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REVIEW

A Review of Basal-Bolus Therapy Using Insulin Glargine and Insulin Lispro in the Management of Diabetes Mellitus

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Abstract: Basal-bolus therapy (BBT) refers to the combination of a long-acting basal insulin with a rapid-acting insulin at mealtimes. Basal insulin glargine 100 U/mL and prandial insulin lispro have been available for many years and there is a substantial evidence base to support the efficacy and safety of these agents when they are used in BBT or basal-plus therapy for patients with type 1 or type 2 diabetes mellitus (T1DM, T2DM). With the growing availability of alternative insulins for use in such regimens, it seems timely to review the data regarding BBT with insulin glargine 100 U/mL and insulin lispro. In patients with T1DM, BBT with insulin glargine plus insulin lispro provides similar or better glycemic control and leads to less nocturnal hypoglycemia compared to BBT using human insulin as the basal and/or prandial component, and generally provides similar glycemic control and rates of severe hypoglycemia to those achieved with insulin lispro administered by continuous subcutaneous insulin infusion (CSII). Studies evaluating BBT with insulin glargine plus insulin lispro in patients with T2DM also demonstrate the efficacy and safety of these insulins. Available data suggest that BBT with insulin glargine and insulin lispro provides similar levels of efficacy and safety in pediatric and adult populations with T1DM and in adult patients and those aged more than 65 years with T2DM. These insulin preparations also appear to be safe and effective for controlling T2DM in people of different ethnicities and in patients with T1DM or T2DM and comorbidities.
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Keywords: Basal-bolus therapy; Insulin glargine; Insulin lispro; Lilly insulin glargine; Type 1 diabetes mellitus; Type 2 diabetes mellitus

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INTRODUCTION

Insulin treatment of type 1 (T1DM) and type 2 (T2DM) diabetes mellitus has progressed considerably since the discovery of insulin in 1922 [1] and its subsequent purification and crystallization [2]. Initially, only animal insulin was available to diabetics, and animal insulin is

associated with adverse effects such as insulin allergy, insulin resistance, and insulin lipodystrophy [3–5]. However, in the 1980s, recombinant DNA technology enabled the development of synthetic human insulin, which replaced animal insulin as it was found to be less likely to produce adverse effects and it could be mass-produced. In the late 1980s and early 1990s, it became apparent that better glucose control would require new insulin preparations with a faster onset and shorter duration of action, enabling prandial insulin to be administered closer to mealtimes, as well as long-acting preparations with a flatter time–action profile and less variable bioavailability, including formulations suitable for once-daily dosing [6–9]. Molecular genetic techniques provided opportunities to create insulin analogues by changing the structure of the native protein and improving its therapeutic properties [8–10].

The crucial importance of an exogenous basal-bolus insulin supply to control blood glucose concentrations in patients with absolute insulin deficiency disease (i.e., T1DM) is well recognized. However, in T2DM, the initial relative insulin deficiency progresses with the decline in β-cell function, which again makes a combination of basal and prandial insulin the most effective insulin strategy [5, 11, 12].

This article reviews the current evidence concerning a widely used basal-bolus strategy combining insulin glargine 100 U/mL with insulin lispro in patients with T1DM and T2DM. The review does not consider all insulins and, as such, does not include other established or new insulins used in basal-bolus regimens unless they have been directly compared with insulin glargine 100 U/mL plus insulin lispro. An introductory summary of key information about the individual agents leads into a discussion of their combined use in basal-bolus therapy (BBT). In addition, the use of this BBT in special populations is considered. The information provided is based on previously conducted and published studies and does not contain any studies with human participants or animals performed by any of the authors.

INSULIN LISPRO

Structure, Pharmacokinetics, and Pharmacodynamics

The first genetically engineered rapid-acting insulin analogue (RAIA) to become available was insulin lispro, which was approved for clinical use in Europe and the USA in 1996 [13]. The B26–30 region of the insulin molecule is not critical for binding to the insulin receptor, but it is important in mediating the formation of insulin dimers [9, 14]. The insulin lispro molecule is created by reversing the normal sequence of proline at position 28 of the B chain and lysine at position 29 (Fig. 1) [8]. This reversal causes a decreased tendency for self-association [13, 15, 16]; consequently, insulin lispro has faster absorption, higher peak serum levels, and a shorter duration of action compared with regular human insulin (RHI) [9, 13, 17, 18]. In patients with T1DM treated with multiple daily injections, insulin lispro can be associated with fewer hypoglycemic events than RHI [13]. Importantly, structural modifications at these positions do not affect the receptor-binding domain of the molecule [16] or the affinity for the insulin receptor [9]. Although the affinity of insulin lispro for the insulin-like growth factor-1 (IGF-1) receptor is slightly higher than that of RHI, this difference in affinity is not large enough to cause a difference in cell-growth-stimulating activity [16]. Insulin lispro has essentially the same effect on lipogenesis as RHI [19].

Pharmacokinetic (PK)/pharmacodynamic (PD) studies indicate that the action of insulin lispro starts within 15 min, peaks in approximately 40–90 min, and disappears within 2–4 h of subcutaneous (SC) injection [18, 20, 21].

After insulin lispro, two other RAIAs, insulin aspart and insulin glulisine, were developed. Although studies have shown some differences in various PK parameters between RAIAs [22–26], overall there do not appear to be substantial differences in their effectiveness at controlling postprandial glucose levels and blood glucose profiles [19, 23–28]. However, there are some differences in the indications

