

The Use of Premixed Insulin Analogues in the Treatment of Patients with Type 2 Diabetes Mellitus: Advantages and Limitations

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ABSTRACT

Background: Intensive, target-oriented therapy is the standard of care in the management of patients with type 2 diabetes mellitus (DM). Early and aggressive use of insulin that is as close as possible to the physiologic pattern of insulin secretion from healthy pancreatic β -cells is advocated to achieve glycemic goals and reduce complications of DM.

Objective: The objective of this article was to review the characteristics, advantages, and drawbacks of premixed insulin analogues and to evaluate their role in the treatment of patients with type 2 DM.

Methods: A PubMed search of articles from 1990 to 2006 was undertaken using the search terms *type 2 diabetes, basal-bolus therapy, premixed insulins, biphasic insulins, and insulin analogues*. Pertinent content from relevant articles was extracted and combined with the authors' knowledge, experience, and clinical expertise.

Results: The advent of insulin analogues has streamlined the treatment of patients with DM. When to initiate insulin during the course of treatment is the subject of much debate. Insulin therapy targeting both fasting and postprandial hyperglycemia is important in achieving optimal blood glucose (BG) control in patients with type 2 DM. A practical and feasible option is the use of ≥ 1 injection of premixed insulin analogues. Premixed insulin preparations provide both basal and prandial coverage because of their biphasic pharmacokinetic properties. Clinical trials have shown that these agents improve glycemic control, are associated with an acceptably low rate of severe hypoglycemia, and have a high degree of patient acceptance. Limitations include the inability to adjust the long- and short-acting components separately, to use a flexible regimen of self-titration and premeal bolus-insulin calculations, and to adequately treat postlunch and early-morning BG elevations.

Conclusion: Clinicians should be aware of premixed insulin analogues' advantages and limitations so that these agents can be used appropriately in the treatment of patients with type 2 DM. (*Insulin*. 2007;2:68–79) Copyright © 2007 Excerpta Medica, Inc.

Key words: type 2 diabetes mellitus, basal-bolus therapy, premixed insulin, biphasic insulin, insulin analogues.

INTRODUCTION

Communities nationally and globally are confronting an epidemic of type 2 diabetes mellitus (DM) due to changes in lifestyle.^{1,2} Aggressive therapy is becoming the standard of care to prevent long-term complications of DM. However, according to some reports,^{3,4} overall glycemic control remains unsatisfactory. Many treatment options exist for patients with type 2 DM, including dietary changes, physical activity, oral antidiabetic drugs (OADs), the new injectable medications (eg, pramlintide, exenatide), and insulin. In addition to the timing and dose of insulin initiation, type of insulin and frequency of injection are key factors to consider when choosing a particular regimen. Several different types of insulin exist, each with its own pharmacokinetic (PK) properties and duration of action.

In general, insulins are classified according to duration of action: rapid-, short-, intermediate-, and long-acting types. A combination of intermediate- and long-acting (basal) insulin and rapid- or short-acting (bolus) insulin is frequently necessary to achieve good glycemic control that is as close as possible to the physiologic pattern of insulin secretion from healthy pancreatic β -cells. However, regimen complexity, patient preference, and other practical factors may dictate the treatment option chosen. Often, simplicity and convenience must be balanced against metabolic control. For example, a regimen requiring only 1 or 2 injections of long-acting insulin may encourage compliance but lead to suboptimal prandial control. On the other hand, a true basal-bolus regimen of ≥ 4 daily injections may enhance control but discourage compliance.

Premixed insulins offer an attractive option between these 2 extremes; they deliver both rapid- and long-acting insulin components in a single convenient injection. Because the primary barrier to achieving good glycemic control remains lack of insulin use in patients who can benefit from it, premixed insulins can potentially help an important subset of patients.

Premixed insulins offer an attractive option between 2 extremes; they deliver both rapid- and long-acting insulin components in a single convenient injection.

These preparations are composed of a single type of insulin that is γ modified to have dual-action PK profiles (a short-acting peak and a longer basal release) and are biphasic rather than truly premixed (eg, a mixture of neutral protamine Hagedorn [NPH] and regular human insulin [RHI]). However, in keeping with commonly used nomenclature, the term *premixed* is used in this article.

The objective of this article was to review the characteristics, advantages, and drawbacks of premixed insulin analogues and to evaluate their role in the treatment of patients with type 2 DM.

MATERIALS AND METHODS

A PubMed search of articles from 1990 to 2006 was undertaken using the search terms *type 2 diabetes*, *basal-bolus therapy*, *premixed insulins*, *biphasic insulins*, and *insulin analogues*. Pertinent content from relevant articles was extracted and combined with the authors' knowledge, experience, and clinical expertise.

