

# Insulin Aspart in the Management of Diabetes Mellitus: 15 Years of Clinical Experience

Kjeld Hermansen<sup>1</sup> · Mette Bohl<sup>1</sup> · Anne Grethe Schioldan<sup>1</sup>

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**Abstract** Limiting excessive postprandial glucose excursions is an important component of good overall glycemic control in diabetes mellitus. Pharmacokinetic studies have shown that insulin aspart, which is structurally identical to regular human insulin except for the replacement of a single proline amino acid with an aspartic acid residue, has a more physiologic time–action profile (i.e., reaches a higher peak and reaches that peak sooner) than regular human insulin. As expected with this improved pharmacokinetic profile, insulin aspart demonstrates a greater glucose-lowering effect compared with regular human insulin. Numerous randomized controlled trials and a meta-analysis have also demonstrated improved postprandial control with insulin aspart compared with regular human insulin in patients with type 1 or type 2 diabetes, as well as efficacy and safety in children, pregnant patients, hospitalized patients, and patients using continuous subcutaneous insulin infusion. Studies have demonstrated that step-wise addition of insulin aspart is a viable intensification option for patients with type 2 diabetes failing on basal insulin. Insulin aspart has shown a good safety profile, with no evidence of increased receptor binding, mitogenicity, stimulation of anti-insulin antibodies, or hypoglycemia compared with regular human insulin. In one meta-analysis, there was evidence of a lower rate of nocturnal hypoglycemia compared with regular human insulin and, in a trial that specifically included patients with a history of recurrent hypoglycemia, a significantly lower rate of severe

hypoglycemic episodes. The next generation of insulin aspart (faster-acting insulin aspart) is being developed with a view to further improving on these pharmacokinetic/pharmacodynamic properties.

## Key Points

Insulin aspart has an improved pharmacokinetic profile compared with regular human insulin and thus demonstrates a greater glucose-lowering effect.

The safety and efficacy of insulin aspart has been demonstrated via randomized controlled trials in diverse patient populations with type 1 or type 2 diabetes mellitus.

Step-wise intensification is an appropriate treatment option with insulin aspart.

There is some evidence that patients with a history of recurrent hypoglycemia may have a lower incidence of severe episodes using insulin aspart.

## 1 Introduction

Recent global data continue to confirm that the number of people with diabetes mellitus is increasing worldwide, with 387 million people (8.3 % of the world's population) living with diabetes in 2014 [1]. Landmark trials such as the Diabetes Control and Complications Trial (DCCT) and its observational follow-up trial (Epidemiology of Diabetes

✉ Kjeld Hermansen  
kjeld.hermansen@aarhus.rm.dk

<sup>1</sup> Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Tage-Hansens Gade 2, 8000 Aarhus C, Denmark

Interventions and Complications; EDIC) in type 1 diabetes (T1D) [2–6] and the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetes (T2D) [7–9] have demonstrated the importance of achieving glycemic control as close to the non-diabetic range as safely as possible in order to reduce the risk of microvascular complications. Implications for preventing macrovascular disease are less clear, as subsequent randomized trials have produced results challenging the idea that aggressive glucose control should be pursued in all patients due to increased risk of adverse events [10–15]. Thus, guidelines recommend that the decision to pursue tight glucose control in T2D, typically as measured by glycated hemoglobin (HbA<sub>1c</sub>), is one that should be tailored carefully to individual patients [16]. Early intensive therapy may be more suitable for younger patients with a shorter duration of disease, with less aggressive therapy being considered for older patients with long-standing diabetes and a history of cardiovascular disease (CVD) or other comorbidities [11–13, 16, 17].

A limitation of using HbA<sub>1c</sub> to assess the adequacy of glycemic control is that patients may have acceptable overall HbA<sub>1c</sub> levels while still experiencing excessive elevations in postprandial glucose. The relative contribution of postprandial glucose excursions to overall hyperglycemia has been shown to be predominant in those patients with better glycemic control, in contrast to elevations in fasting blood glucose (FBG), which increases in contribution when patients have poorer control as measured by higher HbA<sub>1c</sub> [18]. Some studies have indicated that postprandial glucose is a predictor of CVD or mortality independent of fasting glucose levels [19–24]; however, the current evidence for this is still highly controversial [25].

At concentrations found in pharmaceutical formulations, monomers of regular human insulin (RHI) form dimers, which in the presence of zinc ions at neutral pH tend to assemble into larger hexamers [26, 27]. This self-assembly has the undesirable effect of delaying absorption after subcutaneous (SC) injection, as the hexamers must first dissociate before they can be absorbed into the bloodstream via capillaries in the SC tissue [28]. Delayed absorption of RHI can fail to prevent excessive postprandial glucose excursions, resulting in suboptimal glycemic control. Prolonged duration of action could lead to delayed hypoglycemia, including nocturnal episodes [29, 30]. The non-physiological action profile is also inconvenient for patients, who must inject 30 min prior to eating in order to better synchronize insulin availability with carbohydrate absorption [29, 31]. The rapid-acting analog, insulin aspart, introduced over 15 years ago, is formulated to attempt to overcome these limitations.

The goal of this review was to summarize 15 years of clinical experience with insulin aspart in diverse

populations of patients with T1D or T2D. We identified medical literature in the English language since 2002 using Medline and The Cochrane Library. EMBASE was searched from 2010. Bibliographical information and abstracts were also provided by Novo Nordisk. The index terms used in Medline, EMBASE, and The Cochrane Library were insulin aspart, diabetes mellitus, insulin analog, pharmacodynamics, pharmacokinetics, and therapeutic use. Searches were last updated 11 May 2015. Pharmacodynamic and pharmacokinetic data and primary studies in patients with type 1 or 2 diabetes mellitus or gestational diabetes mellitus who received insulin aspart were included. We excluded studies on insulin aspart used in co-formulation with insulin degludec, studies of biphasic insulin aspart, basal–bolus studies where basal insulins were different in each arm but insulin aspart was used as bolus insulin in both study arms, individual case reports, use of insulin aspart in short-term intensive therapy for newly diagnosed patients, studies focusing primarily on delivery devices or inhaled insulin, in-vitro studies focusing on analog measurement techniques for insulin analogs, and studies conducted in animals. We also excluded trials where multiple rapid-acting analogs were administered or where the primary goal was to compare basal insulins and the results for insulin aspart could not be isolated.

## 2 Pharmacokinetic and Pharmacodynamic Properties of Insulin Aspart

### 2.1 Structure

Insulin aspart is structurally identical to both RHI and endogenous insulin, except for replacement of a single proline amino acid at position 28 in the C-terminal area of the insulin B-chain with an aspartic acid residue [32, 33]. This substitution weakens the natural tendency towards self-association between insulin monomers, thereby inhibiting aggregation into hexamers and accelerating absorption after SC injection [26, 33]. Because the aspartic acid substitution on the B-chain does not involve the receptor portion of the insulin molecule, the structural change has no effect on the biological activity of insulin aspart in vivo [34].

### 2.2 Pharmacokinetics (PK)

#### 2.2.1 Comparison with Regular Insulin

The pharmacokinetics (PK) of insulin aspart in healthy volunteers, in patients with diabetes, and in special populations has been reviewed [35]. For example, early studies in healthy volunteers using the euglycemic clamp method

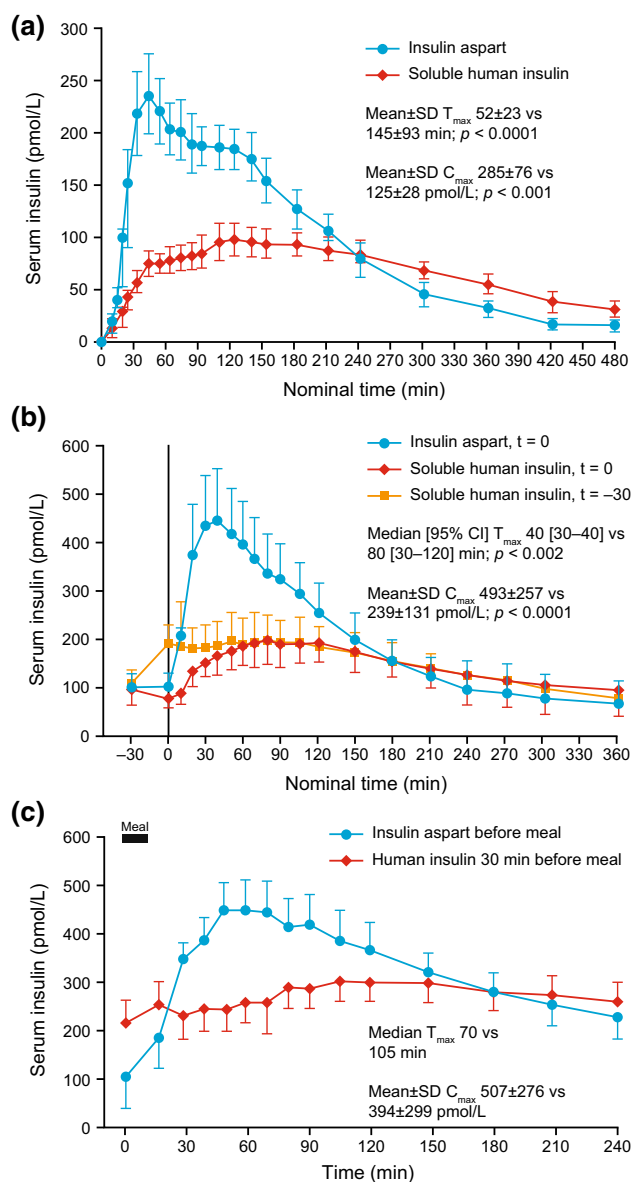
demonstrated that following injection into SC tissue, insulin aspart had faster absorption and higher peak serum levels than RHI [36–38]. A double-blind crossover study in 25 healthy men further demonstrated that the time–action profile of SC insulin aspart more closely resembled normal endogenous post-prandial release of insulin than RHI, achieving more than double the concentration and reaching maximum concentration ( $C_{\max}$ ) in less than half of the time [39] (Fig. 1a). Two studies in healthy Japanese males confirmed these PK properties [40].

These favorable PK trends are maintained in patients with T1D or T2D. In a double-blind, double-dummy crossover study in 22 people with T1D, insulin aspart administered immediately before a standard meal was compared with RHI administered immediately before or 30 min before a meal. The  $C_{\max(\text{insulin})}$  was almost twice as high for insulin aspart ( $p < 0.0001$ ), and time to maximum concentration ( $T_{\max(\text{insulin})}$ ) was reached at around 40 min after dosing for insulin aspart—approximately 60 and 40 min faster than RHI administered immediately before a meal or 30 min before a meal, respectively ( $p < 0.0001$  and  $p < 0.002$ ) [41] (Fig. 1b). Insulin aspart was also compared with RHI in a crossover study in 19 patients with T1D in which area under the concentration–time curve ( $AUC_{\text{insulin}}$ ) was measured after SC administration, combined with consuming a standardized test meal [42].  $AUC_{\text{insulin}}$  was significantly higher for insulin aspart compared with RHI at 0–4 and 0–6 h ( $p < 0.05$ ).

When 20 subjects with T2D were evaluated following a single test meal, it was found that the PK properties of insulin aspart were preserved, but the  $T_{\max}$  varied considerably among individual patients and was not correlated with dose in the range of 0.05–0.22 U/kg [43]. In a randomized, double-blind, crossover trial in 37 patients with T2D, serum insulin concentrations were measured for 240 min following meal ingestion [44] (Fig. 1c). Maximum serum insulin concentration and  $AUC_{\text{insulin}_{0-4\text{ h}}}$  were higher ( $p = 0.023$ ) and median time to maximum serum insulin concentration was 27 min shorter ( $p = 0.039$ ) for insulin aspart than for RHI.

A euglycemic clamp study in 20 non-diabetic subjects demonstrated that the more rapid absorption of insulin aspart compared with RHI was maintained regardless of site of administration (i.e., deltoid, abdomen, or thigh) [38]. However, it has been demonstrated that absorption may be impaired in lipohypertrophic tissue, with  $C_{\max}$  reduced by as much as 25 % in T1D [45].

Distributing the insulin injection volume over a broader area should theoretically enhance absorption. Two studies found improved PK with insulin aspart using a needle-free jet injector, which delivers insulin at high velocity, resulting in distribution over a larger tissue volume than a conventional pen device [46, 47]. Both were randomized,



**Fig. 1** Pharmacokinetics of insulin aspart compared with soluble/regular human insulin in **a** healthy volunteers ( $n = 19$ ), **b** patients with T1D ( $n = 22$ ) and **c** people with T2D ( $n = 37$ ).  $C_{\max}$  maximum concentration,  $SD$  standard deviation,  $t$  time, T1D type 1 diabetes, T2D type 2 diabetes,  $T_{\max}$  maximum time. **a** Reproduced with kind permission from Springer Science + Business Media: Home et al. [39]. **b** Reproduced with permission from American Diabetes Association. Diabetes Care, American Diabetes Association, 1999. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association [41]. **c** Reproduced with permission from Perriello et al. [44], copyright © 2005 John Wiley & Sons, Inc.

glucose clamp, crossover studies, the first in 18 healthy volunteers who received 0.2 U/kg insulin aspart delivered by each of the two devices [46]. The time to peak insulin concentration was >50 % shorter with the jet injector (31  $\pm$  3 vs 64  $\pm$  6 min,  $p < 0.0001$ ) and peak insulin

concentrations were significantly increased. The second study was conducted in 24 patients (12 with T1D and 12 with T2D) [47]. The time to peak insulin concentration was also shorter using the jet injector compared with the pen device in patients with diabetes ( $51.3 \pm 6.4$  vs  $91.9 \pm 10.2$  min;  $p = 0.003$ ). The peak insulin concentrations were similar with each method of administration for jet injector and pen device, respectively.

### 2.2.2 Comparison with Rapid-Acting Insulins

There are few head-to-head studies comparing the PK of insulin aspart with other rapid-acting insulin analogs. One randomized, double-blind study in 20 fasting healthy male volunteers compared insulin aspart and insulin lispro following a single SC injection [48]. Consistent with higher serum insulin concentrations, a stronger suppression of C-peptide was observed during the first 80 min after injection with insulin aspart compared with insulin lispro. This was in contrast to a randomized, single-blind, crossover study in 14 people with T1D [49] that showed similar peak concentrations for insulin aspart and insulin lispro, but more rapid increase and somewhat faster decline with insulin lispro following a standardized meal. A subsequent study in seven C-peptide-negative patients with T1D was conducted in a hospital setting, where they were fed a standardized evening meal and blood glucose (BG) was stabilized overnight with an intravenous (IV) infusion of regular insulin [50]. In that study, free serum insulin concentrations were similar for insulin aspart and insulin lispro, and the PK properties were indistinguishable. Another randomized, double-blind, glucose clamp, crossover trial in 24 patients with T1D showed equivalent PK profiles for insulin aspart and insulin lispro [51].

Insulin aspart and insulin glulisine were compared in a euglycemic clamp study in 12 healthy adult volunteers [52]. Rate of absorption was more rapid for insulin glulisine; however, those results concerning insulin concentrations should be interpreted with caution due to the different assays used. Insulin aspart was also compared with insulin glulisine in 30 insulin-naïve, obese patients with T2D in a randomized crossover study [53]. Subjects received their allocated insulin treatment 2 min prior to consuming a standardized meal. The peak insulin concentration was highest with insulin glulisine ( $p < 0.0001$ ).

