

Review of biphasic insulin aspart in the treatment of type 1 and 2 diabetes

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Background: Insulin is an effective treatment for achieving glycemic control and preventing complications in patients with diabetes. In order to make insulin therapy more acceptable to patients, newer formulations of insulin have been developed, such as biphasic insulins. Biphasic insulins conveniently provide both prandial and basal insulin in a single injection. One of the most well-studied biphasic insulins is biphasic insulin aspart 70/30.

Objective: Our goal was to review the current literature on the safety and efficacy of biphasic insulin aspart in type 1 and type 2 diabetes.

Methods: A MEDLINE search was conducted using the terms “biphasic insulin aspart” to identify clinical studies and reviews.

Results: Biphasic insulin aspart more effectively reduces post-prandial glucose compared to other biphasic insulins and basal insulins. Compared to biphasic insulin aspart, fasting glucose levels are lower with NPH, similar with glargine, and similar or lower with biphasic human insulin. Treat-to-target trials have shown that a goal HbA1c below 6.5 or 7% can be achieved with biphasic insulin aspart. The risk of hypoglycemia is similar to or less than that seen with other biphasic insulins or NPH insulin.

Conclusion: Biphasic insulin aspart 70/30 is a safe and effective treatment option for patients with diabetes.

Keywords: biphasic insulin aspart, insulin, diabetes

Introduction

Diabetes currently affects more than 20 million people in the United States and 246 million people worldwide (CDC 2005; International Diabetes Federation 2007). Unfortunately, the prevalence of this global healthcare epidemic is on the rise and it is projected to affect 366 million people in the world by 2030 (Wild 2004). Diabetes is a chronic disease that is associated with significant morbidity and mortality, both of which contribute substantially to the healthcare costs of society (Johnson et al 2006; Nolan et al 2006). As a result, extensive research has been undertaken to identify effective interventions for reducing microvascular and macrovascular complications in patients with diabetes. Two landmark studies, the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes and the UK Prospective Diabetes Study (UKPDS) in type 2 diabetes, demonstrated that intensive glycemic control reduces the risk of microvascular complications (UKPDS Group 1998; DCCT Group 2000). More recently, the Epidemiology of Diabetes Interventions and Complications (EDIC) trial, a follow-up to the DCCT, showed that intensive glycemic control also reduces the risk of macrovascular complications in type 1 diabetes (Nathan et al 2005). As a result of these and other studies, the American Diabetes Association (ADA) currently recommends maintaining glycosylated hemoglobin (HbA1c) <7.0% to prevent microvascular and macrovascular complications (ADA 2007). The International Diabetes Federation (IDF) and the American College of Endocrinology (ACE) guidelines are even more

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stringent and recommend a goal HbA1c $\leq 6.5\%$ (IDF Clinical Guidelines Task Force 2006; Lebovitz et al 2006).

In all patients with type 1 diabetes and in many with type 2 diabetes, insulin therapy is necessary for achieving these glycemic goals. Individuals with type 1 diabetes have an absolute deficiency in insulin due to complete islet cell destruction (Daneman 2006). As a result, patients with type 1 diabetes must take exogenous insulin to sustain life, prevent diabetic ketoacidosis, achieve glycemic control, and prevent serious long-term complications. In contrast, several different treatment options are available for achieving glycemic control in type 2 diabetes. These options include insulin, oral anti-hyperglycemic agents, and newer injectables such as exenatide and pramlintide (Sicat and Morgan 2007). Despite the presence of these multiple treatment modalities, insulin remains an important therapy for patients with type 2 diabetes. This is because the natural history of type 2 diabetes is characterized by progressive loss of beta cell function (Stumvoll et al 2005). As a result, exogenous insulin therapy often becomes necessary to achieve adequate glycemic control, even in type 2 diabetes (Tibaldi and Rakel 2007). Insulin therapy, when delivered appropriately, is almost always effective in achieving glycemic control in type 2 diabetes, even after other agents have failed (Mudaliar and Edelman 2001). Thus, insulin therapy is important in the treatment of both type 1 and type 2 diabetes.

Unfortunately, insulin therapy is currently being underutilized in the most common type of diabetes, type 2 diabetes. More than half of patients with type 2 diabetes do not meet the current standards of glycemic control and many of these patients are not on insulin therapy (Koro et al 2004). To improve glycemic control in type 2 diabetes and prevent long-term complications, there has been increasing inertia in recent years to facilitate earlier initiation of insulin therapy in patients with uncontrolled type 2 diabetes (Blonde 2005). In an attempt to make insulin therapy more acceptable and practical for patients and their physicians, simpler, more convenient insulin formulations have been developed, such as biphasic (pre-mixed) insulin.

Currently available biphasic insulins include biphasic human insulins and the newer biphasic insulin analogs. Biphasic human insulins, such as biphasic human insulin 70/30, have been in use for many years. Biphasic human insulins are mixtures of human neutral protamine Hagedorn (NPH) insulin and soluble human (Regular) insulin. The mealtime component of biphasic human insulins, soluble human insulin, has a delayed onset of action and prolonged duration. When soluble human insulin is administered subcutaneously, alone or as a biphasic insulin in combination

with NPH, it peaks in about 2–3 hours and remains in the circulation for up to 6 hours (Home et al 1999). Because of this delayed onset of action, biphasic human insulin can result in early post-prandial hyperglycemia followed by subsequent hypoglycemia. To minimize this risk, biphasic human insulin should be administered 30 minutes before a meal. As this is not very practical, biphasic human insulin is often inappropriately taken during or even after a meal.

In contrast, biphasic insulin analogs, such as biphasic insulin aspart 70/30 and biphasic insulin lispro 75/25, have more desirable pharmacological properties as they exhibit a more rapid onset of action and a shorter duration of action. Consequently, biphasic insulin analogs reduce post-prandial glucose (PPG) more effectively and are more physiologic than biphasic human insulins. Biphasic insulin analogs are also more convenient as they can be injected anytime within 15 minutes before to immediately after a meal. The use of biphasic insulin analogs, particularly biphasic insulin aspart, both as monotherapy and as an adjunct to other therapies, has been the subject of interest in a number of recent trials and reviews (Halimi et al 2005; Rolla and Rakel 2005; Garber 2006). This review will focus on the use of biphasic insulin aspart in the treatment of both type 1 and type 2 diabetes.

Methods

A MEDLINE search was conducted using the terms “biphasic insulin aspart” to identify clinical studies and reviews of biphasic insulin aspart in humans published through March of 2007. Twenty-five original articles and 4 review articles that reported on the efficacy or safety of biphasic insulin aspart in patients with type 1 or type 2 diabetes were reviewed. Additional relevant articles were obtained from the reference lists of these articles.

Biphasic insulin aspart

Biphasic insulin aspart 70/30 (NovoLog[®] Mix 70/30, Novo Nordisk, Bagsvaerd, Denmark) is the most well studied biphasic insulin analog, even more extensively studied than biphasic insulin lispro 75/25 (Humalog[®] Mix 75/25, Eli Lilly and Company, Indianapolis, Indiana). Biphasic insulin aspart 70/30, is an admixture consisting of 70% intermediate-acting protamine-crystallized insulin aspart (not NPH) and 30% rapid-acting non-protaminated (soluble) insulin aspart. Biphasic insulin aspart 70/30 has a single peak, which comes from its soluble component. Compared to biphasic human insulin 70/30 (NPH/Regular), biphasic insulin aspart 70/30 has a more rapid and higher peak for more effective mealtime coverage (Figure 1) (Jacobsen et al 2000; Hermansen,

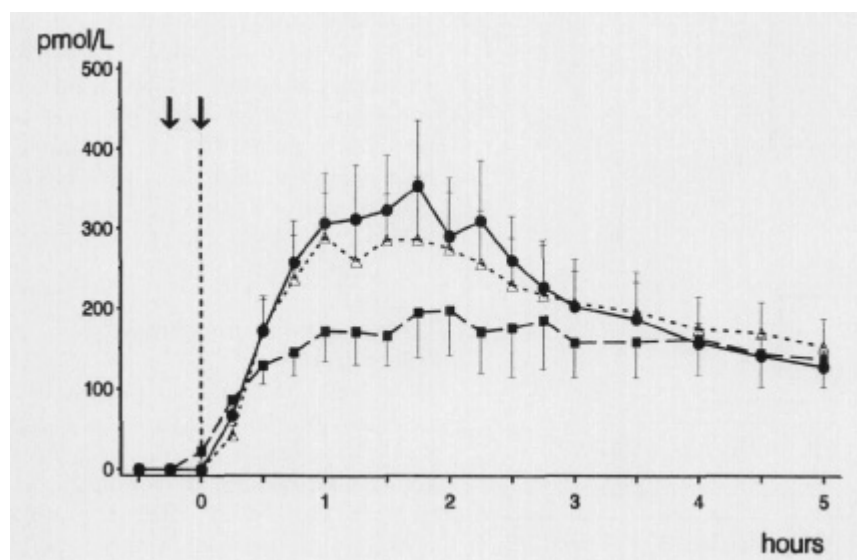


Figure 1 Mean postprandial insulin profiles in patients with type 2 diabetes after injection of biphasic insulin aspart 70/30 (●), biphasic insulin lispro 75/25 (Δ), and biphasic human insulin 70/30 (■). Reprinted with permission from Hermansen K, Colombo M, Storgarrd H, et al. 2002. Improved postprandial glycemic control with biphasic insulin aspart relative to biphasic insulin lispro and biphasic human insulin in patients with type 2 diabetes. *Diabetes Care*, 25:883–8. Copyright © 2002 American Diabetes Association.

