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REVIEW

Use of 50/50 Premixed Insulin Analogs in Type 2 Diabetes: Systematic Review and Clinical Recommendations

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ABSTRACT

Introduction: Premixed insulin analogs represent an alternative to basal or basal–bolus insulin regimens for the treatment of type 2 diabetes (T2D). “Low-mix” formulations with a low rapid-acting to long-acting analog ratio (e.g., 25/75) are commonly used, but 50/50 formulations (Mix50) may be more appropriate for some patients. We conducted a systematic literature review to assess the efficacy and safety

of Mix50, compared with low-mix, basal, or basal–bolus therapy, for insulin initiation and intensification.

Methods: MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, ClinicalTrials.gov, LillyTrials.com, and NovoNordisk-trials.com were searched (11 or 13 Dec 2016) using terms for T2D, premixed insulin analogs, and/or Mix50. Studies (randomized, nonrandomized, or observational; English only) comparing Mix50 with other insulins (except human) and reporting key efficacy [glycated hemoglobin (HbA1c), fasting and postprandial glucose] and/or safety (hypoglycemia, weight gain) outcomes were eligible for inclusion. Narrative reviews, letters, editorials, and conference abstracts were excluded. Risk of bias in randomized trials was assessed using the Cochrane tool.

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Results: MEDLINE and EMBASE searches identified 716 unique studies, of which 32 met inclusion criteria. An additional three studies were identified in the other databases. All 19 randomized trials except one were open label; risk of other biases was generally low. Although not conclusive, the evidence suggests that Mix50 may provide better glycemic control (HbA1c reduction) and, particularly, postprandial glucose reduction in certain patients, such as those with high carbohydrate diets and Asian patients, than low-mix and basal therapy. Based on this evidence and our experience, we provide clinical guidance on factors to consider when deciding whether Mix50 is appropriate for individual patients.

Conclusions: Mix50 may be more suitable than low-mix therapy for certain patients. Clinicians should consider not only efficacy and safety but also patient characteristics and preferences when tailoring insulin treatment to individuals with T2D.

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Keywords: Biphasic insulin; Diabetes mellitus; Type 2; Insulin lispro; Insulin aspart; Practice guideline; Systematic review

INTRODUCTION

The progressive nature of type 2 diabetes (T2D) requires continual monitoring and frequent treatment adjustment [1–6]. To minimize the adverse consequences of prolonged hyperglycemia, people with T2D are treated to reach individualized glycated hemoglobin (HbA1c) targets (often <6.5% or <7% (<48 or <53 mmol/mol) [2–5]). If HbA1c targets cannot be attained with non-insulin treatments, insulin should be initiated to replace or supplement other therapies.

Most international guidelines recommend that people with T2D initiate insulin with basal therapy, e.g., once-daily insulin glargine or neutral protamine Hagedorn (NPH), with or without concomitant oral hypoglycemic agents (OHAs) [1–6]. Some guidelines suggest premixed insulin analogs, i.e., mixtures of a rapid-acting insulin analog and a long-acting

protamine suspension of that analog, as an alternative to initiation with basal insulin [3, 4, 6]. The most commonly used premixed insulin analogs have a low ratio of rapid-acting to long-acting insulin analog (“low mix”), such as 25% insulin lispro, 75% insulin lispro protamine (Lispro 25; Humalog[®] Mix25[™] or Mix75/25[™]; Eli Lilly and Company) or 30% rapid-acting insulin aspart, 70% long-acting insulin aspart (biphasic insulin aspart 30 [BIAsp30]; NovoMix[®] 30; Novo Nordisk). However, formulations with equal proportions (“mid mix” or Mix50) of rapid- and long-acting insulin lispro (Lispro 50; Humalog[®] Mix50[™] or Mix50/50[™]; Eli Lilly and Company) or insulin aspart (BIAsp50; NovoMix[®] 50; Novo Nordisk) are also available, as is a “high-mix” formulation with 70% rapid-acting, 30% long-acting insulin aspart (BIAsp70; NovoMix[®] 70; Novo Nordisk). Premixed insulins, when given before meals, have the advantage of targeting both fasting and postprandial glucose levels with a single injection.

Intensification of insulin therapy should be considered for patients who do not reach HbA1c targets on once-daily basal or premixed analog therapy. The most common approach to intensification is basal–bolus therapy, in which prandial injections of rapid-acting insulin are added to basal therapy. Premixed insulin analogs can be employed for intensification by using two or, occasionally, three injections before meals. Regimens based on premixed analogs can be simpler than basal–bolus regimens, as the patient only requires one type of injection device. Conversely, basal–bolus regimens offer greater flexibility than premixed analogs. Most treatment guidelines suggest that both basal–bolus and premixed insulin analogs are appropriate options for intensification [1–6]. However, these guidelines do not provide advice regarding the choice of premixed ratio (i.e., low, mid, or high mix).

Several groups have published clinical guidance on the use of low-mix insulin analogs [7, 8]. However, to our knowledge, only one group has made clinical recommendations on the use of mid-mix (or high-mix) premixed analogs [9]. These recommendations, published in 2011 as part of a consensus statement, rely on

clinical evidence from just four studies [9]. Thus, recent evidence-based guidance on the use of Mix50 is lacking. Further, Mix50 may be more appropriate than other insulin therapy options for certain patients, such as those with high carbohydrate diets who require greater control of postprandial glucose. We therefore conducted a systematic review to assess the current evidence of the efficacy and safety of Mix50, compared with low-mix analogs, basal therapy, and basal-bolus therapy, for people with T2D requiring insulin initiation or intensification. Based on this evidence and our experience, we provide clinical recommendations and practical guidance on the use of Mix50.

METHODS

Literature Search Strategy

The following online databases were searched on 11 or 13 December 2016: MEDLINE via PubMed; EMBASE via Ovid; Cochrane Database of Systematic Reviews; ClinicalTrials.gov results database; LillyTrials.com; and NovoNordisk-trials.com. Search terms were optimized for each database. For MEDLINE, the search comprised “(diabetes mellitus, type 2 OR type 2 diabetes OR type II diabetes OR non-insulin dependent diabetes OR NIDDM) AND (insulin lispro OR insulin aspart OR biphasic insulins) AND (mix* OR premix* OR 50/50),” where asterisk indicates truncation. For EMBASE, the search comprised “(non insulin dependent diabetes OR diabetes mellitus, type 2 OR type 2 diabetes OR type II diabetes OR non-insulin dependent diabetes OR NIDDM) AND (insulin lispro OR insulin aspart) AND (mix* OR premix* OR 50/50).” The Cochrane Database of Systematic Reviews, ClinicalTrials.gov (restricted to trials with study results posted), LillyTrials.com, and NovoNordisk-trials.com sites were searched using “(insulin lispro OR insulin aspart).” Relevant studies were cross-checked against MEDLINE and EMBASE results to identify duplicate studies. All searches were restricted to reports in the English language only; there was no restriction on publication date.

Study Eligibility Criteria

Studies were considered for inclusion if they involved adults (≥ 18 years) with T2D who were treated with Mix50 in any regimen as initiation or intensification. Studies that compared Mix50 with any other insulin therapy, except human insulins, were eligible; although basal and premixed human insulins are still available, they are not commonly used in current clinical practice and have different pharmacokinetic profiles compared with analogs [1, 10]. Meta-analyses, systematic reviews, randomized controlled trials (RCTs), nonrandomized clinical trials, and prospective and retrospective observational studies were eligible for inclusion; narrative reviews, letters, editorials, commentaries, and conference abstracts were excluded.

Studies were eligible for inclusion if they reported any of the following outcomes: change from baseline (or end point levels) in HbA1c, fasting blood (FBG) or plasma (FPG) glucose, postprandial blood or plasma glucose (PPG), or self-monitored blood glucose (SMBG); proportion of patients achieving HbA1c targets; incidence of hypoglycemia; weight gain; patient-reported outcomes (e.g., quality of life, treatment satisfaction); or adherence.

Study Selection

The output from the MEDLINE and EMBASE searches was imported into a reference manager and duplicates removed. Titles and abstracts were screened against the inclusion criteria for potential eligibility. A subset of articles required review of the full text to establish eligibility. Studies identified in the other databases were compared against eligible studies identified in the MEDLINE and EMBASE database searches and duplicates removed. The bibliographies of relevant systematic reviews were manually screened for additional articles. Searches and screening were performed by a contracted medical writer using a search strategy and inclusion/exclusion criteria developed and approved by three of the authors (GD, GK, TW).

All authors agreed on the final studies for inclusion.

Data Extraction

Data relevant to the prespecified outcomes listed above were extracted into standardized data tables. Data extracted included article citation, country/region, sponsor, study design, duration, patient eligibility criteria, number of patients enrolled and completed, treatment regimens, efficacy outcomes, safety outcomes, and patient-reported outcomes. For presentation and interpretation of results, studies were grouped by whether Mix50 was used for initiation or intensification and by whether Mix50 was compared with low-mix insulin analogs, basal insulin, or basal–bolus regimens, resulting in six main sets of studies.

Risk of Bias Assessment

The risk of bias was assessed for RCTs using the Cochrane Collaboration tool [11]. The risk of bias for nonrandomized studies was not formally assessed, but the inherent biases associated with these studies were acknowledged.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

Literature Search Results

A total of 915 articles were retrieved from MEDLINE ($n = 214$) and EMBASE ($n = 701$) (Fig. 1). After removing duplicates, the titles and abstracts of 716 articles were screened. Of these, 684 articles were excluded, most commonly because they did not include data on Mix50 or they were the wrong type of publication (e.g., narrative review article). There were 32 articles that met the eligibility criteria

for inclusion in this review. Searching the other databases identified three additional, unpublished studies that met the eligibility criteria, for a total of 35 included articles or studies (hereafter referred to simply as “studies”) (Fig. 1; Table S1 in the Electronic supplementary material, ESM).

Characteristics of Included Studies

Of the 35 studies, there were two systematic reviews or meta-analyses [12, 13], 19 RCTs [14–32] (including three crossover studies [19, 25, 28]), two post hoc analyses of pooled data from RCTs [33, 34], ten prospective, non-randomized, observational or interventional studies [35–44], one retrospective observational study [45], and one consensus statement [9] (Table S1 in the ESM). Sample sizes ranged from 13 [42] to 744 [23]; overall, the studies enrolled more than 6000 patients. The studies were conducted in a broad range of countries from North America, South America, Europe, Africa, and Asia.

Nine studies examined Mix50 for insulin initiation [14, 16, 18–20, 22, 29, 31, 32] (Table 1), and 13 studies examined Mix50 for intensification [15, 17, 21, 23–27, 34, 36, 40–42] (Table 2). The remaining 13 studies were not included in these sets for reasons such as combining initiation and intensification or not comparing Mix50 with other insulins [9, 12, 13, 28, 30, 33, 35, 37–39, 43–45] (Table 3). There were no reports of patient adherence with Mix50.

