


REVIEW

Efficacy and Safety of Rapid-Acting Insulin Analogs in Special Populations with Type 1 Diabetes or Gestational Diabetes: Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: To assess the efficacy and safety of three available rapid-acting insulin analogs (insulins lispro, aspart and glulisine, respectively) in pregnant women, children/adolescents and people using continuous subcutaneous insulin infusion (CSII) with type 1 diabetes.

Methods: PubMed, EMBASE and Cochrane Reviews were searched electronically, and their bibliographies examined to identify

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suitable studies for review and inclusion in a meta-analysis. Eligible studies were randomized controlled trials that reported data on relevant clinical outcomes. A different reviewer abstracted data for each of the three subpopulations, and one reviewer abstracted data for all three. Any differences were resolved by consensus or by consulting a fourth reviewer.

Results: In people on CSII, rapid-acting insulin analogs lowered postprandial plasma glucose post-breakfast to a greater extent than did regular human insulin (RHI) (mean difference: -1.63 mmol/L [95% confidence interval -1.71 ; -1.54]), with a comparable risk of hypoglycemia and a trend for lower glycosylated hemoglobin. In the pediatric population, glycemic control was similar with rapid-acting insulin analogs and RHI, with no safety concerns. Meta-analysis indicated severe hypoglycemic events were comparable for rapid-

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acting insulin analogs versus RHI (risk difference: 0.00 [95% confidence interval –0.01; 0.01]). In the pregnancy group, insulin lispro and insulin aspart were safe and effective for both mother and fetus, with glycemic control being at least as good as with RHI. There were no data on insulin glulisine during pregnancy.

Conclusion: Rapid-acting insulin analogs appear generally safe and effective in these special populations; however, additional trials would be helpful.

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Keywords: CSII; Pediatrics; Pregnancy; Rapid-acting insulin analogs; Type 1 diabetes

INTRODUCTION

Many people with type 1 diabetes (T1D) receive insulin therapy [1]. Rapid-acting insulins are typically used to control postprandial plasma glucose (PPG) excursions, whereas long-acting basal insulins are used to control fasting glucose. Rapid-acting insulins are used as part of a basal–bolus injection regimen as well as for continuous subcutaneous insulin infusion (CSII). Three rapid-acting insulin analogs (RAIAs) are currently available in the USA and Europe: insulin lispro (Humalog[®]; Eli Lilly, Indianapolis, IN, USA), insulin aspart (Novolog[®] in the USA and NovoRapid[®] in the EU; Novo Nordisk, Bagsværd, Denmark) and insulin glulisine (Apidra[®]; Sanofi Aventis, Bridgewater, NJ, USA). All three of these RAIAs are also approved for the pediatric T1D patient population, although the ages on the product inserts for which there are data vary by product as well as by country (e.g. USA: insulin lispro, children ≥ 3 years of age; insulin aspart, ≥ 2 years; insulin glulisine, ≥ 4 years [2–4]; EU: insulin lispro, age not specified; insulin aspart, ≥ 1 years; insulin glulisine, ≥ 6 years) [5–7]. In addition, despite the concerns in some countries, the use of RAIAs is very high in T1D patients in general and is almost 100% among those patients using CSII [8].

The three insulin analogs lispro, aspart and glulisine differ in how their molecular structure has been modified from human insulin [9] and

in the chemical composition of their formulations [10], but their pharmacokinetic (PK) and pharmacodynamic (PD) profiles are similar (Electronic Supplementary Material [ESM] Table S1). A large body of clinical studies indicates that these three RAIAs have similar efficacy and safety [11] and that they are preferred over regular human insulin (RHI) for use in adults with T1D due to their lower risk of hypoglycemia [12].

However, certain subgroups of patients with T1D (e.g. children and adolescents, pregnant women and people using CSII) are typically excluded from trials conducted for regulatory approval to ensure a more homogeneous group of patients.

A consequence of excluding these patients from regulatory trials is that there is some uncertainty about the clinical profile of RAIAs in patients who may have unique metabolic, developmental, cognitive or behavioral issues that materially affect the suitability of any medication. With RAIAs in widespread clinical use, it is timely to examine the available evidence for their performance in special populations. Thus, we performed a systematic review and meta-analysis of published data (PROSPERO registration #CRD42016043006).

METHODS

Sources of Data and Search Criteria

The search terms “insulin lispro” (MeSH Terms) OR “insulin” (All Fields) AND “lispro” (All Fields) OR “insulin lispro” (All Fields) OR “lispro” (All Fields) OR aspart (All Fields) OR glulisine (All Fields) were used to search the PubMed, EMBASE and the Cochrane Reviews databases electronically on 1 June 2016 to identify records for further examination. The titles and abstracts (and, when necessary, full papers) were then screened to identify papers potentially reporting relevant *in vivo* data on safety or efficacy in randomized controlled trials (RCTs) involving one of three special populations (children and adolescents with T1D; pregnant women with pre-gestational T1D or gestational diabetes [GDM]; people with T1D using CSII). We did

not set a date range and therefore included any study published up to the date of the search. Reference lists of retrieved publications and targeted review articles of RAIAs were also searched to identify additional records that might be provisionally relevant.

Selection of Studies and Eligibility Criteria

Records identified as provisionally relevant were then further examined for eligibility to verify that they were indeed RCTs, either blinded or open-label and of parallel or crossover design, in one of the target special populations and that they reported data on one of the identified clinical outcomes of interest. Eligibility for the three study populations was as follows: for the pregnancy population, women with either pre-gestational T1D or GDM; for the pediatric population, children or adolescents aged < 18 years with T1D; for the CSII population, people with T1D of any age using an insulin pump.

The criterion for the treatment in eligible studies was the administration of one of the three RAIAs compared with either RHI or each other; trials in which the effect of the RAIAs could not be isolated (as in basal-bolus trials in which different basal insulins were used in each arm) were excluded. We did not pre-specify a minimum duration for the studies, although very short-term (e.g. 1- to 2-day meal tests designed to study PK/PD) were excluded. Outcome measures of interest included glycated hemoglobin (HbA1c), fasting blood glucose (FBG) or plasma glucose, PPG after any or all of the three main meals, hypoglycemia, hyperglycemia, diabetic ketoacidosis and/or pump/catheter occlusion and, for pregnancy, fetal outcomes.

Data Extraction

A standardized data abstraction form was adapted for use in this systematic review. A different reviewer abstracted data for each of the three subpopulations (KN, NS, SR) using the inclusion and exclusion criteria, and one reviewer abstracted data for all three of the subpopulations. Any differences were resolved

by consensus or, if necessary, by consulting a fourth reviewer (PS) not involved in the original data abstraction process for that population. All reviewers are qualified at a post-doctorate level.

Data Synthesis and Statistical Analysis

For each of the three populations, whenever possible, we extracted data on glycemic control (HbA1c at baseline and end of trial; percentage of patients achieving HbA1c target[s] as specified in individual trials; 7- or 8-point self-measured blood glucose [SMBG]); and safety endpoints (e.g. severe, nocturnal, overall hypoglycemia; hyperglycemia/ketosis; fetal outcomes). For completeness, we also extracted other secondary endpoints if available. Each of the retrieved studies was assessed for study quality, including sample size, reporting of methods, reporting of results and risk of bias. Finally, using this information, we graded each study according to the following scale (–, +, ++), with – indicating poor quality, + indicating average quality and ++ indicating good quality.

All authors reviewed the available outcomes data for each eligible study and decided which studies had efficacy and/or safety data that would be suitable for data combination and meta-analysis within each of the three special populations. Suitability was determined by authors' assessment of comparability of the outcomes assessed.

Meta-analysis was conducted using Review Manager 5 (RevMan 5.3 [<http://community.cochrane.org/tools/review-production-tools/revman-5>]) software for Cochrane Reviews. Two different outcome measures were used for the safety variables in the meta-analysis (namely risk difference for severe and any hypoglycemic episodes per month) and three outcome measures for the efficacy variables (namely mean difference in fasting and postprandial blood glucose [BG] and in HbA1c). All models were run as random-effects models. Statistical heterogeneity was calculated by using the I^2 statistic, and publication bias was assessed by using a funnel plot and the Egger's test.

Compliance with Ethics Statement

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

Our search of the PubMed, EMBASE and the Cochrane Reviews databases resulted in the identification of seven eligible studies in pregnancy, nine in pediatric patients and 13 in people using CSII. Records were assessed to be ineligible and thereby excluded from the systematic review and meta-analysis for numerous reasons, including the study not being a RCT (observational studies, letters, case reports or review articles were excluded); ineligible population; *in vitro* or animal studies; study dealt with one of the RAIs in

mixture formulations; outcomes of interest were not reported; PK/PD studies in which basal insulins were the focus of the study; study primarily addressing stability in pumps; health–economics studies without efficacy or safety outcomes; paper written in a language other than English; duplicate record; or study not applicable to this review for other reasons. A flow diagram showing the number of retrieved, excluded and included records is shown in Fig. 1. Prior to submission of this manuscript (August 2017), PubMed and the Cochrane Reviews were searched as previously described and no additional studies that would have been provisionally eligible were identified.

