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Insulin aspart vs. human insulin in the management of long-term blood glucose control in Type 1 diabetes mellitus: a randomized controlled trial

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Abstract

Aims To compare the efficacy of insulin aspart, a rapid-acting insulin analogue, with that of unmodified human insulin on long-term blood glucose control in Type 1 diabetes mellitus.

Methods Prospective, multi-centre, randomized, open-labelled, parallel-group trial lasting 6 months in 88 centres in eight European countries and including 1070 adult subjects with Type 1 diabetes. Study patients were randomized 2:1 to insulin aspart or unmodified human insulin before main meals, with NPH-insulin as basal insulin. Main outcome measures were blood glucose control as assessed by HbA_{1c}, eight-point self-monitored blood glucose profiles, insulin dose, quality of life, hypoglycaemia, and adverse events.

Results After 6 months, insulin aspart was superior to human insulin with respect to HbA_{1c} with a baseline-adjusted difference in HbA_{1c} of 0.12 (95% confidence interval 0.03–0.22) %Hb, $P < 0.02$. Eight-point blood glucose profiles showed lower post-prandial glucose levels (mean baseline-adjusted –0.6 to –1.2 mmol/l, $P < 0.01$) after all main meals, but higher pre-prandial glucose levels before breakfast and dinner (0.7–0.8 mmol/l, $P < 0.01$) with insulin aspart. Satisfaction with treatment was significantly better in patients treated with insulin aspart (WHO Diabetes Treatment Satisfaction Questionnaire (DTSQ) baseline-adjusted difference 2.3 (1.2–3.3) points, $P < 0.001$). The relative risk of experiencing a major hypoglycaemic episode with insulin aspart compared to human insulin was 0.83 (0.59–1.18, NS). Major night hypoglycaemic events requiring parenteral treatment were less with insulin aspart (1.3 vs. 3.4% of patients, $P < 0.05$), as were late post-prandial (4–6 h) events (1.8 vs. 5.0% of patients, $P < 0.005$).

Conclusions These results show small but useful advantage for the rapid-acting insulin analogue insulin aspart as a tool to improve long-term blood glucose control, hypoglycaemia, and quality of life, in people with Type 1 diabetes mellitus.

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Keywords hypoglycaemia, insulin analogue, insulin aspart, insulin therapy, quality of life, rapid-acting insulin, Type 1 diabetes mellitus

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Abbreviations DCCT, Diabetes Control and Complications Trial; DTSQ, Diabetes Treatment Satisfaction Questionnaire; ICH, International Conference of Harmonization; HbA_{1c}, glycated haemoglobin A_{1c}; NPH, neutral protamine Hagedorn; RR, relative risk

Introduction

A major aim of modern diabetes therapy is to intensify the management of blood glucose levels in order to prevent or delay the development of long-term complications [1,2]. Intensified insulin therapy is designed to mimic more closely physiological insulin secretion profiles, and it has been assumed that this is the reason for the improved HbA_{1c} observed in the DCCT [3–5]. Rapid-acting insulin analogues have the advantage of being able to mimic the meal-time insulin response more closely than can injection of unmodified human insulin, even although they are usually administered immediately prior to the meal [3,6–9].

Insulin aspart is an insulin analogue in which the substitution of the B28 proline with aspartic acid reduces the tendency to form hexamers at concentrations found in the subcutaneous depot [10]. This promotes enhanced absorption from the depot, as it is no longer limited by dissolution of the hexamers [10,11]. Clinical experimental trials with insulin aspart and other rapid-acting insulin analogues have demonstrated improved post-prandial glucose control in comparison with human insulin [8–12].

The present study was performed to evaluate the effects of insulin aspart as meal-related insulin in long-term clinical use. The open-labelled design allowed the time of injection for both meal-time insulins to be in line with their individual recommendations, human insulin 30 min before meals and insulin aspart at meal-time. As this was the first large scale long-term trial of insulin aspart, dose recommendations were for a unit-for-unit transfer from human insulin, and no specific treatment algorithm or other modifying advice was used.

Patients and methods

Methods

This was a multi-centre, randomized, open-labelled, parallel-group study conducted at 88 European centres in Austria (3), Denmark (5), Finland (4), Germany (32), Norway (5), Sweden (5), Switzerland (1), and the United Kingdom (33). The study was approved by national regulatory agencies and local ethics committees and monitored in accordance with good clinical research practice. Written informed consent was obtained from all subjects.

