Evolution of Insulin: From Human to Analog

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ABSTRACT

The development of insulin analogs has made improved treatment of type 2 diabetes possible. In this article, structural alterations, pharmacokinetics and pharmacodynamics, clinical end points, and safety issues are reviewed for the currently available basal insulins, rapid-acting insulins, and premixes. The flatter activity profiles of insulin glargine and insulin detemir translate into good clinical efficacy with a lower risk of hypoglycemia relative to neutral protamine Hagedorn insulin. Weight gain is consistently lower with insulin detemir than with neutral protamine Hagedorn insulin. Insulin degludec, licensed in Europe and Japan but not yet in the United States, has a mean half-life of 25.4 hours, a duration of action of >42 hours, and low variability. In trials in type 2 diabetes, rates of nocturnal hypoglycemia were lower with insulin degludec than with insulin glargine, and more flexible; once-daily dose timing was shown to be possible. Insulin lispro, insulin aspart, and insulin glulisine are rapidly absorbed after injection and thus provide better coverage of the post-prandial glucose surge compared with human insulin. Trials and meta-analyses show that reductions in glycated hemoglobin are similar and control of postprandial glucose is better with the rapid-acting analogs versus human insulin. Convenience is greater for patients because the analogs can be injected just before a meal. In premix or biphasic insulins, a proportion of the rapid-acting analog is protaminated, providing both rapid-acting and intermediate-acting components in one formulation, thus reducing the number of injections required. Alterations to human insulin have resulted in improvements in safety, efficacy, tolerability, and convenience for patients.

KEYWORDS: Analog insulin; Human insulin; Hypoglycemia; Insulin evolution; Type 2 diabetes

The history of insulin therapy has been one of continually evolving improvement. Since insulin was first isolated in 1921, milestones in this evolution have included the development of a slower-acting preparation in the late 1940s, neutral protamine Hagedorn insulin, and the use of recombinant technology to enable production large amounts of insulin in 1977 (Figure 1). This synthetic insulin was named “human insulin” to distinguish it from the earlier preparations derived from animal sources. Further milestones were the introduction of rapid-acting insulin analogs in the 1990s and long-acting basal analogs in the early 2000s.

The ever-increasing prevalence of type 2 diabetes and longer life expectancy of patients with diabetes mean that the use of and demand for insulin therapy will continue to grow. This article reviews recent developments in insulin that have improved the treatment of type 2 diabetes. We will focus first on the basal or long-acting insulin analogs, because these are the most widely prescribed insulins in type 2 diabetes. We will then briefly consider the rapid-acting analogs, used primarily in advanced type 2 diabetes, and premix insulins, which may be used to initiate or optimize insulin therapy.

BASAL INSULINS

Where Are We Currently?

Currently, widely used basal insulins are the intermediate-acting neutral protamine Hagedorn insulin and the basal analogs insulin glargine (Lantus; Sanofi, Paris, France) and...
insulin detemir (Levemir; Novo Nordisk Inc, Plainsboro, NJ). One additional analog, insulin degludec (Tresiba; Novo Nordisk Inc), has been licensed for use in Europe and elsewhere, but approval in the United States will be contingent on the results of a dedicated cardiovascular outcomes trial that is currently in progress.

Use of the basal analogs has enabled patients with type 2 diabetes to achieve equivalent levels of glycemic control, with a lower associated risk of hypoglycemia, compared with neutral protamine Hagedorn insulin.1-4 However, only a proportion of patients achieve levels of glycemic control that meet current guidelines, suggesting there is still room for improvement. Indeed, although the aim is for exogenous basal insulin to match the body’s own physiologic basal insulin output as closely as possible, subcutaneous injection substantially changes the kinetics of insulin exposure. Endogenous insulin is secreted by the pancreas directly into the portal vein, from where it is transported to the liver. On the other hand, subcutaneously administered insulin is absorbed into the systemic circulation, so for sufficient insulin to reach the liver and suppress endogenous glucose output, peripheral tissues are inevitably overexposed. This overexposure has been suggested as one of the possible causes of insulin-associated weight gain, a concern that deters many patients from initiating insulin therapy.5

