Hypoglycemics, Insulins Review

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FDA-Approved Indications

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	
insulin aspart (Novolog®)	--	Novo Nordisk	To improve glycemic control in adults and children with diabetes mellitus
insulin aspart (Novolog® Mix)	70/30	Novo Nordisk	For the treatment of patients with diabetes mellitus for the control of hyperglycemia
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	For once 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 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
insulin lispro (Humalog® Mix)	50/50, 75/25	Lilly	For the treatment of patients with diabetes mellitus for the control of hyperglycemia

Overview

It is estimated that 23.6 million Americans have diabetes.[1] Diabetes causes 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 complications including blindness, renal dysfunction resulting in dialysis or transplantation, and nontraumatic amputations.[2]

There are now multiple agents available for the treatment of diabetes when patients do not meet glycemic goals with oral antidiabetic agents. Insulin products are used as replacement therapy in the management of both type 1 and type 2 diabetes. Exogenous insulin supplements deficient levels of endogenous insulin, and temporarily restores the ability of the body to properly utilize carbohydrates, fats, and proteins.

The 2009 update to the American Diabetes Association (ADA) Consensus Algorithm lists three steps in the treatment of type 2 diabetes. Consistent with prior editions of the algorithm, the first step is the initiation of metformin concurrent with lifestyle interventions at the time of diagnosis.[3,4] If metformin therapy and lifestyle interventions fail to achieve or sustain glycemic goals, step two proposes the addition of either basal insulin or a sulfonylurea, other than glyburide. If step two recommendations are not successful in producing target glycemic goals, step three suggests adding or intensifying insulin therapy. When adding insulin to the regimen of a patient currently treated with a sulfonylurea, the sulfonylurea should be discontinued. For those patients who were started on basal insulin in step two, insulin intensification may include the addition of a rapid- or short-acting insulin. For diabetic patients with advanced stages of chronic kidney disease, the 2007 American Association of Clinical Endocrinologists Diabetes Mellitus Guidelines cite insulin as the therapeutic option of choice.[5]

Pharmacology

Insulin, secreted from the beta cells of the pancreas, 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)[6,7]	Crystalline regular insulin is prepared by precipitation in the presence of zinc chloride at a neutral pH.	0.5-1	2-5	8-12	NPH
Rapid-acting	insulin aspart (Novolog)[8]	Consists of human insulin aspart in a clear aqueous solution. Created when the amino acid proline is substituted with aspartic acid at position B28.	0.17-0.33	1-3	3-5	NPH
	insulin glulisine (Apidra)[9]	Created when the amino acid asparagine at position B3 is replaced by lysine and the lysine at position B29 is replaced by glutamic acid.	More rapid than regular insulin	0.92	0.9-2.6	NPH
	insulin lispro (Humalog)[10]	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	6-8	NPH
Rapid/ Intermediate-acting combination products	insulin aspart (Novolog Mix)[11]	Suspension containing insulin aspart protamine crystals and soluble insulin aspart.	More rapid than regular insulin	1-4	Up to 24 hours	None
	insulin lispro (Humalog Mix)[12,13]	Suspension containing insulin lispro protamine suspension and insulin aspart injection.	More rapid than regular insulin	Earlier than regular insulin	Similar to corresponding Humulin mixes	None

Pharmacokinetics

Comparison of Insulin Products (continued)

Type of Insulin	Drug	Composition of Insulin	Onset (hrs)	Peak (hrs)	Duration (hrs)	Compatibility for Mixing
Intermediate-acting	human insulin NPH (Humulin N, Novolin N)[14,15]	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	24	Regular, aspart, lispro, and glulisine
Long-acting	insulin detemir (Levemir)[16,17]	Created when the amino acid threonine in position B30 is omitted and a C14 fatty acid chain is added to amino acid B29	0.8-2.0	6-8 (maximum effect seen from 3-14 hours after dose)	5.7-23.2	None
	insulin glargine (Lantus)[18]	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)	24 (only studied up to 24 hrs)	None

Contraindications/Warnings[19,20,21,22,23,24,25,26,27,28]

Insulin is contraindicated during episodes of hypoglycemia.