Patients

Patients (n = 1070) with Type 1 diabetes were randomized between insulin treatments, 1065 received the trial agents, and 1011 completed the trial. A total of 1047 patients were included in the intention-to-treat analysis and 1006 patients in the per-protocol analysis (Fig. 1). The people recruited were adult men and women judged by the investigators to have Type 1 diabetes by WHO criteria [13], with a duration of diabetes of $\geqslant$ 2 years and treated with insulin for 1 years. For inclusion body mass index was < 35.0 kg/m^2 and $HbA_{1c} \leqslant$ 11.0% (reference value < 6.0%). People with active proliferative retinopathy or nephropathy (serum creatinine > 150 μmol/l), recurrent severe hypoglycaemia, significant cardiovascular disease, systemic corticosteroid treatment, or requiring > 1.4 U.kg^{-1}.day^{-1} insulin, pregnant, or abusing drugs, were excluded from the trial.

Protocol and measurements

During the 4-week run-in period soluble human insulin was administered as meal-time insulin and NPH-insulin was administered as basal insulin once or twice daily. The number of NPH-insulin injections was in general determined by the patient's previous practice, and was not to be changed before or after randomization. Patients were asymmetrically randomized in a 2:1 ratio to receive 6 months' treatment with either insulin aspart (NovoRapid, Novo Nordisk, Bagsvaerd, Denmark) or soluble human insulin (Actrapid, Novo Nordisk) as meal-time insulin, both with neutral protamine Hagedorn (NPH) insulin (Insulatard, Novo Nordisk) as basal insulin.

Study visits were scheduled at screening, 2 weeks into the run-in period, at randomization (baseline), 2 weeks after randomization and then monthly. At each visit measures of efficacy were made (see below), insulin dose adjustments advised, adverse events recorded, and insulin use monitored.

Insulin aspart (100 U/ml) was administered subcutaneously (SC) in the anterior abdominal wall immediately before main meals, and human insulin (100 IU/ml) was advised to be administered SC 30 min before main meals. Injections were made using a pen injector (NovoPen 1.5®, Novo Nordisk). Self blood glucose monitoring was performed using OneTouch II meters (LifeScan, Milpitas, CA). These profiles were used for insulin dose adjustment with target blood glucose values of 5.0–8.0 mmol/l pre-prandially and at bed-time, and < 10.0 mmol/l 1–3 h after meals. Eight-point blood glucose profiles (pre-prandially, 90 min post-prandially, bed-time, and 02.00 h) were requested before randomization and after 5 and 6 months' treatment.

Glycated haemoglobin as HbA_{1c} was measured during the screening phase, at randomization, and after 3 and 6 months' treatment.

Hypoglycaemia and adverse events

Hypoglycaemia was classified as minor (symptomatic events dealt with by the patient), or major grade A (requiring third party help), or major grade B (parenteral glucose or glucagon

administered). Other adverse events were recorded at each visit and classified according to normal pharmaceutical clinical trial guidelines.

Biochemical analyses

Safety haematology and biochemistry tests, drugs-of-abuse screen, HbA_{1c} (by BioRad Diamat Automated Glycosylated Haemoglobin Analyser, Hemel Hempstead, UK; normal < 6.0%), and serum lipids (total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides) were measured using standard laboratory techniques at a central laboratory (Clinical Research Laboratories Europe, Zaventem, Belgium).

Quality-of-life assessment

The Diabetes Treatment and Satisfaction Questionnaire [14] was completed by patients participating in the UK at baseline and at 6 month (insulin aspart $n = 271$, human insulin $n = 148$). The six items on treatment satisfaction were scored together (maximum score 36). The two items on perceived hypoglycaemia and hyperglycaemia (maximum score 6 each) were analysed separately.

Statistical analyses

The sample size was based on an ICH guideline aiming at randomizing 1000 subjects to treatment [15]. At a withdrawal rate of 15%, approximately 850 subjects would be evaluable. An assumed baseline variance for HbA_{1c} of 1.50% (as in the DCCT [1]), gave a probability of detecting non-inferiority of 0.98, if the true difference in HbA_{1c} was 0.20%.