Colombo et al 2002; McSorley et al 2002). When injected subcutaneously, protaminated insulin aspart crystals exhibit a delayed absorption pattern such that the duration of action of the intermediate component of biphasic insulin aspart is similar to human NPH insulin. The incorporation of protaminated insulin aspart in biphasic insulin aspart 70/30 conveniently eliminates the need for a separate basal insulin injection. When intermediate acting protamine-crystallized insulin aspart and rapid-acting non-protaminated insulin aspart are combined to form biphasic insulin aspart 70/30, the peak action of the biphasic insulin aspart occurs between one and four hours after injection with a total duration of action measured as long as 24 hours (NovoLog Mix® 70/30 product label).

An additional advantage of biphasic insulin aspart therapy is that its physiologic time-action profile makes it particularly effective in reducing postprandial hyperglycemia, which is being increasingly recognized as an important target in glycemic management (Boehm et al 2004; Halimi et al 2005; ADA 2007). In patients with HbA1c <7.3%, a significant proportion of overall glycemic control may be explained by elevations in PPG (Landgraf 2004). PPG remains elevated in many patients, even after fasting plasma glucoses have been lowered close to goal (Monnier et al 2003). Excursions in PPG have particular importance because they correlate more closely with progression of cardiovascular disease than either fasting glucose levels or HbA1c (Temelkova-Kurktschiev et al 2000; DECODE Study Group 2003). In addition, treat-to-target studies have shown that more focused attention to

PPG can slow the progression of atherosclerotic disease in diabetes (Leiter et al 2005).

Conventional basal-bolus therapy, consisting of three daily injections of rapid- or short-acting insulin at every meal and one or two additional basal insulin injections, target both PPG and fasting plasma glucose; however they are not always practical as they require multiple daily injections. Biphasic insulin therapy is more convenient than conventional basal-bolus therapy as it delivers basal-bolus insulin in fewer injections. A single injection of biphasic insulin aspart delivers both insulin coverage for a meal (prandial insulin) and more long-lasting insulin coverage (basal insulin), thus targeting PPG, while also maintaining control of fasting plasma glucose.

Another advantage of using biphasic insulin aspart is that it can be conveniently administered with an easy-to-use pen delivery device known as the FlexPen® (Novo Nordisk, Bagsvaerd, Denmark). Pen delivery systems are easier to use than insulin syringes and thus may improve adherence to insulin therapy (Korytkowski et al 2005). Compared to other pen delivery device systems, the FlexPen® is especially easy to use and well-liked by patients. In a recent multicenter, open-label, crossover study, 133 patients with type 2 diabetes and HbA1c $8.5 \pm 1.1\%$ were randomized to twice-daily injections of biphasic insulin aspart 70/30 versus biphasic lispro insulin 75/25 via pen delivery systems. The ease of use and patient preferences for the biphasic insulin aspart pen (Novolog Mix 70/30 Flexpen®) versus the biphasic insulin lispro pen (Humalog Mix 75/25 Humalog Pen®) were assessed. Despite comparable HbA1c

levels and safety profiles, patients preferred the biphasic insulin aspart pen and experienced fewer problems with it than with the biphasic insulin lispro pen. The majority (74.6%) of patients preferred the convenience of the biphasic insulin aspart pen whereas only 14.3% preferred the biphasic insulin lispro pen (Niskanen et al 2004). In another randomized, crossover study involving 23 adult patients with type 1 diabetes, described in detail below, even though pen delivery devices were used to deliver both treatment regimens, 19 (83%) of patients preferred continuing with thrice-daily injections of biphasic insulin aspart with the option of additional bedtime NPH, whereas only 4 patients chose to continue on regular insulin three times a day plus bedtime NPH (Chen, et al 2006).

Biphasic insulin aspart in type 2 diabetes

In patients with type 2 diabetes, several studies have shown that biphasic insulin aspart 70/30 twice daily at breakfast and dinner is more effective in controlling PPG than other insulin regimens. In a systematic review of 21 published clinical trials comparing the efficacy of biphasic insulin aspart 70/30 with other treatment strategies in patients with type 2 diabetes, Halimi et al found that biphasic insulin aspart 70/30 twice daily reduced PPG to a greater extent than biphasic human insulin 70/30 twice daily, NPH twice daily, or insulin glargine once daily. Fasting plasma glucose levels with biphasic insulin aspart were greater than with NPH insulin, but not significantly different from insulin glargine. As many of the reviewed studies were not treat-to-target, reductions in HbA1c with biphasic insulin aspart were similar to that seen with other insulins. Treat-to-target trials have shown that glycemic targets, such as the American Diabetes Association (ADA) recommended goal HbA1c <7%, can be effectively achieved with intensification of biphasic insulin aspart therapy. In fact, many patients with type 2 diabetes may be able to achieve glycemic targets with the simple addition of once daily biphasic insulin aspart 70/30. Finally, this review found that the risk of major hypoglycemia is not increased, and the risk of minor hypoglycemia is similar with biphasic insulin aspart compared to the other insulins (Halimi et al 2005). Other studies in patients with type 2 diabetes have compared biphasic insulin aspart 70/30 to biphasic insulin lispro 75/25, exenatide, and different oral anti-hyperglycemic agents. These studies are reviewed below.

Biphasic insulin aspart compared to biphasic human insulin in type 2 diabetes

In a small randomized, double-blind, crossover study of 13 patients with type 2 diabetes and a mean baseline HbA1c of

7.7%, overall PPG excursions were significantly improved with twice daily biphasic insulin aspart 70/30 compared to twice daily biphasic human insulin 70/30. Both insulins were associated with 7 or fewer minor hypoglycemic events where patients experienced hypoglycemic symptoms but did not need assistance to relieve them. There were no major hypoglycemic events requiring the assistance of another person or injections of glucose or glucagon (McSorley et al 2002). This was not a treat-to-target study as its purpose was to compare the pharmacokinetics and pharmacodynamics of biphasic insulin aspart with biphasic human insulin. In another randomized crossover study of 31 patients with type 2 diabetes with a mean HbA1c of $8.7 \pm 1.3\%$, when biphasic insulin aspart 70/30 was injected at the start of a standardized test meal, post prandial glucose was significantly less compared to biphasic human insulin 70/30 injected 15 minutes before or at the start of the test meal. If however, the biphasic insulin aspart was injected 15 minutes after the start of a meal, the PPG profile was comparable to biphasic human insulin (Kapitza et al 2004).

A larger, 24-week, randomized, multicenter trial of 428 patients with type 2 diabetes confirms that biphasic insulin aspart lowers PPG more effectively than biphasic human insulin. The mean increment in PPG after breakfast was significantly lower with biphasic insulin aspart 70/30 immediately before meals than with biphasic human insulin 70/30 thirty minutes before meals (mean \pm SEM, 73.8 ± 2.9 mg/dL versus 103.3 ± 5 mg/dL; $p < 0.0001$) (Iwamoto 2003). However, there were no statistically significant differences in the HbA1c between the two groups at the end of the 24 weeks ($7.31 \pm 0.04\%$ versus $7.2 \pm 0.06\%$, for biphasic insulin aspart and biphasic human insulin, respectively) and also at the end of 48 weeks ($7.37 \pm 0.04\%$ versus $7.35 \pm 0.07\%$). During the trial the fasting blood glucose decreased slightly in both groups, although by the end of the 24 weeks it was significantly higher in the biphasic insulin aspart group compared to the biphasic human insulin group (160.2 ± 2.3 versus 145.3 ± 3.9 mg/dL, $p = 0.001$), when adjusting for baseline values. Fifty-six percent of those in the biphasic insulin aspart group and 57% of those in the biphasic human insulin group had at least one episode of hypoglycemia. The biphasic insulin aspart group had a 30% lower risk of minor hypoglycemia compared to the biphasic human insulin group, however this was not statistically significant (relative risk 0.69; 95% CI 0.46–1.04). Major episodes of hypoglycemia requiring the assistance of another person were rare. It is important to note that this trial was designed as a noninferiority trial, not as a treat-to-target study. Therefore, it does not fully assess the HbA1c lowering efficacy of biphasic insulin aspart.