Furthermore, the pharmacokinetic profile of injected insulin differs from that of endogenous insulin secretion, in which a steady rate of basal output is augmented by rapidly produced peaks in response to meals. Absorption of an insulin injection tends to follow a profile that increases to a peak before “tailing-off.” In the case of basal insulins, this profile is protracted, but it may be only a poor approximation of the smooth flat profile of basal endogenous insulin secretion seen in the healthy state. This discrepancy increases the risk of hypoglycemia when insulin levels are too high relative to food intake or hyperglycemia when levels are low.6 The profile of absorption also can vary between patients and even from injection to injection in the same patient. Therefore, the blood glucose—lowering effect may vary not only across the day but also day to day,7 making it difficult to calculate correct dosing. Finally, with once-daily dosing, subcutaneously injected basal insulin can become depleted in <24 hours, increasing the risk of hyperglycemia during the periods with no or insufficient insulin present.6

Method of Protraction of Basal Insulin Analogs

Different approaches have been taken to modify the kinetics of basal insulins to retard absorption from the injection depot. Protraction initially was achieved through varying the components of the insulin mixture in the pharmaceutical formulation. For example, neutral protamine Hagedorn insulin consists of a complex of insulin and zinc with protamine, a fish protein that reduces its solubility.8 This gave rise to an intermediate-acting insulin with a duration of action of 12 to 18 hours, with glucose-lowering effect peaking at approximately 4 hours.9 A disadvantage of neutral protamine Hagedorn insulin is its need for resuspension before injection, which is a major source of variability in the actual dose given.9

The next step was to modify the structure of the insulin molecule itself, by replacing or removing amino acid residues in the A or B chains, and in some cases adding side chains (Figure 2). Insulin glargine was modified by the
addition of 2 arginine residues to the C-terminus of the B-chain and the substitution of glycine for asparagine at position A21, resulting in a shift in isoelectric point that reduces its solubility at the physiologic pH of subcutaneous tissue. When injected as an acidic solution into neutral tissue, insulin glargine forms precipitates that subsequently dissolve slowly.

With insulin detemir, the threonine residue at position B30 was deleted and a myristic fatty acid side chain was added to the lysine residue at position B29. The effect was to protract absorption, initially by increasing hexamer stability and promoting dihexamerization at the depot site, and subsequently by reversible binding of these side chains to albumin—both in the subcutaneous tissue and after absorption into the circulation.

In insulin degludec, the threonine residue at position B30 is deleted and the ε-amino group of LysB29 is acylated with a 16-carbon fatty acid side-chain via a γ-L-glutamic acid linker. In pharmaceutical formulation, insulin degludec is assembled as stable dihexamers in the presence of phenol;
after injection, phenol is rapidly eliminated and the dihexamers link up to form large soluble multihexamer chains. Insulin monomers are gradually released from the ends of these multihexamers as zinc diffuses away from the injection depot site. Pegylated insulin lispro, a basal analog currently in development, is discussed in the article by Sorli in this supplement.

**Pharmacokinetics and Pharmacodynamics of the Basal Insulin Analogs**

Pharmacodynamic data for insulin usually are shown as continuous profiles obtained using clamp studies, which measure the glucose infusion rate needed to maintain a prespecified “clamped” glycemic level after administration of insulin. These studies most often are performed in patients with type 1 diabetes to avoid the confounding effects of endogenous insulin secretion. Although clamp studies have their shortcomings (few extend for >24 hours, and most are single-dose studies because of constraints on the patients, who must fast for the duration of the clamp), they are at present the best method available for measuring insulin activity profiles.

The activity profiles of insulin glargine are flatter than those of neutral protamine Hagedorn insulin in type 1 diabetes and type 2 diabetes. Likewise, insulin detemir exhibits flatter activity profiles than neutral protamine Hagedorn insulin in both type 1 diabetes and type 2 diabetes. Neither analog showed a completely peakless profile; rather, both showed a gentle increase and decrease in activity. Both analogs have shown a mean duration of action of approximately 24 hours in clamp studies using clinically relevant doses. Insulin degludec has been shown to have a smooth, stable pharmacodynamic profile over 24 hours at steady state; a mean half-life of 25.4 hours, twice that of insulin glargine (12.5 hours), and a duration of action of >42 hours.