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

Precautions

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.[29,30] Insulin aspart (Novolog) and insulin glulisine contain approximately half the amount of cresol that insulin lispro contains.

Alkaline phosphatase elevations have been reported with human insulin aspart.

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

Drug Interactions[31,32,33,34,35,36,37,38,39,40]

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, alcohol, sulfonamide antibiotics, nonselective beta-blockers, and alpha-adrenergic blockers.

Substances that may increase insulin requirements include oral contraceptives, thiazides, glucocorticoids, growth hormone, and thyroid hormones.

Adverse Effects[41,42,43,44,45,46,47,48,49,50]

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.

Special Populations[51,52,53,54,55,56,57,58,59,60]

Pediatrics

Human insulin (Humulin, Novolin) products have been used in all age groups. Human insulin lispro (Humalog) can be used in children greater than three years of age, and human insulin aspart (Novolog) can be given to pediatric patients over the age of two years. 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) is approved for type 1 diabetes in pediatric patients as well, with pharmacokinetic data in patients as young as six years. 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.[61] 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, p=0.02). The percentage of symptomatic hypoglycemic events was similar between groups; however, fewer patients in the insulin glargine group reported severe hypoglycemia (23 versus 29 percent) and severe nocturnal hypoglycemia (13 versus 18 percent), 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.[62] The multinational, randomized, open-label, parallel-group trial was four months in duration. HbA_1c 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.[63] The mean HbA_1c 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).

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. [64] 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.

Pregnancy

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

In 322 pregnant women with type 1 diabetes, meal-time regular insulin or insulin aspart was administered in an open-label, parallel-group, multicenter study.[65] Patients had $HbA_1c \leq 8$ percent at confirmation of pregnancy, and insulin doses were titrated toward predefined glucose targets and HbA_1c <6.5 percent. Major hypoglycemia occurred at a rate of 1.4 versus 2.1 episodes/year-exposure with insulin aspart and regular insulin, respectively (relative risk 0.72 [95% CI, 0.36-1.46]). The risk of major nocturnal hypoglycemia was 52 percent (RR 0.48 [0.20-1.143]) lower with insulin aspart compared with regular insulin. The HbA_1c for insulin aspart patients was comparable with human insulin in second and third trimesters, and a total of 80 percent of subjects achieved $HbA_1c \leq 6.5$ percent. Maternal safety profiles and pregnancy outcomes were similar between treatments.

Renal impairment

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

Ethnicity

In an open-label, randomized, parallel, multinational, 24-week, non-inferiority study, 443 Asian patients with type 2 diabetes received either insulin glargine (Lantus) daily or NPH insulin at bedtime, in addition to oral glimepiride.[66] HbA_1c levels decreased in the insulin glargine and NPH groups over the study period (-0.99 versus -0.77 percent; p=0.03). The number of

hypoglycemic episodes was significantly lower with insulin glargine compared to NPH insulin ($p<0.004$), including severe ($p<0.03$) and nocturnal ($p<0.001$) cases.

A six-month multicenter, open-label, randomized trial in Japan enrolled 160 patients with type 2 diabetes mellitus.[67] Patients were assigned to one of two groups: those who received twice daily injections of biphasic insulin aspart (Novolog Mix) and those on injections of insulin aspart (Novolog) three times daily with or without multiple daily injections of NPH insulin. At six months, HbA_1c decreased by approximately 2.5 percent in both groups. No incidence of major hypoglycemia was observed in either regimen.

A 24-week, multi-center, open-label, randomized, parallel trial randomized 192 Western Pacific patients to biphasic insulin aspart (Novolog Mix) treatment once daily at dinnertime or continuation of oral antidiabetic therapy.[68] Those not reaching treatment targets on biphasic insulin aspart were switched to twice daily administration at week 14 (n=50). Significantly greater reductions in HbA_1c were seen with once and twice daily biphasic insulin aspart versus oral therapy (1.24 versus 1.34 versus 0.67 percent; $p<0.01$). Hypoglycemic episodes were reported in 54 percent of the patients taking biphasic insulin aspart and 30 percent of the patients taking oral antidiabetic agents.

