

Clinical efficacy and safety of insulin aspart compared with regular human insulin in patients with type 1 and type 2 diabetes: a systematic review and meta-analysis

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KEY WORDS

insulin aspart, insulin therapy, rapid-acting insulin analog, type 1 diabetes mellitus, type 2 diabetes mellitus

ABSTRACT

INTRODUCTION Prandial insulin is a key component in insulin treatment of type 1 diabetes mellitus (T1DM) and in many patients with type 2 diabetes mellitus (T2DM). The evidence-based data supporting the choice of an insulin preparation are still limited.

OBJECTIVES We performed a systematic review to summarize and update the evidence on relative efficacy and safety of insulin aspart (IAsp) and regular human insulin (RHI) in both types of diabetes.

METHODS Randomized controlled trials comparing IAsp with RHI in patients with either T1DM or T2DM and conducted until May 2013 were retrieved from a systematic search of MEDLINE, EMBASE, and Cochrane Library.

RESULTS Of 16 relevant trials, 11 involved patients with T1DM and 5—with T2DM. In the T1DM population, IAsp, when compared with RHI, provided a greater reduction in hemoglobin A_{1c} (HbA_{1c}) levels (weighted mean difference [WMD], −0.11%; 95% confidence interval [CI], −0.16 to −0.05; WMD, −1.2 mmol/mol; 95% CI, −1.7 to −0.5), and improved postprandial glucose levels following breakfast (WMD, −1.40 mmol/l; 95% CI, −1.72 to −1.07), lunch (WMD, −1.01 mmol/l; 95% CI, −1.61 to −0.41), and dinner (WMD, −0.89 mmol/l; 95% CI, −1.19 to −0.59). The risk of nocturnal hypoglycemia was lower in T1DM patients receiving IAsp (relative risk, 0.76; 95% CI, 0.64–0.91), while no difference was observed for severe hypoglycemia. In T2DM patients, IAsp led to a greater reduction in HbA_{1c} levels (WMD, −0.22%; 95% CI, −0.39 to −0.05; −2.4 mmol/mol, −4.3 to −0.5) and postprandial blood glucose. The risk of overall hypoglycemia and severe adverse effects was comparable between the groups.

CONCLUSIONS IAsp provides better glycemic control when compared with RHI in patients with T1DM and T2DM. Fewer T1DM patients treated with IAsp experienced nocturnal hypoglycemia, while both interventions showed a comparable risk of severe hypoglycemic events in both types of diabetes.

INTRODUCTION The clinical practice guidelines recommend the use of insulin preparations in all patients with type 1 diabetes mellitus (T1DM) and in subjects with type 2 diabetes mellitus (T2DM) with uncontrolled glycemia despite the use of combined therapy including several oral antidiabetic drugs (OADs) or a glucagon-like peptide 1

(GLP-1) agonist.^{1–6} Insulin therapy is also recommended as a first-line treatment in T2DM subjects with highly uncontrolled hyperglycemia.¹ In patients with T1DM, in whom insulin secretion is completely abolished because of β -cell destruction, the current guidelines recommend intensive insulin therapy mimicking physiological insulin

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profile. This can be achieved with either multiple daily insulin injections (MDI) or continuous subcutaneous insulin infusion (CSII) using insulin pumps.^{1,4,6} Unlike in T1DM, most T2DM patients retain some endogenous insulin secretion, although the disease is characterized by progressive β -cell insufficiency.² Therefore, treatment of T2DM should be individualized based on the degree of insulin deficiency and some clinical factors. In T2DM, intensive insulin therapy is usually used in relatively young and active subjects in whom OADs, GLP-1 agonists, or simple regimens of insulin therapy are ineffective.¹⁻⁵ Long-term studies demonstrated that intensive hypoglycemic therapy is effective in lowering hemoglobin A_{1c} (HbA_{1c}) levels and reducing the risk of microvascular complications in patients with both T1DM and T2DM.⁷⁻¹¹ As the number of relatively young T2DM patients with long life expectancy is growing, intensive insulin therapy is becoming increasingly common in this type of diabetes.¹² However, intensive blood glucose control predisposes to severe hypoglycemia and increased body weight when compared with conventional therapies.^{7-9,13} Severe hypoglycemia is associated with many unfavorable clinical outcomes¹⁴; therefore, the choice of an optimal diabetes treatment should include a consideration of its potential to control glycemia as well as associated risk of hypoglycemia.

Available insulin preparations show different pharmacological properties with respect to the time of onset, peak activity, and duration of action.¹⁵ Regular human insulin (RHI) has been an integral component of intensive insulin treatment for several decades. RHI provides effective meal-time coverage; however, it also presents several limitations related to its pharmacological profile. RHI is characterized by a delayed time of onset (about half an hour after the injection) with the maximum activity and serum concentration levels after 2 to 3 hours, and prolonged action lasting 6 to 8 hours. Therefore, patients should administer RHI about 30 minutes before meals and consume a snack several hours later to avoid late hypoglycemia.¹⁶ To overcome these limitations, rapid-acting insulin analogs (RAAs) have been designed. Insulin aspart (IAsp) is one of the 3 RAAs available on the market, the 2 other being insulin lispro and glulisine. IAsp was developed by a modification of human insulin through a single amino-acid substitution of proline by aspartic acid in the 28th position of the B chain. IAsp is characterized by a faster onset of activity (about 15 minutes after the injection), maximum activity at about 1.5 hour, and a time duration no longer than 3 to 4 hours.¹⁷ In clinical practice, this eliminates the need for an interval between insulin injection and meals as well as the requirement of snack to avoid late hypoglycemia after meals.¹⁵ Therefore, IAsp mimics the natural insulin response to a meal in superior way when compared with RHI, which facilitates better postprandial glycemic control.¹⁸

