Diversity in diabetes: the role of insulin aspart

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Summary

Diabetes management is changing not only with novel treatments but also in patient demography. This presents clinical challenges and influences our view of diabetes therapies. Insulin analogues have been developed to overcome some of the limitations of traditional human insulins, with the aim of providing a more physiological pharmacokinetic/pharmacodynamic profile. The rapid-acting insulin analogue insulin aspart has been investigated in many clinical trials over the past 10 years and the aim of this review is to present the insulin aspart clinical trial data from across the spectrum of patients with diabetes. Five studies have looked at insulin aspart use (including continuous subcutaneous insulin infusion) in children and adolescents, where the analogue was as effective and well tolerated as soluble human insulin. One large-scale, randomized, controlled trial in pregnant women with type 1 diabetes observed trends towards a reduction in major hypoglycaemia, fewer preterm deliveries and lower birthweight with insulin aspart compared with soluble human insulin. Two 6-month, randomized, controlled, multicentre, multinational, parallel-group, open-label trials reported significant reductions in haemoglobin A₁c and major nocturnal hypoglycaemia with insulin aspart compared with soluble human insulins in patients with type 1 diabetes. There are fewer data involving insulin analogue use in hospitals and in elderly patients with diabetes, but some recent studies have investigated insulin aspart in the emergency department, intensive/non-intensive care setting and in a pharmacokinetic/pharmacodynamic study in patients aged ≥65 years. In summary, the evidence would suggest that insulin aspart is suitable for use in a variety of patients with diabetes. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords insulin aspart; rapid-acting insulin analogues; elderly; children; pregnancy; diabetes

Introduction

There have been multiple changes in the management of diabetes in the past decade. One of the main shifts has been the movement of treatment focus away from speciality care towards primary care. Initiation and intensification of insulin therapy is no longer the domain of the diabetes care specialist. This has altered our approach to insulin therapy, in particular increasing our recognition of the importance of individualized treatment. However, not only management but also patient demography have changed: increasing numbers of children are being diagnosed with type 1 or type 2 diabetes [1,2]; and, as the ageing population continues to rise, increasing numbers of elderly patients are being treated with insulin [3]. These challenges in clinical practice continue to evolve.

Diabetes is a life-long condition, irrespective of age at diagnosis, and specific management considerations must be borne in mind throughout
all stages of patients' lives. Recent data have pointed to a 'metabolic memory' effect, whereby even brief initial periods of poor glycaemic control may adversely affect future risk of complications and long-term outcomes (particularly cardiovascular) [4,5]. Other studies have shown an adverse effect of hypoglycaemia, resulting from intensive insulin therapy, on cardiovascular risk outcomes and mortality in patients with type 2 diabetes [6]. This area is controversial, with data both conflicting and unclear [7].

When setting goals to minimize chronic complications, avoid hypo- and hyperglycaemia and optimize quality of life, these must be customized to the individual patient through education, relevant treatment aims and appropriate use of available tools to facilitate care. These considerations have together changed the way we view insulin therapy, especially now that a range of tools is available, including insulin analogues.

Insulin analogues were developed with the aim of addressing some of the drawbacks of conventional human insulin, in particular the inappropriate pharmacokinetic/pharmacodynamic (PK/PD) profile. The relatively slow dissociation of soluble human insulin hexamers in the interstitium following subcutaneous administration produces a peak insulin concentration in the circulation around 2 h after injection [8]. This does not closely match the physiological prandial insulin response, potentially resulting in postprandial hyperglycaemia and delayed postprandial hypoglycaemia in patients with diabetes. Planning the required interval between injection and eating is also particularly inconvenient for patients. The rapid-acting insulin analogues insulin aspart, insulin lispro and insulin glulisine are absorbed more rapidly into the circulation and reach a higher peak insulin concentration than soluble human insulin [9]. PK/PD data have shown that for both insulin glulisine and insulin aspart, the duration of action does not increase with increasing doses, unlike soluble human insulin [10,11].

Providing adequate basal insulin levels in patients with diabetes is also challenging. There is a need for sufficient concentrations to achieve daytime, overnight and fasting glycaemic control while limiting the occurrence of nocturnal hypoglycaemia. Neutral protamine Hagedorn (NPH) insulin has a duration of action of around 13 h (therefore often necessitating twice-daily administration) and a peak action at 4–8 h which, with bedtime administration, could contribute to nocturnal hypoglycaemia [12]. The basal insulin analogues insulin detemir and insulin glargine were therefore designed to offer a smoother, more protracted duration of action than NPH insulin. The combination of a basal and rapid-acting insulin analogue offers a more physiological insulin profile than can be achieved with conventional human insulins, with the aim of providing improved efficacy and tolerability for patients.

One of the rapid-acting insulin analogues, insulin aspart, has been available for 10 years and like all analogues is currently used for treating the increasingly diverse diabetes population. The aim of this review is to provide an overview of insulin aspart clinical data over the last 10 years and to examine its use across the spectrum of patients with diabetes.

**Children with diabetes**

The prevalence and incidence of children with type 1 or type 2 diabetes are increasing. More than 70 000 children develop type 1 diabetes every year and rates of diagnosis are expected to double between 2005 and 2020 [1,2]. While the incidence of type 2 diabetes in children is still low in Europe, rates of diagnosis in children under 15 years are projected to increase by 70% by 2020, and globally, type 2 diabetes now accounts for up to 45% of new diabetes cases in children [1,2].

