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


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Abstract

Background. – Insulin aspart (IAsp) is one of the three rapid-acting insulin analogues (RAAs) registered for the treatment of diabetes. However, there is an ongoing debate concerning the efficacy and safety of RAAs. For this reason, a systematic review-based study was performed to compare clinical outcomes of treatment with IAsp and regular human insulin (RHI) as well as biphasic insulin aspart and premixed human insulin in type 1 and type 2 diabetes (T1DM, T2DM) patients.

Methods. – Relevant articles were identified by a systematic search through the electronic medical databases (MEDLINE, EMBASE, CENTRAL) up to July 2009.

Results. – A total of 28 trials fulfilled the inclusion criteria, including 17 studies of T1DM, 10 of T2DM and one study of both. For T1DM, pooled data for HbA1c (13 studies) demonstrated lower levels with IAsp than with RHI (WMD = −0.11%; 95% CI: −0.16 to −0.06). In addition, meta-analysis revealed statistically significant differences in favour of IAsp for postprandial glucose (PPG) after breakfast, lunch and dinner, but not for fasting glucose (FG). The Diabetes Treatment Satisfaction Questionnaire evaluating treatment flexibility showed IAsp benefits compared with RHI (WMD = 0.31; 95% CI: 0.15 to 0.47). Safety analyses (three studies) showed a significant reduction in nocturnal hypoglycaemia risk with IAsp (RR = 0.67; 95% CI: 0.54 to 0.83), and no difference in severe hypoglycaemias and a slight increase in any hypoglycaemic episodes with RAAs (RR = 1.06; 95% CI: 1.01 to 1.10). For T2DM, a meta-analysis of nine studies revealed no significant differences between IAsp and RHI in HbA1c (WMD = −0.04%; 95% CI: −0.10 to 0.03), whereas PPG was significantly lower in the IAsp group (WMD = −1.18 mmol/L; 95% CI: −1.88 to −0.47). No studies of treatment satisfaction or quality of life were identified.

Conclusion. – Analyses based on a systematic review showed that treatment with IAsp in T1DM patients resulted in moderately better metabolic control and treatment satisfaction than RHI. In T2DM patients, meta-analysis showed improvement in PPG, but not in any other outcomes.

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Keywords: Type 1 diabetes mellitus; Type 2 diabetes mellitus; Rapid-acting analogues; Insulin aspart; Human insulin; Comparison; Efficacy; Safety; Meta-analysis; Review

Abbreviations: BIASp, biphasic insulin aspart; BHI, biphasic human insulin; CI, confidence interval; DHP, Diabetes Health Profile; DM, diabetes mellitus; DTSQ, Diabetes Treatment Satisfaction Questionnaire; DSQOLS, The Diabetes-Specific Quality-of-Life Scale; FG, fasting plasma glucose; HbA1c, glycated haemoglobin; IAsp, insulin aspart; PPG, postprandial glucose; MDI, multiple daily insulin; QOL, quality of life; PBG, post-breakfast glucose; PLG, post-lunch glucose; PDG, post-dinner glucose; RAA(s), rapid-acting analogue(s); RCT(s), randomized controlled trial(s); RHI, regular human insulin; RR, relative risk; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; WMD, weighted mean difference.

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Résumé

Comparaison de l’efficacité et de la sécurité d’emploi de l’analoge rapide aspart et de l’insuline rapide humaine dans le diabète de type 1 et 2.


Méthodes. — Les articles pertinents ont été identifiés grâce à une recherche systématique sur Medline, Embase et Central jusqu’en juillet 2009.

Résultats. — Nous avons identifié 28 études qui répondaient aux critères d’inclusion, dont 17 études dans le DT1, dix études dans le DT2, et une étude dans le DT1 et DT2. Dans le DT1, les résultats de 13 études ont montré que les taux d’HbA1c atteints avec l’IAsp étaient plus bas qu’avec l’insuline humaine (WMD = −0,11 %; IC à 95 %: −0,16 à −0,06). La méta-analyse a mis en évidence une différence statistiquement significative en faveur de l’IAsp pour la glycémie post-prandiale (GPP) après petit-déjeuner, déjeuner et dîner, mais non pour la glycémie à jeun (GAJ). La partie du questionnaire DTSQ qui a évalué la flexibilité du traitement montrait un bénéfice en faveur de l’IAsp par rapport à l’IH (WMD = 0,31; IC à 95 %: 0,15 à 0,47). L’analyse de la tolérance a montré une diminution significative du risque d’hypoglycémie nocturne dans le groupe IAsp (RR = 0,67; IC à 95 %: 0,54 à 0,83), sans différence concernant les hypoglycémies sévères et avec une légère augmentation des hypoglycémies totales pour les analogues rapides de l’insuline humaine. La méta-analyse des neuf études réalisées dans le DT2 n’a montré aucune différence sur l’HbA1c entre l’IAsp et l’IH (WMD = −0,04 %; IC à 95 %: −0,10 à 0,03), une glycémie post-prandiale significativement plus basse dans le groupe IAsp (WMD = −1,18 mmol/L; IC à 95 %: −1,88 à −0,47). Aucune étude concernant la satisfaction par rapport au traitement ou la qualité de vie n’a été identifiée dans le DT2.

