Review Article

Efficacy and safety of biphasic insulin aspart and biphasic insulin lispro mix in patients with type 2 diabetes: A review of the literature

Ajay Kumar

Diabetes Care and Research Centre, Patna, Bihar, India

ABSTRACT

Type 2 diabetes (T2D) represents an escalating burden worldwide, particularly in China and India. Compared with Caucasians, Asian people with diabetes have lower body mass index, increased visceral adiposity, and postprandial glucose (PPG)/insulin resistance. Since postprandial hyperglycemia contributes significantly to total glycemic burden and is associated with heightened cardiovascular risk, targeting PPG early in T2D is paramount. Premixed insulin regimens are widely used in Asia due to their convenience and effectiveness. Data from randomized controlled trials and observational studies comparing efficacy and safety of biphasic insulin aspart 30 (BIAsp 30) with biphasic insulin lispro mix (LM 25/50) and versus other insulin therapies or oral antidiabetic drugs (OADs) in T2D demonstrated that BIAsp 30 and LM 25/50 were associated with similar or greater improvements in glycemic control versus comparator regimens, such as basal–bolus insulin, in insulin-naïve, and prior insulin users. Studies directly comparing BIAsp 30 and LM 25 provided conflicting glycemic control results. Safety data generally showed increased hypoglycemia and weight gain with premixed insulins versus basal–bolus insulin or OADs. However, large observational trials documented improvements in glycated hemoglobin, PPG, and hypoglycemia with BIAsp 30 in multi-ethnic patient populations. In summary, this literature review demonstrates that premixed insulin regimens are an appropriate and effective treatment choice in T2D.

Key words: Biphasic insulin aspart, biphasic insulin lispro mix, postprandial glucose, premixed insulin, type 2 diabetes

Introduction

Diabetes management guidelines focus on treatment individualization, including ethnic/cultural needs and risk of hypoglycemia and weight gain.[1] Asian patients have higher postprandial glucose (PPG) levels compared with other regional groups[2] and currently, a large proportion of Asian patients with type 2 diabetes (T2D) are treated with human premixed insulin.[3] This review examines studies of efficacy and safety involving insulin analogs, biphasic insulin aspart 30 (BIAsp 30), and biphasic insulin lispro mix (LM 25/50).

Corresponding Author: Dr. Ajay Kumar, Diabetes Care and Research Centre, GC1B, Near Over Bridge, Kankarbagh, Patna - 800 020, Bihar, India. E-mail: drajaykr@yahoo.com

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.179993

Diabetes: An Ever-increasing Public Health Burden

Globally, the number of people with diabetes continues to rise year on year, providing a major challenge to public health and an enormous economic burden.[1,4] The International Diabetes Federation estimates 382 million people globally had diabetes in 2013, with more than 160 million from China and India alone.[4] T2D accounts for approximately 90% of all cases worldwide, and a worrying

Cite this article as: Kumar A. Efficacy and safety of biphasic insulin aspart and biphasic insulin lispro mix in patients with type 2 diabetes: A review of the literature. Indian J Endocr Metab 2016;20:288-99.

trend is the increasing diagnosis of T2D in children and adolescents.[5]

In addition to economic development, rapid transitions to Western lifestyles, and increasing obesity rates,[4,6] other more inherent reasons might explain the escalating burden of T2D in regions such as Asia.[2,7-11] For example, in a study of healthy lean individuals, Asian patients had higher PPG levels and lower insulin sensitivity than Europeans in response to a 75 g carbohydrate load.[2] A change in dietary patterns from traditional high-fiber, low-fat diets to Westernized diets (i.e. high intake of fats, carbohydrates, and trans-fatty acids) has been linked to postprandial hyperglycemia and hyperinsulinemia.[11]

Importance of Targeting Postprandial Glucose

While T2D therapy is directed toward lowering glycated hemoglobin (HbA1c) levels with emphasis on fasting plasma glucose (FPG), targeting PPG excursions is also important for achieving HbA1c goals.[12] In T2D, the contribution of PPG toward total glycemic burden is enormous at any level of glycemic control. Furthermore, PPG contribution relative to FPG is greatest when HbA1c is <7.5%,[13] yet many patients experience significant PPG excursions even in the context of good glycemic control according to HbA1c and FPG.[14,15]

PPG elevations are detectable early in T2D progression.[12] They result from loss of first-phase insulin secretion, decreased insulin sensitivity in peripheral tissues, and diminished suppression of hepatic glucose output after meals due to insulin insufficiency.[12,16] Since postprandial hyperglycemia is an earlier biochemical abnormality than fasting hyperglycemia,[17] any treatment strategy addressing PPG may help to reduce the risk of complications.[18] In the presence of insulin resistance, fasting insulin response is maintained in early T2D, while insulin response to meal-related hyperglycemia is inadequate,[17] highlighting the importance of targeting PPG early in the disease course.[18] Epidemiological study data have demonstrated a correlation between poor PPG control and development of cardiovascular disease,[19] retinopathy, cognitive dysfunction, and cancer.[12]

Treatment Options: Rationale for Premixed Insulin

The progressive decline in β-cell function, which occurs years before T2D is diagnosed,[20] means that many patients will eventually require insulin,[1,21] long considered the most effective antihyperglycemic medication available.[22] Substantial barriers to initiating insulin include the fear of hypoglycemia and weight gain;[23] it is therefore important to weigh glycemic benefits and hypoglycemia/weight gain risk when choosing an insulin regimen. There are three types of insulin therapy available for T2D: basal only, basal plus prandial (with premixed insulin or self-mixed basal–bolus insulin), and prandial only. While basal insulin is recommended in Europe and the USA, premixed insulin is the initial choice for 75% of South Asian patients[24] and the most widely prescribed treatment in Asia.[3] The simple nature of the regimen suits its use in primary care practice and in populations with different dietary habits and cultures; these constitute key reasons for its widespread use in Asia.[3,25,26] Premixed insulins comprise basal and prandial insulins in one injection, making them convenient to administer. Treatment can be intensified from once (od) to 3 times daily (tid) and can be used in insulin-naive patients.[27,28]

Literature Appraisal

This review summarizes randomized controlled trials (RCTs) and observational studies evaluating efficacy and safety of two commonly used premixed insulin analogs for T2D: BIAsp 30 and LM 25/50. A literature search was conducted using PubMed with the search terms "efficacy and safety of BIAsp odds ratio (OR) BIAsp in type 2 diabetes" and "efficacy and safety of biphasic insulin LM OR Humalog Mix in type 2 diabetes" over the past 10-year (as few citations were retrieved for BIAsp 30 vs. LM 25 with the 10 years filter, the literature analysis included one paper from 2002). The initial search returned 88 citations (BIAsp, 63; LM, 25). Articles were excluded if they evaluated only patient-reported outcomes, were *post hoc* analyses not relevant to the focus of this review, or they comparative studies with incretin mimetics. Cost-benefit analyses are important; however, the inclusion of these was beyond the scope of the current review. While insulin pump therapy is available in India,[29] relevant studies are not discussed as neither BIAsp 30 nor LM 25/50 is approved for insulin pump use.

Biphasic Insulin Aspart 30

BIAsp 30 comprises 30% soluble rapid-acting insulin aspart (IAsp; prandial component) and 70% intermediate-acting crystallized protamine-complexed IAsp (basal component).[30] BIAsp 50 and BIAsp 70 are available for patients who require more prandial insulin; however, these formulations are not the focus of this review. BIAsp 30 is a well-established T2D treatment, available

since 2002, which is associated with a wealth of clinical data from RCTs and observational studies of its efficacy and safety compared with other oral glucose-lowering therapies in a diverse range of patient populations.