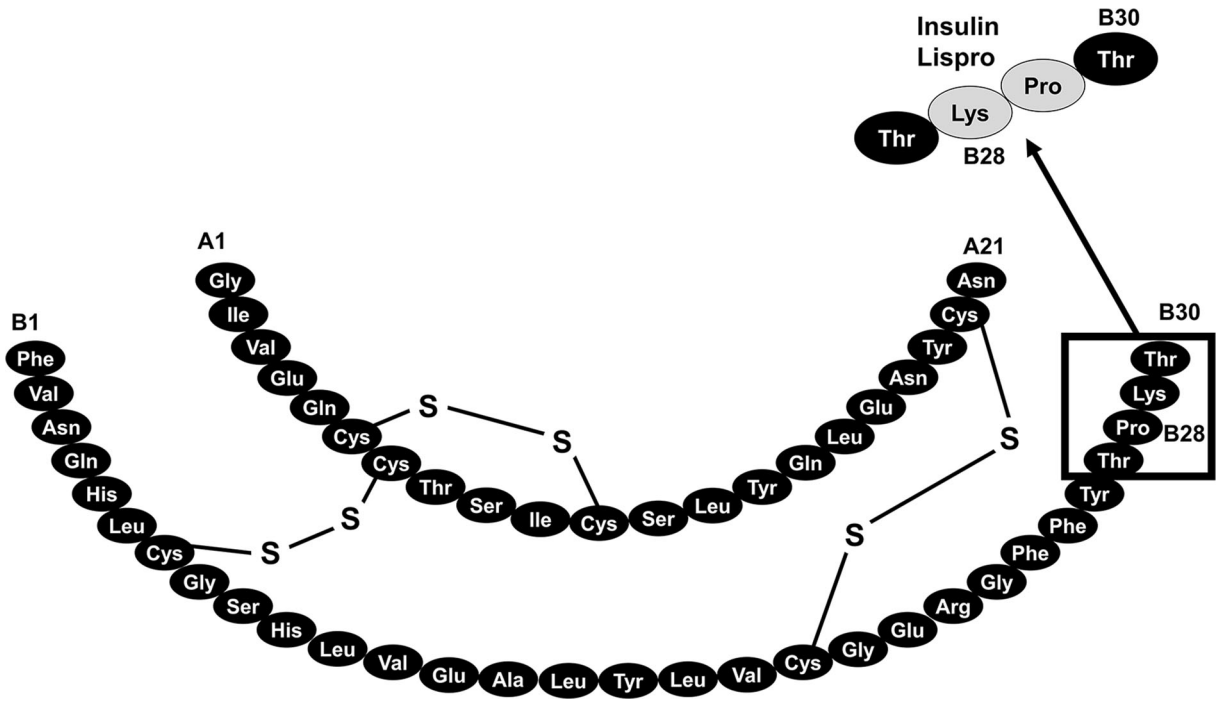

Fig. 1 Structure of insulin lispro. *Ala* alanine, *Arg* arginine, *Asn* asparagine, *Cys* cysteine, *Gln* glutamine, *Glu* glutamic acid, *Gly* glycine, *His* histidine, *Ile* isoleucine, *Leu* leucine, *Lys* lysine, *Phe* phenylalanine, *Pro* proline, *Ser* serine, *Thr* threonine, *Tyr* tyrosine, *Val* valine

and the patient populations studied with the three analogues [29–31].

Efficacy and Safety

Insulin lispro is one of the most studied and widely used rapid-acting insulins. As expected for a RAIA, insulin lispro significantly improves postprandial blood glucose levels compared with RHI when administered as prandial insulin in conjunction with basal insulin, leading to a lower rate of hypoglycemic events [32–35]. This was observed even when insulin lispro was administered immediately before meals and RHI was injected 30–45 min before meals. However, in most cases, the beneficial effects of insulin lispro on postprandial blood glucose levels and frequency of hypoglycemic events were not accompanied by improvements in glycosylated hemoglobin (HbA1c) compared with RHI [33–35]. The most likely explanation for this is the inability of the long-acting insulins that were administered with insulin lispro and RHI to provide true basal coverage, meaning that increased preprandial blood glucose concentrations were present in patients on insulin lispro. Supporting this theory, a clinically and statistically significant decrease in HbA1c level was seen when insulin lispro was used in conjunction with two or more daily injections (instead of one) of neutral protamine Hagedorn (NPH) insulin [36–38].

Insulin lispro is the only rapid-acting analogue which also has a 200 U/mL formulation. Insulin lispro 200 U/mL has the same PK/PD, efficacy, and safety profiles as lispro 100 U/mL [39, 40], but the 200 U/mL pen had a lower glide force and was preferred by patients [41, 42].

No differences have been reported between insulin lispro and RHI regarding the likelihood of allergic reactions, nonhypoglycemic adverse events, or abnormal laboratory values [34, 35, 43]. The immunogenicity of insulin lispro is similar to that of RHI [43], and antibodies against insulin lispro rarely develop and do not affect dose requirements [43]. Interestingly, there have been reports of patients with

severe resistance to RHI due to antibody formation that was successfully overcome by switching to insulin lispro [44–47].

INSULIN GLARGINE

Structure, Pharmacokinetics, and Pharmacodynamics

Insulin glargine is a long-acting biosynthetic human insulin analogue that was first approved for use in patients with T1DM and T2DM in the USA and Europe in 2000 (Lantus® insulin glargine) [48–50].

The structure of insulin glargine was designed by substituting an asparagine residue with a glycine at position 21 of the A chain and elongating the B chain at the C-terminus by adding two arginine residues (Fig. 2) [50, 51]. Modification of the B chain shifts the isoelectric point of insulin glargine, while the glycine substitution stabilizes the hexamer structure, and contributes to delayed delivery from SC depots, increased bioavailability, and maintenance of stability in acidic solutions [3, 50, 52]. After SC injection, insulin glargine precipitates in SC tissues, which delays its absorption and prolongs its duration of action [51–53]. Insulin glargine must not be mixed with other insulins, as it precipitates and the PK and PD profiles are altered.

Insulin glargine generally behaves like RHI regarding insulin receptor binding, receptor autophosphorylation, phosphorylation of signaling elements, and promotion of mitogenesis in muscle cells, apart from an increased binding affinity for the IGF-1 receptor in in-vitro (but not in cell-based) models [54, 55]. The growth-promoting activity of insulin glargine in muscle cells and its maximal metabolic activity do not differ from the effects of native human insulin, but the lipogenic activity of insulin glargine is slightly less than that of RHI [56].

The PD properties of insulin glargine differ from those of RHI. Insulin glargine exerted a glucose-lowering effect for 24 h after a single