Conclusions. — L’analyse fondée sur une revue systématique de la littérature indique que le traitement par IAsp permet un meilleur contrôle métabolique et une plus grande satisfaction vis à vis du traitement dans le DT1. Dans le DT2, la méta-analyse a montré une amélioration de la glycémie post-prandiale mais non des autres critères.

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Mots clés : Diabète de type 1 ; Diabète de type 2 ; Traitement ; Analogues rapides ; Insuline aspart ; Insuline humaine ; Efficacité ; Sécurité ; Comparaison ; Méta-analyse ; Revue générale

1. Introduction

The main goal of diabetes mellitus (DM) treatment, apart from control of body mass, blood pressure and lipid profile, is to keep blood glucose levels as close to the normal range as possible. Several types of insulin, such as regular human insulin (RHI), rapid-acting insulin analogues (RAAs), neutral protamine insulin and long-acting analogues, are available for diabetic patients. They vary in pharmacological profiles of biological activity, such as in their time of action onset, time to peak concentration and duration of action. These differences contribute to the clinical indications for the use of each type of insulin [1].

Current insulin therapy aims to mimic both basal and prandial physiological hormone secretion to achieve near-normal glycaemia. RHI has been used in clinical practice for years as a meal-time insulin, and has proved to be an efficient and safe tool for glycaemic control in both type 1 (T1DM) and type 2 (T2DM) diabetes mellitus. However, its pharmacokinetic and pharmacodynamic profiles have never been considered optimal [2]. RHI starts its action approximately 30–45 min after injection and lasts for about 6–8 h [3]. Thus, patients are advised to take shots approximately 30 min prior to a meal. However, most diabetic patients ignore this recommendation and, instead, use shorter or even no interval between injection and meals [4].

In addition, as peak RHI concentrations occur at 2–4 h after injection, snacks are recommended to avoid hypoglycaemia. In the Diabetes Control and Complications Trial (DCCT), it was established that intensive insulin therapy based on RHI enables reduction of the risk of chronic diabetes complications in T1DM patients, but that it also predisposes to a higher risk of hypoglycaemic episodes and weight gain than does conventional therapy [5,6]. Similarly, it was found that, in T2DM patients, any improvement in glycaemic control was also accompanied by such side-effects [7].

The idea behind the development of RAAs of human insulin was to overcome the pharmacokinetic limitations of RHI by introducing slight, but precisely designed, changes in the amino-acid sequence of the native peptide chain. These modifications were expected to change its properties in such a way as to allow analogues to mimic physiological insulin secretion and activity more closely, including, in particular, a rapid increase in circulating hormone levels soon after eating [8].

The first RAA was introduced more than 15 years ago [9,10], and was soon followed by two other molecules. However, it is still unclear whether or not they benefit diabetic patients through improved glycaemic control and, even more important, by the reduction in the risk of chronic complications and the extended life expectancy as a result of the use of these new compounds. Nevertheless, some advantages of RAAs over RHI have been suggested. In one systematic review of trials published before September 2005, it was reported that RAAs provided slightly better glycaemic control than RHI in T1DM, but not in T2DM, patients as measured by glycated haemoglobin (HbA1c) levels [11]. However, a recent meta-analysis suggested that the use of RAAs in T2DM resulted in better HbA1c without increasing the risk of severe hypoglycaemic episodes [12]. This meta-analysis also reported on the combined data for all three RAAs currently available on the market (aspart, lispro and glulisine). While the pharmacokinetics and pharmacodynamics of these compounds are similar, they are not identical and neither are some of their biological properties such as receptor-binding. Nevertheless, none of these earlier meta-analyses reported on the effect of RAAs on
postprandial glucose (PPG) levels, which are considered an independent risk factor for vascular complications in diabetes [13]. Thus, as new clinical trials are published, there is a need to analyze the emerging data and to investigate each RAA separately.

For this reason and for the first time, this extensive systematic review-based study was carried out to compare outcomes of treatment with insulin aspart (IAsp) and RHI, as well as biphasic insulin aspart (BIAsp) and biphasic human insulin preparations (BHI) in T1DM and T2DM patients.

2. Patients and methods

2.1. Inclusion criteria

This meta-analysis was based on the results of randomized controlled trials (RCTs) that enrolled patients with either T1DM or T2DM and with no restrictions on age. Also included were studies with durations of at least 4 weeks comparing IAsp with RHI or BIAsp with BHI. As trials lasting less than 12 weeks do not yield sufficient fully relevant information on HbA1c, a subgroup analysis was performed for HbA1c that included only trials with treatment durations of 12 weeks or more.

2.2. Exclusion criteria

Studies with sample sizes less than ten subjects or lasting less than 4 weeks, or associated with other types of diabetes (gestational, secondary), were excluded from the analyses.