Overview of Randomized Controlled Trials of Biphasic Insulin Aspart 30

Compared with basal and basal–bolus insulin regimens

Table 1 provides an overview of efficacy and safety data for BIAsp 30 compared with basal or basal–bolus insulin collated from 11 RCTs in patients of differing ethnicities.[31-40] Notably, there tended to be greater HbA1c reductions in studies comparing BIAsp 30 and the basal insulin glargine in insulin-naive patients.[31-34] Yang *et al.* reported that BIAsp 30 was noninferior to glargine in an Asian population and demonstrated significantly lower PPG levels 2 h postmeal) without increased risk of hypoglycemia or weight gain.[35] Comparisons of BIAsp 30 and basal–bolus regimens meanwhile showed similar (nonsignificant treatment-group differences) HbA1c reductions.[38,39]

As might be expected, greater reductions in glucose levels were associated with an increased risk of hypoglycemia (in all but one study).[34] Where a significantly greater reduction in HbA1c was reported for BIAsp 30 than glargine, more patients experienced a hypoglycemic event (HE) (minor) or there was a greater relative risk of an event.[31-33] In terms of change in body weight, BIAsp 30 and all comparators led to an increase from baseline, with no difference between study groups.[31-40]

Compared with biphasic human insulin

In all but one study, there was no significant difference in HbA1c between BIAsp 30 and biphasic human insulin (BHI) [Table 2].[41-44] In one single-center study of obese, insulin-naive patients with T2D, a significant difference in change in HbA1c from baseline favored BIAsp 30 combined with metformin at 3 months.[45]

Significant differences favoring BIAsp 30 over BHI 30 were reported for PPG levels in the three studies evaluating this measure.[42,44,46] In terms of safety, there were generally no treatment differences for weight change or hypoglycemia [Table 2]. An exception was a 24-month study, which demonstrated a significant reduction in year 2 with BIAsp 30 twice daily (bid) versus BHI 30 bid for major hypoglycemia.[41] Also in terms of safety, a Japanese study found switching from BHI 30 to BIAsp 30 was associated with improved postprandial hyperglycemia (measured by 1,5-anhydroglucitol) and decreased cardio-ankle vascular index (a reflection of arterial stiffness).[47]

Compared with oral glucose-lowering therapies

Most of the studies comparing BIAsp 30 od, bid, or tid with oral antidiabetic drugs (OADs) reported a significant HbA1c reduction favoring premixed insulin regimens [Table 3].[48-51] These studies demonstrated additional benefits for BIAsp 30 over comparator OADs in terms of PPG levels [Table 3]. One study comparing BIAsp 30 bid with glibenclamide (both plus metformin) in patients uncontrolled on prior OADs demonstrated no treatment difference in glycemic control.[52] Nevertheless, in a subgroup of patients with HbA1c ≥9% at baseline, BIAsp 30 was associated with significantly greater glycemic control than glibenclamide plus metformin ($P < 0.05$).

In general, few major HEs were reported for treatments; however, BIAsp treatment tended to be associated with more minor HEs.[48-51] Likewise, the effect on weight favored OADs, including glibenclamide plus metformin and metformin/pioglitazone, over BIAsp.[49-52]

Overview of Key Observational Studies of Biphasic Insulin Aspart 30

While RCTs provide the most rigorous means of determining a cause-effect relationship between treatments and outcomes,[53] observational, nonrandomized studies have an important and complementary role, allowing recruitment of larger patient cohorts in a setting more closely reflecting clinical practice. As such, they can help corroborate RCT results.

A number of such studies (i.e. IMPROVE[54] and PRESENT[55]) have examined the safety and effectiveness of BIAsp 30 across different countries and ethnicities. Collectively, these 6 months trials demonstrated improved glycemic control, as shown by reductions in HbA1c, FPG, and PPG levels from baseline, in patients initiating insulin with, or switching to, BIAsp 30.[54,55] Similar findings have been observed in the A_1chieve study, a prospective, multicenter, open-label, noninterventional, 24-week study of 66,726 patients from 30 countries across four continents, using insulin analogs (including BIAsp 30, insulin detemir, and IAsp).[56] Numerous country-specific findings from A_1chieve have shown improvements from baseline to week 24 in HbA1c, PPG, hypoglycemia, and quality of life.[57-60]

Biphasic Insulin Lispro Mix 25/50

LM 25 comprises 25% rapid-acting insulin lispro and 75% intermediate-acting insulin lispro protamine suspension. Also available is LM 50, which comprises 50% rapid-acting lispro and 50% lispro protamine suspension.[61] Numerous

Table 1: Randomized controlled trials comparing biphasic insulin aspart 30 with (a) basal and (b) basal–bolus insulin regimens in type 2 diabetes

Reference	Study design	Patients	BIAsp 30 versus comparator(s)			
			HbA1c	PPG	Hypoglycemia	Mean body weight change
(a) basal						
Raskin *et al.*[31]	28-week, OL, MC, R; BIAsp 30 bid (n=117) versus glargine od (n=116)	Insulin-naive, uncontrolled on OADs (n=233)	Significantly greater reduction with BIAsp 30 versus glargine (−2.79 vs. −2.36, P<0.01) 66% versus 40% achieved HbA1c target <7% (P<0.001)	Sum of three prandial PG increments: 97.4 versus 129.6 mg/dL (P<0.05)	Minor: 43% versus 15% (P<0.05) Major: 1 episode (glargine)	Increased in both groups: 5.4 kg versus 3.5 kg (P<0.01)
Kann *et al.*[32]	26-week, M, O-L, R; BIAsp 30 bid + metformin (n=128) versus glargine od + glimepiride (n=127)	Insulin-naive (n=258)	Significantly greater reduction with BIAsp 30 versus glargine (between treatment difference −0.5%; (P=0.0002)	Mean prandial PG increment: 1.4 mmol/L versus 2.2 mmol/L (P=0.0002)	Minor: 20% versus 9% (P<0.05) Major: 1 episode in each group	0.7 kg versus 1.5 kg (P<0.0001 vs. baseline for comparator only)
Strojek *et al.*[33]	26-week, M, O-L, R, P-G; BIAsp 30 od (n=239) versus glargine od (n=241) both combined with metformin + glimepiride	Insulin-naive (n=480)	Significantly greater reduction with BIAsp 30 versus glargine (between-treatment difference −0.16%; P=0.029) Greater between-treatment difference in Asian versus Caucasian population (P<0.016)†	Lower PG levels postdinner (treatment difference −0.52 mmol/L; P=0.04) and at bedtime (−0.78 mmol/L; P<0.01)	RR of any HE: 6.5 ep/year versus 4.8 ep/year (1.41; P=0.034) No difference between treatments in Asian sub-population	No difference between treatments (data not reported)
Kalra *et al.*[34]	26-week, M, O-L, R, P-G; BIAsp 30 od (n=76) versus glargine od (n=79), both combined with metformin + glimepiride	Asian, insulin-naive (n=155)	Significantly greater reduction with BIAsp 30 versus glargine: −1.22% versus −0.87% (between-treatment difference −0.36%; P=0.015)	PG at bedtime was lower with BIAsp 30 (P=0.0078)	Minor: 39.5% versus 30.4% (P=NS) Major: 1.3% versus 2.5% (P=NS)	Increased in both groups: 0.80 kg versus 1.16 kg (P=NS)
Yang *et al.*[35]	24-week, M, R, O-L, P-G; BIAsp 30 od (n=261) versus glargine od (n=260), both combined with metformin + glimepiride	Chinese and Japanese insulin-naive (n=521)	Noninferiority demonstrated with BIAsp 30 versus glargine (between-treatment difference −1.28 mmol/mol)	Lower PG levels postdinner: 1.51 mmol/L treatment difference (P<0.001)	All HEs: 59.4% versus 56.9% (P=NS)	Between-treatment difference (−0.12 kg; P=NS)
Holman *et al.*[36]‡	3-year, O-L, R, M; BIAsp 30 bid (n=235), prandial IAsp tid (n=239), basal IDet od or bid (n=234)	Uncontrolled on OADs (n=708)	No significant difference between treatments (−1.3 vs. −1.4 [IAsp] and −1.2 [IDet]; P=NS) 49.4% versus 67.4% (P<0.001) and 63.2% (P=0.02), respectively, achieved HbA1c target ≤7%	−61 mg/dL versus −85 mg/dL [IAsp; P<0.001] and −67 mg/dL [IDet; P=0.04]	No significant difference between groups: 49.4% (BIAsp) versus 51.0% (IAsp) and 44.0% (IDet)	Increased in all groups: 5.7 kg versus 6.4 kg [IAsp] and 3.6 kg [IDet; P=0.005 vs. BIAsp]
Ligthelm *et al.*[37]	24-week, O-L, P-G, R; BIAsp 30 bid + metformin versus glargine od + metformin and secretagogs	Uncontrolled on basal insulin + OADs (n=137)	No significant difference between treatments: −1.3% versus −1.2% (difference of −0.06%; P=NS)	Glucose increment averaged over 3 meals was lower with BIAsp 30 (treatment difference: −17.8 mg/dL; P=0.001)	Minor: 6.4 events/patient/year versus 3.4 events/patient/year (P<0.05)	Increased in both groups: 3.1 kg versus 1.4 kg (P=0.0004)
(b) basal–bolus						
Ligthelm *et al.*[38]	16-week, OL, MC, R; BIAsp 30 tid (n=196)* versus basal-bolus (IAsp + NPH qid; n=198)	Uncontrolled on od or bid insulin (n=394)	Non-inferiority demonstrated with BIAsp vs comparator: Mean HbA1c at week 16: 7.81 versus 7.86% (P=NS)	No significant difference in prandial PG increment profiles	No significant difference in HEs: Major: 3.1% versus 1.0% (P=NS)	~2 kg increase in both treatment groups
Hirao *et al.*[39]	6-month, M, O-L, R; BIAsp 30 bid (n=80) versus IAsp tid±NPH (multiple injections) (n=80)	Japanese, insulin-naive (n=160)	No significant difference between treatments: reduction of ~2.5% in both treatment groups (P=NS)	No data reported	No major HEs reported	Increase in BMI: 1.47 kg/m^2 versus 0.69 kg/m^2 (P<0.05)

Contd...