As mentioned earlier, within-subject variability (defined as inconsistency of the blood glucose—lowering profile from one injection to the next in a single subject) can make it difficult to dose insulin correctly and safely reach glycemic targets. Pharmacodynamic variability is assessed using repeat clamp studies. The area under the glucose infusion rate profiles over specific time periods, for example, 24 hours, and the maximum glucose infusion rate are measured, and a coefficient of variation determined. Insulin detemir showed significantly lower within-subject variability than both neutral protamine Hagedorn insulin and insulin glargine, with coefficient of variation values as follows: glucose infusion rate profiles over 24 hours 27% (insulin detemir), 68% neutral protamine Hagedorn insulin, 48% insulin glargine; maximum glucose infusion rate 23%, 46%, and 36%, respectively (P < .001 for all comparisons). Insulin degludec, in turn, has shown a lower day-to-day within-subject variability in total glucose-lowering effect than insulin glargine in patients with type 1 diabetes.

Renal and hepatic impairment can affect the metabolism of many drugs, including insulin, which is partly metabolized through the kidneys. The prescribing information for both insulin glargine and insulin detemir advises possible reductions in dose in patients with renal or hepatic impairment, because of reduced insulin metabolism. In this author’s opinion, the ability to use a basal insulin analog without needing to be concerned about renal or hepatic impairment would be particularly advantageous in treating patients with diabetes hospitalized for other reasons, who are at major risk of experiencing hypoglycemia.

**Clinical End Points**

Although preclinical evidence is useful, it is the clinical efficacy and safety that ultimately determine whether a new insulin represents a step forward from existing products. In diabetes, the key criteria for judging clinical efficacy are glycemic control and hypoglycemia; other outcomes of interest include weight change and insulin dose. Because glycemic control and hypoglycemia are linked, modern clinical trials are “treat-to-target” trials in which basal insulin is titrated to achieve a similar fasting plasma glucose value. This should result in similar glycated hemoglobin (HbA1c) values at the end of the trial, which means that any differences in the incidence/severity of hypoglycemia can be interpreted without having to try to correct for different levels of glycemic control.

**Clinical Trials in Type 2 Diabetes**

Patients with type 2 diabetes who used insulin glargine or insulin detemir in basal—oral therapy achieved similar glycemic control to those using neutral protamine Hagedorn, with lower rates of hypoglycemia, particularly nocturnal hypoglycemia (Table 1). A comparison of insulin glargine with insulin detemir in basal—oral therapy showed similar efficacy for both analogs.

When used in basal—bolus therapy in type 2 diabetes, insulin detemir was shown to effectively reduce HbA1c without increasing hypoglycemia, relative to neutral protamine Hagedorn insulin. Insulin glargine and insulin detemir have been compared in basal—bolus therapy in type 2 diabetes. Overall, for use in type 2 diabetes (basal—oral or basal—bolus), glycemic control was similar with the 2 analogs, which was not surprising because the trials were treat-to-target in design. Weight gain has been consistently lower with insulin detemir. On the other hand, there is evidence that twice-daily dosing—required by some patients—may be needed more frequently with insulin detemir than with insulin glargine, and that unit doses may be higher with insulin detemir. These are overall impressions based on mean results and supported by a Cochrane review of the literature. In practice, therapy needs to be individualized for each patient according to factors such as their age and comorbidities.
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<td>Hypoglycemia similar</td>
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<td>Hypoglycemia lower: Estimated RR degludec/glargine, 0.82 (P = .0359)</td>
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<td>Nocturnal hypoglycemia similar</td>
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<td>Nocturnal hypoglycemia lower: Estimated RR degludec/glargine, 0.75 (P = .0399)</td>
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Phase 3 treat-to-target studies of insulin degludec for basal—oral therapy in type 2 diabetes showed that glycemic control with insulin degludec was similar to that with insulin glargine, and rates of nocturnal hypoglycemia were lower or similar.29 In a treat-to-target trial of basal—bolus therapy in type 2 diabetes, glycemic control was similar with insulin degludec and insulin glargine, with lower rates of overall confirmed hypoglycemia and nocturnal confirmed hypoglycemia in the insulin degludec group.30 A further study showed that insulin degludec can be dosed once daily in a more flexible manner, at intervals of between 8 and 40 hours, without losing efficacy or increasing hypoglycemia.31

