DM

A randomized trial of insulin aspart with intensified basal NPH insulin supplementation in people with Type 1 diabetes

J. H. DeVries, A. Lindholm*, J. L. Jacobsen*, R. J. Heine, P. D. Home†,
The Tri-Continental Insulin Aspart Study Group

Department of Endocrinology, VU University Medical Centre, Amsterdam, the Netherlands, *Novo Nordisk A/S, Bagsvaerd, Denmark, and †Department of Diabetes and Metabolism, University of Newcastle upon Tyne, Newcastle upon Tyne, UK

Accepted 13 January 2003

Abstract

Aims Insulin aspart has been shown to improve post-prandial and overall glycaemic control in people with Type 1 diabetes. We hypothesized that insulin aspart with intensified basal NPH insulin supplementation would result in better overall glycaemic control than human regular insulin with standard basal NPH insulin.

Methods The trial was conducted in 43 centres in seven countries. People with Type 1 diabetes were randomized to mealtime insulin aspart with up to four daily NPH doses if meals were > 5 h apart and a 25% increase in bedtime NPH dose (n = 187), or to mealtime human unmodified insulin with once or twice daily basal NPH insulin (n = 181). Efficacy and safety were evaluated at 12 weeks (primary evaluation period) and 64 weeks.

Results At 12 and 64 weeks there was no statistically significant difference in HbA_{1c} between the insulin aspart and regular insulin groups: –0.09 (95% confidence interval (CI) –0.23, +0.05)% and –0.14 (–0.32, +0.04)%. Post-prandial glucose values were lower and the area under the 24-h self-monitored blood glucose curve above 7.0 mmol/l was 28% smaller with insulin aspart (35.2 ± 3.2 vs. 48.9 ± 3.1 mmol/l h, P = 0.0015). No significant differences were found in mild or severe hypoglycaemia, or adverse event rate. At 64 weeks treatment satisfaction was higher in the insulin aspart group (difference 1.57 (95% CI 0.49, 2.64) points, P = 0.004), while quality of life was not different.

Conclusions Improved post-prandial glycaemic control and treatment satisfaction with insulin aspart were confirmed. Intensifying basal insulin supplementation resulted in a similar HbA_{1c} decrement as previously found with the use of insulin aspart and standard NPH insulin supplementation. This does not support routinely basal NPH insulin intensification when using rapid-acting insulin analogues in daily practice.

Diabet. Med. 20, 312–318 (2003)

Keywords Type 1 diabetes, insulin analogues, glycated haemoglobin HbA_{1c}, hypoglycaemia, quality of life

Abbreviations DTSQ, Diabetes Treatment Satisfaction Questionnaire

Introduction

Insulin aspart is a novel insulin analogue with a more rapid onset and a shorter duration of action after subcutaneous administration compared with human unmodified (regular)

Correspondence to: J. Hans DeVries MD, Department of Internal Medicine, Academic Medical Centre, PO Box 22 660 NL 1100 AD, Amsterdam, the Netherlands. E-mail: j.h.devries@amc.uva.nl

insulin [1]. The use of insulin aspart has been shown to improve post-prandial glycaemic control and diminish the hypoglycaemia event rate, especially at night, in a study where premeal human insulin was replaced by insulin aspart [2]. Moreover, two large-scale studies showed a significant improvement in overall glycaemic control [3]. The first confirmed the diminished hypoglycaemia rate, while the latter showed increased treatment satisfaction.

Two small-scale studies with rapid-acting insulin analogues suggest that overall glycaemic control can be improved by intensifying basal insulin supplementation. These intensifications included a 25% increase in the night time NPH insulin dose and an additional basal insulin dose with mealtime intervals of more than 5 h [4,5]. Several other studies, using insulin lispro, showed improved glycaemic control when basal NPH insulin supplementation was optimized by increasing the number of NPH injections to three to four per day in intensively coached and compliant people [6–10].

The main objective of the present study was to investigate whether increased dosage and frequency of basal insulin injections in combination with premeal insulin aspart would result in improved overall glycaemic control. Therefore, we compared in a large-scale multicentre study two algorithm-driven insulin therapy regimens, one consisting of premeal insulin aspart with an intensified basal NPH insulin supplementation, and the other of premeal human regular insulin with one or two daily doses of basal insulin. After a 12-week phase of intensive treatment, subjects were followed for an additional year at 3-month intervals to approach the real-life situation as closely as possible within a clinical trial.