Risk of Bias

Because all RCTs (and post hoc analyses of RCTs) except one [28] were open label, we classified the risk of bias for blinding of participants and personnel as high (Table 4). However, open-label RCTs are an accepted study design in insulin trials because of the need for dose titration to minimize hypoglycemia. Information on random sequence generation and allocation concealment was lacking in 8 of the 21 RCTs or post hoc analyses, and information regarding preplanned study outcomes,

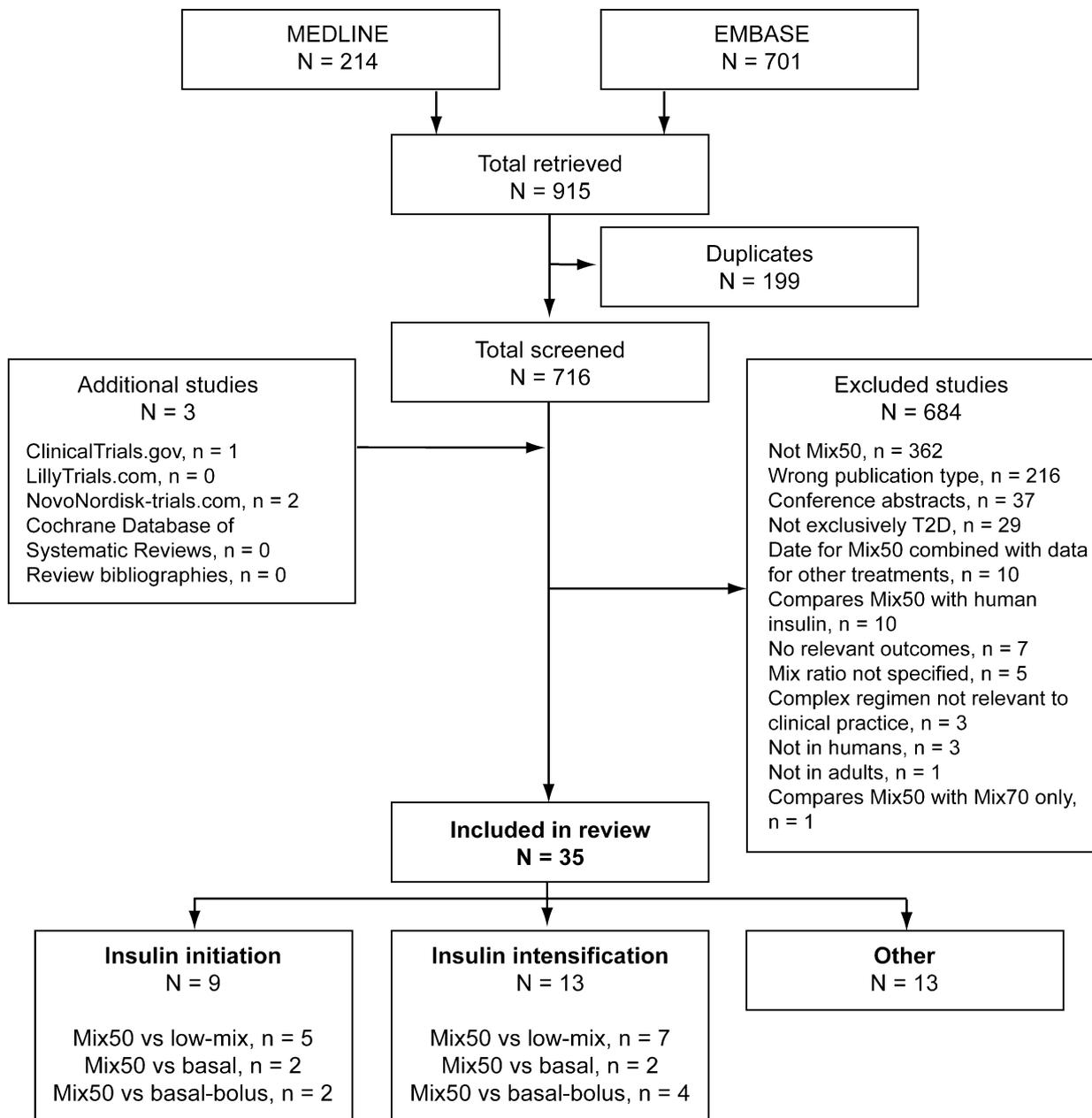


Fig. 1 Literature search flow diagram. *Low-mix* premixed insulin analog containing 25% or 30% rapid-acting component, *Mix50* premixed insulin analog containing

50% rapid-acting component, *Mix70* premixed insulin analog containing 70% rapid-acting component, *T2D* type 2 diabetes

which could be used to detect potential selective outcome reporting, was lacking in 11 of the 21 studies. In these cases, we classified the risk of these types of bias as “unclear.” For objective outcome measures such as HbA1c and glucose levels, we considered the risk of bias due to

inadequate blinding of assessors as low for most RCTs; however, we recognize that the risk of bias associated with an open-label study is high for certain, patient-reported outcomes, such as undocumented (i.e., self-reported) symptomatic hypoglycemia and quality of life measures.

Table 1 Summary of outcomes from studies of Mix50 for insulin initiation

First author (or study identifier), [reference], and countries	Study design Duration	Treatment groups	HbA1c change ^a	FBG/FPG change ^a	PBG/PPG change ^a	Hypoglycemia definition and incidence	Body weight/BMI change ^a
<i>Mix50 vs. low mix</i>							
Chen [14] China, Japan	RCT, OL subgroup analysis of Warada [31] 26 weeks	Lispro 50 BID (<i>n</i> = 160) vs. Lispro 25 BID (<i>n</i> = 168)	LS mean change (%) CHO intake \geq median (≥ 230.8 g): -1.67 vs. -1.35 ($P = 0.024$) CHO intake \geq median ($\geq 54\%$ of energy): -1.79 vs. -1.43 ($P = 0.009$) Fat intake \geq median (≥ 56.5 g): -1.83 vs. -1.48 ($P = 0.013$) Fat intake \geq median ($\geq 31\%$ of energy): -1.87 vs. -1.51 ($P = 0.014$) Protein intake \geq median (≥ 66.0 g): -1.82 vs. -1.50 ($P = 0.027$) Protein intake \geq median ($\geq 15\%$ of energy): -1.79 vs. -1.45 ($P = 0.022$) Energy intake $<$ median (< 1714.5 kcal): -1.77 vs. -1.45 ($P = 0.026$) Treatment differences for CHO, fat, or protein intake $<$ median and energy intake \geq median $P = \text{NS}$	NR Pre-morning meal SMBG (mg/dL) LS mean change -39.51 vs. -44.67 ($P = 0.079$)	NR	Symptomatic or asymptomatic with PG ≤ 3.9 mmol/L or probably symptomatic without PG measurement Total: 61.3% vs. 59.5% Nocturnal: 10.6% vs. 11.9% Severe (requiring assistance): 0% vs. 0%	LS mean change in BW (kg) $+2.08$ vs. $+2.17$ ($P = 0.796$)
Domeki [16] Japan	RCT, OL 48 weeks	Lispro 50 (<i>n</i> = 36) vs. BIAsp30 (<i>n</i> = 36) Before dinner + injections before breakfast and before lunch after 16 and 32 weeks, respectively, if HbA1c $\geq 7.4\%$	Baseline/end point mean values (%) 9.6 (<i>n</i> = 36)/7.7 (<i>n</i> = 13) vs. 9.9 (<i>n</i> = 36)/8.2 (<i>n</i> = 9), $P = \text{NS}$	Baseline/end point mean FPG (reported as mol/L) 130 (<i>n</i> = 36)/90 (<i>n</i> = 13) vs. 138 (<i>n</i> = 36)/105 (<i>n</i> = 9), $P = \text{NS}$	NR	Symptomatic overall: 8.3% vs. 8.3% Severe: 0% vs. 0%	Baseline/end point mean BMI (kg/m^2) 24.5 (<i>n</i> = 36)/27.2 (<i>n</i> = 13) vs. 24.4 (<i>n</i> = 36)/30.5 (<i>n</i> = 9), $P = \text{NS}$

Table 1 continued

First author (or study identifier), [reference], and countries	Study design Duration	Treatment groups	HbA1c change ^a	FBG/FPG change ^a	PBG/PPG change ^a	Hypoglycemia definition and incidence	Body weight/BMI change ^a
Su [29] China	RCT, OL, subanalysis of Watada [31] 26 weeks	Lispro 50 BID (<i>n</i> = 76) vs. Lispro 25 BID (<i>n</i> = 80)	LS mean change (%) -1.99 vs. -1.58 (<i>P</i> < 0.001) Subgroup analysis: Men: -2.11 vs. -1.65 (<i>P</i> = 0.017) Women: -1.91 vs. -1.44 (<i>P</i> = 0.014) Age < 65 years: -2.08 vs. -1.62 (<i>P</i> = 0.006) Age ≥ 65 years: -1.92 vs. -1.31 (<i>P</i> = 0.018) Baseline HbA1c ≥ 8.4%: -2.92 vs. -2.11 (<i>P</i> < 0.001) Baseline PPG ≥ 13.5 mmol/L: -2.60 vs. -1.84 (<i>P</i> < 0.001) Baseline mean BG excursion ≥ 4.4 mmol/L: -2.31 vs. -1.66 (<i>P</i> = 0.001) Baseline FPG ≥ 9.0 mmol/L: -2.65 vs. -1.94 (<i>P</i> = 0.001) Treatment differences for baseline HbA1c < 8.4%, baseline PPG < 13.5 mmol/L, baseline mean BG excursion < 4.4 mmol/L, and baseline FPG < 9.0 mmol/L, <i>P</i> = NS	LS mean change in FBG (mmol/L) -2.12 vs. -2.50 (<i>P</i> = 0.180)	NR LS mean change in SMBG was significantly greater in the Lispro 50 group vs. Lispro 25 after morning (<i>P</i> = 0.028) and evening (<i>P</i> = 0.001) meals	Symptomatic or asymptomatic with PG ≤ 3.9 mmol/L or probably symptomatic without PG measurement Episodes per person per year Total: 3.45 vs. 2.97 Nocturnal: 0.43 vs. 0.30 Severe (requiring assistance): no events in either group	LS mean difference (Lispro 50–Lispro 25) in change in BW (kg) 0.07 kg (<i>P</i> = 0.896)

Table 1 continued

First author (or study identifier), [reference], and countries	Study design Duration	Treatment groups	HbA1c change ^a	FBG/FPG change ^a	PBG/PPG change ^a	Hypoglycemia definition and incidence	Body weight/BMI change ^a
Warada [31] China, Korea, Japan, and Turkey	RCT, OL 26 weeks	Lispro 50 BID (<i>n</i> = 196) vs. Lispro 25 BID (<i>n</i> = 207)	LS mean change (%) −1.69 vs. −1.52 Lispro 25 was noninferior to Lispro 50 and Lispro 50 was noninferior to Lispro 25 Subgroup analysis: Baseline HbA1c ≥ median (≥ 8.4%): −2.35 vs. −2.05 (<i>P</i> = 0.026) Baseline PPG ≥ median (≥ 13.30 mmol/L): −2.26 vs. −1.94 (<i>P</i> = 0.027) CHO intake ≥ median (≥ 230.8 g): −1.67 vs. −1.35 (<i>P</i> = 0.024) CHO intake ≥ median (≥ 54% of energy): −1.79 vs. −1.43 (<i>P</i> = 0.009) Treatment differences for baseline HbA1c, baseline PPG, baseline FPG, and CHO intake < median and baseline FPG ≥ median <i>P</i> = NS	LS mean change in FBG (mmol/L) −1.99 vs. −2.37 <i>P</i> = 0.046	Improvement in PBG was significantly greater with Lispro 50 than Lispro 25 after morning (<i>P</i> = 0.038) and evening (<i>P</i> < 0.001) meals	Symptomatic or asymptomatic with PG ≤ 3.9 mmol/L or probably symptomatic without PG measurement Incidence per person per year Total: 6.343 vs. 5.661, <i>P</i> = 0.463 Nocturnal: 0.731 vs. 0.828, <i>P</i> = 0.688 Severe (requiring assistance): 0.073 vs. 0 (no events), <i>P</i> value ND	LS mean change in BW (kg) + 2.32 vs. + 2.31, <i>P</i> = 0.975
Zafar [32] China	RCT, OL 12 weeks	Lispro 50 BID (<i>n</i> = 73) vs. Lispro 25 BID (<i>n</i> = 73)	Mean change (%) −4.2 vs. −3.6 (<i>P</i> < 0.05)	Mean change in FBG (mmol/L) −2.6 vs. −1.1 (<i>P</i> < 0.05)	Mean change in PBG (mmol/L) −4.2 vs. −2.0 (<i>P</i> < 0.05)	Minor (BG ≤ 3.9 mmol/L; self-treatable): 6.84% vs. 5.48% (<i>P</i> = NS) Nocturnal: 0% vs. 2.74% (<i>P</i> = NS) Major (neurological symptoms; requiring assistance): 0% vs. 0%	Mean change in BW (kg) + 1.92 vs. + 2.03 (<i>P</i> = NS)