Real-Life Observational Studies
Real-life observational studies have lent support to the expectations of good efficacy and safety raised by the clinical trials of insulin glargine and insulin detemir. For example, an observational study showed that 12,216 patients with type 2 diabetes who received insulin glargine as add-on treatment to oral antidiabetic agents demonstrated improved glycemic control without weight gain and with a low incidence of hypoglycemia at 9 and 12 months.32 In the observational study Predictable Results and Experience in Diabetes through Intensification and Control to Target: An International Variability Evaluation (PREDICTIVE), 14-week follow-up of patients who switched to insulin detemir from other insulin regimens showed improved glycemic control, a reduction in major hypoglycemia, and a small decrease in mean body weight in type 2 diabetes (n = 12,981).33

Long-term Safety
In modifying biological molecules such as insulin, it is essential to ensure that their potencies with respect to other endocrinological actions are not altered so as to be potentially harmful. With insulin, the main concern is that molecular alterations could increase the risk of mitogenic activity by increasing residence time on the insulin receptor or increasing the affinity of the ligand for insulin-like growth factor-1 receptors.34,35 Concerns were recently expressed that insulin glargine could increase the incidence of cancer, possibly as a result of an increased affinity ratio for insulin-like growth factor-1 receptors versus insulin receptors, relative to human insulin.34,36,37 However, these concerns were based on epidemiologic analyses with some methodological shortcomings, for example, the confounding effects of cancer incidence being associated with obesity, diabetes, and increasing age. Subsequently, concerns about cancer risk with insulin glargine appear to have been refuted by the publication in 2012 of the Outcome Reduction With Initial Glargine Intervention (ORIGIN) study, one of only a few studies reporting on the long-term safety of a basal insulin analog.38 The study examined the use of insulin glargine to target normal fasting plasma glucose levels in more than 12,000 people with cardiovascular risk factors plus impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes. At 6-year follow-up, insulin glargine had a neutral effect on the incidence of cancer.38 Although increased affinity for the insulin-like growth factor-1 receptor is an unwanted characteristic in an insulin analog, it would not necessarily result in mitogenic effects. The increased affinity of the analog is still likely to be orders of magnitude lower than its affinity for the insulin receptor or the affinity of insulin-like growth factor-1 for its own receptor, and the analog would need to reach cells expressing the receptor in high enough concentrations to elicit a mitogenic response.36 In addition, insulin glargine is quickly transformed to its M1 metabolite, which has shown a lower affinity for insulin-like growth factor-1 than insulin glargine or, indeed, human insulin, after subcutaneous injection in male subjects with type 1 diabetes.39

In vitro molecular characterization studies showed that insulin detemir has an insulin-like growth factor-1 receptor:insulin receptor binding affinity ratio of 1 relative to human insulin and a similar dissociation pattern from insulin receptors to that of human insulin.34 Similarly with insulin degludec, insulin-like growth factor-1 receptor:insulin receptor affinity and mitogenic:metabolic potency ratios are not increased relative to human insulin.40 For a discussion of the possibility of cardiovascular
effects arising from long-term use of insulins, see the article by Moghissi and King in this supplement.

RAPID-ACTING INSULINS

Where Are We Currently?
A major disadvantage of exogenous human insulin is that it cannot match the rapid surge observed with physiologic insulin secretion after meals, which suppresses increases in postprandial glucose. Human insulin has a slower onset of action (with a peak effect 3 hours after dosing) and longer duration of action (extending >8 hours) compared with this endogenous postprandial surge. The rapid-acting analogs were developed to speed up insulin absorption relative to human soluble insulin, and thereby more effectively minimize postprandial glucose excursions and reduce the risk of hypoglycemia due to exogenous insulin concentrations remaining high for longer than needed. Three rapid-acting analogs are currently available: insulin lispro (Humalog; Eli Lilly and Company, Indianapolis, Ind), insulin aspart (NovoLog; Novo Nordisk Inc), and insulin glulisine (Apidra; Sanofi). In the United States, the use of rapid-acting analogs is widespread and human soluble insulin is now rarely used.

Rapid-acting insulin analogs are generally prescribed in type 2 diabetes only when basal insulin or (less commonly) use of oral agents has failed to achieve glycemic control. The analogs can then be used as 1, 2, or 3 times per day additions to basal therapy or to provide so-called complementary insulin therapy or supplementary insulin therapy, in which oral antidiabetic therapy is supplemented with prandial insulin only. The latter approach is favored in some countries but has not been widely adopted in the United States. Rapid-acting analogs also are used in continuous subcutaneous insulin infusion. Premix formulations of the rapid-acting analogs, used to initiate insulin therapy in type 2 diabetes, are described separately.