Pregnancy

Characteristics of the seven eligible studies in pregnancy (two in pre-gestational T1D [13–15] and four in GDM [16–19], with two reporting different outcomes from the same population

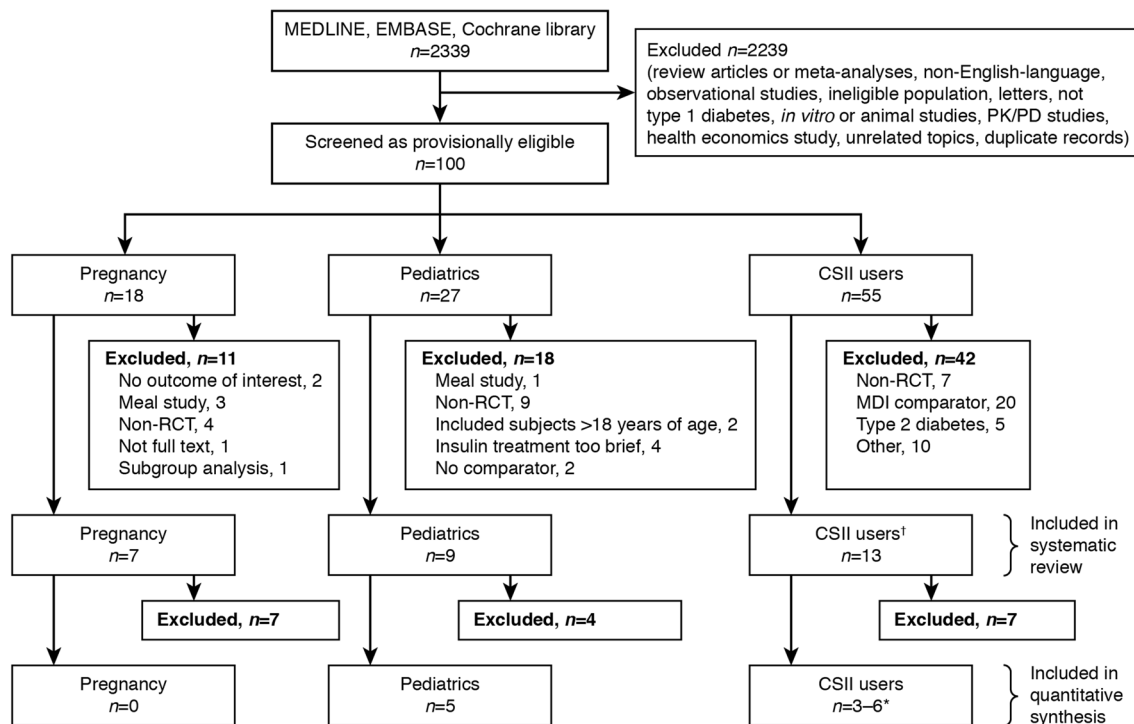


Fig. 1 Flow diagram showing the number of retrieved, excluded and included records. The dagger (†) indicates that the continuous subcutaneous insulin infusion (CSII) group included two pediatric CSII studies. The asterisk (*) indicates that in the CSII meta-analyses, the number of studies included varied depending on the outcome assessed. MDI Multiple daily injections, PD pharmacodynamics, PK pharmacokinetics, RCT randomized controlled trial

Table 1 Study outcomes: pregnancy

First author, year of study	HbA1c outcomes		BG levels		Hypoglycemia		Secondary outcomes		
	Analog (n) vs. comparator (n)	Definition	Results	Definition	Results (mmol/L)	Definition	Measures	Results	
Hod, 2008 [13] and Mathiesen, 2007 [14]	Aspart (157) vs. RHI (165)	Tested in early pregnancy and end of each trimester (1) Mean difference (95% CI) between aspart and RHI at end of second trimester (%) (2) Mean difference at end of third trimester	(1) -0.04% (-0.18; 0.11) (p = NS)	8-point SMBG performed for 1 week in each trimester (1) Mean 24-h BG at first trimester (2) Mean 24-h BG at second trimester (3) Mean 24-h BG at third trimester (4) Mean difference in post-breakfast glucose in aspart vs. RHI in first trimester (5) Mean difference in post-breakfast BG in second trimester (6) Mean difference in post-breakfast BG in third trimester	(1) 6.82 vs. 6.82 (2) 6.96 vs. 7.10 (3) 6.23 vs. 6.48 (4) NR, p = 0.044 (5) NR, p = 0.153 (6) NR, p = 0.0007	Self-reported diary (1) Relative risk (95% CI) of major nocturnal hypoglycemia (2) Relative risk (95% CI) of major hypoglycemia in aspart vs. RHI	(1) Mean (± SD) overall treatment satisfaction score (2) Corrected BW (SEM) (3) Preterm birth (4) Neonatal hypo	(1) 87.6 ± 12.0 vs. 83.4 ± 15.3 (p = 0.03) (2) 3438 (71.5) vs. 3555 (72.9) (p = 0.09) (3) 20.3% vs. 30.6% (p = 0.05) (4) 33.6 vs. 39.7%	
Persson, 2002 [15]	Lispro (16) vs. RHI (17)	Tested monthly (1) Median (range) HbA1c at baseline (6–8 weeks gestation) (%) (2) Median HbA1c at 24 weeks gestation (3) Median HbA1c before delivery	(1) 6.5 (4.8–8.6) vs. 6.6 (4.5–8.6) (2) 5.4 (4.3–5.9) vs. 5.3 (4.7–6.7), p = NS (3) 5.2 (4.6–5.9) vs. 5.0 (4.6–6.7), p = NS	Combined values in second and third trimester of 6-point SMBG (1) Mean (± SD) post-breakfast BG (mmol/L) glucose increase (2) Mean post-breakfast glucose increase (3) Mean post-lunch glucose increase (4) Mean post-dinner glucose increase	(1) 6.50 ± 3.18 vs. 8.56 ± 3.55 (p < 0.01) (2) 0.40 ± 3.20 vs. 1.81 ± 3.42 (p < 0.01) (3) 0.70 ± 3.16 vs. 0.60 ± 3.34 (p = NS) (4) -0.24 ± 3.10 vs. 0.28 ± 2.94 (p < 0.04)	Self-reported diary (1) Number of patients experiencing severe hypo (2) Rate of biochemical hypo (BG < 3.0) (%)	(1) Progression of retinopathy, % in each group (2) Neonatal outcomes (i.e., anthropometry, complications, malformations, symptomatic hypo)	(1) 0 vs. 2 (2) 5.5 vs. 3.9 (p < 0.05)	(1) 18.8 vs. 35.2 (2) No difference in perinatal outcome or neonatal complications

Table 1 continued

First author, year of study	HbA1c outcomes		BG levels		Hypoglycemia		Secondary outcomes	
	Analog (n)	comparator (n)	Definition	Results	Definition	Results (mmol/L)	Measures	Results
Meacci, 2003 [17]	Lispro (25) vs. RHI (24)	Tested at diagnosis of GDM and delivery (1) Mean difference (\pm SD) from pre-intervention to delivery (%)	9-point SMBG performed weekly from diagnosis to 38 weeks gestation (1) Mean (\pm SD) 1-h post-breakfast BG (2) Mean BG 1-h post-lunch BG (3) Mean BG 1-h post-evening meal BG (4) Mean total BG 1-h postprandial BG (5) Mean total preprandial BG (6) Mean total 2-h postprandial BG	(1) -0.3 ± 0.3 vs. -0.3 ± 0.1 ($p = \text{NS}$)	NR	(1) post-BF: 5.93 ± 0.62 vs. 6.84 ± 0.7 ($p < 0.002$) (2) post-lunch: 5.91 ± 0.66 vs. 6.63 ± 0.88 ($p < 0.01$) (3) post-dinner: 6.21 ± 0.49 vs. 6.71 ± 0.62 ($p < 0.05$) (4) total: 6.02 ± 0.59 vs. 6.72 ± 0.73 ($p < 0.01$) (5) 4.08 ± 0.45 vs. 4.13 ± 0.73 ($p = \text{NS}$) (6) 5.20 ± 0.62 vs. 5.44 ± 0.69 ($p = \text{NS}$)	(1) Neonates with cranial-thoracic circumference (CC/CT) ratio 10-25th centile, % (b) Neonatal anthropometry (BW, ponderal index) and complications	(1) 12% vs. 37.5% ($p < 0.05$) (2) No difference between groups
Di Gianni, 2007 [16]	Aspart (31) vs. lispro (33) vs. RHI (32)	NR	5-point SMBG (1) Mean (\pm SD) 1-h post-breakfast BG	NR	Number of patients experiencing any hypo	(1) 6.75 ± 1.12 vs. 6.6 ± 1.05 vs. 7.5 ± 1.3 ($p < 0.05$)	(1) Neonatal anthropometry: BW, CC/CT ratio (2) Macrosomia	(1) Higher BW in RHI than aspart/lispro groups (2) Macrosomia: 9.6%, 12.1%, 15.6% ($p = \text{NS}$) CC/CT ratio lower in RHI than other two groups ($p = 0.03$)

Table 1 continued

First author, year of study	HbA1c outcomes		BG levels		Hypoglycemia		Secondary outcomes	
	Analog (n) vs. comparator (n)	Definition	Results	Definition	Results (mmol/L)	Definition	Measures	Results
Perttinen, 2007 [18]	Aspart (14) vs. RHI (13)	Tested at diagnosis of GDM and delivery	(1) 5.1 ± 0.4 vs. 5.3 ± 0.3 (2) 5.4	Measured on standardized mixed meal test after 6 weeks (1) Time-adjusted mean (± SD) glucose (2) Time-adjusted mean change in glucose from baseline (no insulin) (3) Mean glucose at 30 min time point of meal test (4) Mean glucose at 60 min time point of meal test	(1) 4.2 ± 0.57 vs. 4.8 ± 0.86 (2) -1.09 ± 0.55 vs. -0.54 ± 0.74 (p = 0.003) (3) 4.7 ± 0.19 vs. 5.1 ± 0.23 (p = 0.03) (4) 5.4 ± 0.21 vs. 6.2 ± 0.33 (p < 0.01)	Self-reported diary (1) % of subjects (number of events) experiencing symptomatic hypo (2) % of subjects (number of events) experiencing minor hypo	(1) Insulin-specific antibodies (2) Cross-reactive antibody binding (± SD) at 36/40 and 6/52 post-partum (%) (3) Mean neonatal birth weight (± SD) (kg) (4) Mean birth length (± SD) (cm)	(1) Low insulin-specific antibodies in both groups (2) 1.4 ± 3.0 vs. 1.5 ± 2.3 and 2.3 ± 5.4 vs. 6.5 ± 13.7 (3) 3.1 (0.5) vs. 3.0 (0.5) (p = NS) (4) 49 (2.3) vs. 48 (2.4) (p = NS)
Jovanovic, 1999 [19]	Lispro (19) vs. RHI (23)	Tested at baseline and 6 weeks after randomization	Mean (± SEM) HbA1c at: (1) 5.47 ± 0.09 vs. 5.24 (p = NS) (2) Mean at 6 weeks (3) Mean change from baseline to 6 weeks (% reduction)	6-point SMBG (1) Mean (± SEM) post-breakfast hyperglycemia rate (individual patient % of all readings ≥ 6.67 mmol/L), (%) (2) Mean post-lunch hyperglycemia rate (3) Mean post-evening meal hyperglycemia rate (4) Mean total postprandial hyperglycemia rate	(1) 5.5 ± 0.30 vs. 7.3 ± 0.4 (p = NS) (2) 4.5 ± 1.1 vs. 6.8 ± 0.86 (p = NS) (3) 2.0 ± 0.51 vs. 2.6 ± 0.54 (p = NS) (4) 4.0 ± 0.49 vs. 5.5 ± 0.47 (p < 0.05)	Self-reported diary and meter check (1) Mean (± SEM) pre-breakfast hypo rate (individual patient % of all readings < 3.1 mmol/L) (%) (2) Mean pre-lunch hypo rate (3) Mean post-evening meal hypo rate (4) Mean total preprandial hypo rate	(1) Change in insulin-specific and cross-reactive response from baseline to delivery (2) Neonatal anthropometry (3) Neonatal glucose	(1) 0.65 ± 0.13 vs. 0.93 ± 1.04 (p < 0.05) (2) 0.78 ± 0.37 vs. 1.98 ± 0.81 (3) 1.26 ± 0.43 vs. 1.43 ± 0.86 (4) 0.88 ± 0.25 vs. 2.20 ± 0.86

Aspart Insulin aspart, BF breakfast, BG blood glucose, BW body weight, CC/CT ratio of the cardiac circumference to the thoracic circumference, CI confidence interval, hypo hypoglycemia, GDM gestational diabetes, glulisine insulin glulisine, HbA1c glycated hemoglobin, lispro insulin lispro, NR not reported, NS not significant, RHI regular human insulin, SD standard deviation, SEM standard error of the mean, SMBG self-measured blood glucose

and therefore described in a single row [13, 14]), are summarized in ESM Table S2, and the results of those studies are shown in Table 1. Most (4/6 trials) involved < 50 participants. Study quality assessment is shown in ESM Table S3. Three studies were graded as –, two were graded as + and one was graded as ++.