2.3. Search strategy

An extensive search of MEDLINE, EMBASE, CENTRAL, and the Centre for Reviews and Dissemination was systematically performed. References listed in the retrieved articles were also used. The final search was carried out in July 2009. Verification of the abstracts was done in two stages. Two experienced reviewers independently identified the relevant abstracts, and selected studies according to the criteria described above and extracted the data for analysis. In cases of disagreement, the final decision was achieved by consensus or with the assistance of a third independent expert based on verification of the full text. The quality of RCTs was also assessed, using the parameters proposed by Jadad et al. [14].

2.4. Outcome measures

Our systematic review aimed to identify studies in which clinically important efficacy endpoints, such as mortality and chronic complications (retinopathy, nephropathy, neuropathy, cardiovascular events), were evaluated, but no studies with these endpoints were found. For this reason, the principal efficacy outcomes of IAsp compared with RHI were used surrogates of these endpoints in DM, including levels of fasting glucose (FG) and PPG or HbA1c at the end of the trial. In addition, data on weight gain, quality of life (QOL) and incidences of nocturnal, severe or any hypoglycaemia (number of patients with at least one event) were also extracted. Separate analyses were performed for trials involving both T1DM and T2DM patients.

2.5. Statistical analysis

Dichotomous data were pooled using relative risk (RR). The results of the meta-analysis for continuous endpoints were expressed as weighted mean difference (WMD) or standardized mean difference (SMD). If meta-analysis for continuous endpoints was not possible due to a lack of pertinent data (mean, standard deviation), then attempts were made to extract values from aggregated data (differences between groups), and a modified method was applied for pooling data (known as ‘inverse variance’ in The Cochrane Handbook for Systematic Reviews of Interventions). Two kinds of meta-analysis were carried out: a basic meta-analysis (if means and standard deviation or standard error values were available); and a modified meta-analysis (if only differences between groups were reported). In all cases, the results were presented with 95% confidence intervals (95% CI). Also, it was assumed that the studies included in our analysis were not homogeneous if the P value for a statistical heterogeneity test was lower than 0.1 (P < 0.10). Thus, if clinical trials were heterogeneous (P < 0.10), their results were pooled using a random-effects model. Otherwise, a fixed-effects model was applied. StatsDirect version 2.6.2 software was used for all meta-analyses.

3. Results

The electronic database search identified 4504 articles. Of these, 445 studies were classified as potentially relevant and were passed for further assessment based on full texts. Ultimately, 28 trials met the inclusion criteria for the present review (Fig. 1).