Table 1: Contd...

			(b) basal-bolus			
Reference	**Study design**	**Patients**	**BIAsp 30 versus comparator (s)**			
			HbA1c	**PPG**	**Hypoglycemia**	**Mean body weight change**
Liebl *et al.*[40]	26-week, M, R; BIAsp 30 bid (n=178) versus basal-bolus (IDet od + IAsp at mealtimes; n=541)	Uncontrolled on OADs (n=719)	Significantly less reduction with BIAsp 30 versus comparator. Reduction in both groups: −1.23% versus −1.56% (P=0.0052) 50% versus 60% achieved HbA1c target ≤7% (P value not reported)	Lower with comparator: Treatment difference: 0.63 (P<0.05), 1.81 mmol/L and 0.76 mmol/L (P<0.001) after breakfast, lunch, and dinner, respectively	Major: 0% versus 0.9% Minor: 28% versus 31% (P values not reported)	Increased in both groups: 2.1 kg versus 2.4 kg (P=NS)

*Patients randomized to BIAsp were treated according to individual needs using BMI as a surrogate index of insulin resistance: BIAsp 70 (BMI ≤30 kg/m²) or BIAsp 50 (BMI >30 kg/m²) with breakfast and lunch and BIAsp 30 with dinner); †*post hoc* analysis; ‡*P* values for IAsp versus IDet not given in table for brevity. BIAsp: Biphasic insulin aspart, bid: Twice daily, HE: Hypoglycemic episode, IAsp: Insulin aspart, IDet: Insulin detemir, od: Once daily, NPH: Neutral protamine Hagedorn, OAD: Oral antidiabetic drug, OL: Open-label, qid: Four times daily, MC: Multicenter, BMI: Body mass index, P-G: Parallel-group, PG: Plasma glucose, PPG: Postprandial glucose, R: Randomized, S-C: Single-center, T2D: Type 2 diabetes, tid: Three times daily, HbA1c: Glycated hemoglobin, NS: Not significant

reports from RCTs and observational studies, albeit fewer than recovered for BIAsp, demonstrate the efficacy and safety of LM 25 and LM 50 in T2D in Eastern and Western patient populations.[62-71] The following provides a brief review of findings for insulin-treated and insulin-naive patients.

Overview of Randomized Controlled Trials of Lispro Mix 25/50

Compared with basal and basal–bolus insulin regimens

Table 4 outlines key results of studies of LM 25 and LM 50 compared with basal or basal–bolus insulin regimens in patients uncontrolled on prior therapy with/without insulin. In studies comparing LM 25 or LM 50 with glargine, greater HbA1c reductions were reported, and PPG control was significantly improved with premixed insulin.[62,64,66,69] In the 24-week initiation phase of the Durability of Basal versus LM 75/25 Insulin Efficacy (DURABLE) study comparing LM 25 bid with glargine od, each in addition to OADs, LM 25 significantly decreased HbA1c and was associated with lower PPG levels after morning and evening meals.[66] However, the incidence of hypoglycemia was significantly greater with LM 25, as was weight gain. In the maintenance phase of DURABLE, patients reaching target HbA1c ≤7.0% at the end of the 24-week initiation phase were monitored for up to an additional 24 months.[68] This long-term follow-up showed a significantly greater proportion of patients treated with LM rather than insulin glargine maintained HbA1c goals and maintained goals for significantly longer. Furthermore, at study end, there was no difference between treatments regarding hypoglycemia and weight gain. In a recent *post hoc* analysis of DURABLE that examined the impact of race/ethnicity on the efficacy and safety of insulin regimens, significant differences were observed in the degree of reduction in HbA1c (smaller) and the proportion of patients reaching glycemic targets of <7% (fewer) in Asian compared with Caucasian patients.[71] Moreover, weight gain and rate of hypoglycemia were lower in Asian patients irrespective of treatment. These results demonstrate that racial/ethnic differences in outcomes are important considerations when designing insulin-based treatment plans.

Of three studies comparing LM 25 or LM 50 with glargine plus lispro, two showed no significant differences in HbA1c levels,[67,70] and one showed significantly better reduction with the basal–bolus regimen over LM 50 tid.[63]

Compared with biphasic human insulin or oral glucose-lowering therapies

The literature search failed to retrieve any relevant publications assessing LM 25/LM 50 with BHI or with OADs.

Overview of Key Observational Studies of Lispro Mix 25/50

As the literature search did not retrieve any observational studies evaluating LM 25, LM 50 is the focus of this section.

The effect of LM 50 tid versus lispro tid plus sulfonylureas (SUs) was evaluated over 24 weeks in an observational, interventional trial of 31 Japanese patients with T2D poorly controlled with submaximal SU doses.[72] While there was a significant improvement in HbA1c from baseline to week 24 in both treatment groups (P < 0.00001), a similar proportion of patients achieved target HbA1c <7.0% (LM 50, 67%; prandial–bolus, 69%). Significantly fewer minor HEs occurred with LM 50 versus lispro (0.60 vs. 4.48 episodes/person/year; P = 0.03); however, weight gain significantly increased from baseline with the premixed treatment (P < 0.05) but remained unchanged in the comparator group.

Table 2: Randomized controlled trials comparing biphasic insulin aspart 30 and biphasic human insulin 30 in type 2 diabetes

Reference	Study design	Patients	BIAsp 30 versus comparator			
			HbA1c	PPG	Hypoglycemia	Mean body weight change
Velojic-Golubovic *et al.*[45]	3-month, S-C; BIAsp 30 bid (*n*=20) versus BHI 30 bid (*n*=30), each + metformin	Insulin-naive, obese (*n*=50)	Significant difference between BIAsp 30 versus BHI 30: decrease from baseline −2.50% versus −1.18% (treatment difference 1.33%; *P*<0.05) 65% versus 30% metformin <7% target (*P*<0.05)	Decreased by 6.38 mmol/L versus 4.34 mmol/L (*P*<0.05)	Total: 6 episodes (1 major) versus 14 episodes (4 major); *P*=NS	0.3 kg versus 1.2 kg (*P* value not reported)
Boehm *et al.*[41]	24-month (initial 3 months + 21-month extension), MC, R, C; BIAsp 30 bid (*n*=58) versus BHI 30 bid (*n*=67)	*n*=190 (*n*=125 entered extension)	No significant difference between BIAsp 30 and BHI 30 at 24 months (BIAsp-BHI: 0.03%; *P*=NS)	Not reported	Major HEs Year 1: 5% versus 8% (*P*=NS) Year 2: 0% versus 10% (*P*=0.04)	0.05 kg versus 2.00 kg (*P*=NS)
Abrahamian *et al.*[42]	24-week, M, O-L, R, P-G; BIAsp 30 tid (*n*=89) versus BHI 30 bid (*n*=88)	*n*=177	No significant difference between BIAsp 30 versus BHI: Decreased from 9.8% at baseline to 7.6% versus 7.7% after 24 weeks (*P*=NS)	Postlunch: 156 mg/dL versus 176 mg/dL (*P*=0.0289); postdinner: 154 mg/dL versus 182 mg/dL (*P*=0.0022)	Minor: 130 episodes versus 185 episodes (*P* value not reported) Major: 2 episodes versus 0 episodes	Not reported
McNally *et al.*[43]	M, R, D-B, 2-period (2×16 weeks), crossover; BIAsp 30 bid (*n*=80) versus BHI 30 bid (*n*=80)	Pretreated with insulin (*n*=160)	No significant difference between treatment arms: Decreased from 7.46% to 7.28% versus 7.22% (between-treatment difference 0.06%; *P*=NS)	Not reported	Minor: 90% versus 84% Major: 2 episodes versus 7 episodes (no *P* value reported)	Not reported
Temizel *et al.*[44]	1-year, retrospective; BIAsp 30 bid (or biphasic insulin lispro) (*n*=71) versus BHI 30 bid (*n*=69)	*n*=140	No significant difference between premixed insulin and BHI 30	Not reported	Mild: 0.72 events/person/month versus 0.65 events/person/month (*P*=NS) Severe: 0.06 events/person/month versus 0.04 events/person/month (*P*=NS)	Increased in both groups: 2.08 kg versus 2.29 kg (*P*=NS)
Schmoelzer *et al.*[46]	S-C, OL, R, crossover; BIAsp 30 od versus BHI 30 od	*n*=12 already receiving premix insulin	Not reported	Maximum increase of PPG reduced (5.27 mmol/L vs. 7.10 mmol/L; *P*=0.007)	Not reported	Not reported