Women with Pre-Existing T1D

Persson et al. compared treatment with insulin lispro with RHI treatment in a group of 33 pregnant women with T1D and found that the BG level was significantly lower after breakfast (but not after other meals) with insulin lispro (0.40 ± 3.20 vs. 1.81 ± 3.42 mmol/L; $p < 0.01$) [15] (Table 1). The 95% confidence interval (CI) was not significantly different between treatments, either at 24 weeks gestation or before delivery. The incidence of severe hypoglycemia was low (zero and two episodes for insulin lispro and RHI, respectively) and there were no differences in perinatal outcomes or neonatal complications.

The largest trial was an international, parallel-group trial enrolling 322 women with T1D who at enrollment were pregnant for ≤ 10 weeks or planning to become pregnant. Women were randomized to either insulin aspart or RHI, both in combination with neutral protamine Hagedorn insulin as the basal insulin [14]. HbA1c levels were comparable in the two groups at the end of the second and third trimesters (treatment difference, insulin aspart–RHI: -0.04% [95% CI $-0.18; 0.11$], -0.4 mmol/mol [95% CI $-2.0; 1.2$]; and -0.08% [95% CI $-0.23; 0.06$], -0.9 mmol/mol [95% CI $-2.5; 0.7$], respectively). Mean plasma glucose levels at 90 min post-breakfast were significantly lower in those women receiving insulin aspart arm than in those receiving RHI ($p = 0.044$ and $p = 0.001$ for end of first and third trimesters, respectively). The mean PPG increment across all meals was lower for the insulin aspart arm than for the RHI arm at the end of the first and third trimesters (estimated treatment difference: -0.75 [95% CI $-1.25; -0.25$], $p = 0.003$ and -0.40 [95% CI $-0.80; -0.01$], $p = 0.044$, respectively). The risk of major hypoglycemic events was numerically lower, but not significantly different, for

insulin aspart (rate ratio 0.72 [95% CI 0.36; 1.46]).

In a publication reporting additional data on pregnancy outcomes by Mathiesen et al. [14], Hod et al. [13] indicated that preterm delivery occurred in 20.3 and 30.6% of pregnancies in women receiving insulin aspart and RHI, respectively ($p = 0.053$). Other secondary publications from these trials indicated that there were 137 and 131 live births, 14 and 21 fetal losses, and six and nine congenital malformations in these groups of women on insulin aspart and RHI, respectively. Furthermore, maternal and cord blood antibody levels for both RHI and insulin aspart remained low for both treatments and were similar at 36 weeks gestation for the 97 women who participated in the substudy [20]. In a secondary analysis of data from the same trial, Lloyd et al. reported that these benefits were attained without increasing the cost of treatment compared to RHI [21].

Women with GDM

The characteristics of four RCTs using RAIAs in GDM are summarized in ESM Table S2 [16–19]. The results indicate that insulin lispro was at least as effective as RHI and sometimes demonstrated improved glycemic control (ESM Table S2) [16, 17, 19]. Insulin aspart was associated with significantly lower post-meal BG compared with RHI [16, 18]. In the single trial involving a head-to-head comparison of insulin aspart and insulin lispro, mean 1-h post-breakfast BG was similar for the two products (6.75 ± 1.12 vs. 6.6 ± 1.05 mmol/L, respectively) [16].

In Mecacci et al. [17], hypoglycemia was not reported and, in another trial, there were no hypoglycemic events reported for insulin aspart, insulin lispro or RHI [16]. In a study of women ($n = 27$) using insulin aspart or RHI, the reported percentage of participants experiencing symptomatic hypoglycemic events was similar for both treatments (71 vs. 69%), but more participants using insulin aspart reported minor hypoglycemia (79 vs. 39%) [18]. In the latter case, this was largely due to two participants being prone to hypoglycemia. Neonatal

outcomes (weight, length, physical exam) were good for both insulin aspart and RHI.

Meta-Analysis

The pregnancy studies were deemed to be too heterogeneous or to lack relevant information for meta-analysis of either efficacy or safety outcomes for any of the three RAIAs.

Children and Adolescents

There were nine eligible studies involving pediatric patients with T1D [22–30]. The characteristics of these studies are presented in ESM Table S4 and the results are shown in Table 2. Three trials compared insulin aspart with RHI [22, 23, 28], five compared insulin lispro with RHI [24–27, 30] and one compared insulin lispro with insulin glulisine [29]. Most (5/9; 55.5%) trials involved < 50 participants. Study quality assessment is shown in ESM Table S5. Four studies were graded as –, two were graded as + and three were graded as ++. Trials using RAIAs in CSII in children are discussed in the section “Patients Treated with CSII”.

Overall, glycemic control (either HbA1c or PPG) with insulin lispro or insulin aspart was equivalent to or better than that with RHI. This was also true with respect to incidence of hypoglycemic episodes or other adverse events. There were no head-to-head trials comparing all three RAIAs in pediatric participants. However, a large ($n = 572$), open-label, parallel-group, non-inferiority trial compared insulin glulisine with insulin lispro [29]. Insulin glulisine was demonstrated to be non-inferior to insulin lispro (treatment difference in HbA1c: -0.06% [95% CI $-0.24; 0.12$]; -0.7 [95% CI $-2.6; 1.33$] mmol/mol). More children achieved American Diabetes Association (ADA) age-specific HbA1c targets (at the time of the study: < 6 years, HbA1c > 7.5 to% < 8.5% [> 58 to < 69 mmol/mol]; 6–12 years, HbA1c < 8.0% [< 64 mmol/mol]; 13–17 years, HbA1c < 7.5% [< 58 mmol/mol]; currently, the ADA recommends HbA1c < 7.5% [< 58 mmol/mol] across all pediatric age groups [1]) with insulin glulisine than with insulin lispro (overall population: 38.4 vs. 32.0% for insulin glulisine and

insulin lispro, respectively; $p = 0.039$). The frequencies of hypoglycemic events and other adverse events were similar.

Meta-Analysis

Data on glycemic control were deemed to be too heterogeneous or to lack relevant information for meta-analysis, but the data on severe hypoglycemic outcomes were able to be combined from five studies (Fig. 2a). Overall, the number of severe hypoglycemic events was low (total of 14), and a random-effects model using generic inverse variance showed no difference in risk of severe hypoglycemia with insulin analog treatment, risk difference 0 (95% CI $-0.01; 0.01$). Funnel plots suggested that there was no publication bias (data not shown).

Patients Treated with CSII

The largest number of eligible studies ($n = 13$) was identified for people using CSII [31–43], of which two were carried out in pediatric populations [42, 43] (ESM Table S6). The results are presented in Table 3, and the study quality assessment is shown in ESM Table S7. Two studies were graded as –, three were graded as + and seven were graded as ++. One of the studies consisted of two substudies, one of which was graded as +, and the second was graded as ++ due to the double-blind component.

Eight studies compared an RAIA with RHI and all involved insulin lispro [32, 34–38, 41], with one being a pediatric trial [42]. All were crossover trials of 1–4 months' duration. All indicated that insulin lispro was associated with improved glycemic control (HbA1c) and an incidence of hypoglycemic events that was similar to or lower than RHI.

Three studies involved head-to-head comparisons of insulin lispro versus insulin aspart [33, 39, 43], with an additional trial also comparing RHI [31]. The largest of the three trials was a 16-week, open-label RCT in 298 subjects with T1D aged 4–18 years [43] (ESM Table S6). At 16 weeks, the HbA1c in subjects receiving insulin aspart was deemed to be non-inferior to the HbA1c in those receiving insulin lispro, and

Table 2 Study outcomes: pediatrics

First Author, year	Analog (n) vs. comparator (n)	HbA1c outcomes		BG levels		Hypoglycemia		Secondary outcomes	
		Definition	Results	Definition	Results (mmol/L)	Definition	Results	Measures	Results
Philotheou, 2011 [29]	Glulisine (275) vs. lispro (295)	Tested at baseline and endpoint (1) Adjusted mean change (\pm SD) from baseline to endpoint (2) Difference between treatments in adjusted means (95% CI) for difference from baseline to endpoint (3) % achieving ADA age-specific HbA1c targets at endpoint	(1) $+0.10 \pm 0.08$ vs. $+0.16 \pm 0.07$ (2) -0.06 (-0.24 ; 0.12) (3) 38.4 vs. 32.0 ($p = 0.0039$)	3-point SMBG at endpoint (1) Adjusted mean (\pm SEM) of pre-breakfast BG (p value for difference between groups) (2) Adjusted mean (\pm SEM) of pre-main meal BG (3) Adjusted mean (\pm SEM) of 2-h post main meal	(1) 8.77 ± 0.21 vs. 9.46 ± 0.21 ($p = 0.014$) (2) 9.76 ± 0.24 vs. 9.80 ± 0.23 ($p = 0.894$) (3) 9.20 ± 0.22 vs. 9.04 ± 0.21 ($p = 0.564$)	Reported from month 4 to treatment end (1) Severe hypo (\pm SD): BG < 2.0 mmol/L and third-party assistance required or prompt recovery following glucose treatment, number of episodes per patient-month (2) Nocturnal hypo (3) Any hypo	(1) 0.06 ± 0.24 vs. 0.07 ± 0.27 (2) 0.21 ± 0.50 vs. 0.20 ± 0.80 (3) 3.10 ± 4.33 vs. 2.91 ± 4.35	Mean (\pm SD) increase total daily dose of insulin from baseline, units/day	2.53 ± 0.68 vs. 4.91 ± 0.65 ($p = 0.007$)
Pankowska, 2010 [28]	Aspart (20) vs. RHI (21)	Tested at baseline, midpoint and endpoint (1) Mean HbA1c (\pm SD) at 13 weeks after treatment (2) Mean HbA1c at 26 weeks after treatment	(1) 7.4 ± 0.9 vs. 7.6 ± 1.1 (2) 7.6 ± 0.9 vs. 7.6 ± 1.0	24-h glycemic control measured using CGMS for 72 h at endpoint (1) Mean (\pm SD) of area under glucose curve, mmol/h/L (2) Difference between maximum and minimum glucose levels over 24 h	(1) 219.8 (12.8) vs. 211.8 (10.9) ($p = 0.55$) (2) 4.0 vs. 4.0 ($p = \text{NS}$)	Self-reported by parent during CGM period (1) Severe hypo: BG < 2.8 mmol/L accompanied by CNS symptoms requiring external help, number of episodes per patient-year of exposure (2) Minor hypoglycemia: BG < 2.8 mmol/L that were asymptomatic or self-treatable (3) Symptoms-only hypoglycemia	(1) 0.1 vs. 0.0 ($1/20$) vs. ($0/21$) (2) 18 vs. 20 (3) 1.1 vs. 1.4	Treatment satisfaction: SD values for mean change in treatment satisfaction score at end of study	5.6 vs. 4.4 ($p = 0.04$)