Insulin analogue use is increasing in children with type 1 diabetes in Europe, including use from the time of diagnosis [13]. Rapid-acting insulin analogues provide the possibility of immediate preprandial or even postprandial administration in children and adolescents [14–20]. Children are spontaneous and may have unpredictable sleep patterns and eating behaviours [21]. Consequently, their insulin regimens need to be flexible. It is possible that rapid-acting insulin analogues may have a more suitable PK/PD profile than soluble human insulin to cover unplanned snacks or extra meals in children. The PK/PD profile of insulin aspart compared with that of soluble human insulin was investigated in a small single-dose, randomized, double-blind, two-period cross-over study of children and adolescents with type 1 diabetes [22] (Table 1). Following a single subcutaneous dose (0.15 U/kg) of insulin aspart or human insulin 5 min before breakfast, blood samples were taken at intervals for 5 h following the meal for glucose, insulin and C-peptide levels. The results showed that adolescents had higher maximum serum insulin as well as area under the curve (AUC₀–₅)h insulin concentrations than the younger age group. This small study demonstrates that the PK/PD characteristics of insulin aspart compared with human insulin are preserved in children and adolescents as in adults with diabetes [23,24].

Two clinical studies have been conducted with insulin aspart in children and adolescents (with ages ranging from 2 to 17 years) [14,15]. The feasibility of postprandial compared with preprandial insulin administration was demonstrated in a randomized, multicentre study with an open-label, two-period cross-over design involving 76 children and adolescents with type 1 diabetes (Table 1) [14]. Glycaemic control (measured by fructosamine and 9-point blood glucose profiles) was similar between the two administration timings, except for postprandial glucose following breakfast (Table 1). Treatment satisfaction measured by a modified version of the Diabetes Treatment and Satisfaction Questionnaire was comparable between the groups for parents and adolescents. Parents did significantly prefer preprandial administration when asked the question, 'Would you recommend the form
Table 1. Clinical studies of insulin aspart in children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Study type</th>
<th>Patients</th>
<th>Aim/method</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Mortensen et al. [22]</td>
<td>Single-dose, randomized, double-blind, two-period cross-over study</td>
<td>6–12 years (9 children) 13–17 years (9 adolescents) with type 1 diabetes</td>
<td>Pharmacokinetic/ pharmacodynamic profile comparison of insulin aspart versus soluble human insulin</td>
<td>In both groups, insulin aspart produced a significantly higher ($C_{\text{max}}$ mol) and earlier ($t_{\text{max}}$ min) maximum insulin concentration than human insulin: overall results of mean ± standard deviation $C_{\text{max}}$ of 881 ± 321 pmol/L for insulin aspart versus 422 ± 193 pmol/L for human insulin, $p &lt; 0.001$; and median $t_{\text{max}}$ of 40 versus 75 min, respectively, $p &lt; 0.001$. Mean ± standard deviation glucose levels following insulin administration were also lower with insulin aspart compared with human insulin: $\Delta C_{\text{max glu}}$ of 7.6 ± 5.1 versus 9.4 ± 4.4 mmol/L, respectively, $p &lt; 0.05$.</td>
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<tr>
<td>Danne et al. [14]</td>
<td>12-week, randomized, multicentre, open-label, two-period cross-over study</td>
<td>6–12 years (42 children) 13–17 years (34 adolescents) with type 1 diabetes</td>
<td>Comparison of pre- (immediately before eating) and post- (no later than 30 min after the start of the meal) prandial administration of insulin aspart (as part of a basal–bolus regimen)</td>
<td>Mean ± standard deviation glycaemic control (measured by change in fructosamine before and after each 6-week treatment period) was similar between both administration timings: 366.8 ± 73.7 to 378.0 ± 89.7 μmol for preprandial administration and 383.5 ± 83.3 to 385.4 ± 77.3 μmol for postprandial administration. However, lower mean postprandial glucose levels 120 min after breakfast were reported with preprandial versus postprandial insulin aspart administration (difference of $-2.08 ± 0.74$ mmol/L, $p = 0.016$). Three major hypoglycaemic episodes occurred in the study, two with preprandial and one with postprandial administration. The number of overall hypoglycaemic episodes decreased over the study for both administration timings: preprandial insulin aspart from 1.36 to 0.99 episodes/week, postprandial insulin aspart from 1.23 to 0.86 episodes/week. Glycaemic control was similar between insulin aspart and soluble human insulin: mean HbA1c, 7.7 versus 7.6%, respectively, and postprandial plasma glucose increments, 2.0 versus 1.6 mmol/L. The relative risk of hypoglycaemia was also similar: insulin aspart/soluble human insulin (95% confidence interval): 1.06 (0.96–1.17), $p = 0.225$.</td>
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<tr>
<td>Danne et al. [21]</td>
<td>Randomized, multicentre, two 12-week period cross-over trial</td>
<td>2–7 years (26 children) with type 1 diabetes</td>
<td>Comparison of soluble human insulin injected 30 min before eating and insulin aspart administered within 30 min of starting eating</td>
<td>Glycaemic control was similar between insulin aspart and soluble human insulin: mean HbA1c, 7.7 versus 7.6%, respectively, and postprandial plasma glucose increments, 2.0 versus 1.6 mmol/L. The relative risk of hypoglycaemia was also similar: insulin aspart/soluble human insulin (95% confidence interval): 1.06 (0.96–1.17), $p = 0.225$.</td>
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<tr>
<td>Weinzimer et al. [25]</td>
<td>16-week randomized, open-label, parallel group, multicentre study</td>
<td>4–18 years (298 children) with type 1 diabetes</td>
<td>Comparison of insulin aspart and insulin lispro delivered through CSII</td>
<td>The CSII group achieved significantly lower HbA1c levels than the basal–bolus group (7.2 versus 8.1%, respectively, $p &lt; 0.05$), with similar basal insulin doses but a significantly lower total insulin dose (0.9 ± 0.2 U/kg in CSII group versus 1.2 ± 0.2 U/kg in glargine group ($p = 0.003$). Five episodes (in four subjects) of severe hypoglycaemia were experienced in the basal–bolus group versus two episodes (in two subjects) treated with CSII.</td>
</tr>
<tr>
<td>Doyle et al. [26]</td>
<td>16-week, open-label, randomized, parallel trial</td>
<td>8–21 years (32 children and adolescents) with type 1 diabetes</td>
<td>Comparison of insulin aspart in CSII with an insulin aspart plus insulin glargine basal–bolus regimen</td>
<td>The CSII group achieved significantly lower HbA1c levels than the basal–bolus group (7.2 versus 8.1%, respectively, $p &lt; 0.05$), with similar basal insulin doses but a significantly lower total insulin dose (0.9 ± 0.2 U/kg in CSII group versus 1.2 ± 0.2 U/kg in glargine group ($p = 0.003$). Five episodes (in four subjects) of severe hypoglycaemia were experienced in the basal–bolus group versus two episodes (in two subjects) treated with CSII.</td>
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CSII, continuous subcutaneous insulin infusion; HbA1c, haemoglobin A1c.
of insulin treatment your child received to someone else?' (difference in score of 0.49, \( p = 0.01 \)).