3.1. T1DM studies

3.1.1. Study characteristics

Of the 18 retrieved studies, 14 involved adult patients with T1DM [15–28], and four included children and/or adolescents [29–32]. Mean baseline HbA1c ranged from 6.9% [26] to 9.6% [32]. Thirteen studies were RCTs with a parallel design, and five were RCTs with a crossover design. Only two were double-blind [21,22], and adequate allocation concealment was provided in only three of the 18 studies [21,22,28]. In two of the RCTs, insulin was administered by continuous subcutaneous insulin infusion (CSII) [16,17]; in the rest of the studies, it was by subcutaneous insulin injection. In 13 trials, patients were under a basal–bolus scheme (multiple daily insulin injections, MDI), usually using IAsp or RHI added to neutral protamine Hagedorn (NPH) insulin; in three studies, biphasic insulin was administered. In most of the trials, insulin doses were adjusted according to target values of FG, preprandial glucose and PPG levels. However, none of these trials was designed to treat to any specific HbA1c target (Table 1).
Table 1
Studies included in the systematic review of studies of type 1 diabetic patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients’ characteristics at baseline</th>
<th>Study design</th>
<th>Jadad et al. score</th>
<th>Allocation concealment</th>
<th>Insulin regimen (basal insulin)</th>
<th>Treatment target</th>
<th>Treatment duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampudia-Blasco et al., 2005</td>
<td>28/26 32.3 14.5 8.5 24.8</td>
<td>PS</td>
<td>R1 B0 W0</td>
<td>NC</td>
<td>MDI (glargine)</td>
<td>NR</td>
<td>6</td>
</tr>
<tr>
<td>Arslanian et al., 2005</td>
<td>187/96 11.7 4.7 8.3 21.2</td>
<td>PS</td>
<td>R1 B0 NR</td>
<td>NC</td>
<td>MDI (NPH)</td>
<td>NR</td>
<td>6</td>
</tr>
<tr>
<td>Bode et al., 2001</td>
<td>19/10 36.6 2–25 7.2 25.3</td>
<td>PS</td>
<td>R1 B0 W1</td>
<td>NA</td>
<td>BiBpic</td>
<td>NR</td>
<td>7 weeks</td>
</tr>
<tr>
<td>Bode et al., 2002</td>
<td>59/59 42.7 ≥ 1 7.4 26.3</td>
<td>PS</td>
<td>R2 B0 W1</td>
<td>NA</td>
<td>CSII</td>
<td>NR</td>
<td>4</td>
</tr>
<tr>
<td>Boehm et al., 2002</td>
<td>88/102 &gt; 18 NR ≤ 11.0% ≤ 35 PS</td>
<td>PS</td>
<td>R2 B0 W1</td>
<td>NA</td>
<td>CSII</td>
<td>NR</td>
<td>4</td>
</tr>
<tr>
<td>Bott et al., 2003</td>
<td>283/141 36.9 12.4 7.5 24.3</td>
<td>PS</td>
<td>R1 B0 W0</td>
<td>NA</td>
<td>MDI (NPH)</td>
<td>NR</td>
<td>6</td>
</tr>
<tr>
<td>Chen et al., 2006</td>
<td>27 44.8 19.5 NR 24.4 CO</td>
<td>PS</td>
<td>R1 B0 W1</td>
<td>NA</td>
<td>BiBpic</td>
<td>NR</td>
<td>2 × 3</td>
</tr>
<tr>
<td>Cherubini et al., 2006</td>
<td>30 8.1 5.2 7.5 18</td>
<td>PS</td>
<td>R1 B0 W0</td>
<td>NA</td>
<td>MDI (NPH)</td>
<td>NR</td>
<td>4.5</td>
</tr>
<tr>
<td>Dunne et al., 2007</td>
<td>26/26 5 1.8 7.8 NR CO (no wash-out period)</td>
<td>CO (4-week wash-out)</td>
<td>R1 B0 W0</td>
<td>NA</td>
<td>MDI (NPH)</td>
<td>NR</td>
<td>2 × 3</td>
</tr>
<tr>
<td>DeVries et al., 2003</td>
<td>186/181 36.9 14.9 8.38 25.5</td>
<td>PS</td>
<td>R2 B0 W1</td>
<td>A</td>
<td>MDI (NPH)</td>
<td>NR</td>
<td>16</td>
</tr>
<tr>
<td>Heller et al., 2004</td>
<td>155 35.7 ≥ 2 8.6 24</td>
<td>CO (4-week wash-out)</td>
<td>R2 B1 W1</td>
<td>A</td>
<td>MDI (NPH)</td>
<td>NR</td>
<td>2 × 4</td>
</tr>
<tr>
<td>Home et al., 1998</td>
<td>104 34.3 14.8 7.1 25.3 CO</td>
<td>CO</td>
<td>R1 B1 W1</td>
<td>NC</td>
<td>MDI (NPH)</td>
<td>NR</td>
<td>2 × 1</td>
</tr>
<tr>
<td>Home et al., 2000</td>
<td>707/358 38 15 7.97 25 PS</td>
<td>PS</td>
<td>R1 B0 W1</td>
<td>NA</td>
<td>MDI (NPH)</td>
<td>PMG</td>
<td>6</td>
</tr>
<tr>
<td>Iwamoto et al., 2001</td>
<td>143/62 33.4 10.6 7.5 22.0</td>
<td>PS</td>
<td>R1 B0 W0</td>
<td>NC</td>
<td>MDI (NPH)</td>
<td>NR</td>
<td>6</td>
</tr>
<tr>
<td>Mathiesen et al., 2007</td>
<td>157/165 29.0 12.0 6.9 24.7</td>
<td>PS</td>
<td>R2 B0 W0</td>
<td>NC</td>
<td>MDI (NPH)</td>
<td>PMG, PPG</td>
<td>9</td>
</tr>
<tr>
<td>Mortensen et al., 2006</td>
<td>86/81 14.4 NR 9.6 21.2</td>
<td>PS</td>
<td>R1 B0 W0</td>
<td>NC</td>
<td>BiBpic</td>
<td>FBG, PPG</td>
<td>4</td>
</tr>
<tr>
<td>Raskin et al., 2001</td>
<td>596/286 39.2 15.7 7.9 25.6</td>
<td>CO</td>
<td>R1 B0 W1</td>
<td>NC</td>
<td>MDI (NPH)</td>
<td>NR</td>
<td>6</td>
</tr>
<tr>
<td>Tamas et al., 2001</td>
<td>213/213 36 14.10 8.325 24.1</td>
<td>PS</td>
<td>R2 B0 W0</td>
<td>A</td>
<td>MDI (NPH)</td>
<td>PMG, PPG</td>
<td>3</td>
</tr>
</tbody>
</table>

CO: crossover study; PS: parallel study; R: randomization; R1: random allocation performed; R2: random allocation with appropriate method of randomization; B: blinding; B0: no double-blind; B1: double-blind; B2: double-blind with adequate blinding method; W: withdrawal; W0: no information on reasons for withdrawal; W1: information on reasons for withdrawal provided; A: adequately reported; NA: not adequately reported; NC: not clear; MDI: multiple daily insulin injections; CSII: continuous subcutaneous insulin infusion; NPH: neutral protamine Hagedorn; NR: not reported; FBG: fasting blood glucose; PPG: postprandial glucose; PMG: premeal glucose.
3.1.2. Outcomes