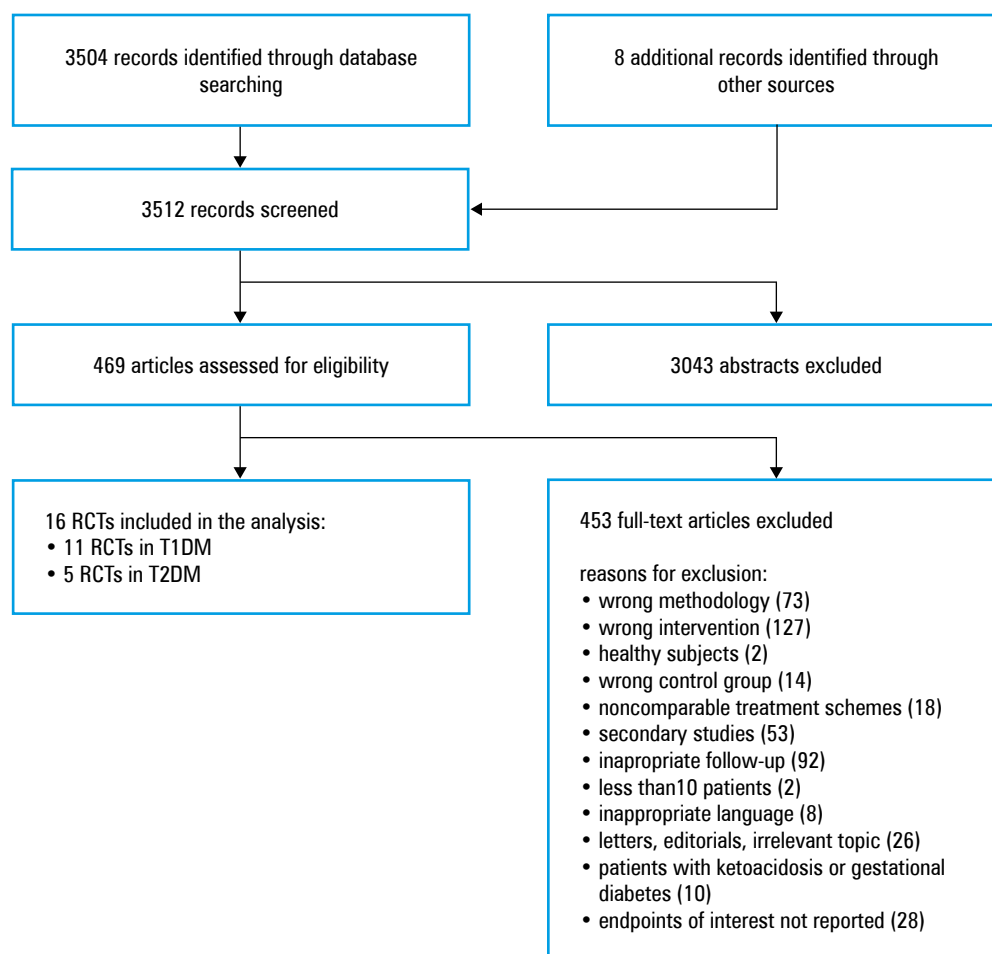
The relative efficacy and safety of IAsp and RHI in diabetic patients has been a matter of ongoing debate. Some new evidence have been published since we first compared both interventions as a prandial or premixed approach in a systematic review.¹⁸ We hope that the inclusion of new data into our analysis will improve its credibility and allow to conduct an assessment in a much more homogenous group of studies. The aim of the current study was to perform a systematic review to summarize and update the evidence on relative efficacy and safety of IAsp and RHI in both types of diabetes in patients receiving prandial insulin treatment.

METHODS Search strategy We carried out a systematic search of major medical databases including Medline (via PubMed), EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify relevant clinical evidence. The search strategy comprised keywords referring to diabetes mellitus and IAsp, which were combined with appropriate Boolean operators. Finally, the results of the systematic search were limited to records containing keywords relating to randomized controlled trials (RCTs). Databases were searched until May 2013. We also screened registers of ongoing clinical trials (clinicaltrials.gov, ISRCTN.org), proceedings of meetings organized by the associations active in the field of diabetes (American Diabetes Association, European Association for the Study of Diabetes), and references of identified articles to retrieve potentially relevant information.

Inclusion and exclusion criteria Eligible RCTs should directly compare IAsp with RHI in patients with T1DM or T2DM using prandial insulin therapy with or without basal insulin and provide similar other antidiabetic medications in both treatment arms. Studies with at least 12 weeks of follow-up were included. Studies were excluded from this analysis when patients had pregestational or gestational diabetes, less than 10 patients were recruited for the study, or if the studies were designed to compare different schemes of prandial insulin treatment in each group, that is, MDI vs. CSII. Studies published in languages other than English, French, and German were also not considered in this review.

Study selection and credibility assessment Two independent analysts retrieved articles at each stage of the selection process and assessed credibility of the included trials. Any discrepancies between the analysts were solved by consensus or a third party. Methodological quality was assessed according to the criteria proposed by Jadad et al.¹⁹ Scores from 0 to 5 points were granted depending on the fulfillment of the following criteria: randomization and its method, blinding and correctness of its method, and information concerning patients lost to follow-up. A higher number of granted points reflected higher credibility

FIGURE 1 Study selection diagram
Abbreviations: RCTs, randomized controlled trials; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus



of the clinical trial. Moreover, the risk of potential bias was also assessed on the basis of other criteria proposed in the Cochrane Handbook for Systematic Reviews of Interventions, namely, allocation concealment, intention-to-treat analysis, and completeness of follow-up.²⁰

Outcome of interest Reduction of the mean HbA_{1c} level during the study was the primary endpoint in this analysis. Key secondary measures included mean glucose level after breakfast, lunch, and dinner. We also assessed the risk of overall, severe, and nocturnal hypoglycemic events.

Statistical analysis Continuous and dichotomous endpoints were presented with weighted mean difference (WMD) and relative risk (RR), respectively, all of them together with 95% confidence intervals (CIs). The between-study heterogeneity was examined using the Cochran Q test and the I^2 statistics and was considered significant when either a P value was less than 0.1 or I^2 was 50% or higher. When homogeneity was confirmed, treatment effects were accumulated using the fixed effect inverse-variance model. In cases of statistically significant heterogeneity, the DerSimonian and Laird random effect model was applied.²⁰ Significance of the overall effect was tested with the Z test, assuming a P value of less than 0.05 as the level of significance. The results were processed using Sophie v. 1.5.0 (a meta-analysis software

by HTA Consulting, verified and producing consistent results with STATA v. 10.0).

RESULTS Study flow The search in electronic databases resulted in 3504 records, of which 469 were selected for full-text assessment after duplicate removal and abstract analysis. A total number of 453 publications were considered irrelevant and were excluded due to the reasons presented in the publication flow diagram, mainly owing to incorrect interventions, inadequate length of follow-up, and incorrect methodology. Finally, 16 RCTs were considered relevant for the current review (FIGURE 1), including 11 papers referring to T1DM and the remaining 5 involving T2DM patients.

Patients with type 1 diabetes mellitus Study characteristics A total number of 11 RCTs comparing IAsp with RHI in an overall number of 3447 patients with T1DM were retrieved, including 4 studies recruiting children²¹⁻²⁴ and 7 trials involving adult patients (FIGURE 1).²⁵⁻³¹ The mean duration of diabetes was between 1.8 and 5.2 years and 4.7 and 15.7 years in studies recruiting children and adults, respectively. The mean HbA_{1c} levels at baseline ranged from 7.3% (56 mmol/mol) to 8.6% (70 mmol/mol) in all identified studies. In 10 studies, patients received intensive insulin therapy by MDI using either neutral protamine Hagedorn (NPH) insulin (8 RCTs) or long-acting

TABLE Characteristics of studies identified within a systematic review for patients with type 1 and type 2 diabetes mellitus