THE PROGRESSIVE NATURE OF TYPE 2 DIABETES MELLITUS AND UNDERUSE OF INSULIN THERAPY

The United Kingdom Prospective Diabetes Study,⁵ the largest trial of glycemic control in type 2 DM, found that DM progresses inexorably when patients are treated with the OADs metformin and glyburide, and escalation of OAD therapy is needed to maintain glycemic control. The traditional approach to treatment of patients with type 2 DM is OAD monotherapy, often in a sequential manner, slowly progressing to combination treatment and eventually to insulin.⁶

In contrast to treatment of patients with type 1 DM, insulin is not considered an essential component of therapy in patients with type 2 DM, and its role in type 2 DM is not clearly defined. It is commonly relegated to "last-resort" use, when all other avenues have been exhausted.⁷ Providers may be reluctant to initiate insulin therapy due to "clinical inertia,"⁸ while most patients' well-known aversion to injection increases the delay in insulin initiation. Studies have shown that insulin therapy is started too late in the course of DM due to provider and patient resistance and lack of awareness about potential benefits.^{9,10} Although clinicians

worry about hypoglycemia, weight gain, and increased cardiovascular risk, these concerns have been shown to be unfounded.¹¹

Studies have shown that insulin therapy is started too late in the course of DM due to provider and patient resistance and lack of awareness about potential benefits.

Early use of insulin in the setting of progressive deterioration of metabolic control is advocated in patients with type 2 DM to attain optimal recommended glycemic targets.^{12,13} Studies have demonstrated the benefits of basal, as well as mealtime, short-acting insulin.^{14,15} Early, intensive insulin therapy is now advocated to improve glycemic control and reduce the risk of complications in patients with type 2 DM.¹⁶

In addition to insulin's PK properties, a patient's blood glucose (BG), carbohydrate intake, and physical activity levels help determine the dose and pattern of insulin needed. It is not enough to start a patient on insulin—a critical element is its proper, physiologic use.

THE BASAL-BOLUS CONCEPT OF INSULIN ADMINISTRATION

The method of delivery of multiple-dose insulin injections in patients with type 2 DM has changed in recent years. Insulin therapy is commonly initiated by adding once- or twice-daily long-acting insulin to existing OAD monotherapy or multitherapy. This therapeutic approach commonly results in improved glycemic control, but it can cause several problems. Hypoglycemia, especially nocturnal, is always a concern and a possible adverse effect of insulin therapy. The long-acting insulin analogues detemir and glargine go some way in addressing this issue.^{17,18} In addition, inadequate monitoring and titration after initiation of insulin therapy can result in suboptimal control.

The latest concept in BG management is that of limiting glycemic variability, which proposes that frequent and extreme BG variations are risk factors for heightened endothelial inflammation, oxidative stress, and possibly clinically evident vascular complications in patients with DM independent of glycosylated hemoglobin (A1C) value.¹⁹ Perhaps the most problematic barrier to achieving good glycemic control is the issue of meal-associated hyperglycemia, which many advocate should be treated aggressively.²⁰ Basal insulin replacement can lower fasting and premeal BG readings, but its limitation is revealed in the form of postprandial hyperglycemia, resulting in persistently elevated A1C levels.²¹ A1C level has been shown to be an independent risk factor for cardiovascular disease, and how postprandial versus fasting BG elevations contribute to the overall burden of hyperglycemia appears to be more significant when A1C levels are lower, but still above goal, for most patients.¹⁴ In other words, basal insulin therapy will

reduce an extremely high A1C but will not, by itself, help patients attain the desired A1C goal of as close to 6.0% as possible unless meal-associated glycemic excursions are also addressed.

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To mimic the function of the healthy pancreas, therapy must therefore address both fasting and postmeal hyperglycemia. Frequent premeal and postmeal BG self-monitoring is necessary to identify trends, manage patterns, and implement the “basal-bolus” concept.²² Each component of this regimen comes from a different type of insulin with a specific and predictable PK profile. Doses are adjusted based on daily self-monitored BG readings that reveal the pharmacodynamic (PD) characteristics of the different insulins, with the aim of dovetailing insulin to BG levels; this helps patients minimize glycemic variations and achieve an individually targeted A1C level.

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A combination of intermediate- or long-acting (eg, NPH or insulin glargine or detemir) and short- or rapid-acting (eg, RHI or insulin lispro, aspart, or glulisine) insulins may be used in several different ways. Separate injections of insulin can be mixed in the same syringe if timing and compatibility allow or they can be used in insulin pen devices. Such an approach can work well for meticulous patients who check BG levels several times a day and do not mind multiple daily injections or mixing varying doses of insulin. However, many patients may consider this detailed method of insulin administration to be overwhelming and inconvenient.

One solution is to use insulins that are already mixed in a fixed ratio of short-acting and basal components—premixed insulins. Premixed insulins can provide both meal and “background” coverage and theoretically address fasting, nocturnal, and prandial aspects of BG management. Premixed insulins can be either human (RHI and NPH) mixtures or analogues.

PREMIXED INSULIN ANALOGUE PREPARATIONS

The advent of recombinant DNA technology has introduced new, synthetic insulins with improved time–action profiles by

making them more similar to physiologic insulin release, avoiding insulin-glucose mismatch, and minimizing intra-individual variability. Analogues can be long acting or rapid acting. The profiles of 2 rapid-acting analogues have been further modified, creating biphasic—or premixed—preparations.