HbA1c levels were measured in 16 studies, but only 13 of them were included in the meta-analysis. Three trials [20,30,31] were not included due to a lack of sufficient numerical data. Of the 13 included trials, five reported significant improvements in HbA1c with IAsp, whereas the remaining eight detected no differences between treatment groups. The pooled results of all 13 studies showed that IAsp decreased HbA1c levels by −0.11% (95% CI: −0.16 to −0.06; Fig. 2). No heterogeneity was observed among these trials [Cochran Q = 14.55 (df = 12); \( P = 0.27 \); \( I^2 = 17.5\% \)], but they differed in terms of insulin regimens. In nine trials, a basal–bolus regimen based on NPH insulin or a long-acting insulin analogue was used; in two studies, IAsp was compared with RHI administered as CSII and, in two others, biphasic insulin aspart (BIAsp) was compared with biphasic human insulin (BHI). Despite the statistical homogeneity between trials, a subgroup meta-analysis was performed, and revealed differences favouring IAsp given as CSII (WMD = −0.31%; 95% CI: −0.55 to −0.08) and as the basal–bolus subgroups (WMD = −0.12%; 95% CI: −0.17 to −0.06), whereas no differences were found between mixtures (WMD = 0.18%; 95% CI: −0.03 to 0.39).

Self-measured PPG after the three main meals was reported in ten studies; however, only five studies were pooled for post-breakfast and post-lunch glucose levels, and six for post-dinner levels. The remaining studies were excluded from the meta-analysis due to a lack of sufficient numerical data. The meta-analyses showed significant differences in PPG after breakfast, lunch, and dinner with IAsp (Table 2). In all except one study, blood PPG was measured 90 min after meals; in the one exception, data for PPG time of measurement were not provided [29]. Thus, in the sensitivity analysis, SMD was calculated instead of WMD. The meta-analyses were also carried out after exclusion of the results obtained by Arslanian et al. [29]. In these analyses, PPG results significantly favoured IAsp (data not shown). In a few small studies, data were expressed as the daily PPG increment [18,26,31,32] but, due to methodological reasons, their results were not pooled with PPG levels after meals.

FG was reported in 12 studies, and three showed RHI superiority over IAsp; in the remaining nine studies, the differences were not significant. Five studies provided numerical data for pooling the results, whereas four of them found no differences in FG between treatment groups. The combined results also showed no differences between groups, although statistical

Table 2
Summary of the pooled results for fasting glucose (FG), postprandial glucose (PPG) and hypoglycaemic episodes in type 1 (T1DM) and type 2 (T2DM) diabetes patients.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies (n)</th>
<th>Patients (n)</th>
<th>Estimates [95% CI]</th>
<th>Reference number</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1DM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBG</td>
<td>5</td>
<td>2820</td>
<td>−1.43 [−1.75; −1.11]</td>
<td>[25,28,29,31,32]</td>
</tr>
<tr>
<td>PLG</td>
<td>5</td>
<td>2712</td>
<td>−1.11 [−1.61; −0.61]</td>
<td>[25,28,31,33]</td>
</tr>
<tr>
<td>PDG</td>
<td>6</td>
<td>3138</td>
<td>−0.97 [−1.25; −0.69]</td>
<td>[25,28,31–33]</td>
</tr>
<tr>
<td>FG</td>
<td>5</td>
<td>2138</td>
<td>0.15 [−0.55; 0.86]</td>
<td>[20,25,28,32,33]</td>
</tr>
<tr>
<td>All hypoglycaemic episodes</td>
<td>6</td>
<td>2220</td>
<td>1.06 [1.01;1.10]</td>
<td>[20,28–30,32,36]</td>
</tr>
<tr>
<td>Nocturnal hypoglycaemic episodes</td>
<td>3</td>
<td>2065</td>
<td>0.67 [0.54;0.83]</td>
<td>[21,28,31]</td>
</tr>
<tr>
<td>Severe hypoglycaemic episodes</td>
<td>7</td>
<td>2358</td>
<td>0.92 [0.75;1.12]</td>
<td>[21,24,27,28,30,32,36]</td>
</tr>
<tr>
<td><strong>T2DM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPG (daily mean)</td>
<td>3</td>
<td>134</td>
<td>−1.18 [−1.88; −0.47]</td>
<td>[40,41,45]</td>
</tr>
<tr>
<td>PBG</td>
<td>3</td>
<td>512</td>
<td>−0.83 [−1.45; −0.21]</td>
<td>[40–42]</td>
</tr>
<tr>
<td>PLG</td>
<td>2</td>
<td>225</td>
<td>−1.32 [−2.16; −0.49]</td>
<td>[37,41]</td>
</tr>
<tr>
<td>All hypoglycaemic episodes</td>
<td>5</td>
<td>882</td>
<td>1.04 [0.92;1.17]</td>
<td>[38,39,42–44]</td>
</tr>
<tr>
<td>Nocturnal hypoglycaemic episodes</td>
<td>1</td>
<td>93</td>
<td>0.65 [0.28;1.48]</td>
<td>[43]</td>
</tr>
<tr>
<td>Severe hypoglycaemic episodes</td>
<td>2</td>
<td>206</td>
<td>0.67 [0.17;2.53]</td>
<td>[39,44]</td>
</tr>
</tbody>
</table>

PBG: post-breakfast glucose; PLG: post-lunch glucose; PDG: post-dinner glucose.
heterogeneity was observed \[\text{Cochrane } Q = 14.69 \text{ (df = 4); } P = 0.0054; I^2 = 72.8\%\].