Other

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

Dosages

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 cartridges (Novolin N, R, 70/30) 3 mL prefilled pen (Humulin N, 70/30) 3 mL prefilled Innolet (Novolin N, R, 70/30)
insulin aspart (Novolog)		5-10 minutes before eating	10 mL vial, 3 mL cartridge, 3 mL prefilled FlexPen
insulin glulisine (Apidra)		Within 15 minutes before a meal or within 20 minutes after starting a meal	10 mL vial, 3 mL cartridge, 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 cartridge, 3 mL prefilled KwikPen, 3 mL prefilled pen
insulin aspart/ protamine aspart (Novolog Mix)	Dosing should be titrated to glycemic control	Dosed within 15 minutes of meal initiation twice daily before breakfast and supper	10 mL vial, 3 mL prefilled FlexPen
insulin lispro/ protamine lispro (Humalog Mix)			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 in the evening or twice daily	10 mL vial, 3 mL prefilled FlexPen
insulin glargine (Lantus)	Usual starting dose is 10 units, and ranges between 2 - 100 units	Once daily at anytime during the day	10 mL vial, 3 mL cartridge, 3 mL prefilled SoloStar pen

Regular insulin, insulin glulisine (Apidra), and insulin aspart (Novolog) can be administered intravenously.

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 intercurrent conditions such as illness, emotional disturbances, or stress.

All of the insulin products are available in cartridge and/or pen delivery systems. The FlexPen delivery system was redesigned and launched in a prefilled pen for insulin detemir (Levemir), insulin aspart, and insulin aspart/protamine aspart (Novolog Mix).[69] 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.

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.[70] 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.[71]

The SoloStar® prefilled pen devices for insulin glargine (Lantus) and insulin glulisine (Apidra) are useful for patients that require larger doses of insulin.[72,73] This pen system is able to dial up to 80 units of insulin in one-unit increments. Patients can dial up to 60 units of insulin in one-unit increments with the HumaPen MEMOIR™ for insulin lispro. The HumaPen MEMOIR is also a reusable insulin pen device that stores up to the last 16 insulin doses (including priming doses). Patients can track the date, time, and amount of these doses. [74]

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.

Clinical Trials

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the 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 patients with type 1 diabetes.[75] Main outcome measures included blood glucose control assessed by HbA_1c, nine-point self-monitored blood glucose profiles, insulin dose, quality of life, hypoglycemia, and adverse events. After 12 weeks of treatment, HbA_1c was significantly lower in the insulin aspart group compared to regular human insulin subjects by 0.17 percent (95% CI, 0.30-0.04, $p<0.05$). Comparison of the blood glucose profiles showed lower blood glucose levels with insulin aspart after breakfast and dinner. 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 ($p=0.005$), and patients found the insulin aspart treatment more flexible ($p=0.022$).

In a six-month, similarly designed trial in 1,070 adults with type 1 diabetes, HbA_1c was significantly lower in the insulin aspart group (0.12 percent reduction in HbA_1c) after six months.[76] The insulin aspart group had lower post-prandial blood glucose levels but had higher preprandial glucose levels before breakfast and dinner. Patients were more satisfied with insulin aspart than with regular insulin. 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, HbA_1c values were significantly lower with insulin aspart than with regular insulin (7.78 versus 7.93 percent; $p=0.005$) at six months.[77] The difference in HbA_1c 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).[78] 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 HbA_1c 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.[79] 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.[80] 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, 0.47-1.09, p=0.12). Mean HbA_1c 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.[81] A total of 204 patients completed the trial according to protocol. The primary endpoint was change in HbA_1c from baseline. HbA_1c decreased 0.91 ± 1.00 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 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.[82] The mean difference between treatment groups in HbA_1c 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 difference was 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.[83] Oral hypoglycemic agents were discontinued. In both groups, HbA_1c 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.[84] 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 HbA_1c < 12 percent who were already taking daily intermediate- or long-acting insulin and a fast-acting human insulin or insulin analogue as bolus insulin.[85] Patients were randomized to insulin detemir or NPH at bedtime in combination with human insulin with main meals. Main outcome measures included HbA_1c, FPG, and hypoglycemia. After six months, FPG was lower with insulin detemir than with NPH (-1.16 mmol/L difference; p=0.001), whereas HbA_1c 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 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 type 2 diabetic patients 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.[86] Morning and evening detemir were associated with reductions in HbA_1c 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 (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).