Structure of the Rapid-Acting Insulin Analogs
In all 3 rapid-acting analogs, small changes have been made in the amino acid sequence of the insulin B chain (Figure 3). These amino acid substitutions destabilize the
natural tendency for insulin monomers to self-associate as dimers and hexamers. As a result, the analogs are absorbed into the circulation more rapidly after subcutaneous injection.44,45

Pharmacokinetics and Pharmacodynamics of the Rapid-Acting Insulin Analogs

Because all 3 rapid-acting analogs are designed to achieve rapid dissociation into monomers in the subcutaneous depot, their pharmacokinetic and pharmacodynamic properties do not differ much from each other. The key feature of all 3 rapid-acting analogs is an earlier insulin peak and a more rapid tailing-off of activity compared with human insulin. The pharmacokinetic and pharmacodynamic of the rapid-acting analogs have been described in a recent systematic review,44 and only a few examples will be cited.

Three studies of insulin aspart in healthy volunteers showed that after subcutaneous injection, the median time to maximum concentration was 40 to 50 minutes, versus 105 to 150 minutes for human insulin (P < .05 in all 3 studies).46-48 Studies in nondiabetic subjects have shown similar patterns of release for insulin aspart, insulin lispro, and insulin glulisine. Two studies that compared insulin lispro directly with insulin aspart or insulin glulisine showed similar pharmacokinetic and pharmacodynamic profiles for all 3 analogs.49,50

Likewise, in studies in patients with type 1 diabetes, all 3 analogs were released more rapidly and reached a higher maximum insulin concentration compared with human insulin.51-53 Figure 4 shows the pharmacokinetic profiles of insulin aspart and insulin glulisine, which, after injection, reach their maximum plasma concentrations at approximately 40 and 55 minutes, respectively. Insulin lispro exhibits a similar profile to both these analogs, reaching its peak plasma concentration approximately 68 minutes after injection. The results obtained in these studies in patients with type 1 diabetes could not be directly compared because of interstudy variability in the comparator (human insulin) and various other parameters. However, within each study, when compared with human insulin administered at the same time (ie, immediately before a meal), maximum glucose concentrations were significantly lower for each of the insulin analogs, insulin lispro (9.9 ± 1.4 mmol/L vs 11.9 ± 2.8 mmol/L [mean ± standard deviation {SD}], P < .05), insulin aspart (13.5 ± 3.5 mmol/L vs 16.4 ± 3.4 mmol/L [mean ± SD], P < .0001), and insulin glulisine (10.0 mmol/L vs 11.6 mmol/L, 95% confidence interval [CI]).51-53 Similar results were seen for glucose excursion measured by area under the curve, with significantly lower values for all 3 analogs when compared with human insulin: insulin lispro: 29.3 ± 5.7 mmol/L·h vs 37.7 ± 11.3 mmol/L·h (mean ± SD) (P < .01); insulin aspart: 14.9 ± 8.7 mmol/L·h vs 21.9 ± 8.5 mmol/L·h (mean ± SD) (P < .0001), and insulin glulisine: 15.5 mmol/L·h vs 18.6 mmol/L·h (95% CI).51-53 In the studies with insulin aspart and insulin glulisine, human insulin also was administered at an additional time point, 30 minutes before a meal, and this resulted in a smaller difference between analog and human insulin.51,52

A study in type 2 diabetes compared insulin aspart injected just before a meal with human insulin injected just before or 30 minutes before a meal.54 The insulin profile of insulin aspart was similar to that observed in the studies in healthy volunteers and patients with type 2 diabetes. The postprandial glucose excursion was smaller in the insulin aspart group (899 ± 609 mmol/L·min) compared with the group that received human insulin injected just before a meal (1102 ± 497 mmol/L·min, P < .01), but did not differ for insulin aspart compared with human insulin injected 30 minutes before a meal (868 ± 374 mmol/L·min).

Dosing at least 30 minutes before a meal is a requirement for human insulin to achieve adequate control of postprandial glucose levels, but many patients are unable to follow this requirement. The fact that all the rapid-acting

![Figure 4](image-url)
Analogs can be administered closer to the start of a meal to translate into greater convenience for patients.