Patients and methods

This 64-week multicentre multinational randomized open-label parallel group trial was conducted in 43 centres in seven countries. The protocol was approved by all appropriate ethical committees. Patients gave written informed consent. The trial was monitored and carried out according to International Conference on Harmonization/Good Clinical Practice guidelines [11].

Patients

People with Type 1 diabetes for > 2 years were included if they were older than 18 years, were on a meal-time plus basal insulin regimen for at least the last 3 months, had an HbA_{1c} of 7.0–10.0%, and had a body mass index (BMI) ≤ 35 kg/m^2. Exclusion criteria included active proliferative retinopathy or nephropathy (serum creatinine > 150 μmol/l), recurrent severe hypoglycaemia (more than two events requiring third-party help in the last 6 months) or hypoglycaemia unawareness (as judged by the investigator), high insulin requirement (use of > 1.4 U/kg body weight), substance abuse and other major disease. Women were excluded if they were pregnant, breast-feeding, or practising inadequate contraception. The two treatment groups were comparable with respect to demographic variables and disease characteristics measured at baseline (Table 1). A trial profile is shown in Fig. 1.

Table 1 Clinical characteristics of the 367 patients randomized to insulin aspart (n = 186) or human insulin (n = 181)

	Insulin aspart	Human insulin
Age (years)	36.9 (28.8, 46.7)	36.9 (28.2, 46.7)
Male sex	116 (62)	111 (61)
Caucasian race	169 (91)	166 (92)
BMI (kg/m^2)	25.3 ± 3.2	25.8 ± 3.4
Smoker	38 (20)	40 (22)
Duration of diabetes (years)	14.2 (8.3, 20.7)	15.6 (9.4, 23.8)
HbA_{1c} (%)	8.36 ± 0.76	8.40 ± 0.77
Basal insulin injections the day before randomization (n/day)		
0	0 (0)*	2 (1)
1	153 (82)	140 (77)
2	32 (17)	38 (21)
3	0 (0)	1 (1)
4	1 (1)	0 (0)
Insulin dose (U/kg body weight)		
Basal insulin	0.31 ± 0.14	0.30 ± 0.12
Mealtime insulin	0.48 ± 0.17	0.42 ± 0.14

Data are presented as n (%), means ± SD or median (25th %, 75th %).
*Two patients reported no basal insulin injection on the day before randomization.

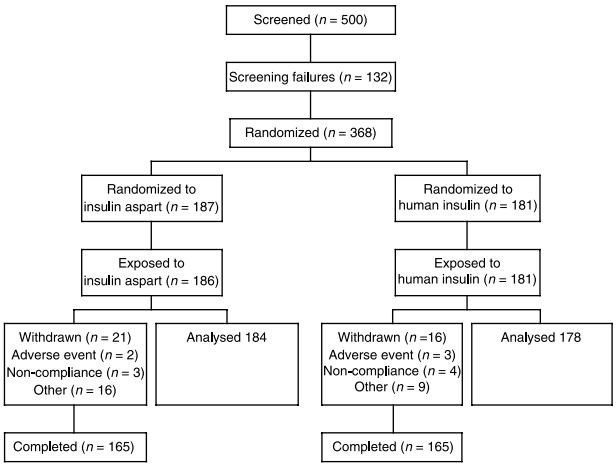

Figure 1 Trial profile.