Study	Design	Number of patients		Mean age, y		Male sex, % of patients		Mean diabetes duration, y		Mean baseline HbA _{1c} , % (mmol/mol)		Mean baseline BMI, kg/m ²		Regimen/basal insulin	Duration of intervention, wk	Jadad score
		IAsp	RHI	IAsp	RHI	IAsp	RHI	IAsp	RHI	IAsp	RHI	IAsp	RHI			
type 1 diabetes																
Ampudia-Blasco, 2005	pg, ol	28	26	32.3 ^a		42 ^a		14.5 ^a		8.5 (69)	8.6 (70)	24.8 ^a		MDI/LAA	26	1/5
Arsanian, 2005	pg, ol	187	96	11.8	11.5	46	56	4.8	4.6	8.3 (67)	8.3 (67)	21.4	20.8	MDI/NPH	24	2/5
Bode, 2002	pg, ol	59	59	42.3	43.1	39	32	≥ 1		7.3 (56)	7.5 (58)	26.7	25.9	CSII	16	1/5
Cherubini, 2006	pg, ol	30		8.1		NA		5.2		7.5 (58)		18.0		MDI/LAA	18	1/5
Danne, 2007	co, ol	26		5.0		65		1.8		7.8 (62)		n/a		MDI/NPH	2×12	1/5
DeVries, 2003	pg, ol	186	181	36.9 ^b	36.9 ^b	62	61	36.9 ^b	36.9 ^b	8.4 (68)	8.4 (68)	25.3	25.8	MDI/NPH	64	3/5
Heller, 2004	co, db	155		35.7		NA		≥ 2		8.6 (70)		24.0		MDI/NPH	2×14	3/5
Home, 2000	pg, ol	707	358	38	38	55	56	15	15	8.0 (64)	8.0 (64)	25.1	24.9	MDI/NPH	26	2/5
Pańkowska, 2010	pg, ol	20	21	5.2	5.4	NA		1.9	2.0	7.4 (57)	7.5 (58)	20.1 ^c	20.1 ^c	MDI/NPH	26	1/5
Raskin, 2000	pg, ol	596	286	38.9	39.9	51	53	15.7	15.8	7.9 (64)	7.95 (63)	25.6	25.7	MDI/NPH	26	1/5
Tamás, 2001	pg, ol	213	213	35.6	36.1	58	55	14.0	14.2	8.4 (68)	8.3 (67)	24.2	24.0	MDI/NPH	64	2/5
type 1 diabetes																
Bretzel, 2004	pg, ol	75	80	61.4	62	59	50	> 1		7.82 (62)	7.83 (62)	29.2	29.3	MDI/NPH	12	2/5
Herrmann, 2013	pg, ol	18	11	58	60	61	73	n/a		8.7 (72)	8.7 (72)	31.5	32.8	MDI/NPH or LAA	104	1/5
Matti, 2012	pg, ol	30	30	54.0	50.2	53	60	5.42	4.93	8.3 (67)	8.1 (65)	24.9	25.2	MDI/ NA	52	3/5
Pala, 2007	co, ol	25		65		28		17.5		7.3 (56)		27.7		MDI/no basal	2×12	1/5
Raskin, 1999	pg, ol	91	91	NA		NA		≥ 2		8.1 (65)	7.9 (63)	NA		MDI/NPH	26	1/5

a values include patients receiving from the third study arm: – insulin lispro (n = 25); **b** median; **c** body weight (kg)

Abbreviations: BMI, body mass index; co, crossover; db, double-blinded; IAsp, insulin aspart; LAA, long-acting insulin analog; MDI, multiple daily insulin; NA, not assessed; NPH, neutral protamine Hagedorn; ol, open-label; pg, parallel-group; RHI, regular human insulin

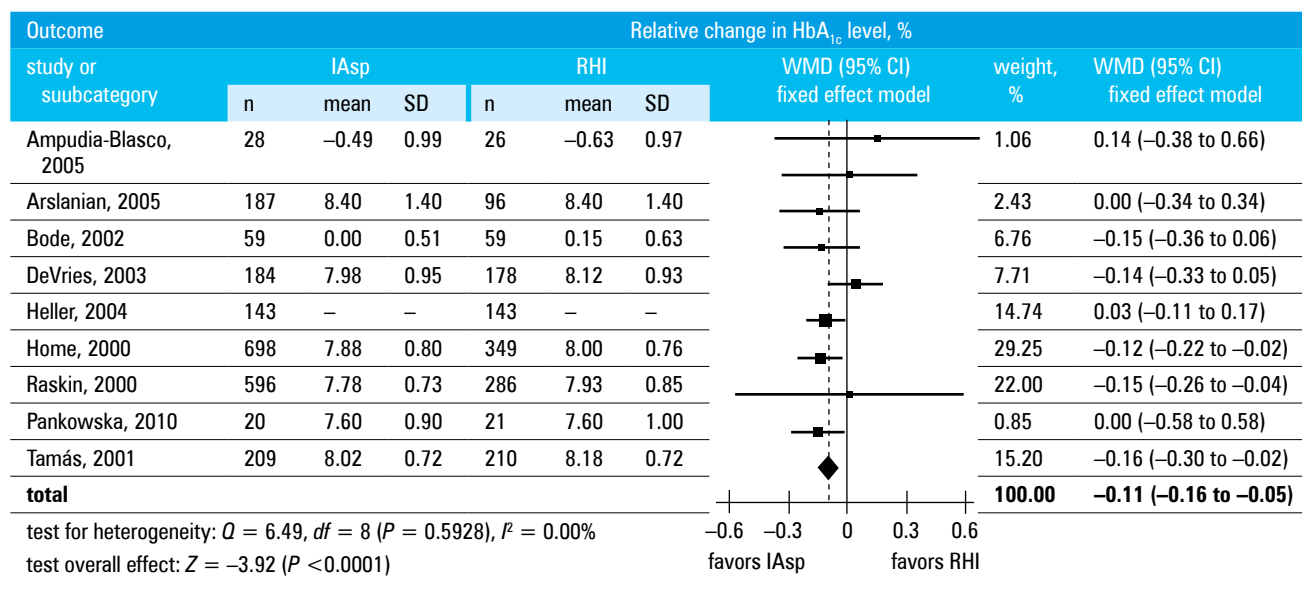


FIGURE 2 Relative change in hemoglobin A_{1c} levels for comparison between insulin aspart and regular human insulin in patients with type 1 diabetes
Abbreviations: CI, confidence interval; HbA_{1c}, hemoglobin A_{1c}; SD, standard deviation; WMD, weighted mean difference; others, see TABLE

insulin analogues (LAAs) (2 RCTs) as basal insulin. In the remaining RCT, insulin was administered via CSII.²⁶ Ten studies were carried out according to a parallel design.^{21,22,24-27,29-31} Two other RCTs were conducted with a cross-over design^{23,28}; however, only 1 study provided an adequate wash-out period before the treatment switch.²⁸ The methodological quality of the included studies ranged from 1 to 3 points, according to the Jadad score, and was most often downgraded because of an open-label design and insufficient information regarding the number of patients lost to follow-up. Allocation concealment was considered adequate in 4 RCTs (TABLE).^{26-28,31}

Glycemic control Glycated hemoglobin Overall, 9 RCTs assessed the change in HbA_{1c} levels during treatment and presented data pertinent for a meta-analysis.^{21,24-31} In 3 of those studies, IAsp showed a greater reduction in HbA_{1c} levels at the end of treatment,²⁹⁻³¹ while in the remaining 6 RCTs, the difference between the groups was not significant. Pooled results revealed a significant advantage of IAsp over RHI with respect to HbA_{1c} reduction (WMD, -0.11%; 95% CI, -0.16 to -0.05; WMD, -1.2 mmol/mol; 95% CI, -1.7 to -0.5), with no evidence for between-study heterogeneity ($P = 0.59$; $I^2 = 0\%$) (FIGURE 2).