BIAsp: Biphasic insulin aspart, BHI: Biphasic human insulin, bid: Twice daily, D-B: Double-blind, HE: Hypoglycemic episode, od: Once daily, OL: Open-label, MC: Multicenter, P-G: Parallel-group, PPG: Postprandial glucose, R: Randomized, tid: Three times daily, S-C: Single-center, T2D: Type 2 diabetes, HbA1c: Glycated hemoglobin, NS: Not significant

Comparative Studies of Biphasic Insulin Aspart 30 and Lispro Mix 25/50

Despite the breadth of data available for premixed insulin regimens, there are very few data comparing BIAsp 30 with LM 25 or LM 50. Indeed, in the last 15 years (search criteria extended for these data), just three studies have been published comparing these therapies.[73-75]

In an open-label, randomized, single-dose, three-way crossover trial, 61 insulin-treated patients received BIAsp 30, BHI 30 or LM 25 immediately before a test meal.[73] PPG control assessed by serum glucose excursions 0–5 h postmeal was significantly improved with BIAsp 30 versus BHI 30 and LM 25, with PPG levels 17% lower compared with BHI 30 (16.6 vs. 20.1 mmol/L; $P < 0.001$) and 10% lower compared with LM 25 (16.6 vs. 18.9 mmol/L; $P < 0.05$). A total of 53 HEs were reported, most of which were mild. By contrast, a 12-week, open-label, two-period, crossover study in 137 patients who had previously received insulin demonstrated no significant difference between BIAsp 30 bid and LM 25 bid in glycemic control, with treatments providing comparable reductions in HbA1c at week 12.[74] There were also no significant treatment differences for hypoglycemia (BIAsp 30, 0.69 episodes/month; LM 25, 0.62 episodes/month; P = NS).

Table 3: Randomized controlled trials comparing biphasic insulin aspart 30 and oral glucose-lowering therapies in type 2 diabetes

Reference	Study design	Patients	HbA1c	PPG	Hypoglycemia	Mean body weight change
Raz *et al.*[48]	18-week, MC, R, O-L, P-G; BIAsp 30 bid + PIO (*n*=93) versus GLIB + PIO (*n*=93) and BIAsp 30 bid (*n*=97)	Uncontrolled on SU (GLIB) (*n*=283)	Significant difference between BIAsp 30 + PIO versus GLIB + PIO (−0.64%; *P*=0.005) and between BIAsp 30 + PIO versus BIAsp 30 (−0.60%; *P*=0.008)	Postbreakfast, postlunch, and postdinner lower with BIAsp + PIO versus GLIB + PIO (*P*<0.05); postdinner versus BIAsp 30 (*P*<0.05)	No major HEs Minor HEs: 15% (BIAsp 30 + PIO) versus 3% (GLIB + PIO) and 12% (BIAsp 30); no *P* values reported	Not reported
Bebakar *et al.*[49]	26-week, MC, O-L, R; BIAsp 30 (od with uptitration to bid)† + OAD (*n*=128) versus OAD mono (*n*=63)	Insulin-naive (*n*=191)	Significant greater reduction with BIAsp 30 od versus OAD mono and with BIAsp 30 od versus OAD mono: (BIAsp 30 od −1.24% and BIAsp 30 bid −1.34% vs. OAD mono −0.67%; *P*<0.01)	Greater reductions at Week 13 with BIAsp 30 od after morning and evening meals (*P*<0.05) Week 26 with BIAsp 30 bid after breakfast (*P*<0.05) and BIAsp 30 od after dinner (*P*<0.05)	54% versus 30% (*P*<0.005) - all classified as minor except one major HE in each group	Increase with BIAsp 30 od and bid versus decrease with OAD (0.96 kg and 1.53 kg vs. −0.18 kg; *P*<0.005)
Raskin *et al.*[50]	34-week, MC, O-L, P-G, R; BIAsp 30 bid + metformin/PIO (*n*=102) versus metformin/PIO (*n*=98)	Insulin-naive (*n*=200)	Significantly greater reduction with BIAsp 30 versus OADs (change from baseline −1.5% vs. −0.2%; *P*<0.0001) HbA1c ≤6.5%: 59% versus 12% (*P*<0.001); <7.0%: 76 versus 24% (*P*<0.001)	Reduced with BIAsp 30 at all-time points (*P*<0.05 vs. metformin/PIO)	Minor: greater with BIAsp 30 (8.3 episodes/patient year vs. 0.1 episodes/patient year; *P*<0.05) Major: 4 episodes with BIAsp 30	Greater increase with BIAsp 30 (4.6 kg vs. 0.8 kg; *P*<0.001)
Ushakova *et al.*[51]	16-week, MC, R, OL-L, P-G; BIAsp 30 tid (*n*=104), BIAsp 30 bid + metformin (*n*=100) versus OADs (*n*=104)	Insulin-naive, uncontrolled on OADs (*n*=308)	Significantly greater reduction with BIAsp 30 and BIAsp 30 + metformin versus OADs (−2.9% and −3.0%, respectively, vs. −2.1%; both *P*<0.001)	Improved with BIAsp 30 and BIAsp 30 + metformin (−6.32 and −6.44 mmol/L vs. −3.59 mmol/L; both *P*<0.001)	No major HEs Minor: 4 and 9 episodes (BIAsp 30 and BIAsp 30 + metformin) versus 1 episode	Increased with BIAsp 30 and BIAsp 30 + metformin (1.71 kg and 1.50 kg) versus −0.75 kg
Kvapil *et al.*[52]*	16-week, MC, OL, R, P-G; BIAsp 30 bid + metformin (*n*=108) versus GLIB + metformin (*n*=114) and BIAsp 30 bid (*n*=107)	Uncontrolled on metformin (*n*=341)	No significant difference with BIAsp 30 versus GLIB + metformin (0.20%; *P*=NS) Significantly lower for BIAsp 30 + metformin versus BIAsp 30 (−0.39%; *P*=0.007)	No significant difference between groups, except postlunch (−0.74 mmol/L with GLIB + metformin vs. BIAsp 30; *P*<0.05)	No major HEs Minor HEs: 23 episodes (BIAsp 30 + metformin) versus 28 (GLIB + metformin) and 20 episodes (BIAsp 30); *P*=NS	Weight increased in all groups; greater with BIAsp 30 versus GLIB + metformin (*P*<0.001)

*Total population results included only; †If HbA1c >8.5% or fasting plasma glucose >7 mmol/L at week 14. BIAsp: Biphasic insulin aspart, bid: Twice daily, GLIB: Glibenclamide, HE: Hypoglycemic episode, od: Once daily, OL: Open-label, MC: Multicenter, P-G: Parallel-group, PIO: Pioglitazone, PPG: Postprandial glucose, R: Randomized, SU: Sulfonylurea, T2D: Type 2 diabetes, tid: Three times daily, HbA1c: Glycated hemoglobin, OAD: Oral antidiabetic drug, NS: Not significant

The third study was not a direct comparison of efficacy between BIAsp 30 and LM 25 or LM 50, but a comparison of LM 50 tid compared with progressive titration of LM 25 or BIAsp 30 bid, administered together with metformin.[75] This 16-week, randomized, parallel-group study of 302 patients failing to achieve glycemic control with BIAsp 30 or LM 25 bid demonstrated no significant treatment difference in mean change from baseline in HbA1c (−1.0% with LM 50 tid, −0.82% with BIAsp 30/LM 25 bid; *P* = NS). While no statistically significant difference was observed between treatments for hypoglycemia, the tid group was associated with greater weight gain than the bid group (1.3 vs. 0.4 kg, respectively; *P* = 0.0009).