Design

After a 2-week run-in, subjects were randomized using a telephone intelligent voice response system to insulin aspart (NovoRapid®; Novo Nordisk, Bagsvaerd, Denmark) or human unmodified insulin (Human Actrapid®; Novo Nordisk) as premeal insulin. People in both arms used intermediate-acting NPH insulin as a basal insulin given at bedtime (Human Insulatard®; Novo Nordisk). In those randomized to insulin

aspart, 80% of the prestudy premeal insulin dose of human insulin dose was given as insulin aspart before meals, and subjects were advised to increase their night time NPH dose by 25% [4]. When time between meals or between dinner and bedtime was > 5 h, additional daytime NPH doses were advised: 40% of the prestudy premeal human insulin dose was given as NPH insulin, and 60% as insulin aspart [5,12]. Human regular insulin was advised to be injected 30 min before meals, insulin aspart immediately before meals. The recommended injection site for mealtime insulin injection was the abdominal wall, for NPH insulin the thigh. One 9-point blood glucose profile (preprandial and 90 min post-prandial, before bed, at 02.00 h and before breakfast the next day) using the One Touch Profile (Lifescan, Milpitas, CA, USA) was requested in the week before each trial visit, to be noted in a diary. Dosage adjustment advice was derived from an algorithm working from self-monitored blood glucose profiles, adjusting insulin aspart on the basis of post-prandial measurements, NPH on preprandial measurements and human mealtime insulin on both preprandial and post-prandial measurements. The algorithm advised adjusting insulin doses when glucose measurements were outside a range of 5.0–7.0 mmol/l preprandially and 5.0–9.0 mmol/l post-prandially in both groups. Patients were seen for trial visits at 2, 4, 8 and 12 weeks, and four times thereafter, at 13-week intervals. Telephone contact was used as required on an investigator-driven basis.

Measurements

Glycaemic control was assessed using the 9-point blood glucose profiles and HbA_{1c} values. HbA_{1c} was measured at each visit using ion-exchange high-pressure liquid chromatography (reference range 4.8–6.7%) at Covance Laboratories (Hamburg, Germany).

Hypoglycaemic events were self-reported. They were classified as major or minor. Major hypoglycaemic episodes were defined by the requirement of third-party help, including i.v. glucose or i.m. glucagon. Minor episodes were all other symptomatic hypoglycaemic events. Other adverse events were recorded at each visit and classified according to pharmaceutical guidelines.

Diabetes-specific quality of life was measured using the Diabetes Health Profile [13]. Treatment satisfaction was measured using the Diabetes Treatment and Satisfaction Questionnaire (DTSQ) [14]. Questionnaires were completed at baseline, and at 12, 38 and 64 weeks.

Statistical analysis

The primary efficacy outcome measure was the change in HbA_{1c} from baseline to 12 weeks. This was analysed by analysis of variance using all post-baseline values with covariate adjustment for baseline value, country and centre. Assuming a standard deviation of HbA_{1c} of 1.0%, 400 randomized subjects would have given the trial a 85% power to detect a difference of 0.3%. Secondary efficacy assessments were the 9-point home blood glucose profiles, hypoglycaemic event rates and quality of life endpoints. The areas under the curve > 7.0 mmol/l and < 3.5 mmol/l from the 9-point home blood glucose profiles were calculated. Time points of the 9-point home blood glucose profiles and derived blood glucose end points were analysed using repeated measures ANCOVA as above. From the 9-point blood glucose profiles, the value reported before breakfast is the average of the before breakfast values of day 1 and day 2. The primary outcome measure for hypoglycaemia was time to first major hypoglycaemia, analysed by Cox-regression with treatment group as factor, secondary outcomes were rates of major, major daytime, major night time and minor hypoglycaemia. Hypoglycaemic event rates were compared using Fisher's exact test. The domains as described by the developers of the quality of life questionnaires were analysed as endpoints using the χ^2 test.

All results were analysed using the intention-to-treat population, defined as all subjects with at least one post-baseline value recorded. The last observation carried forward approach was used for patients who dropped out prior to later visits. *P*-values < 0.05 were considered statistically significant. All analyses were predefined in a statistical analysis plan, except as stated. Statistical analyses were made using SAS for UNIX version 6.12 (SAS Institute, Cary, NC, USA).

Results

Drop-outs and adverse events

Of the 368 people randomized, 186 of the 187 in the insulin aspart group began treatment, as did all 181 randomized to the human insulin group. The intention-to-treat populations (those who had at least one study visit after exposure to the trial medication) included 184 and 178 people, respectively. The withdrawal rates (21 and 16 people, respectively) did not differ between patient arms. In both treatment arms 165 people completed the study (Fig. 1).

