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Aims

The aim of this analysis was 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 in the prandial insulin therapy

Introduction

- Prandial insulin is a key component in insulin treatment of type 1 diabetes mellitus (T1DM) and in many type 2 diabetes mellitus (T2DM) patients,

- The use of RHI for mealtime coverage has several limitations related to its pharmacological profile and may increase the risk of hypoglycemia due to undesired prolonged activity, [1]

- IAsp is a rapid-acting insulin analog, characterized by faster onset of activity and shorter time duration, which allows for a precise control of prandial glycemia. [2]

Methods

A systematic search of electronic medical databases (MEDLINE, EMBASE, Cochrane CENTRAL) and associations active in field of diabetes was carried out until May 2013. Inclusion and exclusion criteria were as follows:

Inclusion criteria	
→ Population	Patients with T1DM or T2DM
→ Intervention vs comparator	IAsp vs RHI
→ Endpoints	• Reduction of glycated hemoglobin (HbA1c) • Glycemia after major meals (breakfast, lunch, dinner) • Risk of hypoglycemia (overall, serious and nocturnal).
→ Methodology	• Randomized controlled trials (RCTs) with follow-up ≥ 12 weeks
Exclusion criteria	• Pregestational or gestational diabetes • Less than 10 patients included • Comparison of different methods of insulin treatment • Language other than English, French, German or Polish

Results were reported as weighted mean difference (WMD) and relative risk (RR) for continuous and dichotomous data, respectively, together with 95% confidence interval [95%CI]. Whenever possible results were pooled with meta-analysis.

Characteristics of included studies

A total number of 3512 abstracts were screened of which 469 positions were considered potentially relevant. Finally, 16 RCTs fulfilled prespecified inclusion criteria and were included in this analysis (Figure 1).

Figure 1. Study selection diagram.
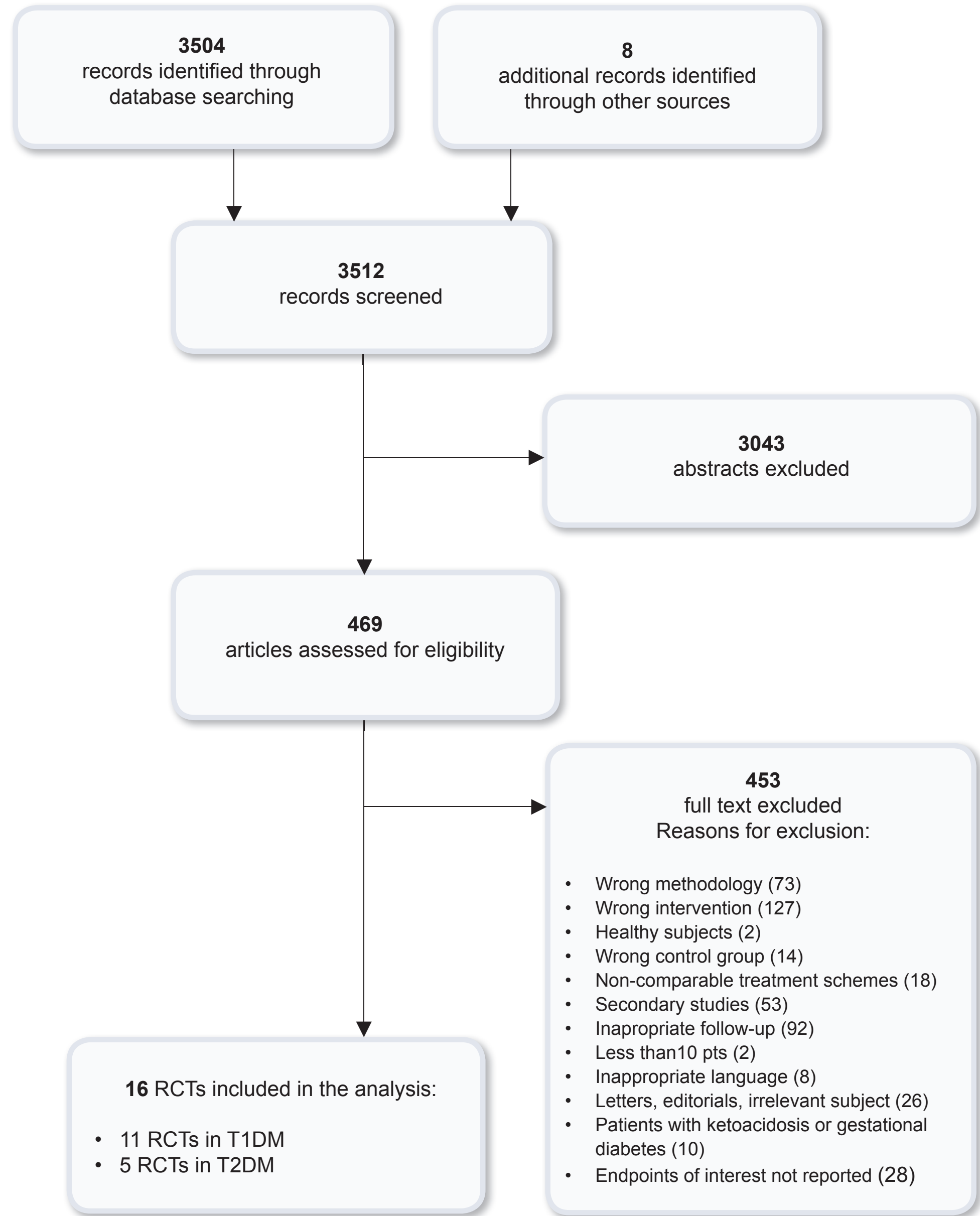
Eleven RCTs compared IAsp with RHI in an overall number of 3447 patients with T1DM, including 4 studies recruiting children [3–6] and 7 trials carried out on adult patients (Figure 1).[7–13] The mean duration of diabetes was between 1.8-5.2 years and 4.7-15.7 years in studies recruiting children and adults, respectively. Themean HbA1c level at baseline ranged from 7.3% to 8.6% in all identified studies. In 10 studies, patients received intensive insulin therapy by MDI using either NPH (8 RCTs) or long-acting insulin analogues (2 RCTs) as basal insulin. In the remaining one, the RCT investigated insulin was administered via continuous subcutaneous insulin infusion CSII (Table 1). [8]