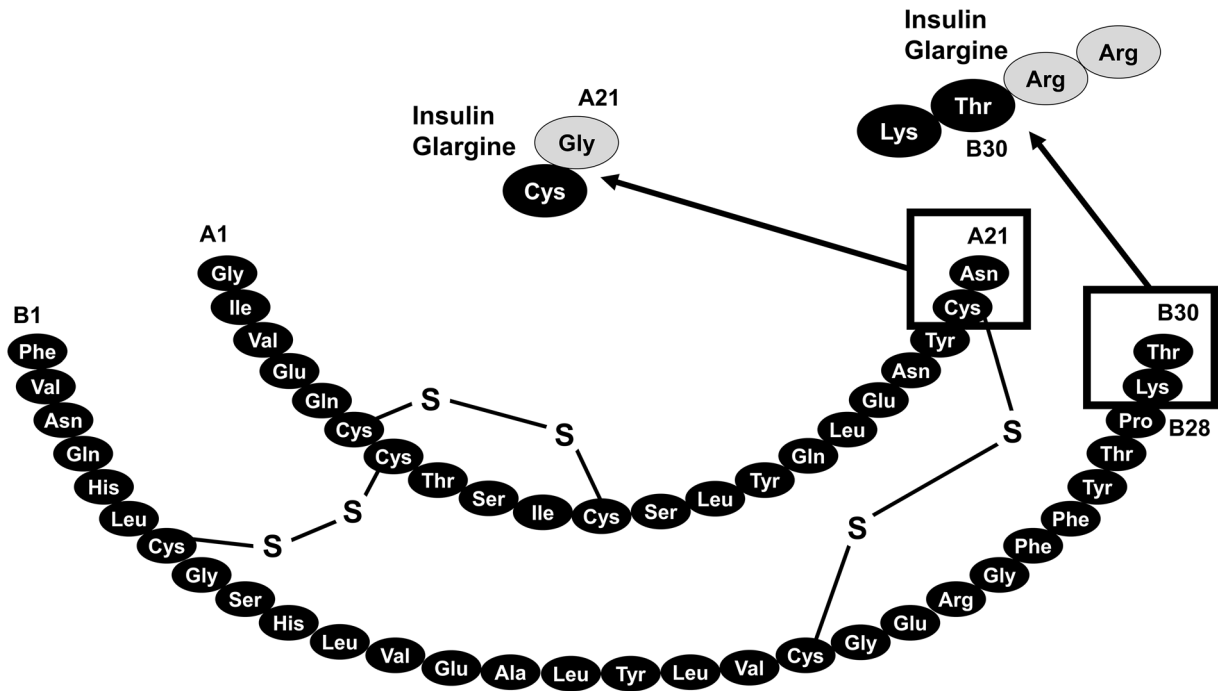

Fig. 2 Structure of insulin glargine. *Ala* alanine, *Arg* arginine, *Asn* asparagine, *Cys* cysteine, *Gln* glutamine, *Glu* glutamic acid, *Gly* glycine, *His* histidine, *Ile* isoleucine, *Leu* leucine, *Lys* lysine, *Phe* phenylalanine, *Pro* proline, *Ser* serine, *Thr* threonine, *Tyr* tyrosine, *Val* valine

daily injection, without a pronounced plasma peak, and induced a smoother metabolic effect than NPH insulin [3, 57]. Although it is recognized that the effect of NPH insulin can vary with injection site, changes in injection site do not alter the time–action profile of insulin glargine [3, 52].

Efficacy and Safety

One of the first studies to evaluate insulin glargine showed that once-daily injections of this analogue in patients with T1DM who were also receiving prandial RHI resulted in similar glycemic control to that provided by four daily injections of NPH insulin plus prandial RHI (same total number of insulin units) [58]. Subsequently, large, multicenter clinical trials in patients with T1DM and T2DM generally demonstrated that insulin glargine provided lower fasting blood glucose levels and less frequent hypoglycemic episodes than NPH insulin when administered alone or with premeal RHI [3, 59–63].

Given that a reduced frequency of hypoglycemia was generally observed in these studies, the target fasting blood glucose level can be lower than the target that has traditionally been used with NPH insulin [62, 64]. Patients treated with insulin glargine had less pharmacodynamic variability than patients treated with NPH insulin [65], possibly because, unlike NPH insulin [66], insulin glargine does not need to be resuspended prior to use.

Phase III study data raised no significant safety concerns for insulin glargine [51, 60, 63]. Retinopathy progression was noted in one study in patients with T2DM [67]. However, a review of all clinical trial data for insulin glargine concluded that the data did not support progression of retinopathy in patients with either T1DM or T2DM [60, 67]. Subsequently, a large, randomized trial in patients with T2DM demonstrated that, despite slightly more severe diabetic retinopathy at baseline in the group treated with insulin glargine, the progression of retinopathy was similar in insulin glargine-treated patients and NPH-treated patients over a 5-year period [68].

More recently, epidemiological studies suggested that insulin glargine might be associated with an increased risk of cancer [69, 70], but this was not confirmed by the ORIGIN trial, which showed that treatment with basal insulin glargine for more than 6 years had a neutral effect on cancers [71]. Exposure to insulin glargine is very limited as it is rapidly metabolized, primarily to the metabolite M1 [72], which mediates most of the glucodynamic effects, has slightly lower receptor binding affinity than human insulin, and does not exceed the mitogenic potential of human insulin [73].

Insulin glargine 100 U/mL is regarded as a standard-of-care basal insulin [74]. Recently, Lilly insulin glargine (Abasaglar®), the first biosimilar insulin to receive marketing authorization in the European Union, has become available [75]. It has an identical primary amino-acid sequence to that of the insulin glargine reference product (Lantus® insulin glargine), and phase I and phase III studies (in particular ELEMENT-1 and ELEMENT-2) have demonstrated that Lilly insulin glargine has similar PK/PD profiles, efficacy, and safety to the insulin glargine reference product [76–80].

BASAL-BOLUS THERAPY WITH INSULIN LISPRO AND INSULIN GLARGINE IN ADULTS WITH DIABETES

In patients with severe insulin deficiency, insulin therapy should replace both basal and prandial insulin requirements, matching the physiologic pattern of insulin secretion as closely as possible [81]. The basal-bolus approach involves multiple daily injections (MDI), with a long-acting insulin used as the basal insulin and a rapid-acting insulin adminstered at mealtimes [81, 82]. Long-acting insulin analogues generally reduce HbA1c to a similar extent to synthetic human insulins, but may be associated with less nocturnal hypoglycemia [83–85]. RAIAs are often preferred over RHI for mealtime insulin administration because they are absorbed more rapidly, can be given nearer to the meal, their action better simulates the

physiological insulin response to meals, and they are associated with less hypoglycemia [83, 86, 87].

Insulin glargine 100 U/mL and insulin lispro have both been available for many years, have been widely studied, and can be considered first-line options for use as the basal and bolus components, respectively, of BBT [87]. A search of the PubMed database up to October 3, 2017 was performed to identify papers about BBT involving insulin glargine 100 U/mL plus insulin lispro in patients with T1DM or T2DM that were published in English. The search was limited to human data, and the following search string was used: ((basal insulin) OR (basal bolus therapy) OR basal-plus OR basal-bolus OR basal bolus premixed) AND (insulin glargine OR Lantus OR "Lantus SoloStar" OR Basaglar OR Abasaglar OR insulin lispro OR Humalog OR basal g OR flexpen OR Novorapid OR LY2963016 OR (LY2963016 AND lispro)) OR (insulin glargine biosimilar) NOT Letter. Additional papers were detected from bibliographies of the identified articles. Clinical trials, observational studies, and review articles were considered; trials could be of any duration and could involve adult patients of any age or pediatric populations. Only studies in which one treatment arm clearly comprised BBT with insulin glargine 100 U/mL plus insulin lispro (and no other insulin preparation) were retained. Comparisons with non-insulin therapy were excluded. The initial search identified 994 papers, of which 39 met the criteria for inclusion. The remainder of this section focuses on studies in adults; pediatric data are discussed later.

