# Improved Glycemic Control With Insulin Aspart

## A multicenter randomized double-blind crossover trial in type 1 diabetic patients

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OBJECTIVE — To compare glycemic control obtained with the new rapid-acting insulin analog insulin aspart with that obtained with unmodified human insulin using algorithm-driven dosage adjustment.

RESEARCH DESIGN AND METHODS — This was a multicenter randomized double-blind crossover study of 90 male subjects with type 1 diabetes. Insulin aspart or soluble human insulin was administered before meals, and NPH insulin was administered at bedtime as basal therapy. Each 4-week study period ended with a 24-h inpatient serum insulin and plasma glucose profile.

RESULTS — The 24-h plasma glucose control obtained with insulin aspart, as assessed by excursions of blood glucose outside a predefined normal range (4.0–7.0 mmol/l), was superior (22% reduction in excursion, $P < 0.01$). Fructosamine levels remained unchanged with insulin aspart, with daytime glycemic control superior but nighttime glycemic control inferior. Eight-point home blood glucose profiles confirmed that insulin aspart significantly improved postprandial blood glucose control after lunch and dinner ($P < 0.05$) without deterioration of preprandial blood glucose control. Hypoglycemic episodes requiring third-party intervention were significantly fewer with insulin aspart than with human insulin (20 vs. 44 events, $P < 0.002$). Insulin aspart was well tolerated.

CONCLUSIONS — In comparison with human insulin, insulin aspart can improve postprandial glycemic control as assessed by a reduction in hyper- and hypoglycemic excursions in people with type 1 diabetes. For its full potential to be realized, it will need to provide better control of nighttime hyperglycemia.

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The Diabetes Control and Complications Trial (DCCT) and other studies have confirmed the rationale for recommending a regimen of mealtime plus basal insulin in the management of type 1 diabetes by demonstrating the relationship between metabolic control and risk of secondary diabetic complications (1–4). Thus, improvement in metabolic control should be a major aim of insulin therapy. However, standard human insulin regimens have a number of disadvantages regarding the desired pharmacokinetics and the variability of absorption after subcutaneous administration (5–8).

Endogenous insulin release after a meal begins more rapidly and is of shorter duration than that achieved with exogenously administered unmodified insulin after subcutaneous injection (8,9). Part of the reason for this difference is that the passage of insulin from the injection site to the bloodstream is delayed as a result of hexamer formation at the concentrations found in the insulin vial and subcutaneous depot (10). Brange et al. (11) designed the insulin analog insulin aspart so that the insulin molecules repel each other, leading to reduced hexameric binding. This simple approach results in markedly improved absorption kinetics after subcutaneous absorption, with a concentration profile more closely resembling the mealtime physiological profile (12–15). Experimentally, the pharmacodynamic/physiological effect is a reduced postprandial hyperglycemic excursion (13,14).

Extensive preclinical testing of insulin aspart has shown that the chemical and biological properties of human insulin have been preserved in terms of potency and of the binding characteristics to the insulin receptor as well as to the IGF-1 receptor (16).

The aim of the present study was to assess these advantages of insulin aspart in people with type 1 diabetes. Previous studies of short-acting insulin analogs have been flawed by inherent bias caused by clinicians' greater experience of using unmodified human insulin and by the lack of a double-blind design (17). Accordingly, we chose an algorithm-driven dosage adjustment protocol and a strictly randomized double-blind design.

## RESEARCH DESIGN AND METHODS

— A multicenter randomized double-blind crossover trial in people with type 1 diabetes was conducted in 11 sites in the U.K. The study was approved

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Abbreviations: $C_{max}$, maximum concentration; $C_{min}$, minimum concentration.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Patient characteristics*

| | |
|---|---|
| *n* | 104 |
| Age (years) | 34.3 ± 8.6 |
| Height (m) | 1.78 ± 0.62 |
| BMI (kg/m$^2$) | 25.3 ± 2.3 |
| Duration of diabetes (years) | 14.8 ± 8.7 |
| $HbA_{1c}$ (%) | 7.1 ± 1.0 |

Data are means ± SD. Normal $HbA_{1c}$ is <5.8%.

by the U.K. Medicines Control Agency and local ethics committees. Written informed consent was obtained from the participating subjects. A total of 104 subjects with type 1 diabetes were randomized, and 90 completed the trial (1 subject was withdrawn because of an adverse event, 3 violated the protocol, and 10 felt unable to continue with the demands of the protocol). The diagnosis of type 1 diabetes was confirmed by medical history and a meal-stimulated serum C-peptide level ≤0.10 nmol/l.

