Biphasic Insulin Analogs for Treatment of Diabetes: A Review

J Tibaldi

Abstract

Diabetes mellitus (DM) is associated with a huge social and economic burden. Achieving guidelines glycemic targets can help reduce the burden of type 2 DM (T2DM)-related complications; however many patients fail to meet these goals. The introduction of insulin analogs, including biphasic insulin analogs, has helped to reduce barriers to patient adherence and to improve outcomes. This review examines the clinical benefits and cost utility of biphasic insulin analogs versus other treatment approaches, in particular human biphasic insulins. Biphasic insulin analogs have a greater flexibility of dosing as compared to equivalent human insulin preparations, resulting in greater convenience and patient satisfaction, and in observational studies, improved efficacy in terms of glycemic control in patients inadequately controlled on human biphasic insulin. Biphasic insulin analogs have shown improved postprandial glucose (PPG) control and a reduced risk of hypoglycemia compared with biphasic human insulin. Treatment with biphasic insulin analogs is cost-effective versus other options in the long term. Biphasic insulin analog treatment of uncontrolled T2DM should be considered an appropriate investment of healthcare resources.

INTRODUCTION

It is well known that diabetes mellitus (DM) is associated with a huge social and economic burden, representing the third most common reason for hospitalization (as a first-listed diagnosis) in the U.S. in 2006 and accounting for 10.6 percent of hospital discharges (1). In 2005, discharge data from patients with diabetes as a first-listed diagnosis documented approximately 2.8 million days of hospital stay, corresponding to an average length of stay of 4.7 days (1).

In 2007, the costs for DM were $174 billion in the U.S., composed of $116 billion in direct medical expenditure and $58 billion attributed to lost productivity (i.e., through disability, work loss, and premature mortality) (2). Healthcare costs were also estimated to be more than twice as high in patients with diabetes versus the general population (2).

In terms of direct costs for diabetes, drug costs are only one factor for consideration and account for approximately 10 to 20 percent of such expenditure. A much larger proportion of direct costs are attributable to the costs of healthcare services directly related to DM or associated with complications of this condition. For example, a breakdown of DM costs in the U.S. in 2007 assigned amounts as follows: $27.7 million for outpatient medication and supplies, $65.8 million for institutional care, and $22.7 million for outpatient care (2).

Costs associated with episodes of hypoglycemia are a particularly important factor to be taken into consideration – approximately 90 percent of all patients who receive insulin have experienced such episodes (3). The mean cost of hypoglycemia has been estimated in two studies of claims data in patients using insulin. One study estimated the costs of moderate-to-severe hypoglycemia at $1186 per episode (4). A second study estimated annualized costs of $3241 per patient with a diagnosis of hypoglycemia (based on reimbursed prescriptions and medical encounters that are reported to third-party payers; omitted more mild episodes that did not lead to a medical consultation) (5). Of course, the burden of hypoglycemia is not purely financial, with major hypoglycemia (assistance required and potentially life-threatening if inadequately treated) placing a huge emotional strain on patients and their families. Even minor hypoglycemia (episodes that can be self-treated by consuming fast-acting carbohydrates) or fear of hypoglycemia can interfere with quality of life, adversely impact on adherence, and thereby indirectly influence treatment costs (6,7).

Cardiovascular disease (CVD) is one of the most expensive complications experienced by patients with T2DM; in one
study, subjects with both CVD and diabetes cost $10,172 per person per year, over 50 percent of which was incurred in the inpatient setting (8). In another study that compared patients with and without diabetes, direct cardiovascular (CV) costs were significantly greater in patients with diabetes for follow-up CV events subsequent to the index hospitalization and first recurrence, increasing from $8,805 in Year 1 to $12,163 in Year 3 (p≤0.0002) (9). Assessment of glycosylated hemoglobin (A1C) levels is also an important predictor of healthcare costs in diabetes. In one study, higher A1C predicted higher costs for patients with baseline A1C ≥7.5 percent (10). In addition, a modeling study estimated that the costs of treating diabetes-related complications increased considerably with relatively small increases in A1C, and these costs escalated faster at higher levels (11). Moreover, a sustained reduction in A1C level among adult diabetic patients has been associated with significant cost savings within 1 to 2 years of improvement (12).