Biphasic insulin aspart compared to biphasic insulin lispro in type 2 diabetes

Only one study has compared the effectiveness of biphasic insulin aspart 70/30 and biphasic insulin lispro 75/25 (75% protaminated lispro and 25% soluble lispro), another commercially available biphasic insulin analog. This was an open-label, three period crossover study in which 61 insulin-treated patients with type 2 diabetes and HbA1c $8.3 \pm 1.1\%$ received a single injection of biphasic insulin aspart 70/30, biphasic insulin lispro 75/25, and biphasic human insulin 70/30, before breakfast on each of 3 separate days (Hermansen, Colombo et al 2002). Significantly fewer PPG excursions were observed after biphasic insulin aspart 70/30 compared to after biphasic insulin lispro 75/25 and to after biphasic human insulin 70/30, which suggests that biphasic insulin aspart more effectively reduces PPG compared to other biphasic insulins (Figure 2). The mean baseline fasting serum glucose was comparable between the two groups (151.2–154.8 mg/dL). A total of 53 hypoglycemic episodes were reported during the study days, including 23 episodes with biphasic insulin aspart, 11 episodes with biphasic human insulin, and 19 episodes with biphasic insulin lispro. Most of these episodes were mild, based on symptoms only, not confirmed with blood glucose measurement, and resolved spontaneously. There were a few severe hypoglycemic episodes requiring assistance from another person, including 2 episodes with biphasic insulin aspart, 2 episodes with biphasic human insulin, and 5 episodes with biphasic insulin lispro.

Biphasic insulin aspart as an adjunct to oral anti-hyperglycemic drugs in type 2 diabetes

Due to progressive loss of beta cell function in type 2 diabetes, oral anti-hyperglycemic drugs (OHD) gradually lose their effectiveness over time, and supplementation with exogenous insulin often becomes necessary (Mudaliar and Edelman 2001; Stumvoll et al 2005; Tibaldi and Rakel 2007). Biphasic insulin aspart has been shown to be an effective adjunctive therapy for patients with type 2 diabetes who are failing OHD. Several studies suggest that when HbA1c levels are elevated in type 2 diabetics on OHD therapy, adding biphasic insulin aspart may more effectively improve glycemic control compared to adding another OHD.

A recent multinational, open-label, 16-week trial showed that when patients with type 2 diabetes are failing monotherapy with metformin, adding biphasic insulin aspart

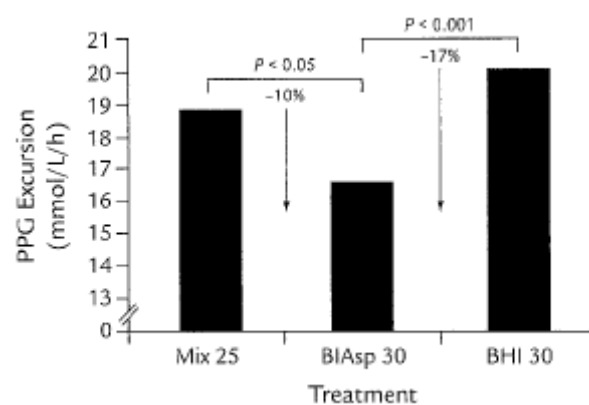


Figure 2 Total post-prandial glucose (PPG) excursions (0–5 hours) with biphasic insulin aspart 70/30 (BIAsp 30) compared to biphasic insulin lispro 75/25 (Mix 25), and biphasic human insulin 70/30 (BHI 30) in an open-label, 3-period, crossover study of 45 patients with type 2 diabetes. Reprinted from Halimi S, Raskin P, Liebl A, et al. 2005. Efficacy of biphasic insulin aspart in patients with type 2 diabetes. *Clin Ther*, 27: S57–74. Copyright © 2005 with permission from Excerpta Medica, Inc.

70/30 more effectively reduces HbA1c, compared to adding glibenclamide (glyburide) (Kvapil et al 2006). In this study, 329 patients with type 2 diabetes who had elevated HbA1c (7.5%–13%) on metformin alone were randomized to receive biphasic insulin aspart 70/30 alone, biphasic insulin aspart 70/30 plus metformin, or glibenclamide plus metformin. Biphasic insulin aspart was initiated at a total daily dose of 0.2–0.3 units/kg of body weight. Half the total daily dose was given immediately before breakfast and the other half was given immediately before the evening meal. Insulin doses were titrated every 1–7 days in increments of 2–4 units per injection to achieve a target blood glucose 90–144 mg/dL. The breakfast dose was adjusted based on the post-breakfast and pre-dinner blood glucose values and the dinner dose was adjusted based on the post-dinner, bedtime, and pre-breakfast blood glucose values. By the end of the trial, HbA1c levels had decreased by more than 1.5% in all three treatment groups. The combination biphasic insulin aspart plus metformin group had significantly greater reductions in HbA1c compared to the biphasic insulin aspart monotherapy group (mean treatment difference $0.39 \pm 0.15\%$, $p = 0.007$). Furthermore, in a subpopulation of 193 patients with HbA1c $\geq 9\%$ at baseline, the HbA1c at the end of the trial was significantly lower in the biphasic insulin aspart plus metformin group compared to the glibenclamide plus metformin group (mean treatment difference, $0.46 \pm 0.21\%$, $p = 0.027$). There was no difference in the mean prandial blood glucose increment (the average increment in blood glucose following breakfast, lunch, and dinner) between groups, however the glucose increment following lunch was significantly lower in the glibenclamide plus metformin group compared to

the biphasic insulin aspart only group (-20.2 ± 5.9 mg/dL, $p < 0.001$) and also compared to the biphasic insulin aspart plus metformin group (-12.6 ± 5.9 mg/dL, $p = 0.036$). The incidence of minor hypoglycemia defined as blood glucose < 50 mg/dL with or without symptoms and not requiring the assistance of another person, was low and similar between treatment groups. In each treatment group, there were approximately 0.04 episodes per patient per week of minor hypoglycemia or hypoglycemia symptoms not confirmed by blood glucose measurement. There were no major hypoglycemic episodes, defined as blood glucose < 50 mg/dL, requiring assistance, and requiring food or IV glucose. Body weight increased in all three groups with a mean weight gain of 1.6 kg in the biphasic insulin aspart only group, 0.8 kg in the biphasic insulin aspart plus metformin group, and 0.1 kg in the glibenclamide plus metformin group. In conclusion, this study showed that in patients with uncontrolled type 2 diabetes on metformin alone, adding biphasic insulin aspart is more effective in reducing HbA1c than adding a sulfonylurea, especially when the HbA1c is $\geq 9\%$. This is to be expected as higher HbA1c levels reflect greater loss of beta cell function and decreased likelihood of responding to the addition of a sulfonylurea. This study also reassures us that biphasic insulin aspart can be added to metformin without inducing major hypoglycemia or increasing the risk of minor hypoglycemia or symptoms of hypoglycemia.

In an open-label, multicenter study, 246 patients with type 2 diabetes who were failing OHD therapy with glibenclamide monotherapy or glibenclamide combination therapy with mean HbA1c 9.5% (range 7.4%–14.7%), were randomized to 18 weeks of biphasic insulin aspart 70/30 twice daily, biphasic insulin aspart 70/30 twice daily plus pioglitazone, or pioglitazone plus glibenclamide (Raz et al 2005). Combination biphasic insulin aspart plus pioglitazone was more efficacious in lowering HbA1c than combination glibenclamide plus pioglitazone (mean [SD] treatment difference, -0.64% [0.23%]; $p = 0.005$) or even biphasic insulin aspart alone (mean (SD) treatment difference -0.60% [0.22%]; $p = 0.008$). The fasting blood glucose was significantly lower in the biphasic insulin aspart plus pioglitazone group than in the glibenclamide plus pioglitazone group (mean \pm SD, 153 ± 45 versus 169 ± 65 mg/dL; $p = 0.012$). The hypoglycemia event rate was low (fewer than 1 episode per patient-week in the biphasic insulin aspart only group) and there were no major hypoglycemic episodes. Edema was reported in $\geq 9\%$ of patients in each treatment group, but there were no episodes of serious edema. Weight gain was more common in the biphasic insulin aspart plus pioglitazone group, where

it affected 8% of patients. The mean weight gain was 4 kg and felt to be consistent with improved glycemic control. However, recent data suggest that patients on insulin may be at increased risk for cardiac complications related to rosiglitazone use. Therefore, thiazolidinediones should be used with caution in combination with insulin.

Biphasic insulin aspart versus NPH or glargine in type 2 diabetes

When insulin therapy is initiated in patients with type 2 diabetes who are failing OHD, a common practice is to add a once-daily bedtime dose of basal insulin, either NPH or the insulin analog glargine (Lantus[®], Sanofi-Aventis Pharmaceuticals, Paris, France) (RiddLe et al 2003). As basal insulins primarily target fasting plasma glucose and do not address postprandial hyperglycemia, several studies have investigated whether biphasic insulin aspart may be a more effective first-line adjunct insulin therapy in insulin-naïve type 2 diabetic patients who are failing OHD therapy.