## Patients

The patients recruited were men with type 1 diabetes, aged 18–60 years, with a BMI <29.0 kg/m$^2$ and an $HbA_{1c}$ <9.0% (normal, <5.8%) (Table 1). For at least 1 month before the study, the patients were required to use human unmodified premeal insulin plus NPH insulin as basal insulin administered only at bedtime. People with active proliferative retinopathy or nephropathy, recurrent severe hypoglycemia, insulin resistance, other systemic diseases, or drug abuse were excluded from the trial. Women were excluded pending reproductive toxicology information on insulin aspart.

## Design

After a 4-week run-in period in which treatment consisted of human unmodified insulin plus bedtime NPH insulin, patients were randomized to premeal insulin aspart (Novo Nordisk, Bagsvaerd, Denmark) or human unmodified insulin (Actrapid; Novo Nordisk) for 4 weeks. Patients then crossed over to treatment with the other premeal insulin for another 4 weeks.

Throughout the trial, patients were asked to take the premeal insulin injections just before eating. This timing is preferred by patients, is usually used by patients treated with human insulin even when they are advised otherwise, and is safer unless blood glucose is self-monitored before each injection (18–21). In all patients, NPH insulin (Human Insulatard, Novo Nordisk) was taken once daily at bedtime. Injections were made using a pen injector (Novo Nordisk). Daily four-point preprandial blood glucose profiles using the Medisense Companion 2 (Medisense, Abingdon, U.K.) and weekly eight-point blood glucose profiles (premeal, postmeal, bedtime, and 0200) were requested. The blood glucose profiles provided the basis for insulin dosage adjustment in collaboration with the treating physician and with the use of a purpose-defined dosage algorithm for hyper- and hypoglycemia (Fig. 1).

The algorithms were designed to improve consistency between centers and thus improve study power. Targets for blood glucose control were premeal and 0200 levels of 4.0–7.0 mmol/l and postprandial blood glucose levels of <10.0 mmol/l in the absence of hypoglycemic episodes. Study visits took place every 2 weeks, with telephone contact occurring weekly or more frequently when dosage adjustment was necessary according to the daily self-monitoring results.

At the end of each study period, a 24-h plasma glucose and serum insulin profile was performed. Insulin aspart and human insulin were administered before meals, and NPH insulin was administered at 2230. Starting at 1800, blood samples were taken every 30 min for 2 h after each meal, and hourly for the rest of the sampling period. Dinner was served at 1800, breakfast at 0800, and lunch at 1300. Content and quantity of meals were standardized during profile days.

Serum fructosamine concentration was measured at baseline and at the end of each 4-week treatment period.

## Hypoglycemia and adverse events

Hypoglycemia was classified as minor (the patient dealt with the episode themselves) or major (the person required help from a third party). Other adverse events were recorded at each visit and classified according to normal pharmaceutical guidelines.