A total number of five RCTs comparing IAsp with RHI in an overall number of 451 adult patients with T2DM were identified (Figure 1). [14–18] The mean duration of diabetes ranged from 4.6 to 17.5 years, while the mean HbA1c at baseline was between 7.3% and 8.7% in respective trials. In four of the included studies, patients received intensive insulin treatment by MDI [14, 15, 18], while the remaining two RCT compared IAsp with RHI, both administered without the use of basal insulin (Table 1) [16, 17]

Methodological quality of all included studies ranged from 1 to 3 points, according to the Jadad score, and was most often downgraded due to lack of double blinding and insufficient information regarding number of patients lost to follow-up.

Table 1. Relative change in HbA1c levels for comparison between IAsp and RHI in patients with T1DM

Study	Methodology	No. of patients IAsp/RHI	HbA1c level [%] IAsp/RHI	Insulin scheme/ basal insulin	OI [weeks]
T1DM					
Ampudia-Blasco 2005 [7]	pg, ol	28/26	8,5/8,6	MDI/LAA	26
Arslanian 2005 [3]	pg, ol	187/96	8,3/8,3	MDI/NPH	24
Bode 2002 [19]	pg, ol	59/59	7,3/7,5	CSII	16
Cherubini 2006 [4]	pg, ol	30	7,5	MDI/LAA	18
Danne 2007 [5]	c-o, ol	26	7,8	MDI/NPH	2x12
DeVries 2003 [9]	pg, ol	186/181	8,4/8,4	MDI/NPH	64
Heller 2004 [10]	c-o, db	155	8,6	MDI/NPH	2x14
Home 2000 [11]	pg, ol	707/358	8,0/8,0	MDI/NPH	26
Pańkowska 2010 [6]	pg, ol	20/21	7,4/7,5	MDI/NPH	26
Raskin 2000 [12]	pg, ol	596/286	7,9/7,95	MDI/NPH	26
Tamás 2001 [13]	pg, ol	213/213	8,4/8,3	MDI/NPH	64
T2DM					
Bretzel 2004 [14]	pg, ol	75/80	7,82/7,83	MDI/NPH	12
Herrmann 2013 [15]	pg, ol	18/11	8,7/8,7	MDI/NPH or LAA	104
Maiti 2012 [16]	pg, ol	30/30	8,3/8,1	MDI / no basal	52
Pala 2007 [17]	c-o, ol	25	7,3	MDI / no basal insulin	2x12
Raskin 1999 [18]	pg, ol	91/91	8,1/7,9	MDI/NPH	26