Table 1 continued

First author (or study identifier), [reference], and countries	Study design Duration	Treatment groups	HbA1c change ^a	FBG/FPG change ^a	PBG/PPG change ^a	Hypoglycemia definition and incidence	Body weight/BMI change ^a
<i>Mix50 vs. basal</i>							
Jacober [19] United States	RCT, OL, crossover 8 months	Lispro 50/Lispro 25 T1D (Lispro 50 before breakfast and lunch, Lispro 25 before dinner) vs. glargine OD (<i>n</i> = 60 crossover)	LS mean change from pretherapy (%): -1.01 vs. -0.75 (<i>P</i> = 0.0068)	Mean FBG at end point (mg/dL) Approx. 125 for both groups (<i>P</i> = NS) (presented in figure, data NR; change values NR)	NR	Symptomatic and/or BG ≤ 4.0 mmol/L; self-reported Mean episodes per patient/30 days: 4.71 vs. 2.31 (<i>P</i> = 0.0010) Nocturnal: 0.94 vs. 0.93 (<i>P</i> = 0.9701)	LS mean change in BW from pretherapy (kg) 1.98 vs. 1.52 (<i>P</i> = 0.457)
Kazda [22] Germany	RCT, OL 24 weeks	Lispro 50 T1D (<i>n</i> = 54) vs. insulin lispro T1D (<i>n</i> = 52) vs. glargine OD (<i>n</i> = 53)	Mean change (%) -1.2 vs. -1.1 vs. -0.3 (<i>P</i> < 0.001 Lispro 50 vs. glargine; <i>P</i> = 0.001 insulin lispro vs. glargine)	Mean change in FBG (mmol/L): -0.9 vs. -0.9 vs. -2.6 (<i>P</i> < 0.001 Lispro 50 vs. glargine; <i>P</i> < 0.001 insulin lispro vs. glargine)	Mean change in PBG (mmol/L): -2.8 vs. -3.0 vs. -2.6 vs. glargine; <i>P</i> < 0.01 insulin lispro vs. glargine) Mean change in PBG excursions (mmol/L): -1.8 vs. -2.1 vs. -0.1 (<i>P</i> < 0.001 Lispro 50 vs. glargine; <i>P</i> < 0.001 insulin lispro vs. glargine)	Symptomatic and/or BG < 3.0 mmol/L; self-reported Mean episodes per 100 patient-days: 1.5 vs. 1.4 vs. 1.0 Severe: none in any group	Mean change in BW (kg): + 1.8 vs. + 2.3 vs. + 0.7 Mean change in BMI (kg/m ²): + 0.6 vs. + 0.9 vs. + 0.2 (<i>P</i> = 0.19 Lispro 50 vs. glargine; <i>P</i> = 0.048 insulin lispro vs. glargine)
<i>Mix50 vs. basal-bolus</i>							
Giugliano [18] Brazil, Canada, Egypt, India, Mexico, Portugal, Romania, Spain, and Turkey	RCT, OL 48 weeks	Lispro 50 and/or Lispro 25 OD, BID, or TID, titrated with algorithm (<i>n</i> = 171) vs. glargine OD + insulin lispro OD, BID, or TID, titrated with algorithm (<i>n</i> = 173)	LS mean change (%): -1.57 (<i>P</i> = 0.556) vs. -1.65	NR	NR	Symptomatic and/or BG ≤ 4.2 mmol/L; self-reported Mean incidence per patient per year: 9.63 vs. 8.13 (<i>P</i> = 0.435) Nocturnal: 1.91 vs. 1.09 (<i>P</i> = 0.066) Severe: 0.09 vs. 0.12 (<i>P</i> = 0.852)	Mean change in BW (kg): + 2.31 vs. + 2.32 (<i>P</i> = 0.819)

Table 1 continued

First author (or study identifier), [reference], and countries	Study design Duration	Treatment groups	HbA1c change ^a	FBG/FPG change ^a	PBG/PPG change ^a	Hypoglycemia definition and incidence	Body weight/BMI change ^a
Jain [20] Australia, Canada, France, Greece, India, Republic of Korea, Mexico, Russia, and Spain	RCT, OL 36 weeks	Lispro 50 OD, BID, or T1D, titrated with algorithm (<i>n</i> = 242) vs. glargine OD + insulin lispro OD, BID, or T1D, titrated with algorithm (<i>n</i> = 242)	LS mean change (%): -1.76% vs. -1.93% (<i>P</i> = 0.097) Noninferiority of Lispro 50 to G + L not achieved	LS mean FBG at week 36 (mmol/L): 7.0 vs. 6.5 (<i>P</i> = 0.010; change values NR)	LS mean post-dinner PBG at week 36 (mmol/L): 9.3 vs. 9.8 (<i>P</i> = 0.010; change values NR) For post-breakfast and post-lunch PBG, <i>P</i> = NS (presented in figure, change values NR)	Symptomatic and/or BG < 3.9 mmol/L, % patients with episodes: 74.5% vs. 74.6% (<i>P</i> = NS) Nocturnal: 46.9% vs. 46.7% (<i>P</i> = NS) Severe (requiring assistance): 3.4% vs. 2.1% (<i>P</i> = NS)	LS mean change in BW (kg): + 3.09 vs. + 3.19 (<i>P</i> = 0.803)

BLAsp30 30% soluble insulin aspart, 70% protamine-crystallized insulin aspart, *BG* blood glucose, *BID* twice daily, *BMI* body mass index, *BW* body weight, *CHO* carbohydrate, *FBG* fasting blood glucose, *FPG* fasting plasma glucose, *G + L* insulin glargine plus insulin lispro, *HbA1c* glycated hemoglobin, *Lispro 25 25%* insulin lispro, 75% insulin lispro protamine suspension, *Lispro 50 50%* insulin lispro, 50% insulin lispro protamine suspension, *LS* least squares, *ND* not determined, *NR* not reported, *NS* not significant, *OD* once daily, *OL* open-label, *PBG* postprandial blood glucose, *PG* plasma glucose, *PPG* postprandial plasma glucose, *RCT* randomized controlled trial, *SMBG* self-monitored blood glucose, *T1D* three times daily

^a Mean change from study baseline to study end point, except where indicated

Table 2 Summary of outcomes from studies of Mix50 for insulin intensification

First author (or study identifier), [reference], and countries	Study design Duration	Treatment groups	HbA1c change ^a	FBG/FPG change ^a	PBG/PPG change ^a	Hypoglycemia incidence	Body weight/ BMI change ^a
<i>Mix50 vs. low mix</i>							
Cucinotta [15] Europe (18 countries)	RCT, OL 36 weeks	BLAsp50 T1D (<i>n</i> = 201) vs. BLAsp30 BID (<i>n</i> = 200) vs. BLAsp70 T1D (<i>n</i> = 198)	Mean change (%) -1.9 vs. -1.6 vs. -1.6 (<i>P</i> = 0.004 vs. BLAsp50 vs. BLAsp30)	FPG at 36 weeks was higher for BLAsp70 (<i>P</i> < 0.05) but not for BLAsp50 (<i>P</i> = NS) compared with BLAsp30 (presented in figure; change values NR)	Mean PPG increment significantly lower with both BLAsp50 (<i>P</i> = 0.0002) and BLAsp70 (<i>P</i> < 0.0001) vs. BLAsp30 (presented in figure; data NR)	Symptomatic and/or BG < 3.1 mmol/L; self-reported Episodes per year: Over 24 h Major (requiring assistance): 0.0 vs. 0.0 vs. 0.1 Minor: 9.3 vs. 7.9 vs. 13.3 Nocturnal Major: 0.0 vs. 0.0 vs. 0.0 Minor: 1.3 vs. 1.6 vs. 1.6 RR of 24-h minor episodes significantly higher with BLAsp70 vs. BLAsp30 (<i>P</i> = 0.0002), but not with BLAsp50 vs. BLAsp30 (<i>P</i> = 0.2185)	Baseline-adjusted change in BW (kg): ~ + 4 vs. ~ + 3.5 vs. ~ + 4 (<i>P</i> = NS)
Farcasiu [17] Hungary, Croatia, Poland, Romania, South Africa, and Turkey	RCT, OL 16 weeks (+ 2-week lead-in with previous Lispro 25 or BLAsp30 BID)	Lispro 50 T1D (<i>n</i> = 151) vs. Lispro 25/BLAsp30 BID (<i>n</i> = 151)	Mean change (%) -1.0 vs. -0.82 (<i>P</i> = NS)	FPG at 16 weeks (mg/dL): 161.1 vs. 153.9 (<i>P</i> = 0.0129)	Mean change in post-lunch PBG (mg/dL): -64.8 vs. -41.5 (<i>P</i> < 0.05) Mean change in post-lunch BG excursion (mg/dL): -38.4 vs. -9.2 (<i>P</i> < 0.001)	Symptomatic and/or PG ≤ 70 mg/dL LS mean episodes/patient/30 days: Overall: 0.56 vs. 0.61 (<i>P</i> = 0.7230) Nocturnal: 0.04 vs. 0.13 (<i>P</i> = 0.0063) Severe (requiring assistance): 0.00 vs. 0.01 (<i>P</i> = 0.8876)	Mean change in BW (kg): + 1.3 vs. + 0.4 (<i>P</i> = 0.0009)