Postmeal glucose Four RCTs reported the level of postprandial blood glucose after individual daily meals and provided numerical data required for a meta-analysis.^{27,29-31} Pooled results demonstrated an advantage of IAsp over RHI with respect to the postprandial glucose level, which was measured 90 minutes following each meal, including breakfast (WMD, -1.40 mmol/l; 95% CI, -1.72 to -1.07), lunch (WMD, -1.01 mmol/l; 95% CI, -1.61 to -0.41), and dinner (WMD, -0.89 mmol/l; 95% CI, -1.19 to -0.59). Statistical heterogeneity was

observed in the meta-analysis for glycemic control following lunch ($P = 0.04$; $I^2 = 69\%$); however, this could be associated with a relatively low number of the included trials. No statistical heterogeneity was demonstrated in the remaining meta-analyses (FIGURES 3, 4, and 5).

Hypoglycemia None of the identified studies reported the number of patients with at least 1 hypoglycemic episode regardless of their severity. The risk of severe hypoglycemia requiring third-party assistance was assessed in 5 RCTs presenting data pertinent for meta-analysis.^{21,24,26,29,31} Pooled results demonstrated a comparable risk of severe hypoglycemia between treatment groups (RR = 0.85; 95% CI, 0.66–1.08). Four RCTs reported the risk of nocturnal hypoglycemia, of which 2 studies reported a significantly lower risk of events in the IAsp group, while in 2 others, the between-group differences were not significant.^{21,26,29,30} A meta-analysis of all studies confirmed a lower risk of nocturnal hypoglycemia in patients receiving IAsp compared with their counterparts treated with RHI (RR = 0.76; 95% CI, 0.64–0.91), with no evidence for between-study heterogeneity ($P = 0.13$, $I^2 = 46\%$).

Patients with type 2 diabetes mellitus **Study characteristics** A total number of 5 RCTs comparing IAsp with RHI in an overall number of 451 adult patients with T2DM were identified (FIGURE 1).³²⁻³⁶ The mean duration of diabetes ranged from 4.6 to 17.5 years in respective trials, while the mean HbA_{1c} at baseline was in the range of 7.3% (56 mmol/mol) to 8.7% (72 mmol/mol). Only in 1 study, the mean baseline body mass index exceeded 30 kg/m², suggesting obesity in the majority of the subjects.³³ Two RCTs recruited T2DM patients who were previously treated with insulin,^{32,36} two others enrolled insulin-naïve subjects,^{33,35} and

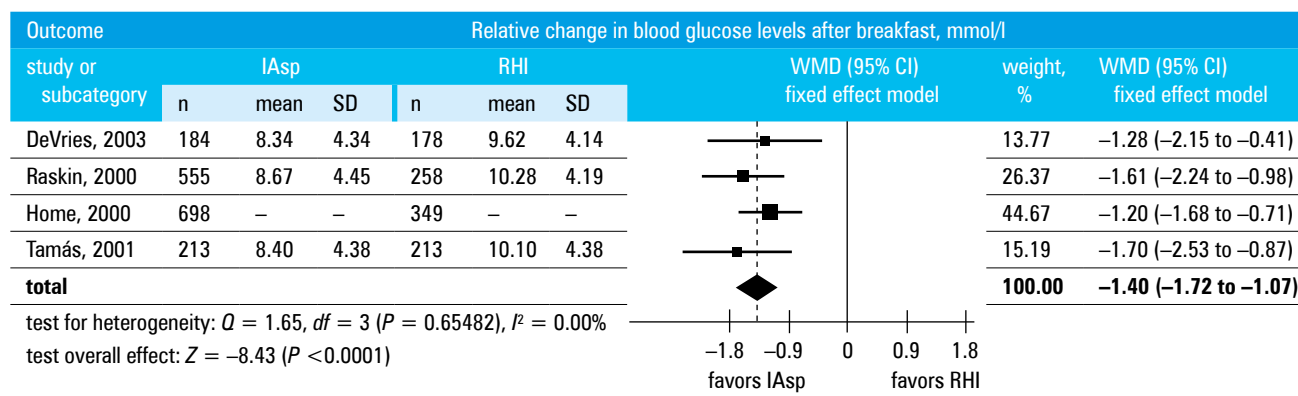


FIGURE 3 Relative change in blood glucose levels after breakfast for comparison between insulin aspart and regular human insulin in patients with type 1 diabetes
Abbreviations: see [TABLE](#) and [FIGURE 2](#)

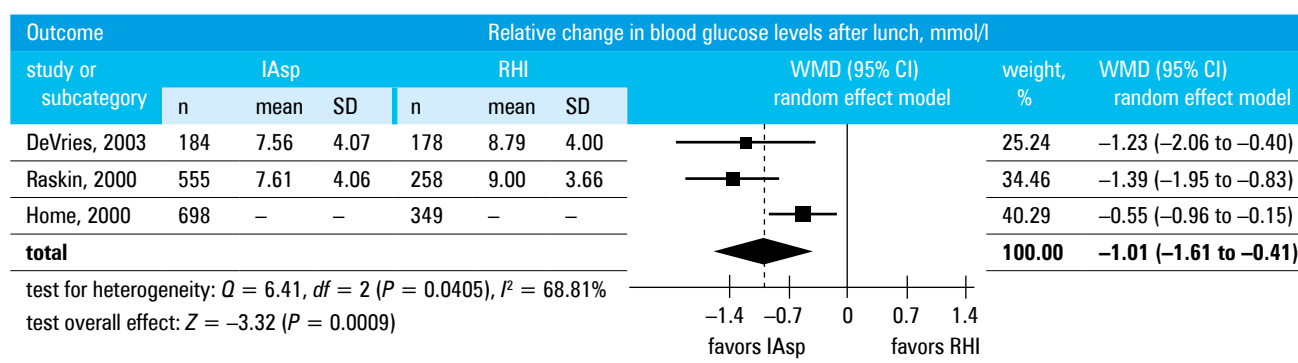


FIGURE 4 Relative change in blood glucose levels after lunch for comparison between insulin aspart and regular human insulin in patients with type 1 diabetes
Abbreviations: see [TABLE](#) and [FIGURE 2](#)