For the primary endpoint, HbA_{1c} at 6 months, the comparison between insulins was based on a combined closed test procedure of non-inferiority, with a subsequent superiority test [16]. Data was analysed using ANOVA with HbA_{1c} at baseline as

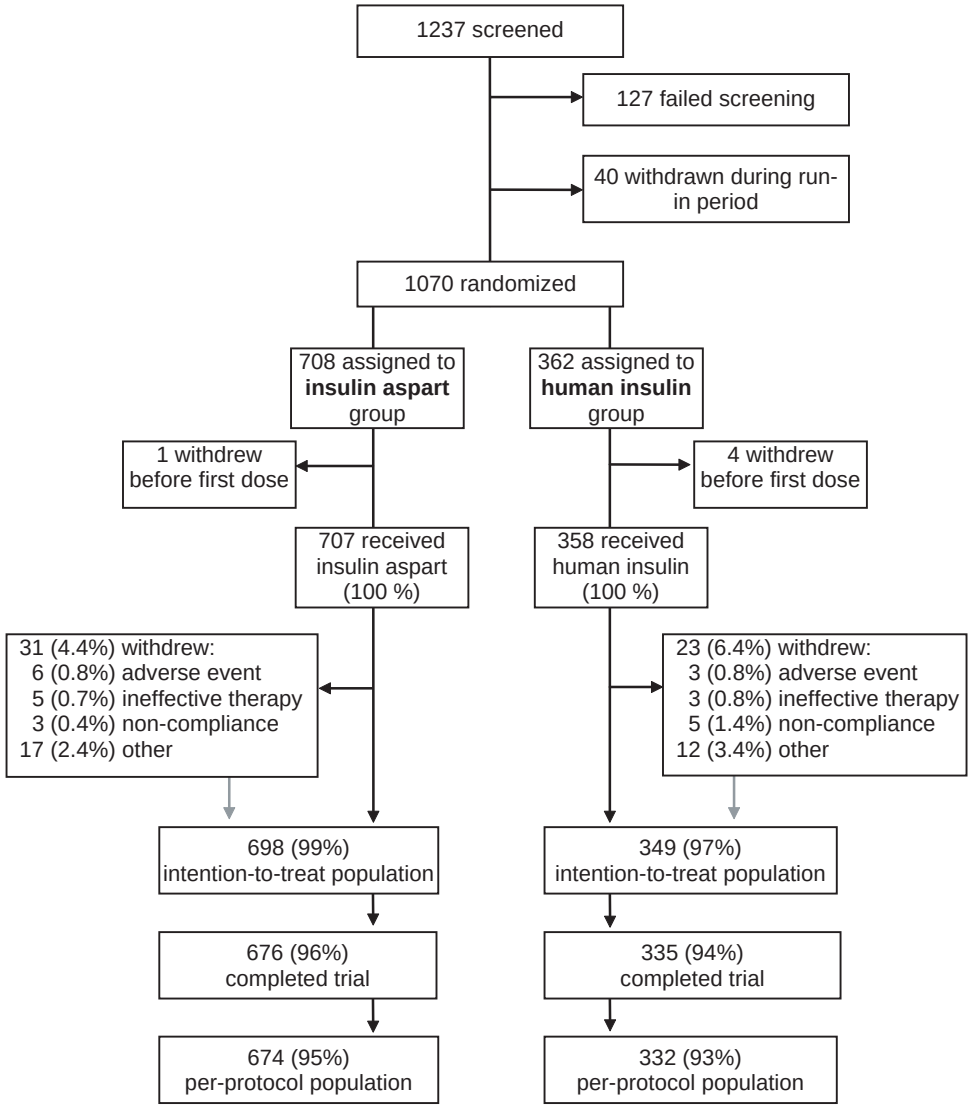

Figure 1 Trial profile showing subject flow, randomization, withdrawal, completion and numbers included for statistical analyses.

covariate, and treatment and centre as fixed effects. Treatment-by-centre interaction and covariate adjustment for rate of hypoglycaemia and its interaction with treatment were also investigated.

Individual time points of the 8-point blood glucose profile at 6 months were compared by ANOVA as above. Prandial blood glucose increment was defined as the average change from before to 90 min after the meal, over the three meals. Prandial blood glucose increment, insulin dose and DTSQ scores were compared between treatments using ANOVA, with covariate adjustment for baseline values.

The incidence of hypoglycaemia was compared using a model based on the Poisson distribution [17], including rate of hypoglycaemia in the run-in period, country and exposure time. The Mantel–Haenszel χ^2 test was used to compare the number of patients experiencing at least one nocturnal (0.00–06.00 h), daytime or post-prandial major hypoglycaemic episode between treatments.