Table 2 continued

First Author, year	HbA1c outcomes		BG levels		Hypoglycemia		Secondary outcomes		
	Analog (#) vs. comparator (#)	Definition	Results	Definition	Results (mmol/L)	Definition	Measures	Results	
Cherubini, 2006 [22]	Aspart (NR) vs. RHI (NR)	Tested at baseline and 6-weekly during study (1) Change in HbA1c (\pm SD) over the study period	(1) 7.5 ± 0.8 to 7.0 ± 0.4 vs. 7.5 ± 1.4 to 7.4 ± 0.5 ($p = 0.018$)	7-point SMBG during study period (1) Mean 2-h postprandial BG (2) Mean fasting BG (3) Mean afternoon BG at endpoint (4) Decrease in mean daily BG variability from baseline	(1) 7.38 ± 1.0 vs. 7.94 ± 1.06 ($p = 0.175$) (2) Analog < RHI, $p = 0.012$ (3) 8.89 ± 2.89 vs. 9.17 ± 2.72 ($p = 0.113$) (4) Analog = RHI, $p > 0.237$	Self-reported (1) Severe hypo: BG < 2.8 mmol/L, number of episodes per patient per day (2) Any hypo: BG < 3.9 mmol/L	NR	(1) 0.045 vs. 0.035 ($p = 0.209$) (2) 0.214 vs. 0.18 ($p = 0.117$)	NR
Fairchild, 2000 [25]	Lispro (35) vs. RHI (35)	Tested at baseline and 6-weekly during study (1) Mean HbA1c (\pm SD) at endpoint	(1) 8.33 ± 0.89 vs. 8.14 ± 0.77 ($p = \text{NS}$)	7-point SMBG done weekly or 2-weekly (1) Mean BG (\pm SD) at 03:00 h (2) Mean difference (95% CI) in 03:00 h BG between groups	(1) 10.57 ± 0.26 vs. 9.02 ± 0.46 ($p = 0.001$) (2) 2.35 ($-3.98; -0.72$) $p = 0.01$	Self-reported and BG meter analysis (1) Severe hypos: hypo associated with convulsion or coma (2) Total recorded hypos, number of episodes per patient per 3 months (3) Total recorded hypos from 06:00 to 12:00 h (4) Hypos with BG < 3.0 mmol/L	Treatment satisfaction questionnaire Number (%) preferring this type of insulin over the other one	(1) 0.032 vs. 0.065 ($p = \text{NS}$) 1/35 vs. 2/35 (2) 13.47 vs. 10.77 ($p = \text{NS}$) (3) 5.69 vs. 3.31, difference 2.4 ± 5.1 ($p = 0.02$) (4) analog = comparator ($p = \text{NS}$)	28 (80) vs. 7 (20)

Table 2 continued

First Author, year	Analog (n) vs. comparator (n)	HbA1c outcomes		BG levels		Hypoglycemia		Secondary outcomes	
		Definition	Results	Definition	Results (mmol/L)	Definition	Results	Measures	Results
Ford-Adams, 2003 [26]	Lispro (23) vs. RHI (23)	Tested at baseline and 4-monthly during study	<p>(1) 8.9 ± 0.3 vs. 8.4 ± 0.3 ($p = 0.14$)</p> <p>(2) 8.5 ± 0.2 vs. 8.8 ± 0.3 ($p = 0.47$)</p>	<p>Overnight metabolic study</p> <p>(1) Mean BG (\pm SD) at start of overnight profile</p> <p>(2) Mean fasting BG</p> <p>(3) AUC of BG (\pm SD) from post-EM to bedtime, mmol/min/L</p> <p>(4) AUC of BG from 22:00 to 04:00 h</p>	<p>(1) 6.5 ± 1.0 vs. 7.1 ± 1.1 ($p = 0.5$)</p> <p>(2) 6.1 ± 0.8 vs. 6.3 ± 0.9 ($p = 0.8$)</p> <p>(3) 138 ± 12 vs. 170 ± 13 ($p = 0.03$)</p> <p>(4) 158 ± 13 vs. 145 ± 12 ($p = 0.3$)</p>	<p>Self-reported</p> <p>(1) Severe hypo: convulsions or requiring glucagon, number of episodes</p> <p>(2) Symptomatic hypoglycemia, number of episodes per patient per week (\pm SD)</p> <p>Overnight metabolic profile</p> <p>(3) Prevalence of low BG from post-EM to 22:00 h: BG < 3.5 mmol/L, %</p> <p>(4) Prevalence of low BG from 22:00 to 04:00 h</p> <p>(5) Prevalence of low BG from 04:00 to 07:00 h</p>	<p>(1) 2/23 vs. 1/23</p> <p>(2) 1.6 ± 0.3 vs. 1.7 ± 0.3 ($p = 0.2$)</p> <p>(3) 9 vs. 6 ($p = 0.06$)</p> <p>(4) 8 vs. 13 ($p = 0.01$)</p> <p>(5) 27 vs. 22 ($p = 0.11$)</p>	<p>Mean (range) total daily insulin dose, units/kg</p>	<p>0.97 (0.68–1.26) vs. 0.96 (0.53–1.22) ($p = 0.2$)</p>
Holcombe, 2002 [27]	Lispro (457) vs. RHI (457)	Tested at baseline and 2-monthly during study	<p>(1) 8.41 ± 1.4 vs. 8.80 ± 1.5 ($p = \text{NS}$)</p> <p>(2) 8.69 ± 1.52 vs. 8.70 ± 1.65 ($p = \text{NS}$)</p>	<p>8-point BG profiles on 2 days at baseline and end of each treatment period</p> <p>(1) Mean (\pm SD) BG concentrations at 03:00 h</p> <p>(2) Mean fasting BG concentrations</p> <p>(3) Mean BG 2-h post-breakfast</p> <p>(4) Mean BG 2-h post-dinner</p> <p>(5) Mean BG 2-h post-mid-day meal</p>	<p>(1) 9.7 ± 3.9 vs. 8.8 ± 3.7 ($p < 0.001$)</p> <p>(2) 10.2 ± 3.5 vs. 9.6 ± 3.4 ($p = 0.005$)</p> <p>(3) 9.7 ± 4.0 vs. 10.6 ± 4.3 ($p < 0.001$)</p> <p>(4) 8.6 ± 3.5 vs. 9.3 ± 3.7 ($p = 0.003$)</p> <p>(5) 8.1 ± 3.4 vs. 8.5 ± 3.4 ($p = \text{NS}$)</p>	<p>Self-reported</p> <p>(1) Severe hypo: needing third-party assistance or intravenous glucose or glucagon injection, number of patients</p> <p>(2) Nocturnal hypoglycemia: from midnight to 06:00 h</p> <p>(3) Any hypoglycemia: symptoms present or measured</p> <p>BG < 3.0 mmol/L, number of episodes per patient per month</p>	<p>(1) 5 vs. 5</p> <p>5/457 vs. 5/547</p> <p>(2) 1.0 ± 1.9 vs. 1.7 ± 2.6 ($p < 0.001$)</p> <p>(3) 4.02 ± 4.5 vs. 4.37 ± 4.5 ($p = 0.023$)</p>	<p>(1) Mean (\pm SD) total daily insulin dose, units/kg</p> <p>(2) Mean (\pm SD) daily dose of short- and rapid-acting insulin</p>	<p>(1) 1.08 ± 0.32 vs. 1.05 ± 0.30 ($p < 0.001$)</p> <p>(2) 0.54 ± 0.24 vs. 0.53 ± 0.20 ($p = \text{NS}$)</p>