Adverse event rates in the insulin aspart and human insulin arms did not differ. Two male, 54- and 60-year-old participants died, both in the human insulin group. These deaths were classified as sudden, and were assessed by local investigators as not being related to the trial product, or to hypoglycaemia. No significant differences were found in body weight (data not shown).

Insulin dosing

The doses of basal insulin and meal-related insulin at 12 and 64 weeks differed significantly between treatments (Tables 2 and 3). The basal insulin dose increased by 36% at 12 weeks and the meal-related component reduced by 13% for insulin aspart relative to baseline, as intended by the dosage algorithm. In the aspart group, 45 patients (24.6%) used three or four daily NPH injections at 12 weeks compared with two patients (1.1%) in the human regular insulin group.

Table 2 Insulin dose, measures of blood glucose control, hypoglycaemia event rates and treatment satisfaction, at 12 weeks of the 64-week trial

	Insulin aspart	Human insulin	Difference (95% CI)	*P*
Insulin dose (U/kg)				
Basal	0.41 ± 0.01	0.32 ± 0.01	0.08 (0.06, 0.10)	< 0.001
Meal related	0.39 ± 0.01	0.46 ± 0.01	–0.07 (–0.09, –0.05)	< 0.001
HbA_{1c} (%)	7.98 ± 0.07	8.12 ± 0.07	–0.09 (–0.23, 0.04)*	0.216
Blood glucose (mmol/l)				
Pre-breakfast	8.22 ± 0.24	8.71 ± 0.24	–0.49 (–1.10, 0.11)	0.112
Post-breakfast	8.27 ± 0.32	9.31 ± 0.32	–1.04 (–1.86, –0.21)	0.0137
Pre-lunch	7.05 ± 0.25	7.12 ± 0.25	–0.08 (–0.73, 0.57)	0.812
Post-lunch	7.40 ± 0.25	8.37 ± 0.25	–0.97 (–1.62, –0.32)	0.0037
Pre-dinner	7.34 ± 0.30	7.39 ± 0.30	–0.06 (–0.84, 0.73)	0.884
Post-dinner	8.22 ± 0.28	8.87 ± 0.28	–0.65 (–1.37, 0.08)	0.081
Bed time	9.16 ± 0.30	8.85 ± 0.30	0.30 (–0.49, 1.10)	0.451
Night (02.00 h)	8.62 ± 0.28	8.42 ± 0.27	0.19 (–0.52, 0.90)	0.593
Hypoglycaemia rate				
Major (events/year)	1.25	1.10	RR 1.16 (0.62, 2.19)	0.723
Minor (events/month)	3.12	3.64	RR 0.91 (0.75, 1.12)	0.385
DTSQ (points)	30.3 ± 0.42	29.5 ± 0.42	0.83 (–0.16, 1.82)	0.100

Data are presented as means ± SE, or mean difference (95% CI). Hypoglycaemia is mean with relative risk (RR) (95% CI).
DTSQ, Diabetes Treatment Satisfaction Questionnaire (scale 0–36, high values indicate high treatment satisfaction).
*The difference as calculated by ANOVA is given, which is not necessarily the same as the difference between raw means.

Table 3 Insulin dose, measures of blood glucose control, hypoglycaemia event rates and treatment satisfaction, at 64 weeks

	Insulin aspart	Human insulin	Difference (95% CI)	*P*
Insulin dose (U/kg)				
Basal	0.41 ± 0.01	0.32 ± 0.01	0.09 (0.07, 0.10)	< 0.001
Meal related	0.41 ± 0.01	0.47 ± 0.01	–0.07 (–0.09, –0.04)	< 0.001
HbA_{1c} (%)	8.08 ± 0.08	8.22 ± 0.07	–0.14 (–0.32, 0.04)*	0.128
Blood glucose (mmol/l)				
Pre-breakfast	8. 05 ± 0.26	8.29 ± 0.25	–0.23 (–0.91, 0.44)	0.494
Post-breakfast	8.34 ± 0.32	9.62 ± 0.31	–1.27 (–2.11, –0.44)	0.0029
Pre-lunch	7.11 ± 0.28	7.13 ± 0.27	–0.02 (–0.76, 0.73)	0.967
Post-lunch	7.56 ± 0.30	8.79 ± 0.30	–1.23 (–2.04, –0.43)	0.0029
Pre-dinner	7.19 ± 0.30	7.59 ± 0.29	–0.40 (–1.20, 0.40)	0.329
Post-dinner	7.45 ± 0.30	9.14 ± 0.29	–1.69 (–2.48, –0.89)	< 0.001
Bed time	8.27 ± 0.29	8.93 ± 0.28	–0.66 (–1.41, 0.10)	0.087
Night (02.00 h)	7.95 ± 0.31	8.27 ± 0.30	–0.32 (–1.14, 0.50)	0.445
Hypoglycaemia rate				
Major (events/year)	0.91	0.79	RR 1.29 (0.89, 1.87)	0.218
Minor (events/month)	1.90	2.35	RR 0.87 (0.69, 1.11)	0.254
DTSQ (points)	30.7 ± 0.5	29.1 ± 0.5	1.57 (0.49, 2.64)	0.004