Analyses were based on the intention-to-treat population. A 5% level of statistical significance was used. Statistical analyses were made using SAS for UNIX version 6.11 (SAS Institute, Cary, NC) and the Cox regression analysis with the S-plus version 4.0 release 3 for Microsoft Windows (Seattle, WA). Results are stated as mean adjusted for baseline values and centre effect (SE), or mean treatment difference (95% confidence interval (CI)), or as indicated.

Results

Withdrawals

Of the 1070 patients randomized, 94% completed 6 months, giving 347 patient-years on insulin aspart and 172 patient-years on soluble human insulin. There were no differences in baseline characteristics between the two groups (Table 1). There were also no differences regarding reasons for withdrawal (insulin aspart 4%, human insulin 6%).

Insulin dose

The doses of meal-related insulin did not change from baseline to 6 month (Tables 1 and 2). There was no difference between groups at 6 month. The baseline dose of NPH-insulin was similar for the two study groups (Table 1), but at 6 month the NPH-insulin dose was 8.5%

Table 1 Clinical characteristics of the Type 1 diabetic patients studied

	Insulin aspart	Human insulin
n	707	358
Age (years)	38 (11)	38 (12)
Sex (M)(%)	55	56
Ethnic group (Europid)(%)	99	99
Body mass index (kg/m^2)	25.1 (3.1)	24.9 (3.0)
Smoking (%)	23	26
Duration of diabetes (years)	15 (10)	15 (10)
HbA_{1c} (%)	7.96 (1.16)	7.98 (1.17)
NPH injections > 1/day (%)	41	38
Insulin dose (U/kg)		
Meal-time	0.40 (0.15)	0.41 (0.17)
Basal	0.29 (0.12)	0.29 (0.12)

Mean (SD), count or percentage.
HbA_{1c} normal < 6.0%.

Table 2 Measures of efficacy at 6 months in people with Type 1 diabetes treated with insulin aspart or soluble human insulin

	Insulin aspart		Human insulin		Insulin aspart–human insulin		
	Mean	(SE)	Mean	(SE)	Mean	(95% CI)	*P*-value
HbA_{1c} (%)	7.88	(0.03)	8.00	(0.04)	–0.12	(–0.03 to –0.22)	< 0.02
Blood glucose (mmol/l)							
Pre-breakfast	8.5	(0.13)	7.7	(0.18)	0.79	(0.36–1.21)	< 0.001
Post-breakfast	8.9	(0.15)	10.1	(0.21)	–1.20	(–0.71 to –1.68)	< 0.0001
Pre-lunch	7.1	(0.13)	7.3	(0.18)	–0.18	(–0.60–0.23)	NS
Post-lunch	8.0	(0.12)	8.5	(0.17)	–0.55	(–0.15 to –0,96)	< 0.01
Pre-dinner	8.0	(0.13)	7.3	(0.18)	0.69	(0.25–1.13)	< 0.01
Post-dinner	8.4	(0.14)	9.0	(0.19)	–0.63	(–0.18 to –1.07)	< 0.01
Bed-time	8.7	(0.14)	8.7	(0.19)	0.04	(–0.42–0.49)	NS
Night (02.00 h)	8.4	(0.14)	8.0	(0.19)	0.39	(–0.05–0.83)	NS
Prandial increment	0.54	(0.09)	1.69	(0.12)	–1.15	(–1.43 to –0.87)	< 0.0001
DTSQ (points)	32.0	(0.3)	29.7	(0.4)	2.27	(1.22–3.32)	< 0.0001
Insulin dose (U/kg)							
Meal-related	0.395	(0.004)	0.400	(0.005)	–0.005	(–0.018–0.008)	NS
Basal	0.319	(0.002)	0.294	(0.003)	0.025	(0.017–0.033)	< 0.0001

DTSQ, Diabetes Treatment Satisfaction Questionnaire.
All estimates are adjusted for baseline value and centre.

higher in subjects treated with insulin aspart compared to human insulin (difference 0.025 U/kg, Table 2).