## 2.3 Pharmacodynamics (PD)

### 2.3.1 Comparison with Regular Insulin

The faster absorption and higher peak concentration of insulin aspart compared with RHI results in an improved pharmacodynamic (PD) profile. As demonstrated during

several euglycemic clamp studies in healthy subjects, peak glucose infusion rates were significantly higher and occurred significantly earlier with insulin aspart than with RHI (Table 1) [34, 36–38, 40]. Nevertheless, there may be considerable variability in insulin action across patients. In one study of nine healthy volunteers, intra-individual variability in insulin action for both insulin aspart and human insulin was in the range of 10–30 %, even under strictly controlled conditions [54].

In order to examine the effect of high doses of insulin aspart, particularly during the late metabolic period, insulin aspart was compared with RHI using doses of 6, 12, and 24 (I)U in 16 healthy subjects during a randomized, double-blind, crossover study [30]. Results showed that insulin aspart had lesser late metabolic action than RHI at 12 and 24 (I)U ( $p < 0.05$ ). Duration of action was shorter at all three doses ( $p < 0.01$ ), and the early metabolic effect was also stronger for all three doses ( $p < 0.05$ ) compared with RHI.

In patients with T1D, insulin aspart demonstrates improved postprandial glucose lowering compared with RHI. In a crossover study of 22 subjects with T1D, serum glucose excursions were significantly lower with insulin aspart injected immediately before a meal ( $891 \pm 521$  mmol  $\times$  L<sup>-1</sup>  $\times$  min<sup>-1</sup>) compared with RHI administered immediately before eating ( $1311 \pm 512$  mmol  $\times$  L<sup>-1</sup>  $\times$  min<sup>-1</sup>,  $p < 0.0001$ ) or 30 min before eating ( $1106 \pm 571$  mmol  $\times$  L<sup>-1</sup>  $\times$  min<sup>-1</sup>,  $p < 0.02$ ) [41]. In a randomized, crossover study in 19 adults with T1D, both glucose  $C_{\max}$  and  $AUC_{0-4\text{ h}}$  were lower for insulin aspart than for RHI following a single standardized test meal (treatment ratio 0.80 [95 % CI 0.63–1.01];  $p < 0.05$ , and 0.76 [0.63–0.91];  $p < 0.05$ , respectively) [42].

Insulin aspart has also demonstrated an improved PD profile in people with T2D [44, 55, 56]. In one double-blind, crossover study, 25 patients with T2D received either insulin aspart immediately before a meal, or RHI administered either 30 min prior to or immediately before a meal [55]. Postprandial glucose [PPG] excursions, as estimated using the absolute incremental area over baseline ( $AUC_{\text{glucose}}$ ) was lower when insulin aspart was compared with RHI administered at mealtime ( $AUC_{\text{glucose}}$  899  $\pm$  609 vs 1102  $\pm$  497 mmol/L/min,  $p < 0.01$ ) but there was no difference when RHI was administered 30 min prior to mealtime ( $AUC_{\text{glucose}}$  868  $\pm$  374,  $p = 0.44$ ). Similarly,  $C_{\max}$  glucose was lower for insulin aspart compared with RHI at mealtime (10.8  $\pm$  2.2 vs 12.0  $\pm$  2.4 mmol/L,  $p < 0.02$ ), but not different when RHI was administered 30 min prior to mealtime (11.1  $\pm$  1.8 mmol/L,  $p = 0.97$ ). In another randomized, double-blind, crossover trial, insulin aspart at mealtime was compared with RHI injected 30 min prior to eating [44]. Results indicated that PPG excursions were 20 % lower with insulin aspart (treatment

**Table 1** Pharmacodynamic results from euglycemic clamp studies comparing insulin aspart with RHI in healthy male volunteers

Study	Number of subjects	Insulin	Peak glucose infusion rate (mg/min/kg) <sup>A</sup> ± SD	Time to peak glucose infusion (min) ± SD
Heinemann et al. 1993 [36]	14	Insulin aspart	12.2 ± 3.1 <sup>a</sup>	104 ± 27 <sup>b</sup>
		RHI	10.6 ± 2.7	165 ± 42
Heinemann et al. 1996 [37]	24	Insulin aspart	10.2 ± 2.3 <sup>c</sup>	105 ± 18 <sup>b</sup>
		RHI	8.4 ± 2.0	148 ± 27
Heinemann et al. 1998 [54]	19	Insulin aspart	11.2 ± 2.8	104 ± 16
		RHI	9.5 ± 2.3	156 ± 29
Mudaliar et al. 1999 [38]	20	Insulin aspart <sup>B</sup>		94 ± 46 <sup>b</sup>
		RHI <sup>B</sup>		173 ± 62
		Insulin aspart <sup>C</sup>		111 ± 59 <sup>b</sup>
		RHI <sup>C</sup>		192 ± 51
		Insulin aspart <sup>D</sup>		145 ± 122 <sup>a</sup>
		RHI <sup>D</sup>		193 ± 60
Engwerda et al. 2011 [46]	18	Insulin aspart (needle-free device)	6.49 ± 0.58	51 ± 3 <sup>d</sup>
		Insulin aspart (pen)	6.09 ± 0.56	105 ± 11

GIR glucose infusion rate, RHI regular human insulin, SD standard deviation

<sup>a</sup>  $p < 0.05$ ; <sup>b</sup>  $p < 0.001$ ; <sup>c</sup>  $p = 0.001$ ; <sup>d</sup>  $p < 0.0001$ , all vs comparator treatment

<sup>A</sup> After subtraction of mean baseline GIR

<sup>B</sup> Injected into abdomen

<sup>C</sup> Injected into deltoid

<sup>D</sup> Injected into thigh

ratio 0.80 [95 % CI 0.66–0.98];  $p = 0.034$ ), with maximum serum glucose levels being similar for the two treatments.

A randomized, placebo-controlled, crossover study examined the effect of a fixed, weight-based dose of insulin aspart on PPG in people with T2D in a real-life setting. Patients followed their typical diet and the effect on glucose fluctuation was evaluated using continuous glucose monitoring (CGM) [57]. A dose of 0.06 U/kg was chosen based on earlier work (described previously), and insulin aspart was administered 30 min prior to meals. Over a 24-h period, the duration of BG values >8 mmol/L was shorter for insulin aspart when compared with placebo ( $8.1 \pm 1.4$  vs  $12.7 \pm 1.3$  h, respectively;  $p < 0.03$ ) and the  $AUC_{\text{glucose} > 8 \text{ mmol/L}}$  was less for insulin aspart than for placebo ( $0.6 \pm 0.2$  mmol/L/h vs  $1.2 \pm 0.2$  mmol/L/h, respectively;  $p < 0.001$ ).

With the rationale that postprandial administration might allow for better matching insulin dose to actual carbohydrate intake, CGM in a hospital setting was used to compare PPG excursions with preprandial insulin aspart or postprandial insulin glulisine in 12 patients with T2D, all using insulin glargine once daily at bedtime [56]. Results indicated that multiple daily injections of either insulin aspart (−10 to 0 min) or insulin glulisine (0 to 5 min) resulted in similar daily BG excursions.

### 2.3.2 Comparison with Rapid-Acting Analogs

Head-to-head trials comparing insulin aspart to insulin lispro have generally shown comparable PD [50, 51]. In a randomized, double-blind crossover study in 20 healthy male volunteers, following a single injection of insulin aspart or insulin lispro, plasma glucose concentrations after 50 min were lower using insulin aspart when compared with insulin lispro ( $3.2 \pm 0.1$  vs  $3.5 \pm 0.1$  mmol/L, respectively;  $p = 0.026$ ) [48]. Blood glucose  $t_{\text{min}}$  was  $59.3 \pm 3.4$  min and  $63.5 \pm 5.3$  min, for insulin aspart and insulin lispro, respectively, which was not significantly different.

Insulin aspart and insulin glulisine were compared in a euglycemic clamp study in 12 healthy adult volunteers [52]. The area under the glucose infusion rate curve ( $AUC_{\text{GIR}_{0-30 \text{ min}}}$ ) indicated a greater early metabolic effect for insulin glulisine ( $30.3 \pm 26.4$  vs  $16.2 \pm 18.4$  mg/kg;  $p = 0.04$ ) and an earlier onset of action as indicated by time to 10 % of  $\text{GIR}_{\text{max}}$  (9 vs 17 min;  $p = 0.01$ ), which was consistent with the faster absorption discussed under PK. Insulin aspart was also compared with insulin glulisine in 30 insulin-naïve, obese patients with T2D in a randomized, crossover study [53]. Subjects received their allocated insulin treatment 2 min prior to consuming a standardized meal. The  $AUC_{\text{glucose}}$  during the first hour



after injection (149 vs 158 mg\*h/dL,  $p = 0.046$ ) as well as maximal glucose concentration (170 vs 181 mg/dL,  $p = 0.03$ ) was significantly lower with insulin glulisine. However, for the total study period of 360 min, plasma glucose concentration and glucose excursions were similar for the two treatments. A randomized, crossover study in 12 patients with T2D was conducted in a hospital setting to compare insulin aspart with insulin glulisine after a single bout of exercise [58]. Both insulins were injected SC immediately before breakfast. One hour after eating, subjects began controlled aerobic exercise on a bicycle. PPG levels were significantly lower in the insulin aspart group at 90, 120, and 150 min after exercise (all  $p < 0.05$ ), although the advantage was confined to patients with body mass index (BMI)  $< 25 \text{ kg/m}^2$ .

Finally, the PD findings comparing delivery of insulin aspart using a jet injector versus a pen device mirrored the improved PK findings [46, 47]. Results for the first study in healthy volunteers are shown in Table 1. In the second study, the glucose clamp technique was used to assess BG levels after a test meal. Jet injection reduced BG levels during the first hour after injection when compared with the pen device ( $154.3 \pm 20.8$  vs  $196.3 \pm 18.4 \text{ mmol} \cdot \text{min} \cdot \text{L}^{-1}$ , respectively;  $p = 0.041$ ), but there was no difference in BG levels over the next 5 h.

## 2.4 PK/PD in Special Populations

### 2.4.1 Elderly Patients

It is important to determine whether the faster absorption, shorter time to peak activity, and shorter duration of action of insulin aspart compared with RHI observed in younger people are maintained in the elderly, who may be more likely to have compromised renal or hepatic function. In one randomized, double-blind, crossover study, 19 elderly ( $\geq 65$  years) subjects with uncomplicated T2D were given a single injection of insulin aspart or RHI during a euglycemic clamp [59]. Insulin aspart was associated with higher early metabolic activity [ $\text{AUC}_{\text{GIR}} (0-120 \text{ min})$  ( $255 \pm 196$  vs  $110 \pm 68 \text{ mg/kg}$ ;  $p < 0.0001$ ) and  $\text{AUC}_{\text{GIR}} (0-300 \text{ min})$  ( $931 \pm 584$  vs  $677 \pm 407 \text{ mg/kg}$ ;  $p = 0.0001$ )] and lower late metabolic activity [ $\text{AUC}_{\text{GIR}} (300-600 \text{ min})$  ( $353 \pm 188$  vs  $683 \pm 372 \text{ mg/kg}$ ;  $p = 0.0006$ )] compared with RHI. As would be expected, PK parameters such as  $C_{\text{max}}$ ,  $T_{\text{max}}$ , and  $\text{AUC}_{\text{insulin}} (0-60, 0-120 \text{ and } 0-300 \text{ min})$  were higher for insulin aspart (all  $p < 0.01$ ).

In 19 patients with T2D (mean age  $72 \pm 1$  year), insulin aspart was given immediately prior to a liquid test meal or RHI 30 min prior [60]. Unlike the trial described above, the insulin and glucose profiles were nearly identical for the two insulins.

### 2.4.2 Children and Adolescents with Type 1 Diabetes

The PK/PD properties of insulin aspart are important to evaluate in children, particularly because PPG excursions may be marked, and clinical consequences of hypoglycemia of concern [61]. One randomized, double-blind, crossover study compared insulin aspart and RHI in nine children aged 6–12 years and nine adolescents aged 13–17 years [62]. Insulin aspart demonstrated a significantly shorter time to  $C_{\text{max}}$  than RHI [median (interquartile range)  $T_{\text{max ins}} 40.0$  (40–50) min vs 75.0 (60–120) min, respectively;  $p < 0.001$ ]. The maximum insulin concentration was higher for insulin aspart compared with RHI ( $p < 0.0001$ ), and was slightly greater in the older (13–17 years) age group, compared with children aged 6–12 years. With respect to PD, the estimated geometric mean ratio for  $\Delta C_{\text{max}}$  insulin aspart/RHI was 0.68 [95 % CI 0.47–0.99];  $p < 0.05$ . However,  $\Delta \text{AUC}_{\text{glucose } 0-4 \text{ h}}$  and  $T_{\text{max glucose}}$  were not significantly different.

### 2.4.3 In Continuous Subcutaneous Insulin Infusion

The time to steady-state concentration of insulin aspart in continuous subcutaneous insulin infusion (CSII) was studied in 10 healthy volunteers, 18–31 years of age, with or without an initial SC bolus [63]. The calculated steady-state concentration did not differ with use of an initial SC bolus, although use of a bolus resulted in an initial overshoot of insulin aspart with a significantly higher AUC ( $p < 0.001$ ). There was a non-significant trend towards longer time to steady state using a bolus compared with no bolus (233 vs 166 min, respectively;  $p = 0.068$ ). Mathematical modeling results suggested that time to achieve steady state concentration could be shortened by administration of a mean bolus of 0.89 U, compared with omitting the bolus.

In children, the effect of using a diluted (20 U/mL) concentration of insulin aspart compared with the standard concentration (100 U/mL) in CSII was evaluated to determine if dilution could accelerate absorption [61]. In this two-period, crossover study, eleven children aged 3.8–7 years were randomized to either diluted or standard concentrations of insulin aspart. There was no difference in  $T_{\text{max}}$  ( $p = 0.59$ ); however, the diluted formulation showed less inter-subject variability compared with the standard formulation (SD 8.7 vs 14.4 min, respectively;  $p = 0.047$ ). There was also no difference in metabolic clearance of insulin ( $p = 0.47$ ) and background plasma insulin concentration ( $p = 0.66$ ). Thus, given that the PK of insulin aspart remains unchanged in CSII after fivefold dilution, there may be some advantages in using a diluted solution to dampen variability in absorption for adolescents.

A retrospective study of 5804 plasma insulin measurements from 70 adults and children treated with CSII examined the reproducibility of insulin aspart PK [64]. There were no differences associated with gender, and <20 % of inter-subject variability in PK parameters was associated with gender, BMI, total daily insulin dose, HbA<sub>1c</sub>, and diabetes duration. Metabolic clearance rate was found to be highly reproducible. Bioavailability of insulin aspart was assessed when administered as SC bolus every hour, via CSII, or via continuous IV infusion [65]. Mean serum insulin aspart concentrations were not significantly different for the three modes of administration ( $p = 0.17$ ) and there was no difference in the AUC<sub>glucose infusion rate</sub> ( $p = 0.37$ ).

One randomized, crossover, euglycemic clamp study that used CSII in 17 adolescents with T1D compared the PD of insulin aspart with insulin lispro [66]. At days 1 and 4, there were no statistically significant differences in AUC<sub>GIR</sub>, GIR<sub>max</sub>, T<sub>max</sub> GIR, time to discontinuation of exogenous glucose, time to half-maximal increase of peak action or time to half-maximal decrease from peak action.