The other study conducted in 26 children with diabetes was a randomized, multicentre, 12-week, cross-over trial of prandial insulin aspart versus prandial soluble human insulin (both in basal–bolus regimens with NPH insulin) (Table 1) [15]. Insulin aspart and soluble human insulin were mixed with NPH insulin to avoid too many injections. One drawback to the use of rapid-acting insulin analogues in children is that more injections may be required, due to their short duration of action compared with soluble human insulin. The study found that prandial administration of insulin aspart in preschool children was as effective and well tolerated as prandial soluble human insulin (Table 1). A modified version of the Diabetes Treatment and Satisfaction Questionnaire was used to assess parental satisfaction with their child's treatment, and showed that parents significantly preferred insulin aspart to soluble human insulin in response to the question, 'How satisfied would you be to continue your child's present form of insulin treatment?' (difference in score of 1.1, \( p = 0.045 \)). Measuring treatment satisfaction is, however, limited in an open-label study.

While these studies are small and have limitations, they do include some very young children and at least demonstrate the feasibility of rapid-acting insulin analogues in this population. While no data exist specifically to support the flexibility of administration timings with rapid-acting insulin analogues in children and adolescents, it is logical, for example, that being able to adjust insulin doses postprandially according to carbohydrate content may be more convenient for children and/or their caregivers.

Administering insulin can be a challenge for school-age children: lunchtime insulin doses may have to be administered at home, by a school nurse (if insured/legally allowed) or by a parent coming into school. Pen devices are useful for insulin administration in children due to their ability to deliver low doses (0.5 U). The majority of European paediatric/adolescent patients with diabetes have multiple daily insulin injections [27], but continuous subcutaneous insulin infusion (CSII) administration is also increasing, including in young children [27]. A 16-week, randomized, multicentre, open-label, parallel-group study in almost 300 children with type 1 diabetes reported that insulin aspart CSII was as effective and well tolerated as insulin lispro CSII (Table 1) [25]. A second 16-week, open-label, randomized, parallel-group study in 32 children and adolescents with type 1 diabetes demonstrated better glycaemic control with insulin aspart CSII than with insulin aspart plus insulin glargine basal–bolus treatment, but both regimens were similarly well tolerated (Table 1) [26].

The above studies have demonstrated that insulin aspart use in children and adolescents is generally well tolerated. Other safety aspects of insulin aspart use in children have also been investigated. A non-randomized, single-centre, retrospective case-control study reported on insulin antibodies (i.e. antibodies against insulin aspart as well as antibodies cross-reacting with human insulin and insulin aspart) in 72 children and adolescents newly diagnosed with type 1 diabetes over 30 months treated with either human insulin or insulin aspart [28]. Antibodies against insulin aspart remained low throughout the study, while increases in human insulin-croix-reacting antibodies were observed in both groups. However, there were no significant differences between treatments (mean \( \pm \) standard deviation: 48.8 \( \pm \) 21.5% with human insulin and 40.2 \( \pm \) 17.9% with insulin aspart, \( p = 0.16 \)) and there were no associations with efficacy or safety.