Overall blood glucose control

HbA_{1c} was significantly improved with insulin aspart as compared to soluble human insulin. After 6 months' treatment the mean HbA_{1c} decreased from 7.96 to 7.86% in the insulin aspart group while it was unchanged in the human insulin group (7.98%). The baseline and centre adjusted difference in HbA_{1c} after 6 month was 0.12% units (Table 2). The effect of insulin aspart on HbA_{1c} was still significant after adjustment for the NPH insulin dose (0.10% units; 95% CI 0.004–0.20; $P < 0.05$). In patients randomized to insulin aspart the mean baseline and 6 month HbA_{1c} values were 8.23 and 8.05% in those treated with NPH insulin once daily, and 7.54 and 7.58% in those treated with NPH insulin twice daily.

Eight-point blood glucose profiles

Post-prandial blood glucose control was significantly better with insulin aspart than with human insulin. After 6 months, the insulin aspart group had significantly lower blood glucose levels after breakfast, lunch, and dinner (differences 0.6–1.2 mmol/l, Table 2) but higher before breakfast and dinner (0.7–0.8 mmol/l, Table 2) compared to human insulin (Fig. 2).

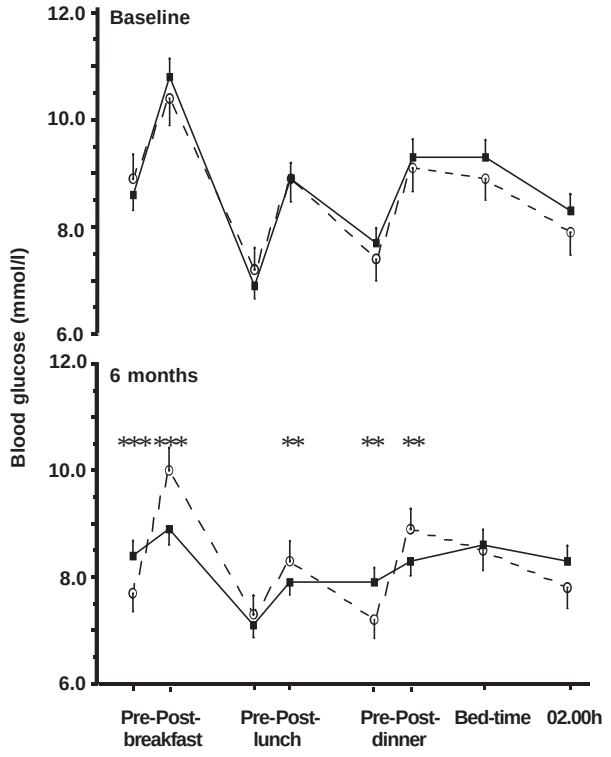

Figure 2 Self-monitored blood glucose profiles in Type 1 diabetic patients using insulin aspart (■) or soluble human insulin (○) at baseline and after 6 months. Mean ± 2 SE. $^{**}P < 0.01$, $^{***}P < 0.001$ between insulin regimens.

The average prandial blood glucose increment decreased from a baseline of 2.0 (SD 2.4) to 0.6 (2.2) mmol/l in the insulin aspart group while it remained unchanged at 1.7 (2.6 and 2.2) mmol/l in the human insulin group. The baseline-adjusted difference between the groups at 6 months was 1.15 mmol/l ($P < 0.0001$, Table 2).

Quality of life

The DTSQ showed significant overall improvement in treatment satisfaction with insulin aspart with largest differences between treatments related to the convenience, flexibility and satisfaction-to-continue-present-treatment items (baseline insulin aspart 30.1 points, human insulin 29.9 points; endpoint difference 2.3 points, Table 2). There were no differences regarding the perceived frequency of hyperglycaemia or hypoglycaemia.

Hypoglycaemia

Hypoglycaemic events are summarized in Table 3. The relative risk (RR) estimate of major hypoglycaemia was 0.83 (95% CI 0.59–1.18; NS) for insulin aspart vs. human insulin. The proportion of subjects with major hypoglycaemia in the insulin aspart group fell from 11% in the first 3 months of treatment to 8% in the last 3 months, while in the human insulin group the proportion was unchanged at 11% (NS). Major events requiring parenteral administration of glucose or glucagon (grade B) occurred in 22 subjects (42 events, 0.12/patient-year) in the insulin aspart group, and 17 subjects (26 events, 0.15/patient-year) in the human insulin group (NS).