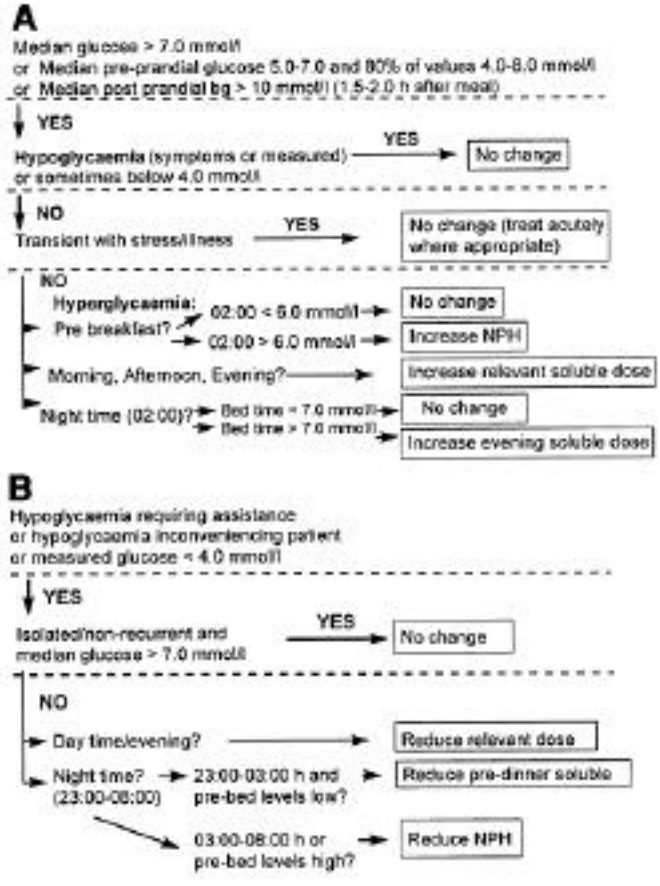


**Figure 1**—*Algorithms used to increase or reduce dosage of insulin in cases of hyperglycemia (A) or hypoglycemia (B). bg, blood glucose.*

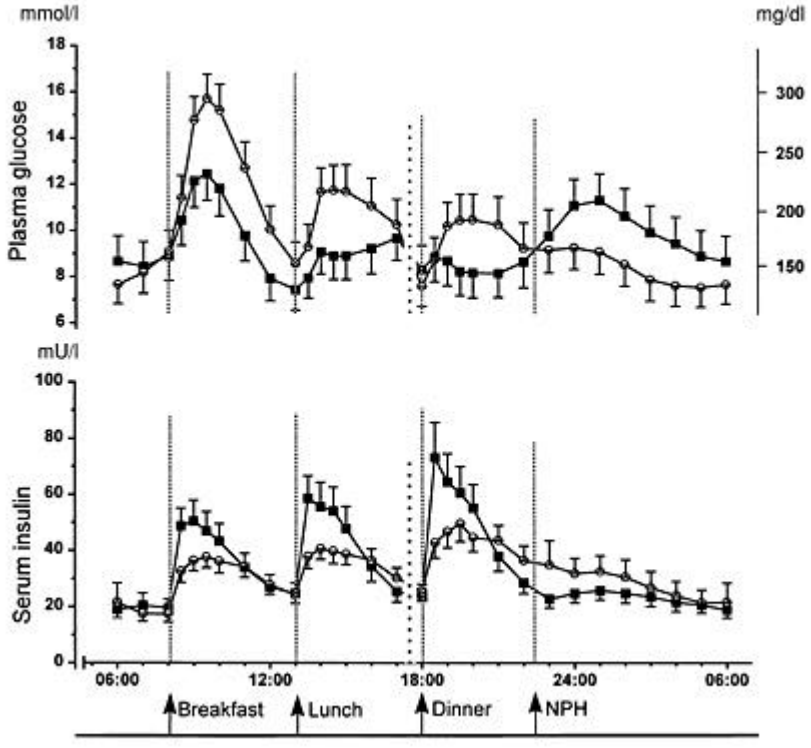


**Figure 2**—*Serum insulin and plasma glucose profiles in type 1 diabetic patients using insulin aspart (■) or unmodified human insulin (○) before main meals. Sampling began at 1800 for each profile. Data are means ± 2 SEM during a 24-h period.*

### Biochemical analysis

Plasma glucose, serum insulin, and serum fructosamine concentrations were measured using standard laboratory techniques at the Bioanalytical Research Company (Ghent, Belgium). Total serum human insulin and insulin aspart concentrations were assayed using a commercial radioimmunoassay kit (Pharmacia, Uppsala, Sweden) validated for both insulins at concentrations <600 pmol/l.

A standard biochemical and hematologic clinical profile was measured before and after the study and assayed by standard methods. Drugs-of-abuse screening and measurement of insulin antibodies were performed before and after the study by standard methods.

### Statistical analysis

The primary efficacy assessment was fructosamine level at the end of each treatment period. The secondary efficacy assessments were 24-h inpatient plasma glucose profiles, eight-point blood glucose profiles (last week of treatment period), ratio of mealtime to basal insulin dose, and incidence of hypoglycemia (during last 2 weeks of treatment).

With an intrapatient coefficient of variation for fructosamine of 20% and a significance level of 5%, a sample size of 80 would detect a true difference (ratio of the clinically significant difference to the intrapatient SD) of 0.50 (10%/20%) with the required certainty (power >80%). The sample size is consistent with previous studies of this kind in type 1 diabetes. All the tests were two-tailed, and the significance level was set at 5% for all analyses. Efficacy results are presented using the intention-to-treat population. Statistical analyses were made using SAS for UNIX version 6.09 (SAS Institute, Cary, NC).