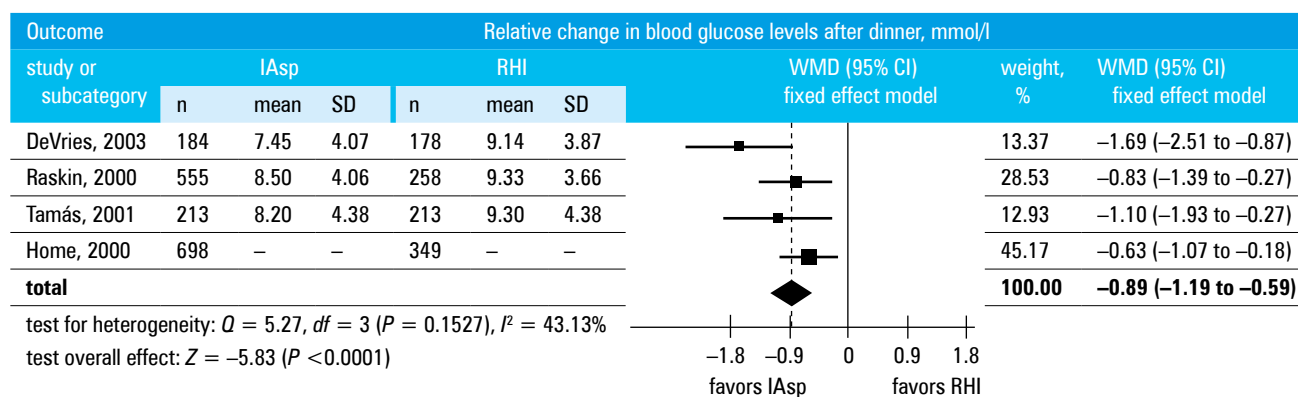


FIGURE 5 Relative change in blood glucose levels after dinner for comparison between insulin aspart and regular human insulin in patients with type 1 diabetes
Abbreviations: see [TABLE](#) and [FIGURE 2](#)

the remaining study did not report information regarding previous insulin use.³⁴ In 4 of the included studies, patients received intensive insulin treatment by MDI,^{32,33,35,36} while the remaining 1 RCT compared IAsp with RHI, both administered twice daily together with OADs, but without the use of basal insulin.³⁴ In 2 RCTs, all recruited patients received NPH as basal insulin,^{32,36} and in the other, participants were treated with either NPH or insulin detemir.³³ In another RCT, the type of basal insulin was not reported.³⁴ In

the remaining 1 RCT, diabetes was treated only with prandial insulin and OADs.³⁵ The follow-up duration of the respective studies ranged from 3 to 24 months. Methodological quality of the included studies ranged from 1 to 3 points, according to the Jadad score, and was most often downgraded owing to the lack of double blinding and insufficient information regarding the number of patients lost to follow-up. None of the studies reported the use of a method providing adequate allocation concealment ([TABLE](#)).

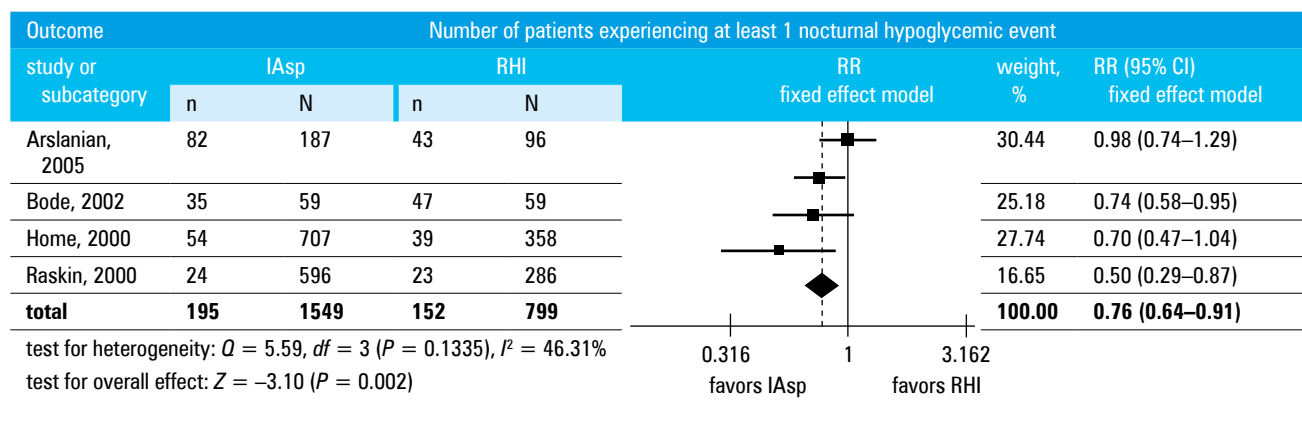


FIGURE 6 Risk of nocturnal hypoglycemic episodes for comparison between insulin aspart and regular human insulin in patients with type 1 diabetes
Abbreviations: RR, relative risk; others, see TABLE and FIGURE 2

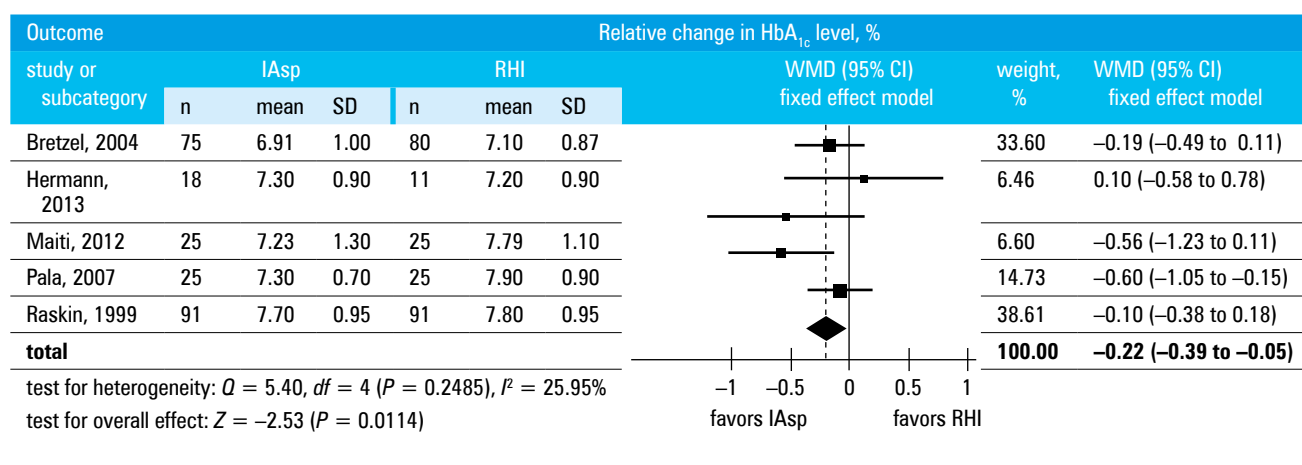


FIGURE 7 Relative change in hemoglobin A_{1c} levels for comparison between insulin aspart and regular human insulin in patients with type 2 diabetes
Abbreviations: see TABLE and FIGURE 2

Glycemic control Glycated hemoglobin All 5 RCTs assessed the level of HbA_{1c} at the end of the study and presented data pertinent for a meta-analysis.^{32–36} Pooled results demonstrated that patients treated with IAsp had better glycemic control compared with their counterparts from the RHI arms (WMD, −0.22%; 95% CI, −0.39 to −0.05; WMD, −2.4 mmol/mol; 95% CI, −4.3 to −0.5) (FIGURE 7). No significant between-study heterogeneity was observed ($P = 0.25$; $I^2 = 26\%$).