#### 2.4.4 In Obesity and Renal/Hepatic Impairment

It is important to assess whether obesity, renal and/or hepatic impairment might affect insulin absorption. In one study, several groups of patients were evaluated [67]. This included 23 T1D patients with BMI values >19 kg/m<sup>2</sup>, another group of 18 patients with T1D and varying degrees of renal function (normal renal function, mild renal impairment, moderate renal impairment, severe renal impairment not yet requiring hemodialysis), and a third group of 24 patients without diabetes but with varying degrees of hepatic impairment. Correlation and regression analyses indicated there were no clinically important relationships between insulin aspart PK and BMI, renal impairment, or hepatic impairment.

Insulin requirements of adult (20–85 years) patients were reported in an observational study of 346 people with T1D including 50 pump users and varying degrees of renal dysfunction determined as the estimated glomerular filtration rate (eGFR) [68]. Consistent with the results of Holmes et al. described above [67], there was no relationship between renal function and the requirements of short-acting insulin. However, results from insulin lispro users ( $n = 118$ ) indicated a significant relationship between dose and eGFR over the measured ranges: subjects with eGFR <60 mL/min required approximately 32.6 % less insulin lispro than those with normal renal function ( $p = 0.002$ ).

#### 2.4.5 In Pregnancy

In one short-term crossover study, PK and PD were assessed after a test meal (breakfast) in 15 women with

gestational diabetes treated with either no exogenous insulin, RHI, or insulin aspart [69]. The mean  $\pm$  SE peak insulin concentration was significantly lower during the meal in which no exogenous insulin was administered ( $72.6 \pm 9.7$   $\mu$ U/mL) than with either regular insulin ( $84.7 \pm 10.8$   $\mu$ U/mL;  $p = 0.034$ , compared with no insulin) or insulin aspart ( $95.9 \pm 10.9$   $\mu$ U/mL;  $p = 0.009$ ). AUC<sub>glucose</sub> at 120, 180, and 240 min was not significantly different when comparing RHI with no exogenous insulin, but AUC<sub>glucose</sub> for insulin aspart was lower compared with no insulin ( $p = 0.018$  and  $p = 0.005$ , for 180 and 240 min, respectively).

### 3 Clinical Efficacy of Insulin Aspart

As summarized in Table 2, numerous randomized trials as well as observational studies have been published describing the use of insulin aspart in basal–bolus regimens in patients with T1D and T2D, use with oral antidiabetic medications in T2D, or use with basal insulin used as needed in T2D. There are also numerous studies reporting efficacy of insulin aspart in CSII in comparison with RHI as well as other rapid-acting analogs (described in Table 3 and discussed separately). Studies done with the primary goal of comparing different basal insulins (e.g., insulin degludec vs insulin glargine) and in which insulin aspart was used in both trial arms are not discussed here.

#### 3.1 Patients with Type 1 Diabetes (T1D)

In studies in adult patients with T1D, in which insulin aspart was used in basal–bolus regimens and where both trial arms used neutral protamine Hagedorn (NPH) as the basal insulin, insulin aspart demonstrated improved PPG control compared with RHI after breakfast, lunch, and dinner [70–72], after breakfast and dinner [75], or after lunch and dinner [73] (Table 2a). In studies from 12 weeks to 3 years in duration, HbA<sub>1c</sub> was significantly lower in patients using insulin aspart compared with RHI [70, 71, 74, 75] (Table 2a). In three other trials involving adults, one of 8 weeks [76], one of 16 weeks [77] and one of 64 weeks [72], end-of-trial HbA<sub>1c</sub> was comparable in both treatment arms. End-of-trial HbA<sub>1c</sub> was significantly lower with insulin aspart in one 18-week study in which an all-analog regimen (insulin aspart + insulin detemir) was compared with RHI + NPH [78]. Results for adolescents are discussed in a later section, as are results using CSII.

#### 3.2 Patients with Type 2 Diabetes (T2D)

Studies using insulin aspart in patients with T2D are summarized in Table 2b. As these data demonstrate,

**Table 2** Efficacy of insulin aspart by injection in adults with (a) T1D, (b) T2D, (c) T1D or T2D

Study (duration)	No. of patients	Insulin treatment (baseline) <sup>A</sup>	Mean HbA <sub>1c</sub> at study end, % (baseline) ± SD	Mean FPG at study end, mmol/L (baseline FPG)	Postprandial plasma glucose at study end, mmol/L (baseline) <sup>A</sup> ± SD			
					O/TM	B	L	D
<b>(a) T1D: randomized studies</b>								
Home et al. (1998) (4 weeks) [73]	90	IAsp + NPH HI + NPH	7.88 (7.96) <sup>b,B</sup>	8.5 <sup>g,B</sup>		6.4	7.2	8.8 <sup>a,B</sup>
Home et al. (2000) (6 months) [70]	1065	IAsp + NPH HI + NPH	8.00 (7.98)	7.7	8.9 <sup>c,B</sup>	8.5	8.0 <sup>d,B</sup>	8.4 <sup>d,B</sup>
Home et al. (2006) (36 months; extension of Home et al. (2000) [74])	753	IAsp + NPH HI + NPH	7.97		10.1			9.0
Raskin et al. (2000) (24 weeks) <sup>C</sup> [71]	882	IAsp + NPH HI + NPH	7.78 (7.90) <sup>e,B</sup>		8.6 <sup>a,B</sup>	7.57 <sup>a,B</sup>		8.46 <sup>a,B</sup>
Raskin et al. (2000) (52 weeks) [71]	714	IAsp ± NPH HI ± NPH	7.93 (7.95)		10.2	8.96		9.29
Tamás et al. (2001) (12 weeks) <sup>C</sup> [75]	423	IAsp ± NPH HI ± NPH	7.91 (7.95) <sup>n,B</sup>	8.8	8.4 <sup>c,B</sup>	8.6 <sup>D</sup>		8.2 <sup>d,B</sup>
DeVries et al. (2003) (64 weeks) [72]	368	IAsp + NPH HI + NPH	8.02 (8.36) <sup>a,B</sup>	9.3	10.1	8.6 <sup>D</sup>		9.3
Hermansen et al. (2004) (18 weeks) [78]	595	IAsp + NPH HI + NPH	8.08	8.05	8.34 <sup>f,B</sup>	7.56 <sup>B</sup>		7.45 <sup>g,B</sup>
Heller et al. (2004) (16 weeks) [77]	155	IAsp + NPH HI + NPH	8.22	8.29	9.62	8.79		9.14
Brock Jacobsen et al. (2011) (crossover study, 8-week periods) [76]	16	IAsp + IDet HI + NPH	7.88 (8.48) <sup>g,B</sup>	7.58 (8.83)				
<b>(a) T1D: observational studies</b>								
Krzyniński et al. (2010) (single-arm, follow-up study, 13 weeks) [85]	950	IAsp + NPH or IDet (NPH or IDet)	7.48 ± 1.00 <sup>c,E</sup>	118.22 ± 27.60 <sup>c,E</sup>	7.68 ± 1.45 <sup>c,E</sup>	7.73 ± 1.45 <sup>c,E</sup>		7.61 ± 1.56 <sup>c,E</sup>
<b>(b) T2D: randomized studies</b>								
Bretzel et al. (2004) (3 months) [79]	231	IAsp ± NPH HI ± NPH HPI	Δ0.91 ± 1.00 (7.82) <sup>h,E</sup>	(161.70 ± 53.66)	(9.62 ± 3.19)	(9.59 ± 2.88)		(9.33 ± 2.69)
			Δ0.73 ± 0.87 (7.83)					
			Δ0.65 ± 1.10 (7.78) <sup>i,E</sup>					



**Table 2** continued

Study (duration)	No. of patients	Insulin treatment (baseline) <sup>A</sup>	Mean HbA <sub>1c</sub> at study end, % (baseline HbA <sub>1c</sub> ) ± SD	Mean FPG at study end, mmol/L (baseline FPG)		Postprandial plasma glucose at study end, mmol/L (baseline) <sup>A</sup> ± SD				
				O/TM	B	L	D			
Raslová et al. (2004) (22 weeks) [83]	395	IAsp + IDet HI + NPH	7.46 (8.16) 7.52 (8.08)	7.28 7.32						
Gallagher and Home (2005) (crossover study, 6 week periods) [80]	21	IAsp ± NPH HI ± NPH	7.04 (7.8) <sup>g,E</sup> 7.15 (7.8) <sup>g,E</sup>	7.9 ± 0.4 <sup>h,E</sup> 9.3 ± 0.4	9.2 ± 0.6 10.2 ± 0.6	7.1 ± 0.5 <sup>h,E</sup> 9.0 ± 0.6				
Gallagher and Home (2005) (crossover study, 6 week periods) [80]	18	IAsp HI	6.94 (7.8 ± 0.7) 7.07 (7.8 ± 0.7)	7.0 6.5						
Pala et al. (2007) (crossover study, 90 day periods) [82]	30	IAsp HI	7.3 <sup>a,E,B</sup> (7.8) 7.9 (7.7)	10.7 (11.3) 11.3 (11.6)	17.5 (22.1) 20.9 (20.2)					
Meneghini et al. (2011) (48 weeks) STEP-Wise trial [91]	296	SimpleSTEP ExtraSTEP	7.5 ± 1.1 (8.7 ± 1.0) 7.7 ± 1.2 (8.9 ± 1.2)	7.49 ± 2.78 (8.10 ± 2.89) 7.38 ± 2.89 (8.27 ± 2.89)	Δ -2.0 ± 2.0 Δ -1.77 ± 1.88					
Cucinotta et al. (2012) (26 weeks) [89]	4099	IAsp ± basal HI ± basal	7.63 (8.02) 7.6 (7.82)	Δ -11.8 Δ -6.3	Δ -7.2 Δ -5.8	Δ -8.0 Δ -5.0	Δ -6.5 Δ -3.7			
Herrmann et al. (2013) (24 months) [81]	29	IAsp ± IDet HI ± IDet	7.3 ± 0.9 <sup>a,E</sup> (8.7 ± 1.6) 7.2 ± 0.9 <sup>a,E</sup> (8.7 ± 1.6)							
Rodbard et al. (2014) (32 weeks) FullSTEP trial [92]	401	IAsp step-wise + IDet IAsp + IDet basal-bolus	Δ -0.98 (7.9 ± 0.6) Δ -1.12 (7.9 ± 0.6)	7.01 (7.0 ± 1.9) 7.12 (6.9 ± 1.6)	Δ1.28 <sup>k,E</sup> Δ1.64					
(b) T2D: observational studies										
Chlup et al. (2007) (before-after study, 52 weeks) [84]	57	IAsp (HI)	7.5 ± 0.20 (8.4 ± 0.23) <sup>g,E</sup>	9.7 (9.7)	10.6 (11.2)	10.3 (10.1)	10.4 (10.5)			
Krzyszmiń et al. (2010) (single-arm, follow-up study, 13 weeks) [85]	1332	IAsp + NPH or IDet	7.60 ± 0.90 <sup>c,E</sup> (8.81 ± 1.4)	6.94 ± 1.33 <sup>c,E</sup> (9.12 ± 2.40)	8.03 ± 1.44 <sup>c,E</sup> (2.41 ± 2.73)	8.35 ± 1.44 <sup>c,E</sup> (11.08 ± 2.75)	8.06 ± 1.42 <sup>c,E</sup> (10.49 ± 2.64)			
Randeree et al. (2013) (single arm, before/after study, 24 weeks; A <sub>1</sub> chieve study) [88]	Insulin-experienced: 561 Insulin-naïve: 1465	IAsp	7.4 <sup>g,E</sup> (9.1)	7.1 <sup>g,E</sup> (9.9)	9.9 <sup>g,E</sup> (13.4)					

Table 2 continued

Study (duration)	No. of patients	Insulin treatment (baseline) <sup>A</sup>	Mean HbA <sub>1c</sub> at study end, % (baseline HbA <sub>1c</sub> ) ± SD	Mean FPG at study end, mmol/L (baseline FPG)		Postprandial plasma glucose at study end, mmol/L (baseline) <sup>A</sup> ± SD	
				O/TM	B	L	D
Latif et al. (2013) (single-arm, before/after study, 24 weeks, A <sub>1</sub> chieve study) [87]	≤40 years: 571 >40–65 years: 2801 >65 years: 660	IAsp + basal (insulin-naïve)	7.4 <sup>C,gs,E</sup> (9.75)	Δ -4.4 ± 4.5 <sup>gs,E</sup> (11.3 ± 4.5)	Δ -5.9 ± 4.9 <sup>gs,E</sup> (14.8 ± 5.0)		
			7.4 <sup>C,gs,E</sup> (9.65)	Δ -3.9 ± 3.7 <sup>gs,E</sup> (10.9 ± 3.6)	Δ -5.5 ± 4.7 <sup>gs,E</sup> (14.4 ± 4.7)		
			7.4 <sup>C,gs,E</sup> (9.60)	Δ -3.6 ± 4.3 <sup>gs,E</sup> (10.7 ± 4.2)	Δ -5.6 ± 4.3 <sup>gs,E</sup> (14.7 ± 5.1)		
(c) T1D or T2D							
Gao et al. (2009) [143]	220	IAsp + NPH	7.7 ± 1.3 (9.3 ± 1.4)		Δ14.6 ± 5.3 <sup>dB</sup>		
		HI + NPH	7.7 ± 1.2 (9.2 ± 1.2)		Δ8.4 ± 4.1		

B after breakfast, D after dinner, FPG fasting plasma glucose, HI human insulin, HPI human premix insulin, IAsp insulin aspart, IDet insulin detemir, IGl<sub>1a</sub> insulin glulisine, L after lunch, NPH neutral protamine Hagedorn, O overall, SD standard deviation, T1D type 1 diabetes, T2D type 2 diabetes, TM test meal, SimpleSTEP addition of insulin aspart to the largest meal, ExtraSTEP addition of insulin aspart to meal with largest postprandial glucose increment, Δ mean change

<sup>a</sup>  $p < 0.05$ , <sup>b</sup>  $p < 0.02$ , <sup>c</sup>  $p < 0.0001$ , <sup>d</sup>  $p < 0.01$ , <sup>e</sup>  $p = 0.005$ , <sup>f</sup>  $p = 0.0029$ , <sup>g</sup>  $p < 0.0001$ , <sup>h</sup>  $p = 0.025$ , <sup>i</sup>  $p = 0.006$ , <sup>j</sup>  $p = 0.011$ , <sup>k</sup>  $p = 0.0459$ , <sup>m</sup>  $p = 0.02$ , <sup>n</sup>  $p = 0.046$

A Baseline value before switching in single-arm studies

B Between groups

C Additional data from review by Heller et al. [90]