The Diabetes Treatment Satisfaction Questionnaire (DTSQ) was used to assess treatment satisfaction in three studies, but the part concerning treatment flexibility was assessed in only two of them. Patients in the IAsg group scored significantly better for total DTSQ (SMD = 0.30; 95% CI: 0.20 to 0.40) as well as for DTSQ treatment flexibility (WMD = 0.31; 95% CI: 0.15 to 0.47). Meta-analysis for QOL was not possible due to a lack of pertinent data, as QOL was evaluated in only two of the identified studies. Also, statistically significant superiority of IAsg was found, using the Diabetes-Specific Quality-of-Life Scale (DSQOLS), in only one study in the part of the DSQOLS concerning dietary restrictions, where a slight, but significant, improvement in QOL was reported in 23% of the IAsg group and in 14% of the RHI group [19]. The other study reported no statistical difference in QOL based on the Diabetes Health Profile (DHP) questionnaire.

Data for the incidence of hypoglycaemic episodes were reported in seven trials, in one of which the incidence of overall hypoglycaemia was significantly lower in the RHI group. In the remaining six studies, no differences were detected. In these studies, hypoglycaemic episodes were reported by patients in their diaries. Our meta-analysis, which included these six studies, revealed a significantly higher rate of hypoglycaemic episodes with IAsg (number needed to harm: 23.72; 95% CI: 13.03 to 131.37), with an RR of 1.06 (95% CI: 1.01 to 1.10). Severe hypoglycaemic episodes were reported in eight trials, but none of them revealed any differences between treatment groups. The pooled results of the seven of these eight trials with sufficient numerical data also showed no significant differences between the IAsg and RHI groups.

In three studies, nocturnal hypoglycaemic episodes were recorded and, in two of them, a significantly lower risk of those episodes was observed with IAsg. The meta-analysis incorporating all three studies revealed a risk reduction of 0.33 (95% CI: 0.17 to 0.46) with IAsg (Table 2).

Data on body mass changes were reported in six studies, although none of them reported any differences between treatments in either body mass index (BMI) or weight gain. However, as in only one of these studies were all of the important numerical values (means and standard deviation or CI) available, meta-analysis was not possible.

### 3.2. T2DM studies

#### 3.2.1. Study characteristics

A total of 11 trials included adult patients with T2DM [18,33–42]. Mean baseline HbA1c ranged from 7.3% [41] to 9.8% [33], and mean baseline BMI was between 28 kg/m² [41]...
Table 3
Studies included in the systematic review for patients with type 2 diabetes (T2DM).

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients’ characteristics at baseline</th>
<th>Study design</th>
<th>Allocation concealment</th>
<th>Insulin regimen</th>
<th>Treatment target</th>
<th>Treatment duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients (n/n)</td>
<td>Age (years)</td>
<td>Diabetes duration (years)</td>
<td>HbA1c (%)</td>
<td>BMI (kg/m²)</td>
<td>Jadad et al.</td>
</tr>
<tr>
<td>Abrahamian et al., 2005</td>
<td>89/88</td>
<td>62.5</td>
<td>11.1</td>
<td>9.8</td>
<td>28.1</td>
<td>PS</td>
</tr>
<tr>
<td>Boehm et al., 2002</td>
<td>88/102</td>
<td>&gt; 18</td>
<td>NR</td>
<td>≤ 11.0%</td>
<td>≤ 35</td>
<td>PS</td>
</tr>
<tr>
<td>Bretzel et al., 2004</td>
<td>75/80</td>
<td>61.7</td>
<td>NR</td>
<td>7.8</td>
<td>29.3</td>
<td>PS</td>
</tr>
<tr>
<td>Dashora et al., 2009</td>
<td>31/31</td>
<td>63.8</td>
<td>12</td>
<td>8.3</td>
<td>30</td>
<td>CO</td>
</tr>
<tr>
<td>Gallagher et al., 2005</td>
<td>21/66</td>
<td>66</td>
<td>11</td>
<td>7.8</td>
<td>30</td>
<td>CO (no wash-out period)</td>
</tr>
<tr>
<td>Gallagher et al., 2007</td>
<td>18</td>
<td>65</td>
<td>13</td>
<td>7.8</td>
<td>32</td>
<td>CO</td>
</tr>
<tr>
<td>Iwamoto et al., 2003</td>
<td>321</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>PS</td>
</tr>
<tr>
<td>Kilo et al., 2003</td>
<td>46/47</td>
<td>56.3</td>
<td>9.4</td>
<td>9.4</td>
<td>30.5</td>
<td>PS</td>
</tr>
<tr>
<td>McNally et al., 2007</td>
<td>80/80</td>
<td>62.25</td>
<td>11.8</td>
<td>7.5</td>
<td>30.1</td>
<td>CO (no wash-out period)</td>
</tr>
<tr>
<td>Pala et al., 2007</td>
<td>25/25</td>
<td>65</td>
<td>17.5</td>
<td>7.3</td>
<td>27.7</td>
<td>CO (no wash-out period)</td>
</tr>
<tr>
<td>Raskin et al., 1999</td>
<td>91/91</td>
<td>NR</td>
<td>NR</td>
<td>8.0</td>
<td>NR</td>
<td>PS</td>
</tr>
</tbody>
</table>

