insulin NPH, both in combination with a daily fixed dose of glimepiride, in terms of glycemic control and incidence of hypoglycemia.[132] Patients with poorly controlled type 2 diabetes on oral antidiabetic agents (HbA1c 7.5 to 10.5 percent) received glimepiride plus insulin glargine (n=231) or insulin NPH (n=250) using a forced titration algorithm. Insulin glargine and insulin NPH achieved similar HbA1c reductions. Confirmed nocturnal hypoglycemia was significantly lower with insulin glargine versus insulin NPH (16.9 versus 30 percent; p<0.01).

insulin glargine (Lantus) and human insulin 70/30

In a 24-week, multinational, multicenter, open-label, parallel-group clinical trial, 371 insulin-naïve patients with poor glycemic control on a sulfonylurea plus metformin were randomized to daily morning insulin glargine plus glimepiride and metformin or to insulin 70/30 twice daily without oral antidiabetic agents.[133] Mean HbA1c decrease from baseline was significantly more pronounced (-1.64 versus -1.31 percent, p=0.0003), and more patients reached HbA1c less than 7 percent without confirmed nocturnal hypoglycemia (45.5 versus 28.6 percent, p=0.0013) with the insulin glargine arm than with insulin 70/30. Similarly, FBG decrease was greater in the insulin glargine group (adjusted mean difference -17 mg/dL; p<0.0001), and more patients reached target FBG under 100 mg/dL with insulin glargine than with insulin 70/30 (31.6 versus 15 percent, p=0.0001). Insulin glargine patients

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had fewer confirmed hypoglycemic episodes than insulin 70/30 patients (4.07 versus 9.87 episodes/patient-year, p<0.0001).

insulin glargine (Lantus) and insulin detemir (Levemir)

In a 52-week multinational, open-label, parallel-group, treat-to-target, non-inferiority trial 443 patients with type 1 diabetes and a mean age of 42 years; a mean body mass index of 26.5; a mean HbA1c of 8.1 percent and a mean duration of diabetes of 17.2 years were randomized to receive either insulin detemir or insulin glargine for 52 weeks.[134] Insulin aspart was administered in both groups as the mealtime insulin. The basal insulin was initially administered once daily in the evening for both groups. If patients in the insulin detemir group achieved target plasma glucose levels before breakfast but not before dinner, administration was changed to twice a day regimen. Insulin glargine patients continued with once daily administration throughout the trial. The primary efficacy endpoint was HbA1c after 52 weeks while the secondary endpoints included the number of patients achieving an HbA1c level less than or equal to 7 percent with or without a major hypoglycemic episode in the last month of treatment and FBG. Results after 52 weeks showed no significant differences in mean HbA1c between insulin detemir and insulin glargine groups (7.57 and 7.56 percent, respectively; mean difference, 0.01%; 95% CI, -0.13 to 0.16)). Additionally, there was no significant difference in the proportion of patients receiving insulin detemir and insulin glargine in achieving an HbA1c value equal to or lower than 7 percent without major hypoglycemia (31.9 and 28.9 percent, respectively). In addition, there were no significant differences in estimated mean FPG (8.58 and 8.81 mmol/L; mean difference, -0.23 mmol/L; 95% CI, -1.04 to 0.58) or in basal insulin doses. The relative risks for total and nocturnal hypoglycemia were not significantly different between insulin detemir and insulin glargine (0.94 and 1.12, respectively; p=NS).

In a 24-week, multinational, open-label, treat-to-target trial, 973 insulin-naïve patients with type 2 diabetes and an HbA1c of 7 to 10.5 percent were randomized to insulin detemir twice daily or insulin glargine once daily.[135] Patients in this study had been treated with metformin for three months or greater prior to the study. The primary outcome was the percentage of patients reaching an HbA1c of less than 7 percent without symptomatic hypoglycemia. In the insulin glargine and insulin detemir groups, 27.5 and 25.6 percent of patients, respectively, reached HbA1c of less than 7 percent. It was demonstrated that insulin glargine once-daily is non-inferior to insulin detemir twice-daily regarding the percentage of patients who achieve a target HbA1c without hypoglycemia. Insulin detemir-treated patients had less weight gain and more often achieved HbA1c of less than 6.5 percent (p=0.017). However, the drop-out rate and daily insulin doses were lower in the insulin glargine group.

insulin glargine (Lantus), insulin detemir (Levemir), and insulin aspart (Novolog)

In a 26-week, multicenter, open-label, parallel-group trial, 320 type 1 diabetics received either insulin detemir twice daily or insulin glargine once daily, each in combination with premeal insulin aspart.[136] After 26 weeks, HbA1c decreased from 8.8 to 8.2 percent in the insulin detemir group and from 8.7 to 8.2 percent in the insulin glargine group. The overall risk of hypoglycemia was similar; however, the risk of severe and nocturnal hypoglycemia was 72 and 32 percent lower, respectively, with insulin detemir than with insulin glargine (p<0.05). Body weight gain was not significantly different between treatment arms.