For fructosamine, a standard two-way crossover analysis conducted on log-transformed values was applied. For the 24-h plasma glucose profile, maximum ($C_{max}$) and minimum ($C_{min}$) concentrations were compared in four time intervals: 1800–2200, 2300–0800, 0830–1300, and 1330– 1700. The plasma glucose excursion was calculated as the sum of the portions of the total area under the curve that lay above 7.0 mmol/l and above the curve that lay below 4.0 mmol/l. Statistical analysis of the secondary end points described above were performed on log-transformed values, to correct skewed distributions.

Ratio of mealtime to basal insulin dose and insulin antibodies were analyzed with Wilcoxon's signed rank test on the paired differences between treatments. Time points of the 24-h profile and the eight-point blood glucose profiles were compared using an analysis of variance. Within-patient variability was measured as the SD over the eight time points and compared with the Wilcoxon's signed rank test. The number of hypoglycemic events were compared using the signed rank test. Results are presented as means ± SD unless otherwise specified.

## RESULTS

### Insulin dosage

There was no difference in the bolus to basal insulin ratio between the insulin aspart period (1.66 ± 0.72) and the human insulin period (1.71 ± 0.78). The mean doses given were 40.9 ± 13.6 U/day for insulin aspart, 39.7 ± 13.5 U/day for human insulin, 27.8 ± 11.3 U/day for bedtime NPH insulin during the insulin aspart period, and 26.8 ± 12.0 U/day during the human insulin period.

### Serum insulin concentration

After the prebreakfast subcutaneous injection of insulin aspart, the time to $C_{max}$ was shorter for insulin aspart than for human insulin (42 ± 58 vs. 88 ± 66 min, respectively; $P < 0.05$). Postbreakfast insulin $C_{max}$ values were higher than after injection of human insulin, 60 ± 37 vs. 44 ± 20 mU/l ($P < 0.05$), with a more rapid disappearance (Fig. 2). Insulin concentrations were lower in the early part of the night ($P < 0.01$) (Table 2) with insulin aspart than with human insulin (26 ± 16 vs. 32 ± 27 mU/l at 0100; $P < 0.001$).

### Blood glucose control

Overall 24-h glucose control, as assessed by the excursion of plasma glucose outside the predefined range (4.0–7.0 mmol/l), was significantly improved with insulin aspart, with the excursion 78% of that obtained with human insulin (4,713 ± 4,310 vs. 5,260 ± 3,361 mmol · $l^{-1}$ · min; $P < 0.01$). When separated into positive and negative excursions (>7.0 and <4.0 mmol/l, respectively), the overwhelming gain (96%) was in the positive excursion, and this excursion was significantly smaller with insulin aspart, whereas the negative excursion was not. In predefined time intervals, daytime glucose

Table 2—*Derived parameters from the 24-h plasma glucose profiles obtained with insulin aspart and human insulin*

| Clock time | Insulin aspart | Human insulin | *P* value |
|---|---|---|---|
| Plasma glucose $C_{max}$ (mmol/l) | | | |
| 0830–1300 | 13.8 ± 5.4 | 16.7 ± 4.8 | <0.0001 |
| 1330–1700 | 11.3 ± 4.7 | 13.3 ± 5.4 | <0.0001 |
| 1800–2200 | 11.2 ± 5.4 | 12.2 ± 5.4 | NS |
| 2300–0800 | 13.5 ± 5.3 | 12.6 ± 4.3 | NS |
| Plasma glucose $C_{min}$ (mmol/l) | | | |
| 0830–1300 | 6.1 ± 3.9 | 7.2 ± 3.9 | <0.02 |
| 1330–1700 | 6.6 ± 4.0 | 7.8 ± 4.4 | <0.001 |
| 1800–2200 | 5.5 ± 3.5 | 5.9 ± 3.9 | NS |
| 2300–0800 | 6.1 ± 4.4 | 4.8 ± 3.2 | <0.01 |
| Serum insulin AUC (mU · $l^{-1}$ · min) | | | |
| 0830–1300 | 9,966 ± 6,223 | 8,798 ± 4,201 | <0.01 |
| 1330–1700 | 9,141 ± 5,995 | 7,888 ± 3,550 | <0.01 |
| 1800–2200 | 11,920 ± 7,539 | 10,234 ± 5,315 | <0.02 |
| 2300–0800 | 12,078 ± 7,261 | 13,897 ± 13,005 | <0.01 |

Data are means ± SD. AUC, area under the curve.

control, as assessed by $C_{max}$ and $C_{min}$, was significantly lower with insulin aspart than with human insulin (Table 2). During the night, $C_{min}$ was significantly lower with human insulin than with insulin aspart (Table 2 and Fig. 2).