D Data estimated from graph

E From baseline

**Table 3** Efficacy of insulin aspart in CSII therapy

Study (duration)	No. of patients	Insulin treatment (baseline) <sup>A</sup>	Mean HbA <sub>1c</sub> at study end, % (baseline HbA <sub>1c</sub> ) ± SD	Other endpoints (baseline) ± SD
<i>(a) Insulin aspart (CSII) vs MDI: randomized trials</i>				
De Vries et al. (2002) (crossover, 16-week periods) <sup>B</sup> [119]	79 Adults T1D	IAsp CSII IAsp + NPH	Δ -0.91 ± 1.28 <sup>a,C</sup> (9.27 ± 1.4) Δ -0.07 ± 0.70 (9.25 ± 1.4)	SD of 9-point SMBG values, -1.35 ± 1.88 mmol/L <sup>b,D</sup> SD of 9-point SMBG values, -0.40 ± 1.77 mmol/L
Raskin et al. (2003) (24 weeks) [117]	132 Adults T2D	IAsp CSII IAsp + NPH	7.6 ± 1.22 (8.2 ± 1.37) <sup>b,C</sup> 7.5 ± 1.17 (8.0 ± 1.08) <sup>b,C</sup>	PPG (90 min post-breakfast), 9.2 ± 2.6 mmol/L <sup>i,D</sup> PPG (90 min post-breakfast), 10.7 ± 3.6 mmol/L
Doyle et al. (2004) (16 weeks) [113]	32 Children (8–21 years) T1D	IAsp CSII IAsp + IGljar	7.2 ± 1.0 (8.1 ± 1.2) <sup>b,c,C,D</sup> 8.1 ± 1.2 (8.2 ± 1.1)	SMBG at lunch, dinner and bedtime were all significantly lower for IAsp CSII <sup>d,D</sup>
Hirsch et al. (2005) (crossover, 5-week periods) [115]	100 Adults T1D	IAsp CSII IAsp+IGljar	IAsp CSII IAsp+IGljar	Serum fructosamine, 343 ± 47 μmol/L <sup>g,D</sup> AUC <sub>glucose</sub> ≥140mg/dL, 464 ± 452 mg·h·sdL <sup>-1</sup> d <sup>i,D</sup> Serum fructosamine, 355 ± 50 μmol/L AUC <sub>glucose</sub> ≥140mg/dL, 777 ± 746 mg·h·sdL <sup>-1</sup>
Skogsberg et al. (2008) (24 months) [99]	72 Children (7–17 years) T1D	IAsp CSII IAsp MDI	6.5 ± 0.4 (8.2 ± 0.4) 6.7 ± 0.5 (8.4 ± 0.5)	Treatment satisfaction scores, 3.5 ± 0.5 <sup>k,D</sup> Treatment satisfaction scores, 2.5 ± 0.5
Pańkowska et al. (2010) (26 weeks) [98]	61 Children (<7 years) T1D	IAsp CSII IAsp+NPH BRHI+NPH	7.6 ± 0.6 (7.7 ± 0.7) 7.6 ± 0.9 (7.6 ± 0.8) 7.6 ± 1.0 (7.6 ± 1.1)	24 h AUC <sub>glucose</sub> , 200.1 ± 12.7 24 h AUC <sub>glucose</sub> , 219.8 ± 12.8 24 h AUC <sub>glucose</sub> , 211.8 ± 10.9
Bergental et al. (2010) (1 year) [112]	329 Adults T1D	IAsp CSII IAsp + IGljar MDI	Δ -1.0 ± 0.7 <sup>d,D</sup> (8.3 ± 0.5) Δ -0.4 ± 0.8 (8.3 ± 0.5)	Reach HbA <sub>1c</sub> ≤7.0 %, 57/166 (34 %) <sup>d,D</sup> Reach HbA <sub>1c</sub> ≤7.0 %, 19/163 (12 %)
Lv et al. (2013) (<2 weeks; time to reach glucose target) [118]	156 Children (7–18 years) T1D	IAsp CSII IAsp + IGljar MDI	Δ -0.4 ± 0.9 <sup>d,D</sup> (8.3 ± 0.6) Δ + 0.2 ± 1.0 (8.3 ± 0.5)	Reach HbA <sub>1c</sub> ≤7.0 %, 10/78 (13 %) Reach HbA <sub>1c</sub> ≤7.0 %, 4/78 (5 %)
	119 Adults T2D	IAsp CSII IAsp + IGljar IAsp + IDet	(9.86 ± 1.69) (9.25 ± 1.54) (9.56 ± 1.49)	FBG, 6.03 ± 0.47 mmol/L FBG, 5.98 ± 0.72 mmol/L FBG, 6.17 ± 0.53 mmol/L

Table 3 continued

Study (duration)	No. of patients	Insulin treatment (baseline) <sup>A</sup>	Mean HbA <sub>1c</sub> at study end, % (baseline HbA <sub>1c</sub> ) ± SD	Other endpoints (baseline) ± SD
Gao et al. (2014) (12 weeks) [114]	200 Adults T2D	IAsp CSII  IAsp + IGlir	7.11 ± 1.32 (10.79 ± 1.42)  7.51 ± 1.28 (10.86 ± 1.36)	FBG, 6.76 ± 1.13 mmol/L <sup>n,D</sup> (FBG, 8.61 ± 3.12 mmol/L)  FBG, 6.85 ± 1.26 mmol/L <sup>n,D</sup> (FBG, 8.68 ± 3.32 mmol/L)
Insulin aspart (CSII) vs MDI: observational studies				
Kawamura et al. (2008) (6 months, single-arm, before/after study) [116]	26 Children (6–18 years) T1D	IAsp CSII (MDI varied regimens)	7.4 ± 0.8 (7.8 ± 1.8)	
(b) Insulin aspart vs buffered RHI, both in CSII: randomized trials				
Bode and Strange 2001 (7 weeks) [120]	29 Adults T1D	IAsp CSII BRHI CSII	6.9 ± 0.6 (7.2 ± 0.8) 7.1 ± 0.6 (7.2 ± 0.9)	FBG, 7.9 ± 2.8 mmol/L FBG, 8.0 ± 2.6 mmol/L
Bode et al. (2002) (16 weeks) [121]	146 Adults T1D	IAsp CSII BRHI CSII ILisp CSII	Δ0.00 ± 0.51 (7.3 ± 0.7) Δ0.15 ± 0.63 (7.5 ± 0.8) Δ0.18 ± 0.84 (7.3 ± 0.7)	
Insulin aspart vs buffered RHI, both in CSII: observational studies				
Chlup et al. (2004) (~90 weeks, single-arm before/after study) [122]	21 Adults T1D	IAsp CSII (BR HI CSII)	7.53 <sup>b,D</sup> (7.89)	
(c) Insulin aspart (CSII) vs insulin lispro and insulin glulisine: randomized trials				
Weinzimer et al. (2008) (16 weeks) [128]	298 Children (4–18 years) T1D	IAsp CSII ILisp CSII	7.9 ± 0.93 (8.0 ± 0.94) 8.1 ± 0.85 (8.1 ± 0.84)	FPG, 9.2 ± 3.7 mmol/L (FPG, 9.5 ± 4.3 mmol/L) FPG, 10.0 ± 4.6 mmol/L (FPG, 9.9 ± 3.8 mmol/L)
Bartolo et al. (2008) (crossover study, 3 days) [131]	17 Adults T1D	IAsp CSII  ILisp CSII		ΔBG <sub>90 min</sub> 0.51 ± 2.03 mmol/L <sup>c,D</sup> ΔBG <sub>120 min</sub> 0.36 ± 2.11 mmol/L <sup>o,D</sup> %postprandial values <sub>0–120 min</sub> within target range, 59.8 ± 29.1 % ΔBG <sub>90 min</sub> -0.67 ± 2.42 mmol/L ΔBG <sub>120 min</sub> -0.67 ± 2.11 mmol/L %postprandial values <sub>0–120 min</sub> within target range, 48.6 ± 30.6 %
van Bon et al. (2011) (crossover study, 13-week periods) [127]	288 Adults T1D	IAsp CSII IGlu CSII ILisp CSII	7.26 ± 0.76 (7.33 ± 0.71) 7.32 ± 0.73 (7.31 ± 0.71) 7.31 ± 0.74 (7.28 ± 0.71)	Reach HbA <sub>1c</sub> <7.0, 31 % Reach HbA <sub>1c</sub> <7.0, 28 % Reach HbA <sub>1c</sub> <7.0, 30 %

**Table 3** continued

Study (duration)	No. of patients	Insulin treatment (baseline) <sup>A</sup>	Mean HbA <sub>1c</sub> at study end, % (baseline HbA <sub>1c</sub> ) ± SD	Other endpoints (baseline) ± SD
Thrasher et al. (2014) (crossover study, 16-week periods) [126]	122 Adults T2D	IAsp CSII ILisp CSII	7.4 ± 0.12 (7.4 ± 0.9) 7.5 ± 0.12 (7.4 ± 0.9)	
Dzygalo and Szybowska, (2014) (crossover study, 2 visits) [125]	64 Children (10.3–17.9 years) T1D	IAsp CSII IGlu CSII		PPG, iAUC ~338 ± 51.8 min × mmol/L PPG, iAUC ~403 ± 48.9 min × mmol/L
Tamborlane et al. (2015) (two crossover studies; 8- and 12-week periods, respectively) [130]	132 Adults T1D	IAsp CSII ILisp CSII	Δ0.0 (7.3 ± 0.7) Δ0.06 (7.3 ± 0.7)	Mean difference, daily mean SMBG 0.22 mmol/L [95 % CI -0.07 to 0.52]
	133 Adults T1D	IAsp CSII ILisp CSII	Δ -0.31 (7.5 ± 0.7) <sup>m,c,d</sup> Δ -0.15 (7.5 ± 0.7)	Mean difference, daily mean SMBG 0.18 mmol/L [95 % CI -0.10 to 0.47]
(c) Insulin aspart (CSII) vs insulin lispro and insulin glulisine: observational studies				
Alemzadeh et al. (2007) (1-year, single-arm, before/after study) [124]	14 Children (~3–5 years) T1D	IAsp CSII (IAsp + IGlargin)	7.8 ± 0.4 (8.0 ± 0.5)	Sensor MBG, 10.27 ± 4.38 mmol/L (Sensor MBG, 11.82 ± 5.22 mmol/L) MAGE, 9.32 ± 1.22 mmol/L <sup>c,m</sup> (MAGE, 11.65 ± 1.72 mmol/L)
Wittlin et al. (2008) (16 weeks, single-arm, before/after study) [129]	513 Adults T1D or T2D	IAsp CSII (ILisp CSII)	7.9 ± 1.1 <sup>e,d</sup> (8.1 ± 1.1)	FBG, 7.72 ± 3.33 mmol/L <sup>f,d</sup> (FBG, 8.30 ± 3.59 mmol/L)

BG blood glucose, BRHI buffered regular human insulin, CSII continuous subcutaneous insulin infusion, FBG fasting blood glucose, HI human insulin, IAsp insulin aspart, iAUC incremental Area Under Curve, IDet insulin detemir, IGlargin insulin glargine, IGLisp insulin lispro, MAGE mean amplitude of glycemic excursion, MBG mean blood glucose, MDI multiple daily injections, NPH neutral protamine Hagedorn insulin, PPG postprandial glucose, RHI regular human insulin, SD standard deviation, SMBG self-measured blood glucose, T1D type 1 diabetes, T2D type 2 diabetes, Δ mean change

<sup>a</sup>  $p = 0.002$ , <sup>b</sup>  $p < 0.05$ , <sup>c</sup>  $p < 0.02$ , <sup>d</sup>  $p < 0.001$ , <sup>e</sup>  $p = 0.014$ , <sup>f</sup>  $p = 0.004$ , <sup>g</sup>  $p = 0.0001$ , <sup>h</sup>  $p = 0.039$ , <sup>j</sup>  $p = 0.019$ , <sup>k</sup>  $p = 0.001$ , <sup>m</sup>  $p < 0.0001$ , <sup>n</sup>  $p < 0.005$ , <sup>o</sup>  $p < 0.03$

<sup>A</sup> Baseline value before switching in single-arm studies, <sup>B</sup> analyzed as a parallel-trial due to high dropout rate after crossover [ $\mu = 17/79$  (22 %)], <sup>C</sup> from baseline, <sup>D</sup> between groups



insulin aspart decreased HbA<sub>1c</sub> from baseline in five randomized studies [79–83]. HbA<sub>1c</sub> was also reduced in one 52-week study [84] and in one 13-week study in which patients switched from RHI to insulin aspart [85]. In another randomized study, baseline and end-of-trial HbA<sub>1c</sub> remained similar for both insulin aspart and RHI [86].

In two large observational studies, HbA<sub>1c</sub>, PPG and fasting plasma glucose (FPG) levels were significantly reduced after switching to insulin aspart, one in which patients used insulin aspart with a basal insulin [87], and another in which basal insulin was not used [88]. In both studies, oral antidiabetic drugs (OADs) were allowed. In a third large observational study comparing insulin aspart with RHI (use of basal insulin was optional), HbA<sub>1c</sub> was decreased from baseline in both groups ( $p < 0.0001$ ). FPG and PPG values after each meal were also reduced from baseline in both groups ( $p \leq 0.05$  for most comparisons) [89].

### 3.3 Meta-Analysis in T1D and T2D

A meta-analysis of ten published and unpublished randomized trials of basal–bolus therapy in T1D and T2D with a minimum duration of 12 weeks has further confirmed significantly better glucose control with insulin aspart treatment compared with RHI (mean overall difference between treatments in HbA<sub>1c</sub>  $-0.1\%$  [95% CI  $-0.15$  to  $-0.04$ ];  $p < 0.001$ , favoring insulin aspart) [90]. PPG was significantly lower after treatment with insulin aspart compared with RHI, but the analysis did present a significant level of heterogeneity ( $p < 0.001$ ).

### 3.4 Intensification of Treatment with Insulin Aspart

#### 3.4.1 Intensification with All-Analog Regimens

Due to the inevitable decline in  $\beta$ -cell function characterizing T2D, patients typically require progressive intensification of therapy when diet, exercise, and metformin cannot maintain adequate glycemic control. Typically, this begins with adding a second OAD, drugs of the incretin class, a basal insulin or a premixed insulin. Eventually many patients require full basal–bolus regimens to ensure adequate prandial coverage and acceptable overall glucose control [16]. Basal–bolus regimens comparing insulin aspart with RHI in T1D or T2D have been discussed above. Trials have also compared all-analog regimens with RHI regimens. For example, one 18-week trial compared insulin aspart with insulin detemir versus RHI in combination with NPH [78]. Results demonstrated a lower HbA<sub>1c</sub> in the arm using an all-analog regimen (HbA<sub>1c</sub> 7.88% vs 8.11%; mean difference  $-0.22\%$  point [95% CI  $-0.34$  to  $-0.10$ ];  $p < 0.001$ ), indicating that insulin aspart could be used

effectively with a basal insulin analog in a full basal–bolus regimen.

#### 3.4.2 Step-Wise Addition of Insulin Aspart

A full basal–bolus regimen may be intimidating for patients with T2D due to the complexity of these regimens and risk of hypoglycemia. Therefore, some patients may initially intensify treatment by using a premixed insulin to improve prandial coverage. Another option that has been examined is the step-wise addition of insulin aspart injections to basal insulin. Two trials have demonstrated the efficacy and feasibility of this approach [91, 92]. The first was a randomized, controlled, parallel-group trial of 48 weeks' duration in which 296 patients with T2D already using basal insulin were randomized to either the SimpleSTEP regimen (addition of insulin aspart at the anticipated largest meal of the day;  $n = 150$ ) or the ExtraSTEP regimen (addition of insulin aspart with the meal having the highest measured increase in postprandial glucose;  $n = 146$ ) [91]. Both groups administered insulin detemir once daily at bedtime. HbA<sub>1c</sub> decreased by about 1.2% in both groups, and the strategies were equally effective at lowering HbA<sub>1c</sub> (treatment difference  $-0.06\%$  [95% CI  $-0.29$  to  $0.17$ ]). Insulin aspart dose was identical in each arm (0.53 U/kg). The decrease in PPG increment was similar in both groups, suggesting that the sequential addition of prandial insulin aspart to one or more meals improves glycemic control in those who need intensification beyond basal insulin (Table 2b).