CO: crossover study; PS: parallel study; NR: not reported; A: adequately reported; NA: not adequately reported; NC: not clear; R: randomization; R1: random allocation performed; R2: random allocation, with appropriate method of randomization; B: blinding; B0: no double-blind; B1: double-blind; B2: double-blind with adequate blinding method; W: withdrawal; W0: no information on reasons for withdrawal; W1: information on reasons for withdrawal provided; MDI: multiple daily insulin injections; NPH: neutral protamine Hagedorn; FG: fasting glucose; PMG: premeal glucose; PPG: postprandial glucose.
and 32 kg/m² [36]. Six studies were RCTs with a parallel design and five were RCTs with a crossover design. However, only two studies were double-blind [37,40], and adequate allocation concealment was provided in only one of these 11 studies [40]. In all of these studies, insulin was administered by subcutaneous injection: in five studies, patients received either BIAsp or BHI, while six trials compared IAasp with RHI in a basal–bolus regimen (MDI). In most of the trials, insulin doses were adjusted according to target values of FG, preprandial glucose and PPG levels, although none of them used HbA1c as a primary treatment target (Table 3). PPG and FG were self-measured by patients, and all hypoglycaemic episodes were recorded in their diaries.

3.2.2. Outcomes

HbA1c levels were reported in ten studies, but one of them [39] was not included in the meta-analysis due to a lack of numerical data. Of the nine meta-analyzed trials, all except one reported no statistical superiority of IAasp over RHI in lowering HbA1c. In addition, the meta-analysis revealed no significant differences in HbA1c between the IAasp and RHI groups (Fig. 3), and no significant heterogeneity was observed across these trials [Cochran Q = 13.14 (df = 8); P = 0.107]. Sensitivity analysis pooled the results of all studies except one (McNally et al. [40]), in which all participants used a continuous glucose monitoring system (CGMS). After excluding the latter study’s results from the meta-analysis, a significant difference with IAasp was demonstrated (WMD = −1.18 mmol/L; 95% CI: −1.88 to −0.47). Glucose was measured 2 h after meals in two studies, and after 90 min in one. In the sensitivity analysis, SMD showed better results for IAasp than for RHI (data not shown). Meta-analysis of glucose levels after breakfast and lunch showed significant differences with IAasp, whereas a lack of sufficient data for pooling prevented PPG analysis after dinner. FG was reported in four studies, two of which showed a significant superiority of RHI over IAasp, and the combined results were associated with a significant difference with RHI. However, there were no differences in the risk for either hypoglycaemic episodes (RR = 1.04; 95% CI: 0.92 to 1.17) or severe hypoglycaemic episodes between the analyzed treatment groups. Nocturnal hypoglycaemic events were reported in only one study, which revealed no difference between IAasp and RHI (Table 2). No studies of treatment satisfaction and QOL in T2DM patients were identified.

Data for body mass were reported in only three studies. In all of them, weight gains were numerically lower in the IAasp group than in the RHI group. In one study, no significant differences between groups were observed while, in the other two studies, no statistical analyses were performed. Thus, meta-analysis was not possible due to incomplete data.

4. Discussion

Meta-analysis is a scientific tool that can help to answer important clinical questions concerning, for example, the differences in efficacy and safety between alternative therapeutic approaches. The studies included in the present meta-analyses were found using a systematic literature review that searched several medical databases (MEDLINE, EMBASE, the Cochrane
in HbA1c levels favouring IAsp. In the present study, a larger number of clinical trials have been included. In addition, analyses of subgroups in the studies were performed according to therapeutic approaches and methodological design. Also, PPG—an endpoint not discussed by Singh et al. [43]—was evaluated in the present meta-analyses. As expected, a statistically significant PPG reduction was found in the groups receiving IAsp. The included studies were relatively homogeneous as to the time of glycaemic measurement—90 min after a meal in most cases. In addition, in T1DM patients, the results were presented in two ways. Four studies reported mean daily PPG increments, representing the difference between PPG and preprandial glucose levels. However, as these studies were relatively small, the results are imprecise. A more reliable conclusion, based on ten trials (involving greater than 3000 patients), can be drawn based on the PPG reported after breakfast, lunch and dinner separately. After each of these main meals, PPG was significantly lower in the IAsp group than in the controls. The between-group difference was largest after breakfast (−1.4 mmol/L) and smallest after dinner (−0.97 mmol/L). In some included trials, values for PPG were reported only after selected meals, while insignificant differences were mentioned without numerical data, thus making pooling impossible. This may have led to an unintentional reporting bias and overestimation of IAsp superiority in lowering PPG.