Currently available premixed insulin analogues include insulin aspart 70/30 (NovoLog[®] Mix 70/30; Novo Nordisk Inc., Princeton, New Jersey), insulin lispro 75/25 (Humalog Mix[®] 75/25[™]; Eli Lilly and Company, Indianapolis, Indiana), and insulin lispro 50/50 (Humalog Mix[®] 50/50[™]; Eli Lilly and Company). In Europe, insulin aspart 70/30 and insulin lispro 75/25 are known as NovoMix[®] 30 and Humalog[®] Mix 25[™], respectively. These dual-release formulations combine a 25% to 50% soluble, rapid-acting component with a protaminated insulin analogue portion that has a prolonged duration of action. The result is a product that provides biphasic coverage. Compared with human premixed insulins, the premixed biphasic analogues have a faster onset of action (5–15 minutes) and earlier peak (1–2 hours) for the first component and a relatively peakless second component lasting ≤16 hours.^{23,24} These characteristics lead to an improved PD effect, with favorable biochemical and physiologic BG-lowering actions in vivo (**Figure 1**).

The premixed insulin analogues have several clinical advantages. These preparations’ rapid-acting components are absorbed faster and provide better postprandial coverage compared with human insulin premixed formulations. They possess a more physiologic time–action profile, thereby theoretically lowering the risk of hypoglycemia, especially at night. Patients can conveniently time their injections 0 to 15 minutes before eating. The analogues can even be administered immediately after mealtime if eating patterns or amounts are unpredictable. Thus, there would conceivably be less worry about both day and nocturnal hypoglycemic episodes.

EVIDENCE FOR THE USE OF PREMIXED INSULIN ANALOGUES FROM CLINICAL TRIALS

Human premixed insulins have long been a popular way to treat patients with type 2 DM. Their limitations include the inflexible necessity for injection 30 minutes before meals, a high incidence of hypoglycemia, and the difficulty some patients experience in using them to optimize BG control in everyday living. Because of their favorable PK and PD properties,^{24–26} premixed insulin analogues have a distinct advantage over human premixed insulin. They can be injected at or after a meal, making them much more flexible and patient-friendly than human premixed insulins.^{27–29} Hermansen et al³⁰ also demonstrated that both types of premixed analogues (lispro mix 25 or lispro 75/25 and biphasic insulin aspart 30 [BIAsp 30] or aspart 70/30) achieved better postprandial BG control than premixed human insulins. In that trial, BIAsp 30 also demonstrated better postprandial BG control than lispro mix 25, most likely due to its higher proportion of fast-acting insulin. Similar results were seen when Boehm et al³¹ compared BIAsp 30 with human pre-