**IMPROVING GLYCEMIC CONTROL TO REDUCE COMPLICATIONS**

Key clinical trials such as the Diabetes Complications and Control Trial (DCCT) and follow-up studies and the United Kingdom Prospective Diabetes Study (UKPDS) have shown that improving glycemic control reduces microvascular and macrovascular complications (13–16). For example, it is estimated that every percentage drop in A1C can reduce the risk of microvascular complications by almost 37 percent and the risk of DM-related mortality by 21 percent (p<0.001) (14). Based on these findings, the American Diabetes Association (ADA) and the American College of Endocrinology (ACE)/American Association of Clinical Endocrinologists (AACE) have issued recommended target levels for A1C: <7.0 and ≤6.5 percent, respectively (17–20). A management approach centered around achieving these goals and improving glycemic control may reduce the costs of DM, primarily by delaying or preventing the complications of the disease and the associated morbidity and mortality.

Despite the proven importance of achieving glycemic goals, survey data have shown that many patients fail to achieve these targets (21,22). One possible reason for this is the delay in initiating insulin that can occur with the stepwise approach to therapy in patients with T2DM (23–25). Due to the progressive loss of beta cells in T2DM, most people eventually require insulin therapy to maintain glucose control. In addition, healthcare providers and patients can be reluctant to start insulin therapy (26–28). In recent decades, insulin analogs have been developed with the aim of overcoming some of the disadvantages of conventional human insulins (29). In addition, different formulations of insulin have been developed to simplify diabetes treatment. In particular, biphasic (also referred to as premix) insulin analogs with dual-release properties provide a more convenient insulin regimen and may therefore have an important role in reducing barriers to insulin therapy and increasing patient adherence and outcomes. ACE/AACE guidelines recommend biphasic insulin formulations as one of the first-line options when A1C is >9.0 percent (18,20).

This review provides an overview of the clinical benefits and cost utility of biphasic insulin analogs compared with other treatment approaches and with human biphasic insulins in particular.

**BIPHASIC INSULIN ANALOGS**

The goal of insulin administration is to mimic normal physiologic secretion of insulin in order to control both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG). Biphasic insulin regimens use a single insulin preparation to deliver prandial and basal insulin requirements and are administered as once-, twice-, or three-times-daily injections. Human premixed insulin formulations contain 70 percent NPH and 30 percent regular human insulin as the basal and prandial components, respectively (e.g. biphasic human insulin 70/30). In contrast, biphasic insulin analogs are derived from rapid-acting insulin analogs (insulin aspart or insulin lispro) and consist of a mixture of a rapid-acting insulin analog and its intermediate-acting protaminated form (protaminated insulin aspart or protaminated insulin lispro) as the basal component (e.g. biphasic human insulin 70/30, insulin lispro mix 75/25-Mix 75/25, or insulin lispro mix 50/50-Mix).

Biphasic insulin analogs offer several advantages compared with other insulin regimens. First, these formulations are more convenient, as they mean fewer injections and less monitoring compared with basal-bolus therapy; the need for fewer injections may be easier to accept, particularly for patients first transitioning to insulin therapy. Second, the rapid-acting component of premixed insulin analogs mimics the physiological mealtime profile of insulin more closely than regular human insulin as a result of its more rapid absorption and clearance, meaning that these agents can be administered closer to mealtimes (30,31). This greater degree of flexibility in dosing time provides greater
convenience and satisfaction for patients and may result in improved adherence compared with premixed human insulin (32). Premixed insulin analogs have also been associated with fewer major hypoglycemic episodes compared with premixed human insulin (33). Finally, as discussed in more detail below, premixed insulin analogs have shown improved glycemic control compared with human insulin premixes and basal insulins.

It should be noted that the basal components of all biphasic insulins have an intermediate-acting profile rather than the more physiologic profile of the long-acting insulin analogs, insulin detemir and glargine, whose duration of action can last for up to 24 hours. As a result, premixed insulin analogs are best suited for patients with regular mealtime schedules, as patients with irregular mealtimes are more vulnerable to hypoglycemic episodes with these formulations.

USE OF BIPHASIC INSULIN ANALOGS FOR INSULIN INITIATION AND TITRATION

Although a basal-bolus regimen is the most physiologic insulin regimen, many patients with uncontrolled T2DM (A1C ≥9 percent) are reluctant to begin insulin therapy with this intensive approach. Instead, clinicians often start with less intensive regimens and then adjust as needed; for example, adding either a basal or premixed insulin to oral antidiabetic drugs (OADs). The ability to use premixed insulin analogs in once-, twice- or three-times-daily regimens provides a simple approach for initiation and titration to meet glycemic goals. Furthermore, costs may be reduced, as there is only one medication to purchase and less blood testing may be needed.