With insulin aspart, 54 subjects (8%) had a major nocturnal event compared to 39 subjects (11%) with human insulin (RR 0.70; 95% CI 0.47–1.04; $P = 0.076$), while 11% of subjects in both treatment groups experienced a daytime major hypoglycaemic event. Significantly fewer patients on insulin aspart (1.3%) experienced nocturnal major B hypoglycaemia compared to human insulin (3.4%; RR 0.38; 95% CI 0.17–0.87; $P < 0.05$).

Post-injection major hypoglycaemia within 1 h from starting a meal occurred in 1.1% of subjects on insulin aspart and 0.6% of subjects on human insulin (NS), while events 4–6 h after a meal occurred in 1.8% of subjects on insulin aspart and in 5.0% subjects on human insulin (RR 0.37; 95% CI 0.19–0.72; $P < 0.005$).

The relative risk for minor hypoglycaemia was 1.01 (95% CI 0.89–1.16; NS) for insulin aspart vs. human insulin. Minor hypoglycaemia was most frequently reported between 10.00 and 16.00 h, and 2–4 h after a meal in both treatment groups.

Adverse events

Adverse events were equally distributed between treatments (Table 4). All events leading to withdrawal from insulin aspart were hypoglycaemia-related except one case of urticaria and one death from myocardial infarction (both assessed as unrelated to trial drug). There were three events of ketoacidosis in each treatment group.

Discussion

The present study compares insulin aspart as meal-related insulin to unmodified human insulin in people with Type 1 diabetes managed in a wide variety of centres across Europe. The study was randomized but not double-blind, the latter so that advice on the timing of insulin dosage before meals could follow the currently approved recommendations for human insulin (at least 30 min prepprandially), and intended recommendations for insulin aspart (immediately before meals). While it is recognized that most patients do not follow such recommendations when using human insulin for reasons of convenience and safety [18,19], adherence is expected to improve in the more rigorous conditions of a clinical trial. Furthermore, regulatory authorities expect such recommendations to be followed in major phase 3 studies. The lack of double-blinding carries a risk of favouring a new agent, but any such advantage would be expected to fade in these longer studies, and has not been evident with insulin lispro, where the analogue was found to have no overall advantage in terms of blood glucose control [20,21].

Table 3 Hypoglycaemia rates in the Type 1 diabetic patients during treatment with insulin aspart and human insulin

		Insulin aspart				Human insulin			
		Patients		Events†		Patients		Events†	
		n	%	*n*	/patient-year	*n*	%	*n*	/patient-year
Patients		707	(100)			358	(100)		
Hypoglycaemic episodes									
Minor		563	(80)	10113	7.64	270	(75)	4322	7.54
Major	all	111	(16)	314	0.81	65	(18)	152	0.97
	night	54	(7.6)	116	0.34	39	(10.9)	55	0.46
grade A	all	97	(14)	272	0.83	51	(14)	126	0.94
	night	46	(6.5)	99	0.32	27	(7.5)	40	0.38
grade B	all	22	(3.1)	42	0.09	17	(4.7)	26	0.12
	night	9	(1.3)*	17	0.03	12	(3.4)	15	0.05

Hypoglycaemia: grade A requiring assistance but not parenteral glucose/glucagon, grade B requiring or treated with parenteral glucose or glucagon.
†Estimated incidence rate was obtained by a generalized linear Poisson regression model (with adjustment for the number of episodes during the run-in period, country and accounting for overdispersion) standardizing to subjects from UK with no run-in episodes of the particular type.
*$P < 0.05$ compared to human insulin.

Table 4 Adverse events (except hypoglycaemia) in the Type 1 diabetic patients during 6 months' treatment with insulin aspart and soluble human insulin

	Insulin aspart				Human insulin			
	Patients		Events		Patients		Events	
	n	%	*n*	/patient-year	*n*	%	*n*	/patient-year
Patients	707	(100)			358	(100)		
Adverse events								
All	484	(68)	1600	4.6	233	(65)	752	4.4
Serious events	31	(4)	36	0.10	21	(6)	25	0.15
Deaths	1	(< 1)	1	< 0.01	0	(0)	0	0
Non-serious events	478	(68)	1564	4.5	228	(64)	727	4.2

However, studies of this kind using new agents with very different pharmacokinetic properties from the standard therapy, place the new insulin at considerable disadvantage compared to human insulin. Firstly, the insulin doses and snacking habits at study entry will have been optimized for the human insulin regimen, often over many years. Secondly, the investigators' mindset is likely to be largely determined by years of experience with the pharmacokinetics of human insulin, and, in a study with a large number of centres and thus few patients per centre, adequate experience is unlikely to be obtained by any investigator to use the new insulin to its full advantage. Thirdly, experience and fear of hypoglycaemia will often be deeply ingrained in the habits of the insulin-users (people with diabetes), and any lesser experience of hypoglycaemia, in particular the erratic and infrequent major events, is unlikely within the 6 months of the study to allow changes in target blood glucose levels that might be to the advantage of the rapid-acting analogue.