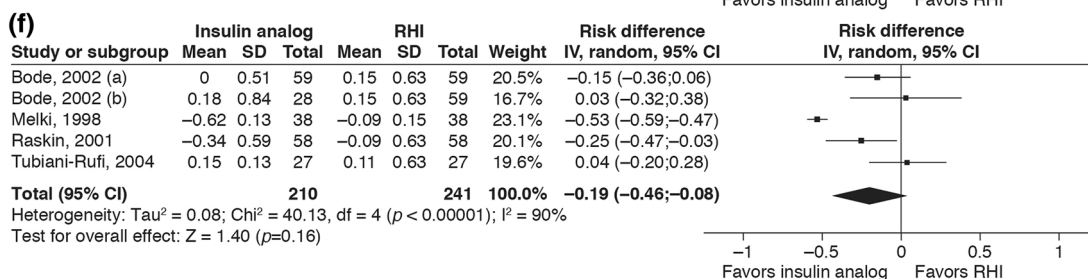
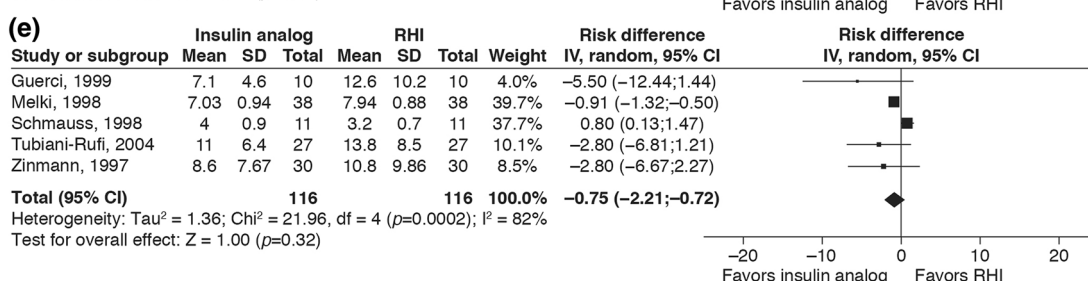
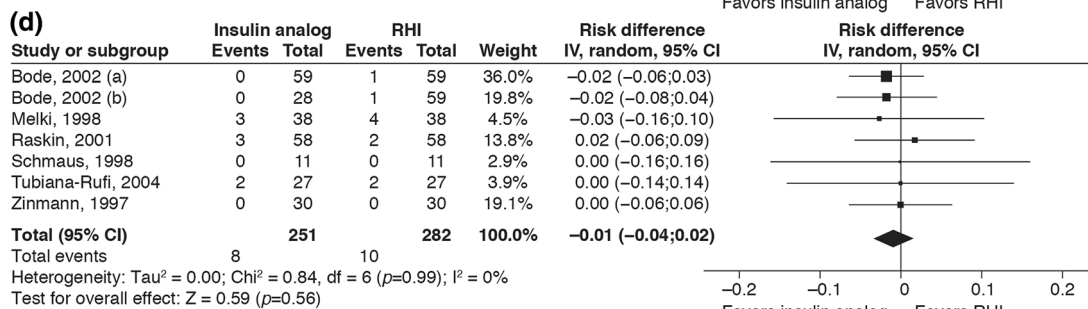
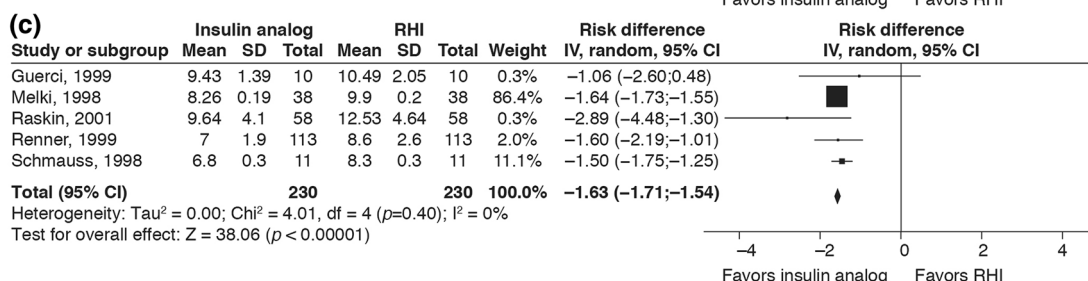
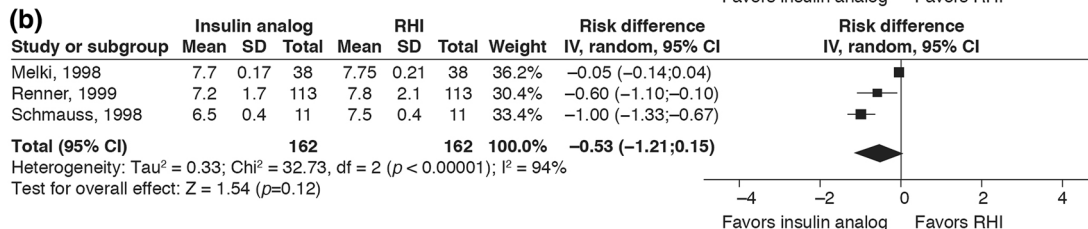
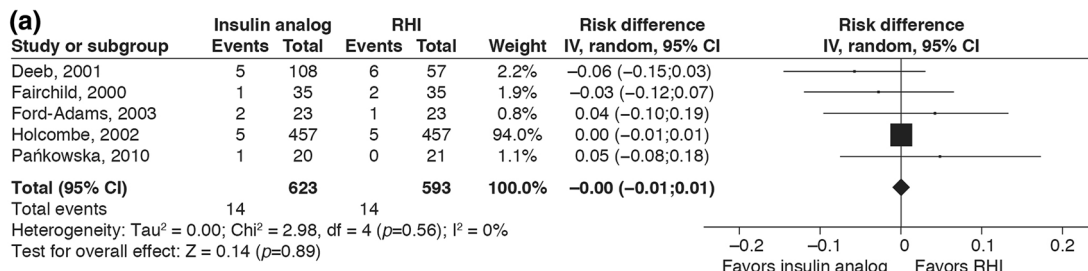
Table 2 continued

First Author, year	Analog (#) vs. comparator (#)	HbA1c outcomes		BG levels		Hypoglycemia		Secondary outcomes	
		Definition	Results	Definition	Results (mmol/L)	Definition	Results	Measures	Results
Deeb, 2001 [24]	Lispro before meals (analog 1, 53) vs. lispro after meals (analog 2, 55) vs. RHI (57)	Tested at baseline and 3-monthly during study (1) Mean (\pm SD) HbA1c at endpoint	(1) 8.40 \pm 1.1 vs. 8.54 \pm 1.0 vs. 8.43 \pm 1.0 (p = NS)	7-point SMBG profiles on 2 days at baseline and end of each treatment period (1) Overall mean BG (\pm SD) (2) Mean BG 2-h post-breakfast (3) Mean BG pre-lunch (4) Mean BG 2-h post-lunch (5) Mean BG 2-h post-dinner BG	(1) 9.6 \pm 1.6 vs. 10.1 \pm 1.6 vs. 10.0 \pm 1.7 (p = 0.007 analog 1 vs. analog 2, p = 0.024 for trend) (2) 11.7 \pm 4.4, 13.5 \pm 5.5, 15.0 \pm 5.4 (p < 0.001 analog 1 vs. comparator; p = 0.023 analog 1 vs. analog 2) (3) 8.7 \pm 3.9 vs. 8.3 \pm 3.1 vs. 8.3 \pm 3.1 vs. 9.5 \pm 4.1 (p = NS analog 1 vs. analog 2, p = 0.037 analog 1 vs. RHI) (4) Analog 1 = analog 2 = RHI (p = NS) (5) 8.8 \pm 5.0 vs. 9.9 \pm 4.7 vs. 10.8 \pm 5.4 (p = NS analog 1 vs. analog 2, p = 0.006 analog 1 vs. RHI)	Self-reported (1) Severe hypo: needing third-party assistance, resulting in a coma, or requiring intravenous glucose or glucagon, number of patients (2) Any hypoglycemia: symptomatic or measured BG < 3.5 mmol/L, number of episodes per 30 days	(1) 2 vs. 3 vs. 6 (p = NS) 5/108 vs. 6/57 (2) 14.7 \pm 11.9 vs. 13.6 \pm 9.3 vs. 13.8 \pm 9.8 (p = NS)	Mean total daily insulin dose, units/kg	0.21 vs. 0.23 vs. 0.25 (p = NS)

Table 2 continued

First Author, year	HbA1c outcomes		BG levels		Hypoglycemia		Secondary outcomes	
	Analog (n) vs. comparator (n)	Definition	Results	Definition	Results (mmol/L)	Definition	Measures	Results
Tupola, 2001 [30]	Lispro (22) vs. RHI (22)	Tested at baseline and 3-monthly during study (1) Mean (\pm SD) change in HbA1c from baseline to endpoint	(1) 0.2 ± 0.8 vs. -0.4 ± 0.7 ($p = 0.1$)	7-point SMBG profiles on 1 day per month over study period (1) Mean BG (\pm SD) pre-breakfast (2) Mean BG pre-dinner (3) Mean BG at bedtime (4) 1-h and 2-h postprandial BG excursions	(1) 11.5 ± 4.5 vs. 8.4 ± 3.8 ($p = 0.02$) (2) 11.7 ± 6.0 vs. 9.6 ± 5.7 ($p = 0.4$) (3) 11.5 ± 5.0 vs. 10.6 ± 6.0 ($p = 0.8$) (4) Analog = RHI ($p = \text{NS}$)	Self-reported and BG meter analysis (1) Severe hypo: loss of consciousness during a hypoglycemic episode (2) Nocturnal hypoglycemia: from 11:00 to 06:00 h (3) Hypoglycemia: symptoms present or BG < 3 mmol/L, number of episodes per patient per month	(1) Total daily insulin dose (2) Patient satisfaction: number (%) of patients/families who wanted to continue this type of insulin	(1) Analog = RHI ($p = \text{NS}$) (2) 18 (82) vs. 4 (18)
Danne, 2007 [23]	Aspart (23) vs. RHI (25)	Tested at baseline and 3-monthly during study (1) HbA1c at endpoint	(1) Analog = RHI ($p = \text{NS}$)	7-point SMBG during study period (1) Daily BG variations	(1) Analog = RHI ($p = \text{NS}$)	Self-reported (1) Major hypoglycemia: those that parents could not handle on their own, number of episodes (2) Any hypoglycemia, number of episodes per week (3) Relative risk of hypoglycemia (95% CI); relative risk for analog/RHI	WHO-DTSQs (1) Mean score (\pm SD) for question on continuing present form of insulin (2) Mean score (\pm SD) for question on recommending this form of insulin to others	(1) 4.8 ± 1.5 vs. 3.7 ± 1.8 ($p = 0.045$) (2) 5.0 ± 1.4 vs. 4.2 ± 1.8 ($p = 0.051$)

ADA American Diabetes Association, AUC area under the curve, CGM continuous glucose monitoring, CNS central nervous system, DTSQ Diabetes Treatment Satisfaction Questionnaire, DKA diabetic ketoacidosis, EM evening meal, WHO World Health Organization



◀ **Fig. 2** Meta-analyses of key outcomes. **a** Forest plot showing the difference in risk of severe hypoglycemic episodes with insulin analog treatment compared to regular human insulin (RHI) in a pediatric population. **b** Forest plot showing the difference in the mean fasting blood glucose level with insulin analog treatment compared to RHI treatment in the CSII sub-review. **c** Forest plot showing the difference in mean postprandial blood glucose (BG) level with insulin analog treatment compared to RHI treatment in the CSII sub-review. **d** Forest plot showing the difference in risk of severe hypoglycemic episodes with insulin analog treatment compared to RHI treatment in the CSII sub-review. **e** Forest plot showing the mean difference in the rate of any hypoglycemic episodes with insulin analog treatment compared to RHI treatment in the CSII sub-review. **f** Forest plot showing the difference in glycated hemoglobin (HbA1c) with insulin analog treatment (lispro or aspart) compared to RHI in the CSII sub-review.