The ease of transitioning patients to insulin therapy with premixed insulin analogs has been illustrated by the 1-2-3 Study (34). In this observational study of 100 patients with T2DM inadequately controlled on oral agents with or without basal insulin, addition and self-titration of biphasic insulin aspart once, twice, or three times daily enabled 41, 70, and 77 percent of patients to achieve an A1C goal of <7.0 and 21, 52, and 60 percent of patients to achieve an A1C goal of ≤ 6.5 percent (34). In a more recent study, 150 patients with T2DM inadequately controlled using OAD therapy or existing insulin regimens were started on biphasic insulin aspart once, twice, or three times daily and self-titrated according to a predefined dosing schedule (35). The starting dose of biphasic aspart was dependent on previous insulin therapy (naive, basal or premixed) and A1C levels (<8.5 or ≥8.5 percent). After 18 months, all patients experienced significant reductions in A1C, FPG and PPG irrespective of pre-study regimen and 91 percent of patients achieved A1C <7 percent (35).

Results from several other clinical trials have indicated that the use of twice-daily premixed insulin aspart or lispro is superior to once-daily insulin glargine for lowering A1C in patients with inadequately controlled T2DM as a consequence of improved postprandial glucose control (36-40).

BIPHASIC INSULIN ANALOG INTENSIFICATION REGIMENS

INTENSIFYING FROM BASAL INSULIN

In clinical trials, intensification with biphasic insulin aspart has been shown to improve glycemic control in patients inadequately controlled on basal insulins (human or analog). This was demonstrated in two recently published observational studies in patients with T2DM: PRESENT (Physicians’ Routine Evaluation of Safety and Efficacy of NovoLog Mix 70/30 Therapy) and IMPROVE™ (41,42).

A subanalysis of the PRESENT study examined patients previously receiving analog basal insulin (AB; n=348), or human basal insulin (HB; n=3414), who were transferred to biphasic insulin aspart (42). All glycemic endpoints (A1C, FPG, and PPG) were significantly improved after 6 months irrespective of the basal insulin previously used (p<0.0001). A1C was reduced by 1.6 and 1.42 percent after AB and HB, respectively (mean A1C 7.8 and 7.9 percent, respectively), FPG by 3.73 mmol/L (67.14 mg/dL) and 2.83 mmol/L (50.94 mg/dL), respectively, and PPG by 5.86 mmol/L (105.48 mg/dL) and 5.09 mmol/L (91.62 mg/dL), respectively. In both AB and HB groups, 24 percent of patients achieved the ADA A1C target of <7 percent at 6 months.

In patients intensifying from basal human insulin, there were significant reductions in the rate of overall hypoglycemia (5.9 to 2.1; p<0.001) and minor hypoglycemia (5.6 to 2.0; p<0.001), but no significant change in those intensifying from basal insulin analog treatment. However, major hypoglycemic episodes were significantly lower after 6 months’ treatment with biphasic insulin aspart in both AB and HB groups (1.1 to 0.03; p=0.04 and 0.39 to 0.1; p<0.001, respectively) (42). The reduced risk of hypoglycemia may be a consequence of a premix insulin analog providing a more appropriate match of insulin supply to physiological need compared with basal insulin. It is important to avoid administering too much basal insulin in
an attempt to control postprandial glucose levels. It should be noted that the reductions in hypoglycemia in the subanalysis of the PRESENT study are in contrast with the increased risk of major hypoglycemia historically reported with declines in A1C following treatment with human insulin (43).

The international IMPROVE observational study investigated the safety and efficacy of biphasic insulin aspart in patients with T2DM in routine care who started insulin therapy with or switched to biphasic insulin aspart from existing insulin regimens. In an analysis of patients previously treated with basal insulin, significant mean reductions at 26 weeks were seen in IMPROVE for A1C (1.72 percent; p<0.0001), FPG (2.35 mmol/L [42.3 mg/dL]; p<0.0001) and PPG (4.36 [78.48], 3.59 [64.62] and 3.44 [61.92] mmol/L [mg/dL] for pre-breakfast, lunch and dinner, respectively; p<0.0001) for patients intensifying treatment from basal insulin (66 percent NPH and 32 percent basal insulin analog) to biphasic insulin aspart. Both major and minor hypoglycemic events also declined at 26 weeks following intensification with biphasic aspart: major events from 2.4 to 0.3 percent, and minor events from 27 to 17 percent (41).