pg – paralel gruop study; ol – open-label study; c-o – crossover study;
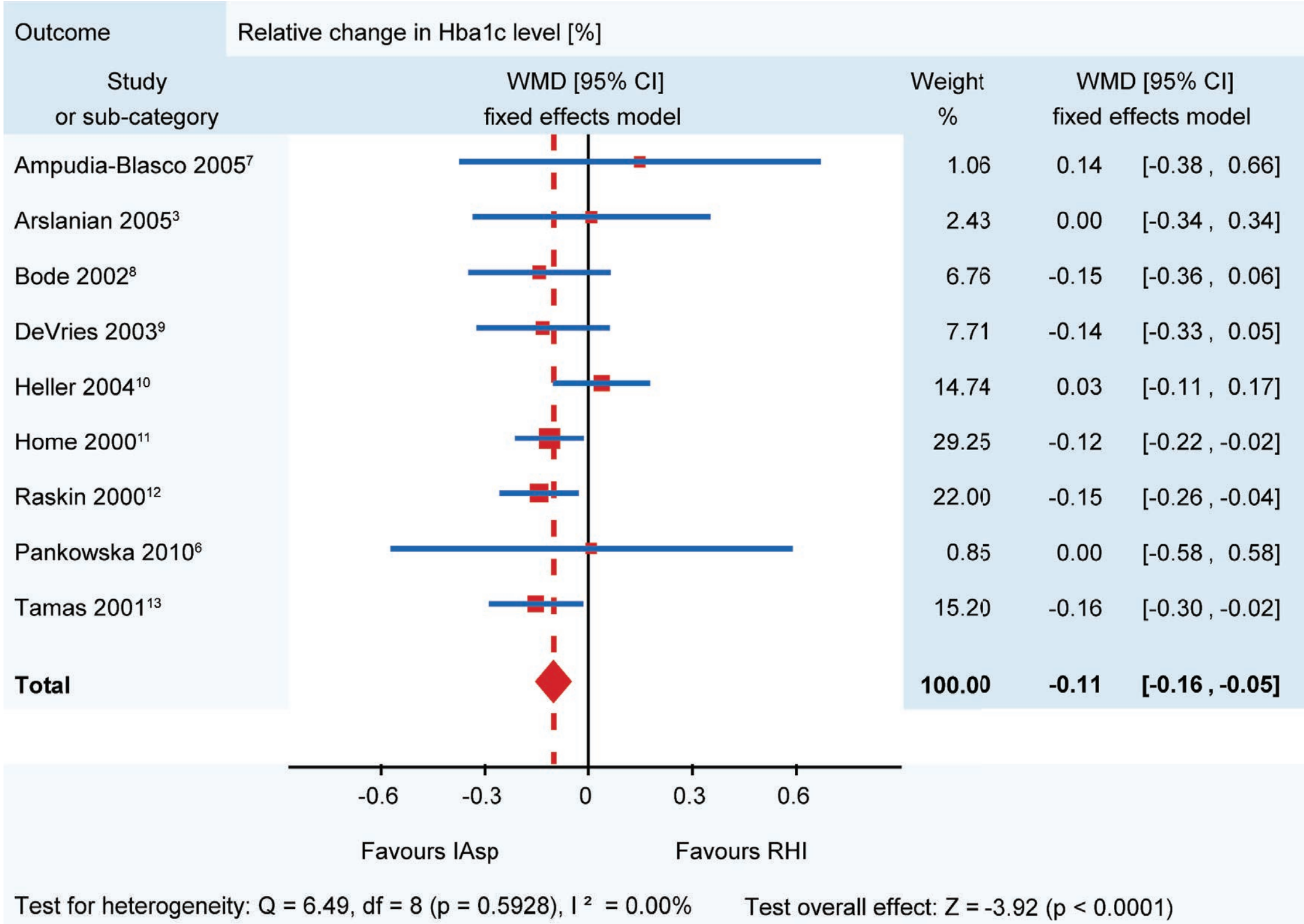
Results

Patients with T1DM

Glycemic control

Glycated hemoglobin (HbA1c): Meta-analysis of 9 RCTs revealed significant advantage of IAsp over RHI with respect to HbA1c reduction during treatment (WMD=-0.11% [-0.16, -0.05]), with no evidence for between-study heterogeneity (p=0.59, I^2=0%) (Figure 2).