In 2005, the INITIATE (INITiation of Insulin to reach A1c Target) study group reported that initiating insulin therapy with twice daily biphasic insulin aspart 70/30 was more effective in achieving HbA1c targets compared to initiating insulin therapy with once daily glargine. They conducted a 28 week open-label, randomized treat-to-target trial, including 233 insulin-naïve patients with type 2 diabetes who were poorly controlled with HbA1c $\geq 8\%$ on $> 1,000$ mg/day of metformin alone or in combination with other OHDs. A total of 263 subjects enrolled into the four-week run-in period, during which the metformin dose was optimized to 1500–2550 mg/day and secretagogues and alpha-glucosidase inhibitors were discontinued. Subjects on pioglitazone remained on it and those on rosiglitazone were switched to pioglitazone. At the end of the 4 week run-in period, 30 of the subjects were removed from the study as they had at least one self-measured plasma glucose ≤ 70 mg/dL or had both fasting plasma glucose (FPG) and presupper plasma glucose levels that were ≤ 140 mg/dL. The remaining 233 patients were randomly assigned to either 5 to 6 units of biphasic insulin aspart 70/30 twice daily or 10–12 units of glargine at bedtime. Insulin doses were titrated weekly for the first 12 weeks and then every 2 weeks to achieve target FPG and presupper plasma glucose of 80–110 mg/dL according to a prespecified algorithm (Raskin et al 2005). At the end of the 28 weeks, the mean HbA1c was 6.9% in the biphasic insulin aspart group and 7.4% in the insulin glargine group ($p < 0.01$). In addition, 66% of people in the biphasic insulin aspart group achieved a HbA1c $< 7\%$, compared to only 40% in the insulin glargine group

($p < 0.001$). The mean HbA1c reduction was greater in the biphasic insulin aspart group compared to the glargine group (mean HbA1c reduction, $-2.79 \pm 0.11\%$ vs $-2.36 \pm 0.11\%$; $p < 0.01$) This effect was more pronounced in patients with baseline HbA1c $>8.5\%$ (mean HbA1c reduction, $-3.13 \pm 1.63\%$ vs $-2.6 \pm 1.5\%$; $p < 0.05$). Mean FPG was similar in the two treatment groups at baseline (252 ± 67.4 versus 243 ± 68.8 mg/dL in the biphasic insulin aspart and glargine groups, respectively; $p > 0.05$), and also the end of the study (127 ± 40.6 versus 117 ± 44.3 mg/dL; $p > 0.05$). Fifty-seven percent of subjects in the glargine group achieved target FPG 80–110 mg/dL, compared to only 36% in the biphasic insulin aspart group. Still, the change in FPG from baseline was similar in both groups (125 ± 72.9 versus 125 ± 74.4 mg/dL in the biphasic insulin aspart and glargine groups respectively). Mean prandial plasma glucose increments (postprandial plasma glucose – preprandial plasma glucose) were significantly lower for breakfast and dinner in the biphasic insulin aspart group compared to the glargine group. Minor hypoglycemia, defined as blood glucose <56 mg/dL with or without symptoms, was greater in the biphasic insulin aspart group than in the glargine group (3.4 ± 6.6 versus 0.7 ± 2 episodes per year, $p < 0.05$). Forty-three percent of subjects in the biphasic insulin aspart group reported minor hypoglycemia, compared to only 10% in the glargine group ($p < 0.05$). However, there was only one episode of major hypoglycemia (defined as an episode with neurological symptoms of hypoglycemia that required assistance and had either a plasma glucose <56 mg/dL or reversal of symptoms after food, glucagon, or intravenous glucose). This episode of major hypoglycemia occurred in the glargine group. No subjects discontinued treatment because of hypoglycemia. Biphasic insulin aspart was also associated with more weight gain compared to insulin glargine (5.4 ± 4.8 vs 3.5 ± 4.5 kg, $p < 0.01$). The total daily insulin dose at the end of the study was greater in the biphasic insulin aspart group than in the glargine group (78.5 ± 39.5 versus 51.3 ± 26.7 units/day).

In a subsequent report, baseline cohort characteristics and treatment effects from INITIATE were entered into the validated CORE diabetes model to simulate the range of diabetic complications and disease progression, and predict life expectancy, quality-adjusted life expectancy, cumulative incidence of complications and direct medical costs over patient lifetimes (Valentine et al 2005). This modeling study found that reducing HbA1c levels with biphasic insulin aspart 70/30 was associated with improved life expectancy (0.19 ± 0.20 years) and quality-adjusted life expectancy (0.19 ± 0.14 quality-adjusted life years [QALYs]). Biphasic

insulin aspart 70/30 was also projected to reduce the incidence of retinopathy and nephropathy complications compared to glargine.

More recently, the INITIATE data were entered into the validated Markov/Monte-Carlo simulation model and long-term treatment with biphasic insulin aspart 70/30 was projected to be cost-effective compared to glargine in patients with type 2 diabetes who fail OHD (Ray et al 2007). The incremental cost-effectiveness ratio was \$46,533 per QALY gained with biphasic insulin aspart vs glargine. Biphasic insulin aspart was even more cost effective than glargine in patients with baseline HbA1c $>8.5\%$, where the incremental cost-effectiveness ratio was only \$34 916 per QALY gained with biphasic insulin aspart. The lifetime cost per patient treated successfully to target HbA1c levels of $<7.0\%$ and $\leq 6.5\%$ were US\$80,523 and US\$93,242 lower with biphasic insulin aspart than with glargine, respectively.

A second, large, open-label study confirms that initiating insulin therapy in type 2 diabetes with biphasic insulin aspart may reduce HbA1c and mean PPG increment to a greater extent than initiating insulin glargine. In this study 255 insulin-naïve patients with type 2 diabetes were randomized to twice-daily biphasic insulin aspart 70/30 plus metformin versus once-daily insulin glargine plus glimepride (Kann et al 2006). The rationale for this study design was that basal insulin might be best used in combination with an insulin secretagogue. The mean HbA1c at baseline was $9.2 \pm 1.5\%$ in the biphasic insulin aspart plus metformin group and $8.9 \pm 1.3\%$ in the glargine plus glimepride group ($p = 0.07$). At the end of 26 weeks, the mean change in HbA1c was statistically significantly greater in the biphasic insulin aspart plus metformin group compared to the insulin glargine plus glimepride group (between-group difference: -0.5% (95% CI = -0.8 to -0.2%), $p = 0.0002$). In addition, the mean increment in PPG was significantly lower in the biphasic insulin aspart plus metformin group than in the insulin glargine plus glimepride group (25.2 ± 25.2 versus 39.6 ± 32.4 mg/dL; $p = 0.0002$). Minor hypoglycemia occurred in 20% of subjects in the biphasic insulin aspart plus metformin group and in 9% of subjects in the other group ($p = 0.01$). One major hypoglycemic episode occurred in each group. The mean change in weight was $+1.5$ kg (95% CI = 0.84 to 2.19 kg; $p < 0.0001$) in the glargine plus glimepride group and $+0.7$ kg (95% CI = -0.07 to 1.42 kg; $p = 0.08$) in the biphasic insulin aspart plus metformin group.

Biphasic insulin aspart has also been compared to NPH insulin in insulin-naïve type 2 diabetic patients failing OHD. In an open-label 12-week study, 140 patients with type 2

diabetes who had HbA1c levels $\geq 7.5\%$ on metformin alone or in combination with sulfonylurea were enrolled. All subjects received metformin monotherapy for 4 weeks and then combination therapy with metformin and a once-a-day insulin for 12 weeks, either biphasic insulin aspart 70/30 once daily before dinner, biphasic human insulin 70/30 thirty minutes before dinner, or NPH insulin once daily at bedtime (Kilo et al 2003). The insulin dose was titrated during the first four weeks to achieve a FPG between 90 and 126 mg/dL. After that, no further adjustments were made in the insulin dose. By the end of the 12 weeks, HbA1c had decreased by 1.3%, 1.2%, and 1.1% in the biphasic insulin aspart, NPH, and biphasic human insulin groups, respectively. There were no statistically significant differences in the 8-point blood glucose profiles, FPG, or HbA1c between the three treatment groups. The largest reductions in HbA1c (-2.3% with biphasic insulin aspart, -1.9% with NPH, -1.8% with biphasic human insulin) were seen in those patients who achieved a final FPG < 126 mg/dL. Overall, FPG values decreased by 31% with biphasic insulin aspart, by 37% with NPH insulin, and by 28% with biphasic human insulin. All three treatment regimens were well tolerated. These results suggest that patients with type 2 diabetes can safely and effectively begin insulin therapy using once-daily injections of biphasic insulin aspart 70/30, biphasic human insulin 70/30, or NPH insulin in combination with metformin.

A recent large multinational randomized non-inferiority trial involving 394 patients with type 2 diabetes found that biphasic insulin aspart given three times a day with meals was as efficacious as a basal-bolus insulin regimen consisting of three injections a day of soluble insulin aspart with meals plus a fourth daily injection of NPH at bedtime (Ligthelm et al 2006). Patients randomized to biphasic insulin aspart received biphasic insulin aspart 70/30 three times a day with meals if their BMI was ≤ 30 kg/m². Those who were randomized to biphasic insulin aspart and had a BMI > 30 kg/m² received biphasic insulin aspart 50/50 with breakfast and lunch and 70/30 with dinner. At the end of 16 weeks, the mean HbA1c decreased from $9.1 \pm 0.7\%$ to $7.8 \pm 1\%$ in both groups. Therefore, in patients with type 2 diabetes, biphasic insulin aspart three times a day with meals was not inferior to the more intensive 4-injections-per-day regimen of insulin aspart with meals plus NPH at bedtime. In addition, the incidence of adverse events and hypoglycemia were similar in the two groups.