INTENSIFYING FROM ONCE-DAILY BIPHASIC INSULIN ANALOG REGIMEN

For patients unable to achieve glycemic control with a biphasic insulin analog regimen, therapy can be intensified through a number of approaches, including increasing dose frequency from either once daily to twice daily or twice daily to three times daily, or by additional injections of a rapid-acting insulin.

A retrospective case series analysis in 12 older patients (aged 52 to 80 years) with T2DM demonstrated the benefits of increasing the frequency of biphasic insulin aspart from a twice-daily regimen to a three-times-daily regimen as an alternative to initiating a basal-bolus regimen; after 6 months, mean A1C decreased from 8.4 to 7.2 percent with only one patient having an A1C value >8 percent (33). Furthermore, no patients reported major or minor hypoglycemic episodes (33).

Switching to three-times-daily biphasic insulin aspart from a twice-daily human premix regimen has also been safely used to intensify treatment for patients inadequately controlled on twice-daily biphasic human insulin (44). In a study in patients with type 1 (28 percent) or type 2 (72 percent) diabetes, after 16 weeks, a three-times-daily biphasic aspart regimen showed significantly better glycemic control than twice-daily human biphasic insulin (A1C 8.35 vs 8.67 percent; p=0.0001). Biphasic insulin aspart three times daily was associated with a higher risk of minor hypoglycemia (relative risk, 1.58; p=0.0038). However, the overall rate of minor hypoglycemia remained low with both the analog and human insulin premixes (13.1 vs 8.3 episodes/patient year, respectively) and rates of major episodes were similar.

Findings from other studies also suggest that use of biphasic insulin analogs may provide efficacy comparable to that of basal-bolus regimens (45,46), although A1C benefits have not been demonstrated across all clinical trials because they were designed to prove noninferiority (47). Increasing the injection frequency of a single formulation of a premixed insulin analog may provide a valuable alternative to basal-bolus therapy, which requires a greater number of injections with two different insulin regimens, and in certain patients has the possibility of error.

COMPARISON OF BIPHASIC INSULIN ANALOGS WITH BIPHASIC HUMAN INSULINS

As discussed above, the faster onset of action of premixed insulin analogs compared with equivalent human insulin preparations means that these agents can be administered closer to mealtimes, therefore affording greater flexibility in dosing (30,31).