Table 2 continued

First author (or study identifier), [reference], and countries	Study design Duration	Treatment groups	HbA1c change ^a	FBG/FPG change ^a	PBG/PPG change ^a	Hypoglycemia incidence	Body weight/ BMI change ^a
NCT00627445 [24] China	RCT, OL 16 weeks (+ 4-week lead-in with previous insulin)	BIAsp50 before breakfast and lunch + BIAsp30 before dinner (<i>n</i> = 219) vs. BIAsp30 BID (<i>n</i> = 222)	LS mean change (%): -1.790 vs. -1.517 (<i>P</i> < 0.001) BIAsp50/ BIAsp30 was non-inferior to, and also superior to, BIAsp30	LS mean change in pre-breakfast SMBG (mmol/L): -2.52 vs. -2.43 (<i>P</i> = 0.516)	LS mean change in PBG (mmol/L): Post-breakfast: -3.92 vs. -4.00 (<i>P</i> = 0.716) Post-lunch: -4.37 vs. -3.15 (<i>P</i> < 0.001) Post-dinner: -3.46 vs. -3.37 (<i>P</i> = 0.746)	Symptomatic and/or PG < 3.1 mmol/L; self-reported Episodes per person per year Total: 11.1 vs. 10.3 (<i>P</i> = 0.1976) Nocturnal: 2.04 vs. 1.23 (<i>P</i> = 0.0130) Major (requiring assistance): 1 vs. 0 events	LS mean change in BW (kg): +1.188 vs. +0.817 (<i>P</i> = 0.0851)
NCT00834262 [40] Israel	Prospective, nonrandomized, OL, observational 13 weeks	BIAsp50 (<i>n</i> = 91) vs. BIAsp30 (<i>n</i> = 106) vs. BIAsp70 (<i>n</i> = 14) vs. combinations (<i>n</i> = 127) Dose and frequency at physician's discretion	Mean change (% [SD]): ^b -0.6 (1.5) vs. -0.7 (1.3) vs. -0.6 (0.9) vs. -0.9 (1.4)	Mean change (mg/dL [SD]): ^b -17.5 (52.3) vs. -50.3 (57.6) vs. -23.5 (74.2)	Mean change in PPG (mg/dL [SD]): ^b Post-breakfast: -44.4 (70.0) vs. -25.1 (53.6) vs. -72.8 (60.2) vs. -35.1 (71.0) Post-lunch: -43.7 (73.1) vs. -27.6 (51.0) vs. -56.9 (58.8) vs. -36.9 (80.3) Post-dinner: -45.3 (71.5) vs. -25.2 (56.2) vs. -75.5 (56.8) vs. -34.4 (86.1)	Symptomatic and/or PG < 3.1 mmol/L; self-reported Episodes per patient-year: 3.8 vs. 2.5 vs. 0.3 vs. 4.1	Mean change in BW (kg): +0.4 vs. +0.8 vs. -0.8 vs. +0.7
Roach [25] India	RCT, OL, DB for pre-breakfast insulin, crossover 16 weeks (+ 4-week lead-in with human insulin 30/70 BID)	Lispro 50 before breakfast + Lispro 25 before dinner vs. Lispro 25 BID (<i>n</i> = 116; crossover)	Mean at 16 weeks (%): 8.14 vs. 8.14 (<i>P</i> = 0.919; change values NR)	Mean FBG at 16 weeks (mmol/L): 9.5 vs. 8.9 (<i>P</i> = 0.129; change values NR)	Mean PBG after CHO-rich breakfast at 16 weeks (mmol/L): 10.9 vs. 12.4 (<i>P</i> = 0.0012; change values NR)	Symptomatic; self-reported % patients with episodes: 32.4% vs. 26.1% (<i>P</i> = 0.078) Severe (requiring assistance): no episodes	NR
Shimizu [41] Japan	Prospective, nonrandomized, interventional 24 weeks	Lispro 50 BID (PPG > 200 mg/dL; <i>n</i> = 20) vs. Lispro 25 BID (PPG < 200 mg/dL; <i>n</i> = 20)	Mean (%) at baseline: 8.3 vs. 8.1 Mean (%) at 24 weeks: 7.5 vs. 7.9	Mean FPG at baseline (mg/dL): 143.0 vs. 150.7 Mean FPG at 24 weeks (not significantly changed from baseline)	Mean PPG at baseline (mg/dL): 228.8 vs. 181.8 (<i>P</i> < 0.05) Mean PPG at 24 weeks (mg/dL): 182.5 vs. NR (not significantly changed from baseline)	Not defined No severe episodes in either group	Mean BW at baseline (kg): 59.1 vs. 59.1 Mean BW at 24 weeks (kg): 60.0 vs. 59.3

Table 2 continued

First author (or study identifier), [reference], and countries	Study design Duration	Treatment groups	HbA1c change ^a	FBG/FPG change ^a	PBG/PPG change ^a	Hypoglycemia incidence	Body weight/ BMI change ^a
Tanaka [42] Japan	Prospective, non-comparative, OL, switching study 2 days	Switched from low-mix to Lispro 50 BID (<i>n</i> = 13)	NR	NR	Post-breakfast PBG lower with Lispro 50 than before switch (<i>P</i> < 0.01)	Symptomatic No hypoglycemic symptoms	NR
<i>Mix50 vs. basal</i>							
Hirsch [34] Australia, Greece, India, The Netherlands, Poland, Puerto Rico, and United States	Post-hoc analysis of Robbins [26] 24 weeks (+ 6-week lead-in with Lispro 25 BID)	Lispro 50 TID (<i>n</i> = 157) vs. glargine OD (<i>n</i> = 158)	Mean change (%): -0.72 vs. -0.35 (<i>P</i> < 0.001)	Mean FBG change (mg/dL): -10.4 vs. -34.9 (<i>P</i> < 0.001)	NR	Symptomatic or BG < 3.5 mmol/L; self-reported Episodes per patient per 30 days: All: 0.65 vs. 0.28 (<i>P</i> = 0.017) Nocturnal: 0.19 vs. 0.16 (<i>P</i> = 0.017)	BW at end point (kg): 89.96 vs. 87.64 (<i>P</i> < 0.001)
Robbins [26] Australia, Greece, India, The Netherlands, Poland, Puerto Rico, and United States	RCT, OL 24 weeks (+ 6-week lead-in with Lispro 25 BID)	Lispro 50 TID (<i>n</i> = 158) vs. glargine OD (<i>n</i> = 159)	Mean change (%): -0.7 vs. -0.4 (<i>P</i> < 0.001)	Mean FBG at 24 weeks (mmol/L): 8.1 vs. 6.5 (<i>P</i> < 0.001) (change values NR)	Mean change in daily 2-h PBG excursion (mmol/L): -1.0 vs. + 0.6 (<i>P</i> < 0.001)	Symptomatic or BG < 3.5 mmol/L; self-reported Episodes per patient per 30 days: entire treatment period: all: 0.8 vs. 0.5 (<i>P</i> = 0.07) Nocturnal: 0.2 vs. 0.3 (<i>P</i> = 0.30) At end point: all: 0.7 vs. 0.3 (<i>P</i> = 0.02) Nocturnal: 0.2 vs. 0.2 (<i>P</i> = 0.62)	Mean change in BW (kg): + 1.2 vs. -0.5 (<i>P</i> < 0.001)
<i>Mix50 vs. basal-bolus</i>							
Ito [36] Japan	Prospective, observational 16 weeks	Lispro 50 or BIAsp50 switched to glargine OD + glulisine BID (<i>n</i> = 28)	Mean change (%): -0.1 (change <i>P</i> = 0.64)	NR	NR	No severe hypoglycemia (symptomatic, requiring assistance)	Mean BW, baseline/end point (kg): 69.3/69.6 (<i>P</i> = 0.38) Mean BMI, baseline/end point (kg/m ²): 25.5/25.6 (<i>P</i> = 0.31)

Table 2 continued

First author (or study identifier), [reference], and countries	Study design Duration	Treatment groups	HbA1c change ^a	FBG/FPG change ^b	PBG/PPG change ^a	Hypoglycemia incidence	Body weight/ BMI change ^a
Jia [21] China, Taiwan, Korea	RCT, OL 24 weeks	Lispro 50 before breakfast and lunch + Lispro 25 before dinner (<i>n</i> = 199) vs. glargine OD + lispro TID (<i>n</i> = 203)	LS mean change (%): −1.1 vs. −1.1 Noninferiority demonstrated	LS mean change in FBG (based on SMBG morning pre-meal) (mmol/L): −0.8 vs. −1.2 (<i>P</i> = 0.002)	LS mean change in PBG (mmol/L): Post-lunch: −3.5 vs. −3.0 (<i>P</i> = 0.005) Post-breakfast and post-dinner: <i>P</i> = NS (presented in figure, values NR)	Symptomatic and PG ≤ 3.9 mmol/L Mean episodes per patient per 30 days: 0.47 vs. 0.41 (<i>P</i> = 0.148) Nocturnal: 0.03 vs. 0.05 (<i>P</i> = 0.235) Severe (requiring assistance): no episodes in either group	Change in BW (kg): +0.8 vs. +0.7 (<i>P</i> = NR)
Miser [23] Argentina, Australia, Brazil, Canada, Greece, Hungary, India, the Netherlands, Romania, Spain, and United States	RCT, OL, substudy 6 months (substudy, after 6 months main study)	Lispro 50 TID (<i>n</i> = 174) vs. glargine OD + insulin lispro TID (<i>n</i> = 171) (Arm B only; received Lispro 25 in main study)	Mean HbA1c (%) at 6 months: 8.2 vs. 8.2 (<i>P</i> = 0.990) Noninferiority of Lispro 50 to G + L was shown	No significant differences in PG at end point (data NR)	NR	Symptomatic or PG ≤ 70 mg/dL; self-reported Mean episodes per patient per year: Overall: 11.1 vs. 12.1 (<i>P</i> = 0.623) Nocturnal: 2.5 vs. 2.4 (<i>P</i> = 0.949) Severe (events; requiring assistance): 2 vs. 0 (<i>P</i> = 0.188)	Mean change in BW (kg): 0.6 vs. 0.9 (<i>P</i> = 0.345)

Table 2 continued

First author (or study identifier), [reference], and countries	Study design Duration	Treatment groups	HbA1c change ^a	FBG/FPG change ^a	PBG/PPG change ^a	Hypoglycemia incidence	Body weight/ BMI change ^a
Rosenstock [27] Puerto Rico and United States	RCT, OL 24 weeks	Lispro 50 T1D (<i>n</i> = 187) vs. glargine OD + insulin lispro T1D (<i>n</i> = 187)	Mean change (%): -1.87% vs. -2.09% (<i>P</i> = 0.021) Noninferiority of Lispro 50 to G + L was not demonstrated	Mean FBG at 24 weeks (mmol/L): 8.8 vs. 8.2 (<i>P</i> = 0.013) (change values NR)	Mean PBG at 24 weeks (mmol/L): Post-breakfast: 9.6 vs. 8.6 (<i>P</i> = 0.002) (change values NR) For post-lunch and post-dinner PBG, treatment difference NS	Symptomatic; self-reported Episodes per patient per year: Overall: 51.20 vs. 48.70 (<i>P</i> = 0.619) Nocturnal: 4.78 vs. 6.17 (<i>P</i> = 0.139) Severe (requiring assistance): 0.10 vs. 0.04 (<i>P</i> = 0.266)	Mean change in BW (kg): 4.0 vs. 4.5 (<i>P</i> = 0.224)

BG blood glucose, *BLA_{sp}30* 30% soluble insulin aspart, 70% protamine-crystallized insulin aspart, *BLA_{sp}50* 50% soluble insulin aspart, 50% protamine-crystallized insulin aspart, *BLA_{sp}70* 70% soluble insulin aspart, 30% protamine-crystallized insulin aspart, *BID* twice daily, *BMI* body mass index, *BHV* body weight, *CHO* carbohydrate, *DB* double-blind, *FBG* fasting blood glucose, *FPG* fasting plasma glucose, *G + L* insulin glargine plus insulin lispro, *HbA1c* glycated hemoglobin, *Lispro 25 25%* insulin lispro, 75% insulin lispro protamine suspension, *Lispro 50 50%* insulin lispro, 50% insulin lispro protamine suspension, *LS* least squares, *NR* not reported, *NS* not significant, *OL* open-label, *PBG* postprandial blood glucose, *PG* plasma glucose, *PPG* postprandial plasma glucose, *RCT* randomized controlled trial, *RR* relative risk, *SD* standard deviation, *SMBG* self-monitored blood glucose, *T1D* three times daily

^a Mean change from study baseline to study end point, except where indicated
^b Standard deviations provided because no statistical comparisons were made