Data are presented as means ± SE, or mean difference (95% CI). Hypoglycaemia is mean with relative risk (RR) (95% CI).
DTSQ, Diabetes Treatment Satisfaction Questionnaire (scale 0–36, high values indicate high treatment satisfaction).
*The difference as calculated by ANOVA is given, which is not necessarily the same as the difference between raw means.

Glycaemic control

The primary efficacy analysis of change in HbA_{1c} showed a non-significant ($P = 0.216$) insulin aspart—human regular insulin difference of –0.09 (95% confidence interval (CI) –0.23, +0.05)% at 12 weeks (Tables 2 and 3). At 64 weeks this difference was –0.14 (95% CI –0.32, +0.04)%, $P = 0.128$. Adjustment for baseline values of age, BMI, duration of diabetes, baseline HbA_{1c}, total daily insulin dose, number of daily basal injections, country and centre did not change the overall

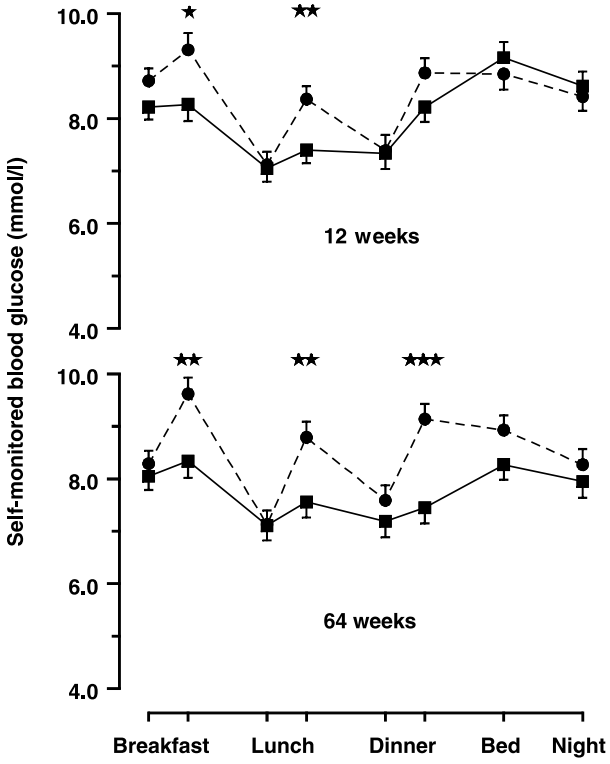

Figure 2 Eight-point 24-h glucose profiles at 12 weeks and 64 weeks. $^{*}P < 0.05$; $^{**}P < 0.005$; $^{***}P < 0.001$.

estimate of treatment effect (data not shown). The area under the 24-h glucose curve above 7.0 mmol/l was 28% smaller in the insulin aspart group (35.2 ± 3.2 vs. 48.9 ± 3.1 mmol/l h ($P = 0.0015$). Post-prandial glucose values were lower in the insulin aspart group than in the human insulin group at 12 and 64 weeks (Fig. 2, Tables 2 and 3).

A *post hoc* analysis in the insulin aspart group showed no significant difference in change in HbA_{1c} from baseline to 12 weeks in those using one or two NPH injections daily vs. those using three or four NPH injections daily: median –0.50 (0.10, –0.80) ($n = 139$) vs. –0.30 (0.00, –1.00) ($n = 45$)% (NS).