In one parallel, double-blind trial, 403 patients with uncontrolled type 2 diabetes on OHD and/or NPH insulin were randomized to receive biphasic insulin aspart 70/30

twice a day or NPH twice a day for 16 weeks (Christiansen et al 2003). The mean baseline HbA1c was $8.8 \pm 1.3\%$ in the biphasic insulin aspart group and $8.8 \pm 1.2\%$ in the NPH group. OHDs were discontinued on randomization. The starting dose of insulin was 8 to 16 Units per day in insulin naïve patients at the discretion of the patient's physician. The starting insulin doses in patients who had been on NPH insulin before the study were based on their previous insulin requirements. Both the NPH and the biphasic insulin aspart were administered immediately before breakfast and dinner. The target range for fasting/preprandial blood glucose was 90 to 144 mg/dL. Insulin doses were titrated according to accepted treatment guidelines. HbA1c significantly decreased from baseline in both groups, however there were no differences between groups. The mean reduction in HbA1c was 0.67% in the biphasic insulin aspart group and 0.61% in the NPH group. Reductions in fasting blood glucose were similar in the two groups (25.2 versus 27 mg/dL in the biphasic insulin aspart and NPH groups, respectively), however the final fasting blood glucose values were 17.1 mg/dL higher in the biphasic insulin aspart group ($p < 0.0001$). The mean postprandial glucose increment was significantly lower in the biphasic insulin aspart group compared to the NPH group. Thus, in patients with type 2 diabetes, biphasic insulin aspart twice daily was as effective in reducing HbA1c and more effective in reducing PPG compared to NPH twice daily. There were no differences in rates of hypoglycemia between the two groups with 33% of subjects in each group reporting minor hypoglycemia episodes, defined as hypoglycemic symptoms with or without confirmation with blood glucose measurement that do not require the assistance of another person. There were 341 minor hypoglycemic episodes in 77 patients in the biphasic insulin aspart group and 285 minor hypoglycemic episodes in 68 patients in the NPH group, but the relative risk between treatments was not significant (RR = 1.21 and 95% CI 0.77–1.9; $p = 0.4$). Approximately 11% of patients in each group experienced one or more minor nocturnal hypoglycemic episodes. Fewer than 2% of subjects in each group experienced major hypoglycemia episodes, defined as an episode requiring the assistance of another person or an injection of glucose or glucagon. In both groups, hypoglycemic episodes were noted to be more frequent during the first week of treatment, but then they decreased in frequency with continued treatment.

In a multicenter open-label observational trial, 41 type 2 diabetics with HbA1c levels above target despite treatment with OHD, alone or in combination with once daily basal insulin NPH or glargine, were switched to a forced titration

algorithm using biphasic insulin aspart 70/30 once daily before supper (Jain et al 2004). In this algorithm, the biphasic insulin aspart dose was regularly adjusted to maintain fasting plasma glucose between 80 and 110 mg/dL. After 16 weeks on this treat-to-target algorithm, 39% of the patients (16 out of 41) achieved a HbA1c <7% and 22% of the patients (9 out of 41) achieved a HbA1c \leq 6.5%.

Together these studies support the use of biphasic insulin aspart as a viable and efficacious insulin therapy for patients with type 2 diabetes who are failing OHD. Initiating once-daily injections of biphasic insulin aspart 70/30 at dinner appears to be as effective in lowering HbA1c as initiating once-daily injections of biphasic human insulin 70/30 at dinner or NPH insulin at bedtime. Initiating twice daily injections of biphasic insulin aspart is more effective in achieving HbA1c targets than initiating insulin glargine once daily. Compared to NPH twice daily, biphasic insulin aspart twice daily is as effective in reducing HbA1c and more effective in reducing PPG. Finally, biphasic insulin aspart three times a day with meals is as efficacious in lowering HbA1c levels in patients failing OHD as a basal-bolus insulin regimen consisting of three injections a day of soluble insulin aspart with meals plus a fourth daily injection of NPH at bedtime. Overall, biphasic insulin aspart is more efficacious than insulin glargine and as efficacious as NPH or biphasic human insulin in lowering HbA1c levels in patients failing OHD. Biphasic insulin aspart reduces PPG excursions, and is effective in achieving HbA1c goals. Furthermore, biphasic insulin aspart is convenient, cost effective and well tolerated in patients with type 2 diabetes.

Biphasic insulin aspart compared to exenatide

Patients failing OHD have the option of initiating exenatide, a glucagon like peptide-1 (GLP-1) analog that increases glucose dependent insulin secretion, suppresses glucagon secretion, slows gastric emptying, and decreases food intake. Exenatide reduces HbA1c by only about 1%, but its main advantage is that it promotes weight loss. Thus many patients failing OHD are started on exenatide rather than insulin. In a recently published non-inferiority trial, 501 patients with type 2 diabetes who were failing OHD therapy with metformin and a sulfonylurea (baseline mean HbA1c 8.6% and Fasting serum glucose 198 mg/dL) were randomized to receive either twice-daily injections of exenatide or twice-daily injections of biphasic insulin aspart 70/30 (Nauck et al 2007). The starting dose of insulin for each patient was chosen by the investigator following randomization. Investigators

were instructed to adjust insulin doses to optimize glycemic control, while avoiding significant hypoglycemia. Patients were contacted at regular intervals to discuss their glycemic control, but no forced titration schedule was used in this study. Options available to help guide investigators in intensification of insulin therapy include a titration guideline indicating minimal targets of <126 mg/dL for fasting glucose and <180 mg/dL for 2 hour postprandial glucose. Ultimately, the decision of whether or not to adjust insulin was left up to each investigator's clinical judgment. On entry into the study, prior metformin and sulfonylurea doses were continued. If hypoglycemia occurred, the sulfonylurea dose was reduced by 50% in the exenatide group and the insulin dose was reassessed in the biphasic insulin aspart group. Mean reduction in HbA1c was similar in the two groups (mean \pm SEM change in HbA1c, $-1.04 \pm 0.07\%$ with exenatide, and $-0.89 \pm 0.06\%$ with biphasic insulin aspart) suggesting noninferiority of exenatide compared to biphasic insulin aspart, with respect to change in HbA1c. The mean change in fasting serum glucose from baseline to week 52 was 32.4 ± 3.6 mg/dL in the exenatide group and 30.6 ± 3.6 mg/dL in the biphasic insulin aspart group. The difference between the two groups in mean change in HbA1c (exenatide-insulin) was -1.8 mg/dL (95% CI -10.8 to 7.2 mg/dL; $p = 0.69$). Greater reductions in PPG were reported with exenatide (morning meal $p < 0.001$, mid-day meal $p = 0.002$, and evening meal $p < 0.001$). However, these results should be interpreted with some skepticism as 80% of patients in the exenatide group were maximized on exenatide (10 μ g a day), whereas there was no algorithm for titrating the insulin aspart. The mean total daily dose of biphasic insulin aspart at 52 weeks was only 24 units, suggesting that the biphasic insulin aspart group may have been under treated. Furthermore, the mean HbA1c at baseline was only 8.6% in this study. It is unlikely that exenatide would be as effective as insulin in achieving glycemic goals in patients with a higher HbA1c as reduction in HbA1c with exenatide is only about 1%.

A steady decline in the mean body weight was noted in the exenatide group throughout the study, while the biphasic insulin group gained weight. By the end of the 52 weeks the difference in mean change in body weight between groups was -5.5 ± 0.2 kg (95% CI -5.9 to -5 kg; $p < 0.001$). There were statistically significant reductions in the mean systolic blood pressure (-5 ± 15 mmHg, $p < 0.001$) and the mean diastolic blood pressure (-2 ± 10 mmHg, $p = 0.03$) in the exenatide group. There were no significant changes in blood pressure in the biphasic insulin group. Exenatide was associated with a higher incidence of gastrointestinal adverse events

than biphasic insulin aspart. Hypoglycemia rates were similar in the two treatment groups (4.7 ± 0.7 events per patient-year in the exenatide group versus 5.6 ± 0.7 events per patient-year in the biphasic insulin group). There were no episodes of severe hypoglycemia.