Table 3 Summary of outcomes from additional studies of Mix50

First author and [reference]	Study type	Patient population	Reason for exclusion from quality assessment	Relevant efficacy outcomes	Relevant safety outcomes
Akahori [35]	Observational Approx. 11 months	T2D with poor glycemic control Lispro 50 (<i>n</i> = 19) vs. BIAsp30 (<i>n</i> = 20)	Combined initiation and intensification	Mean HbA1c (%): Baseline, 9.9 vs. 10.1 Week 12, 6.9 vs. 7.0 Week 48, 7.0 vs. 7.3 (<i>P</i> = 0.03) HbA1c < 6.9% at week 48: 60.0% vs. 25.0% (<i>P</i> = 0.01) Mean FBG (mg/dL): baseline, 119.4 vs. 122.6 Week 48, 127.4 vs. 132.6 (<i>P</i> = NS) Mean PPG after 1 week (mg/dL): Post-breakfast, 147.6 vs. 170.0 (<i>P</i> = 0.34) Post-lunch, 146.9 vs. 161.0 (<i>P</i> = 0.51) Post-dinner, 116.0 vs. 204.0 (<i>P</i> = 0.01)	No major and few minor (symptoms only) hypoglycemic episodes (<i>P</i> = NS) No significant changes in BMI in either group
Brito [9]	Consensus statement	Patients currently on BIAsp30 who require intensification	Presents clinical evidence for use of high-mix insulin analogs (based on 4 studies of BIAsp30, BIAsp50, and BIAsp70)	Patients poorly controlled on low-mix insulin BID or T1D considered most likely to benefit from switching to high-mix insulin analogs Patients with normal FPG but elevated PPG may benefit most from BIAsp70 Patients with elevated FPG and PPG levels may benefit most from BIAsp50 Provides algorithms for intensification, depending on patient's PPG and FBG	PPG should not exceed 9 mmol/L as long as hypoglycemia is avoided Down-titration recommended if major or recurrent minor hypoglycemia occurs
Cho [45]	Retrospective observational Approx. 2 weeks (perioperative)	Patients requiring intensive insulin treatment to stabilize glycemic control before surgery Lispro 50 T1D (<i>n</i> = 20) vs. basal-bolus (insulin type NR; <i>n</i> = 27)	Perioperative	Lispro 50 T1D and basal-bolus therapy were equally effective in controlling BG at 1 day before or 7 days after surgery	No differences in hypoglycemia (symptomatic or BG < 60 mg/dL), infections, or surgical complications between Lispro 50 T1D and basal-bolus therapy

Table 3 continued

First author and [reference]	Study type	Patient population	Reason for exclusion from quality assessment	Relevant efficacy outcomes	Relevant safety outcomes
Davidson [33]	Post-hoc analysis of ethnicity, including 2 RCTs involving Lispro 50 [26, 27]	Patients treated with Lispro 50, Lispro 25, basal (glargine or NPH), or basal-bolus (G + L)	Basal and basal-bolus groups combined	<p>Lispro 50: no effect of ethnicity on change in HbA1c, % of patients achieving HbA1c targets, or FPG at end point</p> <p>Lispro 25: change in HbA1c significantly lower in Asian (−0.8%) and Latino/Hispanic (−0.9%) patients compared with Caucasian patients (−1.3%; $P < 0.05$)</p> <p>Significantly fewer Asian patients achieved HbA1c < 7.0% compared with Caucasian patients (2.3% vs. 23.3%; $P < 0.05$)</p> <p>Basal/basal-bolus: change in HbA1c significantly greater in Latino/Hispanic (−0.9%) patients compared with Caucasian patients (−0.3%; $P < 0.01$)</p> <p>Significantly more Latino/Hispanic patients achieved HbA1c < 7.0% compared with Caucasian patients (36.5% vs. 14.0%; $P < 0.01$)</p>	<p>Lispro 50: no effect of ethnicity on BW or hypoglycemia (definitions varied among studies), except a higher rate of severe episodes in Asian patients compared with Caucasian patients ($P < 0.01$)</p> <p>Lispro 25; no effect of ethnicity on BW or hypoglycemia</p> <p>Basal/basal-bolus: no effect of ethnicity on BW or hypoglycemia</p>
Ilag [12]	SR of 7 RCTs, including 3 RCTs involving Lispro 50 [19, 22, 26]	T2D requiring insulin initiation or intensification	Combined initiation and intensification; did not conduct MA	<p>Changes in HbA1c, range:</p> <p>Lispro 50: −0.72% to −1.2%</p> <p>Glargine: −0.3% to −0.75% ($P \leq 0.007$)</p> <p>More patients achieved HbA1c target with Lispro 50 vs. glargine</p> <p>FBG was lower with glargine vs. Lispro 50 in 2 trials and NR in 1 trial</p> <p>PPG was lower with Lispro 50 vs. glargine in 2 trials and similar in 1 trial</p> <p>Insulin doses were higher with Lispro 50 than with basal</p>	<p>More hypoglycemic episodes with Lispro 50 than with basal (definitions varied among studies)</p> <p>No significant difference in BW gain between treatments or NR</p>
Mashitani [37]	Noncontrolled, interventional, 24 weeks	Insulin-naive patients poorly controlled on SU Lispro 50 OD ($n = 15$)	Did not compare Lispro 50 with low-mix, basal, or basal-bolus	<p>Mean (SD) HbA1c (%):</p> <p>Baseline, 9.0 (0.9)</p> <p>Week 24, 7.5 (0.9) ($P < 0.01$ vs. baseline)</p> <p>HbA1c < 7.0: 60%</p> <p>Significantly lower SMBG values at all time points except after dinner compared with baseline</p>	No significant changes in BW

Table 3 continued

First author and [reference]	Study type	Patient population	Reason for exclusion from quality assessment	Relevant efficacy outcomes	Relevant safety outcomes
Nakashima [38]	Nonrandomized, interventional 48 weeks	Patients (no insulin for ≥ 6 months) who required intensification Lispro 50 OD, increased to BID or T1D if required ($n = 135$)	Did not compare Lispro 50 with low-mix, basal, or basal-bolus	Mean change in HbA1c (%): -1.29 ($P < 0.001$ vs. baseline) HbA1c $< 6.9\%$: 18.5% HbA1c $< 7.4\%$: 52.6%	Hypoglycemia incidence (symptomatic, self-reported): Any episode: 65.9% Daytime: 65.9% Nocturnal: 5.9% Daytime severe: 2.2% Nocturnal severe: 0.7% All severe hypoglycemic episodes (requiring assistance) occurred in patients on Lispro 50 T1D who did not achieve HbA1c targets Mean change in BW (kg): $+ 1.3$ ($P < 0.001$ vs. baseline) Mean change in BMI (kg/m^2): $+ 0.48$ ($P < 0.001$ vs. baseline)
NCT00755833 [39]	Observational 8 weeks to 17 months	T2D treated with biphasic human insulin requiring intensification B1Asp50 T1D ($n = 63$) vs. B1Asp50 BID ($n = 43$) vs. B1Asp50 BID + B1Asp30 OD ($n = 65$)	Compared different B1Asp50 regimens	B1Asp50 BID vs. B1Asp50 T1D vs. B1Asp50/30 at 12 months Mean change (SD) in HbA1c (%): -0.6 (0.8) vs. -1.3 (1.8) vs. -1.3 (1.3) ($P < 0.0001$ vs. baseline for each treatment) HbA1c $\leq 6.5\%$: 7.0% vs. 11.1% vs. 7.7% HbA1c $< 7\%$: 20.9% vs. 15.9% vs. 13.8% Mean (SD) change in FPG (mmol/L) for all patients combined: -1.3 (3.6) ($P < 0.0001$ vs. baseline) Mean (SD) change in PPG (mmol/L) for all patients combined: -2.5 (3.0) ($P < 0.0001$ vs. baseline)	Major hypoglycemic episodes (not defined) in last 3 months for all patients combined: 4.5% at 12 months Mean change in BW at 12 months for all patients combined (kg): $+ 1.1$ ($P < 0.0001$ vs. baseline)
Qayyum [13]	SR, MA of 45 trials, including 3 RCTs involving Lispro 50 [19, 22, 26]	T2D requiring insulin initiation or intensification	Combined initiation and intensification	Mean difference (95% CI) of change in HbA1c (%): glargine vs. Lispro 50 = -0.40 ($-0.65, -0.15$) (significant in favor of Lispro 50) Mean difference (95% CI) of change in FBG/PPG (mg/dL): glargine vs. Lispro 50 = 24.7 (19.0, 30.4) (significant in favor of glargine) Mean difference (95% CI) of change in PBG/PPG (mg/dL): glargine vs. Lispro 50 = -32.6 ($-48.2, -17.1$) (significant in favor of Lispro 50)	Hypoglycemia (definitions varied among studies) (OR [95% CI]): combined premixed analogs (Lispro 25, B1Asp30, Lispro 50) vs. basal insulin = 2.02 (1.35, 3.04) Pooled difference (95% CI) in change in BW (kg): combined premixed analogs (Lispro 25, B1Asp30, Lispro 50) vs. basal insulin = 2.0 (1.1, 3.0)

Table 3 continued

First author and [reference]	Study type	Patient population	Reason for exclusion from quality assessment	Relevant efficacy outcomes	Relevant safety outcomes
Schwartz [28]	RCT, crossover	T2D using insulin (but not glargine) <i>N</i> = 23	Single-dose study	Incremental AUC of serum glucose over 4 h after test meal significantly lower with Lispro 50 than with Lispro 25 ($P < 0.025$) Mean 2-h PPG (mg/dL): Lispro 50 vs. Lispro 25: 159 vs. 198 ($P < 0.05$) Mean maximal PPG (mg/dL): Lispro 50 vs. Lispro 25: 194 vs. 222 ($P = \text{NR}$)	No serious adverse events
Suzuki [30]	RCT 12 months	T2D with HbA1c $\geq 7\%$ despite maximal OHAs Lispro 50 ($n = 12$) vs. Lispro 50 + SU ($n = 10$)	Unclear whether patients were insulin-naïve or insulin-treated at baseline (mean [SD] insulin dose at baseline = 0.23 [0.18] U/kg) Does not compare Mix50 with other insulin	Mean change in HbA1c (%): Lispro 50 vs. Lispro 50 + SU = -2.02 vs. -1.55 ($P = 0.16$) HbA1c $< 7.0\%$: Lispro 50 vs. Lispro 50 + SU = 66.7% vs. 50.0% ($P = 0.22$) HbA1c $< 6.5\%$: Lispro 50 vs. Lispro 50 + SU = 41.7% vs. 20.0% ($P = 0.14$)	Incidence of slight hypoglycemia (not defined) same in both groups; no serious hypoglycemia (not defined) Mean change in BMI (%): Lispro 50 vs. Lispro 50 + SU = 7.0 vs. 4.5 ($P = 0.08$)
Tanaka [43]	Observational 6 months	Patients with poor glycemic control with insulin and/or OHAs Lispro 50 T1D ($n = 35$)	Combined initiation and intensification; did not compare Lispro 50 with low mix, basal, or basal-bolus	Mean (SD) HbA1c (%): baseline, 10.1 (1.6) 6 months, 6.8 (1.1) ($P < 0.001$ vs. baseline)	Mean (SD) BW (kg): baseline, 59.7 (10.8) 6 months, 61.1 (9.7) ($P < 0.05$ vs. baseline)
Yamashiro [44]	Observational 24 weeks	Insulin-naïve; HbA1c $> 7.5\%$; receiving SU \pm biguanides \pm alpha-glucosidase inhibitors Lispro 50 ($n = 15$) vs. prandial insulin lispro + SU ($n = 16$)	Did not compare Lispro 50 with low mix, basal, or basal-bolus HbA1c $< 7\%$: 67% vs. 69% Mean FPG (mg/dL): Baseline, 207.8 vs. 178.1 Week 24, 142.7 vs. 132.1	Mean HbA1c (%) Baseline, 10.3 vs. 9.2 Week 24, 6.8 vs. 6.8 HbA1c $< 7\%$: 67% vs. 69% Mean FPG (mg/dL): Baseline, 207.8 vs. 178.1 Week 24, 142.7 vs. 132.1	Mean minor hypoglycemic episodes (symptomatic and/or BG < 70 mg/dL; self-reported) per patient/year: 0.60 vs. 4.48 ($P = 0.03$) No major (requiring assistance) hypoglycemic episodes Mean BW (kg): Baseline, 62.1 vs. 60.3 Week 24, range 61.2–63.3 ($P < 0.05$ change from baseline) vs. 58.5–59.1 ($P = \text{NS}$ change from baseline)