Type 2 diabetics (n=476) with HbA_1c 7.5-10.0 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.[87] At 24 weeks, HbA_1c 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 $HbA_1c \leq 7.0$, 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).[88] Outcome measures at one year were HbA_1c, the proportion of patients with a HbA_1c of 6.5 percent or less, the rate of hypoglycemia, and weight gain. At one year, HbA_1c 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 $HbA_1c \leq 6.5$ percent were 17.0, 23.9, and 8.1 percent; respective mean numbers of hypoglycemic events per patient per year

were 5.7, 12.0, 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 with type 1 diabetes randomized to insulin detemir or NPH insulin. Insulin aspart was given to both groups at meals.[89] After six months, comparable HbA_1c 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 in self-measured FPG was lower with insulin detemir 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.[90] Insulin aspart was the mealtime insulin. With both insulin detemir groups, before breakfast and at bedtime or at a 12-hour interval, 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). 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. Although HbA_1c for each insulin detemir group was not different from the NPH group at endpoint, HbA_1c for the pooled insulin detemir groups was significantly lower than for the NPH group (mean difference -0.18 percent; p=0.027). Within-person between-day variation in self-measured pre-breakfast plasma glucose was lower for both detemir groups (both p<0.001). 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=0.040, respectively).

A multinational, open-label, parallel-group trial studied 505 patients with type 2 diabetes.[91] Patients were randomized to insulin detemir or NPH, receiving basal insulin either once or twice daily, and insulin aspart at mealtimes. After 26 weeks of treatment, significant reductions in HbA_1c 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 HbA_1c 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.[92] HbA_1c 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.

insulin detemir (Levemir), insulin NPH (Novolin N), insulin aspart (Novolog), and 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.[93] Glycemic control with insulin detemir/insulin aspart was improved in comparison with NPH insulin/regular human insulin (HbA_1c 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 insulin detemir in combination with insulin aspart at meals or insulin NPH in combination with regular human insulin at meals.[94] Basal insulins were administered either once or twice daily. At 22 weeks, HbA_1c 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) with intermittent insulin lispro over 16 weeks.[95] NPH insulin patients maintained their regimen of either once daily or twice daily injections whereas insulin glargine patients received once daily injections at bedtime. 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 HbA_1c 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, 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.[96] A small decrease in HbA_1c 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. 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.

Patients with type 1 diabetes were treated for up to 28 weeks with insulin glargine (n=199) or NPH insulin (n=195) in addition to preprandial regular insulin in a randomized, parallel-group study.[97] 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 HbA_1c 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.[98] Lispro insulin at meal-time was continued in both groups. Mean daily blood glucose was lower with insulin glargine ($p<0.05$). HbA_1c 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 ($HbA_1c > 7.5$ percent) were randomized to either bedtime insulin glargine or NPH and also continued their prestudy medications.[99] Mean FPG at end point was similar with insulin glargine and NPH (117 versus 120 mg/dL), as was HbA_1c (6.96 versus 6.97 percent). A majority of patients (approximately 60 percent) attained HbA_1c 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.[100] The treatment groups showed similar improvements in HbA_1c from baseline to end point on intent-to-treat analysis. The mean change in HbA_1c 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 during the treatment period after the dose-titration phase compared to 35.5 percent for NPH patients (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 type 2 diabetes mellitus patients 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.[101] HbA_1c 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. HbA_1c 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.[102] Previous oral antidiabetic therapy was continued throughout the study. At 52 weeks, there was a trend toward a decrease in HbA_1c 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 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 glargine versus NPH were studied in 125 poorly controlled type 1 diabetes patients.[103] Patients received preprandial insulin lispro and either 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 HbA_1c was 8.3 versus 9.1 percent for the glargine versus NPH groups, but HbA_1c was lower in the 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 glargine (p<0.01). The mean values for end-point FBG were 7.9 versus 9.0 mmol/L in favor of glargine (p<0.05). Significantly fewer moderate or severe nocturnal hypoglycemic episodes were observed in the 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.[104] Type 2 diabetes patients poorly controlled on oral antidiabetic agents (HbA_1c 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 HbA_1c reductions. Confirmed nocturnal hypoglycemia was significantly lower with insulin glargine versus insulin NPH (16.9 versus 30.0 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.[105] Mean HbA_1c decrease from baseline was significantly more pronounced (-1.64 versus -1.31 percent, p=0.0003), and more patients reached HbA_1c 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 had fewer confirmed hypoglycemic episodes than insulin 70/30 patients (4.07 versus 9.87 episodes/patient-year, p<0.0001).