A number of comparative studies of biphasic insulin analogs and biphasic human insulin preparations have been conducted and are summarized in Table 1. In general, findings of these studies have shown that biphasic insulin analogs reduce A1C and FPG to a similar extent as biphasic human insulin, but provide improved postprandial control. Compared with biphasic human insulin, PPG reductions of 5.4 to 30.6 mg/dL have been reported for biphasic insulin aspart or biphasic insulin lispro 75/25 in clinical trials (29).
Table 1: Trials comparing glycemic control with biphasic insulin analogs and premixed human insulin formulations in patients with type 2 diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Insulin</th>
<th>No. patients</th>
<th>Duration</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boehm et al.</td>
<td>BIAsp 70/30 bid</td>
<td>268</td>
<td>12 weeks</td>
<td>A1C was similar between groups at 12 weeks</td>
</tr>
<tr>
<td></td>
<td>BIAsp 70/30 bid</td>
<td></td>
<td></td>
<td>PPG was significantly lower with BIAsp than BIH after each meal, mean difference (mg/dL) (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>BIH 70/30 bid</td>
<td></td>
<td></td>
<td>(9.24 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>BIAsp 70/30 bid</td>
<td>125</td>
<td>24 months</td>
<td>No significant difference in A1C after 24 months between BIAsp and BIH groups (p=0.01)</td>
</tr>
<tr>
<td></td>
<td>BIH 70/30 bid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceenest et al.</td>
<td>BIAsp 70/30 bid</td>
<td>604</td>
<td>16 weeks</td>
<td>Glycemic control with BIAsp was superior to BIH at 16 weeks: mean A1C 9.55% vs 9.07% (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>BIH bid</td>
<td></td>
<td></td>
<td>PPG was significantly lower with BIAsp, mean difference at 16 weeks (3.96 mg/dL) (p&lt;0.0001)</td>
</tr>
<tr>
<td>Henrikson et al</td>
<td>BIAsp 70/30 bid</td>
<td>61</td>
<td>5 days</td>
<td>PPG control was significantly superior with BIAsp compared with either BIH or BIH 17% lower (p&lt;0.001) and 16% lower (p&lt;0.002)</td>
</tr>
<tr>
<td></td>
<td>BIH 70/30 bid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inzito (51)</td>
<td>BIAsp 70/30 bid</td>
<td>425</td>
<td>24-45 weeks</td>
<td>BIAsp was as effective as BIH for A1C at 24 and 45 weeks</td>
</tr>
<tr>
<td></td>
<td>BIH 70/30 bid</td>
<td></td>
<td></td>
<td>Mean PPG was significantly lower in the BIAsp group after breakfast than in the BIH group: 73.5 vs 163.3 (p&lt;0.0001)</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>BIAsp 70/30 bid</td>
<td>131</td>
<td>12 weeks</td>
<td>A1C reductions were similar between groups: 1.3%, 1.2% and 1.1%</td>
</tr>
<tr>
<td></td>
<td>BIH 70/30 bid</td>
<td></td>
<td></td>
<td>in BIAsp, BIH and BIH, respectively</td>
</tr>
<tr>
<td></td>
<td>BIH 70/30 bid</td>
<td></td>
<td></td>
<td>PPG reductions were also similar: 31%, 27% and 26%, respectively</td>
</tr>
<tr>
<td>McGorey et al.</td>
<td>BIAsp 70/30 bid</td>
<td></td>
<td>4 weeks</td>
<td>Mean daily PPG excursion was lower for BIAsp (16.9 mmol/L) than BIH (17.5 mmol/L) (p=0.02)</td>
</tr>
<tr>
<td></td>
<td>BIH 70/30 bid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moosh et al.</td>
<td>BIAsp 70/30 bid</td>
<td></td>
<td>30</td>
<td>A1C 1.7% lower with BIAsp and 5.1% lower with treatment with BIH (p=0.04)</td>
</tr>
<tr>
<td></td>
<td>BIH 70/30 bid</td>
<td></td>
<td></td>
<td>PPG was significantly lower with BIAsp than BIH after the morning (p=0.017) and evening (p=0.013)</td>
</tr>
<tr>
<td></td>
<td>BIH 70/30 bid</td>
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<td></td>
<td></td>
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<tr>
<td>Schwartz et al.</td>
<td>BIAsp 70/30 bid</td>
<td></td>
<td>35</td>
<td>A1C improved to a significantly higher with BIAsp than with BIH 75.25 (p&lt;0.001) and BIH 50.30 (p=0.001)</td>
</tr>
<tr>
<td></td>
<td>BIH 70/30 bid</td>
<td></td>
<td></td>
<td>Mean 2-hour PPG values were 213, 186 and 159 mg/dL, respectively (p=0.05 for all regimens)</td>
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</tbody>
</table>

In a 48-week, randomized, open-label trial in patients with T2DM, the post-breakfast PPG was 29 percent lower with biphasic insulin aspart twice daily than biphasic human insulin twice daily (p<0.001) (51). Boehm et al also reported significantly lower mealtime self-measured blood glucose increases in patients with Type 1 or Type 2 diabetes treated with a twice-daily injection of biphasic insulin aspart compared with biphasic human insulin (48). The number of major hypoglycemic episodes with biphasic insulin aspart was also half that with biphasic human insulin, while in a 1-year extension of this study, there were no major hypoglycemic episodes observed with biphasic insulin aspart compared with an incidence of 10 percent with biphasic human insulin in patients with T2DM (49).

Effects of insulin lispro 75/25 compared with human insulin premix have been reported in a 6-month randomized, open-label, two-period crossover study. In this study, treatment with insulin lispro 75/25 resulted in better postprandial glycemic control after the morning and evening meals compared with treatment with premixed human insulin (54).