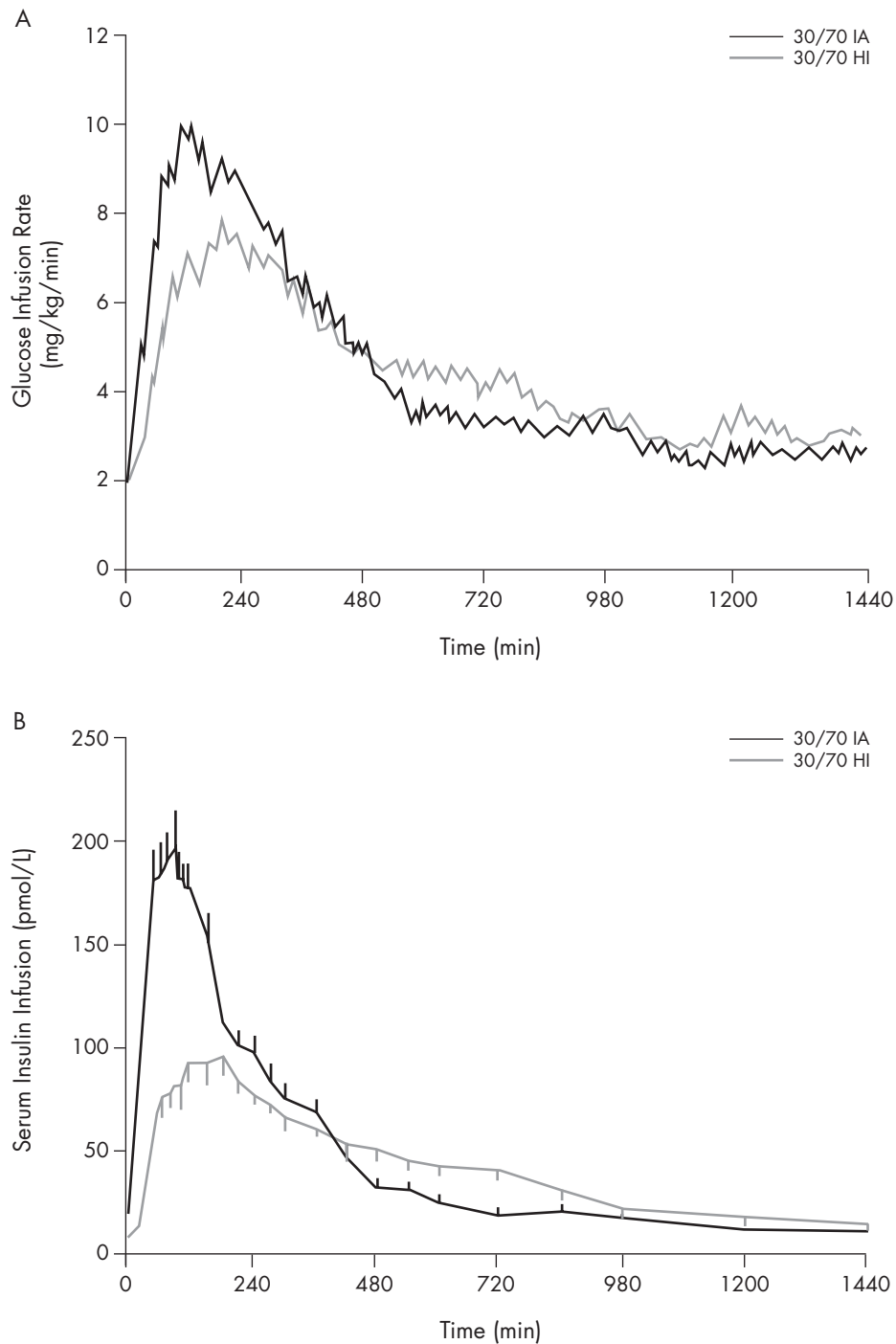


Figure 1. (A) Glucose infusion rates and (B) serum insulin concentrations (mean [SE]) after SC injection of either premixed rapid-acting analogue insulin aspart (30/70 IA) or a mixture of soluble regular human insulin/neutral protamine Hagedorn (30/70 HI). Copyright © 1997 American Diabetes Association. From *Diabetes Care*, Vol. 20, 1997;1612–1614.²⁴ Reprinted with permission from The American Diabetes Association.

mixed insulin. Other studies^{32,33} have shown that compared with premixed human insulins, premixed insulin analogues are associated with markedly less hypoglycemia, especially nocturnal hypoglycemia.

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Insulin analogue mixtures are intended for twice-daily injection—before breakfast and the evening meal. Large clinical studies have revealed that when used in this manner, they can achieve superior control compared with a single daily injection of a basal insulin analogue, a widely used treatment option when insulin therapy is initiated in patients with type 2 DM. A recent publication reports on a study comparing the PK and PD aspects of these 2 types of insulins.³⁴ In a euglycemic clamp setting, BIAsp 30, given as 2 split doses, was compared with a single dose of insulin glargine; AUC for insulin plasma levels and glucose infiltration rate (GIR) were measured. The total daily dose of both insulins was the same (0.5 U/kg). The PK and PD profiles, as measured by the plasma insulin and GIR, were 28% and 32% greater after 2 SC doses of BIAsp 30 compared with 1 dose of insulin glargine. The authors also found that plasma C-peptide concentrations fell below baseline after both injections of BIAsp 30 but remained unaltered after insulin glargine injection. They surmised that an acute prandial delivery of insulin may protect pancreatic β -cells from excessive stimulation (providing β -cell “rest”) and thereby slow cell death in patients with type 2 DM.

In the 28-week, treat-to-target INITIATE study,³⁵ BIAsp 30 was compared with insulin glargine, and both insulins were used in combination with metformin. Doses for patients in both groups were titrated to a strict algorithm. The primary end point was an A1C level $\leq 6.5\%$, with an A1C level target $< 7.0\%$ as the secondary end point. Of the patients treated with BIAsp 30, 42% reached an A1C $\leq 6.5\%$ and 66% reached an A1C level $< 7.0\%$. In the insulin glargine group, 28% reached an A1C level $\leq 6.5\%$ and 40% reached an A1C level $< 7.0\%$ (**Figure 2**). Only 1 patient receiving insulin glargine had a major hypoglycemic episode, and minor hypoglycemia occurred more often in patients receiving premixed insulin than in those receiving insulin glargine (43% vs 16%, respectively).

The EuroMix study³⁶ examined the same 2 insulins as part of 2 different regimens. A combination of BIAsp 30 plus metformin was compared with insulin glargine plus insulin glimepiride, both widely used treatment combinations in patients with type 2 DM. Results were similar to those from the INITIATE study,³⁵ with the BIAsp 30 plus metformin

group achieving better glycemic control than the insulin glargine plus insulin glimepiride group. In a crossover study design, Malone et al³⁷ demonstrated the superiority of insulin lispro mix 25 over insulin glargine. All 3 studies showed that the premixed insulins' superiority compared with insulin glargine derived from their better control of postprandial BG values, since the level of fasting BG was similar with both treatment regimens. None of the studies found a higher rate of major hypoglycemia in patients using premixed insulin analogues compared with those using the basal-only insulin analogue. Although the frequency of minor hypoglycemic events was higher with premixed preparations, investigators and patients considered them acceptable and relatively easy to manage.