Postmeal glucose None of the identified studies presented numerical data allowing a comparison of the two types of insulin with respect to the efficacy of postprandial glucose control following any of the daily meals. Nevertheless, 1 RCT demonstrated that the mean level of blood glucose following major meals in patients treated with IAsp was lower by 0.96 mmol/l compared with the RHI group ($P < 0.05$ in each study).³⁴ Two other studies also reported a lower postmeal glucose level in the IAsp arm (by 0.44 mmol/l and 3.40 mmol/l in respective studies); however, none of them presented the results of statistical comparison or appropriate estimates of data dispersion required for a meta-analysis.^{32,35}

Hypoglycemia Two RCTs assessed the proportion of patients with at least 1 hypoglycemic episode during study treatment, regardless of severity.^{32,33} Pooled results demonstrated no significant between-group differences in the risk of overall hypoglycemia (RR, 1.00 [0.70, 1.44]). Of 2 RCTs assessing the risk of severe hypoglycemia, one recorded no events in either group, while the other reported no significant difference between the study arms.^{35,36} Neither study reported the risk of nocturnal hypoglycemia.

DISCUSSION In this systematic review, we compared the efficacy and safety of IAsp and RHI in T1DM and T2DM patients receiving prandial insulin therapy. Some evidence for IAsp superiority was identified. First, our meta-analysis demonstrated that IAsp compared with RHI in patients with T1DM provided favorable glycemic control, as assessed by HbA_{1c} levels. It also reduced glucose fluctuations following all 3 major daily meals. At the same time, IAsp substantially reduced the risk of nocturnal hypoglycemia compared with RHI and demonstrated a comparable safety profile with respect to the risk of overall and severe hypoglycemic events. The estimates

of clinical efficacy of IAsp in patients with T1DM are highly consistent with our previous findings¹⁸ and the results presented by other authors.³⁷⁻³⁹ Additionally, we demonstrated a higher efficacy of IAsp over RHI in terms of HbA_{1c} reduction in patients with T2DM treated with prandial insulin. This is a new finding, which has not been presented in any previous systematic reviews or meta-analysis.

We believe that the above findings were possible owing to novel evidence and improved methodological quality. For example, in our former meta-analysis, we adopted relatively less stringent criteria allowing for the inclusion of studies with relatively high degrees of heterogeneity with respect to population, intervention, and methodology. This high between-study variation, particularly the inclusion of studies with biphasic insulin in the same meta-analysis with RCTs assessing IAsp, along with an insufficient number of relevant RCTs available at that time, were the main reasons why we were unable to demonstrate superiority of IAsp over RHI in T2DM. In the current report, we included new studies, which were published since 2010 and, therefore, could not be considered in older reports.^{24,33,34} One of these new studies enrolled children with T1DM,²⁴ while 2 others were carried out in patients with T2DM.^{33,34} The inclusion of new evidence allowed us to use more rigid criteria in order to improve the credibility of evidence by ensuring an appropriate level of between-study homogeneity, particularly in the population with T2DM, where data availability has been limited so far. Indeed, we excluded RCTs with a follow-up shorter than 12 weeks, which is a rational approach as the level of HbA_{1c}, the primary endpoint of the current analysis, reflects changes in blood glucose over the period of the last 3 months. Moreover, this analysis was focused only on the assessment of the prandial insulin therapy (in all but 1 study, the intensive insulin therapy model was applied) that included IAsp; therefore, studies comparing biphasic insulin aspart with RHI were considered irrelevant. Finally, we also excluded studies enrolling solely pregnant women, analyzed in our previous work, as being not representative for the entire T1DM population. Altogether, the inclusion of new RCTs and the adoption of a more coherent methodology have led to reduced heterogeneity and improved precision of efficacy estimates. This allowed us to demonstrate a significant advantage of IAsp over RHI in glycemic control in both types of diabetes mellitus.

A recent meta-analysis based on individual patient data (IPD) included a total number of 10 RCTs comparing IAsp with RHI, both used in basal-bolus regimen together with NPH, in patients with T1DM (6 RCTs), T2DM (3 RCTs), or a mixed population of both types of diabetes (1 RCT).⁴⁰ All trials were pooled together and no separate analysis for each diabetes type was performed. The results of the meta-analysis showed that IAsp reduced HbA_{1c} by 0.1% (1.1 mmol/mol)

as compared with RHI; this was accompanied by lower postprandial blood glucose levels. Consistent with our results for T1DM, the authors also demonstrated a lower risk of nocturnal hypoglycemia in the IAsp group; however, the overall proportion of patients experiencing hypoglycemic episodes was comparable in both arms. The high consistency of our results in T1DM and those presented by Heller et al.⁴⁰ is of interest as the methodologies of both reports varied substantially. First, the other meta-analysis included solely trials with available IPD, of which some have not been published yet. Second, the authors decided to perform one single analysis for both types of diabetes presenting one single estimate, which could be the source of considerable heterogeneity. Finally, several available studies but with unavailable IPD were excluded from the analysis. Although a meta-analysis by Heller et al.⁴⁰ was based on specific information, which could not be easily assessed, it provided valuable complementary and supportive data to our work.

Two milestone prospective diabetes studies, The UK Prospective Diabetes Study (UKPDS) and Diabetes Control and Complications Trial (DCCT), demonstrated that more intensive therapies, although improving glycemic control, are almost inevitably associated with an increased risk of severe hypoglycemia.⁷⁻⁹ More recently, these results were confirmed by a meta-analysis of 67 RCTs showing that the degree of HbA_{1c} reduction correlated with the risk of overall, severe, and nocturnal hypoglycemia.⁴¹ Therefore, hypoglycemia is often considered a barrier for effective glycemic control. Interestingly, our results demonstrated that IAsp as compared with RHI allows for better glycemic control without an increased risk of hypoglycemia; moreover, a decreased risk of nocturnal events was observed in the T1DM cohort. This phenomenon can probably be attributed to the favorable pharmacokinetic properties of IAsp, which provide very short-acting activity and, thus, limit the risk of late falls in glucose levels.¹⁷ IAsp also allows for a more precise adjustment of the insulin concentration in response to an increase in blood glucose levels following daily meal intake, which is reflected in a higher clinical efficacy with respect to postprandial glucose control. These properties are of clinical value because postprandial glucose fluctuations contribute to 52% to 59% of total hyperglycemia in patients with intensified therapy for T2DM.⁴²

Unlike IAsp, the activity of RHI is still significant several hours after the injection, which predisposes a patient to hypoglycemia, particularly during the night. Nocturnal hypoglycemia is frequent in patients treated with insulin, and although it usually has an asymptomatic course it may lead to significant clinical consequences, including sudden death.^{43,44} As reported by the DCCT trial, 55% of all severe hypoglycemic events occur during the night.⁴⁵ Patients who once experienced nocturnal hypoglycemia tend to reduce their adherence to insulin treatment or

even intentionally reduce their insulin dose.^{46,47} Therefore, IAsp may provide particular clinical benefit in patients at risk of nocturnal hypoglycemia, especially those with T1DM.