Type 1 Diabetes Mellitus

Insulin is the cornerstone of treatment for patients with T1DM, with the initial dosage generally based on body weight (0.4–1.0 U/kg/day total insulin) [88]. Intensive insulin therapy (≥ 3 injections per day or CSII) improves glycemic control and produces better long-term outcomes than 1–2 insulin injections per day [89–91]. Consequently, American Diabetes Association (ADA) guidelines recommend that most people with T1DM should receive either MDI (≥ 3 prandial insulin injections and 1 or 2 basal insulin injections per day) or CSII [92].

Insulin Glargine Plus Insulin Lispro Versus Human Insulin

BBT using insulin glargine 100 U/mL plus insulin lispro was compared with BBT using other insulin combinations that utilized human insulin for the basal and/or prandial component in seven studies in adults with T1DM, all of which had randomized, open-label [93–97], or single-blind [98] designs (Table 1). Overall, these studies indicate that insulin glargine plus insulin lispro provides similar or better glycemic control to and less nocturnal hypoglycemia than regimens including human insulin. Overall, insulin glargine plus insulin lispro reduced HbA1c by 0.1–1.0% (1–11 mmol/mol) compared with baseline, whereas the change seen with recombinant or synthetic human insulin as the basal and/or prandial component ranged from an increase of 0.1% (1 mmol/mol) to a reduction of 0.6% (7 mmol/mol) (Table 1). The mean number of episodes of nocturnal hypoglycemia per month was 0.53–2.0 with insulin glargine plus insulin lispro, compared with 0.55–3.6 for regimens including human insulin (Table 1).

Only one of these studies compared insulin glargine plus insulin lispro with a combination of two human insulin products in patients with T1DM [93]. In this randomized crossover study ($n = 56$), insulin glargine plus insulin lispro provided better glycemic control than NPH insulin plus RHI, as indicated by a significantly lower HbA1c after 16 weeks of treatment [7.5% vs. 8.0% (59 vs. 64 mmol/mol); $p < 0.001$], together with an 8% lower 24-h blood glucose AUC ($p = 0.037$). In addition, the rate of symptomatic nocturnal hypoglycemia was 44% lower with insulin glargine plus insulin lispro than with the comparator regimen (0.66 vs. 1.18 episodes/month; $p < 0.001$) [93]. Moreover, recipients of insulin analogue therapy reported greater satisfaction with treatment [94].

The other studies ($n = 34$–619 patients) compared BBT with insulin glargine plus insulin lispro with BBT using either insulin glargine

Table 1 Clinical trials comparing basal-bolus therapy with insulin glargine 100 U/mL plus insulin lispro with other basal-bolus regimens in patients with type 1 diabetes mellitus

	Study design; treatment duration (prior treatment, as specified)	Treatment	*N*	Mean change from baseline		Nocturnal hypoglycemia (episodes per mon[a])
				HbA1c (%) [mmol/mol]	Fasting blood glucose (mmol/L)	
Comparisons with human insulin						
IGlar + LIS vs. NPH + RHI						
Ashwell et al. [93]	R, OL, C, M; 16 wk	IGlar + LIS	56	NR[b]	NR[b]	0.66 ± 0.02
	(No previous IGlar; insulin [MDI] for ≥ 1 year)	NPH + RHI	56	NR[b]	NR[b]	1.18 ± 0.02
				NR[b]	NR[b]	$p < 0.001$
IGlar vs. NPH						
Rossetti et al. [95]	R, OL; 3 months	IGlar[c] + LIS	17	− 0.4 [− 5]	NR	2.0 ± 0.19[d,e]
	(NPH + LIS [MDI])	NPH + LIS	17	+ 0.1 [+ 1]	NR	3.6 ± 0.4[d,e]
				$p < 0.04$	$p < 0.05$	$p < 0.05$[d,e]
Porcellati et al. [96]	R, OL; 1 year	IGlar + LIS	61	− 0.5 [− 6]	NR[f]	1.2 ± 0.2[d,e]
	(NPH + LIS [MDI])	NPH + LIS	60	0 [0]	NR[f]	3.2 ± 0.3[d,e]
				$p < 0.05$	NR[f]	$p < 0.05$[d,e]
Fulcher et al. [99]	R, SB, M; 30 wk	IGlar + LIS	62	− 1.0 [− 11]	− 3.46	0.22[g,h]
	(Insulin for ≥ 1 year)	NPH + LIS	63	− 0.5 [− 6]	− 2.34	0.37[g,h]
				$p < 0.01$	$p < 0.05$	$p = 0.02$[g,h]
Bolli et al. [97]	R, OL, M; 24 wk	IGlar + LIS	85	− 0.6 [− 7]	− 1.56	0.18 ± 0.25[d,i]
	(NPH + RHI or LIS [MDI])	NPH + LIS	90	− 0.6 [− 7]	− 0.54	0.16 ± 0.25[d,i]
				NS	$p = 0.0064$	$p = 0.383$[d,i]
Raskin et al. [98]	R, OL, M; 16 wk	IGlar + LIS	310	− 0.1 [− 1]	− 2.33 ± 0.26	1114[j]
	(NPH + LIS [MDI] for ≥ 3 months)	NPH + LIS	309	− 0.1 [− 1]	− 0.69 ± 0.26	992[j]
				NS	$p = 0.0001$	$p = 0.06$[j]
LIS vs. RHI						
Brunetti et al. [100]	R, OL, M, NI; 16 wk	IGlar + LIS	193	NR	NR	0.022[d,g]
	(NPH or IGlar + prandial insulin [MDI])	IGlar + RHI	202	NR	NR	0.021[d,g]
				NS[k]	NS[k]	$p = 0.742$[d,g]

Table 1 continued

	Study design; treatment duration (prior treatment, as specified)	Treatment	*N*	Mean change from baseline		Nocturnal hypoglycemia (episodes per mon[a])
				HbA1c (%) [mmol/mol]	Fasting blood glucose (mmol/L)	
Comparisons with other insulin analogues						
LIS vs. GLU						
Dreyer et al. [101]	R, OL, M; 26 wk	IGlar + LIS	333	− 0.1 [− 1]	NR	0.53 ± 0.84
	(Insulin for > 1 year)	IGlar + GLU	339	− 0.1 [− 1]	NR	0.55 ± 0.94
				NS	NR	NR
Kawamori et al. [102]	R, OL, M, NI; 28 wk	IGlar + LIS	135	0.04 [0.5]	NR	0.01[g]
	(BBT for ≥ 12 wk)	IGlar + GLU	132	0.01 [0.1]	NR	0.00[g]
				NS[l]	NR	$p = 0.6637$[g]

BBT basal-bolus therapy, *C* crossover, *CI* confidence interval, *GLU* insulin glulisine, *HbA1c* glycated hemoglobin, *IGlar* Lantus® insulin glargine, *LIS* insulin lispro, *M* multicenter, *MDI* multiple daily injections, *mon* months, *N* number of patients, *NI* noninferiority, *NPH* neutral protamine Hagedorn insulin, *NR* not reported, *NS* not significant, *OL* open-label, *R* randomized, *RHI* regular human insulin, *SB* single-blind, *wk* weeks

