A Direct Efficacy and Safety Comparison of Insulin Aspart, Human Soluble Insulin, and Human Premix Insulin (70/30) in Patients With Type 2 Diabetes

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OBJECTIVE — Because there are limited data on the comparison of insulin aspart and mixed insulin in type 2 diabetes, this trial was performed to compare the efficacy and safety of preprandial insulin aspart with human soluble insulin (HI) and human premix (70% NPH/30% regular) insulin (MIX).

RESEARCH DESIGN AND METHODS — A total of 231 type 2 diabetic patients were randomized to insulin aspart ($n = 75$), HI ($n = 80$), or MIX ($n = 76$) for 3 months. Insulin aspart and HI were administered with or without bedtime NPH insulin. A total of 204 patients completed the trial according to protocol. HbA_{1c}, 7-point blood glucose, insulin dosage, and hypoglycemic episodes were recorded. The primary end point was "change of HbA_{1c}" from baseline to last visit. Analysis for equivalence was performed by *t* tests with three subtests.

RESULTS — HbA_{1c} decreased 0.91 ± 1.00 for insulin aspart, 0.73 ± 0.87 for HI, and 0.65 ± 1.10 for MIX with the following confidence intervals: insulin aspart HI (−0.21 to 0.57, $P = 0.025$), insulin aspart MIX (−0.17 to 0.69, $P = 0.092$), and HI-MIX (−0.33 to 0.48, $P = 0.006$). Postprandial blood glucose decreased in the insulin aspart group: 0.44 mmol/l to >1.67 mmol/l compared with HI and 1.1 mmol/l to >1.67 mmol/l compared with MIX. Preprandial insulin doses were similar in the insulin aspart and HI groups (10–14.5 U). Hypoglycemic events per month were 0.56 HI, 0.40 insulin aspart, and 0.19 MIX.

CONCLUSIONS — Statistically, insulin aspart was not equivalent to another treatment in terms of HbA_{1c} reduction. Insulin aspart treatment resulted in improved HbA_{1c} and postprandial blood glucose. The application of insulin aspart was safe and well tolerated.

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The major therapeutic goals in subjects with type 2 diabetes are to optimize blood glucose control, to reduce overweight, and to normalize lipid disturbances and elevated blood pressure. It has been shown that the intensive management of type 2 diabetes reduces the risk for chronic complications (1). Diet and exercise, aiming at weight reduction, are the cornerstones of therapy. However, pharmacological treatment with oral hypoglycemic agents (OHAs) or insulin is often required (2–13).

Insulin aspart is a rapid-acting human insulin analog: replacement of proline at position B28 by aspartic acid reduces the tendency for self-association to hexamers and dimers and leads to faster absorption into the blood stream (14). Because of its short-acting profile, insulin aspart is administered immediately before main meals (15,16). Postprandial administration was also demonstrated to be a feasible therapeutic option (17). Several clinical studies showed that insulin aspart is as effective as human soluble insulin (HI) in type 1 diabetic patients (18–23).

There are only limited data for insulin aspart in type 2 diabetes and no comparisons so far among preprandial use of HI, a short-acting insulin analog, and standard human premix insulin (MIX) in a type 2 diabetic population. The aim of the present trial was to compare the efficacy and safety of three different therapeutic regimens in type 2 diabetic patients: *1*) preprandial insulin aspart with or without additional NPH insulin once daily at bedtime; *2*) preprandial HI with or without additional NPH insulin once daily at bedtime; and *3*) MIX (70% NPH/30% regular) once or twice daily.

The intensive management of blood glucose reduces the incidence of progression of diabetes complications in type 2 diabetic patients (1,24) but may require multiple-injection regimens for insulin, which is not desirable for all people with type 2 diabetes. Therefore, we wanted to find out whether MIX (70% NPH/30% regular) was as effective as insulin aspart and HI in controlling HbA_{1c}.

RESEARCH DESIGN AND METHODS

— The study was approved by 18 ethics committees responsible for the 30 centers participating in the trial, and the study was performed in accordance with the principles expressed in the Declaration of Helsinki (25). All subjects gave written informed consent before entry.

Of the 231 randomized type 2 diabetic patients, 204 patients completed the trial according to protocol. Patients were men and women (age ≥35 years) with type 2 diabetes according to World

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Abbreviations: HI, human soluble insulin; MIX, human premix insulin; OHA, oral hypoglycemic agent; WHO, World Health Organization.