There are too few studies to form any conclusions regarding the comparative efficacy and safety of BIAsp 30 and LM 25/LM 50. Whether additional, comparative, studies are required is questionable given that a systematic review of three head-to-head trials of premixed insulin analogs revealed no differences in FPG, PPG, or HbA1c reduction between BIAsp 30, LM 25, and LM 50.[76]

Discussion

This review provides an overview of RCTs and observational studies comparing the efficacy and safety of BIAsp 30 and LM 25/LM 50 with other insulin therapies and OADs in patients with T2D. Although BIAsp 50 and BIAsp 70 are available for patients who require more prandial/bolus insulin, BIAsp 30 is the focus of this review given the experience accumulated over the years of use with this formulation. Overall, premixed insulin analogs were

Table 4: Randomized controlled trials comparing lispro mix 25/lispro mix 50 with (a) basal and (b) basal–bolus insulin regimens in Type 2 diabetes

Reference	Study design	Patients	LM 25/LM 50 versus comparator (s)			
			HbA1c	PPG	Hypoglycemia	Mean body weight change
(a) basal						
Comparison with basal regimens						
Malone *et al.*[62]	MC, R, prospective, O-L, crossover (2×16-week); LM 25 bid (*n*=52) versus glargine od (*n*=53), both with metformin	Insulin-naive (*n*=105)	Significantly greater decrease with LM 25 versus glargine (−1.3% vs. −0.9%; *P*=0.003) ≤7% target HbA1c: 42% versus 18%; *P*<0.001	Similar postlunch but lower postbreakfast (156.4 mg/dL vs. 171.1 mg/dL; *P*=0.012) and dinner (164.8 mg/dL vs. 193.8 mg/dL; *P*<0.001)	Low in both groups, but higher with LM 25 (0.68 episodes/patient/30 days vs. 0.39 episodes/patient/30 days; *P*<0.05)	Similar gain in both groups (2.8% vs. 2.9%; *P*=NS)
Robbins *et al.*[64]	24-week, MC, R, O-L, P-G; LM 50 tid + metformin (*n*=157) versus glargine od + metformin (*n*=158)	Previously treated with OADs (*n*=315)	Significantly greater reduction with LM 50 versus glargine (−0.7% vs. −0.4%; *P*<0.001) HbA1c ≤7%: 56.3% versus 39.7% (*P*=0.005); ≤6.5%: 46% versus 21% (*P*=0.001)	Lower with LM 50 (postbreakfast: 8.7 mmol/L vs. 9.2 mmol/L, *P*<0.05; postlunch: 8.4 mmol/L vs. 9.8 mmol/L, *P*<0.001; postsupper: 8.7 mmol/L vs. 10.7 mmol/L, *P*<0.001)	Overall HEs: 28.8% versus 17.7% (*P*=0.02)	Weight gain with LM 50 (1.2 kg) versus weight loss (−0.5 kg; *P*<0.001)
Milicevic *et al.*[65]*	24-week, MC, R, O-L, P-G; LM 50 (am)/LM 25 (pm) (*n*=68) versus. GLIB + NPH insulin (*n*=67)	Uncontrolled on OADs (*n*=135)	Significantly greater reduction with LM 25/LM 50 versus NPH (−1.31% vs. −0.5%; *P*=0.01)	Lower with LM 25/LM 50 (11.13 mmol/L vs. 14.46 mmol/L; *P*=0.0001)	Higher with LM 25/LM 50 (0.22 episodes/patient/30 days vs. −0.08 episodes/patient/30 days; *P*=0.037)	Weight gain similar for both groups (1.42 kg vs. 1.20 kg; *P*=NS)
Buse *et al.*[66]	24-week, MC, R, O-L, P-G; LM 25 bid (*n*=1045) versus glargine od (*n*=1046), both + OADs	Insulin-naive (*n*=2091)	Significantly greater reduction with LM 25 versus glargine (−1.8% vs. −1.7%, *P*=0.005) HbA1c <7%: 47.5% versus 40.3%; *P*<0.001)	Lower levels with LM 25 after morning (167 mg/dL vs. 172 mg/dL; *P*<0.05) and evening (163 mg/dL vs. 176 mg/dL; *P*<0.001) meals	Overall: 57.1% versus 51.8% (*P*=0.016)	Weight gain 3.6 kg versus 2.5 kg (*P*<0.001)
Sakharova *et al.*[69]	6-month, S-C, O-L, crossover; LM 25 bid versus glargine od	Uncontrolled on OADs (*n*=14)	Significantly greater reduction with LM 25 versus glargine (−2.5% versus −1.7%; *P*=0.009)	23% lower with LM 25 (153 mg/dL vs. 199 mg/dL; *P*=0.001)	No major HEs; no significant difference between groups in minor HEs (3.2 vs. 0.9; *P*=NS)	Weight gain not significantly different between groups (2.4 kg vs. 1.7 kg; *P*=NS)
Buse *et al.*[68]†	≤24-month, MC, R, O-L, P-G; LM 25 bid (*n*=473) versus glargine od (*n*=419), both + OADs	Insulin-naive (patients had completed 24-week initiation study with HbA1c ≤7%)	Significantly longer time of maintaining target HbA1c goal ≤7% longer with LM 25 versus glargine (16.8 months vs. 14.4 months; *P*<0.05) More LM 25 patients maintained HbA1c goal (43% vs. 35%; *P*=0.006)	Lower levels with LM 25 evening PPG (*P*<0.001)	Overall: 49.9% versus 45.3% (*P*=NS)	No difference during maintenance phase (1.6 kg vs. 1.8 kg; *P*=NS)
(b) basal–bolus						
Comparison with basal–bolus regimens						
Bowering *et al.*[70]	48-week, MC, O-L, R; LM 25 od to tid (*n*=214) versus glargine+lispro (*n*=212)	Insulin-naive, uncontrolled on OADs (*n*=426)	No significant difference between LM 25 and glargine + lispro (LM 25-glargine + lispro difference: −0.4%)	No difference between groups in mean change from baseline (5.24 mmol/L vs. 4.89 mmol/L; *P*=NS)	No difference in overall rate/30 days (1.71 vs. 1.96)	Weight gain of 2.78 kg versus 2.92 kg (no *P* value reported)
Jain *et al.*[67]	36-week, MC, O-L, R; LM 50 od to tid (*n*=242) versus glargine + mealtime lispro (*n*=242)	Uncontrolled on OADs (*n*=484)	No significant difference in reduction between treatment arms (−1.76% vs. −1.93%; *P*=NS)	Evening PPG lower with LM 50 (167.4 mg/dL vs. 176.4 mg/dL; *P*=0.010)	No difference in overall incidence (74.5% vs. 74.6%; *P*=NS)	No difference between groups (3.09 kg vs. 3.19 kg; *P*=NS)

Contd...

Table 4: Contd...