Important limitations of our report include the low quality of most studies identified within this systematic review. Some RCTs were only presented in an abstract form without a subsequent presentation in full-text publications, which limits the availability of the data required for credibility assessment.^{21,25,36} Between-study variability in insulin regimen, duration of intervention period and study design could also potentially confound the results of our meta-analysis. These limitations are inherent problems of most secondary studies in diabetes that attempt quantitative data synthesis; therefore, the results of the current and other meta-analyses should be interpreted with caution and revised when new evidence becomes available.

In summary, IAsp demonstrates better glycaemic control with respect to HbA_{1c} and prandial glucose fluctuations compared with RHI in patients with both T1DM and T2DM receiving a prandial insulin regimen therapy. Additionally, IAsp is associated with fewer nocturnal hypoglycemic events in the T1DM population and has a comparable safety profile with respect to severe hypoglycemia in all patients, regardless of the type of diabetes mellitus.

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REFERENCES

- American Diabetes Association (ADA). Standards of medical care in diabetes—2013. *Diabetes Care*. 2013; 36 Suppl: S11-S66.
- Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012; 35: 1364-1379.
- International Diabetes Federation. Global Guideline for Type 2 Diabetes. 2012. Available from: <http://www.idf.org/sites/default/files/IDF%20T2DM%20Guideline.pdf>. Accessed December 2, 2013.
- IDF/ISPAD. Global IDF/ISPAD guideline for diabetes in childhood and adolescence. 2011. Available from: <http://www.idf.org/sites/default/files/Diabetes-in-Childhood-and-Adolescence-Guidelines.pdf>. Accessed December 2, 2013.
- NICE. Type 2 diabetes: the management of type 2 diabetes [Internet]. 2008. Available from: <http://www.nice.org.uk/CG66>. Accessed December 2, 2013.
- Cyganek K, Klupa T, Szopa M, et al. Medical care of pregnant women with type 1 diabetes: current guidelines and clinical practice. *Pol Arch Med Wewn*. 2013; 123: 59-65.
- The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med*. 1993; 329: 977-986.
- Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998; 352: 854-865.
- Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998; 352: 837-853.
- Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008; 359: 1577-1589.
- Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005; 353: 2643-2653.
- Donner T, Muñoz M. Update on insulin therapy for type 2 diabetes. *J Clin Endocrinol Metab*. 2012; 97: 1405-1413.
- Maraka S, Morey-Vargas OL, Montori VM. Should we use intensive hypoglycemic treatment in patients with advanced type 2 diabetes? *Pol Arch Med Wewn*. 2014; 124: 657-658.
- Zoungas S, Patel A, Chalmers J, et al. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med*. 2010; 363: 1410-1418.
- DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: Scientific review. *JAMA*. 2003; 289: 2254-2264.
- Rolla A. Pharmacokinetic and Pharmacodynamic Advantages of Insulin Analogues and Premixed Insulin Analogues Over Human Insulins: Impact on Efficacy and Safety. *Am J Med*. 2008; 121 (6 Suppl): S9-S19.
- Ma Z, Parkner T, Frystyk J, et al. A comparison of pharmacokinetics and pharmacodynamics of insulin aspart, biphasic insulin aspart 70, biphasic insulin aspart 50, and human insulin: a randomized, quadruple crossover study. *Diabetes Technol Ther*. 2012; 14: 589-595.
- Rys P, Pankiewicz O, Łach K, et al. Efficacy and safety comparison of rapid-acting insulin aspart and regular human insulin in the treatment of type 1 and type 2 diabetes mellitus: a systematic review. *Diabetes Metab*. 2011; 37: 190-200.
- Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996; 17: 1-12.
- Higgins JT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011] [Internet]. The Cochrane Collaboration; 2011. www.cochrane-handbook.org. Accessed April 22, 2013.
- Arslanian S, Foster C, Wright NM, et al. Insulin aspart compared to regular insulin and insulin lispro in basal bolus therapy with NPH to treat pediatric patients with type 1 diabetes mellitus. *Diabetologia*. 2005; 48 (Suppl 1): A327.
- Cherubini V, Iannilli A, Iafusco D, et al. Premeal insulin treatment during basal-bolus regimen in young children with type 1 diabetes. *Diabetes Care*. 2006; 29: 2311-2312.
- Danne T, Råstam J, Odendahl R, et al. Parental preference of prandial insulin aspart compared with preprandial human insulin in a basal-bolus scheme with NPH insulin in a 12-wk crossover study of preschool children with type 1 diabetes. *Pediatr Diabetes*. 2007; 8: 278-285.
- Pańkowska E, Nazim J, Szalecki M, Urban M. Equal metabolic control but superior caregiver treatment satisfaction with insulin aspart in preschool children. *Diabetes Technol Ther*. 2010; 12: 413-418.
- Ampudia-Blasco FJ, Girbes J, Sanz J, et al. Regular insulin is as effective as rapid-acting insulin analogs in combination with glargine insulin in type 1 diabetic patients. *Diabetologia*. 2005; 48 (Suppl 1): A92.
- Bode B, Weinstein R, Bell D, et al. Comparison of insulin aspart with buffered regular insulin and insulin lispro in continuous subcutaneous insulin infusion: a randomized study in type 1 diabetes. *Diabetes Care*. 2002; 25: 439-444.
- DeVries JH, Lindholm A, Jacobsen JL, et al. A randomized trial of insulin aspart with intensified basal NPH insulin supplementation in people with Type 1 diabetes. *Diabet Med J Br Diabet Assoc*. 2003; 20: 312-318.
- Heller SR, Colagiuri S, Vaaler S, et al. Hypoglycaemia with insulin aspart: a double-blind, randomised, crossover trial in subjects with type 1 diabetes. *Diabet Med J Br Diabet Assoc*. 2004; 21: 769-775.
- Home PD, Lindholm A, Riis A. Insulin aspart vs. human insulin in the management of long-term blood glucose control in Type 1 diabetes mellitus: a randomized controlled trial. *Diabet Med J Br Diabet Assoc*. 2000; 17: 762-770.
- Raskin P, Guthrie RA, Leiter L, et al. Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. *Diabetes Care*. 2000; 23: 583-588.
- Tamás G, Marre M, Astorga R, et al. Glycaemic control in type 1 diabetic patients using optimised insulin aspart or human insulin in a randomised multinational study. *Diabetes Res Clin Pract*. 2001; 54: 105-114.
- Bretzel RG, Arnolds S, Medding J, Linn T. A direct efficacy and safety comparison of insulin aspart, human soluble insulin, and human premix insulin (70/30) in patients with type 2 diabetes. *Diabetes Care*. 2004; 27: 1023-1027.
- Herrmann BL, Kasser C, Keuthage W, et al. Comparison of insulin aspart vs. regular human insulin with or without insulin detemir concerning adiposity and metabolic effects in patients with type 2 diabetes mellitus.