Squares and diamonds represent the difference in HbA1c after intervention with the two treatments for each study (horizontal lines are 95% CI) and for all the studies combined, respectively. The I^2 value refers to the statistical heterogeneity for the pooled analysis. A random-effects model using generic inverse variance showed a mean difference in HbA1c of -0.19% (95% CI $-0.46; 0.08$); -2.1 (95% CI $-5.0; 0.9$) mmol/mol with insulin analog compared to RHI at the end of the treatment period. The squares and the diamond in **a**, **d**, **e** represent the difference in risk for each study (horizontal lines represent 95% CI) and for all studies combined, respectively. The squares and the diamond in **b**, **c** represent the difference in the glucose levels between the two treatment arms for each study (horizontal lines are 95% CI) and for all the studies combined, respectively. The results of these meta-analyses are the mean of post-breakfast BG measurements only. In **a** and **d** ‘Events’ refers to the number of patients experiencing any such episode during the treatment period as a proportion of total number of patients in that treatment group. ‘Rate’ refers to mean (\pm SD) of any episodes of hypoglycemia per 30 days in all the patients in the respective treatment group. In **f** ‘Bode, 2002 (a)’ [31] refers to the observed difference in HbA1c between the subgroup of insulin lispro vs. RHI, and ‘Bode, 2002 (b)’ [31] refers to the subgroup on insulin aspart vs. RHI; the three remaining studies compare lispro vs. RHI. The I^2 value refers to the statistical heterogeneity for this pooled analysis. CI confidence interval, IV inverse variance, SD standard deviation

there were no significant differences in FBG or rates of hyper- and hypoglycemia. However, the daily insulin dose was significantly lower for groups on insulin aspart (0.86 ± 0.237 vs. 0.94 ± 0.233 U/kg, for insulin aspart vs. insulin lispro, respectively; $p = 0.018$) [43]. In two related, 24-week, randomized, crossover trials in adults with T1D, insulin lispro was assessed to be non-inferior to insulin aspart based on SMBG profiles averaged over days 1–6 of treatment, but not when day 6 values alone were compared [39]. In a randomized, parallel-group trial in 146 adults with T1D, mean change from baseline was not significantly different for participants treated with insulin lispro, insulin aspart or RHI for 16 weeks [31]. Rates of hypoglycemia were also similar among treatments.

One RCT compared all three RAIAs in adults [40]. This was a crossover trial with three 13-week periods that was designed to test the superiority of insulin glulisine for unexplained hyperglycemia and/or infusion-set occlusion. It failed to show superiority of insulin glulisine on the primary outcome, but revealed that the monthly rate of unexplained hyperglycemic episodes and/or perceived catheter-set occlusion was significantly higher in insulin glulisine-treated patients than in those receiving the two other analogs [40]. Furthermore, insulin glulisine was associated with a higher frequency of symptomatic hypoglycemia, whereas HbA1c and 7-point SMBG were similar for all three insulin analogs [40].

Meta-analysis

Data on mean FBG and mean PPG for patients using CSII were sufficiently consistent to permit some meta-analysis, as were some of the hypoglycemic outcomes. Funnel plots suggested that there was no publication bias, although the number of studies in the meta-analysis with FBG outcomes was small (funnel plots not shown). Meta-analysis was performed for RAIAs versus RHI for FBG (three studies) (Fig. 2b), PPG (five studies) (Fig. 2c), severe hypoglycemic episodes (six studies) (Fig. 2d), any hypoglycemic episodes (five studies) (Fig. 2e) and HbA1c (four studies) (Fig. 2f). A random-effects model using generic inverse variance showed a mean difference in FBG of -0.53 mmol/L

Table 3 Study outcomes: continuous subcutaneous insulin infusion

First author, year	Analog (#) vs. comparator (#)	HbA1c outcomes		BG levels		Hypoglycemia		Secondary outcomes	
		Definition	Results	Definition	Results (mmol/L)	Definition	Results	Measures	Results
Zimmann, 1997 [41]	Lispro (30) vs. RHI (30)	Tested monthly (1) Mean (± SE) baseline HbA1c in all patients (2) Mean endpoint HbA1c (3) Difference in endpoint HbA1c between treatments	(1) 8.03 ± 0.13 (2) 7.66 ± 0.13 vs. 8.00 ± 0.16 (3) - 0.34 (p = 0.0041)	8 point-SMBG profile done weekly (1) Mean fasting BG (2) Mean post-prandial BG	(1) No significant difference between treatments (2) Lower with lispro than with RHI (p < 0.05)	Self-reported diary (1) Any hypo at baseline: BG < 3 mmol/L or compatible symptoms, episodes per 30 days (± SE) (2) Any hypo during treatment (3) Biochemical hypo at baseline: BG < 3 mmol/L only (4) Biochemical hypo during treatment (5) Severe hypo	(1) 12.7 ± 1.6 (2) 8.6 ± 1.4 vs. 10.8 ± 1.8 (lispro baseline, RHI p = NS) (3) 8.4 ± 1.3 (4) 6.0 ± 0.9 vs. 7.6 ± 1.3 (lispro baseline, RHI p = NS) (5) 0/30 vs. 0/30	(1) 5-h meal test on subgroup of six patients for postprandial insulin glucose and FFA (2) BW (3) Infusion-set occlusion	(1) Peak free plasma insulin at 45 min for lispro (287 ± 69 pmol/L) vs. 150 min for RHI (294 ± 56). Plasma glucose and FFA markedly reduced for lispro vs. RHI (2) No difference in BW from baseline or between treatments at endpoint (3) No occlusions with either treatment
Melki, 1998 [35]	Lispro (38) vs. RHI (38)	Tested at end of first 3 months (1) Baseline (2) Endpoint (3) Change from baseline to endpoint	(1) 7.74 ± 0.20 vs. 7.97 ± 0.13 (2) 7.11 ± 0.15 vs. 7.88 ± 0.16 (3) - 0.62 ± 0.13 vs. - 0.09 ± 0.15 (p = 0.01)	7 point-SMBG profile done daily during last 30 days of each treatment period (1) Mean BG ± SE (2) Mean preprandial BG (3) Mean 2-h postprandial BG	(1) 7.93 ± 0.15 vs. 8.61 ± 0.18 (p < 0.0001) (2) 7.70 ± 0.17 vs. 7.75 ± 0.21 (p = NS) (3) 8.26 ± 0.19 vs. 9.20 ± 0.20 (p < 0.0001)	Self-reported diary recorded in last 30 days of first treatment period (1) Hypo event: BG < 3 mmol/L, episodes per month (± SD) (2) Very low BG measurement: BG < 2 mmol/L (3) Severe hypo: third-party assistance required	(1) 7.03 ± 0.94 vs. 7.94 ± 0.88 (p = NS) (2) 0.05 ± 0.05 vs. 0.47 ± 0.19 (p < 0.05) (3) 3 vs. 7 (3/38 vs. 4/38)	(1) Ketoacidosis (2) BW (3) Glucose variability (4) Patient preference (5) Technical problems	(1) No episodes in either group (2) No difference (3) Significantly lower overall mean and postprandial glycemic fluctuation with lispro than RHI, SD of BG in mmol/L (± SE): 3.44 ± 0.10 vs. 3.80 ± 0.10 (p < 0.0001) and 3.58 ± 0.10 mmol/L vs. 3.84 ± 0.10 (p < 0.02) (4) All seven questions on non-validated questionnaire in favor of lispro (p < 0.0001) (5) Insulin precipitation in catheter, one vs. four episodes; catheter obstruction, nine episodes each

Table 3 continued

First author, year	Analog (<i>n</i>) vs. comparator (<i>n</i>)	HbA1c outcomes		BG levels		Hypoglycemia		Secondary outcomes	
		Definition	Results	Definition	Results (mmol/L)	Definition	Results	Measures	Results
Schmauss, 1998 [38]	Lispro (11) vs. RHI (11)	Tested 3-monthly	Lispro then RHI vs. RHI then lispro	3-day BG profile done 3-monthly	(1) 6.5 ± 0.4 vs. 7.5 ± 0.4 (<i>p</i> = NS)	Self-reported	(1) 4.0 ± 0.9 vs. 3.2 ± 0.7 (<i>p</i> = NS)	(1) Basal and bolus insulin requirements	(1) No difference
		(1) Baseline	(1) 6.3 ± 0.2 vs. 6.7 ± 0.4 (<i>p</i> = NS)	(1) Mean fasting BG	(2) 6.8 ± 0.3 vs. 8.3 ± 0.3 (<i>p</i> = 0.03)	(1) Hypo: BG < 3.5 mmol/L and/or symptoms, episodes per 30 days (± SD)	(2) 0 vs. 0 (0/11 vs. 0/11)	(2) BMI change	(2) No change in BMI
		(2) End of first 3 months	(2) 5.7 ± 0.3 vs. 6.5 ± 0.3 (<i>p</i> = NS)	(2) Mean 2-h postprandial BG		(2) Severe hypo: requiring IV glucose or glucagon		(3) Treatment satisfaction	(3) No difference in treatment satisfaction
Guerci, 1999 [32]	Lispro (10) vs. RHI (10)	Tested monthly	(1) 7.47 ± 0.86 vs. 7.36 ± 0.76 (<i>p</i> = NS)	SMBG done monthly	(1) 9.35 ± 1.17 vs. 9.07 ± 0.43 (<i>p</i> = NS)	Self-reported	(1) 10.1 ± 9.7 vs. 6.9 ± 4.4 (<i>p</i> = NS)	(1) Glucose variability, mean SD of previous months' BG	(1) No difference between treatment groups
		(1) Baseline	(1) 7.07 ± 0.51 vs. 6.97 ± 0.67 (<i>p</i> = NS)	(1) Mean baseline BG	(2) 9.04 ± 0.89 vs. 9.32 ± 1.17 (<i>p</i> = NS)	(1) Incidence of hypo at baseline: BG < 3.5 mmol/L, episodes per 30 days (± SD)	(2) 7.1 ± 4.6 vs. 12.6 ± 10.2 (<i>p</i> = 0.05)	After pump interruption for 5 h:	(2) Until 3 h no difference in PG between groups. From 3 to 5 h, PG higher with lispro (<i>p</i> < 0.01)
		(2) Endpoint of each treatment period	(2) 5.7 ± 0.3 vs. 6.5 ± 0.3 (<i>p</i> = NS)	(2) Mean BG at endpoint	(3) 9.53 ± 1.98 vs. 9.92 ± 1.05 (<i>p</i> = NS)	(2) Incidence of hypo at endpoint		(2) Mean PG	(3) From 3 h onwards, consistently higher for lispro vs. RHI (but <i>p</i> = NS)
		(3) Mean baseline postprandial BG	(4) 9.43 ± 1.39 vs. 10.49 ± 2.05 (<i>p</i> = 0.05)	(3) Mean postprandial BG				(3) Plasma 3-hydroxybutyrate	(4) From 2 h onwards, consistently higher for lispro vs. RHI (<i>p</i> < 0.05)
		(4) Mean postprandial BG at endpoint						(4) Plasma FFA	