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Premixed insulin analogues have also been studied as a once-daily treatment option. Recent studies^{37–40} have shown that BIAsp 30 insulin can be used once daily as initial insulin treatment in patients with type 2 DM. Garber et al⁴¹ found that 41% of patients receiving once-daily BIAsp 30 reached an A1C level $< 7.0\%$ at the end of the first 16-week phase of the study. A1C level with once-daily BIAsp 30 decreased from 8.6% to 6.6%. Treatment was intensified at 16-week intervals to aim for an A1C level $\leq 6.5\%$; if that goal was not reached, patients added a second and then a third injection of BIAsp 30 insulin after each study phase. At the end of the study, 60% of patients had an A1C level $\leq 6.5\%$ and 77.0% had an A1C level $< 7.0\%$ (**Figure 3**). No major nocturnal hypoglycemia was seen in any phase of the study. Daily episodes of major and minor hypoglycemia were not related to the number of injections; as the number of daily injections increased, the frequency of hypoglycemia remained the same. Patient well-being appeared to be related to the level of control achieved and was not influenced negatively by the number of injections required to reach the A1C target.^{38,42}

Although it did not involve the use of premixed insulin analogues, the study by Janka et al⁴³ merits mention. Insulin glargine added to 2 OADs was compared with cessation of OADs and replacement with premixed human insulin twice daily. All patients were insulin naive, taking metformin plus a sulfonylurea, with a mean duration of DM of 10 years, body mass index of 29.5 kg/m², and baseline A1C level of 8.8%. In the basal-insulin group, patients received metformin and glimepiride, while the insulin glargine dosage was titrated to a target fasting BG level of 100 mg/dL (5.6 mmol/L). In the insulin-only group, twice-daily human premixed 70/30 (70% NPH/30% RHI) insulin was titrated to the same target before breakfast and the evening meal, respectively. After 6 months of treatment, the mean A1C level

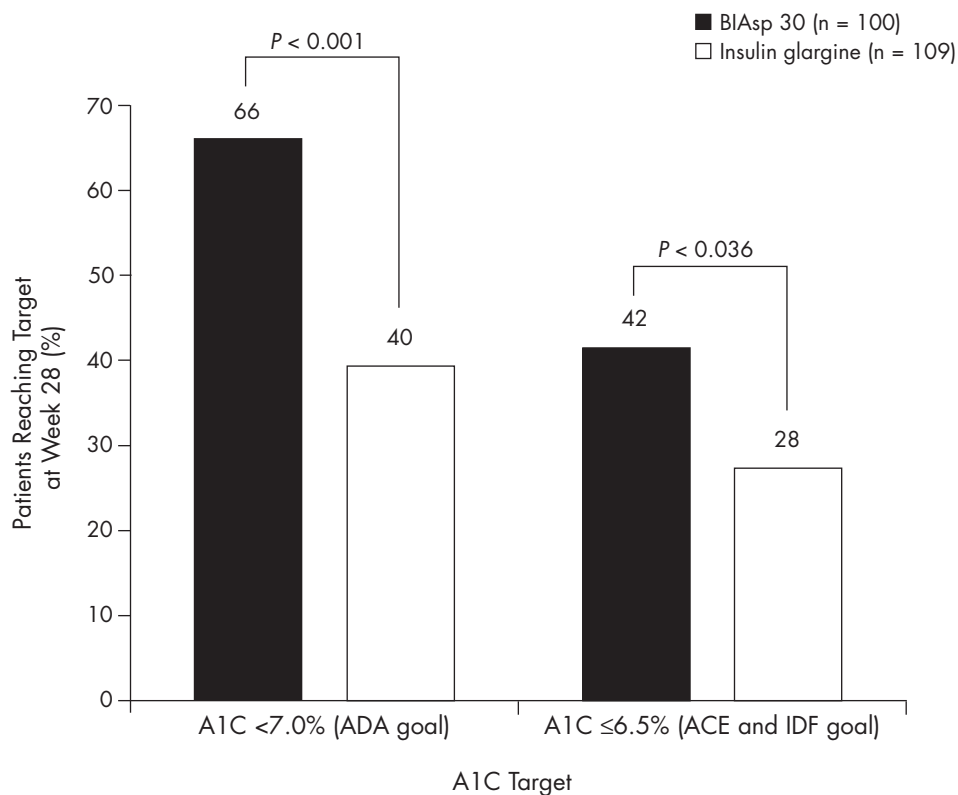


Figure 2. Percentage of patients achieving glycosylated hemoglobin (A1C) targets in the biphasic insulin aspart 30 (BIAsp 30) and insulin glargine groups at the end of the INITIATE study. ADA = American Diabetes Association; ACE = American College of Endocrinology; IDF = International Diabetes Federation. Copyright © 2005 American Diabetes Association. From *Diabetes Care*, Vol. 28, 2005;260–265.³⁵ Reprinted with permission from The American Diabetes Association.

was 7.15% in patients receiving basal insulin plus OADs and 7.49% in patients receiving twice-daily 70/30 insulin alone.

The 8-point self-measured BG profiles before and after treatment showed no advantage in daytime BG levels in patients receiving human premixed insulin versus those receiving basal insulin plus OADs.⁴³ Patients in the insulin-only group required twice as much insulin (mean, 64.5 vs 28.2 U daily), and their rate of confirmed hypoglycemic events (<60 mg/dL) was twice as high (9.9 vs 4.1 per patient-year). Thus, the basal insulin plus OAD regimen was superior both in achieving better glycemic control and in causing less hypoglycemia. Additionally, these findings are consistent with other research showing that metformin, when combined with both premixed and basal insulins, helps to reduce undesired hypoglycemia, weight gain, and excessive insulin dose.⁴⁴

These results cannot be generalized to the premixed analogues because of their different PD profiles. It is difficult to determine if using analogue preparations would have lessened the limiting factor of hypoglycemia and therefore

assisted in intensifying therapy, leading to improved glycemic control. In addition, continuing OAD therapy in patients who received premixed insulin might have yielded different outcomes.