### Diabetes in pregnancy

One of the aims of the St Vincent Declaration in 1989 was that the outcome of diabetic pregnancy should approximate that of non-diabetic pregnancy. Unfortunately, some 20 years on, this goal has still not been realized [29,30]. The basic aims of managing diabetic pregnancy include stringent glycaemic control (and accompanying monitoring) throughout gestation customized to the individual patient. Haemoglobin A1c (HbA1c) levels of <6.1% prepregnancy, fasting plasma glucose levels of 3.5–5.9 mmol/L and postprandial glucose levels of <7.8 mmol/L are recommended [31,32]. It is well recognized that poor glycaemic control is associated with an increased risk of poor maternal/foetal outcomes [33,34] and good glycaemic control reduces this risk [35].

However, achieving strict glycaemic targets is challenging for both the patients and clinician and also has to be balanced against the risk of hypoglycaemia, the consequences of which can be serious for both the mother and baby [36,37]. While the pathophysiology of pregnancy in type 1, type 2 and gestational diabetes is different, the management goals are similar: optimizing glycaemic control, safety and quality of life.

Conceptually, insulin analogues may be helpful in the management of diabetic pregnancy given the desire to optimize postprandial glucose control with the avoidance of hypoglycaemia; a flexible administration may be beneficial if nausea interrupts normal eating habits. One large, prospective, randomized, controlled, multicentre, multinational trial has compared prandial insulin aspart with prandial soluble human insulin (both in combination with basal NPH insulin) in 322 women with type 1 diabetes who were pregnant or planning to become pregnant [38–41] (Table 2). On confirmation of pregnancy all patients had to have an HbA1c \( \leq \) 8.0%, and insulin doses were titrated to achieve preprandial plasma glucose levels between 4.1 and 6.1 mmol/L, 1- and 2-h postprandial plasma glucose levels of <8.6 and <7.5 mmol/L, respectively, and HbA1c \( \leq \) 6.5%. Patients were followed at 12, 24 and 36 weeks’ gestation plus a 6-week postpartum follow-up visit. The primary end-point was major hypoglycaemia (requiring third-party assistance). Obstetric and diabetic complications were
assessed as well as maternal efficacy and safety outcomes. Treatment with insulin aspart resulted in trends towards reductions in major hypoglycaemia (Table 2), with the lack of statistical difference between treatments possibly due to lack of statistical power and to a lower-than-anticipated occurrence of events. There was no difference in HbA1c between treatments (Table 2); however, mean prandial glucose increments were significantly lower with insulin aspart compared with human insulin (Table 2). In general, foetal outcomes were similar between insulin aspart and human insulin, although there was a trend towards fewer preterm deliveries and lower birthweight with aspart (Table 2) [39]. A secondary analysis that focused on those enrolling prior to pregnancy found that these patients experienced better hypoglycaemia outcomes than those already pregnant in the trial (Table 2) [41]. It is possible that initiation of insulin aspart prior to conception resulted in a lower risk of major hypoglycaemia than initiation in early pregnancy. Another secondary analysis of the trial data indicated that insulin antibodies to human insulin or insulin aspart do not develop during pregnancy, and there was no evidence to suggest that insulin aspart crosses the placenta (Table 2) [40]. In the absence of other published randomized controlled trials investigating an insulin analogue in type 1 diabetic pregnancy, these data provide reassurance and evidence of the potential benefit of the use of insulin aspart in this population.

The efficacy and safety of insulin aspart versus human insulin were also investigated in a smaller randomized, controlled, standardized meal-test study of 15 patients with gestational diabetes mellitus [42]. Overall, efficacy and safety were similar between the two treatments, but greater reductions in postprandial glucose were observed with insulin aspart (Table 2).

**Type 1 and type 2 diabetes in the adult population**

It is universally acknowledged that good glycaemic control (HbA1c, fasting plasma glucose and postprandial glucose) is the foundation of diabetes management in any patient. Reducing HbA1c reduces the risk of development and progression of late diabetic complications [43,44]. The importance of postprandial glucose control has come to the fore over recent years with a greater understanding of the induction of oxidative stress from glucose peaks and fluctuations, eventually leading to cardiovascular dysfunction [45]. The contribution of postprandial glucose to overall glycaemic control has also been highlighted over the past decade, along with the realization that postprandial glucose contributes disproportionally to HbA1c control [46].

However, achieving strict HbA1c levels and good glycaemic control can lead to an increase in hypoglycaemia [43,44], which poses challenges for patients and physicians. Particularly, patients fear hypoglycaemia, and they may adjust their insulin to avoid hypoglycaemia, leading to suboptimal control, or they may snack to avoid hypoglycaemia and this might cause weight gain. Hypoglycaemia is a major barrier to insulin therapy [47].