Results similar to those published by Singh et al. [43] were also obtained, suggesting no differences between IAsp and RHI as regards their effects on severe hypoglycaemic episodes in T1DM. However, the risk of nocturnal hypoglycaemia was found to be lower in the IAsp group than in the RHI group, irrespective of the type of insulin therapy (basal–bolus or CSII). While, the authors of the previous meta-analysis identified only one study reporting a benefit with IAsp over RHI in a CSII regimen for hypoglycaemia during the night. In addition, the present meta-analysis evaluated the effects of insulin on all hypoglycaemic episodes, which was not discussed by Singh et al. [43]. Surprisingly, this showed a moderate risk increase in the IAsp group compared with the RHI group.

Pooling the results of the 11 T2DM RCTs suggested no statistically significant difference between IAsp and RHI in changing HbA1c levels. It is also worth noting that one study used CGMS, which does not reflect the current clinical practices (low external validity of the study) [40]. There were also significant differences in favour of IAsp in the present meta-analysis including all relevant studies except for McNally et al. [40]. In addition, the review articles published so far reported unequivocal conclusions as to the effect of analogues on HbA1c reduction in T2DM patients. Mannucci et al. [12] demonstrated that the use of RAAs instead of RHI makes it possible to reduce HbA1c by an additional 0.4%. However, in contrast to our present research, their study was not systematic and was based on only a small number of publications. Although all three RAAs (aspart, lispro and glulisine) were evaluated as a single group, only 11 trials were included, whereas the present meta-analysis considered 11 studies of IAsp alone. In the review by Singh et al. [43], which was also based on a systematic literature search, IAsp as well as insulin lispro were evaluated separately. They found no statistically significant differences between IAsp and RHI with respect to HbA1c reduction in T2DM patients; however, only six RCTs of IAsp were included in that study. The Singh et al. meta-analysis also lacked PPG data. In our systematic review of T2DM patients, as with T1DM, a difference in favour of IAsp was observed with respect to PPG. Furthermore, meta-analyses performed for mean daily PPG, and post-breakfast and post-lunch glucose also revealed differences favouring IAsp. However, due to insufficient numerical data in the included trials, it was not possible to pool the results for post-dinner glucose.

The validity of the results of a meta-analysis depends on the quality of the included studies. In most of the studies in the present analysis, no blinding or allocation concealment was applied, which might be a source of bias. On the other hand, double-blind studies involving insulin with different pharmacokinetic properties, such as time of action onset, may be open to criticism on ethical grounds. It should also be noted that the data reported in some studies were incomplete. While HbA1c levels were measured in most studies, data for PPG or the risk of hypoglycaemic episodes were reported in only some of the published reports. However, a major advantage of the present research is our systematic approach to the problem: all available RCTs comparing IAsp and RHI were included, regardless...
of differences in baseline characteristics, insulin treatment regimens or quality of methodology. Also, to verify the effect of potential confounders on the final results, a sensitivity analysis, consisting of a series of meta-analyses, was performed, and it was demonstrated that the results of the stratified meta-analyses were, in most cases, in accordance with the results of the meta-analyses that included all of the available trials. However, one exception was the insulin treatment regimen for T1DM patients, in whom HbA1c reductions were observed in a subpopulation treated with intensive insulin therapy (CSI or MDI), whereas no differences were found between BIAsp and BHI.

When choosing between insulin analogues and RHI, not only should their differences in glycaemic control and treatment flexibility be considered, but also their oncogenic safety, cost of treatment, type of diet and patients’ preferences. Indeed, studies in vitro [44] have suggested that insulin aspart has slightly less mitogenic potency, although it is unclear whether these differences are clinically relevant.

The cost of insulin analogues is still higher than that of human insulin, although a model-based evaluation has demonstrated that treatment with IAAsp can be a cost-effective option; in some countries, it was even cost-saving, mostly due to an improved QOL and a reduced cost related to diabetes complications. In fact, IAAsp was found to be more effective and less costly than treatment with RHI in Canadian (T1DM), Swedish and Spanish (T2DM) settings [45,46]. Pharmacoeconomic studies carried out in other countries and for different patient subgroups have also revealed similar results in most, but not all, populations [45–49].

5. Conclusion

Analyses based on a systematic review of the literature show that, in T1DM patients, treatment with IAAsp resulted in moderately better metabolic control, as demonstrated by reductions in HbA1c and PPG, and no change in FG. It was also established that using IAAsp instead of RHI resulted in greater treatment satisfaction and a significant reduction for nocturnal hypoglycaemic episodes, but not severe hypoglycaemias or hypoglycaemia in general. In T2DM patients, the present meta-analysis showed some improvement in PPG, but not for the other outcomes.

Conflicts of interest statement

M.T.M. has received fees from Novo Nordisk Poland for lectures and advisory board membership. P.R., O.P., A.K. and K.L. have received fees from HTA Consulting for scientific projects (such as systematic reviews and meta-analyses) financed by Novo Nordisk, Sanofi-Aventis and Eli Lilly. I.S.B. is employed by Novo Nordisk Poland.

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