When insulin lispro and insulin glulisine were compared in obese patients with type 2 diabetes, both were rapidly absorbed. Insulin glulisine showed a faster increase in insulin concentration than insulin lispro, but the 2 analogs produced similar plasma glucose profiles. However, the prescribing information for all 3 rapid-acting analogs recommends that, as with all insulin medicinal products, glucose monitoring should be intensified and the bolus insulin dose adjusted on an individual basis in patients with renal or hepatic impairment.56-58

Clinical End Points
Insulin lispro, insulin aspart, and insulin glulisine have been compared with human insulin in trials of basal–bolus therapy in type 2 diabetes. All 3 analogs showed similar or superior decreases in \( \text{HbA}_1c \) and superior postprandial glucose control versus human insulin (Table 2). Between-group rates of hypoglycemia were similar, with a trend toward reduced nocturnal hypoglycemia in the study with insulin lispro.61

Several meta-analyses of the results from clinical trials of the rapid-acting analogs are available, some of which included premix formulations (Table 3). The studies included were heterogeneous and inconsistent in methods of reporting postprandial glucose or in the definition of hypoglycemia. Overall, the rapid-acting analogs did not differ significantly from human insulin in decreasing \( \text{HbA}_1c \), but postprandial glucose (when analyzed) was significantly lower with the analogs, in particular for post-breakfast and post-dinner values (likely reflecting the fact that premixes are frequently administered in the morning and evening).

The meta-analyses did not find any significant difference in hypoglycemic risk between the analogs and human insulin. A more recent meta-analysis of patient-level data from trials comparing insulin aspart with human insulin in type 1 diabetes and type 2 diabetes concluded that nocturnal hypoglycemia was significantly lower with insulin aspart (unfortunately, the results are not reported by diabetes type).63

In line with the patient-centered approach recommended by the American Diabetes Association/European Association for the Study of Diabetes, the rapid-acting analogs are a useful choice for patients with type 2 diabetes whose \( \text{HbA}_1c \) remains high despite fasting plasma glucose being at target after 3 to 5 months of basal insulin titration. In these patients, more effective control of postprandial glucose is needed.

Long-term Safety
All 3 rapid-acting analogs have a binding affinity for, and residence time on, the insulin receptor that is similar to or lower than that of human insulin.67,68 In different experiments, insulin aspart was shown to have 81% of the affinity of human insulin for the insulin-like growth factor-1 receptor, insulin glulisine 20% to 25%, and insulin lispro 156%. These results suggest that increased mitogenicity should not be a concern, and experiments in cell lines showed that the mitogenic potency of each analog was lower than that of human insulin.67,68 These findings apply to premixes derived from insulin lispro or insulin aspart.

PREMIX INSULINS
Where Are We Currently?
Premix or biphasic insulins were designed to maximize patient convenience and reduce the number of daily injections required by providing both rapid-acting and intermediate-acting components in one formulation. Until

### Table 2 Key Clinical Trials of Insulin Lispro, Insulin Aspart, and Insulin Glulisine in Basal–Bolus Therapy in Type 2 Diabetes

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<th>Treatments Compared</th>
<th>Key Trial</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lispro + basal insulin vs human insulin + basal insulin</td>
<td>Ross et al 2001</td>
<td>HbA1c similar</td>
</tr>
<tr>
<td>Aspart ± NPH vs human insulin ± NPH</td>
<td>Bretzel et al 2004</td>
<td>Hypoglycemia similar</td>
</tr>
<tr>
<td>Glulisine + NPH vs human insulin + NPH</td>
<td>Dailey et al 2004</td>
<td>Mean postprandial glucose lower by 0.44 to &gt;1.67 mmol/L with aspart vs human insulin (no significance testing reported)</td>
</tr>
</tbody>
</table>

*Estimated refers to values estimated from reported final values or from figures.
*HbA1c = glycated hemoglobin; NPH = neutral protamine Hagedorn.
*A third arm, human premix insulin (70% NPH/30% regular), is not reported.
recently, the theoretically ideal combination of a mixture of a rapid-acting and a basal analog has not been possible in practice because the basal analog formulations cannot be mixed with other insulins. Instead, in the premixes, a proportion of the rapid-acting analog is protaminated so that it becomes an intermediate-acting analog.