(b) basal-bolus						
Reference	**Study design**	**Patients**	**LM 25/LM 50 versus comparator (s)**			
			HbA1c	**PPG**	**Hypoglycemia**	**Mean body weight change**
			Comparison with basal-bolus regimens			
Rosenstock *et al.*[63]	24-week, M, R, O-L; LM 50 tid (*n*=187) versus glargine/lispro bid (basal-bolus; *n*=187)	Uncontrolled on glargine + OADs (*n*=374)	Significantly greater decrease with glargine/lispro compared with LM 50 (LM 50: −1.87% vs. glargine/lispro: −2.09%; *P*<0.05) HbA1c <7%: 54% versus 69% (*P*<0.05)	Similar between groups, except morning PPG, which was higher with LM 50 (174 mg/dL vs. 155 mg/dL; *P*=0.002)	No difference in overall rate (51.2 episodes/patient/year vs. 48.7 episodes/patient/year)	No difference (4.0 kg vs. 4.5 kg; *P*=NS)

*Both meals combined, †Maintenance phase of the DURABLE trial (DURABLE initiation phase), in which patients with HbA1c ≤7% were monitored for up to an additional 24 months. LM: Biphasic insulin lispro mix, bid: Twice daily, GLIB: Glibenclamide, HEs: Hypoglycemic episodes, OADs: Oral antidiabetic drugs, od: Once daily, OL: Open-label, MC: Multicenter, NPH: Neutral protamine Hagedorn, P-G: Parallel-group, PPG: Postprandial glucose, R: Randomized, S-C: Single-center, T2D: Type 2 diabetes, tid: Three times daily, NS: Not significant, HbA1c: Glycated hemoglobin

associated with improved glycemic control, as evidenced by reductions from baseline in both HbA1c and in PPG versus comparator regimens.[31-35,37,42,45,46,48-51,62,64-66,68] As such, these data highlight the importance of targeting PPG with an appropriate regimen, and the contribution this makes to the overall achievement of glycemic control. In addition, DURABLE demonstrated long-term treatment with a premixed insulin analog provided modestly improved durability of glycemic control compared with glargine.[68] In general, however, studies found premixed insulin tended to increase minor hypoglycemia and weight gain compared with basal insulin comparators. While such effects present challenges in T2D, these issues can be managed simply by implementing less aggressive insulin titration schedules, regular meals, and dietary/exercise intervention. Regarding comparisons of the insulin analog BIAsp 30 with BHI 30, the PPG and hypoglycemia benefits observed with the premixed insulin analogs may render them the preferred treatment modality.[41,42,45,46] This would be especially true in Asia where a large proportion of patients with diabetes are treated with BHI.

In addition to RCTs, large observational trials are beneficial as they investigate the effectiveness and safety of treatments in a real-life setting (i.e. day-to-day clinical practice). Recent findings from the large, observational A_1chieve study are particularly noteworthy as they showed that, across four continents, patients with T2D treated with BIAsp 30 achieved improvements from baseline, not only in glycemic control, but also in quality of life.[57-60] An improvement in hypoglycemia with BIAsp 30 was also reported in this and other observational trials.[54,55,57-60]

The need to individualize treatment regimens is key in many diseases, including T2D, and is illustrated by the results of a *post hoc* analysis of DURABLE. In this analysis, significant differences were observed between race/ethnic groups in the effect of LM 25 and insulin glargine (e.g., smaller reductions in HbA1c for Asian compared with Caucasian patients).[71] As highlighted in diabetes management guidelines, treatment individualization, focusing on patient preference (including ethnic and cultural needs) is crucial to treatment success.[1] This is particularly relevant for patients requiring insulin, in terms of when and how to initiate and intensify therapy, and choice of regimen. Another important consideration when initiating and intensifying insulin therapy is the cost of treatment in relation to benefits of glycemic control and the risk of short- and long-term complications. There is evidence that insulin analogs can offer cost-effective treatment, having been associated with improved clinical outcomes and an increase in quality-adjusted life-years.[77-80]

Together, these data indicate that premixed insulin regimens are appropriate and convenient treatments for most patients with T2D, offering flexibility in dosing schedule for people with regular eating patterns, and requiring fewer injections compared with basal–bolus regimens. These benefits render premixed insulin analogs the treatment of choice in many Asian countries, including India, where a large proportion of patients are treated in primary care practice.[3]

Acknowledgments

The author accepts a direct responsibility for this paper and is grateful for the editorial assistance provided by Watermeadow Medical, with support from Novo Nordisk, in developing the draft manuscript from an agreed outline. The manuscript has been read and approved by the author, the requirements for authorship have been met, and the author believes that the manuscript represents honest work.

Financial support and sponsorship
Nil.

Conflicts of interest
AK has received payments for conducting clinical trials and in the capacity of advisory board member for new drug development, development of treatment guidelines, and for delivering lectures at national and international conferences from several pharmaceutical companies including Boeringher Ingelheim, Eli Lilly, Johnson and Johnson, Merck, Novo Nordisk, Spherix, Takeda, Novartis, and USV.

References

1. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, *et al.* Management of hyperglycemia in type 2 diabetes: A patient-centered approach: Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364-79.
2. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: The thrifty phenotype hypothesis 1992. Int J Epidemiol 2013;42:1215-22.
3. Das AK, Sahay BK, Seshiah V, Mohan V, Muruganathan A, Kumar A, *et al*. Indian National Consensus Group: National Guidelines on Initiation and Intensification of Insulin Therapy with Premixed Insulin Analogs. Available from: http://www.apiindia.org/medicine_update_2013/chap51.pdf. [Last accessed on 2014 Oct 30].
4. International Diabetes Federation. IDF Diabetes Atlas. 6th ed. Brussels, Belgium: International Diabetes Federation; 2013. Available from: http://www.idf.org/diabetesatlas. [Last accessed on 2014 Nov 30].
5. World Health Organization (WHO). 10 Facts about Diabetes. Available from: http://www.who.int/features/factfiles/diabetes/facts/en/index4.html. [Last updated on 2014 Nov 01; Last accessed on 2014 Nov 30].
6. Ramachandran A, Snehalatha C. Rising burden of obesity in Asia. J Obes 2010;2010. pii: 868573.
7. Huxley R, James WP, Barzi F, Patel JV, Lear SA, Suriyawongpaisal P, *et al.* Ethnic comparisons of the cross-sectional relationships between measures of body size with diabetes and hypertension. Obes Rev 2008;9 Suppl 1:53-61.
8. Lear SA, Humphries KH, Kohli S, Chockalingam A, Frohlich JJ, Birmingham CL. Visceral adipose tissue accumulation differs according to ethnic background: Results of the Multicultural Community Health Assessment Trial (M-CHAT). Am J Clin Nutr 2007;86:353-9.
9. Dickinson S, Colagiuri S, Faramus E, Petocz P, Brand-Miller JC. Postprandial hyperglycemia and insulin sensitivity differ among lean young adults of different ethnicities. J Nutr 2002;132:2574-9.
10. John M, Kalra S, Unnikrishnan AG, Ganapathy B, Baruah MP, Sahay RK. Recommendations for insulin initiation based on ethnicity. Med Hypotheses 2011;77:460-1.
11. Misra A, Khurana L, Isharwal S, Bhardwaj S. South Asian diets and insulin resistance. Br J Nutr 2009;101:465-73.
12. International Diabetes Federation. 2011 Guideline for Management of PostMeal Glucose in Diabetes. Available from: http://www.idf.org/2011-guideline-management-postmeal-glucose-diabetes. [Last accessed on 2014 Nov 30].
13. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: Variations with increasing levels of HbA (1c). Diabetes Care 2003;26:881-5.
14. Bonora E, Calcaterra F, Lombardi S, Bonfante N, Formentini G, Bonadonna RC, *et al.* Plasma glucose levels throughout the day and HbA (1c) interrelationships in type 2 diabetes: Implications for treatment and monitoring of metabolic control. Diabetes Care 2001;24:2023-9.
15. Erlinger TP, Brancati FL. Postchallenge hyperglycemia in a national sample of U.S. adults with type 2 diabetes. Diabetes Care 2001;24:1734-8.
16. Caumo A, Luzi L. First-phase insulin secretion: Does it exist in real life? Considerations on shape and function. Am J Physiol Endocrinol Metab 2004;287:E371-85.
17. Monnier L, Colette C, Dunseath GJ, Owens DR. The loss of postprandial glycemic control precedes stepwise deterioration of fasting with worsening diabetes. Diabetes Care 2007;30:263-9.
18. Ceriello A. The hyperglycemia-induced "metabolic memory": The new challenge for the prevention of CVD in diabetes. Rev Esp Cardiol 2008;8 (Suppl. C):11C-7C.
19. Aryangat AV, Gerich JE. Type 2 diabetes: Postprandial hyperglycemia and increased cardiovascular risk. Vasc Health Risk Manag 2010;6:145-55.
20. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: A progressive disease. U.K. Prospective Diabetes Study Group. Diabetes 1995;44:1249-58.
21. Jabbour S. Primary care physicians and insulin initiation: Multiple barriers, lack of knowledge or both? Int J Clin Pract 2008;62:845-7.
22. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, *et al*. Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009;32:193-203.
23. Korytkowski M. When oral agents fail: Practical barriers to starting insulin. Int J Obes Relat Metab Disord 2002;26 Suppl 3:S18-24.
24. Home P, Naggar NE, Khamseh M, Gonzalez-Galvez G, Shen C, Chakkarwar P, *et al.* An observational non-interventional study of people with diabetes beginning or changed to insulin analogue therapy in non-Western countries: The A1chieve study. Diabetes Res Clin Pract 2011;94:352-63.
25. Singh AK. Science of premix insulin: Where have we reached? Expert Rev Endocrinol Metab 2014;10:65-74.
26. Indian National Consensus Group. Premix insulin: Initiation and continuation guidelines for management of diabetes in primary care. J Assoc Physicians India 2009;57 Suppl:42-6.
27. Garber AJ, Wahlen J, Wahl T, Bressler P, Braceras R, Allen E, *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.
28. Tambascia MA, Nery M, Gross JL, Ermetice MN, de Oliveira CP. Evidence-based clinical use of insulin premixtures. Diabetol Metab Syndr 2013;5:50.
29. Kesavadev J. Continuous insulin infusion systems in type 2 diabetes. J Assoc Physicians India 2011;59 Suppl:41-3.
30. Liebl A, Prusty V, Valensi P, Kawamori R, Christiansen JS, Palmer AJ, *et al.* Ten years of experience with biphasic insulin aspart 30: From drug development to the latest clinical findings. Drugs 2012;72:1495-520.
31. Raskin P, Allen E, Hollander P, Lewin A, Gabbay RA, Hu P, *et al.* Initiating insulin therapy in type 2 Diabetes: A comparison of biphasic and basal insulin analogs. Diabetes Care 2005;28:260-5.
32. Kann PH, Wascher T, Zackova V, Moeller J, Medding J, Szocs A, *et al.* Starting insulin therapy in type 2 diabetes: Twice-daily biphasic insulin Aspart 30 plus metformin versus once-daily insulin glargine plus glimepiride. Exp Clin Endocrinol Diabetes 2006;114:527-32.
33. Strojek K, Bebakar WM, Khutsoane DT, Pesic M, Smahelová A,