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insulin glargine (Lantus) and biphasic insulin aspart (Novolog Mix 70/30)

The 28-week parallel-group study randomized 233 insulin-naive patients on more than 1,000 mg daily metformin alone or in combination with other oral antidiabetic agents to receive biphasic insulin aspart twice daily or insulin glargine at bedtime and titrated to target blood glucose.[137] At study end, the mean HbA1c value was lower in the biphasic insulin aspart group than in the insulin glargine group (6.91 versus 7.41 percent, p<0.01). The HbA1c reduction was greater in the biphasic insulin aspart group than in the insulin glargine group (-2.79 versus -2.36 percent, p<0.01), especially for subjects with baseline HbA1c greater than 8.5 percent (p<0.05). Minor hypoglycemia was greater in the biphasic insulin aspart group than in the insulin glargine group (3.4 and 0.7 episodes/year; p<0.05), and weight gain at study end was greater for biphasic insulin aspart-treated subjects than for insulin glargine-treated subjects (5.4 versus 3.5 kg, p<0.01).

In the randomized, open-label, parallel study, biphasic insulin aspart plus metformin twice daily were compared with insulin glargine plus glimepiride daily in 255 insulin-naïve patients.[138] The primary endpoint was the difference in absolute change in HbA1c between groups after 26 weeks of treatment. HbA1c change was significantly greater in the insulin aspart group than the insulin glargine group (between-group difference: -0.5 percent; p=0.0002). During the maintenance phase, one major hypoglycemic episode occurred in each group; 20.3 and 9 percent of patients experienced minor hypoglycemic episodes in the insulin aspart and insulin glargine groups, respectively (p=0.0124). Insulin glargine patients experienced significant weight gain of 1.5 kg (p<0.0001); the weight change with insulin aspart patients of +0.7 kg was not statistically significant (p=0.0762).

In a 26-week, open-labeled, randomized, parallel-group, multinational, treat-to-target trial, 480 insulin-naïve type 2 patients with diabetes with inadequate control on oral anti-diabetic medications were randomized to receive either biphasic insulin aspart prior to dinner or insulin glargine at bedtime in combination with metformin and glimepiride.[139] A total of 433 patients completed the trial. At the end of treatment, biphasic insulin aspart and insulin glargine reduced the mean HbA1c levels by -1.41 percent and 1.25 percent, respectively (95% CI, -0.3 to -0.02; p=0.029). After 26 weeks, the mean HbA1c levels were 7.1 percent for the biphasic insulin aspart group and 7.3 percent for the insulin glargine group. The relative risk for a nocturnal hypoglycemic episode was greater in the biphasic insulin aspart group than for insulin glargine (relative risk: 2.41; 95%CI, 1.34 to 4.34; p=0.003), although hypoglycemic rates were overall low with three major episodes occurring in each group.

insulin glargine (Lantus) and insulin lispro (Humalog)

In an open-label, multicenter study, 418 patients with type 2 diabetes inadequately controlled with oral hypoglycemic agents were randomized to receive either insulin glargine administered once daily (n=205) or insulin lispro administered three times daily (n=210).[140] The primary efficacy endpoint was the change in HbA1c from baseline to endpoint (week 44). There was no significant difference between the two treatment groups relative to mean reduction in HbA1c. The percentage of patients that reached HbA1c of 7 percent or less was 57 percent in the glargine group and 69 percent in the lispro group. However, the mean change in fasting blood glucose was significantly greater in the insulin glargine group (-4.3 mmol/L) compared to the insulin lispro group (-1.8 mmol/L; p<0.0001). Patients treated with insulin glargine were also shown to have greater reductions in nocturnal blood glucose compared with patients treated with insulin lispro (-3.3 mmol/L versus -2.6 mmol/L; p=0.0041). Hypoglycemic episodes occurred at a rate of 5.2 events per patient per year for insulin glargine and 24

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events per patient per year for insulin lispro (p<0.001). There was no significant difference in mean weight gain between the two treatment groups.