A recent study comparing BIAsp 30 plus metformin and a thiazolidinedione showed superior control versus metformin plus thiazolidinedione alone, and 76% of patients reached an A1C target of 7.0%.⁴⁵ The level of minor hypoglycemia was acceptable, with ~8 minor events occurring per year. In addition, Liebl et al⁴⁶ found that, compared with a basal-bolus regimen with insulins detemir and aspart, BIAsp 30 twice daily was comparable in terms of A1C reduction in insulin-naïve patients, and hypoglycemia rates were low and similar between groups.

USING PREMIXED INSULIN ANALOGUES IN CLINICAL PRACTICE

Table I lists the expected advantages of using premixed insulin analogues in patients with type 2 DM. Because pre-

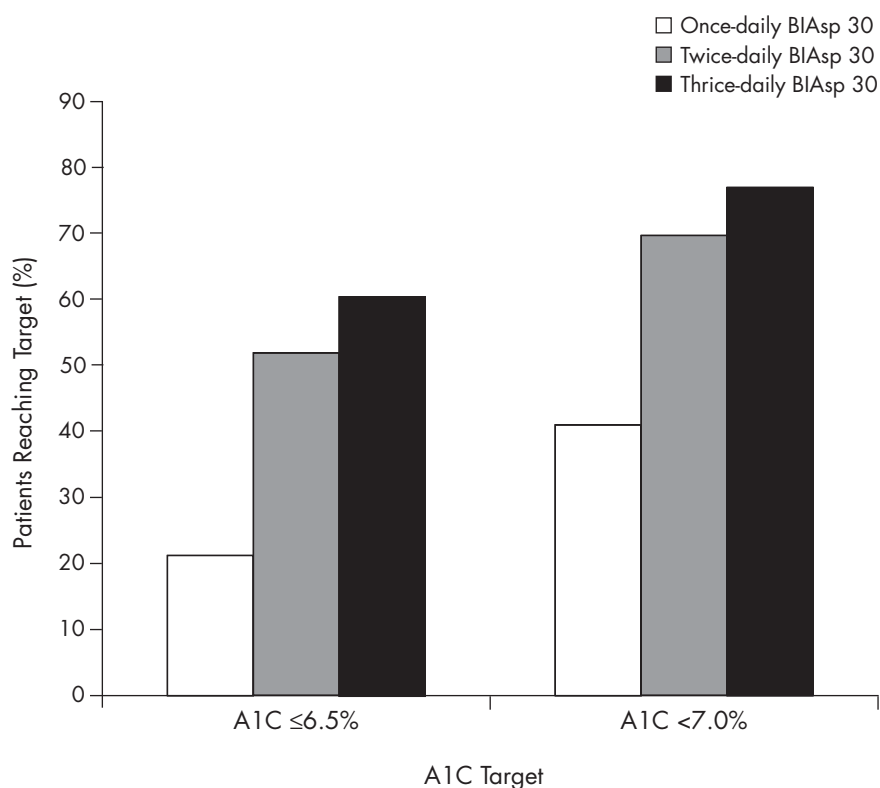


Figure 3. Percentage of patients who reached glycosylated hemoglobin (A1C) targets in the 1-2-3 Study. Biphasic insulin aspart 30 (BIAsp 30) was given once, twice, or thrice daily. From Garber AJ, Wahlen J, Wahl T, et al. Attainment of glycaemic goals in type 2 diabetes with once-, twice-, or thrice-daily dosing with biphasic insulin aspart 70/30 (the 1-2-3 study). *Diabetes Obes Metab.* 2006;8:58–66.⁴¹ Reprinted with permission from Blackwell Publishing.

mixed analogues appear to match physiologic insulin secretion better than human premixed insulin, they are associated with good postprandial control, low rates of hypoglycemia, modest improvements in overall glycemic control, and better patient acceptance, since they can be injected just before or immediately after a meal.

What factors should clinicians consider when deciding whether a patient is a suitable candidate for a premixed insulin analogue or another insulin? This dilemma may be one of the most controversial debates among providers. Based on accumulated evidence and clinical experience, the following scenarios may help clinicians considering biphasic insulin formulations.

Initiating Insulin Therapy

Initiation of insulin therapy is a watershed event for patients with type 2 DM and is usually instituted due to suboptimal control with OAD therapy. Premixed insulin analogues, because they are a convenient fixed-mix combi-

nation of rapid- and long-acting insulin, may provide an attractive and effective option^{44,47,48} compared with basal or bolus insulin alone, a complex multidose regimen, or human premixed insulin. Those options require more frequent daily injections or use of different types of insulin either separately or mixed by the patient before injection (self-mixing). In addition, their PK profile does not closely mimic the physiologic insulin profile seen in healthy subjects after a meal.

Targeting Postprandial Hyperglycemia

Using a basal insulin like NPH, insulin glargine, or insulin detemir alone or in combination with OADs is a popular approach in the treatment of patients with type 2 DM. However, this strategy does not adequately address postprandial BG elevations, and A1C levels remain above recommended targets. The solution would be to add a soluble or rapid-acting insulin before meals or, more conveniently, switch to a twice-daily premixed insulin analogue.³⁶

Table I. Advantages of premixed insulin analogues.