Biphasic insulin aspart in type 1 diabetes

The evidence regarding biphasic insulin aspart therapy is sparser in the literature for type 1 diabetes than for type 2 diabetes. This is probably partially due to the higher prevalence of the latter. In a randomized, crossover study involving 23 adult patients with type 1 diabetes and mean baseline HbA1c 9.2% (range 8.1%–12.3%), biphasic insulin aspart 70/30 three times a day with bedtime NPH if necessary for 12 weeks was superior to a more traditional basal-bolus insulin regimen consisting of soluble human insulin (regular insulin) three times a day and bedtime NPH for 12 weeks [mean and range HbA1c, 8.3% (6.7%–9.8%) after biphasic insulin aspart vs 8.6% (7.4%–11.4%) after regular insulin, $p = 0.013$] (Chen et al 2006). Biphasic insulin aspart was injected immediately before meals. Regular insulin was injected as it had been prior to trial entry and varied anywhere from 0 to 30 minutes before meals. When patients were randomized to the biphasic insulin aspart phase, the initial dose was based on their average daily dose the week before, 30% was given with breakfast, 30% with lunch, and 40% with dinner. In addition, during this phase patients were advised by a diabetes nurse to take bedtime NPH if needed to control fasting hyperglycemia. Eleven of the 23 subjects chose to take bedtime NPH (2–10 units) during the biphasic insulin aspart phase. Those assigned to the regular insulin phase were started on the same doses that they had been on pretrial. Patients adjusted their insulin doses according to their self-monitored blood glucose and with advice from a diabetes nurse. Patients were given targets of 90–144 mg/dL for preprandial blood glucose and 90 to 180 mg/dL for postprandial blood glucose. Although the percent of basal insulin was greater during biphasic insulin aspart treatment, the total daily insulin doses during the two treatment phases were identical, averaging 50 units daily during both treatment phases. HbA1c significantly improved with both treatments, but the improvement was significantly greater with biphasic insulin aspart than with regular insulin, especially in those 11 patients who took bedtime NPH while in the biphasic insulin aspart phase. These 11 patients had a mean HbA1c of 8.7% (7.4%–11.4%) following regular insulin compared to a mean HbA1c of 8.2% (6.7%–9.8%)

following biphasic insulin aspart ($p < 0.05$). Analysis of self monitored blood glucoses revealed significantly lower blood glucoses 2 hours after dinner and at bedtime during the biphasic insulin aspart phase compared to the regular insulin treatment phase. The mean (range) blood glucose 2 hours after dinner was 173 (120–324) mg/dL with regular insulin versus 149 (90–220) mg/dL with biphasic insulin aspart. The mean blood glucose at bedtime was 176 (112–283) mg/dL with regular insulin versus 148 (104–227) mg/dL with biphasic insulin aspart. There were no significant differences between the two treatments in the mean fasting blood glucose [153 (101–225) mg/dL with regular insulin versus 155 (112–227) mg/dL with biphasic insulin aspart]. There were no differences between the two treatments in blood glucoses 2 hours after breakfast, before lunch, 2 hours after lunch, or before dinner. The rate of total hypoglycemic events, defined as either symptoms of hypoglycemia and/or blood glucose < 50 mg/dL, was not significantly different between treatments [median (range), 0.7 (0–3.3) versus 1.2 (0.1–3.1) events per patient per week with the regular insulin and biphasic insulin aspart, respectively]. During biphasic insulin aspart treatment, the rate of total hypoglycemic events was 1.1 (0.3–1.9) events per patient per week in the 12 patients who did not take bedtime NPH compared to 1.2 (0.1–3.1) events per patient per week in the 11 patients who also took bedtime NPH. The rate of nocturnal hypoglycemia occurring between midnight and 4 am was the same during the two treatments, 0.2 (0.1–0.7) events per patient per week. There was one episode of major hypoglycemia during regular insulin treatment and 3 episodes in 2 patients during biphasic insulin aspart treatment. Major hypoglycemia was defined as symptomatic hypoglycemia requiring the assistance of another person. (Chen et al 2006).

In another large study, 104 adult patients with type 1 diabetes and 187 adult patients with type 2 diabetes who were on twice-daily insulin injections with a mean baseline HbA1c of 8% were randomized to twice daily biphasic human insulin 70/30 or biphasic insulin aspart 70/30. After 12 weeks, the mean daily PPG increment was significantly lower with biphasic insulin aspart compared to biphasic human insulin (difference between groups -12.2 mg/dL (90% CI -2.9 to -21.6 mg/dL; $p < 0.02$). (Boehm et al 2002). Blood glucoses after breakfast, before lunch, after dinner and at bedtime were about 18 mg/dL lower in the biphasic insulin aspart group compared to the biphasic human insulin group ($p < 0.05$). Fasting blood glucose was not statistically significantly different between the

two treatment groups (161 ± 5.0 mg/dL in the biphasic insulin aspart group versus 148 ± 4.9 mg/dL in the biphasic human insulin group. The mean difference in fasting blood glucose between the treatment groups (biphasic insulin aspart – biphasic human insulin) is 12 mg/dL (95% CI –0.9 to 25 mg/dL). There was also no significant differences in mean HbA1c between the two treatments (mean \pm SEM, $8.14 \pm 0.06\%$ versus $8.15 \pm 0.06\%$). The number of major hypoglycemic episodes, defined as requiring another person's assistance or IV glucose or glucagon, was twice as great with biphasic human insulin compared to biphasic insulin aspart (42 versus 20 major episodes), however this did not achieve statistical significance, partly because 19 of the 42 episodes in the biphasic human insulin group occurred in only 3 patients. There were 361 minor hypoglycemic episodes with biphasic human insulin and 362 minor episodes with biphasic insulin aspart. Significant risk factors for major hypoglycemia were type 1 diabetes and longer duration of diabetes. Minor hypoglycemia was defined as symptoms of hypoglycemia, confirmed by a blood glucose reading if possible, and not requiring the assistance of another person. The overall risk of major and minor hypoglycemia was not significantly different between the two treatment groups. Thus, compared to biphasic human insulin, biphasic insulin aspart twice daily significantly improved PPG control in patients with type 1 and type 2 diabetes. Overall glucose control or HbA1c and overall risk of hypoglycemia was similar in the two treatment groups. Subsequently, 125 of the patients with type 2 diabetes participated in a 2-year extension of this trial (Boehm et al 2004). After 2 years, mean HbA1c was not statistically different between the two treatment groups ($8.35 \pm 0.20\%$ in the biphasic insulin aspart group vs $8.13 \pm 0.16\%$ in the biphasic human insulin group; adjusted mean difference 0.03% (90% CI –0.29 to 0.34%), $p = 0.89$) However, as this was not a treat-to-target study, it does not address the efficacy of biphasic human insulin aspart for achieving target HbA1c levels. The proportion of patients who experienced a major hypoglycemia episode was similar in both treatment groups during the first year (5% with biphasic insulin aspart and 8% with biphasic human insulin, $p = 0.72$), but was significantly lower in the biphasic insulin aspart group during the second year (0% with biphasic insulin aspart versus 10% with biphasic human insulin, $p = 0.04$). There was no significant difference between the two treatment groups in the proportion of patients experiencing minor hypoglycemia. The change in body weight was 0.05 ± 0.81 kg in the biphasic insulin aspart group and 2 ± 0.69 kg in the biphasic human insulin group

($p = 0.07$). Thus, in patients with type 2 diabetes, biphasic insulin aspart was associated with a reduced rate of major hypoglycemia, despite a similar HbA1c, after 24 months.

A multinational, randomized, open-label, parallel group trial compared biphasic insulin aspart to biphasic human insulin in patients with type 1 diabetes (Mortensen et al 2006). In this study, 167 adolescents, 10–17 years of age, with type 1 diabetes and mean baseline HbA1c of 9.6% were randomized to biphasic insulin aspart 70/30 three times a day before meals or biphasic human insulin 70/30 before breakfast and regular insulin before lunch and dinner. The starting total daily dose of insulin was the same as the total daily insulin dose at screening. If judged necessary by the investigator, additional doses of insulin aspart or regular insulin could be given before snacks or NPH could be given at bedtime. The glycemic goals in this study include fasting blood glucose <144 mg/dL and postprandial blood glucose <180 mg/dL. Dose adjustments were made based on these goals, HbA1c, and frequency of hypoglycemia. At the end of 16 weeks, there were small reductions in HbA1c in both groups. However, the end-of-study HbA1c was similar in the two treatment groups ($9.39 \pm 0.14\%$ with biphasic insulin aspart versus $9.3 \pm 0.15\%$ with human insulin, $p = 0.62$ after adjusting for baseline HbA1c and country). The mean PPG increment in the human insulin group was twice that in the biphasic insulin aspart group (6.7 ± 7.4 mg/dL versus 13.9 ± 7.9 mg/dL); however, this did not achieve statistical significance ($p = 0.47$). Overall, the body mass index (BMI) increased in both groups but significantly less so with biphasic insulin aspart (0.16 ± 0.1 versus 0.56 ± 0.11 , $p = 0.005$). Interestingly, male subjects treated with biphasic insulin aspart had a reduction in their BMI of -0.13 ± 0.16 , whereas male patients treated with human insulin had an increase in BMI of 0.41 ± 0.18 ($p = 0.007$). Females treated with biphasic insulin had a mean increase in BMI of 0.21 ± 0.14 compared to females treated with human insulin who had a mean increase in BMI of 0.43 ± 0.16 ; however, this was not statistically significant ($p = 0.276$). The incidence of major and minor hypoglycemic events was comparable in the two treatment groups. There were 15 major hypoglycemic episodes, 7 in the biphasic insulin aspart group and 8 in the human insulin group. The relative risk of experiencing a major episode was not significantly different in the treatment groups. Most subjects experienced only a few episodes, but a few subjects had a high number of episodes. Ten subjects were responsible for reporting more than 600 (or 30% of) episodes. Six patients in the biphasic insulin aspart group reported 382 episodes and 4 people in the human insulin

group reported 221 episodes. The majority of reported hypoglycemia episodes were symptoms only, and not confirmed by blood glucose measurement.