**SWITCHING FROM BIPHASIC HUMAN INSULINS TO BIPHASIC INSULIN ANALOGS**

Data from the PRESENT study have shown significant mean improvements in glycemic control when patients with uncontrolled glycemia were transferred from biphasic human insulin to biphasic insulin aspart, with reductions over 6 months of 1.6 percent for A1C, 2.92 mmol/L (52.56 mg/dL) for FPG and 4.75 mmol/L (85.5 mg/dL) for PPG. Incidence of hypoglycemia (episodes/patient year) was also reduced from baseline at 6 months: overall (8.9 to 2.2), major (0.7 to 0.1), minor (8.2 to 2.2), and nocturnal (2.9 to 0.5) (56).

The IMPROVE observational study also reported the effect of switching from insulin plus OAD therapy in 9,568 patients with T2DM (51 percent of whom were receiving biphasic human insulin) to biphasic insulin aspart in routine care. Improvements in glycemic control were achieved at 26 weeks, with significant reductions in all efficacy parameters (p<0.0001): 2 percent in A1C, 3.3 mmol/L (59.4 mg/dL) in FPG, 5.1 mmol/L (91.8 mg/dL) in breakfast PPG, 4.2 mmol/L (75.6 mg/dL) in lunch PPG, and 3.2 mmol/L (57.6 mg/dL) in dinner PPG (57). Significant reductions (p<0.001) in this population were also seen in rates (events/patient/year) of major hypoglycemia (0.27 to 0.02), minor hypoglycemia (8.1 to 3.2), and nocturnal hypoglycemia (2.7 to 0.6) (57). Furthermore, the proportion of patients who were extremely/very satisfied with treatment
increased from 13 percent at baseline to 59 percent at 26 weeks.

A subanalysis from IMPROVE in patients switching from human premix insulin to biphasic insulin aspart showed significant improvements in glycemic control (Figure 1) together with a reduced risk of hypoglycemia following the switch to biphasic insulin aspart (58). The mean reduction in A1C from baseline after 6 months was 1.84 percent (p<0.0001) with biphasic insulin aspart, and the percentage of patients achieving A1C <7 percent increased from 6.3 to 40.5 percent. Significant reductions (p<0.0001) were also noted in FPG (3.48 mmol/L [62.64 mg/dL]), breakfast PPG (5.48 mmol/L [98.64 mg/dL]), lunch PPG (5.17 mmol/L [93.06 mg/dL]), and dinner PPG (3.24 mmol/L [58.32 mg/dL]). Major, minor and nocturnal hypoglycemia rates were significantly reduced from baseline (all p<0.0001), irrespective of whether patients switched from human premix insulin to biphasic insulin aspart on a unit-for-unit basis or were transferred to a higher/lower dose.

**Figure 1**

Figure 1: Mean overall reductions in effectiveness parameters with biphasic insulin aspart 30 from baseline to 6 months (adapted from Shah et al. [58]).

It should be noted that although observational studies have the advantage of accessing a broader range of patients compared with randomized controlled trials and occur in “real-world” clinics, they have been viewed as having less validity than randomized, controlled trials and are thought to overestimate treatment effects (59). This assumption has been challenged, however: comparative evaluation of randomized controlled trials and well-designed observational studies (with either a cohort or a case–control design) using the same intervention suggests that the results of observational studies do not systematically overestimate the magnitude of the effects of treatment compared with those in randomized, controlled trials (59,60).

**POTENTIAL CARDIOVASCULAR BENEFITS OF BIPHASIC INSULIN ANALOGS**

Increasing evidence indicates that postprandial hyperglycemia may have a greater effect on the development of cardiovascular complications compared with elevated FPG (61). It has been noted that patients with normal FPG, but unregulated glucose tolerance, have a significantly increased risk of CV events (62). In the Diabetes Intervention Study, blood glucose after breakfast, but not fasting FPG, was identified as a predictor of myocardial infarction (MI) and mortality in newly diagnosed patients with T2DM (63). Similarly, Cavalot et al. showed that PPG is a stronger predictor of CV events than FPG, especially post-lunch (64). The effects of PPG fluctuations on endothelial function have also been investigated using surrogate inflammatory markers (65). Findings suggest that marked fluctuations in glucose seen in patients with diabetes are more damaging on endothelial function than continuously high levels, and that oxidative stress is involved in this pathway.