The FullSTEP trial was a phase IV, 32-week, randomized, parallel-group, treat-to-target, non-inferiority trial that compared a full basal–bolus regimen to a step-wise approach [92]. A total of 401 patients with T2D, from 150 sites in seven nations, participated. Those in the full basal–bolus group administered insulin aspart before each main meal, whereas those in the step-wise group added insulin aspart first to the largest meal and, if HbA<sub>1c</sub>  $\geq 7.0\%$ , added additional boluses at the next largest meal at week 11 and week 22. Both groups used insulin detemir once daily at bedtime as the basal insulin. HbA<sub>1c</sub> and FPG decreased by similar amounts in both groups, but the mean prandial glucose increment was significantly higher for the step-wise group (treatment difference, 0.36 mmol/L [95% CI 0.01–0.71];  $p = 0.046$ ) (Table 2b).

### 3.5 Long-Term Microvascular and Macrovascular Complications

A desirable long-term outcome of better glucose control would be a reduced risk of adverse CVD outcomes, although as multiple reviews have discussed, it has been difficult to demonstrate this unequivocally in large trials

[10, 12–15, 25]. One large observational study using computerized data from patients with T2D in the German Disease Analyzer database (3154 patients using insulin aspart and 3154 patients using RHI) examined several key cardiovascular outcomes [93]. After a mean follow-up of 3.5 years, patients using insulin aspart had a 15 % lower risk of combined macrovascular outcomes (hazard ratio 0.85 [95 % CI 0.75–0.96]), a 42 % lower risk of stroke or transient ischemic attack (0.58 [0.45–0.74]); a 31 % lower risk of myocardial infarction (0.69 [0.54–0.88]), a 16 % lower risk of coronary heart disease (0.84 [0.72–0.94]), and a 20 % lower risk of peripheral vascular disease (0.80 [0.69–0.93]), (all  $p < 0.05$ ) compared with those using RHI. The risk of microvascular complications was not significantly different for users of insulin aspart and RHI (0.96 [0.87–1.06]).

Oxidative stress due to increased glucose fluctuations has been proposed as one possible reason for an association between PPG levels and CVD, but a small ( $n = 43$ ) trial comparing thrice-daily insulin aspart versus once-daily insulin detemir showed significantly lower measures of oxidative stress, based on urinary 8-iso-prostaglandin F<sub>2α</sub> only in the insulin detemir group ( $p = 0.0079$ ) [94]. The absence of a uniformly accepted standard of how to estimate the postprandial hyperglycemia and glycemic variability adds a further challenge to this debate [25].

### 3.6 Special Populations

#### 3.6.1 Children and Adolescents

Control of PPG may be particularly difficult in children, in part due to the high carbohydrate content of breakfast cereals. Postprandial administration theoretically offers a better opportunity for matching insulin dose to the actual meal content. The effect of preprandial (immediately before meal start) compared with postprandial (up to 30 min after start of meal) administration of insulin aspart was evaluated using a randomized, crossover trial design in 76 children and adolescents with T1D aged 6–17 years [95]. With respect to 7-point BG profiles, the treatment difference for pre- to post-comparison was statistically significant at 120 min post-breakfast. In a similar 12-week crossover study in 26 children with T1D, RHI injected 30 min before mealtime was compared with insulin aspart injected at or shortly after meals [96]. The average postprandial increment was similar for both insulins.

Insulin aspart was compared with insulin glulisine in 13 children with T1D, aged 5.4–11.8 years and using multi-injection therapy [97]. Results indicated that use of insulin aspart was associated with a lower postprandial glucose excursion at 2 h ( $+98.6 \pm 66.9$  vs  $+113.5 \pm 65.2$  mg/dL,  $p = 0.01$ ) and BG was lower with insulin aspart even at

4 h ( $129.0 \pm 37.0$  vs  $141.9 \pm 36.5$  mg/dL,  $p = 0.04$ ) after breakfast. In a 26-week, randomized, parallel-group trial in 61 children with T1D, participants were randomized to either insulin aspart multiple daily injection (MDI) or RHI MDI, each with NPH as the basal insulin, or to insulin aspart CSII [98]. After 26 weeks, mean HbA<sub>1c</sub> remained essentially unchanged from baseline and comparable in each of the three groups.

In a randomized, parallel-group trial in 72 children and adolescents aged 7–17 years with T1D, insulin aspart MDI with NPH as the basal insulin ( $n = 38$ ) was compared with insulin aspart CSII ( $n = 34$ ) [99]. After 24 months, there was no difference in HbA<sub>1c</sub> between the groups ( $p = 0.33$ ). Basal–bolus regimens of either insulin aspart + insulin glargine or RHI + NPH were compared after 24 weeks of treatment in a randomized, parallel-group study of 40 children 6–10 years of age [100]. At end of trial, HbA<sub>1c</sub> and FBG were similar in both treatment groups.

The effect of pre-meal insulin treatment with insulin aspart was studied in 30 prepubertal children with T1D using insulin glargine as their basal insulin [101]. Children were randomized to either insulin aspart 2 min before meals or RHI 30 min prior to eating, with the dose estimated using carbohydrate counting; children in the insulin aspart group also received an additional injection before the afternoon snack. At 18 weeks, mean daily BG, glucose variability, and decrease from baseline were similar in both groups. FBG decreased more with RHI ( $p = 0.012$ ) and HbA<sub>1c</sub> decreased from baseline with RHI but not with insulin aspart ( $p = 0.018$ ).

#### 3.6.2 Pregnancy

Pregnant women with diabetes are at risk of adverse maternal and perinatal outcomes [102], which can be mitigated with improved glucose control [103]. In one study, 322 women with T1D on basal–bolus therapy were randomized to either insulin aspart ( $n = 157$ ) or RHI ( $n = 165$ ) as the bolus insulin, with NPH as basal insulin [104]. Change in HbA<sub>1c</sub> with insulin aspart was non-inferior to RHI. However, the mean prandial glucose increment was lower after each main meal with insulin aspart, with the treatment differences being  $-0.75$  mmol/L [95 % CI  $-1.25$  to  $-0.25$ ];  $p = 0.003$  at 12 weeks' gestation and  $-0.40$  mmol/L [95 % CI  $-0.80$  to  $-0.01$ ];  $p = 0.044$  at 36 weeks' gestation.

One randomized, parallel-group trial compared the efficacy of insulin aspart with RHI in basal–bolus therapy in 27 women with gestational diabetes [105]. Women were followed from the time of diagnosis (18–28 weeks) to 6 weeks postpartum. Glycemic control was good and comparable with both insulins during the study period (HbA<sub>1c</sub>  $\leq 6.0$  %). However, change from baseline values

for average PG was greater for insulin aspart when compared with RHI ( $-1.09 \pm 0.54$  vs  $-0.54 \pm 0.74$  mmol/L, respectively;  $p = 0.003$ ).

### 3.6.3 Hospitalized Patients

Consensus guidelines stress the importance of insulin-based treatment for most hospitalized patients with hyperglycemia [106]. Hospitalized patients may have sought emergency care due to diabetic ketoacidosis (DKA), may have been admitted for reasons primarily unrelated to pre-existing diabetes but develop hyperglycemia, or may have been non-diabetic and developed hyperglycemia. Intravenous insulin therapy is often preferred for these patients because it allows rapid adjustment and avoids any problems with absorption due to conditions such as edema or poor perfusion. However, SC administration is less complicated and thus may have advantages for patients in non-intensive care unit (ICU) settings whose BG is not changing rapidly [107, 108].

Observational data from a large ( $n = 3024$ ) group of hospitalized patients (67 % ICU) demonstrated the efficacy of using IV insulin aspart, with mean BG decreasing from 19.8 to 8.6 mmol/L after treatment [109]. Results were similar in ICU and non-ICU patients.

One randomized study examined the efficacy of insulin aspart given either SC every hour ( $n = 15$ ) or every 2 h ( $n = 15$ ), compared with an IV infusion of RHI ( $n = 15$ ) in consecutive patients admitted for treatment of uncomplicated DKA [107]. Mean duration of treatment until correction of hyperglycemia was similar for all three treatments, indicating that insulin aspart administered SC either hourly or every 2 h was an effective alternative to IV administration of RHI.

In another study, emergency department (ED) patients with a history of T2D and a BG  $\geq 200$  mg/dL at presentation were randomized to either insulin aspart every 2 h SC when BG  $> 200$  mg/dL ( $n = 87$ ), or usual care (which could include insulin) per hospital physicians' treatment ( $n = 89$ ) [110]. If subsequently admitted, patients in the intervention group began basal-bolus therapy with insulin detemir. Patients with DKA were excluded from the study. The mean final ED BG was lower in the intervention group when compared with the usual care group ( $217 \pm 71$  vs  $257 \pm 89$  mg/dL, respectively;  $p < 0.01$ ). The mean length of stay in the ED was also similar in both groups. Among patients assigned to usual care who were eventually admitted, most still received insulin (76.9 % basal insulin and 70.4 % bolus). Patient-day-weighted mean glucose was lower for the intervention group ( $163 \pm 39$  vs  $202 \pm 39$  mg/dL for intensive vs usual-care patients, respectively,  $p < 0.01$ ).

Finally, in a study of 130 nonsurgical patients with T2D and BG between 140–400 mg/dL, patients were randomized to basal-bolus therapy either with insulin aspart at mealtimes + insulin detemir ( $n = 67$ ) or RHI (twice daily) + NPH ( $n = 63$ ) [111]. Mean BG was similar at baseline in each group, and after 1 day, improved similarly in both groups ( $p = 0.80$ ).

## 3.7 Insulin Aspart in Continuous Subcutaneous Insulin Infusion (CSII)

### 3.7.1 Insulin Aspart CSII Versus Multiple Daily Injection (MDI)

Several studies in adults and children, and in T1D and T2D, have examined glucose control with insulin aspart used in CSII versus other insulins used in MDI [98, 99, 112–119]. Results are presented in Table 3a. The largest trial studied both children ( $n = 156$ ) and adults ( $n = 329$ ) with T1D for 1 year, and reported significantly greater improvements in HbA<sub>1c</sub> for patients switching to insulin aspart CSII than patients who remained on MDI therapy with insulin aspart concomitant with insulin glargine [112]. One 16-week trial in 32 youths with T1D demonstrated significant improvement from baseline for insulin aspart CSII as well as significantly lower HbA<sub>1c</sub> compared with MDI therapy [113]. The study by Hirsch et al. demonstrated statistically significant differences in serum fructosamine or AUC<sub>glucose  $\geq 140$  mg/dL</sub> with insulin aspart CSII versus MDI [115]. However, other studies have not demonstrated significant improvements in glucose control compared with baseline for insulin aspart CSII or MDI therapy [99, 114, 117].

### 3.7.2 Insulin Aspart Compared with Buffered Regular Human Insulin (RHI), Both in CSII

Three studies have compared insulin aspart CSII with buffered RHI CSII, using change in HbA<sub>1c</sub> as the outcome [120–122] (Table 3b). Randomized trials of 7 weeks in 29 adults with T1D [120] and 16 weeks in 146 adults with T1D [121] demonstrated little change in HbA<sub>1c</sub> from baseline and no between-treatment differences. In contrast, a 90-week study of 21 adults with T1D demonstrated an improvement in HbA<sub>1c</sub> after switching from buffered RHI to treatment with insulin aspart CSII (7.89 % vs 7.53 %, respectively,  $p < 0.05$ ) [122].

Another study highlighted differences in glucose control with insulin aspart compared with buffered RHI in 21 Chinese patients with T1D or T2D [123]. The study demonstrated better BG profiles with insulin aspart overall ( $p < 0.01$ ) as well as before breakfast ( $6.72 \pm 1.24$  vs

$7.84 \pm 1.58$  mmol/L,  $p = 0.01$ ), after breakfast ( $8.96 \pm 2.41$  vs  $11.70 \pm 3.11$  mmol/L,  $p = 0.003$ ) and after dinner ( $8.15 \pm 2.10$  vs  $10.07 \pm 2.36$  mmol/L,  $p = 0.008$ ).

### 3.7.3 Insulin Aspart Compared with Other Rapid-Acting Analogs in CSII

Comparisons of insulin aspart with other analogs in CSII have generally shown no significant differences in HbA<sub>1c</sub> between treatment groups (Table 3) [124–128]. However, one 16-week, single-arm, before-and-after study in 513 adults with T1D or T2D reported a small but statistically significant decrease in both mean ( $\pm$ SD) difference in HbA<sub>1c</sub> ( $-0.1 \pm 0.7\%$ ,  $p = 0.014$ ) and FBG ( $-12.2 \pm 81.0$  mg/dL,  $p = 0.004$ ) after switching from insulin lispro CSII to insulin aspart CSII [129]. Two 24-week, randomized, crossover trials were conducted in subjects with T1D to determine whether glycemic control on day 6 of pump reservoir use of insulin lispro was non-inferior to insulin aspart. Insulin lispro did not achieve non-inferiority to insulin aspart on day 6 of reservoir usage. In one of the studies, greater decrease in HbA<sub>1c</sub> with insulin aspart compared with insulin lispro was noted ( $p < 0.001$ ). Insulin aspart mean self-measured blood glucose (SMBG) profiles were lower than the profiles for insulin lispro in both studies; however, daily mean SMBG was not different for the two insulins [130] (Table 3). In a 3-day, randomized, crossover trial in 17 patients with T1D, CGM was used to assess the combined postprandial control after standardized meals. For breakfast and lunch combined, mean changes in BG values were lower for insulin lispro than for insulin aspart at 90 and 120 min [131] (Table 3).

### 3.8 Flexible Dosing

RHI is typically administered 30 min prior to meals in order to match maximal glucose-lowering action with glycemic load. Pre-meal administration can be inconvenient for patients and also make it difficult to accurately match insulin dose to the anticipated carbohydrate intake. The question of whether injecting closer to or immediately after starting a meal might be equally efficacious was investigated in a randomized, double-blind, crossover trial in 20 patients with T1D in a hospital setting [132]. During each period, one of four treatment combinations was administered: insulin aspart at meal (IASp<sub>0 min</sub>) or at 15 min after the meal began (IASp<sub>+15 min</sub>), and RHI at start of meal (HI<sub>0 min</sub>) and at 15 min prior to the meal start (HI<sub>-15 min</sub>). PG excursions from baseline levels were highest with RHI given at mealtime (17.9 mmol/L/h) compared with other times of administration (13.6, 11.9, and 14.2 mmol/L/h, for HI<sub>-15 min</sub>, IASp<sub>0 min</sub> and IASp<sub>+15 min</sub>, respectively; all  $p < 0.05$  vs RHI given at

mealtimes). The PG excursions for other administration times were not significantly different from each other. In another crossover study, the effect of administering insulin aspart 30, 15, and 0 min prior to starting a meal was examined in ten patients with T1D on three different study days [133]. Each patient's insulin pump was used to deliver the required prandial bolus, and CGM was used to monitor BG. Administration at  $-15$  min resulted in a significantly lower glucose excursion ( $4.77 \pm 0.52$  mmol/L) than at 0 min ( $6.93 \pm 0.76$  mmol/L,  $p = 0.022$ ) and at  $-30$  min ( $6.48 \pm 0.76$  mmol/L,  $p = 0.025$ ).