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.[106] After 26 weeks, HbA_1c 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.

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 with 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.[107] At study end, the mean HbA_1c 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 HbA_1c 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 HbA_1c 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.[108] The primary endpoint was the difference in absolute change in HbA_1c between groups after 26 weeks of treatment. HbA_1c 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).

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).[109] The primary efficacy endpoint was the change in HbA_1c from baseline to endpoint (week 44). There was no significant difference between the two treatment groups relative to mean reduction in HbA_1c or in the number of patients who achieved a HbA_1c of 7 percent or less. 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 24.0 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.

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.[110] 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, HbA_1c was lower with insulin glargine (6.78 versus 6.95 percent, p=0.021), but HbA_1c was reduced significantly from baseline for both therapies (p<0.0001). Noninferiority 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 HbA_1c varied depending on the specific target; statistically significant differences did occur in favor of insulin glargine at HbA_1c<7 percent and HbA_1c <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 the open-label, controlled, multicenter, parallel-group, 12-week study.[111] Changes in mean HbA_1c were -0.26, -0.11, and -0.13 percent in the pre-meal glulisine, post-meal glulisine, and regular insulin groups, respectively. The reduction in HbA_1c was greater for the pre-meal glulisine group in comparison with the regular insulin group (p=0.02) and the post-meal glulisine group (p=0.006); no significant difference was found between post-meal glulisine versus regular insulin. Overall, blood glucose profiles were similar in all three treatment groups but were significantly lower for pre-meal 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 glulisine groups; however, weight decreased in the post-meal glulisine group (-0.3 kg; p=0.03).

Type 2 diabetics who had received at least six months of continuous insulin therapy were randomized in a multinational, controlled, open-label, parallel group, 26-week study.[112] Patients (n=890) received NPH insulin twice daily and either insulin glulisine or regular insulin at least twice daily. There were no differences in HbA_1c 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).

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.[113] Of the 683 patients randomized, 672 received treatment. Over the 26-week study, a similar reduction in mean HbA_1c 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 HbA_1c measurements were collected at baseline, 1.5, 3.5, and 5.5 months.[114] 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). HbA_1c 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.[115] The outcomes examined included fasting glucose, postprandial glucose, HbA_1c, 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 HbA_1c of 8.7 percent, and a mean body mass index (BMI) of 29.4 kg/m^2. 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 HbA_1c (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, 12.0 mg/dL; CI, 6.0 to 18.1 mg/dL). Premixed insulin analogues were also associated with an increased incidence of hypoglycemia (OR, 2.0 [CI, 1.3 to 3.0]) and weight gain (pooled difference, 2.0 kg [CI, 1.1 to 3.0 kg]) compared with long-acting insulins. Premixed insulin analogues were similar to premixed human insulin in decreasing fasting glucose levels, HbA_1c 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 HbA_1c 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 composition of the product, the onset, peak, and duration of activity can vary, but the effects of these products on HbA_1c, 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 HbA_1c 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 HbA_1c 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 cresol 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 a basal insulin, and in combination with oral antidiabetic medications in type 2 diabetics. 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 HbA_1c are comparable with human insulin.

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