The eight-point self-measured blood glucose profiles showed identical prelunch, predinner, and bedtime glucose concentrations, with no suggestion of loss of preprandial glycemic control with insulin aspart (Fig. 3). However, afternoon and evening postprandial concentrations were significantly improved, with values of 6.4 ± 3.0 vs. 8.1 ± 3.7 mmol/l after lunch ($P < 0.05$) and 7.2 ± 3.1 vs. 8.8 ± 3.5 mmol/l after dinner ($P < 0.05$) (Fig. 3). The midmorning and nighttime differences did not reach statistical significance.

There was no difference in blood glucose control as assessed by serum fructosamine, with concentrations of 3.76 ± 0.53 and 3.82 ± 0.56 mmol/l for insulin aspart and human insulin, respectively (NS).

### Hypoglycemia

There were 567 hypoglycemic episodes reported in the insulin aspart period and 615 episodes in the human insulin period (NS). There were significantly fewer major hypoglycemic episodes in the whole insulin aspart period than in the whole human insulin period (20 events in 16 subjects vs. 44 events in 24 subjects, $P < 0.002$). During the last 2 weeks of the study period, there were half as many events in the insulin aspart period than in the human insulin period (11 vs. 22 events, $P < 0.05$).

### Other adverse events

There were 81 treatment-emergent adverse events (excluding hypoglycemia) reported with insulin aspart compared with 66 adverse events with human insulin (NS), and clinicians assessed 5 and 8 events reported with insulin aspart and human insulin, respectively, as having a possible relationship to the insulin. One event of fatigue and anorexia with insulin aspart led to the subject's withdrawal from the study. Serious adverse events were reported in two subjects while using insulin aspart (vomiting and pyrexia in one, hypoglycemia with convulsions in the other), and in two subjects while using human insulin (confusion in one, hypoglycemia with convulsions in the other). There were no clinically significant abnormalities in the biochemical or hematologic profiles, vital signs, or electrocardiograms.

In 83 individuals with antibody measurements before and after the trial, the difference in change from baseline was 0.4 ± 3.0% between treatments (change with insulin aspart minus the change with human insulin, NS).

CONCLUSIONS — The results of this study confirm that insulin aspart, as a consequence of its more rapid subcutaneous absorption (Fig. 2), can achieve improved blood glucose control postprandially when used in a premeal plus basal insulin regimen. Such results are consistent with those described for another insulin analog, insulin lispro (17,22), but these results were achieved for insulin aspart without deterioration of late postprandial blood glucose concentrations (Fig. 3). Furthermore, blood glucose excursions outside the physiological range (4.0–7.0 mmol/l) were significantly reduced on the insulin aspart regimen, with notable reductions in peak concentrations after meals (Table 2).

However, overall blood glucose concentration, as measured by serum fructosamine, was unchanged with the use of insulin aspart, as has been the case in the major clinical lispro studies (17). This find-

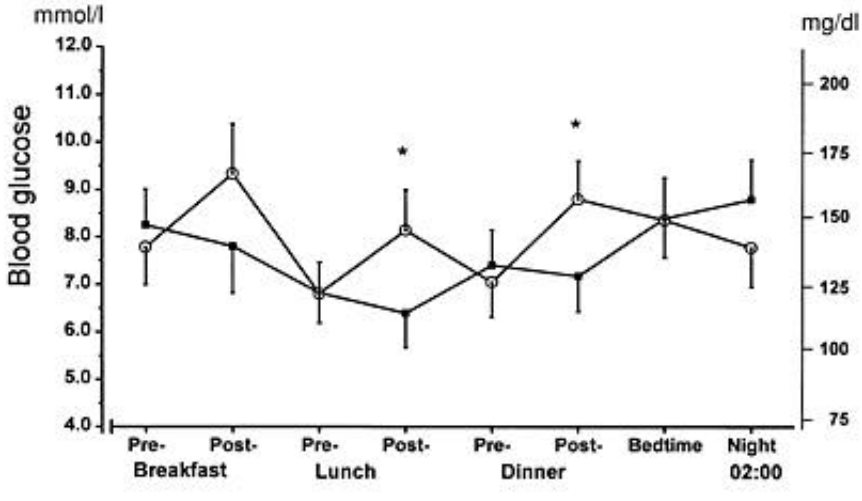


**Figure 3**—*Self-monitored blood glucose profiles for the last week in the study period in type 1 diabetic patients using insulin aspart (■) or human insulin (○). Data are means ± 2 SEM. * $P < 0.05$ between insulins.*