[a] Mean ± SE episodes of nocturnal hypoglycemia per patient per month during treatment period, unless indicated otherwise

[b] HbA1c value at 16 wk lower with IGlar + LIS vs. NPH + RHI [difference − 0.5% (6 mmol/mol), 95% CI − 0.7 to − 0.3% (− 8 to − 3 mmol/mol), $p < 0.001$]; fasting FBG value lower at 16 wk with IGlar + LIS vs. NPH + RHI (difference −1.5 mmol/L, 95% CI − 2.6 to − 0.5, $p = 0.005$)

[c] Data shown are for patients given IGlar at bedtime. Another group received IGlar at dinnertime; there were no significant differences in HbA1c or hypoglycemia results between these two groups

[d] Mean number of episodes per month during the last month of treatment

[e] Hypoglycemia defined as blood glucose < 4.0 mmol/L irrespective of symptoms

[f] Mean daily blood glucose was lower with IGlar vs. NPH (7.6 ± 0.11 mmol/L vs. 8.1 ± 0.22 mmol/L, $p < 0.05$)

[g] Severe nocturnal hypoglycemia

[h] Number of episodes per 100 patient days

[i] Serious nocturnal hypoglycemia (blood glucose < 2.3 mmol/L)

[j] Number of episodes during entire treatment period (16 wk)

[k] Paper states treatments did not differ with respect to HbA1c and FBG at study end

[l] Non-inferiority of IGlar + GLU versus IGlar + LIS was demonstrated based on analysis of covariance of the change in HbA1c and using a prespecified non-inferiority margin (upper 95% CI limit) of 0.45% (5 mmol/mol); the between-group difference in least-squares mean change was 0.1% [1 mmol/mol; 95% CI − 0.1 to 0.2% (− 1 to 2 mmol/mol)]

plus RHI or NPH insulin plus insulin lispro. Insulin glargine plus insulin lispro provided better control of fasting blood glucose [95–99] and/or HbA1c [95, 96, 99] than NPH insulin plus insulin lispro, and similar glycemic control to insulin glargine plus RHI [100]. Half of these studies also found that BBT with insulin glargine plus insulin lispro reduced the frequency of total nocturnal hypoglycemia [95, 96] or severe nocturnal hypoglycemia [99] versus NPH insulin plus insulin lispro (mean episodes of nocturnal hypoglycemia per month 1.2–2.0 vs. 3.2–3.6; see Table 1 for individual study results).

Insulin Glargine Plus Insulin Lispro Versus Other Insulin Analogues

When compared with BBT utilizing other insulin analogues in T1DM, BBT with insulin

Table 2 Clinical trials comparing basal-bolus therapy with insulin glargine 100 U/mL plus insulin lispro to continuous subcutaneous insulin infusion using insulin lispro in patients with type 1 diabetes mellitus

	Study design; duration (prior treatment, as specified)	Treatment	*N*	Mean change from baseline		Severe hypoglycemia (episodes per patient during treatment[a])
				HbA1c (%) [mmol/mol]	Fasting blood glucose (mmol/L)	
Lepore et al. [104]	OL; 1 year	IGlar + LIS	24	− 0.7 [8]	NR	0.21 ± 0.40
	(NPH + RHI or LIS [MDI] for ≥ 1 year)	LIS CSII	24	− 1.0 [− 11]	NR	0.17 ± 0.37
				NS	NR	NS
Lepore et al. [105]	OL; 1 year	IGlar + LIS	16	NR	NR	0.18
	(NPH + RHI or LIS [MDI] for ≥ 1 year)	LIS CSII	16	NR	NR	0.12
				NS[b]	NS[b]	NS
Bolli et al. [106]	R, OL, M; 24 wk	IGlar + LIS	26	− 0.6 [− 7]	− 2.7	35 ± 35[c]
	(NPH-based MDI regimen)	LIS CSII	24	− 0.7 [− 8]	− 3.3	41 ± 43[c]
				NS	NS	$p = 0.93$[c]
Bruttomesso et al. [107]	R, OL, C, M; 4 mon	IGlar + LIS	39	− 0.1 [− 1]	NR	0.1 ± 0.4
	(LIS or ASP CSII for ≥ 6 mon)	LIS CSII	39	− 0.2 [− 2]	NR	0.1 ± 0.3
				NS	NR	$p = 0.710$
Ruiz-de-Adana et al. [108]	R, OL; 6 mon	IGlar + LIS	23	− 0.3 [− 3][d]	NR	0.05 ± 0.2
	(IGlar + LIS [MDI] for 6 mon)	LIS CSII	15	− 0.9 [− 10][d]	NR	0.29 ± 1
				NR[e]	NR	$p = 0.08$

ASP insulin aspart, *C* crossover, *CSII* continuous subcutaneous insulin infusion, *IGlar* Lantus® insulin glargine, *HbA1c* glycated hemoglobin, *LIS* insulin lispro, *M* multicenter, *MDI* multiple daily injections, *mon* months, *N* number of patients, *NPH* neutral protamine Hagedorn insulin, *NR* not reported, *NS* not significant, *OL* open-label, *R* randomized, *RHI* regular human insulin, *wk* weeks

[a] Total number of episodes per patient during study treatment. Severe hypoglycemia, unless indicated otherwise

[b] Values for changes in HbA1c and FBG were not reported, but paper stated that there were no significant differences in the degree of improvement in HbA1c or fasting plasma glucose between the groups

[c] Overall incidence of hypoglycemia. There were also no significant differences for nonsevere, nocturnal, symptomatic, or asymptomatic hypoglycemia events

[d] All patients underwent a 6-month period of IGlar + LIS prior to randomization to receive CSII or continue with IGlar + LIS. Baseline values were obtained after this initial 6-month period of IGlar + LIS

[e] $p = 0.03$ for comparison of HbA1c values at endpoint [IGlar + LIS 7.6% vs. CSII 7.0% (60 vs. 53 mmol/mol)]

Table 3 Clinical trials comparing basal-bolus therapy with insulin glargine 100 U/mL plus insulin lispro to other insulin regimens in patients with type 2 diabetes mellitus