AUC area under the curve, BG blood glucose, BLA50 50% soluble insulin aspart, BLA70 70% soluble insulin aspart, 30% protamine-crystallized insulin aspart, BID twice daily, BMI body mass index, BH body weight, CI confidence interval, FPG fasting plasma glucose, G + L insulin glargine + insulin lispro, HbA1c glycated hemoglobin, Lispro 25 25% insulin lispro, 75% insulin lispro protamine suspension, Lispro 50 50% insulin lispro, 50% insulin lispro protamine suspension, MA meta-analysis, NPH neutral protamine Hagedorn, NR not reported, NS not significant, OD once daily, OHAs oral hypoglycemic agents, OR odds ratio, PBG postprandial blood glucose, PPG postprandial plasma glucose, RCT randomized controlled trial, SD standard deviation, SMBG self-monitored blood glucose, SR systematic review, SU sulfonylurea, T1D three times daily, T2D type 2 diabetes

Table 4 Summary of risk of bias for randomized trials using the Cochrane tool [11]

First Author and Year (or study identifier)	Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessors ^a	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias
<i>Initiation: Mix50 vs. Low-mix</i>							
Chen 2017 [14]	+	+	-	?	+	?	+
Domeki 2014 [16]	?	?	-	+	+	?	+
Su 2016 [29]	+	+	-	+	+	+	+
Watada 2017 [31]	+	+	-	+	+	+	+
Zafar 2015 [32]	?	?	-	+	?	?	+
<i>Initiation: Mix50 vs. Basal</i>							
Jacobson 2006 [19]	?	?	-	+	+	?	?
Kazda 2006 [22]	?	?	-	+	+	?	+
<i>Initiation: Mix50 vs. Basal-bolus</i>							
Giugliano 2014 [18]	+	+	-	+	+	+	+
Jain 2010 [20]	+	+	-	+	+	?	+
<i>Intensification: Mix50 vs. Low-mix</i>							
Cucinotta 2009 [15]	+	+	-	+	+	+	+
Farcasiu 2011 [17]	?	?	-	+	+	?	+
NCT00627445 [24]	+	+	-	+	+	+	+
Roach 2003 [25]	?	?	-	+	+	?	?
<i>Intensification: Mix50 vs. Basal</i>							
Hirsch 2009 [34]	+	+	-	?	+	-	+
Robbins 2007 [26]	+	+	-	+	+	?	+
<i>Intensification: Mix50 vs. Basal-bolus</i>							
Jia 2015 [21]	+	+	-	+	+	+	+
Miser 2010 [23]	+	+	-	+	+	+	+
Rosenstock 2008 [27]	+	+	-	+	+	+	+
<i>Other</i>							
Davidson 2010 [33]	+	+	-	?	+	-	-
Schwartz 2006 [28]	?	?	+	+	+	?	?
Suzuki 2012 [30]	?	?	-	+	+	?	+

⊕ = low risk; ⊕ = unclear risk; ⊖ = high risk

^a Risk of bias for primary outcome (usually glycated hemoglobin); secondary outcomes that rely on patient reporting (e.g., hypoglycemic episodes, self-monitored blood glucose levels, quality of life measures) may have greater risk of bias

Patients also reported their own diets in the subanalysis by Chen et al. [14] and ethnicities in the post hoc analysis by Davidson et al. [33], which may have affected the subgroup comparisons of HbA1c. Therefore, we classified the blinding of outcome assessors for these two studies as “unclear.” Finally, we considered the risk of selective reporting bias as high for the two pooled analyses because of their post hoc nature [33, 34].

Initiation

Mix50 vs. Low-Mix Insulin Analogs (5 Studies)

Five studies (all RCTs; two were subgroup analyses [14, 29] of one RCT [31]) compared Lispro 50 (total 305 patients) with low-mix insulin analogs (total 316 patients) in insulin-naïve patients poorly controlled on OHAs [14, 16, 29, 31, 32] (Table 1; Table S1 in the

ESM). Four of these studies compared Lispro 50 twice daily (BID) with Lispro 25 BID [14, 29, 31, 32]; one study compared Lispro 50 with BIAsp30 at 1 to 3 injections per day for each treatment [16]. Treatment duration ranged from 12 [32] to 48 weeks [16]. All studies were conducted in Asia (primarily Japan and China).

Lispro 50 resulted in a greater reduction in HbA1c levels compared with low-mix, although the difference was statistically significant in only two studies [29, 32] (Fig. 2; Table 1). The mean change from baseline in HbA1c with Lispro 50 ranged from -1.69% [31] to -4.2% [32] (Fig. 2). In subgroup analyses of one RCT, Lispro 50 was more effective than Lispro 25 at reducing HbA1c among patients with baseline HbA1c, PPG, FPG, or glucose excursions, or carbohydrate, fat, or protein intake, greater than the median level, and in patients with energy intake lower than the median [14, 29, 31]. In addition,

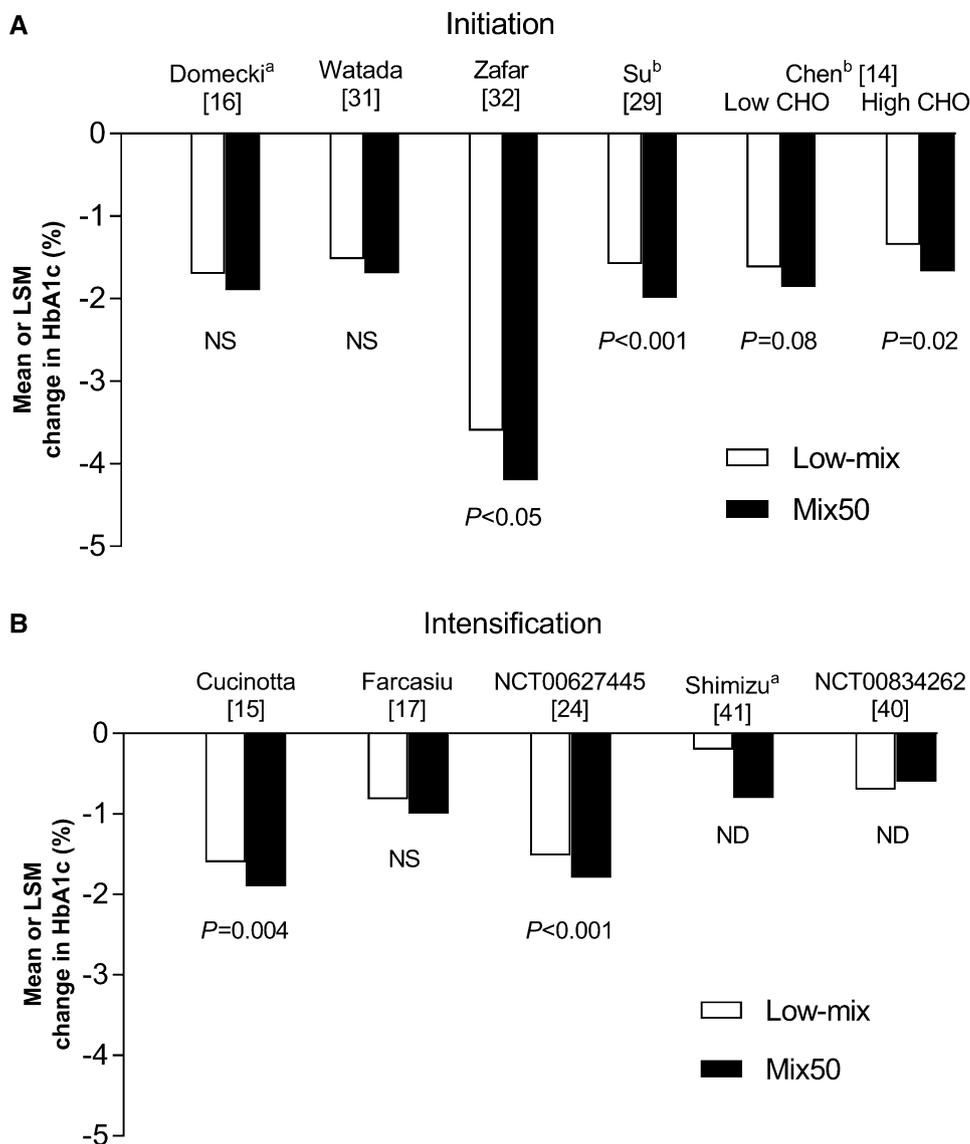


Fig. 2a–b Changes in HbA1c with Mix50 or low-mix insulin analog treatment in studies of initiation (a) or intensification (b). P values shown are comparisons between target groups, where reported. ^aChange from baseline calculated from baseline and end point values. ^bSubanalysis of Watada trial. CHO carbohydrate, HbA1c

glycated hemoglobin, *low-mix* premixed insulin analog containing 25% or 30% rapid-acting component, *LSM* least-squares mean, *Mix50* premixed insulin analog containing 50% rapid-acting component, *ND* not determined, *NS* not significant

Lispro 50 was more effective than Lispro 25 in both men and women and in both older (≥ 65 years) and younger (< 65 years) patients [29]. Where reported, the proportion of patients reaching target HbA1c levels was also greater with Lispro 50 than with low-mix [16, 29, 31] (Table S2 in the ESM). There was no consistent effect of Lispro 50 vs. low-mix on fasting

glucose levels (Table 1). In contrast, Lispro 50 consistently reduced PPG, glucose excursions, and/or average SMBG levels to a greater extent than low-mix (Table 1; Table S2 in the ESM). There were no reported differences between treatments in total daily insulin dose at end point, incidence or rate of hypoglycemia, or in

Initiation	Mix50	Low-Mix	Basal
High post-prandial glucose?	↑↑	↑	↓
High carbohydrate meals?	↑↑	↑	↓
Inconsistent timing and content of meals?	↓	↓	↑↑
Is nocturnal hypoglycemia an issue?	↑↑	↑	↓
Is afternoon hypoglycemia an issue?	↓	↑	↑
Taking sulfonylureas?	↓	↓	↑
Intensification	Mix50	Low-Mix	Basal
Prefers fewer injections or single device?	↑	↑	↓
Able to conduct frequent blood glucose monitoring?	↓	↓	↑
Inconsistent timing and content of meals?	↓	↓	↑↑

Fig. 3 Factors to consider when deciding whether to prescribe Mix50. *Arrows* indicate which insulin types are more (*up arrow*) or less (*down arrow*) suitable for patients with different characteristics. *Low-mix* premixed insulin

analog containing 25% or 30% rapid-acting component, *Mix50* premixed insulin analog containing 50% rapid-acting component

the amount of weight gained (Table 1; Table S2 in the ESM).

Mix50 vs. Basal Insulin (2 Studies)

Two RCTs compared Lispro 50 (with or without one Lispro 25 injection; total 114 patients) with basal insulin (total 113 patients) in insulin-naïve patients (Table 1; Table S1 in the ESM) [19, 22]. One RCT was an 8-month crossover study conducted in the United States that compared Lispro 50 before breakfast and lunch plus Lispro 25 before dinner with basal insulin glargine [19]. The other RCT was a 24-week, 3-arm study conducted in Germany that compared Lispro 50 three times daily (TID) with insulin lispro TID and also with basal insulin glargine [22].