Hypoglycaemia

There were no significant differences between insulin aspart and human insulin arms in the time to first major hypoglycaemia (relative risk at 12 weeks 1.06, 95% CI 0.58, 1.94) or the event rate of major or minor hypoglycaemia (Tables 2 and 3). Furthermore, no differences were found when analysing nocturnal and daytime major hypoglycaemic episodes separately. There was no difference in area under the curve below 3.5 mmol/l from the 9-point home blood glucose profiles.

Quality of life

No significant differences between treatments in the Diabetes Health Profile domain scores were found (data not shown). Treatment satisfaction was similar at 12 weeks in the two treatment groups, but at 64 weeks was higher in the insulin aspart group (difference 1.57 (95% CI 0.49, 2.64) points, $P = 0.004$) (Tables 2 and 3).

Discussion

The present trial confirms that the use of insulin aspart in a multiple injection therapy regimen results in a lowering of post-prandial glucose excursions, and thus area under the blood glucose concentration curve above 7.0 mmol/l, even with a reduced mealtime insulin dose. However, as measured by HbA_{1c}, overall glycaemic control was not improved to a statistically significant extent. The safety of insulin aspart, both with regard to adverse events in general and the hypoglycaemia rate in particular, was also confirmed. No differences in health-related quality of life between the two treatments were found, but treatment satisfaction at 64 weeks was higher in the insulin aspart group.

Two other large-scale trials with insulin aspart in multiple injection therapy regimens using one or two daily NPH injections showed statistically significantly lower HbA_{1c} values (0.12% and 0.15%) in the aspart group [3,15]. The advantage in HbA_{1c} of 0.14% seen in the present trial in the insulin aspart group at 64 weeks is similar to the 0.12% and 0.15% seen in these earlier trials. Thus, the present study is in agreement with those trials, although it appears to lack the statistical power to reach significance in this respect.

Smaller earlier studies using insulin lispro plus basal insulin supplementation of three or four NPH injections daily showed 0.35–0.43% lower HbA_{1c} values, compared with basal bolus regimens with human regular insulin [6–10]. In the current trial, a *post hoc* analysis did not support these observations. We did not find a significant difference in HbA_{1c} in those patients using three or four NPH injections per day at 12 weeks compared with those on one or two NPH injections. This does not exclude that in well-selected patients three or four basal insulin injections may be effective in improving overall glycaemic control by > 0.12–0.15%. However, the required total daily number of injections may then be difficult to accept for many patients. Also, the policy of increasing NPH dosage by 25% in the insulin aspart group, to compensate for the lower early night time insulinaemia in the aspart group, compared with the human insulin group, may have failed.

Another possible explanation for the different findings between our large-scale trial and previous smaller scale studies is that a larger difference in HbA_{1c} can be attained in patients that are more intensively coached (daily telephone contact if needed). Our trial used a large number of treatment centres, and perhaps as a result is closer to current clinical practice. Future randomized trials with rapid-acting insulin analogues as meal-time insulin comparing different modes of basal insulin supplementation, including new long-acting insulin analogues, seem warranted.

A possible explanation for the similar hypoglycaemia rate in both groups could be that increased dosage and number of NPH injections resulted in a relatively higher hypoglycaemia rate in the insulin aspart group. This may explain why the earlier benefit of insulin aspart in lowering the hypoglycaemia event rate was not confirmed in this trial [2,3].

The increased treatment satisfaction seen in the present and in an earlier trial [15] is remarkable in the light of the ceiling effect in the WHO-DTSQ measure [16]. Many people rate their baseline treatment satisfaction so high (27.7 ± 5.9 and 28.3 ± 5.2 in the two treatment groups at baseline in our trial, on a scale of 0–36) that improvement might seem difficult to achieve. The DTSQ-change questionnaire, which was developed in response to this criticism, was not available at the time of execution of the present trial [17].