Thomsen HF, *et al.* Once-daily initiation with biphasic insulin aspart 30 versus insulin glargine in patients with type 2 diabetes inadequately controlled with oral drugs: An open-label, multinational RCT. Curr Med Res Opin 2009;25:2887-94.
34. Kalra S, Plata-Que T, Kumar D, Mumtaz M, Søndergaard F, Kozlovski P, *et al.* Initiation with once-daily BIAsp 30 results in superior outcome compared to insulin glargine in Asians with type 2 diabetes inadequately controlled by oral anti-diabetic drugs. Diabetes Res Clin Pract 2010;88:282-8.
35. Yang W, Xu X, Liu X, Yang G, Seino Y, Andersen H, *et al.* Treat-to-target comparison between once daily biphasic insulin aspart 30 and insulin glargine in Chinese and Japanese insulin-naïve subjects with type 2 diabetes. Curr Med Res Opin 2013;29:1599-608.
36. Holman RR, Farmer AJ, Davies MJ, Levy JC, Darbyshire JL, Keenan JF, *et al.* Three-year efficacy of complex insulin regimens in type 2 diabetes. N Engl J Med 2009;361:1736-47.
37. Ligthelm RJ, Gylvin T, DeLuzio T, Raskin P. A comparison of twice-daily biphasic insulin aspart 70/30 and once-daily insulin glargine in persons with type 2 diabetes mellitus inadequately controlled on basal insulin and oral therapy: A randomized, open-label study. Endocr Pract 2011;17:41-50.
38. Ligthelm RJ, Mouritzen U, Lynggaard H, Landin-Olsson M, Fox C, le Devehat C, *et al.* Biphasic insulin aspart given thrice daily is as efficacious as a basal-bolus insulin regimen with four daily injections: A randomised open-label parallel group four months comparison in patients with type 2 diabetes. Exp Clin Endocrinol Diabetes 2006;114:511-9.
39. Hirao K, Arai K, Yamauchi M, Takagi H, Kobayashi M; Japan Diabetes Clinical Data Management Study Group. Six-month multicentric, open-label, randomized trial of twice-daily injections of biphasic insulin aspart 30 versus multiple daily injections of insulin aspart in Japanese type 2 diabetic patients (JDDM 11). Diabetes Res Clin Pract 2008;79:171-6.
40. Liebl A, Prager R, Binz K, Kaiser M, Bergenstal R, Gallwitz B; PREFER Study Group. Comparison of insulin analogue regimens in people with type 2 diabetes mellitus in the PREFER Study: A randomized controlled trial. Diabetes Obes Metab 2009;11:45-52.
41. Boehm BO, Vaz JA, Brøndsted L, Home PD. Long-term efficacy and safety of biphasic insulin aspart in patients with type 2 diabetes. Eur J Intern Med 2004;15:496-502.
42. Abrahamian H, Ludvik B, Schernthaner G, Prager R, Zellenka U, Knudsen L, *et al.* Improvement of glucose tolerance in type 2 diabetic patients: Traditional vs. modern insulin regimens (results from the Austrian Biaspart Study). Horm Metab Res 2005;37:684-9.
43. McNally PG, Dean JD, Morris AD, Wilkinson PD, Compion G, Heller SR. Using continuous glucose monitoring to measure the frequency of low glucose values when using biphasic insulin aspart 30 compared with biphasic human insulin 30: A double-blind crossover study in individuals with type 2 diabetes. Diabetes Care 2007;30:1044-8.
44. Temizel M, Mert M, Bozbey C, Arman Y, Cevizci E, Altintas N, *et al.* Evaluation of the weight-increasing effects of biphasic analog and regular NPH insulin mixtures in patients with Type 2 diabetes mellitus. J Diabetes 2010;2:250-5.
45. Velojic-Golubovic M, Mikic D, Pesic M, Dimic D, Radenkovic S, Antic S. Biphasic insulin aspart 30: Better glycemic control than with premixed human insulin 30 in obese patients with Type 2 diabetes. J Endocrinol Invest 2009;32:23-7.
46. Schmoelzer I, de Campo A, Pressl H, Stelzl H, Dittrich P, Oettl K, *et al.* Biphasic insulin aspart compared to biphasic human insulin reduces postprandial hyperlipidemia in patients with Type 2 diabetes. Exp Clin Endocrinol Diabetes 2005;113:176-81.
47. Ohira M, Endo K, Oyama T, Yamaguchi T, Ban N, Kawana H, *et al.* Improvement of postprandial hyperglycemia and arterial stiffness upon switching from premixed human insulin 30/70 to biphasic insulin aspart 30/70. Metabolism 2011;60:78-85.
48. Raz I, Stranks S, Filipczak R, Joshi P, Lertoft B, Rastam J, *et al.* Efficacy and safety of biphasic insulin aspart 30 combined with pioglitazone in type 2 diabetes poorly controlled on glibenclamide (glyburide) monotherapy or combination therapy: An 18-week, randomized, open-label study. Clin Ther 2005;27:1432-43.
49. Bebakar WM, Chow CC, Kadir KA, Suwanwalaikorn S, Vaz JA, Bech OM; BIAsp-study group. Adding biphasic insulin aspart 30 once or twice daily is more efficacious than optimizing oral antidiabetic treatment in patients with type 2 diabetes. Diabetes Obes Metab 2007;9:724-32.
50. Raskin P, Matfin G, Schwartz SL, Chaykin L, Chu PL, Braceras R, *et al.* Addition of biphasic insulin aspart 30 to optimized metformin and pioglitazone treatment of type 2 diabetes mellitus: The ACTION Study (Achieving Control Through Insulin plus Oral ageNts). Diabetes Obes Metab 2009;11:27-32.
51. Ushakova O, Sokolovskaya V, Morozova A, Valeeva F, Zanozina O, Sazonova O, *et al.* Comparison of biphasic insulin aspart 30 given three times daily or twice daily in combination with metformin versus oral antidiabetic drugs alone in patients with poorly controlled type 2 diabetes: A 16-week, randomized, open-label, parallel-group trial conducted in russia. Clin Ther 2007;29:2374-84.
52. Kvapil M, Swatko A, Hilberg C, Shestakova M. Biphasic insulin aspart 30 plus metformin: An effective combination in type 2 diabetes. Diabetes Obes Metab 2006;8:39-48.
53. Sibbald B, Roland M. Understanding controlled trials. Why are randomised controlled trials important? BMJ 1998;316:201.
54. Valensi P, Benroubi M, Borzi V, Gumprecht J, Kawamori R, Shaban J, *et al.* Initiating insulin therapy with, or switching existing insulin therapy to, biphasic insulin aspart 30/70 (NovoMix30) in routine care: Safety and effectiveness in patients with type 2 diabetes in the IMPROVE observational study. Int J Clin Pract 2009;63:522-31.
55. Sharma SK, Al-Mustafa M, Oh SJ, Azar ST, Shestakova M, Guler S, *et al.* Biphasic insulin aspart 30 treatment in patients with type 2 diabetes poorly controlled on prior diabetes treatment: Results from the PRESENT study. Curr Med Res Opin 2008;24:645-52.
56. Shah SN, Litwak L, Haddad J, Chakkarwar PN, Hajjaji I. The A1chieve study: A 60 000-person, global, prospective, observational study of basal, meal-time, and biphasic insulin analogs in daily clinical practice. Diabetes Res Clin Pract 2010;88 Suppl 1:S11-6.
57. Kumar A, Sharma SK, Rajput R, Unnikrishnan AG. Initiating therapy or switching to biphasic insulin aspart improves glycaemic control in type 2 diabetes: An Indian experience from the A1chieve study. J Assoc Physicians India 2013;61 1 Suppl:16-20.
58. Lim-Abrahan MA, Yu-Gan S, Jain AB, Sobrepena LM, Racho VA. Safety and effectiveness of biphasic insulin aspart 30 in type 2 diabetes patients switched from biphasic human insulin 30: Results from the Filipino cohort of the A1chieve study. Diabetes Res Clin Pract 2013;100 Suppl 1:S35-40.
59. Soewondo P, Pramono RB, Langi YA, Soetedjo NN, Kshanti IA. Clinical experience with BIAsp 30: Results from the Indonesian cohort of the international A1chieve study. Diabetes Res Clin Pract 2013;100 Suppl 1:S54-9.
60. Hussein Z, Lim-Abrahan MA, Jain AB, Goh SY, Soewondo P. Switching from biphasic human insulin to biphasic insulin aspart 30 in type 2 diabetes: Results from the ASEAN subgroup of the A1chieve study. Diabetes Res Clin Pract 2013;100 Suppl 1:S24-9.
61. European Medicines Agency. Humalog (Insulin lispro). Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000088/human_med_000820.jsp and mid=WC0b01ac058001d124. [Last accessed on 2014 Nov 30].
62. Malone JK, Kerr LF, Campaigne BN, Sachson RA, Holcombe JH; Lispro Mixture-Glargine Study Group. Combined therapy with