In these RCTs, Lispro 50 resulted in a greater reduction in HbA1c levels compared with basal insulin glargine (Table 1). The mean change from baseline in HbA1c with Lispro 50 in each study was -1.01% [19] and -1.2% [22]. The proportion of patients reaching target HbA1c levels was numerically but not statistically (or not verified statistically) greater with Lispro 50 than with glargine (Table S2 in the ESM). One RCT showed a greater decrease in FBG with

glargine than with Lispro 50 [22], whereas the other RCT showed no significant difference in FBG between treatments [19] (Table 1). In both RCTs, Lispro 50 reduced glucose excursions and post-meal SMBG levels but not PPG (reported in one RCT [22]) to a greater extent than glargine (Table 1; Table S2 in the ESM). The total daily insulin dose at end point and the rate of hypoglycemia were both greater for Lispro 50 than for glargine; weight gain was similar or greater for Lispro 50 than for glargine (Table 1; Table S2 in the ESM).

In one RCT, 63.0% of the 54 patients receiving Lispro 50 and 50.9% of the 53 patients receiving glargine reported their treatment satisfaction (assessed with a nonvalidated, 5-point Likert scale) at the end of the 24-week study as high or very high [22]. However, these results should be interpreted with caution, as the treatment satisfaction questionnaire was not a standard validated tool and therefore may not have been reliable. The same study also reported that 83.3% of patients receiving Lispro 50 were willing to continue their current treatment, compared with 77.4% of patients receiving glargine [22].

Mix50 vs. Basal–Bolus (2 studies)

One 36-week RCT [20] and one 48-week RCT [18] compared 1 to 3 injections of Lispro 50 (with or without Lispro 25 injections; total 413 patients) with basal insulin glargine plus 1 or 2 prandial injections of insulin lispro (total 415 patients) in insulin-naïve patients (Table 1; Table S1 in the ESM). Both RCTs were multinational and examined specific algorithms for initiating and intensifying insulin, starting with a single injection of Lispro 50 or glargine and progressively adding mealtime injections of Lispro 50 and/or Lispro 25 or insulin lispro, respectively.

In both RCTs, there was no significant difference between Lispro 50 and basal–bolus insulin in the reduction of HbA1c [18, 20] (Table 1). Despite this, in one RCT, noninferiority of Lispro 50 to basal–bolus could not be demonstrated [20]. The mean change from baseline in HbA1c with Lispro 50 in each RCT was -1.65% [18] and -1.76% [20]. The proportion of patients reaching HbA1c targets also did not differ between treatments, except that one RCT reported that a greater proportion of patients receiving Lispro 50 reached $\text{HbA1c} < 7.0\%$ compared with basal–bolus [18] (Table S2 in the ESM). In contrast, another RCT reported that a mean $\text{HbA1c} < 7.0\%$ was achieved only with thrice-daily basal–bolus therapy and not with once- or twice-daily basal–bolus or with any Lispro 50 regimen [20]. This RCT also reported a higher FBG at end point with Lispro 50 than with basal–bolus [20], whereas the other RCT did not report FBG data [18] (Table 1). There was no consistent effect of Lispro 50 vs. basal–bolus on SMBG levels, including post-meal values (Table S2 in the ESM). The total daily insulin dose at end point was reported in one RCT as greater for Lispro 50 than for basal–bolus [20] (Table S2 in the ESM). There were no significant differences between Lispro 50 and basal–bolus in the incidence or rate of hypoglycemia, or in the amount of weight gained (Table 1). One RCT reported that scores for both the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and the EuroQol EQ-5D increased significantly from baseline in both treatment groups, but with no reported difference between treatments [18].

Intensification

Mix50 vs. Low-Mix Insulin Analogs (7 Studies)

Four RCTs [15, 17, 24, 25] and three nonrandomized studies [40–42] compared Mix50 (total 811 patients) with low-mix insulin analogs (total 828 patients) in patients poorly controlled despite previous treatment with insulin (with or without OHAs) (Table 2; Table S1 in the ESM). In five of these studies, previous treatment consisted of premixed insulin (human or analog, usually low mix). Treatment regimens varied amongst the studies, and treatment duration ranged from 2 days [42] to 36 weeks [15]. The studies were conducted in Europe [15]; Europe, South Africa, and Turkey [17]; China [24]; India [25]; Israel [40]; and Japan [41, 42].

Overall, Mix50 resulted in a greater reduction in HbA1c levels compared with low mix, although the results were not consistent (Fig. 2; Table 2). The treatment difference was statistically significant in two RCTs of BIAsp50 [15, 24], but not in another of Lispro 50 [17]; the fourth RCT of Lispro 50 did not report change from baseline levels, but the end point HbA1c did not differ between groups [25]. The mean change from baseline in HbA1c with Mix50 ranged from -0.6% [40] to -1.9% [15]. Similarly, the proportion of patients reaching target HbA1c levels was greater with Mix50 than with low mix in two RCTs of BIAsp50 [15, 24], but not in a third RCT of Lispro 50 [17] (Table S2 in the ESM). There were no differences between Mix50 and low mix in the effect on FPG/FBG, except in one RCT where FPG at end point was significantly higher with Lispro 50 than with low mix [17] (Table 2). In contrast, Mix50 reduced PPG, glucose excursions, and/or average SMBG levels to a greater extent than low mix (Table 2; Table S2 in the ESM). The total daily insulin dose at end point was higher for Mix50 than for low mix in three of the four studies when statistically compared (Table S2 in the ESM). The relative risk of minor hypoglycemia did not differ between Mix50 and low mix in one RCT of BIAsp50 [15]; the rate of nocturnal hypoglycemia was higher with Mix50 than with low mix in one RCT of BIAsp50 [24], but lower in another RCT of Lispro 50 [17]; other studies did not report any significant

differences in hypoglycemia between treatment groups (Table 2). Weight gain was significantly higher with Mix50 than with low-mix in one RCT of Lispro 50 [17]; the other studies did not report any statistical differences in weight gain between treatments (Table 2).

Mix50 vs. Basal Insulin (2 Studies)

One multinational, 24-week RCT compared Lispro 50 ($n = 158$) with basal glargine ($n = 159$) in patients poorly controlled on insulin (0–2 injections/day) and OHAs [26]; data from this RCT were the only Mix50 data included in a post hoc analysis [34] (Table 2; Table S1 in the ESM). Although this RCT included patients who were insulin-naïve, most patients (78.7%; 248 of 315) were on insulin before the trial [26].

Lispro 50 resulted in a greater reduction in HbA1c levels (-0.72%) compared with basal glargine (-0.35%) [26, 34] (Table 2). The proportion of patients reaching target HbA1c levels was also statistically greater with Lispro 50 than with glargine [26] (Table S2 in the ESM). There was a greater decrease in FBG, and the end point FBG values were lower, with glargine than with Lispro 50 [26, 34] (Table 2). Conversely, Lispro 50 reduced PPG excursions and SMBG at all time points except at 3 am and pre-breakfast (i.e., FBG) to a greater extent than glargine [26] (Table 2; Table S2 in the ESM). In addition, as demonstrated in the post hoc analysis, Lispro 50 was associated with lower glycemic variability (assessed by 5 indices) than glargine [34] (Table S2 in the ESM). The total daily insulin dose at end point, the rate of hypoglycemia, and the amount of weight gained were greater for Lispro 50 than for glargine (Table 2; Table S2 in the ESM).

Mix50 vs. Basal-Bolus (4 Studies)

Three 24-week RCTs compared Lispro 50 (with or without Lispro 25 injections; total 560 patients) with basal-bolus insulin (basal glargine plus prandial insulin lispro; total 561 patients) in patients poorly controlled on basal or premixed insulin BID with or without OHAs [21, 23, 27] (Table 2; Table S1 in the ESM). One of these RCTs [23] was a multinational substudy of patients who required intensification after

6 months of initial treatment with either basal glargine or Lispro 25 BID [46]. The other RCTs were conducted in Asia (China, Taiwan, Korea) [21] and in the United States and Puerto Rico [27]. An additional 16-week nonrandomized study conducted in Japan examined 28 patients who switched from Mix50 to basal insulin glargine plus insulin glulisine BID [36].

In the RCTs, Lispro 50 reduced HbA1c to a similar [21, 23] or lesser [27] extent than basal-bolus insulin (Table 2). In the nonrandomized study, switching from Mix50 to basal-bolus resulted in a nonsignificant decrease in HbA1c (-0.1%) [36] (Table 2). The mean change from baseline in HbA1c with Lispro 50 was -1.1% [21] and -1.87% [27] in the two RCTs that reported this variable. The proportion of patients reaching target HbA1c levels was lower with Lispro 50 than with basal-bolus insulin, although not all differences were statistically significant (Table S2 in the ESM). Lispro 50 was also less effective than basal-bolus at reducing FBG (Table 2). One RCT reported that Lispro 50 was more effective than basal-bolus at reducing post-lunch PPG, with no treatment differences for blood glucose after other meals [21]; another RCT reported that end point PPG post-breakfast, but not after other meals, was significantly higher with Lispro 50 than with basal-bolus [27] (Table 2). In one RCT, the total daily insulin dose at end point was lower for Lispro 50 than for basal-bolus [27]; there were no treatment group differences in dose in the other RCTs [21, 23] (Table S2 in the ESM). There were no reported differences between Lispro 50 and basal-bolus in the incidence or rate of hypoglycemia, or in the amount of weight gained (Table 2).

In one RCT, there were no differences in the change in DTSQ treatment satisfaction or perceived frequency of hyperglycemia scores (both status and change versions of the DTSQ), or in the Experience With Insulin Therapy Questionnaire (EWITQ) scores, between Lispro 50 (+ Lispro 25) and basal-bolus therapy [21]. However, the DTSQ (status version) perceived frequency of hypoglycemia was significantly higher in the Lispro 50 (+ Lispro 25) group than in the basal-bolus group ($P = 0.017$) [21]. In the nonrandomized study, there was no significant

change in DTSQ treatment satisfaction, perceived hyperglycemia, or perceived hypoglycemia scores after patients switched from Mix50 to basal–bolus [36].

Other Studies (13 Studies)

Although the remaining studies could not be included in the summaries above for various reasons (shown in Table 3), several of these studies are noteworthy. The two systematic reviews combined studies of initiation and studies of intensification [12, 13]. One systematic review [13] conducted a meta-analysis of three RCTs [19, 22, 26], which suggested that Lispro 50 was more efficacious than basal glargine at reducing HbA1c and PPG, but that glargine was more efficacious than Lispro 50 at reducing FBG. This systematic review also concluded that premixed analogs (Lispro 25, BIAsp30, Lispro 50) are associated with a greater incidence of hypoglycemia and more weight gain [13]. The other systematic review supported these general conclusions, although no meta-analysis was conducted [12].

One post hoc analysis that included two RCTs involving Lispro 50 examined the effect of ethnicity on the response to Lispro 50 vs. Lispro 25 vs. combined basal or basal–bolus therapy in patients requiring intensification [33] (Table 3). There was no effect of ethnicity on the efficacy or safety of Lispro 50, except a significantly higher rate of severe hypoglycemia in Asian patients compared with Caucasian patients. The analysis also suggested that Lispro 25 may be less effective at reducing HbA1c in Asian and Latino–Hispanic patients, and basal/basal–bolus therapy more effective in Latino–Hispanic patients, compared with Caucasian patients [33].

A consensus statement published in 2011 presented clinical evidence on the use of BIAsp50 and BIAsp70 in patients currently on BIAsp30 who required intensification [9]. The statement recommended several patient subgroups who may benefit the most from premixed BIAsp with higher ratios of rapid-acting insulin aspart, including: patients poorly controlled on low-mix insulin BID or TID; patients

with elevated FPG and PPG levels may benefit most from BIAsp50; and patients with normal FPG but elevated PPG may benefit most from BIAsp70 [9]. The consensus statement also provided specific algorithms and dosing titration schedules for intensification, depending on each patient's PPG and FPG levels [9].