Figure 2. Relative change in HbA1c levels for comparison between IAsp and RHI in patients with T1DM

Postmeal glucose: Pooled results demonstrated an advantage of IAsp over RHI with respect to post-prandial glucose level, which was measured 90 minutes following each meal, including breakfast (WMD=-1.40mmol/L [-1.72, -1.07]), lunch (WMD=-1.01mmol/L [-1.61, -0.41]) and dinner (WMD=-0.89mmol/L [-1.19, -0.59]) (Figure 3, Figure 4 and Figure 5). Statistical heterogeneity was observed in the meta-analysis for glycemic control following lunch (p=0.04, I^2=69%); however, this can be associated with the relatively low number of included trials. No statistical heterogeneity was demonstrated in the remaining meta-analyses.

Figure 3. Relative change in post breakfast blood glucose levels for comparison between IAsp and RHI in patients with T1DM
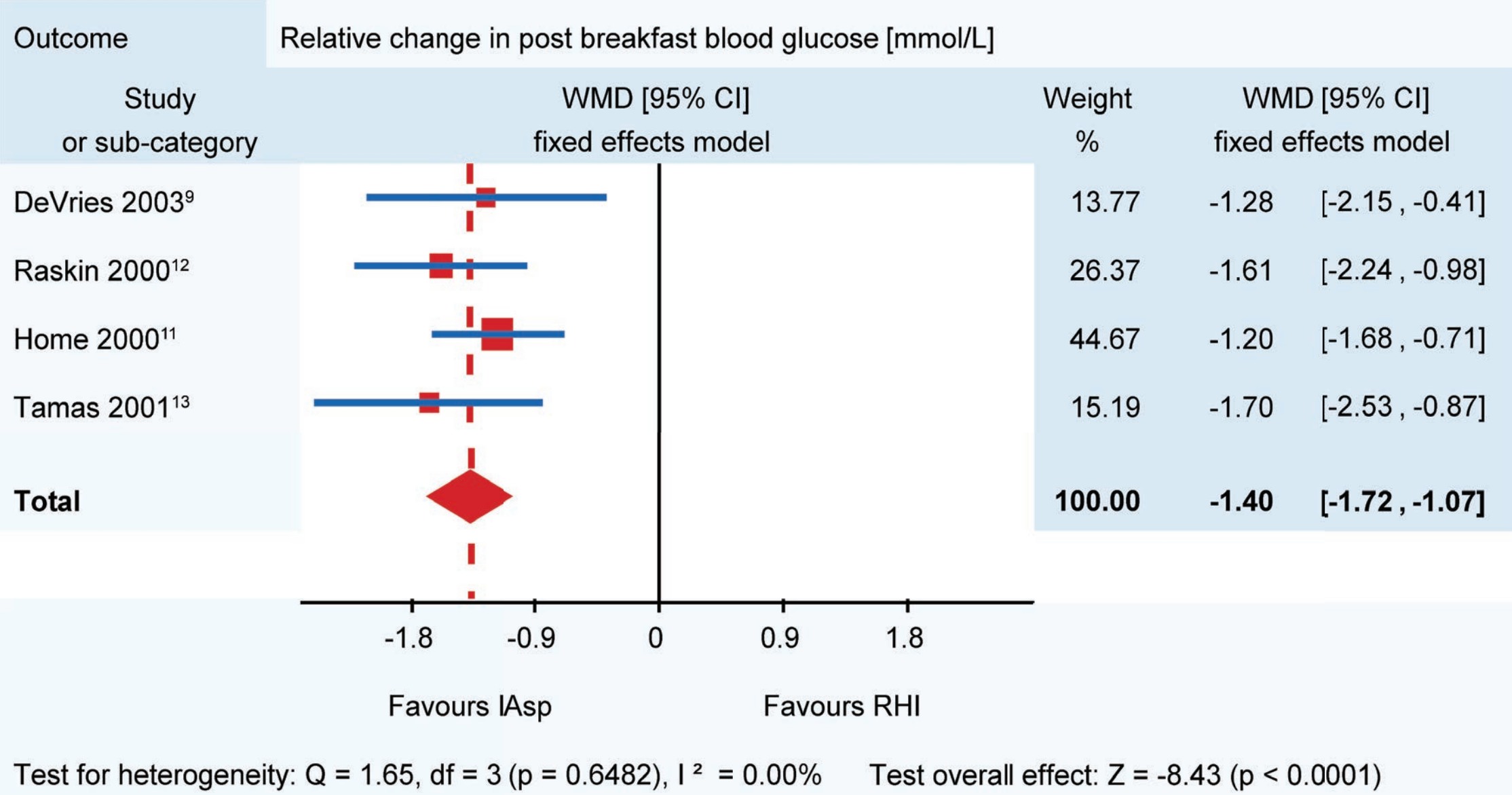