Provide basal and prandial insulin coverage
Ease transition from OADs to insulin therapy
Provide better control of postprandial hyperglycemia than OADs or basal-only insulin regimens
Reduce risk of severe hypoglycemia compared with premixed human insulin
Enhance patient convenience and acceptance (eg, easy to time with meals, availability of dual-action profile [biphasic] insulin in 1 injection, no mixing of short- and long-acting insulins)
Reduce errors in dosing

OADs = oral antidiabetic drugs.

Advancing from Basal-Only to Basal-Bolus Insulin Therapy

Patients who are no longer achieving optimal control with basal insulin alone and require progression to a true basal-bolus regimen may find a premixed insulin analogue to be a desirable option.⁴⁹

Possible Reduction in the Rate and Severity of Treatment-Related Hypoglycemia

Late postprandial and nocturnal hypoglycemia is a risk with human insulins (eg, RHI, NPH, or a combination). Better dovetailing of insulin to ambient BG levels afforded by premixed analogues, and their lack of a significant peak effect, reduces insulin-glucose mismatch and the risk of hypoglycemia.^{31,32} Switching from premixed human to premixed analogue insulin may be helpful in this regard.

Convenience

Premixed insulin analogues do not require mixing of 2 separate insulins and can be given immediately before or after a meal. This enhanced flexibility and convenience improve quality of life and treatment satisfaction.^{50,51} Moreover, availability in disposable pen form obviates drawing up insulin from a vial. After injection is initiated, the insulin aspart 70/30 pen can be used for ≤ 14 days⁵² and the insulin lispro 75/25 and insulin lispro 50/50 pens for ≤ 10 days^{53,54} if kept at room temperature (below 86°F recommended). These features are beneficial for patients with sight and dexterity issues, make it more convenient for eating out and travel, and can reduce errors in dosing.⁵⁵ The net result is a potentially improved level of patient acceptance and adherence to therapy.

A target-oriented titration schedule is crucial to successful implementation of any insulin regimen. The design and results of the INITIATE study³⁵ provide some practical guidelines for adjusting the dose of premixed insulins in clinical practice that Mooradian et al⁵⁶ highlighted in a recent review. A prudent strategy is to start with a total daily dose of 10 to

12 U. If ≥ 2 fasting BG values over 3 consecutive days are above target, the presupper insulin dose is increased in a graded fashion (between 2 and 6 U) depending on the degree of elevation and based on the lower of the readings. The dose may be reduced in a comparable way if hypoglycemia ensues. Similarly, the prebreakfast dose is adjusted depending on presupper BG levels. The doses are maintained when BG levels are within the desired range (usually between 80 and 110 mg/dL [4.4–6.05 mmol/L]). Although many variables affect it, as a rough guide, the usual total daily insulin requirement in patients with type 2 DM is between 0.5 and 1.0 U/kg. In this manner, the insulin regimen is tailored to the glycemic profile and individualized to the particular patient.

No clear-cut recommendations exist on whether to continue, adjust, or stop OADs when premixed insulin is initiated. This remains largely a matter of clinician preference, although customizing therapy to specific clinical situations and patient characteristics makes sense.⁵⁷ Combining insulin with a sulfonylurea may be at least clinically advantageous, and consideration should be given to reducing or eliminating the latter as the premixed analogue dose is titrated, especially if hypoglycemia occurs. The continuation of either metformin or a thiazolidinedione (eg, rosiglitazone, pioglitazone) is helpful in counteracting insulin resistance and reducing the total insulin dose required.⁵⁸ Metformin could limit the problem of weight gain commonly encountered in insulin-treated patients, while the mealtime use of an α -glucosidase inhibitor agent (eg, acarbose, miglitol) may decrease the number of daily insulin injections.⁵⁹ Conversely, the presence of comorbid conditions such as nephropathy and congestive heart failure may contraindicate the use of metformin and thiazolidinediones with insulin. Careful assessment of all relevant clinical aspects is therefore essential for safe and effective advancement from OADs to premixed insulin analogues.

The issue of cost frequently dictates the type of insulin or regimen prescribed. Although insulin analogues tend to be more expensive than traditional human preparations, they may be cost-effective in the long run when used in an intensive management strategy⁵⁰ if they reduce hypoglycemia and encourage compliance. Whether they will lead to sustained and significant improvement in glycemic control and thereby translate into reduced diabetic complications compared with human premixed insulin or other regimens remains to be demonstrated.

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LIMITATIONS OF PREMIXED INSULIN ANALOGUES

Although premixed insulin analogues are an effective and simple option when insulin therapy is initiated or intensified

in patients with type 2 DM, they are not—like most therapies—without limitations.⁶⁰ **Table II** summarizes potential limitations of therapy with premixed insulin analogues.