In summary, several studies suggest that biphasic insulin aspart 70/30 may be a safe and effective alternative for some patients with type 1 diabetes. Compared to a basal-bolus regimen of regular insulin three times a day before meals plus NPH at bedtime, biphasic insulin aspart three times a day before meals \pm bedtime NPH more effectively reduces HbA1c while maintaining similar rates of hypoglycemia. Another study involving both type 1 and type 2 diabetics showed that biphasic insulin aspart twice daily significantly improves PPG control while achieving similar HbA1c levels compared to biphasic human insulin twice daily. The overall risk of hypoglycemia was similar in the two treatment groups, however having type 1 diabetes was a risk factor for major hypoglycemia. In adolescents 10–17 years old, biphasic insulin aspart before breakfast, lunch and dinner is as effective in lowering HbA1c as a regimen of biphasic human insulin before breakfast plus regular insulin before lunch and dinner. Interestingly males treated with biphasic insulin aspart had a slight reduction in BMI, whereas BMI increased in males treated with biphasic human insulin and females treated with biphasic human insulin or biphasic insulin aspart. The incidence of major and minor hypoglycemia was comparable in the two treatment groups. Most subjects experienced only a few episodes, but a few subjects were particularly susceptible to hypoglycemia and reported a high number of episodes.

Biphasic insulin aspart and hyperlipidemia

In the previously described study by Kvapil et al involving 341 patients with type 2 diabetes, triglyceride levels decreased by 44–53 mg/dL in the two biphasic insulin aspart groups and by only 18 mg/dL in the glibenclamide plus metformin group. However, there were no statistically significant differences between the treatment groups in the mean triglyceride level at the end of the 16 weeks (176 ± 106 mg/dL with biphasic insulin aspart versus 202 ± 132 mg/dL with biphasic insulin aspart plus metformin versus 176 ± 97 mg/dL with glibenclamide plus metformin). HDL cholesterol increased slightly by 4–8 mg/dL in all three treatment groups, but this did not meet statistical significance (Kvapil et al 2006). In the 1-2-3 study of 100 patients with type 2 diabetes, discussed in detail below, significant improvements were seen in fasting lipids with biphasic insulin aspart 70/30, including a 20% decrease in triglycerides, 9% increase in HDL cholesterol,

and 5% decrease in total cholesterol. There was no change in LDL cholesterol (Garber et al 2006).

Studies on the effects of biphasic insulin aspart versus biphasic human insulin on postprandial hyperlipidemia in patients with diabetes have been inconsistent. One small study of 12 patients with type 2 diabetes found a significant reduction in postprandial hyperlipidemia with biphasic insulin aspart compared to biphasic human insulin (maximum increase in triglycerides, 205 ± 90.4 mg/dL with biphasic human insulin vs 145 ± 60.6 mg/dL with biphasic insulin aspart, $p = 0.014$) (Schmoelzer et al 2005). A randomized crossover study of 50 patients with type 1 diabetes reported a reduction in postprandial glucose with biphasic insulin aspart 70/30 compared to biphasic human insulin 70/30, but there were no differences in the postprandial free fatty acid or triglyceride levels between the two treatments (Hermansen, Vaaler et al 2002).

Optimal dosing frequency of biphasic insulin aspart

The optimal dosing frequency of biphasic insulin aspart when used in combination with OHD in those that have failed OHD alone has been investigated. The results of the 1-2-3 study suggest that in many patients with type 2 diabetes, biphasic insulin aspart 70/30 may need to be titrated to three daily injections to achieve optimum glycemic control (Garber et al 2006). This was a 48-week observational study that enrolled 100 patients with type 2 diabetes with a HbA1c of 7.5%–10% on at least two OHDs or on one OHD plus once-daily basal insulin. The basal insulin was discontinued on entry into the study, while the OHDs were continued as previously. All subjects were initiated on once daily dinnertime biphasic insulin aspart 70/30 (12 units or 70%–100% of prior basal insulin dose). Under the guidance of the investigator, subjects self-titrated their biphasic insulin aspart dose every 3–4 days to a target fasting blood glucose of 80–110 mg/dL. If a subject's HbA1c was greater than 6.5% by week 15, oral insulin secretagogues were discontinued and a second injection of biphasic insulin aspart 70/30 was initiated at a dose of 3–6 units with breakfast. Subjects adjusted their breakfast dose every 3–4 days to achieve pre-dinner blood glucose levels 80–110 mg/dL. They continued to adjust their dinner dose to achieve fasting blood glucose levels 80–110 mg/dL. After another 16 weeks, if a subject's HbA1c was still greater than 6.5%, a third injection of biphasic insulin aspart was added at a dose of 3 units with lunch. This lunchtime dose was adjusted to achieve a PPG of 100–140 mg/dL 2 hours after

lunch. Subjects were also allowed to continue to adjust their breakfast and dinner doses, but were cautioned not to adjust more than one dose at a time. The addition of once-daily biphasic insulin aspart at dinner allowed 21% of patients to achieve a HbA1c <6.5%, and 41% of patients to achieve a HbA1c <7.0%, in accordance with IDF and ADA guidelines. When patients were titrated to twice-daily biphasic insulin aspart, 52% achieved a HbA1c <6.5%, and 70% achieved a HbA1c <7.0%. Upwards titration to thrice daily dosing of biphasic insulin aspart allowed 60% of patients to achieve a HbA1c <6.5%, and 77% to achieve a HbA1c <7.0%. The mean HbA1c for all patients decreased from $8.6 \pm 0.8\%$ at baseline to $6.6 \pm 0.9\%$ at the end of the study. Self monitored fasting blood glucose also decreased significantly from a baseline of 175–180 mg/dL to 115–120 mg/dL after biphasic insulin treatment. The mean laboratory-measured fasting plasma glucose was 125 ± 59 mg/dL for at the end of the study. Most (84%) of patients reported minor hypoglycemia, defined as blood glucose <56 mg/dL, with or without symptoms, that the patient was able to treat themselves. The minor hypoglycemia rate was 15.4, 22.4, and 12 events per patient year during once-daily, twice-daily, and thrice-daily dosing, respectively. Thus, increasing the number of daily injections does not appear to significantly increase the risk for minor hypoglycemia. Interestingly, approximately half of all the minor hypoglycemia episodes were reported by only 13 patients. Perhaps in such patients who are particularly susceptible to hypoglycemia, a less aggressive titration schedule may have reduced the frequency of hypoglycemia. Major hypoglycemia, defined as blood glucose <56 mg/dL with CNS symptoms and requiring the assistance of another person, was reported by 7 patients. The risk of major hypoglycemia was similar with the once-daily, twice-daily, and thrice-daily treatments. There were no nocturnal major hypoglycemic episodes. There were 33 patients who reported two or fewer minor or major hypoglycemia episodes. No patient withdrew from the study because of hypoglycemia. This trial demonstrated that biphasic insulin aspart 70/30 can be safely and effectively titrated to achieve glycemic control in the majority of patients with uncontrolled type 2 diabetes.

In another randomized, open-label study of 177 patients with type 2 diabetes, biphasic insulin aspart with breakfast, lunch, and dinner significantly improved post lunch and post dinner glucose profiles compared to biphasic insulin aspart twice daily (post lunch 156 vs 176 mg/dL, $p = 0.0289$ and post dinner 154 vs 182 mg/dL $p = 0.002$) (Abrahamian et al 2005). The mean difference in HbA1c between treatment

groups was 0.08% after 24 weeks, but this was not statistically significant.

Safety profile of biphasic insulin aspart

Hypoglycemia

The most common side effect of all insulin products is hypoglycemia, emphasizing the importance of self monitoring blood glucose in all patients on insulin therapy. This is no surprise as hypoglycemia is the major limiting factor in achieving glycemic control in patients on insulin. Care should be taken when any kind of insulin is used in combination with beta blockers and clonidine as these drugs may mask symptoms of hypoglycemia (Provider 2006).

A systematic review of randomized comparative studies involving the use of biphasic insulin aspart 70/30 in type 2 diabetes showed that the rates of minor hypoglycemia with biphasic insulin aspart 70/30 varied across studies, but was generally not different from the rates seen with biphasic human insulin 70/30, biphasic insulin lispro 75/25, or NPH insulin (Halimi et al 2005). The rates of severe hypoglycemic events with biphasic insulin aspart 70/30 were low. Compared to biphasic human insulin 70/30, the rates of severe hypoglycemia with biphasic insulin aspart 70/30 were either similar or lower.