### 3.9 Quality of Life/Treatment Satisfaction with Insulin Aspart

Studies have evaluated quality of life (QoL) and/or treatment satisfaction using insulin aspart in children [98], adults with T1D [134], and adults with T1D or T2D using CSII [129]. In the pediatric study comparing insulin aspart CSII, insulin aspart MDI, and RHI MDI, both groups randomized to insulin aspart indicated an increase in treatment satisfaction, with the greatest increase being for insulin aspart CSII [98]. In a 6-month, randomized trial, treatment satisfaction was compared in 424 patients with T1D, 283 using insulin aspart MDI and 141 using RHI, with each group using NPH for the basal component [134]. At end of trial, treatment satisfaction on two different validated scales was higher with insulin aspart ( $p < 0.01$ ), mainly due to increased dietary and leisure time flexibility ( $p < 0.0001$ ). QoL was improved with respect to diet restrictions ( $p < 0.01$ ). Finally, in a 16-week, open-label, multicenter study, 513 adults ( $\geq 18$  years) with T1D or T2D previously using insulin lispro CSII were switched to insulin aspart CSII [129]. Average overall treatment satisfaction scores (Diabetes Treatment Satisfaction Questionnaire, DTSQ) for the two insulins were not significantly different. However, the average overall score on the Insulin Treatment Satisfaction Questionnaire (ITSQ) was significantly greater for insulin aspart than for insulin lispro (treatment difference 1.7;  $p = 0.001$ ).

## 4 Safety and Tolerability of Insulin Aspart

### 4.1 General Adverse Event Profile

#### 4.1.1 Receptor Binding and Mitogenicity

Insulin and insulin-like growth factor (IGF)-1 binding properties are important to evaluate with any new insulin to ensure that the safety profile is not adversely affected by the molecular modifications introduced during the bio-engineering process [135]. Insulin aspart was one of



several insulin formulations evaluated in an in-vitro study. In that study, insulin aspart was shown to be equipotent to RHI in binding to the insulin receptor [135]. Insulin aspart also dissociated from the insulin receptor at a rate similar to RHI, and had a similar metabolic potency. Furthermore, evaluation of mitogenic potency using human osteosarcoma cells indicated that insulin aspart was slightly less mitogenic than RHI [135].

The effect of insulin aspart, RHI, and two biphasic insulin aspart formulations on the circulating IGF system was studied in vivo in 19 patients [136]. Despite differences in glucose-lowering profiles after a single SC injection, insulin aspart and RHI demonstrated parallel decreases in IGF-binding protein (IGFBP)-1 levels during the first 3 h, and had similar profiles and AUCs for total IGF-1, IGFBP-2, and IGFBP-3. There were minor and clinically unimportant differences in IGFBP-1 during the later part of the study (6–9 h) between insulin aspart and RHI. Neither insulin changed total serum IGF-1 from baseline. Another in vivo evaluation of insulin-like growth factors was done as part of a randomized, two-period (8 weeks) crossover study in 16 patients with T1D treated with either insulin aspart + NPH or RHI + NPH [76]. Results indicated no statistically significant differences between treatment groups in total IGF-I, free IGF-I, total IGF-II, IGFBP-1 or IGFBP-2.

#### 4.1.2 Anti-Insulin Antibodies

Development of antibodies to SC administered insulin is common, and although they usually are not associated with clinical symptoms [137], there is a hypothetical concern that modifications to the insulin molecule could increase antigenicity and that anti-insulin antibodies could alter PK and/or PD properties. Antibodies of interest would include those specific to RHI or insulin aspart, as well as cross-reactive antibodies [138]. These were measured in a variety of patient populations: adults with T1D or T2D [71, 138]; pregnant women with T1D [139]; adults with T2D [137]; children with T1D [138], and women with gestational diabetes [105], all discussed below.

In one study of adults with T1D or T2D, insulin antibody results were combined from three trials, for a total of 1396 patients randomized to insulin aspart and 740 to RHI, with NPH as the basal component [138]. Insulin aspart-specific and RHI-specific antibody levels remained undetectable in most patients throughout the studies. Most patients had cross-reacting antibodies at baseline, which transiently increased with insulin aspart treatment; there were no adverse clinical effects that could be linked to antibody levels. There was also no correlation with absolute levels of antibodies and clinical efficacy or glycaemic parameters. Increased antibody levels were not

associated with an increased insulin dose, and in one case, there was an inverse relationship. Additional detail was obtained from the full publication of a study of patients with T1D (whose data also contributed to the combined analysis by Lindholm et al. [138], discussed previously) [71]. In that group, 882 patients enrolled in the study for 6 months ( $n = 596$  for insulin aspart and  $n = 286$  for RHI) with 714 being followed up to 12 months. Throughout the trial, insulin aspart-specific antibodies remained low (1 % binding). Primarily due to a spike in cross-reacting antibodies in 22 (4 %) insulin aspart-treated patients, those on insulin aspart had significantly greater binding than RHI (treatment difference 5.8 % [95 % CI 4.06–7.64]) [71]. However, by 12 months, mean cross-reacting antibodies had returned to baseline in patients using insulin aspart.

In another study, insulin antibodies were detected in 48/118 (40.7 %) patients with T2D who used insulin, including 26/47 (55.3 %) using insulin aspart or biphasic insulin aspart, and surprisingly in 7/263 patients who had never used insulin [137]. A multiple regression analysis showed that insulin aspart was more antigenic than RHI. Total serum insulin levels were higher in patients (on any insulin) with insulin antibodies compared with patients without antibodies ( $615.0 \pm 576$  vs  $279.5 \pm 28.1$  pmol/L, respectively,  $p < 0.001$ ). However, free serum insulin levels were not different with or without antibodies.

Antibody response was compared in a retrospective study of 72 children or adolescents (age 2–17 years) newly diagnosed with T1D and treated with RHI ( $n = 30$ ) or insulin aspart ( $n = 42$ ), and all using NPH as the basal insulin. Insulin aspart-specific and cross-reacting antibodies were measured at diagnosis and every 3–6 months for 30 months [140]. Insulin aspart-specific antibodies remained low during the period of the study, but the level of cross-reacting antibodies increased after 9 months to 48.8 % for RHI and 40.2 % for insulin aspart, and remained high, with no difference between treatments. However, there was no detectable influence of these elevated antibody levels on efficacy or safety.

Antibody response was also reported in a study of 27 women with gestational diabetes randomized to insulin aspart or RHI and treated from diagnosis at 18–28 weeks' gestation to 6 weeks postpartum [105]. Antibodies specific to either insulin aspart or RHI remained low (<1 % binding), but cross-reacting antibody binding increased from baseline ( $0.2 \pm 3$  % in both treatments groups) at end of study (insulin aspart  $2.1 \pm 5.4$  %, RHI  $6.4 \pm 13.9$  %). For the insulin aspart group, this was largely due to one patient with binding of 10.1 and 19.2 % at two visits. Both treatments were described as safe in this population. Results from a subset of 97 pregnant women with T1D who participated in a larger trial [104, 141] also indicated that levels of insulin aspart-specific as well as RHI-specific



antibodies were low at baseline and at gestational week 36, with no significant differences between insulin aspart and RHI [139].

## 4.2 Hypoglycemia

### 4.2.1 In Patients with T1D

Randomized trials in T1D where insulin aspart + NPH was compared with RHI + NPH have generally shown no difference in the incidence of overall or major hypoglycemia between treatments [70–72, 75, 77] (Table 4a). Data from a 6-month extension ( $n = 714$ ) of the original 6-month trial with 882 subjects by Raskin et al. [71] indicated that the 24-week results were maintained at 52 weeks. However, two of these trials have demonstrated a significantly lower rate of nocturnal hypoglycemia with insulin aspart compared with RHI [70, 71], whereas another two trials showed no difference [72, 75] (Table 4a). Additionally, although finding no difference in overall incidence of major hypoglycemic events, a trial by Heller et al. [77] indicated that the rate of major nocturnal hypoglycemia was 72 % lower with insulin aspart (0.067 vs 0.225 events/month,  $p = 0.001$ ) [77]. Furthermore, in a study of 16 patients with T1D, in which acute hypoglycemia was induced by IV infusion of either insulin aspart or RHI, both insulins elicited similar symptomatic and counterregulatory responses [142].

### 4.2.2 In Patients with T2D

Results from three unpublished randomized trials of 16–24 weeks (summarized individually in a meta-analysis) indicated no difference in overall hypoglycemia for insulin aspart + NPH compared with RHI + NPH (rate ratios: 1.11 [95 % CI 0.64–1.94],  $p = 0.70$ ; 0.89 [0.44–1.78],  $p = 0.74$ ; and 1.26 [0.17–9.06],  $p = 0.82$  for the three trials, respectively) [90]. Two of these trials reported results for nocturnal hypoglycemia, again indicating no difference between patients receiving insulin aspart and those receiving RHI. In one trial enrolling Chinese patients with either T1D or T2D, results were in favor of RHI for lower overall hypoglycemic episodes [143] (Table 4c). There was no difference in incidence of mild hypoglycemic events in a randomized, two-period (90 days each) crossover trial comparing mealtime insulin aspart and mealtime RHI, both with metformin 500 mg three times daily ( $2.2 \pm 1.7$  vs  $2.3 \pm 1.6$  episodes/month, respectively,  $p = \text{NS}$ ) [82].

The A<sub>1</sub>chieve observational study in patients who started or switched to basal–bolus therapy with insulin aspart has demonstrated reduced risk of hypoglycemia in people

aged  $\leq 40$ , 40–65, and  $> 65$  years [87] (Table 4b). Another analysis of the A<sub>1</sub>chieve study, examining 2026 patients using insulin aspart as the only insulin treatment, indicated that both insulin-naïve and insulin-experienced patients had reduced risk of overall hypoglycemia after adding insulin aspart to their treatment regimen [88].

### 4.2.3 Meta-Analysis of T1D and T2D

In a meta-analysis of ten trials, a fixed effect model indicated a similar rate of overall hypoglycemia for insulin aspart + NPH and RHI + NPH (treatment difference 0.99 % [95 % CI 0.90–1.09],  $p = 0.81$ ); results were comparable using a random effects model [90]. However, the overall rate of nocturnal hypoglycemia was significantly lower for insulin aspart + NPH compared with RHI + NPH (treatment difference 0.76 % [95 % CI 0.67–0.85],  $p < 0.001$ ); results were identical when a random effects model was used.

### 4.2.4 During Step-Wise Addition of Insulin Aspart

Safety of insulin aspart was also evaluated in two studies examining intensification of treatment via step-wise additions of insulin aspart in patients with T2D. In the STEPwise trial, insulin aspart was added to either the largest meal (SimpleSTEP) or to the meal with largest prandial glucose increments (ExtraSTEP). The number of episodes of hypoglycemia was low and similar for both regimens [91] (Table 4b). The FullSTEP trial compared a full basal–bolus regimen with a step-wise addition of insulin aspart, beginning with administration before the largest meal [92]. In that trial, there were fewer overall hypoglycemic events in the step-wise group (rate ratio 0.58 [95 % CI 0.45–0.75],  $p < 0.0001$ ).

### 4.2.5 In Patients with Recurrent Hypoglycemia

The HypoAna trial examined whether basal–bolus regimens with insulin analogs could reduce the risk of hypoglycemia (compared with regimens with RHI) in those patients with T1D experiencing severe recurrent hypoglycemia at least twice a year [144]. This was a unique study because most clinical trials exclude patients with severe hypoglycemia. In this blinded endpoint, two-period (1 year each), crossover trial, 159 adult patients were randomized to either insulin aspart + insulin detemir or RHI + NPH. Due to 18 withdrawals, the intention-to-treat population was 141 patients [145]. There were 157 episodes of severe hypoglycemia with the all-analog treatment, compared with 242 episodes with the RHI regimen. Use of insulin analogs resulted in an absolute rate reduction of 0.51 episodes [95 % CI 0.19–0.84] per patient-year,

**Table 4** Incidence of hypoglycemia in clinical trials using insulin aspart by injection

Study (duration)	No. of patients	Insulin treatment (baseline) <sup>A</sup>	Incidence of hypoglycemic events (%) of patients)			Rate of hypoglycemic episodes per patient—year (insulin aspart)		
			All	Major	Nocturnal	All rate ratio [95 % CI]	Major relative risk [95 % CI]	Nocturnal rate ratio [95 % CI]
(a) T1D: randomized trials								
Home et al. (1998) (4 weeks) [73]	90	IAsp + NPH HI + NPH	10,430 (80.9)	20 <sup>a,b</sup> 44	1520 (51.1)	30.0	0.81	4.4
Home et al. (2000) <sup>C</sup> (6 months) [70] <sup>p</sup>	1065	IAsp + NPH HI + NPH	4480 (77.7)	152 (18)	1011 (57.3)	26.0	0.97	5.9
Home et al. (2006) (36 months; extension of Home et al. 2000) [74]	753	IAsp + NPH HI + NPH		820 (29) 261 (31)		1.18 [0.98–1.42]	0.83 [0.59; 1.18]	0.75 [0.60–0.93] <sup>b</sup>
Raskin et al. (2000) <sup>C</sup> (24 weeks) [71] <sup>p</sup>	882	IAsp + NPH HI + NPH	13,019 (89.9)		1545 (59.9)	45.2	1.00 [0.72; 1.39]	5.4
Tamás et al. (2001) <sup>C</sup> (12 weeks) [75] <sup>p</sup>	423	IAsp + NPH HI + NPH	6521 (87.1)		1030 (66.4)	47.5	0.94 [0.79–1.11]	7.5
DeVries et al. 2003 <sup>C</sup> (64 weeks) [72] <sup>p</sup>	368	IAsp + NPH HI + NPH	5129 (89.8)		796 (68.3)	24.1	0.91 [0.65–1.08]	3.7
Hermansen et al. (2004) (18 weeks) [78]	595	IAsp + IDet HI + NPH	6167 (91.7)		1029 (74.0)	29.5	0.79 [0.89–1.87]	4.9
Heller et al. (2004) (16 weeks) [77]	155	IAsp + NPH HI + NPH	2497 (75)		271 (38.7)	0.79 <sup>A</sup>	1.29 [0.89–1.87]	0.79 [0.59–1.06]
Brock Jacobsen et al. (2011) (crossover, 8-week periods) [76]	16	IAsp + NPH HI + NPH	3192 (82.9)		608 (60.3)	0.83 [0.64–1.08]	0.89 [0.35–2.22]	0.45 <sup>A</sup> [0.35–0.58] <sup>c</sup>
(a) T1D: observational studies								
Krzymień et al. (2010) (13 weeks, single-arm, before/after study) [85]	950	IAsp + NPH or IDet (NPH or IDet)					0.72 [0.47–1.09]	0.14 [0.10–0.20] <sup>a</sup>