ing is not necessarily an adverse one, because major episodes of hypoglycemia were halved with the use of insulin aspart in the present study, and a reduction in hypoglycemia is associated with a tendency to somewhat higher blood glucose levels and thus with some increase in the average blood glucose level.

Nighttime blood glucose levels were higher with insulin aspart than with human insulin, with the crossover of the glucose profiles occurring as early as 2200–2300 (Fig. 2). This phenomenon implies that human insulin contributes significantly to insulin supply from this time on into the early part of the night, and thus to the feared nighttime hypoglycemia. Indeed, short-acting analogs are known to reduce the incidence of nighttime hypoglycemia (23), and on the basis of the present results, insulin aspart would be expected to do the same in patients at risk of nighttime hypoglycemia. In patients without such a risk, there would appear to be an opportunity for an improvement in overall blood glucose control, as the relative hyperglycemia should allow an increase in the evening NPH insulin dose, restoring nighttime glycemic control and perhaps improving prebreakfast glucose levels. Such ideas are currently being studied, but it is perhaps disappointing that the algorithm-driven dosage adjustment did not deliver such an improvement in the current study. The likely explanation is twofold. First, only weekly nighttime self-monitoring was performed, providing little information with which to adjust the evening NPH insulin dosage. Second, because a patient's experience of nighttime hypoglycemia is usually highly adverse, a very good case for an increase in the evening NPH insulin dosage is needed before it becomes acceptable to both patient and physician.

These observations also suggest that short-acting insulin analogs would be better matched by a true basal insulin rather than by the erratically absorbed and rather short-acting NPH insulin. This idea is supported by the observations of Zinman et al. (24), who used pumps to deliver basal insulin supply and were able to show significantly improved overall glycemic control when using short-acting analogs.

Because of the double-blind design of the study, preprandial injection of human insulin was necessary just before the meal, as in other similar studies (25). This timing may be thought to bias the postprandial results in favor of insulin aspart. However, as has been strongly argued by others, human insulin administration ≥30 min before meals can be hazardous unless glucose levels are checked first (19–21). Recently, Torlone et al. (26) showed a decrease in glucose concentration of 2.0 mmol/l when human insulin is administered 30 min before a meal. The experience of the resulting hypoglycemia as well as the obvious inconvenience of early administration (and sometimes the impossibility of predicting the time of the meal) may be the reasons that most patients do not follow this advice even when adequately instructed (18,20). Accordingly, the current study should more closely reflect actual clinical practice.

It is intriguing to note that the nighttime hyperglycemia occurring with insulin aspart persisted until morning, although this finding was not statistically significant. Nevertheless, this effect has been noted in an experimental study performed overnight with insulin lispro (27). In both studies, this effect appears to have occurred despite convergence of serum insulin concentrations for >4 h. It is tempting to hypothesize that in the fasting state, at least, a component of insulin action persists well beyond measurable changes in insulin concentrations, perhaps through changes in insulin sensitivity. This hypothesis would be amenable to testing.

In conclusion, a regimen of mealtime plus basal insulin using insulin aspart can significantly reduce glucose excursion and major hypoglycemic events in people with type 1 diabetes. Further optimization and improvement in overall blood glucose control must await the results of studies of the ideal dosage ratios of insulin aspart and NPH insulin, particularly when administered in the evening.

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## APPENDIX

The following are members of the U.K. Insulin Aspart Study Group: S. Amiel, London; S. Bloom, London; R. Gregory, Leicester; S. Heller, Sheffield; J.P. O'Hare, Bath; P.D. Home, Newcastle upon Tyne; J. McKnight, Edinburgh; M. Nattrass, Birmingham; D. Owens, Cardiff; D. Sandeman, Southampton; and G. Williams, Liverpool, U.K.

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