One obvious limitation of premixed insulin analogues, as with any premixed insulin, is that the different components cannot be individually adjusted. This limits flexibility in changing the rapid-acting component without affecting the long-acting component, and vice versa. Thus, modifications can only be made by increasing or decreasing the total dose at a particular time, rather than having the option of fine-tuning the individual basal or prandial coverage. For example, a patient might require a larger amount as basal insulin, a scenario that is usually seen in extreme or sustained uncontrolled hyperglycemia, corresponding to an A1C level >8.0%.¹⁴ This is seen when the contribution of fasting, premeal, and nocturnal elevated BG is predominant. As glycemic control improves, the contribution of postprandial glucose to overall hyperglycemia increases, necessitating the addition or increase in bolus or prandial insulin to address these glucose excursions. As a result, the basal-bolus insulin ratio shifts according to glycemic pattern and the degree or stage of hyperglycemia. Premixed insulin in different ratios (eg, insulin lispro 50/50) has been made available to overcome this problem.⁶¹ The introduction of BIAsp 50 and BIAsp 70, in which the percentage of soluble rapid-acting insulin aspart is 50% and 70%, respectively, is expected in the near future.⁶²

Similarly, large elevations of BG associated with midday meals may not be adequately covered with 2 injections and may require either 3 injections of premixed insulin⁴¹ or a lunchtime shot of rapid-acting insulin alone.

Patients with type 1 DM who frequently need to change their prandial insulin dose independent of the basal component are not good candidates for premixed insulin. Similarly, patients with type 2 DM who use varying amounts of short-acting insulin based on premeal BG readings and the carbohydrate content of food may find it difficult to use premixed

insulin to optimal advantage. A more complex multiple-dose insulin injection regimen or insulin pump therapy might be a better option in these specific patient groups.

Premixed insulin analogues are injected before meals, providing coverage for the postprandial BG elevation through the rapid-acting component. In some individuals, the duration of action of the longer-acting component of the predinner dose may not last until the next morning, allowing BG levels to rise unchecked secondary to the “dawn phenomenon.”⁶³ This phenomenon is not commonly reported in clinical studies but could occur in real life. This problem could be addressed by using separate doses of short- and long-acting insulins at dinner and bedtime, respectively.

Patients treated with premixed insulin analogues requiring an “as-needed” supplemental dose for addressing episodes of extreme hyperglycemia (eg, during sickness or stress) should keep a supply of rapid-acting insulin available. When patients must fast before a diagnostic or surgical procedure, it is recommended that they take their basal insulin but avoid short-acting insulin. However, with premixed insulin analogue therapy it is not possible to give one component. The temporary administration of rapid- or long-acting insulin alone solves this problem.

Patients treated with premixed insulin analogues requiring an “as-needed” supplemental dose for addressing episodes of extreme hyperglycemia (eg, during sickness or stress) should keep a supply of rapid-acting insulin available.

Finally, a dilemma may be encountered when hospitalized patients receive a scheduled-dose premixed insulin analogue (and therefore are receiving some rapid-acting insulin) and are also given supplemental short-acting insulin several times a day. Long- and rapid-acting SC insulin given separately or, when necessary, as continuous IV RHI (insulin drip) may be preferable in the inpatient setting.

Table II. Potential limitations of premixed insulin analogues in clinical practice.

Ratio of the 2 insulin components cannot be adjusted separately

Regimens based on carbohydrate counting and sensitivity factor are difficult to devise with premixed insulin analogues

Difficulty when used as “supplemental” insulin in place of rapid-acting insulin alone for treatment of hyperglycemic episodes

Insulin coverage may not address the “dawn phenomenon,” early-morning hyperglycemia, and postlunch hyperglycemia

Not suitable when food intake is held (eg, in the inpatient setting)

CONCLUSIONS

Most patients with type 2 DM ultimately require insulin to achieve optimal BG control. Transitioning from OADs to insulin presents a number of options, and a “one-size-fits-all” approach is impractical because of the heterogeneous nature of DM and different patient scenarios. A treatment regimen individualized to each patient’s goals and preferences will work best. Published evidence supports the idea that an insulin regimen that takes into account treatment of both fasting and postprandial hyperglycemia is most efficacious in reducing A1C levels. Furthermore, an emerging concept of minimizing daily glycemic variability in addition to lowering A1C levels to suppress the vascular complications of DM is gaining momentum. A single insulin analogue that contains 2 formulations with 2 PD profiles is an attractive choice, because it provides a basal-bolus therapeutic approach in a convenient way that may enhance patient acceptance. If used early and correctly in the

course of type 2 DM, premixed insulin analogues can help patients minimize hypoglycemia and achieve A1C goals.

Although problems may occur in clinical practice when premixed insulin analogues are prescribed, they are usually minor and temporary. Finding the appropriate application for the use of premixed insulin is paramount, and at times it may be prudent to switch to a different insulin type or regimen. Clinicians should be aware of premixed insulin analogues' advantages and limitations so that these agents can be used appropriately in the treatment of patients with type 2 DM.

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ACKNOWLEDGMENTS

Dr. Rizvi is on the speakers' bureau for sanofi-aventis (Bridgewater, New Jersey). Dr. Ligthelm is an advisor and key speaker for Novo Nordisk Inc. and participates in training courses for diabetes nurses for both Novo Nordisk Inc. and GlaxoSmithKline (Research Triangle Park, North Carolina).

The authors thank Catherine Jones, PhD, and Nicola Duckworth, PhD, for technical assistance during the preparation of the manuscript.

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