insulin lispro Mi×75/25 plus metformin or insulin glargine plus metformin: A 16-week, randomized, open-label, crossover study in patients with type 2 diabetes beginning insulin therapy. Clin Ther 2004;26:2034-44.
63. Rosenstock J, Ahmann AJ, Colon G, Scism-Bacon J, Jiang H, Martin S. Advancing insulin therapy in type 2 diabetes previously treated with glargine plus oral agents: Prandial premixed (insulin lispro protamine suspension/lispro) versus basal/bolus (glargine/lispro) therapy. Diabetes Care 2008;31:20-5.
64. Robbins DC, Beisswenger PJ, Ceriello A, Goldberg RB, Moses RG, Pagkalos EM, *et al.* Mealtime 50/50 basal+prandial insulin analogue mixture with a basal insulin analogue, both plus metformin, in the achievement of target HbA1c and pre- and postprandial blood glucose levels in patients with type 2 diabetes: A multinational, 24-week, randomized, open-label, parallel-group comparison. Clin Ther 2007;29:2349-64.
65. Milicevic Z, Hancu N, Car N, Ivanyi T, Schwarzenhofer M, Jermendy G. Effect of two starting insulin regimens in patients with type II diabetes not controlled on a combination of oral antihyperglycemic medications. Exp Clin Endocrinol Diabetes 2009;117:223-9.
66. Buse JB, Wolffenbuttel BH, Herman WH, Shemonsky NK, Jiang HH, Fahrbach JL, *et al.* DURAbility of basal versus lispro mix75/25 insulin efficacy (DURABLE) trial 24-week results: Safety and efficacy of insulin lispro mix75/25 versus insulin glargine added to oral antihyperglycemic drugs in patients with type 2 diabetes. Diabetes Care 2009;32:1007-13.
67. Jain SM, Mao X, Escalante-Pulido M, Vorokhobina N, Lopez I, Ilag LL. Prandial-basal insulin regimens plus oral antihyperglycaemic agents to improve mealtime glycaemia: Initiate and progressively advance insulin therapy in type 2 diabetes. Diabetes Obes Metab 2010;12:967-75.
68. Buse JB, Wolffenbuttel BH, Herman WH, Hippler S, Martin SA, Jiang HH, *et al.* The DURAbility of Basal versus Lispro mix75/25 insulin Efficacy (DURABLE) trial: Comparing the durability of lispro mix75/25 and glargine. Diabetes Care 2011;34:249-55.
69. Sakharova OV, Lleva RR, Dziura JD, Spollett GR, Howell SK, Beisswenger PJ, *et al.* Effects on post-prandial glucose and AGE precursors from two initial insulin strategies in patients with type 2 diabetes uncontrolled by oral agents. J Diabetes Complications 2012;26:333-8.
70. Bowering K, Reed VA, Felicio JS, Landry J, Ji L, Oliveira J. A study comparing insulin lispro mix25 with glargine plus lispro therapy in patients with Type 2 diabetes who have inadequate glycaemic control on oral anti-hyperglycaemic medication: Results of the PARADIGM study. Diabet Med 2012;29:e263-72.
71. Davidson JA, Wolffenbuttel BH, Arakaki RF, Caballero AE, Jiang HH, Hardin DS. Impact of race/ethnicity on efficacy and safety of two starter insulin regimens in patients with type 2 diabetes: A posthoc analysis of the DURABLE trial. Ethn Dis 2013;23:393-400.
72. Yamashiro K, Ikeda F, Fujitani Y, Watada H, Kawamori R, Hirose T. Comparison of thrice-daily lispro 50/50 vs thrice-daily lispro in combination with sulfonylurea as initial insulin therapy for type 2 diabetes. J Diabetes Investig 2010;1:149-53.
73. Hermansen K, Colombo M, Storgaard H, ØStergaard A, Kølendorf K, Madsbad S. 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 2002;25:883-8.
74. Niskanen L, Jensen LE, Råstam J, Nygaard-Pedersen L, Erichsen K, Vora JP. Randomized, multinational, open-label, 2-period, crossover comparison of biphasic insulin aspart 30 and biphasic insulin lispro 25 and pen devices in adult patients with type 2 diabetes mellitus. Clin Ther 2004;26:531-40.
75. Farcasiu E, Ivanyi T, Mozejko-Pastewka B, Birkus Z, Csog J, Kowalska I, *et al.* Efficacy and safety of prandial premixed therapy using insulin lispro mix50/50 3 times daily compared with progressive titration of insulin lispro mix75/25 or biphasic insulin aspart 70/30 twice daily in patients with type 2 diabetes mellitus: A randomized, 16-week, open-label study. Clin Ther 2011;33:1682-93.
76. Qayyum R, Bolen S, Maruthur N, Feldman L, Wilson LM, Marinopoulos SS, *et al.* Systematic review: Comparative effectiveness and safety of premixed insulin analogues in type 2 diabetes. Ann Intern Med 2008;149:549-59.
77. Gupta V, Baabbad R, Hammerby E, Nikolajsen A, Shafie AA. An analysis of the cost-effectiveness of switching from biphasic human insulin 30, insulin glargine, or neutral protamine Hagedorn to biphasic insulin aspart 30 in people with type 2 diabetes. J Med Econ 2015;18:263-72.
78. Pollock RF, Curtis BH, Smith-Palmer J, Valentine WJ. A UK analysis of the cost-effectiveness of Humalog Mix75/25 and Mix50/50 versus long-acting basal insulin. Adv Ther 2012;29:1051-66.
79. Pollock RF, Curtis BH, Valentine WJ. A long-term analysis evaluating the cost-effectiveness of biphasic insulin lispro mix75/25 and mix50/50 versus long-acting basal insulin analogs in the United States. J Med Econ 2012;15:766-75.
80. Palmer JL, Beaudet A, White J, Plun-Favreau J, Smith-Palmer J. Cost-effectiveness of biphasic insulin aspart versus insulin glargine in patients with type 2 diabetes in China. Adv Ther 2010;27:814-27.