These problems may account for the rather small size of the statistically significant improvement in HbA_{1c} found in the present study. Nevertheless this is the first major multicentre trial of any rapid-acting insulin analogue to show any such improvement. Improvement was previously shown in small experimental studies with insulin lispro in which NPH dosage was specifically targeted for change [22,23]. Whether these changes could be reproduced in formal multi-centre studies is not known. Using the outcome data of the DCCT [1,24], such an improvement in blood glucose control might be expected to reduce retinopathy progression by some 6% over 5 years, as well as improving other microvascular outcomes.

The blood glucose profiles (Fig. 2) confirm that the major advantage from insulin aspart comes, as would be expected from the pharmacodynamic studies [8,9,12,25], from better blood glucose control in the immediate post-prandial period. This is the time at which blood glucose levels were at their highest on human insulin, but the extent to which the peaks of hyperglycaemia post-prandially account for the toxic effects of glucose which lead to microvascular complications is not known, and this important consideration is clearly in need of further study [26].

In the present study, blood glucose levels pre-prandially tended to be higher on insulin aspart than on human insulin, in contrast to a previous report [7]. This can be attributed to the shorter interprandial intervals enforced during the earlier study, and to the use of algorithm-driven insulin dose adjustment necessary to achieve useful changes within a 4-week study. The problem of exhaustion of the subcutaneous depot of rapid-acting analogues has received some attention in the last 2 years, notably in tightly performed experimental studies [27,28], and in exploratory studies in outpatient populations [22]. A consensus has emerged from these studies that more day-time extended-acting insulin will be needed to prevent deterioration in blood glucose control where the late post-prandial period exceeds 4–5 h, and that any such night-time insulin will need to be given only 3–4 h after the evening meal [29], and not as late as possible as at present. None of this information was available at the time of conduct of the present study, and is unlikely to have influenced clinicians' practice to the advantage of the rapid-acting analogue. Further studies are then required with insulin aspart to try and harness these ideas.

Night-time self-monitored blood glucose levels were not statistically significantly higher with insulin aspart, in contrast to previous studies with this and other rapid-acting insulin analogues [7,22], although there was a trend in that direction. A trend consistent with this was found in the hypoglycaemia rate during the night (Table 3), statistically significant different by a large margin (1.3 vs. 3.4% of patients) for the most severe events requiring parenteral management. These observations are consistent with the phase 2 study on insulin aspart [7], and experimental and clinical studies of insulin lispro [20,30]. The increase is now understood to be a result of the absence of the long tail of action of the pre-dinner human insulin. Increasing the dose of extended-acting insulin given at night has been shown to ameliorate the night-time and pre-breakfast hyperglycaemia that can occur with rapid-acting analogue regimens [28,30], but it remains to be seen whether this then loses the advantage of reduced night-time hypoglycaemia. Clinically however, this distinction may not matter; patients are managed as individuals and not as groups, and those with a night hypoglycaemia problem could benefit from a lesser frequency of events, while others benefited from improved blood glucose control.

The treatment satisfaction instrument was only used in the UK, where its validity in the English language has been best documented [14]. Open-label studies of new therapeutic preparations are not a good environment in which to administer treatment satisfaction or quality-of-life questionnaires, because of the possibility of bias. Nevertheless the improvement in satisfaction is highly statistically significant and appears difficult to ignore (Table 2).

No concerns in regard of unanticipated adverse events arose during this intensively monitored study.

In conclusion, insulin aspart is the first rapid-acting insulin analogue for which a small, but significant improvement in overall blood glucose control has been soundly demonstrated for a SC insulin injection regimen. This is achieved in the context of reduction in peak glucose levels during the day, and with apparent advantage for the most severe forms of night-time hypoglycaemia, for late post-prandial hypoglycaemia, and for treatment satisfaction. Application of recently gained knowledge of optimal basal insulin replacement when using rapid-acting analogues should enable significant gains in blood glucose control.

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