A limitation of this large-scale study lies in its multicentre and multinational character. All centres and nationalities have their own therapeutic approaches and attitudes, and patient lifestyles differ between countries. The relatively small number of patients managed by each investigator limits the local experience that can be gained in intensification of basal insulin supplementation, particularly as this was required in the insulin aspart group only. These factors may have diluted possible advantages for the insulin aspart group, and reduced the statistical power of the study. This issue is of some importance for those designing large-scale clinical trials of insulins with new pharmacodynamic properties in the future.

In conclusion, the present large-scale clinical trial confirmed improved post-prandial glycaemic control and treatment satisfaction with the use of insulin aspart. A 25% increase in night time NPH insulin dose and the advice to use additional NPH injections when the time between injections was > 5 h, resulted in a similar HbA_{1c} decrement as reported in trials where human insulin was replaced by insulin aspart using a 1 : 1 ratio without intensification of basal insulin supplementation. This does not support routinely basal NPH insulin intensification when using rapid-acting insulin analogues in daily practice.

Acknowledgements

The study was supported by Novo Nordisk A/S as part of its insulin aspart development programme. P.D.H. and R.J.H. provide research and consultation services to Novo Nordisk on behalf of the University of Newcastle upon Tyne and the VU University Medical Centre, respectively. We thank all the people with diabetes and investigators who invested their time and effort in this study.

The following are members of the Tri-Continental Insulin Aspart Study Group. Australia: Royal North Shore Hospital, St Leonards (E. Wilmhurst), John Hunter Hospital, Newcastle (T. Donnelly), Royal Newcastle Hospital, Newcastle (K. Bowen), Princess Alexandra Hospital, Woolloongabba (D. Cameron), Royal Perth Hospital, Perth (K. Stanton), Ashford International Research Centre, Ashford (A. Roberts), Box Hill Hospital, Box Hill (R. Simpson). Austria: Landeskrankenanstalten, Salzburg (R. Weitgasser). Finland: Peijas Hospital, Vantaa (K. Harno), Päijät-Häme Central Hospital, Lahti (H. Haapamäki), Laakso Hospital, Helsinki (N. Uhlenius), North Karelian Central Hospital, Joensuu (E. Elovaara), Länsi-Pohja Central Hospital, Kemi (P. Nyländen). Germany: Christliches Krankenhaus, Quakenbrück (H. R. Henrichs), Diabetologische Ambulanz, Schwedt (T. Hampel), Krankenhaus Bethanien, Hamburg (M. Dreyer), Universitätsklinik, Bad Oeynhaus (R. Petzoldt), Diabetologische Ambulanz, Dresden (J. Schulze), Medizinische Universitätsklinik Tübingen (R. M. Schmülling). Great Britain: The Ayr Hospital, Ayr (A. Collier), Queen Mary's Hospital, Kent (I. Cranston), Freeman Hospital, Newcastle upon Tyne (P. D. Home), Royal London Hospital (P. Kopelman). The Netherlands: Vrije Universiteit medisch centrum, Amsterdam (J. H. de Vries, R. J. Heine), Westeinde Ziekenhuis, Den Haag (P. H. L. M. Geelhoed-Duyvestein), Medisch Centrum Alkmaar, Alkmaar (W. Bronsveld), Sophia Ziekenhuis, Zwolle (J. E. Heeg), Onze Lieve Vrouwe Gasthuis, Amsterdam (C. B. Brouwer), Medisch Spectrum Twente, Enschede (J. Huisman), Academisch Ziekenhuis Utrecht, Utrecht (M. Castro Cabezas). South Africa: New Groote Schuur Hospital, Observatory (A. Philotheou), Vergelegen Medi Clinic, Somerset West (G. C. Ellis), 102 Parklands Medical Centre, Natal (I. Robertson), Johannesburg Hospital, Johannesburg (J. Wing), University of Natal, Natal (A. A. Motala), Parklands Medical Centre, Natal (M. A. C. Omar). Sweden: University hospital MAS, Malmo (C. D. Agardh), Helsingborg Hospital, Helsingborg (A. Nilsson), Värnamo Hospital (A. Sjögren), Karolinska Hospital, Stockholm (K. Brismar), Huddinge University Hospital, Huddinge (J. Bolinder), Sahlgrenska Hospital, Göteborg (B. Eliasson), Falun Hospital, Falun (P. Hallgren).