**Table 4** continued

Study (duration)	No. of patients	Insulin treatment (baseline) <sup>A</sup>	Incidence of hypoglycemic events (% of patients)			Rate of hypoglycemic episodes per patient—year (insulin aspart)		
			All	Major	Nocturnal	All rate ratio [95 % CI]	Major relative risk [95 % CI]	Nocturnal rate ratio [95 % CI]
<b>(b) T2D: randomized trials</b>								
Raslová et al. (2004) and correction (2006) (22 weeks) [83]	395	IAsp + IDet HI + NPH	333 (38.7)	2 (1.0)	59 (16.2)	0.87 <sup>A</sup> [0.55; 1.37]		0.54 <sup>A</sup> [0.30–0.97] <sup>e</sup>
Meneghini et al. (2011) (48 weeks) STEP-Wise trial [91]	296	SimpleSTEP regimen ExtraSTEP regimen	400 (41.5)	4 (1.0)	113 (22.6)			
Rodbard et al. (2014) (32 weeks) FullSTEP trial [92]	401	Step-wise Basal–bolus	920 (74)	4 (1.3)	132 (32)			
<b>(b) T2D: observational studies</b>								
Krzymień et al. (2010) (single-arm follow-up study, 13 weeks) [85]	1332	IAsp + NPH or IDet (NPH or IDet)					0.94 <sup>E</sup> [0.68–1.31] <sup>a</sup>	
Randeree et al. (2013) (24 weeks) [88]	Insulin-experienced: 561 Insulin-naïve: 1465	IAsp	(7.8)	(0)	(0.9)		1.6 <sup>c,F</sup>	0.1
Latif et al. (2013) (single-arm before/after, 24 weeks) (A)cheive study [87]	≤40 years: 571 >40–65 years: 2801 >65 years: 660	Insulin-naïve switching to IAsp + basal	12.7 <sup>c,F</sup> (27.7)	0.2 <sup>c,F</sup> (6.7)	4.9 <sup>c,F</sup> (13.7)		0.9 <sup>c,F</sup>	0.1
			11.1 <sup>c,F</sup> (18.6)	0 <sup>c,F</sup> (3.6)	4.1 <sup>c,F</sup> (9.2)		3.6	0.7
			11.0 <sup>c,F</sup> (18.3)	0 <sup>c,F</sup> (3.3)	2.9 <sup>c,F</sup> (9.8)		3.4	0.6
<b>(c) T1D and T2D</b>								
Gao et al. (2009) <sup>F</sup> (12 weeks) [143]	220	IAsp RHI	73 (23.6)	0	3 (2.7)		2.9	0.1
			25 (15.5)		5 (3.6)		1.0	0.2
							2.97 [1.40–6.32] <sup>f</sup>	0.97 [0.59–1.58]

HI human insulin, IAsp insulin aspart, IDet insulin detemir, NPH neutral protamine Hagedorn insulin, RHI regular human insulin, NR not reported, T1D type 1 diabetes, T2D type 2 diabetes, SimpleSTEP addition of insulin aspart to the largest meal, ExtraSTEP addition of insulin aspart to meal with largest postprandial glucose increment

<sup>a</sup>  $p < 0.002$ , <sup>b</sup>  $p = 0.01$ , <sup>c</sup>  $p < 0.001$ , <sup>d</sup>  $p = 0.036$ , <sup>e</sup>  $p = 0.04$ , <sup>f</sup>  $p = 0.005$ , <sup>g</sup>  $p < 0.0001$

<sup>A</sup> Relative risk

<sup>B</sup> Between groups

<sup>C</sup> Additional data reported in meta-analysis by Heller et al. [90]

<sup>D</sup> Additional data from review by Heller et al. [90]

<sup>E</sup> Incidence rate ratio, daytime only

<sup>F</sup> From baseline

corresponding to a relative rate reduction of 29 % [95 % CI 11–48],  $p = 0.01$ , compared with the RHI regimen.

#### 4.2.6 In Children and Adolescents

Insulin aspart was compared with RHI in a two-period (12 weeks each) crossover trial in 26 preschool children (age 2.4–6.9 years) using NPH as the basal insulin. The relative risk of hypoglycemia was not significantly different for insulin aspart compared with RHI [96]. Time of dosing has also been examined in a pediatric population. In a randomized, two-period (6 weeks each) crossover trial in 76 children and adolescents (<18 years) treated with a basal–bolus regimen with insulin aspart plus either NPH, lente, or ultralente basal insulin, the incidence of hypoglycemia was similar whether insulin aspart was administered immediately before the start of a meal or up to 30 min after starting the meal [95]. When comparing insulin aspart with RHI, both with NPH, in a 26-week study of 61 children with T1D <7 years of age, the incidence of minor hypoglycemic episodes was similar between treatments [98].

#### 4.2.7 In Hospitalized Patients

Hospitalized patients may frequently present with or develop hyperglycemia, which is itself associated with poorer outcomes [146, 147]. However, control of hyperglycemia must be accomplished without incurring hypoglycemic episodes. In a study of adults with T2D, comparing initiation of insulin aspart in the ED in conjunction with prompt initiation of insulin aspart + insulin detemir for those patients subsequently admitted to the hospital (intensive care group) compared with usual care by physicians, one intensive care patient and six usual care patients had BG <50 mg/dL ( $p = 0.11$ ) [110]. The odds of moderate hypoglycemia were higher in the intensively treated group (OR 1.93 [95 % CI 0.7–5.29]), but were lower for severe hypoglycemia (OR 0.15 [0.018–1.33]). Patients with diabetic ketoacidosis, hyperosmolar non-ketotic syndrome, or critical illness requiring ICU admission or direct surgical intervention were excluded from this study.

Incidence of hypoglycemia was studied in a randomized trial in which 130 hospitalized patients with T2D were allocated to treatment with either insulin aspart + insulin detemir or RHI + NPH [111]. There was no significant difference in the proportion of patients who experienced at least one episode of hypoglycemia (BG <60 mg/dL) during their hospital stay. In a study of 45 consecutive patients admitted to a hospital with diabetic ketoacidosis, SC administration of insulin aspart either every hour ( $n = 15$ )

or every 2 h ( $n = 15$ ), indicated no difference in incidence of hypoglycemia with those receiving RHI IV ( $n = 15$ ), with only one patient in each group experiencing a BG  $\leq 60$  mg/dL (3.3 mmol/L) [107]. A study of 126 patients with refractory hyperglycemia or requiring at least 20 U/day insulin were randomized to either meals with a standard amount of carbohydrates accompanied by fixed dosing, or flexible dosing based on carbohydrate intake [148]. Insulin aspart was administered immediately after the meal. The overall frequency of hypoglycemia was 23 and 39 % in the fixed and flexible meal groups, respectively ( $p = 0.08$ ). Although the difference was not statistically significant, the trend favored the fixed-dose group, despite the fact that insulin dose (including correctional doses) was higher for the fixed-dose group. In one observational study, 203 patients undergoing cardiac surgery were randomized to receive insulin aspart or RHI intravenously. Incidence of hypoglycemia was similar in both groups, with no patients experiencing a severe adverse event, and 24.4 % of patients in the insulin aspart group and 34.1 % in the RHI group experiencing moderate adverse events [149].

#### 4.3 Safety and Tolerability During Pregnancy

Several papers from the same multicenter, multinational, parallel-group randomized trial in 322 women with T1D using basal–bolus therapy randomized to either insulin aspart ( $n = 157$ ) or RHI ( $n = 165$ ), both with NPH as basal insulin, have reported several relevant outcomes: efficacy (discussed in the Efficacy section [104]), fetal and perinatal outcomes [141], and placental transfer of antibodies (discussed under Antibodies [139]). Perinatal mortality was comparable for insulin aspart and RHI (14 and 22/1000 births). However, although not statistically significant, preterm delivery tended to occur less frequently in women using insulin aspart compared with women using RHI (20.3 vs 30.6 %, respectively,  $p = 0.053$ ) [141].

Additional data demonstrating comparable safety of insulin aspart and RHI during pregnancy was obtained from a randomized, parallel-group trial of 27 women with gestational diabetes; all women were using a basal–bolus regimen with NPH as the basal insulin [105]. Women were treated and followed-up from diagnosis of gestational diabetes at 18–28 weeks to 6 weeks postpartum. Nineteen subjects reported symptomatic hypoglycemic events, with similar proportions for both insulins: 10 (71 %) in the insulin aspart group (53 events) and 9 (69 %) in the RHI group (23 events). No major hypoglycemic events were reported during this period. Mean infant weights, lengths, and physical exam findings were similar in each group as well, and no cases of macrosomia were reported.

## 5 Insulin Aspart in CSII

### 5.1 In Vitro/Stability Studies

An essential requirement for use of an insulin product in CSII is adequate in vitro stability in the pump environment, as any degradation or precipitation can alter PK properties and potentially occlude catheters, leading to hyperglycemia and ketoacidosis.

Stability and potency of insulin aspart was determined to be unaffected by simulated ‘worst case’ storage conditions (i.e., agitation) for CSII [150]. Testing performed at 3, 4, and 7 days to detect changes in pH, isoAspB28, desamido insulin aspart, insulin aspart-related impurities, and high-molecular weight proteins indicated no change in any of these from reference values; there was also no evidence of fibrillation or precipitation. A similar simulation study comparing insulin aspart with insulin glulisine indicated that the physical stability of insulin glulisine was reduced at both the needle end and reservoir at day 10 compared with baseline, whereas physical stability increased for insulin aspart in both the needle end and reservoir, with the exception of a sample at a flow rate of 0.9 U/h (simulating an adult user), which still maintained 90 % of physical stability [151]. Another study found that all three rapid-acting insulin analogs maintained physical, chemical, and biological properties after 6 days’ use in the tubeless, skin-adhered, Solo™ MicroPump device [152]. Tendency towards fibrillation, independent of the stabilizing excipients in their respective commercial formulations, was examined for insulin aspart, insulin lispro, and insulin glulisine in a laboratory study simulating worst-case conditions of agitation and heat [153]. Insulin aspart exhibited faster rates of fibrillation than insulin glulisine or insulin lispro when compared after stabilizing excipients were removed. However, the relevance of all of these laboratory findings for clinical use remains to be determined.

Resistance to isoelectric precipitation, which may be particularly problematic at the infusion site, has been shown to be lower with insulin aspart compared with RHI or insulin lispro in an in vitro study using decreasing pH (~7.5 to ~2.6) to stimulate precipitation [154]. Another in vitro study demonstrated that insulin aspart was more resistant to isoelectric precipitation than insulin glulisine [155]. In an in vitro study comparing insulin aspart, insulin lispro, and insulin glulisine, over the entire study period of nine runs of 5 days’ duration, there were 48 occlusions ( $n = 9$  [12.5 %] for aspart;  $n = 13$  [18 %] for insulin lispro, and  $n = 26$  [36 %] for insulin glulisine). Overall, there was one early (within 72 h) occlusion with insulin aspart, three with insulin glulisine, and five with insulin lispro. Insulin aspart had the lowest estimated overall

probability of occlusion (9.2 % [95 % CI 4.0–19.5], 15.7 % [8.1–28.1], and 40.9 % [28.0–55.0], for insulin aspart, insulin lispro, and insulin glulisine, respectively) [156].

It has been postulated that changes in skin temperature below the infusion catheters might interact with choice of insulin to increase risk of occlusion [157]. In a 5-day simulation study using insulin aspart and insulin glulisine, 20 healthy volunteers wore a skin temperature probe and the catheter was inserted into an absorbent sponge in a plastic bag strapped to the abdomen to reproduce the effects of CSII [157]. The risk of occlusion was similar for both insulins (odds ratio 0.87 %,  $p = 0.6$ ) and considered unrelated to local skin temperature below the catheters.

#### 5.1.1 Insulin Aspart CSII Compared with MDI

As shown in Table 5, insulin aspart CSII has shown comparable safety to MDI therapy [98, 112, 113, 116, 117]. These results may appear somewhat at odds with those from a meta-analysis comparing CSII with MDI, which indicated a significantly greater risk of severe hypoglycemia with MDI compared with CSII (rate ratio 4.19 [95 % CI 2.86–6.13]) [158]. However, these results are not directly comparable as, in contrast to the meta-analysis, episodes of severe hypoglycemia were either few or absent in studies comparing insulin aspart CSII with MDI, summarized in Table 5.

#### 5.1.2 Insulin Aspart in CSII Versus RHI and Compared with Rapid-Acting Insulin Analogs

Insulin aspart has also demonstrated comparable safety with RHI when both are used in CSII [99, 118–123] and with other rapid-acting insulin analogs (insulin lispro and/or insulin glulisine) in CSII [124, 126–128] (Table 5).

In a 39-week, randomized, open-label, multicenter, crossover trial in patients with T1D using insulin glulisine, insulin aspart, and insulin aspart in CSII, the primary endpoint of incidence of catheter occlusion and unexplained hyperglycemia [95 % CI] was similar with insulin glulisine (68.4 % [62.7–74.1]), insulin aspart (62.1 % [56.2–68.1];  $p = 0.04$ ) and insulin lispro (61.3 % [55.4–67.3];  $p = 0.03$ ) [127]. In terms of secondary outcomes, the monthly rate of unexplained hyperglycemia or perceived infusion set occlusion was significantly lower with insulin aspart (1.32 [1.02–1.61];  $p < 0.001$ ) and insulin lispro (1.54 [1.24–1.83];  $p < 0.001$ ) compared with insulin glulisine (2.02 [1.73–2.32]).

In one article summarizing the results of two randomized trials ( $n = 265$ ) with a total treatment period of 24 weeks in patients with T1D, subjects treated with



insulin lispro had a lower rate of documented and all-reported hypoglycemia than those treated with insulin aspart (documented hypoglycemia: 9.39 vs 10.84,  $p = 0.003$ ; and 7.57 vs 8.71,  $p = 0.012$ , for trial 1 and trial 2, respectively; all reported hypoglycemia: 15.26 vs 16.91,  $p = 0.006$ ; and 16.74 vs 18.86,  $p < 0.001$ , for trial 1 and trial 2, respectively) [130]. A significantly higher rate per 30 days of unexplained hyperglycemic episodes was noted in the insulin lispro group compared with the insulin aspart group (trial 1: 8.20 vs 6.79,  $p = 0.029$ ; trial 2: 8.05 vs 6.54;  $p = 0.003$ ).

## 5.2 Effect of Insulin Aspart on Weight

Examining the effect of insulin aspart on weight is difficult because of the competing influence of other concurrent therapies that influence weight, particularly basal insulin. For example, less weight gain has been demonstrated in basal-bolus trials with all-analog regimens (insulin aspart + insulin detemir) compared with RHI + NPH in T1D [78] and T2D [83]. However, the contribution of insulin aspart to effects on weight observed in these studies is impossible to separate from that of insulin detemir.

The effect on weight can be more directly assessed in CSII studies where insulin aspart is the sole insulin in a study arm. It is important to recognize that many of these studies are performed in children where, due to normal growth, an increase in weight is expected. Other studies are crossover trials, in which participants are exposed to all trial products. However, in one large (329 adults, 156 children) 1-year trial comparing insulin aspart CSII with insulin aspart + insulin glargine basal-bolus therapy, weight in adults increased by 2.4 and 1.8 kg in CSII and MDI groups, respectively ( $p = 0.19$ ) [112]. However, in a 16-week, parallel-group trial of 146 adults randomized to either insulin aspart CSII or RHI CSII, there were no changes in weight from baseline to end of trial [121].