	Study design; duration (prior treatment, as specified)	Treatment	*N*	Mean change from baseline		Nocturnal hypoglycemia (episodes per year[a])
				HbA1c (%) [mmol/mol]	Fasting blood glucose (mmol/L)	
Comparisons with premixed insulin						
Rosenstock et al. [113]	R, OL, M, NI; 24 wk	IGlar + LIS	187	− 2.1 [− 23]	− 1.88	6.17 ± 10.68
	(IGlar + OAD for ≥ 90 days)	LM 50/50 t.i.d[b]	187	− 1.9 [− 20]	− 0.74	4.78 ± 7.15
				$p = 0.021$[c]	NR[d]	$p = 0.139$
Miser et al. [114]	R, OL, M, NI; 24 wk	IGlar + LIS (Arm A)[e]	199	0.1 [1]	NR	3.0 ± 13.6
	(IGlar + OAD or LM 75/25 + OAD)	LM 75/25 b.i.d. (Arm A)[e]	200	0.0 [0]	NR	2.5 ± 7.0
				NR[f]	NR	$p = 0.657$
		IGlar + LIS (Arm B)[e]	171	0.2 [2.2]	NR	2.4 ± 6.1
		LM 50/50 t.i.d. (Arm B)[e]	174	0.2 [2.2]	NR	2.5 ± 8.1
				NR[f]	NR	$p = 0.949$
Jia et al. [115]	R, OL, M, NI; 24 wk	IGlar + LIS	202	− 1.1 [− 12]	−1.2	0.05 ± 0.21[h]
	(PMI [human insulin-, LIS- or ASP-based] for ≥ 6 mon)	LM 50/50 b.i.d + LM 75/25 o.d.	197	− 1.1 [− 12]	−0.8	0.03 ± 0.09[h]
				NS[g]	$p = 0.002$	$p = 0.235$

Table 3 continued

	Study design; duration (prior treatment, as specified)	Treatment	*N*	Mean change from baseline		Nocturnal hypoglycemia (episodes per year[a])
				HbA1c (%) [mmol/mol]	Fasting blood glucose (mmol/L)	
Comparison with other insulin analogues						
Koivisto et al. [120]	R, OL, M, NI; 24 wk	IGlar + LIS	191	− 1.2 [− 13]	NR	0.09[h]
	(OAD + insulin)	ILPS + LIS	192	− 1.1 [− 12]	NR	0.13[h]
				NR[i]	NR	$p = 0.2$

ASP insulin aspart, *b.i.d.* twice daily, *C* crossover, *CI* confidence interval, *IGlar* Lantus® insulin glargine, *HbA1c* glycated hemoglobin, *ILPS* insulin lispro protamine suspension, *LIS* insulin lispro, *LM 50/50* 50% insulin lispro protamine suspension/50% insulin lispro, *LM 75/25* 75% insulin lispro protamine suspension/25% insulin lispro, *M* multicenter, *mon* months, *N* number of patients, *NI* noninferiority, *NR* not reported, *NS* not significant, *OAD* oral antihyperglycemic drugs, *o.d.* once daily, *OL* open-label, *PMI* premixed insulin, *R* randomized, *t.i.d.* three times daily, *wk* weeks

[a] Mean ± SD number of episodes per patient per year unless indicated otherwise

[b] Evening dose could be changed to LM 75/25 if necessary; this occurred in 55% of patients

[c] Difference in HbA1c change from baseline to endpoint (BBT minus LM 50/50) − 0.2% [− 2 mmol/mol; 90% CI − 0.4 to − 0.1% (− 4 to 1 mmol/mol)]. Protocol-specified lower limit of CI for noninferiority was − 0.3%. Therefore, noninferiority of LM 50/50 was not demonstrated

[d] $p = 0.013$ for comparison of fasting plasma glucose values at endpoint (IGlar + LIS 8.2 mmol/L vs. LM 50/50 8.8 mmol/L)

[e] Substudy of DURABLE study. During a 6-month initiation phase, patients received IGlar once daily or LM 75/25 twice daily. Patients who did not achieve glycemic control then entered the 6-month intensification substudy. Patients on IGlar entered intensification arm A and patients on LM 75/25 entered intensification arm B

[f] Noninferiority of LM 75/25 and LM 50/50 versus BBT was demonstrated based on HbA1c values at endpoint, with 95% CI of − 0.10 to 0.37% (− 1 to 4 mmol/mol) and − 0.25 to 0.25% (− 3 to 3 mmol/mol), respectively; the noninferiority margin was set at 0.4% (5 mmol/mol)

[g] Noninferiority of LM 50/50–LM 75/25 vs. IGlar + LIS was demonstrated based on a noninferiority margin of 0.4% (5 mmol/mol); the between-group difference in least squares mean change was 0% [0 mmol/mol; 95% CI − 0.1 to 0.2% (− 1 to 2 mmol/mol)]

[h] Mean ± SD number of episodes per patient per 30 days

[i] Noninferiority of ILPS + LIS vs. IGLar + LIS was demonstrated based on analysis of covariance of the change in HbA1c and using a prespecified noninferiority margin (upper 95% CI limit) of 0.4% (5 mmol/mol); the between-group difference in least-squares mean change was 0.1% [1 mmol/mol; 95% CI − 0.1 to 0.3% (− 1 to 3 mmol/mol)]

glargine 100 U/mL plus insulin lispro provided similar glycemic control and rates of hypoglycemia to insulin glargine plus insulin glulisine in randomized clinical trials ($n = 672$ and 267, respectively) (Table 1) [101, 102], and lower evening post-prandial glucose levels than insulin detemir plus insulin lispro in a crossover trial ($n = 8$), which could be due to insulin detemir having a shorter duration of action or a slower onset of action [103].

Insulin Glargine Plus Insulin Lispro Versus Insulin Lispro CSII

BBT with insulin glargine 100 U/mL plus insulin lispro was compared with CSII using insulin lispro in five open-label studies in patients with T1DM ($n = 32$–50) (Table 2) [104–108]. The two approaches provided similar glycemic control and frequency of severe hypoglycemia in most studies [104–106], although two reported better glycemic control with CSII [107, 108].

Type 2 Diabetes Mellitus

Pharmacological treatment for patients with T2DM usually starts with a single oral antidiabetic agent (OAD), generally metformin [88]. If maximally titrated OAD monotherapy is inadequate, a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist or insulin, is added [88]. The progressive decline in β-cell function that occurs in T2DM means that most patients eventually need exogenous insulin therapy in combination with other therapies [87, 88].

Treatment Intensification Using Insulin

Insulin is usually added to ongoing treatment with metformin and/or other OADs and possibly GLP-1 receptor agonist therapy. Rapid-acting mealtime insulin may be used as the initial insulin therapy in patients with T2DM [109, 110]. However, it is generally more common to start with a single daily injection of basal insulin [81, 82, 88, 111]. If basal insulin alone does not provide adequate glycemic control, prandial insulin can be added, either as a full basal-bolus regimen (basal insulin with bolus insulin administered at all meals) or in a stepwise fashion, starting with the largest meal ('basal-plus' therapy) and then other meals, as necessary, to reach full BBT [11, 82, 111]. Alternatively, a GLP-1 receptor agonist might be added to basal insulin therapy as the next step [81, 88, 111, 112], or the patient could be switched from basal insulin to premixed insulin (initially administered twice daily, progressing to three times daily if necessary) [81, 88]. The intensification option selected will depend on each patient's clinical circumstances and preferences [81].