Table 3 continued

First author, year	Analog (#) vs. comparator (#)	HbA1c outcomes		BG levels		Hypoglycemia		Secondary outcomes	
		Definition	Results	Definition	Results (mmol/L)	Definition	Results	Measures	Results
Renner, 1999 [37]	Lispro (113) vs. RHI (113)	Tested at baseline and endpoint	(1) 7.24 ± 1.0 (2) 6.77 ± 0.88 vs. 6.90 ± 0.97 (p = 0.02)	8-point daily SMBG	(1) 7.2 ± 1.7 vs. 7.8 ± 2.1 (p = NS)	Self-reported	(1) 12.0 ± 13.9 vs. 11.0 ± 11.2 (p = NS)	(1) Ketosis	(1) Five vs. four patients
		(1) Baseline in all patients		(1) Mean fasting BG (± SD)	(2) 7.0 ± 1.9 vs. 8.6 ± 2.6 (p < 0.001)	(1) BG < 3.5 mmol/L and/or symptoms, mean number of episodes (± SD) per patient per 4 months	(2) Lispro = RHI (p = NS)	(2) Treatment satisfaction (DTSQ)	(2) Patients scored significantly higher on the treatment satisfaction when treated with lispro compared to RHI
		(2) Endpoint		(2) Mean post-breakfast BG	(3) 6.9 ± 1.9 vs. 7.3 ± 2.2 (p = NS)	(2) BG < 3.3 mmol/L, mean number of episodes (± SD) per patient per month	(p = NS)	(3) Occlusion of catheter	(3) Same amount in the two treatments
				(3) Mean pre-lunch BG	(4) 7.6 ± 1.9 vs. 8.7 ± 2.4 (p < 0.001)				
				(4) Mean post-lunch BG	(5) 7.3 ± 1.9 vs. 7.5 ± 1.9 (p = NS)				
				(5) Mean pre-dinner BG	(6) 7.2 ± 1.9 vs. 8.3 ± 1.9 (p < 0.001)				
				(6) Mean post-dinner BG	(7) 7.6 ± 1.8 vs. 8.3 ± 2.0 (p < 0.001)				
				(7) Mean 22:00 h BG	(8) 8.0 ± 2.7 vs. 7.7 ± 2.3 (p = NS)				
Johansson, 2000 [34]	Lispro (41) vs. RHI (41)	Tested at baseline and endpoint	(1) 7.7 ± 0.8 (2) 7.4 vs. 7.6 (p = 0.047)	Last 30 days SMBG	(1) 8.5 vs. 8.4 (p = NS)	Self-reported	(1) 9.7 vs. 8.0 [1.7 (-1.3; 5.3)] (p = NS)	(1) Treatment satisfaction (DTSQ)	(1) No difference between the treatments
		(1) Baseline in all patients		(1) Mean of pre-prandial and bedtime BG	(2) 8.1 vs. 9.6 (p < 0.001)	(1) Any hypo: BG < 3.0 mmol/L and/or symptoms, episodes per 30 days (difference between treatments [95% CI])	(p = NS)		
		(2) Endpoint	(3) -0.2 (-0.3; 0.0) (p = 0.047)		(3) 8.3 vs. 8.9 (p < 0.001)				
		(3) Difference between treatments (95% CI)							

Table 3 continued

First author, year	Analog (n) vs. comparator (n)	HbA1c outcomes		BG levels		Hypoglycemia		Secondary outcomes	
		Definition	Results	Definition	Results (mmol/L)	Definition	Results	Measures	Results
Raskin, 2001 [36]	Lispro (58) vs. RHI (58)	Tested at baseline and endpoint (1) Baseline in all patients (2) Change from baseline	(1) 7.9 ± 1.1 vs. 7.6 ± 0.8 (p = NS) (2) -0.34 ± 0.59 vs. -0.09 ± 0.63 (p = 0.004)	4-point daily SMBG done in last 2 weeks of each treatment period (1) Mean BG (± SD) PG during test meal at end of each treatment period (2) Mean PG 1 h post-meal (3) Mean PG 2 h post-meal	(1) 8.1 ± 2.0 vs. 8.1 ± 1.6 (p = NS) (2) 11.16 ± 4.29 vs. 13.20 ± 4.68 (p = 0.012) (3) 9.64 ± 4.10 vs. 12.53 ± 4.64 (p = 0.001)	Self-reported (1) Any hypo: BG < 3.0 mmol/L and/or symptoms, episodes per 12 weeks (2) Severe hypoglycemia: requiring IV glucose	(1) 8 vs. 11 (p = NS) (2) 3 vs. 3 (p = NS) 3/58 vs. 2/58	(1) BW	(1) No difference between treatments
Tubiani-Rufi, 2004 [42]	Lispro (27) vs. RHI (27)	Tested at baseline and endpoint (1) Difference in HbA1c (± SD) from baseline to end of first treatment sequence	(1) +0.15 ± 0.13 vs. +0.11 ± 0.63 (p = NS)	9-point SMBG on 2 days during each treatment (1) Change in mean post-dinner BG	(1) -0.94 ± 5.05 vs. +1.78 ± 5.94 (p = 0.01)	Self-reported (1) Severe hypoglycemia, episodes per 30 days (2) BG ≤ 3.3 mmol/L (3) BG ≤ 2.2 mmol/L	(1) 2 vs. 2 2/27 vs. 2/27 (2) 11.0 ± 6.4 vs. 13.8 ± 8.5 (p = NS) (3) 0.6 ± 1.1 vs. 1.0 ± 1.1 (p = NS)	(1) BW (2) Glucose variability (SD of SMBG) (3) Infusion-set occlusion (4) Parents' treatment preference (5) Hyperglycemic episodes with ketonuria	(1) No difference between treatments (2) 6.4 ± 1.0 vs. 6.0 ± 0.95 mmol/L (p = 0.01) (3) No difference between treatments (4) 74% want to continue lispro (5) 2.5 ± 2.7 vs. 2.0 ± 3.0 episodes (p = NS)

Table 3 continued

First author, year	Analog (#) vs. comparator (#)	HbA1c outcomes		BG levels		Hypoglycemia		Secondary outcomes		
		Definition	Results	Definition	Results (mmol/L)	Definition	Results	Measures	Results	
Hoogma, 2006 [33]	Glulisine (29) vs. aspart (30)	Tested at baseline and endpoint	(1) 6.8 vs. 7.1 (<i>p</i> = NS) (2) 7.0 vs. 7.2 (3) 0.11	NR	NR	Self-reported (1) Severe hypoglycemia: BG < 2.0 mmol/L and requiring assistance or IV glucose/glucagon, number of patients experiencing at least one in 12 weeks (2) Nocturnal hypoglycemia (3) Symptomatic hypoglycemia	(1) 2 vs. 2 (<i>p</i> = NS) (2) 20 vs. 15 (<i>p</i> = NS) (3) 26 vs. 24 (<i>p</i> = NS)	(1) Infusion-set occlusion (2) Unexplained hyperglycemia: at least one episodes of BG > 19.4 mmol/L, episodes in 12 weeks	(1) No difference between treatments (2) 6 vs. 12 (<i>p</i> = NS)	
		(1) Baseline HbA1c	(− 0.09, 0.31) (<i>p</i> = NS)							
		(2) Endpoint HbA1c								
Weinzimer, 2008 [43]	Aspart (198) vs. lispro (100)	(3) Between-group difference in HbA1c (95% CI) from baseline to endpoint								
		Tested at baseline and endpoint	(1) 8.0 ± 0.94 vs. 8.2 ± 0.84 (<i>p</i> = NS) (2) − 0.15 ± 0.05 vs. − 0.05 ± 0.07 (<i>p</i> = NS) (3) 50.3 vs. 40.4% (<i>p</i> = NS) (4) 59.7 vs. 43.8% (<i>p</i> = 0.04)	8-point SMBG done on 2 days at baseline and before ending treatment	(1) 9.5 ± 4.3 vs. 9.9 ± 3.8 (<i>p</i> = NS) (2) 9.3 ± 3.7 vs. 10.0 ± 4.6 (<i>p</i> = NS) (3) aspart = lispro (<i>p</i> = NS) (4) aspart = lispro (<i>p</i> = NS)	Self-reported (1) Major hypoglycemia: BG < 3.1 mmol/L and requiring assistance or IV glucose/glucagon, episodes per patient per year (2) Nocturnal hypoglycemia: minor or major occurring between midnight and 06:00 h (3) Minor hypoglycemia: BG < 3.1 mmol/L with or without symptoms	(1) 0.4 vs. 0.3 (<i>p</i> = NS) (2) 5.7 vs. 6.2 (<i>p</i> = NS) (3) 77.2 vs. 66.0 (<i>p</i> = NS)	(1) BW (2) Hyperglycemia: BG > 16.7 mmol/L, % patients with episodes (3) DKA, number of patients with episodes	(1) No difference between treatments (2) 11 vs. 17 (<i>p</i> = NS) (3) 1 vs. 2 (<i>p</i> = NS)	
		(1) Baseline								
		(2) Change in HbA1c from baseline to end of treatment								
		(3) Percentage achieving age-specific HbA1c target at baseline								
		(4) Percentage achieving age-specific HbA1c target at endpoint								