In a before-and-after study of 513 adults with T1D or T2D, there was an increase in weight 12 weeks after switching from insulin lispro CSII to insulin aspart CSII (0.58 kg [95 % CI 0.4–0.8]) [129]. However, in a smaller ( $n = 21$  subjects) but much longer before-and-after study comparing RHI CSII and insulin aspart CSII in adults with T1D, BMI was nearly identical 1 year after switching to insulin aspart CSII (23.37 vs 23.70) [84].

## 6 Health Economics

Several trials have compared the cost effectiveness of insulin aspart with that of RHI [159–161] or assessed the health economic implications of intensifying treatment with insulin aspart [162, 163].

With respect to comparisons with RHI, an economic analysis of data from a trial comparing insulin aspart with RHI in 322 pregnant women using basal-bolus therapy with NPH as the basal insulin indicated that the cost of treatment was similar with insulin aspart and RHI (mean per-patient cost was £3222 in the insulin aspart group and £3539 in the RHI group, difference  $-\text{£}318$  [95 % CI  $-\text{£}1353$  to  $\text{£}576$ ],  $p = 0.49$ ) [159].

An economic analysis of data from patients with T2D in four European countries participating in the PREDICTIVE (Predictable Results and Experience in Diabetes Through Intensification and Control to Target: an International Variability Evaluation) study indicated that over a 35-year period, insulin aspart was projected as associated with societal and direct medical cost savings in Sweden (SEK2470 and SEK8248, respectively); with direct medical cost savings in Spain (€1382), but increased direct costs in Italy (€2235) and Poland (€743) [161]. In Germany, a decision analysis model incorporating macrovascular disease incidence in people with T2D indicated that, over a 3-year time frame, insulin aspart was (economically) superior to RHI, with the decreased incidence of macrovascular events resulting in lower costs and improved quality of life [160].

A study using records from 1793 patients with T2D from a large managed care organization in the US, who were intensifying treatment from a basal regimen + OADs to a basal-bolus regimen with insulin aspart, indicated that overall costs and diabetes-related healthcare costs decreased by US\$2283 and US\$2028, respectively ( $p \leq 0.0001$ ). This was attributed to a decrease in the number of in-patient visits (0.50 visits/patient/year;  $p < 0.05$ , for a cost savings of US\$3019/patient) and also to reductions in HbA<sub>1c</sub> (0.5 %;  $p = 0.001$ ) and use of OADs (56 vs 64 %;  $p < 0.0001$ ) [162]. Cost effectiveness of step-wise addition of bolus insulin aspart compared with full basal-bolus therapy in T2D was also evaluated in the FullSTEP trial [163]. Outcomes at end of trial such as hypoglycemic event rates, the proportion of patients achieving HbA<sub>1c</sub> targets, and SMBG were incorporated into the models. The models indicated that in a health plan with 77,000 patients with T2D and with 7.8 % intensifying each year to basal-bolus therapy, step-wise addition of insulin aspart would result in a cost savings of US\$1304 over a full basal-bolus regimen for each patient requiring intensification.

## 7 Future Needs and Opportunities

Fifteen years of clinical use of insulin aspart have demonstrated that it maintains PK and PD properties in a variety of patient populations. However, despite these

**Table 5** Incidence of hypoglycemia and diabetic ketoacidosis with insulin aspart in CSII

Study (duration)	No. of patients	Insulin treatment (baseline) <sup>a</sup>	Safety findings
Insulin aspart (CSII) vs multiple daily doses: randomized trials			
DeVries et al. (2002) (crossover, 16 week periods) [119]	79 Adults T1D	IAsp CSII  IAsp + NPH	0.98 ± 2.02 episodes of mild hypoglycemia per patient—week 3 episodes of severe hypoglycemia 1 episode of DKA 0.02 ± 1.18 episodes of mild hyperglycemia per patient—week 6 episodes of severe hypoglycemia 1 episode of DKA
Raskin et al. (2003) (24 weeks) [117]	132 Adults T2D	IAsp CSII IAsp + NPH	0.8 ± 1.6 hypoglycemic events/patient/30 days, none severe 1.2 ± 3.1 hypoglycemic events/patient/30 days, none severe
Doyle et al. (2004) (16 weeks) [113]	32 Children (8–21 years)	IAsp CSII IAsp + IGlir	1 hospitalization for DKA 5 episodes of severe hypoglycemia in 4 patients 2 hospitalizations for ketosis in 1 patient
Pańkowska et al. (2010) [98]	61 Children (<7 years)	IAsp CSII	0.3 major hypoglycemic events per year 21 minor hypoglycemic events per year 1.2 symptoms-only hypoglycemic events per year 0.1 major hypoglycemic events per year 18 minor hypoglycemic events per year 1.1 symptoms-only hypoglycemic events per year 0 major hypoglycemic events per year 20 minor hypoglycemic events per year
Bergental et al. (2010) (1 year) [112]	329 Adults T1D	IAsp CSII, sensor-augmented  IAsp + IGlir MDI	1.4 symptoms-only hypoglycemic events per year 15.31 episodes of severe hypoglycemia per 100 patient—years 0.01 episodes of DKA per 100 patient—years 17.62 episodes of severe hypoglycemia per 100 patient—years 0 episodes of DKA per 100 patient—years
	156 Children (7–18 years) T1D	IAsp CSII, sensor-augmented  IAsp + IGlir MDI	8.98 episodes of severe hypoglycemia per 100 patient—years 0.02 episodes of DKA per 100 patient—years 4.95 episodes of severe hypoglycemia per 100 patient—years 0.02 episodes of DKA per 100 patient—years
Insulin aspart (CSII) vs multiple daily doses: observational studies			
Kawamura et al. (2008) (6 months, single-arm, before/after study) [116]	26 Children (6–18 years) T1D	IAsp CSII (MDI, varied regimens)	7/22 patients had hypoglycemia, none severe 8/22 patients had hypoglycemia, none severe

Table 5 continued

Study (duration)	No. of patients	Insulin treatment (baseline) <sup>a</sup>	Safety findings
Insulin aspart (CSII) vs buffered RHI: randomized trials			
Bode and Strange (2001) (7 weeks) [120]	29 Adults T1D	IAsp CSII  BR HI CSII	14 (74 %) patients experienced hypoglycemia 2.9 events/patient 6 (60 %) patients experienced hypoglycemia 6.2 events/patient
Bode et al. (2002) (16 weeks) [121]	146 Adults T1D	IAsp CSII BR HI CSII ILisp CSII	3.7 ± 3.6 hypoglycemic episodes per patient per month 4.8 ± 4.2 hypoglycemic episodes per patient per month 4.4 ± 4.7 hypoglycemic episodes per patient per month
Skogsberg et al. (2008) (24 months) [99]	72 Children (7–17 years) T1D	IAsp CSII  IAsp MDI	2.5 ± 0.5 perceived episodes of hypoglycemia No episodes of DKA 3.5 ± 0.5 perceived episodes of hypoglycemia No episodes of DKA
Ly et al. (2013) (<2 weeks; time to reach glucose target) [118]	119 Adults T2D	IAsp CSII IAsp + IGLar IAsp + IDet	0.10 episodes of hypoglycemia per person per day 0.07 episodes of hypoglycemia per person per day 0.05 episodes of hypoglycemia per person per day
Gao et al. (2014) (12 weeks) [114]	200 Adults T2D	IAsp CSII IAsp + IGLar	1.62 % of patients had hypoglycemic events <sup>a</sup> 5.93 % of patients had hypoglycemic events
Insulin aspart (CSII) vs buffered RHI: observational studies			
Chlup et al. (2004) (~90 weeks, single-arm before/after study) [122]	21 Adults T1D	IAsp CSII (BR HI CSII)	No change in frequency of hyper- or hypoglycemia after switching
Insulin aspart vs insulin lispro and insulin glulisine, all in CSII: randomized trials			
Weinzimmer et al. (2008) (16 weeks) [128]	298 Children (4–18 years) T1D	IAsp CSII  ILisp CSII	92.2 hypoglycemic events per patient—year 5.7 nocturnal hypoglycemic events per patient—year 0.4 major hypoglycemic events per patient—year 1 patient experienced DKA 81.3 hypoglycemic events per patient—year 5.7 nocturnal hypoglycemic events per patient—year 0.3 major hypoglycemic events per patient—year 2 patients experienced DKA

**Table 5** continued

Study (duration)	No. of patients	Insulin treatment (baseline) <sup>A</sup>	Safety findings
van Bon et al. (2011) (crossover, 13-week periods) [127]	288 Adults T1D	IAsp CSII  IGlu CSII	65.01 symptomatic hypoglycemic events per patient—year 9.66 nocturnal hypoglycemic events per patient—year 1.38 severe hypoglycemic events per patient—year 73.84 symptomatic hypoglycemic events per patient—year 12.80 nocturnal hypoglycemic events per patient—year 1.63 severe hypoglycemic events per patient—year 1 patient experienced DKA
Thrasher et al. (2014) (crossover, 16-week periods) [126]	122 Adults T2D	ILisp CSII  IAsp CSII	62.69 symptomatic hypoglycemic events per patient—year 9.48 nocturnal hypoglycemic events per patient—year 1.06 severe hypoglycemic events per patient—year 2.38 hypoglycemic events per patient per 30 days 1.52 documented symptomatic hypoglycemic events per patient per 30 days 0.52 nocturnal hypoglycemic events per patient per 30 days 1 case of DKA
Insulin aspart vs insulin lispro and insulin glulisine, all in CSII: observational studies		ILisp CSII	2.24 hypoglycemic events per patient per 30 days 1.25 documented symptomatic hypoglycemic events per patient per 30 days 0.45 nocturnal hypoglycemic events per patient per 30 days
Alemzadeh et al. (2007) (1-year, single-arm before/after) [124]	14 Children (~3–5 years)	IAsp CSII (IAsp + IGlur)	73.1 moderate hypoglycemic events per 100 patient—years 17.5 severe hypoglycemic events per 100 patient—years (92.3 moderate hypoglycemic events per 100 patient—years)
Wittlin et al. (2008) (16 weeks, single-arm, before/after) [129]	513 Adults T1D or T2D	IAsp CSII (ILisp CSII)	22.5 severe hypoglycemic events per 100 patient—years 6 hypoglycemic events during 12 weeks of treatment (1 hypoglycemic event during 4 weeks of treatment)

BR HI buffered regular human insulin, CSII continuous subcutaneous insulin infusion, DKA diabetic ketoacidosis, HI human insulin, IAsp insulin aspart, IDer insulin detemir, IGlur insulin glargine, IGLu insulin glulisine, ILisp insulin lispro, MDI multiple daily injections, NPH neutral protamine Hagedorn insulin, RHI regular human insulin, T1D type 1 diabetes, T2D type 2 diabetes

<sup>a</sup>  $P < 0.01$

<sup>A</sup> Baseline value before switching in single-arm studies

improvements, rapid-acting insulin aspart still does not fully mimic the PK and PD endogenous insulin profile. The next generation of insulin aspart ('faster-acting insulin aspart') is currently in clinical development and preliminary results have been reported [164, 165]. Faster-acting insulin aspart contains excipients nicotinamide and arginine. The excipients result in a stable formulation and faster initial absorption after SC injection [164].

In a glucose clamp crossover study, 52 adult patients with T1D were randomized to either insulin aspart or faster-acting insulin aspart [164]. Faster-acting insulin aspart took less than half of the time to onset of appearance (4.9 vs 11.2 min) and showed higher early exposure. During the first 30 min, area under the serum insulin aspart curve with faster-acting insulin aspart was twofold higher than insulin aspart (treatment ratio 2.05 [95 % CI 1.76–2.38]). Faster-acting insulin aspart had 50 % greater glucose-lowering effect within the first 30 min ( $AUC_{GIR, 0-30 \text{ min}}$  treatment ratio 1.48 [95 % CI 1.13–2.02]).

In a double-blind, randomized crossover study, two formulations of faster-acting insulin aspart (only data for the faster aspart formulation undergoing further development were presented) were compared with insulin aspart in CSII in 43 adults for 14 days [165]. Faster-acting insulin aspart had a significantly greater glucose-lowering effect after a standardized meal than insulin aspart, as shown by a lower mean change in plasma glucose from 0 to 2 h (3.03 and 4.02 mmol/L, respectively; treatment difference  $-0.99$  mmol/L [95 % CI  $-1.95$  to  $-0.03$ ],  $p < 0.05$ ). The mean increment in interstitial glucose (measured with blinded continuous glucose monitoring) was also significantly lower with faster-acting insulin aspart at 60 min (treatment difference  $-0.66$  mmol/L [95 % CI  $-0.95$  to  $-0.37$ ];  $p < 0.001$ ) and 120 min (treatment difference  $-0.58$  [95 % CI  $-0.97$  to  $-0.19$ ],  $p < 0.01$ ) after all meals. The duration of low interstitial glucose (i.e.,  $\leq 3.9$  mmol/L per 24 h) was also significantly longer for insulin aspart compared with faster-acting insulin aspart (2.45 and 2.03 h, respectively, mean difference  $-0.42$  [95 % CI  $-0.72$  to  $-0.11$ ]).

## 8 Conclusion

Insulin aspart is structurally identical to both RHI and endogenous insulin, except for replacement of a single proline amino acid at position 28 in the C-terminal area of the insulin  $\beta$ -chain with an aspartic acid residue. This substitution weakens the natural tendency towards self-association between insulin monomers, thereby accelerating absorption after SC injection. Following SC injection, insulin aspart had a faster absorption, shorter time to peak

activity, and a more rapid and shorter duration of action than RHI.

The PK profiles for insulin aspart and insulin lispro are similar, whereas the absorption of insulin glulisine appears slightly more rapid. Head-to-head trials comparing insulin aspart with insulin lispro have generally shown comparable PD, whereas insulin glulisine had a slightly earlier onset. There seem to be no clinically important relationships between insulin aspart PK and BMI, renal impairment, or hepatic impairment.

In adult patients with T1D, insulin aspart demonstrated improved postprandial glucose control compared with RHI after meals. A meta-analysis of trials of basal-bolus therapy in T1D and T2D has shown significantly better postprandial glucose control with insulin aspart treatment compared with RHI. Insulin aspart significantly reduces  $HbA_{1c}$  compared with RHI in T1D, and in T2D both insulins appear to influence  $HbA_{1c}$  similarly. A meta-analysis in T1D and T2D has shown better  $HbA_{1c}$  reduction with insulin aspart compared with RHI. Furthermore, comparisons of insulin aspart with other analogs in CSII have generally shown no significant differences in  $HbA_{1c}$  between treatment groups, and studies have suggested that insulin aspart has a lower risk of occlusion than either insulin lispro or insulin glulisine. Randomized trials in T1D have generally shown no difference in the incidence of overall or major hypoglycemia between treatments. Insulin aspart administered as CSII and MDI therapy have shown comparable safety.

Despite these improvements, insulin aspart still does not fully mimic the PK and PD properties of the endogenous insulin profile. An ultrarapid-acting insulin—'faster-acting insulin aspart'—appears to have twice-as-fast onset of appearance, 2-fold higher insulin exposure, and 50 % greater insulin action within the first 30 min than insulin aspart. More closely approaching the physiological insulin secretion profile could lead to earlier inhibition of hepatic glucose production and improved postprandial glucose control. The efficacy and safety of faster-acting insulin aspart need to be demonstrated in large clinical trials.

### Compliance with Ethical Standards

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