Insulin Glargine Plus Insulin Lispro Versus Premixed Insulin

Seven studies, all using a randomized, controlled, noninferiority design, compared insulin glargine 100 U/mL plus insulin lispro with premixed insulin with the aim of establishing whether premixed insulin was noninferior to BBT. Overall, study results did not suggest any clinically relevant advantage of premixed insulin over insulin glargine plus insulin lispro [113–119].

Among three studies evaluating full BBT (n = 374, 744, 402) (Table 3), two concluded that premixed insulin (insulin lispro mix 25/75 or 50/50) was noninferior to BBT with insulin glargine plus insulin lispro with respect to HbA1c levels in patients who had failed to achieve glycemic control on their initial insulin regimen (in combination with OADs) [114, 115]. The third study was unable to demonstrate noninferiority for insulin lispro mix 50/50 or 75/25, based on a difference in HbA1c change (BBT minus premixed) of − 0.2% [2 mmol/mol; 90% CI − 0.4 to − 0.1% (− 5 to − 1 mmol/mol)] after 24 weeks, against a noninferiority margin of − 0.3% (3 mmol/mol) [113]. In two of these studies, the total daily insulin dose at study end was similar with both approaches [114, 115]; in the third study, mean total insulin dose was higher in the BBT group than in the premixed-insulin group at study end (146 vs. 123 units, p = 0.002) [113]. Rates of overall and nocturnal hypoglycemia and mean weight gain were similar with both treatment approaches [113–115].

The other four studies evaluated basal-plus therapy or intensification strategies involving one to three doses of insulin lispro (n = 476, 426, 344, 484) [116–119]. In these studies, the addition of an increasing number of prandial insulin injections was effective and safe [116–119]. Three studies found premixed insulin was noninferior to basal-plus therapy with insulin glargine plus insulin lispro [116, 118, 119]. However, one study did not demonstrate noninferiority for insulin lispro mix 50/50, based on a change in HbA1c of − 1.76% (− 19 mmol/mol) versus − 1.93% (− 21 mmol/mol) with insulin glargine plus insulin lispro [between-group difference 0.17% (2 mmol/mol) for premixed minus basal-plus, 95% CI − 0.03 to 0.37 (− 0 to 4 mmol/mol); noninferiority margin 0.3% (3 mmol/mol)] [117]. In this study, HbA1c values were significantly lower in the basal-plus group compared with the premixed insulin group at weeks 12 and 24 weeks, although not at week 36 (study end) [117]. Total daily insulin doses, number of injections, rates of hypoglycemia, and weight changes at study end were similar with both approaches in most studies [116–119], with the

exceptions that the total daily insulin dose and mean daily number of injections were greater [117], nocturnal hypoglycemia was more common [118], and weight gain was greater [116] with premixed than BBT in one study each.

Glargine + Lispro Versus Other Insulin Analogues

A randomized clinical trial (n = 383) showed that similar glycemic control was achieved with insulin glargine 100 U/ml plus insulin lispro BBT and insulin lispro protamine suspension plus insulin lispro BBT in patients with T2DM who no longer achieved glycemic targets on insulin plus OAD treatment (Table 3) [120]. More than 82% of patients in each group received three insulin lispro injections per day throughout the study [120]. In a small crossover study involving 12 patients, BBT with insulin glargine plus insulin lispro was associated with lower pre- and post-dinner glucose levels than BBT with insulin detemir plus insulin lispro [103].

Insulin Administration and Titration Protocols

Various algorithms for starting and intensifying insulin therapy in patients with T2DM are available, such as those provided by the ADA [88] and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) [111].

Only one of the studies evaluating full BBT with insulin glargine 100 U/mL plus insulin lispro in patients with T2DM outlined the dosing algorithms used: insulin doses were adjusted weekly based on mean preprandial blood glucose level and, if a more aggressive approach was needed, total daily insulin requirement [113].

Studies that evaluated progression of insulin therapy, but not necessarily full BBT, used various algorithms based on fasting and/or preprandial blood glucose levels to adjust the dosages of insulin glargine and insulin lispro [117–119]. Importantly, patients can be trained to self-titrate bolus insulin doses safely [121]. In the 24-week AUTONOMY study, patients on optimized basal insulin glargine who were starting to add insulin lispro therapy were able to self-titrate their bolus insulin lispro safely using either of two simple algorithms, with insulin lispro adjusted every other day based on the preprandial reading from the previous 1–3 days [121].

BASAL-BOLUS THERAPY WITH INSULIN LISPRO PLUS INSULIN GLARGINE IN SPECIAL POPULATIONS

Children and Adolescents

The use of BBT with insulin glargine 100 U/mL plus insulin lispro in pediatric patients has been evaluated in a few, mostly small, trials, including two randomized open-label studies [122–124] and one noncomparative study [125]. Overall, these studies found that this regimen was effective and safe in children or adolescents with T1DM.

In a crossover study involving adolescents (aged 12–20 years, currently in puberty) with T1DM (n = 25) who were already receiving multiple injection regimens (not specified further), BBT with insulin glargine plus insulin lispro was at least as effective as NPH insulin plus RHI at maintaining glycemic control, and was associated with a lower incidence of nocturnal hypoglycemia [122]. In the other randomized study (n = 175), insulin glargine plus insulin lispro was at least as effective as intermediate-acting NPH or lente insulin plus insulin lispro, and reduced glucose variability, in children and adolescents (aged 9–17 years) who had previously been receiving intermediate-acting NPH or lente insulin [123, 124]. There was no difference in the rates of hypoglycemia [blood glucose < 2.00 mmol/L (< 36 mg/dL) or severe hypoglycemia requiring assistance] between the groups in the overall analysis [123], but in an analysis of a subset who used continuous glucose monitoring (n = 90), insulin glargine plus insulin lispro reduced the amount of time spent with blood glucose levels < 2.22 mmol/L (< 40 mg/dL) based on such monitoring [124]. Finally, a small (n = 35) noncomparative study suggested that flexible

MDI using insulin glargine plus insulin lispro (with the lispro dose adjusted according to 2-hour postprandial blood glucose measurements) improved glycemic control in preschool children who had previously been receiving twice-daily ultralente insulin plus insulin lispro [125].