Figure 4. Relative change in post lunch blood glucose levels for comparison between IAsp and RHI in patients with T1DM
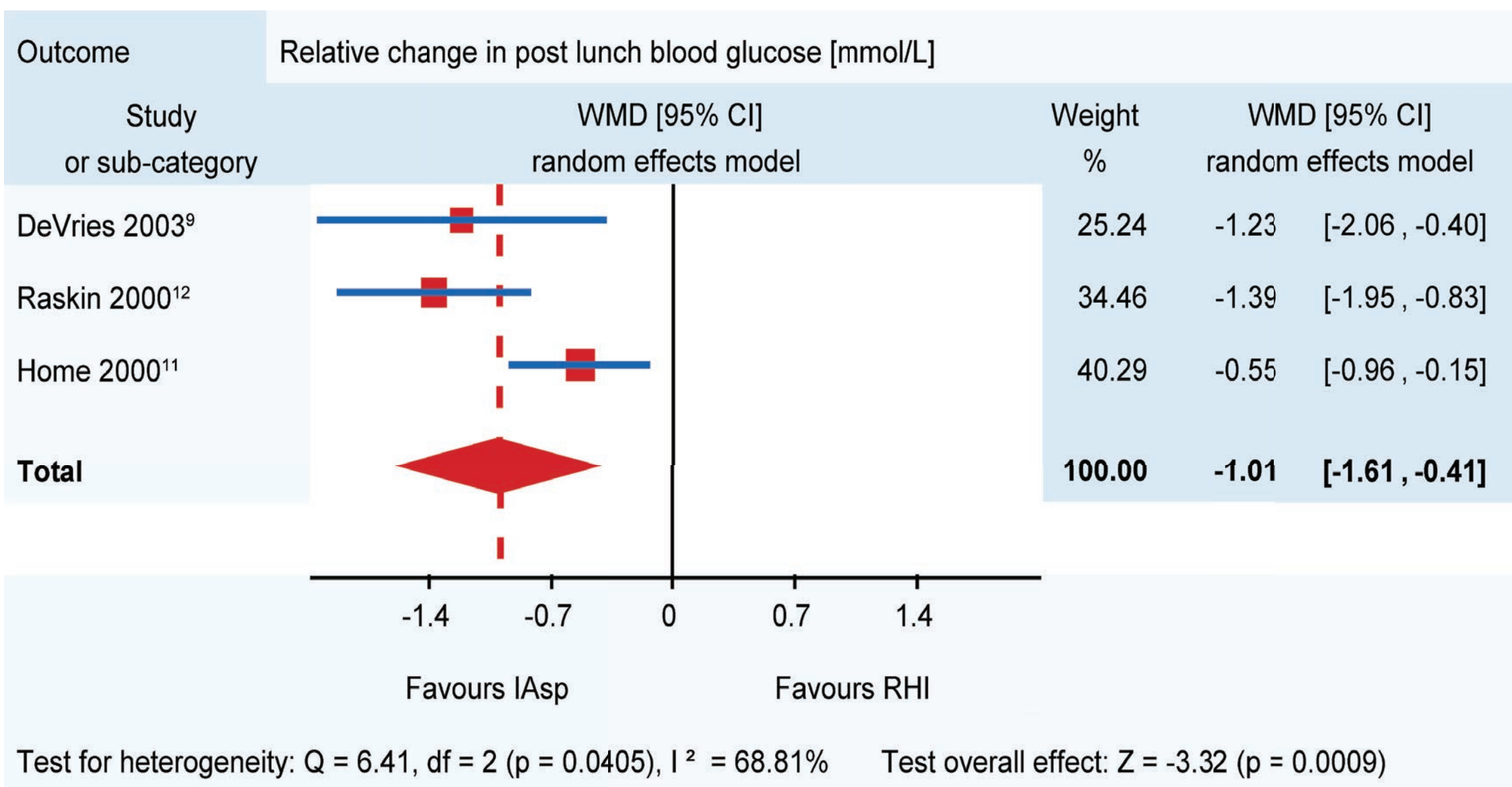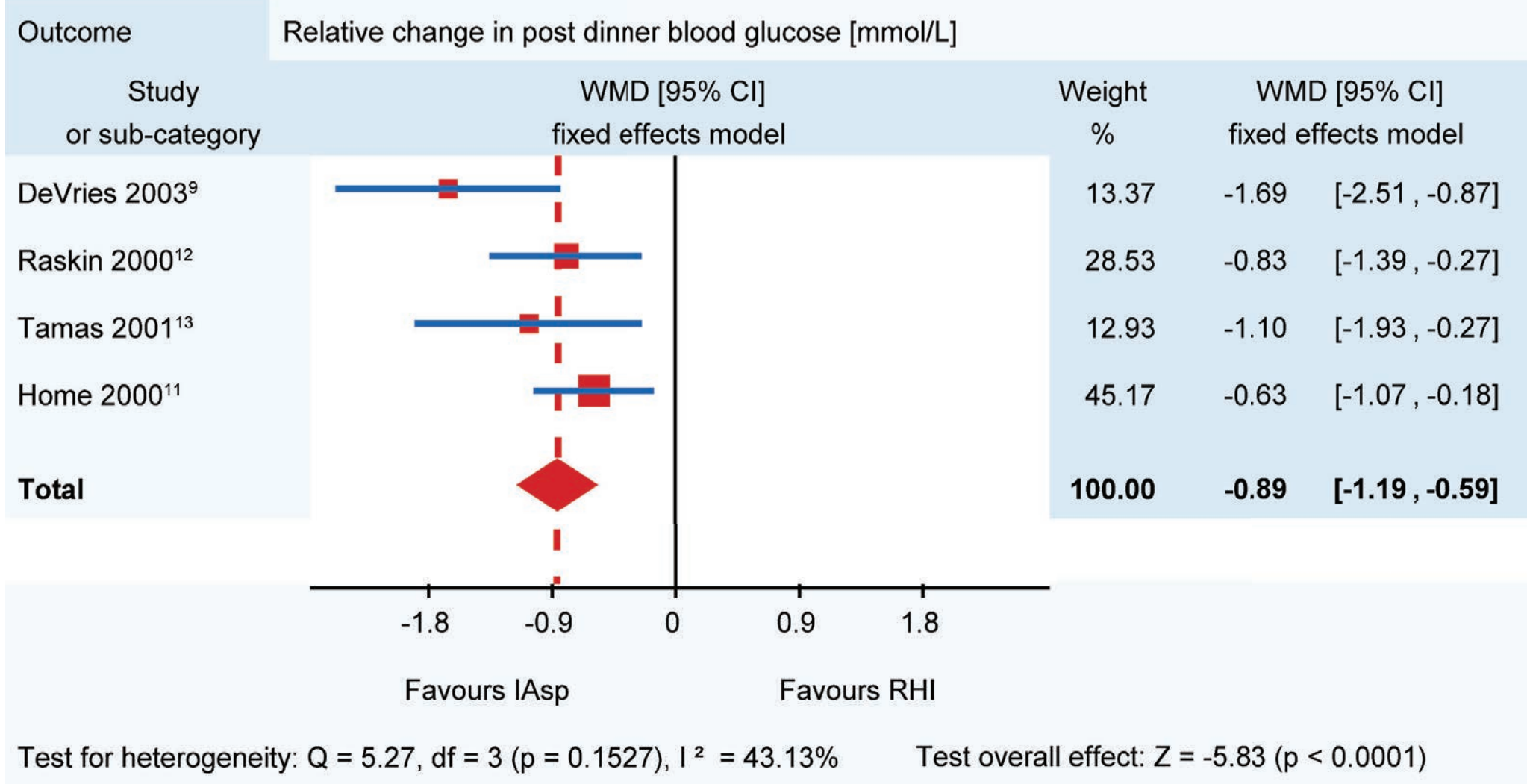