In terms of treatment effects, data have shown that reducing PPG with an OAD can produce a 49 percent relative risk reduction of major CV events (66), and decrease carotid intima media thickness (67), while improving impaired glucose tolerance can reduce the risk of MI (68). Similar data for insulin analog therapy from the Japanese NICE (Nippon Ultrarapid Insulin and Diabetic Complication Evaluation) study showed a cumulative decrease of 43 percent in the CV event rate between patients receiving insulin aspart and regular human insulin (6.4 vs 11.1 percent; p<0.02) (69). In this study, decreases in PPG were significantly lower in the insulin aspart group than in the human insulin group (142 vs 226 mg/dL; p<0.05), while decreases in FPG were similar (128 vs 133 mg/dL) (69).

At present, data documenting decreased postprandial glucose with reductions in CV risk with biphasic insulins are lacking. However, given that that biphasic insulin analogs reduce PPG more effectively than biphasic human insulins and basal insulin analogs (50,70), it could be hypothesized that they may help to reduce the long-term risk of cardiovascular complications. Data suggest that optimum CV benefit may be dependent on early-stage therapy initiation in T2DM. Ceriello and Testa put forward the concept of metabolic memory with respect to the reduction of CV complications, i.e. achieve early control before bad
metabolic memory develops and CV disease is firmly established (65). Further evidence for the concept of metabolic memory is provided in the UKPDS 10-year update presented by Holman et al. (71) and the subset of patients from the VADT (Veterans Affairs Diabetes Trial) study with baseline coronary artery calcium (CAC) data (72). Patients in the UKPDS study who were in the intensive arm and were randomized early in the disease to insulin and a sulphonylurea had lasting macrovascular benefits at 10 years post-study, including risk reductions for MI (15 percent, p=0.01), despite identical A1C levels during the 5 years of post-trial follow-up (71). Similarly, in the VADT study, intensive therapy was associated with decreased CV disease events in patients with low CAC scores, but not in those with high scores, i.e. before the development of more extensive coronary atherosclerosis (72). Thus, it is important to remove any barriers to early glycemic control and give consideration to the timely implementation of premix insulin analog therapy when appropriate.

COST-EFFECTIVENESS AND QUALITY OF LIFE OF BIPHASIC INSULIN ANALOGS

Hypoglycemia and weight gain, both of which can impact on quality of life, have historically been associated with intensive insulin therapy; an incidence of 28 episodes of severe hypoglycemia per 100 patients has been reported in patients with T2DM receiving human insulin for >10 years, while in the UKPDS study, intensive insulin therapy was associated with a 5-kg weight gain (73). As previously discussed in this article, biphasic insulin analogs have a more beneficial effect on hypoglycemia than both basal human insulin and human biphasic insulin (58,74), while the 1.8 percent reduction in A1C reported in the IMPROVE study in patients switching from human biphasic insulin to biphasic insulin analog therapy was achieved without weight gain (58).

A number of recent studies have reported on the cost-effectiveness of biphasic insulin analogs compared with other insulin regimens. Three of these studies have evaluated the long-term clinical and cost outcomes associated with biphasic insulin aspart compared with insulin glargine in insulin-naive patients failing OADs in the U.K. (75), the U.S. (76) and Sweden (77). These studies used data from the INITIATE clinical trial and showed that biphasic insulin aspart was associated with improved clinical outcomes and reduced costs compared with insulin glargine treatment over patient lifetimes.

The U.K.-focused study used the Center for Outcomes Research (CORE) Diabetes Model to evaluate life expectancy, quality-adjusted life years (QALY), cumulative incidence of complications, and direct medical costs over patient lifetimes for biphasic insulin aspart versus insulin glargine. Biphasic insulin aspart was associated with projected improvements in discounted life expectancy (0.19 ± 0.20 years) and quality-adjusted life expectancy (0.19 ± 0.14 QALYs), as well as reduced incidence of retinopathy and nephropathy, compared with insulin glargine. Although total lifetime direct costs were £1,319 higher with biphasic insulin aspart, the authors conclude that this option represents excellent value for money compared with insulin glargine in the U.K (75).

Similar results were seen in the U.S. setting, where improvements in glycemic control were projected to lead to gains favoring biphasic insulin aspart versus glargine in life expectancy (0.19 ± 0.24 years) and quality-adjusted life expectancy (QALE) (0.19 ± 0.17 years). Treatment with biphasic insulin aspart was also associated with reductions in the cumulative incidences of diabetes-related complications, notably in renal and retinal conditions. The incremental cost-effectiveness ratio was $46,533 per QALY gained with biphasic insulin aspart versus glargine (for patients with baseline HbA1c ≥ 8.5 percent, it was $34,916) (76).