Table 3 continued

First author, year	HbA1c outcomes		BG levels		Hypoglycemia		Secondary outcomes		
	Analog (n) vs. comparator (n)	Definition	Results	Definition	Results (mmol/L)	Definition	Results	Measures	Results
Tamborlane, 2015 [39]	Substudy 1 lispro (116) vs. aspart (116) Substudy 2 lispro (118) vs. aspart (118)	Tested at baseline and endpoint (1) Mean (\pm SD) HbA1c at baseline (2) Mean (\pm SEM) endpoint HbA1c (3) Mean change (\pm SEM) in HbA1c from baseline	Substudy 1 (1) 7.3 ± 0.7 (2) 7.34 ± 0.05 vs. 7.28 ± 0.05 ($p = \text{NS}$) (3) 0.06 ± 0.05 vs. -0.00 ± 0.05 ($p = \text{NS}$) Substudy 2 (1) 7.5 ± 0.7 (2) 7.30 ± 0.04 vs. 7.14 ± 0.04 ($p < 0.001$) (3) -0.15 vs. -0.31 ($p < 0.001$)	7-point SMBG done on day 6 of reservoir use (1) Mean (\pm SEM) BG Substudy 1 (1) 9.34 ± 0.14 vs. 9.11 ± 0.14 ($p > 0.05$) Substudy 2 (1) 8.72 ± 0.10 vs. 8.54 ± 0.10 ($p > 0.05$)	Self-reported (1) Severe hypo: requiring third-party assistance, total number of episodes (2) Nocturnal hypo: occurring between bedtime and wake up (3) Symptomatic hypo: BG < 3.9 mmol/L and symptomatic, episodes per 30 days (4) Symptomatic hypo: total number of episodes (5) Asymptomatic: BG < 3.9 mmol/L and no symptoms	(1) 5 vs. 16 (2) lispro = aspart (3) Substudy 1: 9.39 vs. 10.84 ($p = 0.003$) Substudy 2: 7.57 vs. 8.71 ($p = 0.012$) (4) Substudy 1: 15.26 vs. 16.91 ($p = 0.006$) Substudy 2: 16.74 vs. 18.86 ($p < 0.001$) (5) lispro = aspart	(1) Infusion-set occlusion (2) Hyperglycemia: BG > 13.9 mmol/L (> 3 h after eating) or > 16.7 mmol/L (within 3 h after eating), episodes per 30 days (3) DKA, number of episodes	(1) No difference between treatments (2) Substudy 1: 8.20 vs. 6.79 ($p = 0.029$) Substudy 2: 8.05 vs. 6.54 ($p = 0.003$) (3) 4 vs. 0	
Bode, 2002 [31]	Aspart (59) vs. lispro (28) vs. RHI (59)	Tested at baseline and endpoint (1) Mean (\pm SD) HbA1c at baseline (2) Mean change from baseline to endpoint	(1) 7.3 ± 0.7 vs. 7.3 ± 0.7 vs. 7.5 ± 0.8 ($p = \text{NS}$) (2) 0.00 ± 0.51 vs. 0.18 ± 0.84 vs. 0.15 ± 0.63 ($p = \text{NS}$)	8-point SMBG done on 2 days at baseline and endpoint (1) Fasting and pre-meal BG (2) Post-dinner BG (3) BG at 02:00 h	(1) Aspart = lispro = RHI (2) Aspart $<$ lispro = RHI ($p = 0.019$) (3) RHI $<$ aspart = lispro ($p = 0.002$)	Self-reported (1) Severe hypo: BG < 2.8 mmol/L and requiring assistance or IV glucose/glucagon, mean events per patient per 30 days (\pm SD) (2) Nocturnal hypo: minor or major occurring between midnight and 06:00 h (3) Minor hypo: symptomatic and BG < 2.8 mmol/L (4) Minor hypo: symptoms with or without low BG	(1) 0 vs. 0 vs. 1 $0/59$ vs. $1/59$; $0/28$ vs. $1/59$ (2) 0.5 ± 0.83 vs. 0.6 ± 0.61 vs. 0.9 ± 0.97 (aspart vs. lispro vs. RHI) $p = 0.004$ (3) 3.7 ± 3.6 vs. 4.4 ± 4.7 vs. 4.8 ± 4.2 ($p = \text{NS}$) (4) 6.7 ± 5.4 vs. 10.5 ± 8.1 vs. 10.5 ± 8.9 (aspart vs. lispro vs. RHI) $p = 0.044$, aspart vs. RHI $p = 0.034$	(1) BW (2) Unexplained hyperglycemia: BG > 19.4 mmol/L, % patients with at least one episode (3) DKA	(1) No difference in any treatment group (2) 27% vs. 36% vs. 41%, ($p = \text{NS}$) (3) No episodes

Table 3 continued

First author, year	Analog (#) vs. comparator (#)	HbA1c outcomes		BG levels		Hypoglycemia		Secondary outcomes	
		Definition	Results	Definition	Results (mmol/L)	Definition	Results	Measures	Results
van Bon, 2011 [40]	Glulisine (256) vs. aspart (256) vs. lispro (256)	Tested at baseline and endpoint (1) Mean (±SD) HbA1c at baseline (2) Mean HbA1c at endpoint (3) Percentage of patients with HbA1c < 7.0 at endpoint, %	(1) 7.31 ± 0.71 vs. 7.33 ± 0.71 vs. 7.28 ± 0.71 (p = NS) (2) 7.32 ± 0.73 vs. 7.26 ± 0.76 vs. 7.31 ± 0.74 (p = NS) (3) 28 vs. 31 vs. 30 (p = NS)	7-point SMBG 1 day before endpoint (1) Fasting and pre-meal SMBG (2) Mean post-lunch BG (3) Mean nocturnal BG	(1) glulisine = aspart = RHI vs. 8.6 (p < 0.021) (2) (glulisine vs. aspart) 9.2 vs. 8.6 (p < 0.021) (3) (glulisine vs. lispro) 8.8 vs. 8.2 (p < 0.018)	Self-reported (1) Severe hypoglycemia: BG < 2.8 mmol/L and requiring assistance or IV glucose/glucagon, episodes per patient-year (± SD) (2) Nocturnal severe hypo: severe hypo occurring at night (3) Symptomatic hypo: BG < 3.9 mmol/L and symptomatic (4) Nocturnal symptomatic hypo: symptomatic hypo occurring at night	(1) 1.63 ± 450 vs. 1.38 ± 7.73 vs. 1.06 ± 3.81 (p = NS) (2) 0.61 ± 2.20 vs. 0.33 ± 1.18 vs. 0.36 ± 1.40 (glulisine vs. aspart p = 0.044, glulisine vs. lispro p = 0.070) (3) 73.84 ± 82.10 vs. 65.01 ± 72.07 vs. 62.69 ± 72.87 (glulisine vs. aspart p = 0.008, glulisine vs. lispro p < 0.001) (4) 12.80 ± 18.02 vs. 9.66 ± 13.75 vs. 9.48 ± 13.28 (glulisine vs. aspart p < 0.001, glulisine vs. lispro p < 0.001)	(1) Infusion-set occlusion (2) DKA (3) Hyperketonemia, rate per month (± SD)	(1) No difference between groups (2) 1 vs. 0 vs. 0 (3) 0.14 ± 0.43 vs. 0.06 ± 0.22 vs. 0.06 ± 0.18 (glulisine vs. aspart p = 0.01, glulisine vs. lispro p = 0.02)

BMI Body mass index, CI confidence interval, CSMI continuous subcutaneous insulin infusion, DKA diabetic ketoacidosis, FFA free fatty acids, IV intravenous, PG plasma glucose, SE standard error, Aspart insulin aspart, BG blood glucose, BMI body mass index, BW body weight, CI confidence interval, CSI continuous subcutaneous insulin infusion, DKA diabetic ketoacidosis, DTSQ Diabetes Treatment Satisfaction Questionnaire, FFA free fatty acids, glulisine insulin glulisine, IV intravenous, hypo hypoglycemia, Lispro insulin lispro, NR not reported, NS not statistically significant, PG plasma glucose, RHI regular human insulin, SMBG self-measured blood glucose

(95% CI -1.21 ; 0.15), a mean difference for PPG of -1.63 mmol/L (95% CI -1.71 ; -1.54), a risk difference for severe hypoglycemic episodes of -0.01 (95% CI -0.04 ; 0.02) and a mean difference in rate of any hypoglycemic episode of -0.75 (95% CI -2.21 ; 0.72). The mean difference in HbA1c was -0.19% (95% CI -0.46 ; 0.08); -2.1 mmol/mol (95% CI -5.0 ; 0.9) with RAIAs compared to RHI after 3 or 4 months of treatment.

DISCUSSION

This systematic review and meta-analysis summarizes the safety and efficacy of RAIAs in populations of patients who are either typically excluded from clinical trials (i.e. due to pregnancy) or require dedicated trials (i.e. children and adolescents, patients using CSII). Overall, for insulin lispro and insulin aspart, data across all three special populations indicate that their safety and efficacy are comparable with, and in some cases significantly better than, RHI. Data also suggest, from the more limited results available, similar characteristics for insulin glulisine.

There are no head-to-head RCTs individually comparing all three RAIAs with each other in the pediatric CSII setting. However, in 2009, the Institute for Quality and Efficiency in Health Care in Germany, acknowledging the limited amount of data at the time, concluded that there were no significant differences between RHI and any of the three RAIAs in terms of key efficacy and safety endpoints [44]. The UK National Institute for Health and Care Excellence (NICE) guidelines specifically indicate that RAIAs are preferred over RHI for use in CSII for pediatric patients [45].

Given the lack of any major safety concerns when the three RAIAs were studied individually, there is no a priori reason to suspect that head-to-head trials would reveal any substantive differences in safety among them in special populations. However, without randomized comparative trials in these special populations, that conclusion remains speculative. Due to the limited number of studies and the heterogeneity of the outcome measures, only limited meta-

analysis was possible, primarily in the CSII population. Those results indicate that RAIAs in CSII lower post-breakfast BG and possibly HbA1c to a greater extent than RHI, without an increased risk of hypoglycemia. Although many trials have been published using CSII versus multiple daily injections (MDI) in pediatric subjects, we did not review those here because it was impossible to separate the effects of the RAIAs from those of the mode of treatment (CSII or MDI).

CONCLUSIONS

Rapid-acting insulin analogs appear to be safe and effective in these three special populations of people with T1D. However, additional trials would be helpful, and head-to-head trials would be necessary to detect any statistical differences among them, should they exist. The lack of clinically relevant differences in performance among the RAIAs make other factors, such as cost, availability and patient/provider preference, more important. Finally, studies have now been published indicating the PK advantages of a new formulation of insulin aspart in clinical development (faster aspart) over conventional insulin aspart [46], including in pediatric populations [47] and in those using CSII [48]. Studies addressing the performance of new fast-acting insulin aspart versus insulin glulisine and insulin lispro in these special populations in a clinical setting would be advantageous.

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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.

Data Availability. Data used in the meta-analysis are included in Fig. 1.

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