- 34 Maiti R, Jaida J, Leander PJ, et al. Cardioprotective role of insulin: Advantage analogues. *J Res Med Sci.* 2012; 17: 642-648.
- 35 Pala L, Mannucci E, Dicembrini I, Rotella CM. A comparison of meal-time insulin aspart and human insulin in combination with metformin in type 2 diabetes patients. *Diabetes Res Clin Pract.* 2007; 78: 132-135.
- 36 Raskin P, McGill J, Kilo C, Boss A. Human Insulin Analog (Insulin Aspart, IAsp) is Comparable to Human Insulin (HI) in Type 2 Diabetes. *Diabetes.* 1999; 48 (Suppl 1): A355.
- 37 Banerjee S, Tran K, Li H, et al. Short-acting insulin analogues for diabetes mellitus: meta-analysis of clinical outcomes and assessment of cost-effectiveness. *Ott Can Agency Drugs Technol Health.* 2007.
- 38 Singh SR, Ahmad F, Lal A, et al. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. *CMAJ.* 2009; 180: 385-397.
- 39 Garg S, Ampudia-Blasco FJ, Pfohl M. Rapid-acting insulin analogues in Basal-bolus regimens in type 1 diabetes mellitus. *Endocr Pract Off J Am Coll Endocrinol Am Assoc Clin Endocrinol.* 2010; 16: 486-505.
- 40 Heller S, Bode B, Kozlovski P, Svendsen AL. Meta-analysis of insulin aspart versus regular human insulin used in a basal-bolus regimen for the treatment of diabetes mellitus. *J Diabetes.* 2013; 5: 482-491.
- 41 Pontiroli AE, Miele L, Morabito A. Metabolic control and risk of hypoglycaemia during the first year of intensive insulin treatment in type 2 diabetes: systematic review and meta-analysis. *Diabetes Obes Metab.* 2012; 14: 433-446.
- 42 Riddle M, Umpierrez G, DiGenio A, et al. Contributions of basal and postprandial hyperglycemia over a wide range of A1C levels before and after treatment intensification in type 2 diabetes. *Diabetes Care.* 2011; 34: 2508-2514.
- 43 Allen KV, Frier BM. Nocturnal hypoglycemia: clinical manifestations and therapeutic strategies toward prevention. *Endocr Pract Off J Am Coll Endocrinol Am Assoc Clin Endocrinol.* 2003; 9: 530-543.
- 44 Yale JF. Nocturnal hypoglycemia in patients with insulin-treated diabetes. *Diabetes Res Clin Pract.* 2004; 65 (Suppl 1): S41-S46.
- 45 The diabetes control and complications trial research Group Epidemiology of severe hypoglycemia in the Diabetes Control and complications trial. *Am J Med.* 1991; 90: 450-459.
- 46 Fidler C, Elmelund Christensen T, Gillard S. Hypoglycemia: an overview of fear of hypoglycemia, quality-of-life, and impact on costs. *J Med Econ.* 2011; 14: 646-655.
- 47 Brod M, Christensen T, Bushnell DM. Impact of nocturnal hypoglycemic events on diabetes management, sleep quality, and next-day function: results from a four-country survey. *J Med Econ.* 2012; 15: 77-86.

Efektywność kliniczna i bezpieczeństwo stosowania insuliny aspart w porównaniu z insuliną ludzką u pacjentów z cukrzycą typu 1 oraz 2 – przegląd systematyczny i metaanaliza

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SŁOWA KLUCZOWE

analogi
szybkodziałające
insuliny, cukrzyca
typu 1, cukrzyca
typu 2, insulina
aspart, insulinoterapia

STRESZCZENIE

WPROWADZENIE Insulina posiłkowa stanowi kluczową komponentę insulinoterapii w cukrzycy typu 1 (*type 1 diabetes mellitus* – T1DM) i u wielu pacjentów z cukrzycą typu 2 (*type 2 diabetes mellitus* – T2DM). Dane oparte na dowodach naukowych wspierające wybór preparatu insulinowego są w dalszym ciągu nieliczne.

CELE Przeprowadziliśmy przegląd systematyczny w celu podsumowania i aktualizacji dowodów naukowych dotyczących względnej skuteczności i bezpieczeństwa stosowania insuliny aspart (IAsp) oraz insuliny ludzkiej (*regular human insulin* – RHI) w obydwu typach cukrzycy.

METODY Randomizowane badania kliniczne porównujące IAsp z RHI u pacjentów z T1DM lub T2DM przeprowadzone w okresie do maja 2013 roku znaleziono w ramach przeszukiwania systematycznego baz MEDLINE, EMBASE i Cochrane Library.

WYNIKI Z 16 znalezionych badań 11 dotyczyło pacjentów z T1DM, a 5 – pacjentów z T2DM. W populacji z T1DM IAsp w porównaniu z RHI zapewniał większą redukcję poziomu HbA_{1c} (różnica średnich ważonych [*weighted mean difference* – WMD] –0,11%; 95% CI: od –0,16 do –0,05; WMD –1,2 mmol/mol; 95% CI od –1,7 do –0,5) i lepszy poziom glikemii poposiłkowej mierzony po: śniadaniu (WMD –1,40 mmol/l; 95% CI: od –1,72 do –1,07), obiedzie (WMD –1,01 mmol/l; 95% CI: od –1,61 do –0,41) i kolacji (WMD –0,89 mmol/l; 95% CI: od –1,19 do –0,59). Ryzyko nocnej hipoglikemii było niższe u pacjentów z T1DM otrzymujących IAsp (RR 0,76; 95% CI: 0,6–0,91), natomiast w przypadku ciężkiej hipoglikemii nie obserwowano różnic pomiędzy grupami. U pacjentów z T2DM stosowanie IAsp prowadziło do większej redukcji poziomu HbA_{1c} (WMD –0,22%; 95% CI: od –0,39 do –0,05; WMD –2,4 mmol/mol; 95% CI: od –4,3 do –0,5) oraz glikemii poposiłkowej. Ryzyko wystąpienia hipoglikemii ogółem oraz poważnych zdarzeń niepożądanych było porównywalne w obu badanych grupach.

WNIOSKI W porównaniu z RHI IAsp zapewnia lepszą kontrolę glikemii u chorych z T1DM oraz T2DM. Mniej pacjentów z T1DM leczonych IAsp doświadczało hipoglikemii nocnych, podczas gdy w przypadku obu interwencji ryzyko ciężkiej hipoglikemii było porównywalne dla obu typów cukrzycy.

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