In addition to these studies, cost-effectiveness outcomes based on data from the PRESENT and IMPROVE observational studies have recently been published and provide evidence to support the economic value of switching from human insulins to a biphasic insulin analog (78,79). Palmer et al. estimated the long-term clinical and cost consequences of switching to biphasic insulin aspart from biphasic human insulin in a Chinese population, based on data from the IMPROVE study (79). Conversion to biphasic insulin aspart was projected to improve discounted life expectancy by 0.38 years per patient (9.91 vs 9.53 years) and QALE by 0.91 (6.32 vs 5.41 QALYs). In this study, the increased medical costs associated with biphasic insulin aspart were offset by the reduction in diabetes-related complication costs over patient lifetimes, with an overall incremental cost-effectiveness ratio of 1,926 Chinese Yuan (equivalent to $282 at January 15, 2010) per QALY gained.

Using data from the Saudi Arabian PRESENT subgroup, conversion to biphasic insulin aspart from human insulin was projected to increase life expectancy by 0.62 years (11.77 vs 11.15 years) and QALE by 0.96 (7.03 vs 6.07)
QALYs. Direct medical cost savings of Saudi Arabian Riyals 53,879 (equivalent to $14,367 at January 15, 2010) per patient were projected for conversion to biphasic insulin aspart therapy. Cost savings were largely the result of lower costs of hypoglycemia and renal complications (78).

A further pan-European study (Denmark, Finland, Germany, Norway, Spain, Sweden, and the U.K.) has illustrated how biphasic insulin aspart is associated with reduced hypoglycemia-related healthcare costs compared with biphasic human insulin (80). Using the CORE Diabetes Model, biphasic insulin aspart improved QALY by 0.15 to 0.22 years over biphasic human insulin, depending on country. Treatment with biphasic insulin aspart was projected to result in additional QALYs and reduced healthcare costs associated with major hypoglycemic events. Although acquisition costs were higher, the incremental cost per QALY was in the range generally considered to be cost-effective in each country (80).

Adherence to insulin among patients with T2DM has been estimated at 62 to 64 percent (81). Medication nonadherence can negatively impact on treatment costs: one study reported that a 10 percent increase in MPR (medication possession ratio) in patients with DM was associated with a reduction in total healthcare costs of 8.6 percent (82). Biphasic insulin preparations can simplify treatment and require fewer injections and less monitoring than a basal-bolus regimen (83). Given the higher patient satisfaction with biphasic insulin analogs over biphasic human insulins, and the fact that the analog formulations allow more flexible injection timing (32,84), biphasic insulin analogs have the potential to increase adherence-related cost reduction, although direct evidence for this relationship has yet to be shown.

CONCLUSIONS
Biphasic insulin formulations containing both basal and prandial insulin provide an attractive option for patients requiring insulin therapy. Data suggest that biphasic insulin analogs are superior to long- or intermediate-acting insulin in obtaining good metabolic control. They are also considered an attractive alternative to classical basal-bolus therapy, as fewer daily injections are required with only one insulin formulation.

Comparative studies of biphasic insulin analogs and biphasic human insulin preparations have shown that biphasic insulin analogs provide improved postprandial control compared with biphasic human insulin preparations and reduce the number of hypoglycemic episodes. Biphasic insulin analogs can also be administered closer to mealtimes compared with premixed human insulin preparations, affording the patient greater flexibility with mealtime dosing.

The improved balance between glycemic control and the risk of hypoglycemia with biphasic insulin analogs compared with biphasic human insulin also means that these agents have the potential to reduce the costs of treatment of hypoglycemia, hospitalization, and chronic complications, provided they are used in patients with regular eating patterns.

Available pharmacoeconomic modeling studies have shown that treatment with biphasic insulin analogs is cost-effective versus other options in the long term. The use of biphasic insulin analogs for treatment of T2DM should therefore be considered an appropriate investment of healthcare resources.

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CONFLICT OF INTEREST STATEMENT
Author has served on the speaker’s bureau and advisory board for Novo Nordisk. Author has also served on the speaker's bureau for Merck and Daichi Sankyo (not on the subject of insulin).

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Author Information
Joseph M Tibaldi, MD