Figure 5. Relative change in post dinner blood glucose levels for comparison between IAsp and RHI in patients with T1DM

Hypoglycemia

Neither study reported the risk of overall hypoglycemic episodes regardless of their severity. Pooled results of five RCTs demonstrated a comparable risk of severe hypoglycemia between treatment groups (RR=0.85 [0.66, 1.08]). [3, 6, 8, 11, 13] 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 [0.64, 0.91]), with no evidence for between-study heterogeneity (Figure 6). [3, 6, 8, 11, 13]

Figure 6. The risk of nocturnal hypoglycemic episodes for comparison between IAsp and RHI in patients with T1DM
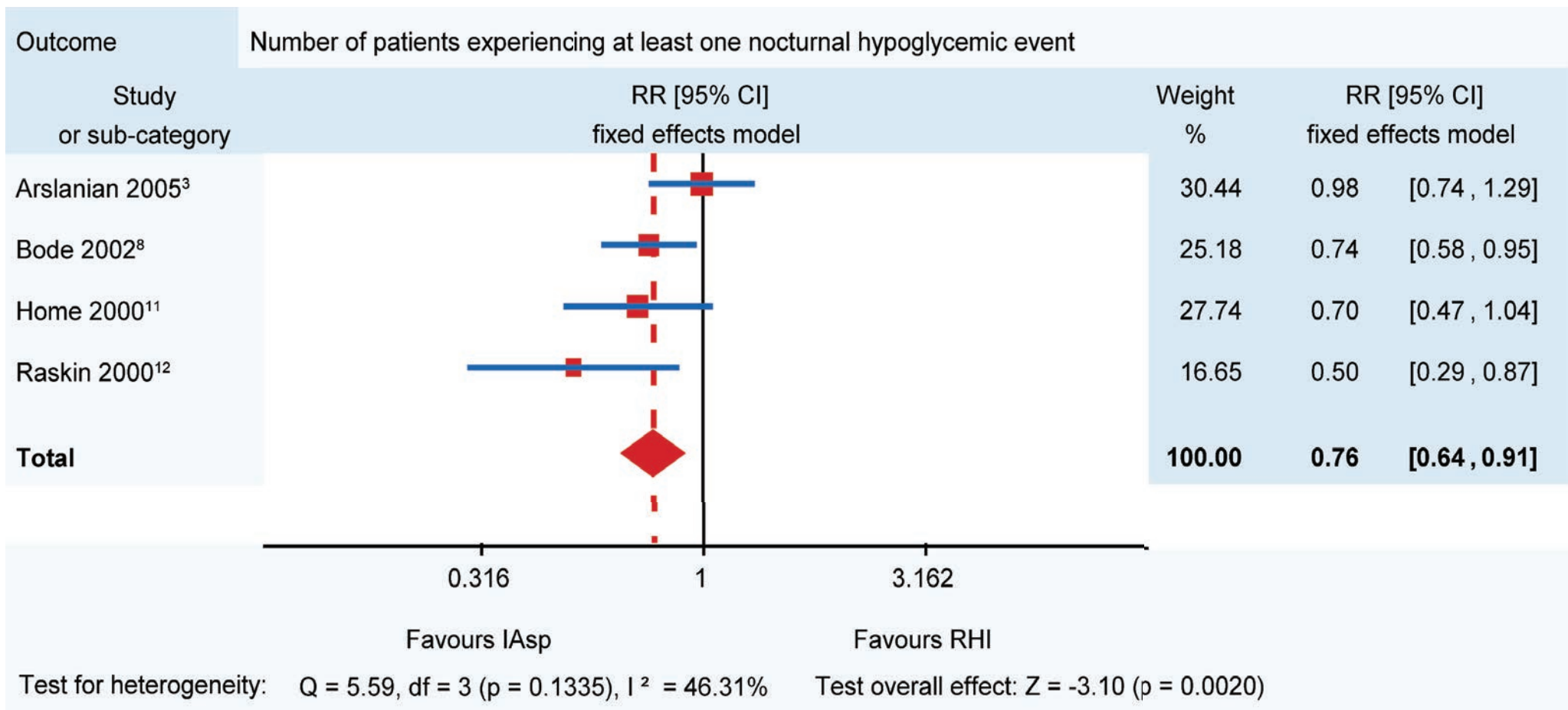

Patients with T2DM

Glycemic control

Glycated hemoglobin (HbA1c): Meta-analysis of all 5 RCTs demonstrated that patients treated with IAsp had better glycemic control compared to their counterparts from RHI arms (WMD=-0.22% [-0.39, -0.05]) (Figure 7). No significant between-study heterogeneity was observed.