In an open-label 24-week trial, 383 insulin-treated patients with type 2 diabetes were randomized to insulin lispro protamine suspension (ILPS) plus lispro or glargine plus lispro.[141] Mean changes at week 24 were -1.05 percent (ILPS) and -1.20 percent (glargine). HbA1c less than seven percent was achieved by 21.7 versus 29.4 percent of patients. Mean basal/mealtime insulin doses at week 24 were 29.6/36.2 IU/day (ILPS) versus 32.8/42.2 IU/day (glargine); the difference was not statistically significant for total dose (p=0.7). In both groups, 56.1/25.7 percent versus 63.6/19.3 percent of patients experienced any/nocturnal hypoglycemia (p=0.2 for both).

insulin glargine (Lantus) and biphasic insulin lispro (Humalog Mix)

Type 2 diabetics (n=374) were randomly assigned to insulin lispro mix 50/50 three times daily with meals or insulin glargine at bedtime plus mealtime insulin lispro in a 24-week, multicenter, open-label, no inferiority trial.[142] Investigators could replace insulin lispro mix 50/50 with 75/25 at the evening meal if the fasting plasma glucose target was unachievable. At week 24, HbA1c was lower with insulin glargine (6.78 versus 6.95 percent, p=0.021), but HbA1c was reduced significantly from baseline for both therapies (p<0.0001). Non-inferiority of insulin lispro mix to insulin glargine was not demonstrated based on the prespecified noninferiority margin of 0.3 percent. The percentages of patients achieving target HbA1c varied depending on the specific target; statistically significant differences did occur in favor of insulin glargine at HbA1c<7 percent and HbA1c <6.5 percent. Rates of hypoglycemia were similar for both groups.

insulin glulisine (Apidra) and regular human insulin

Patients with type 1 diabetes (n=860) received daily insulin glargine and were randomized to either insulin glulisine injected within 15 minutes before or immediately after meals or regular human insulin, injected 30 to 45 minutes before meals in an open-label, controlled, multicenter, parallel-group, 12-week study.[143] Changes in mean HbA1c were -0.26, -0.11, and -0.13 percent in the pre-meal insulin glulisine, post-meal insulin glulisine, and regular insulin groups, respectively. The reduction in HbA1c was greater for the pre-meal insulin glulisine group in comparison with the regular insulin group (p=0.02) and the post-meal insulin glulisine group (p=0.006); no significant difference was found between post-meal insulin glulisine versus regular insulin. Overall, blood glucose profiles were similar in all three treatment groups but were significantly lower for pre-meal insulin glulisine post-breakfast and post-dinner measurements. Severe hypoglycemic episodes were comparable for all groups. Body weight increased (+0.3 kg) in the regular insulin and pre-meal insulin glulisine groups; however, weight decreased in the post-meal insulin glulisine group (-0.3 kg; p=0.03).

Patients with type 2 diabetes who had received at least six months of continuous insulin therapy were randomized in a multinational, controlled, open-label, parallel group, 26-week study.[144] Patients (n=890) received NPH insulin twice daily and either insulin glulisine or regular insulin at least twice daily. There were no differences in HbA1c reductions (insulin glulisine: -0.32 percent; regular insulin: -0.35 percent; p=0.57). Insulin glulisine lowered plasma glucose significantly more versus regular insulin at two hours (14.14 mmol/L versus 15.28 mmol/L; p=0.0025). Nocturnal hypoglycemia from the fourth month to the end of treatment was less frequent with insulin glulisine versus regular insulin (9.1 versus 14.5 percent; p=0.029).

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insulin glulisine (Apidra) and insulin lispro (Humalog)

The objective of the multinational, multicenter, controlled, open-label, randomized, parallel-group study was to compare the efficacy and safety of insulin glulisine to that of insulin lispro in adults diagnosed with type 1 diabetes.[145] Of the 683 patients randomized, 672 received treatment. Over the 26-week study, a similar reduction in mean HbA1c occurred in both groups (adjusted mean change from baseline -0.14 percent in both groups). The basal insulin dose was relatively unchanged from baseline in the insulin glulisine group but increased in the insulin lispro group (insulin glulisine: 0.12 units versus insulin lispro: 1.82 units; p=0.0001). There was no relevant difference between the two groups in the reporting of symptomatic hypoglycemia (overall, nocturnal, or severe).

insulin lispro (Humalog) and regular human insulin

In a 5.5-month randomized, open-label, parallel study of 148 patients with type 2 diabetes receiving either insulin lispro (n=70) or regular human insulin (n=78), eight-point blood glucose profiles and HbA1c measurements were collected at baseline, 1.5, 3.5, and 5.5 months.[146] Two-hour post-breakfast and two-hour post-supper blood glucose levels were significantly lower for insulin lispro than for regular human insulin at the end point (p=0.02 in both cases). HbA1c improved from 10.5 percent (insulin lispro) and 10.3 percent (regular human insulin) to 8 percent in each treatment arm. Hypoglycemia rates were similar during the day with a trend towards a reduced incidence in the night hours with insulin lispro (0.08 episodes/month versus 0.16 episodes/month, p=0.057).