Two landmark studies of insulin aspart treatment involving 1952 patients with type 1 diabetes were published 10 years ago [48,49]. These were randomized, controlled, multicentre, multinational, parallel-group, open-label trials conducted for 6 months which compared insulin aspart with soluble human insulin, both administered before main meals and in combination with NPH insulin. In the European trial, there was a baseline-adjusted difference in HbA1c between the two treatments of 0.12%; 95% confidence interval 0.03–0.22; p = 0.02, in favour of insulin aspart. Insulin aspart treatment also resulted in lower postprandial glucose levels compared with human insulin (mean baseline-adjusted difference of −0.6 to −1.2 mmol/L, p < 0.01). The overall risk of experiencing a hypoglycaemic episode was similar between treatments, although major nocturnal events and late postprandial (4–6 h) hypoglycaemic events were significantly lower with insulin aspart than with human insulin (1.3 versus 3.4% of patients, p < 0.05, and 1.8 versus 5.0% of patients, p < 0.005, respectively). The North American trial reported similar findings [49]. Mean HbA1c values (% ± standard error of the mean) were significantly lower with insulin aspart (7.78 ± 0.03%) than with soluble human insulin (7.93 ± 0.05%, p = 0.005) at 6 months. Similarly, mean postprandial blood glucose levels (mmol/L ± standard error of the mean) were also significantly lower following insulin aspart treatment compared with human insulin at breakfast (8.7 ± 0.2 versus 10.3 ± 0.3), lunch (7.6 ± 0.2 versus 9.0 ± 0.2) and dinner (8.5 ± 0.2 versus 9.3 ± 0.2), p < 0.05. Fewer patients experienced major nocturnal hypoglycaemia with insulin aspart (4%) compared with soluble human insulin (8%, p = 0.013). Treatment satisfaction (Diabetes Treatment and Satisfaction Questionnaire) was only measured in the European trial and found patients significantly in favour of insulin aspart compared with human insulin (particularly for the subitems of convenience, flexibility and satisfaction to continue current treatment) [48]. Overall, there was a significantly higher treatment satisfaction score of 32.0 versus 29.7, p < 0.001.

A smaller, shorter study investigated insulin aspart use in 231 patients with type 2 diabetes [50]. In this 3-month, randomized, controlled trial, insulin aspart resulted in a significant improvement in HbA1c compared with human insulin (0.91 ± 1.00% decrease for insulin aspart versus 0.73 ± 0.87% decrease for human insulin, p = 0.025). Both prandial insulins could be administered with or without bedtime NPH insulin: by trial end 72% of patients in the insulin aspart group and 81% in the human insulin group were taking NPH insulin. Postprandial blood glucose also decreased to a greater extent with insulin aspart compared with soluble human insulin, with a treatment difference of up to 1.67 mmol/L. A similar proportion of patients experienced at least one episode of hypoglycaemia between the two treatments (41% each).
## Table 2. Clinical studies of insulin aspart in diabetic pregnancy

<table>
<thead>
<tr>
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<th>Patients</th>
<th>Aim/method</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Mathiesen et al. [38]</td>
<td>Prospective, randomized, controlled, multicentre, multinational trial</td>
<td>322 women with type 1 diabetes who were pregnant or planning pregnancy</td>
<td>Comparison of prandial insulin aspart with prandial soluble human insulin (both in combination with basal NPH insulin); maternal outcomes</td>
<td>Overall major hypoglycaemia, relative risk insulin aspart/human insulin was 28% lower: 0.720 (95% confidence interval 0.36–1.46), risk of major nocturnal hypoglycaemia was 52% lower [relative risk 0.48 (95% confidence interval 0.20–1.14)], and risk of any nocturnal hypoglycaemia was 24% lower [relative risk 0.76 (95% confidence interval 0.57–1.03)]. HbA1c was comparable with human insulin in second [insulin aspart–human insulin: −0.04 (−0.18 to 0.11)] and third [−0.08 (−0.23 to 0.06)] trimesters. Prandial glucose increments were lower with insulin aspart (insulin aspart–human insulin, in mmol/L) at end of first trimester: −0.75 (95% confidence interval −1.25, −0.25), p = 0.003; and at end of third trimester: −0.40 (−0.80, −0.01), p = 0.044. Overall treatment satisfaction (via the Diabetes Treatment Satisfaction Questionnaire) was significantly higher with insulin aspart (87.6 score) compared with human insulin (83.4 score), p = 0.031</td>
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<tr>
<td>Hod et al. [39]</td>
<td>Prospective, randomized, controlled, multicentre, multinational trial (as above)</td>
<td>As above</td>
<td>As above, with foetal/perinatal outcomes reported</td>
<td>There was a trend towards fewer preterm deliveries with insulin aspart versus soluble human insulin: 20.3 versus 30.6% of pregnancies, respectively (p = 0.053) and lower birthweight; mean (standard error of the mean) birthweight corrected for gestational age was 3438 g (71.5 g) and 3555 g (72.9 g); p = 0.091. Perinatal mortality was 14 and 22 per 1000 births, respectively, and the number of congenital malformations in each group was 6 and 9, respectively</td>
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<td>McCance et al. [40]</td>
<td>Secondary analysis of above trial</td>
<td>As above</td>
<td>As above, with insulin antibody data reported</td>
<td>Median levels of insulin aspart-specific antibodies were low at baseline (0.3% for both groups) and at gestational week 36 (0.2% for the insulin aspart group and 0.3% for the human insulin group). Similarly, human insulin-specific antibodies were at baseline (−0.1% in both groups) and remained low during pregnancy (−0.1% for insulin aspart and 0.0% for human insulin at gestational week 36)</td>
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A small but significant decrease in cross-reacting insulin antibodies was observed during pregnancy (from 6.9 to 3.7% in the insulin aspart group and from 8.6 to 4.1% in the human insulin group): the estimated regression coefficient of cross-reacting insulin antibodies at baseline (for the two groups together) was 0.8266, which was significantly different from 1 (p = 0.0120, r² = 0.7612). Cross-reacting insulin antibodies in cord blood and maternal cross-reacting insulin antibodies at gestational week 36 were significantly correlated (regression coefficient = 0.9271, p < 0.0001, r² = 0.9067), but no treatment effect was found (p = 0.9248). There was no correlation between birthweight and cord-blood human insulin (p = 0.1590) |