Figure 7. Relative change in HbA1c levels for comparison between IAsp and RHI in patients with T2DM
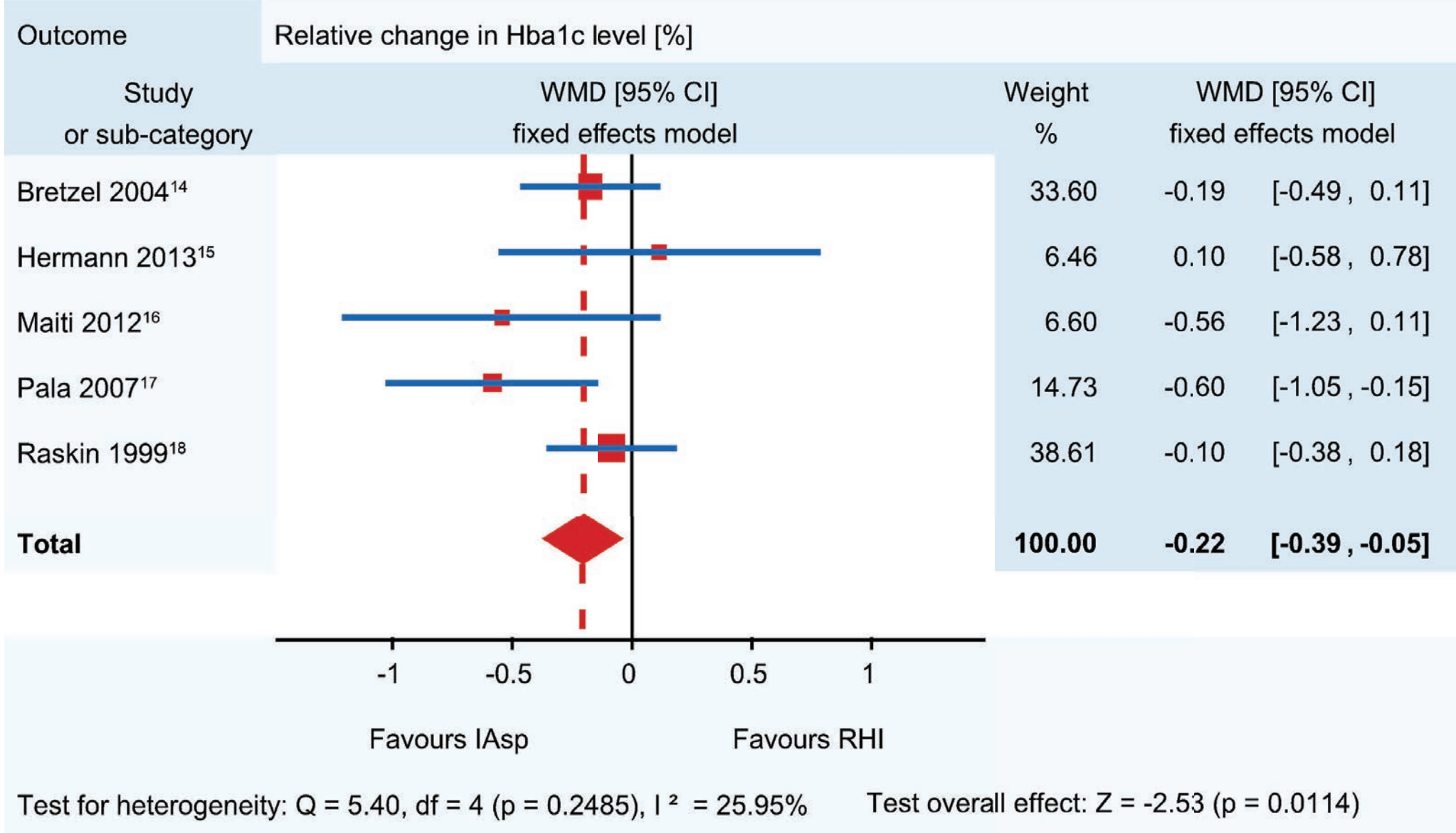
Postmeal glucose: Neither study presented data allowing comparison between IAsp and RHI with respect to postprandial glucose control following any of the daily meals. One RCT demonstrated that the mean level of blood sugar following major meals in patients treated with IAsp was lower by 0.96 mmol/L compared with the RHI group (p<0.05 in each study). [16] Two other studies also reported a lower postmeal glucose level in IAsp arm (by 0.44 mmol/L and 3.40 mmol/L in respective studies) however without any formal statistical comparison. [14, 17]

Hypoglycemia

Pooled results of 2 RCTs demonstrated no significant between-group differences in the risk of overall hypoglycemia (RR=1.00 [0.70, 1.44]). [14, 15] Of two RCTs assessing the risk of severe hypoglycemia, one recorded no events in either group, while the other reported no significant difference between study arms. [17, 18] Neither study reported the risk of nocturnal hypoglycemia.

Conclusions

IAsp provided better glycemic control when compared with RHI in T1DM and T2DM in patients receiving prandial insulin treatment. T1DM patients treated with IAsp were less prone to develop nocturnal hypoglycemia, while both interventions presented a comparable risk of severe hypoglycemic events in both types of diabetes.

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