Elderly Patients

No studies specifically evaluating BBT with insulin glargine 100 U/mL plus insulin lispro in elderly patients (aged ≥ 65 years) were identified, but two studies reported subgroup analyses in patients in this age group with T2DM [120, 121]. According to a post hoc subgroup analysis, BBT with either insulin lispro protamine suspension plus insulin lispro or insulin glargine plus insulin lispro was effective and safe in patients aged > 65 years (n = 89), with mean reductions from baseline at 24 weeks in HbA1c of − 1.0% (11 mmol/mol) and − 1.2% (13 mmol/mol), respectively; these reductions were similar to those achieved in the overall population [− 1.1% (11 mmol/mol) and − 1.2% (13 mmol/mol), respectively] [120]. The proportion of elderly patients reporting at least one hypoglycemic event was similar to that of the overall population for both treatment groups [120]. Subgroup analysis of the AUTONOMY study (n = 255/1112) showed that patients aged ≥ 65 years on basal insulin glargine were able to self-titrate insulin lispro doses safely to achieve insulin intensification [121]. The percentages of patients aged ≥ 65 years who achieved HbA1c targets of ≤ 7.0% (53 mmol/mol) were 58.5% and 58.0% when insulin lispro was self-titrated every day or every 3 days, respectively, and were similar to the percentages achieving this goal in the total population. There was no significant difference in the rate of hypoglycemia between algorithm groups among either the overall population or elderly patients [121].

Patients with Comorbidities

Studies have not been published that specifically evaluated BBT with insulin glargine plus insulin lispro in patients with renal disease or hepatic disease. The product characteristic summaries for insulin glargine and insulin lispro include the warning that insulin requirements may be lower in patients with renal or hepatic impairment due to reduced insulin metabolism, and lower in patients with hepatic impairment due to a reduced capacity for gluconeogenesis [31, 75], although in chronic hepatic impairment, insulin requirements may increase due to greater insulin resistance [31]. However, the summary of product characteristics for insulin lispro also states that renal and hepatic impairment do not affect the glucodynamic response to insulin lispro [31]. Studies showed that the PK and PD characteristics of insulin lispro were maintained in patients with T1DM and diabetic nephropathy [126] and that postprandial glucose levels and hypoglycemia rates were lower with insulin lispro than with RHI in patients with T2DM and compensated nonalcoholic liver disease [127]. Insulin glargine provided better glycemic control than NPH insulin in patients with T2DM on hemodialysis [128]. Overall, insulin glargine and insulin lispro appear to be suitable for use in patients with renal or hepatic disease.

No studies were identified that specifically evaluated BBT with insulin glargine plus insulin lispro in patients with cardiovascular disease. However, in patients with T2DM, the glycemic benefits of insulin glargine were unaltered by cardiovascular risk factors [129]; insulin glargine did not increase the risk of adverse cardiovascular outcomes in patients with preexisting cardiovascular disease or cardiovascular risk factors in the ORIGIN study [130, 131]; and RAIAs, including insulin lispro, had potentially more favorable effects on cardiovascular risk factors such as dyslipidemia and biomarkers of inflammation or atherosclerosis compared with RHI [132].

Two randomized, open-label studies (n = 60, 140) evaluated BBT with insulin glargine plus insulin lispro in hospitalized patients with diabetes [133, 134]. In patients with T2DM on a general medicine ward, BBT with insulin glargine plus insulin lispro permitted better adherence to target insulin timing with respect to meals and reduced the percentage of patient

days in which hypoglycemia < 70 mg/dL occurred when compared with NPH insulin plus RHI [134]. In patients with T2DM undergoing surgery, BBT using insulin glargine plus insulin lispro provided effective glycemic control, with no significant difference in postoperative glucose levels or in overall hypoglycemic episodes compared with insulin detemir plus insulin aspart [133].

Other Patient Populations

Most trials involving insulin glargine plus insulin lispro were conducted in Europe or the USA. However, ethnicity can affect the response of patients with T2DM to insulin therapy [135]. Studies and subgroup analyses have shown that BBT or basal-plus therapy with insulin glargine plus insulin lispro can provide effective glycemic control in South American [136] and East Asian populations [115, 137] with T2DM.

Finally, no studies appear to have specifically evaluated BBT with insulin glargine plus insulin lispro in pregnant women with diabetes; however, available data for the individual agents suggest that both are safe for use in pregnancy [138, 139].

CONCLUSIONS

With the growing availability of alternative insulins for use in BBT, it is timely that this article reviews the current evidence regarding BBT combining insulin glargine 100 U/mL with insulin lispro in patients with T1DM and T2DM, including its use in special populations (children, elderly, pregnant women, patients with comorbidities, and people of different ethnicities).

Insulin glargine 100 U/mL and insulin lispro have both been available for many years, have been studied extensively, and are widely used as the basal and bolus components, respectively, of BBT. Insulin lispro was the first rapid-acting insulin analogue to become available and has been evaluated in a wide range of patients, and insulin glargine is regarded as a standard-of-care basal insulin. Given the length of their availability, a substantial evidence base exists to support the efficacy and safety of these agents as BBT or basal-plus therapy in patients with T1DM and T2DM.

Clinical studies indicate that in patients with T1DM, BBT with insulin glargine plus insulin lispro provides similar or better glycemic control, and less nocturnal hypoglycemia, than BBT involving human insulin as the basal and/or prandial component. Moreover, in patients with T1DM, BBT with insulin glargine 100 U/mL plus insulin lispro generally provides a similar level of glycemic control to that achieved with insulin lispro CSII, with similar rates of severe hypoglycemia.

In patients with T2DM receiving basal insulin, intensification of insulin therapy can generally be achieved by either initiating BBT or progressing to basal-plus therapy and then full BBT with prandial cover for all meals. Progression of insulin therapy can be achieved using various algorithms based on fasting and/or preprandial blood glucose levels to adjust the dosages of insulin glargine and insulin lispro. Algorithms for starting and intensifying insulin therapy are provided by the ADA [88] and the AACE/ACE [111]. Simple algorithms for the titration of prandial insulin lispro can facilitate patient self-management of insulin therapy. Most studies evaluating BBT with insulin glargine plus insulin lispro in patients with T2DM evaluated the noninferiority of premixed insulin versus BBT. These studies found that premixed insulin does not appear to provide any advantage over this BBT with respect to glycemic control or rates of hypoglycemia.

One of the key factors to be considered with insulin therapy is the need to achieve a balance between maintaining good glycemic control and minimizing the risk of hypoglycemic episodes. Studies such as AUTONOMY [121] demonstrate that, if well titrated, insulin therapy enables glycemic targets to be reached safely and simply.

Pooled analyses of studies involving insulin glargine or insulin lispro showed that these agents provided similar levels of efficacy and safety in elderly and young patients. In addition, insulin glargine plus insulin lispro is safe and effective in people of different ethnicities, and these insulins appear to be suitable for use

in other special populations such as pregnant women and patients with comorbidities.

In conclusion, BBT remains a relevant option for patients with T1DM and those with T2DM requiring insulin treatment. In particular, the widely used combination of insulin glargine 100 U/mL plus insulin lispro has established efficacy and safety, and should be considered a first-line option in patients for whom BBT regimens are being considered.

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