Insulin aspart was not detected in cord blood, including those who received intravenous infusion of insulin aspart during delivery |
Table 2. (Continued)

<table>
<thead>
<tr>
<th>Author</th>
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<tbody>
<tr>
<td>Heller et al.</td>
<td>Secondary analysis of above trial</td>
<td>As above</td>
<td>As above, with comparison of hypoglycaemia in those women randomly assigned during early pregnancy with women randomly assigned during preconception</td>
<td>23% of all patients experienced severe hypoglycaemia during pregnancy. The relative risk of severe hypoglycaemia in the first half of pregnancy in women randomized in early pregnancy/preconception was 1.70 (95% confidence interval 0.91–3.18, ( p = 0.097 )); the relative risk in the second half of pregnancy was 1.35 (0.38–4.77, ( p = 0.640 )). In women randomly assigned preconception, severe hypoglycaemia rates occurring before and during the first and second halves of pregnancy and postpartum for insulin aspart compared with human insulin were 0.9 versus 2.4, 0.9 versus 2.4, 0.3 versus 1.2 and 0.2 versus 2.2 episodes/patient/year, respectively (not significant).</td>
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<td>Pettitt et al.</td>
<td>Randomized, parallel-group, open-labelled trial</td>
<td>27 women with gestational diabetes mellitus (age 30.7 ± 6.3 years, HbA1c &lt; 7%)</td>
<td>Comparison of insulin aspart (5 min before meal) and human insulin (30 min before meal). The trial period extended from diagnosis of gestational diabetes (18–28 weeks) to 6 weeks postpartum</td>
<td>HbA1c was ≤6% in both groups throughout the study and no major hypoglycaemia was observed. During the meal test at week 6, mean glucose concentration at 30 min after eating was significantly lower with insulin aspart than with human insulin (4.7 ± 0.19 mmol/L versus 5.1 ± 0.23 mmol/L, respectively; ( p = 0.0278 )). Similarly, the mean peak glucose concentration was significantly lower with insulin aspart than with human insulin (5.4 ± 0.21 mmol/L versus 6.2 ± 0.33 mmol/L, respectively; ( p = 0.0097 )). Change from baseline values for average plasma glucose was lower with insulin aspart versus human insulin: −1.09 ± 0.54 mmol/L versus −0.54 ± 0.74 mmol/L, respectively, ( p = 0.003 ).</td>
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The effect of insulin aspart on hypoglycaemia was explored in a multinational, double-blind, randomized, cross-over trial of two 16-week periods in 155 patients with type 1 diabetes and baseline HbA1c < 8.0% [51]. Patients were symmetrically randomized to insulin aspart or human insulin, both injected 0–5 min before meals, and NPH insulin was given as a basal insulin once or twice daily. Tight glycaemic control was maintained by regular adjustment of insulin doses according to predefined treatment algorithms. While HbA1c was maintained at 7.7% for both treatments, the rate of major nocturnal hypoglycaemia was 72% lower with insulin aspart compared with human insulin (0.067 versus 0.225 events/month; relative risk 0.93; 95% confidence interval 0.87–1.00; \( p = 0.001 \)). The overall rate of major hypoglycaemia did not differ between treatments (relative risk 0.72; 95% confidence interval 0.47–1.09; \( p = 0.12 \)) but minor events were also reduced with insulin aspart (relative risk 0.93; 95% confidence interval 0.87–1.00; \( p = 0.048 \)).

A recent study has also provided long-term data on the efficacy and safety of insulin aspart as part of a basal–bolus regimen with insulin detemir in patients with type 2 diabetes [52,53]. The Treat-To-Target in Type 2 Diabetes study was a 3-year, multicentre, open-label, randomized, controlled clinical trial in 708 patients with type 2 diabetes (HbA1c 7.0–10.0% and on maximally tolerated doses of metformin and sulfonylurea). There is a lack of evidence-based medicine on how best to initiate insulin therapy in patients with type 2 diabetes, and so this study was designed to investigate this. Patients were initially randomly assigned to receive biphasic insulin aspart twice daily, prandial insulin aspart three times daily or basal insulin detemir once daily. Insulin doses were titrated throughout the study and if an HbA1c level of >10.0% or two consecutive HbA1c levels of >8.0% were recorded after 24 weeks in the first year of the trial, or a level of >6.5% was subsequently recorded, the sulfonylurea was discontinued and the original regimen was intensified with a second type of insulin: a lunchtime prandial insulin aspart injection was added to patients taking biphasic insulin aspart; a bedtime basal insulin detemir injection was added to the patients taking insulin aspart and a prandial insulin aspart injection before each meal was added to those patients taking insulin detemir. After 1 year, nearly 75% of patients were taking a second type of insulin so that most of the original insulin aspart and insulin detemir treatment groups were on a basal–bolus regimen [52]. Mean HbA1c levels after 3 years of treatment for the original insulin aspart and original insulin detemir groups were 6.8 and 6.9%, respectively. Over 40% of patients in both these groups achieved HbA1c < 6.5% after 3 years, and over 60% of patients achieved HbA1c < 7.0%. These excellent glycaemic control results were not at the cost of high rates of severe hypoglycaemia: a low proportion of patients experienced major hypoglycaemia over 3 years in the insulin aspart group (2.1%) and in the insulin detemir group (0.9%). Prior to the publication of this study, there were few data investigating insulin initiation and optimization in patients with type 2 diabetes.