Biphasic human insulin (BHI) contains 30% regular human insulin in solution and 70% protaminized regular human insulin. Currently, the most widely used analog premixes are biphasic insulin aspart 30 (BIAsp 30) (NovoLog Mix 70/30; Novo Nordisk Inc) and biphasic insulin lispro (Mix 25) (Humalog Mix 75/25; Eli Lilly and Company). These consist of 70%/75% intermediate-acting protaminized analog suspension and 30%/25% rapid-acting analog solution, respectively. A mixture of insulin lispro with 50/50 proportions of protaminated and rapid-acting components is available but is used less frequently.

The challenges of combining a basal and a rapid-acting insulin in a single formulation recently have been overcome in the form of insulin degludec/insulin aspart (Ryzodeg; Novo Nordisk), a soluble co-formulation of insulin degludec (70%) and insulin aspart (30%). Insulin degludec/insulin aspart has been licensed in Europe and elsewhere but is not yet widely available, and licensing in the United States will await the results of the cardiovascular outcomes trial of insulin degludec.

Premix insulins are typically prescribed as an initiation regimen for patients with type 2 diabetes who do not achieve glycemic control using oral antidiabetic medications or as an optimization regimen for those whose HbA1c values remain too high despite use of a basal analog.

**Pharmacokinetics and Pharmacodynamics of the Premixes**

A recent review of 10 years of experience with biphasic insulin aspart (BIAsp) included a discussion of the pharmacokinetic and pharmacodynamic profiles. The pharmacokinetic profile of BIAsp 30 is closer to that of normal physiologic insulin secretion than the pharmacokinetic profile of BHI, with faster absorption and a higher peak concentration. In healthy subjects, the glucose-lowering effect of BIAsp was earlier and more pronounced than that of BHI, whereas the duration of action of the basal component was similar for the 2 preparations. A 3-way study that compared the pharmacokinetic and pharmacodynamic of BIAsp, Mix 25, and BHI showed that measures of insulin pharmacokinetic and glucose concentrations were

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**Table 3** Selected Meta-analyses of the Efficacy and Safety of the Rapid-Acting Analogs Compared with Human Insulin in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Reference</th>
<th>Included Studies in Type 2 Diabetes</th>
<th>Result: Rapid-Acting Analog Compared with Human Insulin</th>
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<tr>
<td>Siebenhofer et al 2006&lt;sup&gt;65&lt;/sup&gt;</td>
<td>Studies published up to September 2005 Lispro (6 trials) Aspart (1 trial) No glulisine studies</td>
<td>HbA1c: no significant difference Hypoglycemia: no significant difference</td>
</tr>
<tr>
<td>Singh et al 2009&lt;sup&gt;66&lt;/sup&gt;</td>
<td>Studies published up to 2007 Included premix formulations Lispro (11 trials) Aspart (4 trials) No glulisine studies</td>
<td>HbA1c: no significant difference Risk of hypoglycemia: no significant difference</td>
</tr>
<tr>
<td>Mannucci et al 2009&lt;sup&gt;62&lt;/sup&gt;</td>
<td>Studies published up to January 2008 Lispro (7 trials) Aspart (4 trials) Glulisine (2 trials) Included premix formulations</td>
<td>HbA1c: −0.10% in favor of analogs (95% CI, −0.01 to −0.19) In 3 studies, blood glucose was significantly lower with analogs after breakfast (by 0.7 mmol/L) and dinner (by 0.6 mmol/L) (both P &lt; .001) Severe hypoglycemia: no significant difference HbA1c: no significant difference PPG: daily mean PPG lower by 1.18 mmol/L (95% CI, −1.88 to −0.47) with aspart Risk of hypoglycemia: no significant difference</td>
</tr>
<tr>
<td>Rys et al 2011&lt;sup&gt;64&lt;/sup&gt;</td>
<td>Studies published up to July 2009 Included premix formulations Only studies on aspart (6 trials) or BIAsp (4 trials)</td>
<td>HbA1c: −0.10% in favor of aspart (95% CI, −0.15 to −0.04), P &lt; .001 PPG: significantly lower by 0.47 mmol/L (95% CI, −0.70 to −0.25) (P &lt; .001) with aspart Hypoglycemia: no significant difference Nocturnal hypoglycemia: significantly lower with aspart: RR, 0.76 (95% CI, 0.67-0.85) (P &lt; .001) These results are for types 1 and 2 diabetes combined</td>
</tr>
<tr>
<td>Heller et al 2013&lt;sup&gt;63&lt;/sup&gt;</td>
<td>Patient-level data from trials comparing aspart with human insulin. Trials in type 1 diabetes (6 trials, n = 1909), type 2 diabetes (3 trials, n = 219), and types 1 and 2 diabetes combined (1 trial, n = 110)</td>
<td>HbA1c: −0.10% in favor of analogs (95% CI, −0.01 to −0.02) PPG: significantly lower by 0.19 mmol/L (95% CI, −0.40 to −0.01) with aspart</td>
</tr>
</tbody>
</table>