During the first 12 months of the study by Boehm et al described in detail above, there was no significant difference in the rate of major hypoglycemia between biphasic insulin aspart and biphasic human insulin (Boehm et al 2002). However, during the second year of the trial, major hypoglycemic events were significantly reduced in the biphasic insulin aspart group compared to the biphasic human insulin group (Boehm et al 2004). In the second year of this study, using biphasic insulin aspart instead of biphasic human insulin reduced major nocturnal hypoglycemia by 38% and minor nocturnal hypoglycemia by 37%, despite similar HbA1c levels. One possible explanation for the reduced hypoglycemia seen with biphasic insulin aspart is that its mealtime component, rapid-acting insulin aspart, has a shorter duration of action (4 hours) compared to regular insulin (6 hours). Another explanation might be that patients on biphasic human insulin are more likely to inject their insulin inappropriately late as it is difficult to time insulin injections 30 minutes before meals.

In a systematic review of 17 publications through February 2005, including more than 2600 adults with type 2 diabetes [mean (range) baseline HbA1c 8.6% (7.5%–9.9%)] and 104

adults with type 1 diabetes (HbA1c 8.4% (7.2%–10.4%)), the overall incidence of hypoglycemia was comparable between biphasic insulin aspart 70/30, biphasic human insulin 70/30 and biphasic insulin lispro 75/25 (Davidson et al 2005). In this report, hypoglycemic episodes occurred in 43%–57% of patients using biphasic insulin aspart, in 32%–57% of patients receiving biphasic human insulin, and in 28% of patients using basal NPH insulin. Major hypoglycemic events in which symptoms required assistance, glucagon, or IV glucose were reported less often with the use of biphasic insulin aspart (2%–8%) than with the use of biphasic human insulin (2%–14%). This review also found no significant differences in weight gain, formation of cross-reactive antibodies, or adverse events between biphasic insulin aspart and biphasic human insulin. Adverse events were reported in 36%–90% of patients on biphasic insulin aspart, 38%–88% of patients on biphasic human insulin, and 51% of patients on biphasic insulin lispro. Interestingly, the use of OHD was not found to significantly alter the safety profile of biphasic insulin aspart. Efficacy parameters were not assessed in this review.

In another recent study of 157 insulin-naïve patients with type 2 diabetes and HbA1c $\geq 8\%$, subjects were randomized to biphasic insulin aspart 70/30 twice daily plus metformin or insulin glargine once daily plus metformin. In both groups insulin doses were titrated weekly according to a pre-specified algorithm. Subjects in the biphasic insulin aspart group experienced more weight gain and minor hypoglycemic events than subjects in the insulin glargine group (Raskin et al 2007). This may simply be a consequence of better glycemic control, as the proportion of subjects who achieved a HbA1c $< 7\%$ at 28 weeks was greater in the biphasic insulin aspart group than in the insulin glargine group (65% versus 41%, $p = 0.003$). The mean change in HbA1c was $-2.89 \pm -1.6\%$ with biphasic insulin aspart and $-2.46 \pm -1.6\%$ with insulin glargine ($p = 0.035$). There were no major episodes of hypoglycemia, but nocturnal hypoglycemia was reported by 25% of the biphasic insulin aspart group compared to only 10% of the insulin glargine group ($p = 0.021$).

Weight gain

In the above study by Raskin et al weight gain was 5.6 ± 4.6 kg in the biphasic insulin aspart group and 3 ± 4.3 kg in the insulin glargine group ($p = 0.0004$) (Raskin et al 2007). The greater weight gain in the biphasic insulin aspart group may be due to the increase in minor hypoglycemia, as treatment of the hypoglycemia may lead to increased caloric consumption. The greater weight gain may also be a reflection of better glycemic control as improved glycemic control itself is associated with

weight gain and increased risk for hypoglycemia (Henderson et al 2003). Improved glycemic control can lead to weight gain as it reduces glucosuria so that calories are stored rather than lost in the urine. In a systemic review of 21 trials of biphasic insulin aspart in patients with type 2 diabetes, the amount of weight gain seen with biphasic insulin aspart varied from as little as 0.05 kg to as much as 5.4 kg, depending on the duration of treatment, degree of titration, and underlying patient population (Halimi et al 2005).

Insulin antibodies

As with other insulins, cross-reactive antibodies have been reported to develop with the use of biphasic insulin aspart, however the clinical significance of this is not known. In a study of 294 patients with either type 1 or type 2 diabetes, patients were randomized to treatment with either twice daily biphasic insulin aspart or biphasic human insulin 70/30 (Lindholm et al 2002). Patients were then tested for cross-reactive insulin antibodies at 0, 3, 6, and 12 months. During treatment there was an initial 11.2% increase from baseline in cross reactive antibodies in patients receiving biphasic insulin aspart, followed by a decrease over the next several months. However, there was no correlation between cross reactive insulin antibodies and blood glucose control or adverse outcomes. Another 12-week study of multiple daily injections of biphasic insulin aspart in patients with type 1 diabetes also found no differences in long-term glycemic control between patients with different levels of insulin antibodies (Chen et al 2005).

Other potential adverse events

Insulin aspart contains cresol, a compound that can cause local injection reactions and generalized myalgias. Cresol is also a component in insulin detemir, insulin glargine, and lispro (NovoLog Mix[®] 70/30 product label).

Advantages versus disadvantages of biphasic insulin aspart

As large epidemiologic studies suggest that PPG levels correlate better with adverse cardiovascular outcomes and death, one potential advantage of biphasic insulin aspart is better PPG control. Improvements in PPG control may also have the potential to reduce other diabetes complications, but this has yet to be proven in prospective, randomized controlled trials.

An important limitation of biphasic insulin aspart is that it is only available in certain proportions, most commonly 70/30. This limitation, also seen with other biphasic insulins,

Table 1 Commonly used biphasic insulins

| | Commercially available in US | Commercially available in Europe |
|--|------------------------------|----------------------------------|
| Biphasic insulin analogs | | |
| Biphasic insulin aspart 70/30 (70% protamined aspart and 30% soluble aspart) | yes | yes |
| Biphasic insulin aspart 50/50 (50% protamined aspart and 50% soluble aspart) | no | yes |
| Biphasic insulin lispro 75/25 (75% protamined lispro and 25% soluble lispro) | yes | yes* |
| Biphasic human insulins | | |
| Biphasic human insulin 70/30 (70% NPH and 30% regular insulin) | yes | yes* |
| Biphasic human insulin 50/50 (50% NPH and 50% regular insulin) | yes | yes* |

*Commercially available in selected European countries

may not be of particular significance in patients with type 2 diabetes who still maintain some endogenous insulin secretion. Furthermore, using biphasic insulin eliminates the need for patients to mix their own insulin, which can be a potential source of error. Nevertheless, there will be patients who are unable to achieve glycemic goals with biphasic insulins because of its fixed proportions and such patients may benefit from learning how to mix NPH and a rapid-acting insulin, rather than using premixed biphasic insulins.

Another potential limitation of all biphasic insulins are that their basal components exhibit an intermediate NPH-like profile rather than a more physiologic, truly basal insulin profile as is seen with insulin glargine or levemir. NPH peaks several hours after it is injected, requiring patients on biphasic insulins to eat at fixed times of the day. Some patients may even need to have mid-morning and bedtime snacks to avoid hypoglycemia when the NPH insulin peaks. Therefore, some patients may prefer to switch to a more physiologic basal-bolus regimen of glargine or levemir once a day plus rapid-acting insulin three times a day. Glargine and levemir are peakless basal insulins that last 24 hours, however they cannot be mixed with other insulins.

Although basal-bolus insulin regimens are more physiologic, they require four insulin injections daily and are more labor-intensive than biphasic insulin aspart 70/30 which may need to be given once, twice, or maybe thrice daily to achieve glycemic control. Thus for the less adherent patient, biphasic insulin aspart may be preferable to a basal bolus regimen.

Despite these limitations, the above studies show that many patients with type 2 diabetes and some patients with type 1 diabetes can achieve glycemic control safely and effectively with biphasic insulin aspart 70/30. Studies have also shown that the biphasic insulin aspart pen is particularly well-liked by patients because of its convenience and ease of use. Thus, in many patients the potential limitations of biphasic insulin aspart are likely outweighed by its ease of use, convenience, and greater acceptability.

On the other hand, for other patients, such as those who do not consume meals at fixed times, the disadvantages of biphasic insulin aspart may outweigh its advantages, and alternative treatment regimens may be more appropriate. Thus, when deciding on whether or not to initiate biphasic insulin aspart, one must take into consideration patient preferences, compliance, and dietary habits.

Conclusions

In conclusion, the evidence for biphasic insulin aspart supports its role as a safe, and efficacious alternative therapeutic modality for achieving glycemic control in patients with diabetes. Patients with type 2 diabetes who are failing OHD, can be brought to goal with the simple addition of biphasic insulin aspart 70/30 once or twice daily. Compared to other insulins, biphasic insulin aspart 70/30 more effectively reduces post-prandial glucose, which is being increasingly recognized as an important component of good glycemic management. Biphasic insulin aspart has been shown to be as efficacious as other insulins in reducing HbA1c. The rate of hypoglycemia with biphasic insulin aspart is similar to that seen with other insulins. However, there are situations when the disadvantages of biphasic insulin aspart outweigh its advantages, and alternative treatment regimens may be more appropriate.

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