The size, duration and design of the Treat-To-Target in Type 2 Diabetes study, with most patients with type 2 diabetes achieving excellent glycaemic control and low rates of hypoglycaemia when treated with a basal–bolus insulin analogue regimen, have added to the evidence base regarding the treatment of this population.

### Inpatient diabetes and hyperglycaemia

There is an increasing prevalence of diabetes in hospitalized patients (12–25% of patients with diabetes, although this may be underestimated) [54,55]. However, the management of these patients remains challenging. There are few randomized studies to guide us regarding what glycaemic targets need to be achieved and what management strategies result in best clinical outcomes, especially in the non-intensive care unit (non-ICU) populations.

Hyperglycaemia in hospital results from: (1) patients with a known history of diabetes; (2) patients who have diabetes, but are unaware of their condition; and (3) hyperglycaemia as a result of stress. Patients in all three groups should be treated similarly and appropriately, as hyperglycaemia results in poor clinical outcomes, longer hospital stays and increased cost [54,55]. There are, however, several barriers and challenges to managing hyperglycaemia in hospitalized patients. Changes in patient clinical status, unpredictable caloric or carbohydrate intake, initiation or discontinuation of certain medications such as steroids, failure of the clinician to make appropriate treatment adjustments based on daily blood glucose levels, poor coordination of blood glucose testing and prandial insulin administration and poor communication among the multidisciplinary care members [56] are among the many challenges to optimal care of these patients.

Insulin is the most appropriate agent for management of hyperglycaemia among hospitalized patients; intravenous insulin is used in critically ill patients and subcutaneous insulin in non-critically ill patients [57]. There is also agreement that sliding-scale insulin administration should be discouraged as it is not effective and may compromise safety in inpatients [56,58]. The most recent consensus statement from the American Association of Clinical Endocrinologists and American Diabetes Association on inpatient glycaemic control does not state whether human insulin or insulin analogues should be used, but acknowledges this is an area for future research [56].

For patients requiring subcutaneous insulin in hospital, a basal–bolus insulin regimen is recommended [56]. Supplemental (correction) insulin doses should also be used (rapid or short acting), the insulin being the same used at mealtimes. There is not a great deal of evidence demonstrating the use of rapid-acting insulin analogues.
in hospitalized patients; however, it is possible that the PK/PD characteristics of rapid-acting insulin analogues may be beneficial compared with human insulin when postprandial administration [59,60] or quick reduction of hyperglycaemia is required.

Several diverse studies have investigated the use of insulin aspart in hospitalized patients [61–64]. A prospective, randomized, open-label trial in 45 consecutive patients admitted to an emergency department with diabetic ketoacidosis compared subcutaneous insulin aspart every 1 (n = 15) or 2 (n = 15) h, and intravenous infusion of soluble human insulin (n = 15) [61]. The subcutaneous insulin aspart regimens were no different from intravenous insulin infusion with regard to mean duration of treatment until correction of hyperglycaemia (6.9 ± 4 (subcutaneous 1 h), 6.1 ± 4 (subcutaneous 2 h) and 7.1 ± 5 h (intravenous); not significant) or resolution of ketoacidosis (10 ± 3, 10.7 ± 3 and 11 ± 3 h, respectively; not significant). Length of hospital stay, number of hypoglycaemic events and mortality rates were also similar between the treatments. Subcutaneous insulin aspart in an emergency department setting was also investigated in two other studies [62,63]. A hyperglycaemia treatment protocol was tested in 54 consecutive patients with a history of diabetes and an admission blood glucose level of >11.1 mmol/L in a quasi-experimental study using historical-matched controls [62]. The protocol consisted of weight- and blood-glucose-based subcutaneous insulin aspart every 2 h until blood glucose was <11.1 mmol/L. Only 35% of historical controls received insulin therapy.

Treatment with insulin aspart decreased mean blood glucose levels from 18.5 ± 5.8 mmol/L on admission to 8.8 ± 3.8 mmol/L at discharge from the emergency department. This was a significantly greater decline than that seen in the historical control group (17.9 ± 7.0 to 1.34 ± 4.4 mmol/L, p < 0.001).

Subsequently, 69% of insulin aspart-treated patients and 67% of the historical controls were admitted to hospital. Mean length of hospital stay was significantly less with insulin aspart than with historical controls (3.8 ± 3.3 versus 5.3 ± 4.1 days, p < 0.05). Four patients (7.4%) treated with insulin aspart developed a blood glucose level <3.9 mmol/L.