BIAsp = biphasic insulin aspart; CI = confidence interval; HbA1c = glycated hemoglobin; PPG = postprandial glucose.

*Including studies of aspart and BIAsp.
significantly closer to the physiologic ideal with BIASp versus human insulin (Figure 5).72 The measures did not differ significantly between BIASp and Mix 25.

Specific studies of the effects of renal or hepatic impairment on the pharmacokinetic and pharmacodynamic of the premix insulins have not been conducted. As with other insulins, doses of the premix insulins may need to be reduced in such patients.56,73

Clinical End Points

Studies that have compared BIASp with BHI in type 2 diabetes are listed in the recent review.69 In general, HbA1c control was similar and postprandial glucose control was better with BIASp, as would be expected on the basis of the pharmacokinetic profile. This finding also was reported in meta-analyses of trials of rapid-acting analogs72 and trials of BIASp versus BHI.75 Rates of overall hypoglycemia did not differ between treatments in the individual studies or in the meta-analysis by Davidson et al.75 However, the meta-analysis showed that nocturnal hypoglycemia was significantly lower with BIASp versus BHI (rate ratio, 1.24; 95% CI, 1.08-1.43; P < .01).75 Qayyum et al74 did not find any difference in hypoglycemia between BIASp or Mix 25 compared with BHI. A study comparing BIASp 30 and Mix 25 in patients with type 2 diabetes concluded that efficacy and safety are similar for the 2 premixes.76

Numerous studies have compared the premix insulins with basal insulins as initiation regimens in patients with type 2 diabetes. Because the current article is focused on the evolution of insulins, from human to analog preparations, these studies are outside its scope, and we refer the reader to a recent review by Vaag and Lund.77 These authors concluded that there is a lack of consensus on whether insulin therapy should be initiated with a basal or a premix insulin and emphasized the importance of considering real-life factors, such as patient lifestyle and compliance with complex treatment regimens, when prescribing insulin for initiation.

Dosing Convenience

BHI, like human insulin, needs to be given 30 minutes before a meal, a requirement that is impractical for many patients. The premixes, like the rapid-acting analogs, offer greater convenience because they can be administered closer to the start of a meal. Premixes also offer patients the convenience of easy intensification. If control is not achieved with 1 injection daily, second and third injections can be added.

A disadvantage of the premixes is the fact that doses of the rapid- and intermediate-acting components cannot be adjusted individually. For most patients, this constraint is outweighed by the convenience of fewer daily injections, but some patients may prefer to change to basal—bolus therapy as their type 2 diabetes progresses and insulin therapy changes from being used essentially as just a supplement to a full replacement regimen.

CONCLUSIONS

The need for effective insulin therapies is ever increasing as the incidence of type 2 diabetes continues to increase. Two primary concerns of patients are whether an insulin preparation controls their blood glucose adequately without causing hypoglycemia and whether the regimen is simple, convenient, and forgiving if there is a delay in administering it. In terms of the basal analogs, great progress has been made in meeting these requirements. Insulin glargine and insulin detemir offer equivalent glycemic control, with less risk of hypoglycemia, compared with neutral protamine Hagedorn. Insulin degludec, in turn, offers the prospect of once-daily dosing for all patients, greater flexibility of dosing, and even further reductions in the risk of nocturnal hypoglycemia. For the rapid-acting analogs, research efforts are focused on developing molecules that are absorbed into the bloodstream even more quickly after subcutaneous injection. Other approaches to the future of insulin therapy are covered in this supplement.13
increasing recognition of the importance of patient-reported outcomes, more recent trials of insulin therapy are including measures of patient quality of life. The expectation is that features such as a reduced risk of hypoglycemia and increased convenience will be reflected in improved quality of life scores. The story of insulin is one of a molecule that continues to evolve.

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References