META-ANALYSES

A systematic review of 45 studies was performed to compare premixed insulin analogues with any other antidiabetic agents for the treatment of type 2 diabetes in adults.[147] The outcomes examined included fasting glucose, postprandial glucose, HbA1c, and weight gain. Mortality data are scant. Of the 45 studies, 43 were randomized controlled trials. The studies included a total of 14,603 patients with a mean age of 59 years, a median HbA1c of 8.7 percent, and a mean body mass index (BMI) of 29.4 kg/m2. When compared with long-acting insulin analogues, premixed insulin analogues were found to be more effective in reducing postprandial glucose levels (pooled difference, -27.9 mg/dL; CI, -34.3 to -21.5 mg/dL) and HbA1c (pooled difference, -0.39%; CI, -0.5% to -0.3%). However, premixed insulin analogues were found to be less effective than long-acting insulin analogues in reducing fasting glucose levels (pooled difference, 12 mg/dL; CI, 6 to 18.1 mg/dL). Premixed insulin analogues were also associated with an increased incidence of hypoglycemia (OR, 2 [CI, 1.3 to 3]) and weight gain (pooled difference, 2 kg [CI, 1.1 to 3 kg]) compared with long-acting insulins. Premixed insulin analogues were similar to premixed human insulin in decreasing fasting glucose levels, HbA1c levels, and the incidence of hypoglycemia but were more effective in decreasing postprandial glucose levels (mean difference, 21.1 mmol/L; 95% CI, 21.4 to 20.7 mmol/L [219.2 mg/dL; 95% CI, 225.9 to 212.5 mg/dL]). Compared to other non-insulin anti-diabetic agents, premixed insulin analogues were more effective in decreasing fasting glucose levels, postprandial glucose levels and HbA1c levels, but were associated with a higher incidence of hypoglycemia.

SUMMARY

Human insulin products (Humulin and Novolin), produced by recombinant DNA technology, contain the exact same insulin amino acids and have the same action as endogenous insulin. Depending on the

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composition of the product, the onset, peak, and duration of activity can vary, but the effects of these products on HbA1c, FPG, and hypoglycemia are very similar.

Insulin aspart (Novolog), insulin glulisine (Apidra), and insulin lispro (Humalog) are insulin products that have a faster onset of activity and shorter duration of action than human insulin. Insulin aspart and insulin lispro have been shown to decrease HbA1c by an additional 0.1-0.2 percent, decrease the incidence of hypoglycemia episodes by about 20 percent, decrease nocturnal hypoglycemic episodes by 25-50 percent, and decrease FPG levels compared to human insulins. Insulin glulisine studies show an additional decrease in HbA1c of about 0.1 percent, as well. All of these products may be administered with a meal rather than the 30 to 60 minutes prior to a meal for regular human insulin. Insulin aspart vials and cartridges are latex-free, and the solution contains less metacresol than insulin lispro, as does insulin glulisine. All of the rapid-acting insulins are approved for use in pediatric patients as well as for use in external insulin pumps. All are also available in cartridge and pen delivery systems.

The biphasic insulins (Humalog Mix 50/50 and 75/25, Novolog Mix 70/30, and human insulin 70/30) combine both a fast-acting and a long-acting insulin. Their purpose is to decrease the number of injections needed per day for a diabetic patient. Both insulin lispro and insulin aspart combinations have a faster onset of activity and shorter duration of action than biphasic human insulin. Insulin glulisine is not available in such a combination.

Insulin detemir (Levemir) and insulin glargine (Lantus) have changes in the amino acid sequence. They produce a longer duration of action with minimal peak effect and are used as basal insulins. Both may be used in type 1 diabetics as basal insulin, and in combination with oral antidiabetic medications in patients with type 2 diabetes. Each agent consistently controls glycemic levels better than insulin NPH, with less hypoglycemia. Compared to human insulin, these agents decrease episodes of hypoglycemia by 25-50 percent, decrease nocturnal hypoglycemic episodes by 25-33 percent, and generally have lower FPG levels. Effects on HbA1c are comparable with human insulin.

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