A second study has also looked at subcutaneous insulin aspart in the emergency department setting, but was prospective, randomized and controlled [63]. The trial investigated 114 patients with type 2 diabetes and blood glucose >11.1 mmol/L who were randomized to receive weight- and blood-glucose-based insulin aspart every 2 h until blood glucose <11.1 mmol/L, or usual care. Fifty-four percent of usual care patients received subcutaneous insulin aspart. Mean blood glucose decreased by 4.3 mmol/L with insulin aspart treatment and by 3.1 mmol/L with usual care. Thirty-three patients treated with insulin aspart and 36 patients treated with usual care were admitted as inpatients. Those treated with insulin aspart (now added to each meal) also began once-daily insulin detemir, and both were titrated. Inpatient usual care patients were treated by hospital physicians with a mixture of oral agents (19%), NPH insulin and aspart (33%) or glargine and aspart (48%). Mean hospital blood glucose levels were lower for insulin aspart plus insulin detemir (8.2 ± 2.3 mmol/L) compared with usual care [9.9 ± 3.7 mmol/L (p < 0.01)]. Inpatient hypoglycaemia was similar between treatments.

The safety of intravenous insulin aspart use in hospital has been investigated only in a large open-label, observational study [64]. Inpatient hyperglycaemia in either an ICU or a non-ICU setting was treated with intravenous insulin aspart according to clinical practice in India. A total of 2792 patients received this treatment over 6 months; 67.3% of patients received intravenous insulin aspart in an ICU setting. Only 1.6% of patients experienced at least one episode of major hypoglycaemia with intravenous insulin aspart and there were only five serious adverse events, none of which were deemed related to insulin aspart.

### Elderly patients with diabetes

Elderly patients with diabetes tend to have more advanced and pronounced disease than younger patients [65,66], and frequent comorbidity, which can also complicate management [67]. Other challenges in managing elderly patients include the age-related decline in renal impairment and polypharmacy. Both of these put elderly patients at risk of drug accumulation, drug–drug interactions and adverse effects [68,69]. Consequently, it is important that the medications used to treat diabetes in elderly patients do not carry a risk of accumulation and thus cause unnecessary hypoglycaemia or other adverse effects.

The PK/PD of insulin aspart have been investigated in 18 patients with type 1 diabetes with varying degrees of renal impairment [creatinine clearance ranging from <30 mL/min (severe) to >80 mL/min (normal)] [70]. Each patient was given a single subcutaneous injection of insulin aspart followed by a standardized meal. Regression analyses showed no significant difference in PK endpoints between normal and variable degrees of renal impairment: \( C_{\text{max}} \), \( \text{In (AUC}_{0–360} \) and \( t_{1/2} \) (min): \( p = 0.92, p = 0.78 \) and \( p = 0.65 \), respectively. Furthermore, no statistically significant linear observation was observed between creatinine clearance and \( C_{\text{max}}, \text{AUC}_{0–1440} \) and apparent clearance. The PK/PD characteristics of insulin aspart compared with soluble human insulin were also investigated in an elderly population with type 2 diabetes [71]. This was a randomized, single-centre, double-blind, cross-over trial in 19 elderly patients >65 years old) with type 2 diabetes given a single subcutaneous dose of 0.3 U/kg of insulin aspart or soluble human insulin during a euglycaemic clamp procedure. The AUC of the glucose infusion rate from 0 to 120 min after administration of insulins showed a significant difference between insulin aspart and soluble human insulin; the glucose-lowering effect in this 2-h period was on average 111% greater with insulin aspart than soluble human insulin.
(p < 0.0001). However, from 300 to 600 min following insulin administration the glucose-lowering effect was on average 92% greater with soluble human insulin than insulin aspart (p = 0.0006). Other PK/PD parameters also demonstrated an earlier onset of action, higher maximum glucose-lowering effect and time to maximum effect with insulin aspart compared with soluble human insulin, similar to the profile seen in younger patients with diabetes. In summary, there was greater PD activity of insulin aspart in the early phase, which indicated better mealtime glucose control with insulin aspart versus soluble human insulin, and there was significantly lower PD activity in the late phase compared with soluble human insulin.

While there are no large-scale, randomized, controlled trials specifically comparing insulin aspart with soluble human insulin in elderly patients with diabetes, the above studies provide some support for the use of insulin analogues in this population, although data regarding relevant endpoints such as hypoglycaemia are missing and therefore further research is required.

Conclusions

The efficacy, tolerability and safety of insulin aspart have been investigated in a variety of patients and studies since its launch 10 years ago. For the clinician, this means that there is flexibility to adjust insulin aspart treatment across age groups and different stages of life, as supported by the broad prescribing label. There is also the possibility to use insulin aspart in different settings, such as intravenous administration in hospitalized patients or delivery through CSII.

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Conflict of interests

Simon Heller has lectured at symposia supported by Astra Zeneca, Eli Lilly, Johnson & Johnson, Novo Nordisk and Sanofi-Aventis for which he has received payment and undertaken consultancy on behalf of Amylin, Eli Lilly, Mannkind, NovoNordisk and Abbott for which his institution has received payment. David McCance has received sponsorship from Novo Nordisk for speaking at meetings and sitting on advisory panels. Etie Moghissi is a consultant for Novo Nordisk and Lilly, and a speaker for Novo Nordisk and Bristol-Myers Squibb/AstraZeneca. Avideh Nazeri is an employee of Novo Nordisk A/S. Olga Kordonouri has no conflicts of interest.

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