Strengths and Limitations of This Systematic Review

This review is strengthened by its systematic approach to identifying relevant studies, including unpublished studies, the consideration of Mix50 for both initiation and intensification, the comparison of Mix50 with three other general approaches to insulin therapy (low mix, basal, basal–bolus), the diverse range of countries represented, and the risk of bias assessment. Limitations include heterogeneity in the study designs, populations, treatment regimens, durations, and reported outcomes (including the use of self-reporting of hypoglycemic episodes in most studies), the limited number of studies in some settings or comparisons, and the exclusion of articles not written in English.

SUMMARY OF EVIDENCE AND CLINICAL RECOMMENDATIONS

To our knowledge, this is the first systematic review to collate the evidence regarding the relative efficacy and safety of Mix50 as a treatment option for the initiation or intensification of insulin therapy. Overall, the evidence suggests that Mix50 may be more effective in certain patient groups (e.g., those with high-carbohydrate diets, Asian) than low-mix insulin analogs in reducing HbA1c, primarily via reductions in PPG levels, although with a possible increased risk of hypoglycemia. These results indicate that Mix50 represents an alternative treatment option, especially for patients who prefer premixed insulins but require greater glycemic control after meals than that provided by low-mix insulins. In the section

below, we provide practical guidance, based on the collected evidence and our clinical expertise, on the use of Mix50 for insulin initiation and intensification. Importantly, treatment decisions should be individualized for the patient, and the broad range of available therapies and regimens enable flexibility to tailor treatment to the patient.

Insulin Initiation with Mix50

Summary of Evidence

For patients initiating insulin treatment, the evidence suggests that Mix50 may result in better glycemic control than either low-mix insulin analogs or basal therapy with insulin glargine, at least in Asian patients with assumed high-carbohydrate diets (Table 1). The improved glycemic control when using Mix50 is undoubtedly related to the greater reduction of PPG levels (Table 1). Although the risk of hypoglycemia and weight gain is somewhat greater with Mix50 than with basal insulin, this is also true with low-mix insulin analogs [12, 13].

Interestingly, the studies comparing Mix50 with low-mix analogs for initiation were all conducted in Asia, where premixed insulins are more commonly used than in Western countries [31, 47]. Asian patients may require tighter control of PPG in part because of a high-carbohydrate diet [14, 31] and because of greater glycemic responses to certain foods like rice compared with patients of European descent [48]. Indeed, subanalyses of the largest RCT indicate that Lispro 50 has the most benefit relative to Lispro 25 in patients with a high carbohydrate intake, as well as in patients with high baseline HbA1c ($\geq 8.4\%$), PPG (≥ 13.30 or ≥ 13.5 mmol/L), glucose excursion (≥ 4.4 mmol/L), or FPG (≥ 9.0 mmol/L), at least in this Asian study population [14, 29, 31]. None of the studies comparing Mix50 with low-mix analogs for initiation were conducted in non-Asian countries; thus, we do not currently know if Mix50 is more effective than low mix in patients of other ethnicities or with different dietary habits.

Identifying Patients Suitable for Initiation with Mix50 (Fig. 3)

Although Mix50 is not commonly used for the initiation of insulin therapy, there are some patients for whom it may be considered. As mentioned above, this includes patients with large PPG excursions (especially after lunch) and those with carbohydrate-rich diets. Even in the absence of a high-carbohydrate diet, patients with high PPG should be considered for Mix50. Decisions on whether Mix50 or low mix is more suitable are best guided by examining matched pre- and postprandial glucose concentrations, together with HbA1c levels. Patients with certain ethnic backgrounds, such as Asian or Pacific Islander, may also benefit from Mix50, either because of their diet or because of underlying physiological differences in the glycemic response to meals [48, 49].

The risk of hypoglycemia and the patient's ability to manage hypoglycemic episodes is also an important consideration. For example, if nocturnal hypoglycemia is a potential issue, Mix50 at dinner may be a better choice than basal or low-mix insulins. Similarly, Mix50 could be used during Ramadan to reduce PPG after the evening meal, which often contains a large caloric load [50]. Mix50 may also be an appropriate choice for patients at high risk of micro- and macrovascular complications caused by high glycemic variability [51]. Other factors, such as age, physical and mental capabilities, patient preferences, and lifestyle, should be considered when deciding between basal insulin and premixed insulins [7, 8], but apply equally to Mix50 and low-mix options. Many of these factors are less relevant for initial insulin therapy, but become important when the patient eventually requires intensification. Thus, clinicians should assess how the patient will cope best with additional injections and plan accordingly when deciding on initial treatment.

Dose and Regimen for Initiation with Mix50

Guidelines suggest initiating insulin (basal or premixed) at a dose of 10–12 units once daily before the largest meal (usually dinner)

[1, 5, 6, 8]. The dose is then titrated once or twice weekly to achieve FBG levels of approximately 4–7 mmol/L without hypoglycemia. The same general approach can be used with Mix50, although titrating to a target PPG may also be considered. Another option is to split the dose across two injections, before breakfast and before dinner, which may suit patients who require more postprandial control after breakfast (e.g., those who eat a large carbohydrate-rich breakfast) or those at high risk of nocturnal hypoglycemia. In most cases, patients can continue with OHAs, especially metformin; however, discontinuing sulfonylureas should be considered because of the increased risk of hypoglycemia when used in combination with insulin. In addition to the standard information provided when initiating insulin, particular care should be taken to ensure that patients starting on Mix50 (or any prandial insulin) understand the risks and management of hypoglycemia.

Insulin Intensification with Mix50

Summary of Evidence

For patients requiring insulin intensification, the evidence suggests that Mix50 may provide better glycemic control compared with low-mix insulins, but not compared with basal-bolus regimens. Although two RCTs in this review concluded that Mix50, specifically BIA50, provided better glycemic control than low-mix insulins [15, 24], the other two RCTs reported no difference between the Lispro 50 and low mix [17, 25]. The reasons for these discrepancies are unclear, but may be related to differences in treatment regimen, treatment duration, or patient characteristics. However, as observed when used for initiation, Mix50 had a greater effect on PPG levels than low-mix insulins when used for intensification.

Compared with basal-bolus therapy, Mix50 is less efficacious at overall glycemic control, although again, there are inconsistencies between studies. However, there is evidence that Mix50 may have a greater effect on PPG levels than basal-bolus therapy, particularly the levels after breakfast and lunch [21, 27]. Issues

of safety (i.e., hypoglycemia and weight gain) are generally similar between Mix50 and basal-bolus therapy.

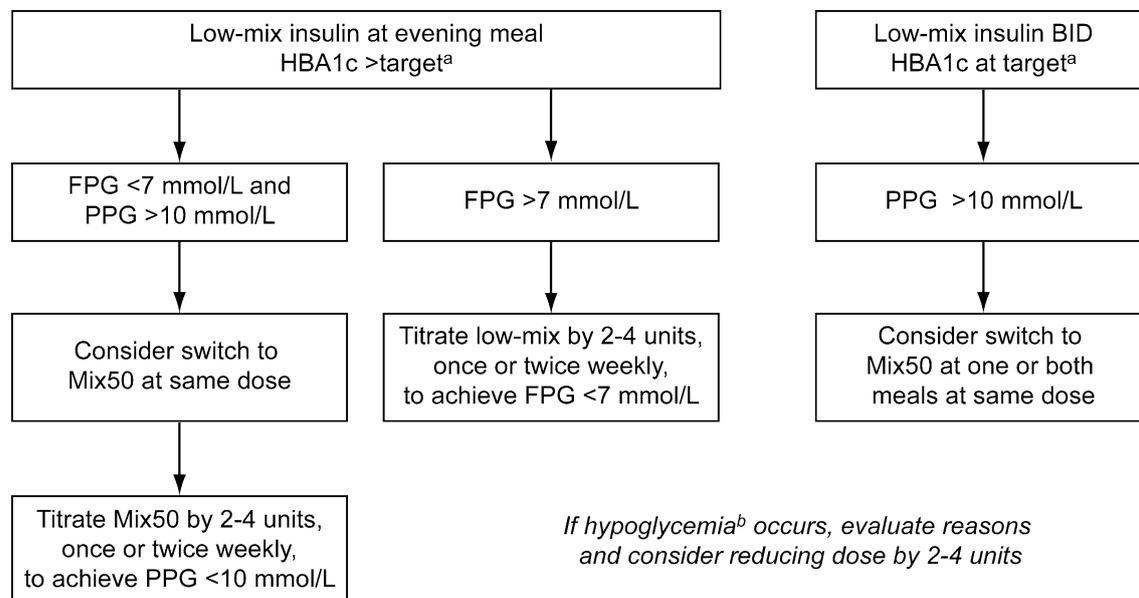
Identifying Patients

Suitable for Intensification with Mix50 (Fig. 3)

Several additional factors should be considered when determining whether Mix50 is suitable for individual patients who require intensification of their current insulin regimen. If the patient is already on a premixed insulin, consider switching from low mix to Mix50 and/or adding doses as part of a BID or TID regimen, especially at the meal(s) with the highest PPG excursions. If FPG target levels are not reached, consider changing the pre-dinner injection to a low-mix insulin and using Mix50 before breakfast (and lunch, if required). However, this option should be weighed against any patient preference for a simpler regimen with a single insulin injection device. Similarly, if the patient is currently on basal therapy, a regimen using Mix50 (or low mix) may be easier for the patient than a basal-bolus regimen, which requires multiple injection devices and frequent glucose monitoring. In contrast, patients with inconsistent timing or content of meals may benefit from the flexible dosing possible with a basal-bolus regimen. As with initiation, paired pre- and postprandial glucose concentrations, as well as the level of carbohydrate consumption, can be used to help decide which premixed insulin is most appropriate for an individual patient.

Dose and Regimen for Intensification with Mix50

When using premixed insulin for intensification, regardless of whether the initial dose is basal or premixed, standard practice is to divide the current total daily dose across two doses injected before breakfast and before dinner [1, 5, 6, 9]. Alternatively, Mix50 can be given before breakfast and a low mix before dinner to provide more overnight basal insulin. For patients currently on low mix, consider using Mix50 before any meal where PPG is > 10 mmol/L [9] or whichever meal routinely has the highest carbohydrate content. Dose



^aIndividualized, but typically 7%

^bIndividualized, but typically blood glucose <4 mmol/L (<5-6 mmol/L in elderly or frail patients)

Fig. 4 Algorithm for switching from low-mix insulin to Mix50. *BID* twice daily, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *low-mix* premixed insulin

analog containing 25% or 30% rapid-acting component, *Mix50* premixed insulin analog containing 50% rapid-acting component, *PPG* postprandial glucose

titration follows the same general pattern as for patients on once-daily insulin [1, 5, 6, 8, 9]. However, the doses should be adjusted independently, depending on the glucose profile; adjust the pre-breakfast dose according to the pre-dinner glucose level and the pre-dinner dose according to the FBG level [6]. A third dose can be added before lunch if target HbA1c or PPG levels are not met. A general guideline for switching patients from low mix to Mix50 is shown in Fig. 4; however, as always, regimens and doses should be tailored to the individual patient.

CONCLUSION

We conducted a systematic literature review to assess the evidence for the use of Mix50 in patients with T2D. In conclusion, the collective evidence suggests that Mix50 is a suitable alternative for both initiation and intensification of insulin therapy that may be more appropriate than low-mix insulins for certain patients.

Clinicians should consider not only efficacy and safety but also patient characteristics and preferences when tailoring insulin treatment to individuals with T2D.

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Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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