References

1 Heinemann L, Kapitza C, Starke AA, Heise T. Time-action profile of the insulin analogue B28Asp. *Diabet Med* 1996; **13**: 683–684.
2 Home PD, Lindholm A, Hylleberg B, Round P. Improved glycemic control with insulin aspart: a multicenter randomized double-blind crossover trial in type 1 diabetic patients. UK Insulin Aspart Study Group. *Diabetes Care* 1998; **21**: 1904–1909.
3 Raskin P, Guthrie RA, Leiter L, Riis A, Jovanovic L. Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. *Diabetes Care* 2000; **23**: 583–588.
4 Ahmed AB, Mallias J, Home PD. Optimization of evening insulin dose in patients using the short-acting insulin analog lispro. *Diabetes Care* 1998; **21**: 1162–1166.
5 Ahmed AB, Home PD. Optimal provision of daytime NPH insulin in patients using the insulin analog lispro. *Diabetes Care* 1998; **21**: 1707–1713.
6 Del Sindaco P, Ciofetta M, Lalli C, Perriello G, Pampanelli S, Torlone E *et al.* Use of the short-acting insulin analogue lispro in intensive treatment of Type 1 diabetes mellitus: importance of appropriate replacement of basal insulin and time-interval injection-meal. *Diabet Med* 1998; **15**: 592–600.
7 Jansson P-A, Ebeling P, Smith U, Conget I, Coves MJ, Gomis R *et al.* Improved glycemic control can be better maintained with insulin lispro than with human regular insulin. *Diab Nutr Metab* 1998; **11**: 194–199.

8 Colombel A, Murat A, Krempf M, Kuchly-Anton B, Charbonnel B. Improvement of blood glucose control in Type 1 diabetic patients treated with lispro and multiple NPH injections. *Diabet Med* 1999; **16**: 319–324.
9 Ciofetta M, Lalli C, Del Sindaco P, Torlone E, Pampanelli S, Mauro L *et al.* Contribution of postprandial versus interprandial blood glucose to HbA1c in type 1 diabetes on physiologic intensive therapy with lispro insulin at mealtime. *Diabetes Care* 1999; **22**: 795–800.
10 Lalli C, Ciofetta M, Del Sindaco P, Torlone E, Pampanelli S, Compagnucci P *et al.* Long-term intensive treatment of type 1 diabetes with the short-acting insulin analog lispro in variable combination with NPH insulin at mealtime. *Diabetes Care* 1999; **22**: 468–477.
11 International Conference on Harmonisation (ICH), Topic E6. *Harmonised Tripartite Guideline for Good Clinical Practice. Step 5, Consolidated Guideline 1.5.96*. London: ICH, 1996.
12 Jacobs MA, Keulen ET, Kanc K, Casteleijn S, Scheffer P, Deville W *et al.* Metabolic efficacy of preprandial administration of Lys (B28), Pro (B29) human insulin analog in IDDM patients. A comparison with human regular insulin during a three-meal test period. *Diabetes Care* 1997; **20**: 1279–1286.
13 Meadows K, Steen N, McColl E, Eccles M, Shiels C, Hewison J *et al.* The Diabetes Health Profile (DHP): a new instrument for assessing the psychosocial profile of insulin requiring patients—development and psychometric evaluation. *Qual Life Res* 1996; **5**: 242–254.
14 Bradley C (ed.). Diabetes Treatment Satisfaction Questionnaire (DTSQ). In *Handbook of Psychology and Diabetes*. Chur, Switzerland. Harwood, 1994: 111–132.
15 Home PD, Lindholm A, Riis A. Insulin aspart vs. human insulin in the management of long-term blood glucose control in Type 1 diabetes mellitus: a randomized controlled trial. European Insulin Aspart Study Group. *Diabet Med* 2000; **17**: 762–770.
16 Pouwer F, Snoek FJ, Heine RJ. Ceiling effect reduces the validity of the Diabetes Treatment Satisfaction Questionnaire. *Diabetes Care* 1998; **21**: 2039.
17 Bradley C. Diabetes Treatment Satisfaction Questionnaire. Change version for use alongside status version provides appropriate solution where ceiling effects occur. *Diabetes Care* 1999; **22**: 530–532.