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

Table 1 —*Baseline demographic data*

	Insulin aspart	Soluble insulin	Premix insulin 70/30
Men/women	44/31	40/40	46/30
Age (years)	61.4 ± 9	62 ± 3.3	63.1 ± 8.9
BMI (kg/m^2)	29.2 ± 3.7	29.3 ± 3.3	29.2 ± 4
HbA_{1c} (%)	7.82 ± 0.13	7.83 ± 0.13	7.78 ± 0.13

Data are means ± SD.

Health Organization (WHO) criteria (26) and whose duration of diabetes was >1 year (Table 1). They were treated with antidiabetic agents (OHAs and/or conventional insulin therapy) for >1 year. HbA_{1c} was ≤10.0%, and BMI was 23–37 kg/m^2. Patients were able to perform blood glucose measurements at home. None had unstable/untreated proliferative retinopathy, clinical significant nephropathy, neuropathy or hepatic disease, heart failure (New York Heart Association III and IV), uncontrolled hypertension, or systemic treatment with corticosteroids or required >1.4 units · kg^{-1} · day^{-1} insulin.

The study was conducted as a multicenter, randomized, open-labeled, three-arm parallel group trial including a screening visit, a randomization visit, followed by a 1- to 3-week titration period, and a 3-month maintenance period. At the first random visit, patients were randomized to either preprandial insulin aspart (100 units/ml, 3-ml Penfill; Novo Nordisk, Bagsvaerd, Denmark), preprandial HI (Actrapid HM, 100 IU/ml, 3-ml Penfill; Novo Nordisk), or MIX (70/30) (Mixtard 30 HM, 100 IU/ml, 3-ml Penfill; Novo Nordisk). NPH insulin (Insulatard HM, 100 IU/ml, 3-ml Penfill; Novo Nordisk) once daily at bedtime could be added to both short-acting insulin preparations. The MIX was used once or twice daily. The trial products were administered using NovoPen3. No combination therapy of insulin with OHAs was allowed after randomization and start of trial medication. Further insulin dose adjustments were performed within the following 1- to 3-week titration period, including 2–4 dose-finding days (second to fifth random visit). The therapeutic aim of the titration period was optimization of glycemic control (80–110 mg/dl or 4.4–6.1 mmol/l). The following 3-month maintenance period included three visits: the first maintenance visit occurred 7 days after the last titration visit, the second maintenance visit occurred after 1.5 months, and the third maintenance visit occurred after another 1.5 months. Patients documented home blood glucose measurements, insulin dosages, and hypoglycemic episodes. Dosage of the trial medication was adjusted by the investigators throughout the trial based on the patient's self-measurements of the 7-point blood glucose profiles measured the day before the first random visit to the third maintenance visit and the incidence of hypoglycemic episodes, which were symptomatic and/or biochemical (i.e., blood glucose ≤45 mg/dl or 2.5 mmol/l) hypoglycemic episodes.

HbA_{1c} was assessed at the screening visit and at the third maintenance visit and was analyzed by a central laboratory (using the high-performance liquid chromatography method [Diamat, reference interval: 4.3–6.1%]). Self-monitoring of blood glucose was performed by the patients using blood glucose meters provided by the sponsor (One Touch Profile; LifeScan). A central laboratory analyzed standard safety laboratory parameters.

Statistical analysis was performed with the intention-to-treat population. The trial was based on equivalence of the primary efficacy end point, the change of HbA_{1c} from baseline (screening visit) to the last (third maintenance) visit. A sample size of 222 patients, including a dropout rate of ~15%, was calculated on the assumption that type I error should not exceed 5% and type II error should not exceed 10%. The primary hypotheses were as follows. The change of HbA_{1c} of treatment A is not statistically different from treatment B with the equivalence difference limit defined as 0.5% HbA_{1c}. Treatment A and B should be replaced as any combination of the investigated treatments. Because three treatments were compared simultaneously, type I (α) error was adjusted according to Bonferroni for three equivalence tests, i.e., each hypothesis was tested with a type I error of 1.67%. The primary hypothesis was evaluated using three two-sided Student's *t* tests each with $\alpha = 1.67\%$ (i.e., 0.83% for each subtest). Consideration of the subgroups (e.g., with or without additional NPH insulin once daily at bedtime) was evaluated as the secondary end point. The incidence of hypoglycemic episodes was tested on the differences among the treatment groups using a Wilcoxon test with $\alpha = 5\%$. Subgroups (i.e., additional treatments) of the main treatment groups were evaluated using the ANOVA technique. The safety analysis included all subjects who had received trial medication. Adverse events were summarized by event frequency and frequencies of subjects with events and also by relation to trial treatment and severity. Furthermore, all adverse events were summarized by WHO-preferred terms. The safety profile, as measured by standard safety parameters, was presented by summary statistics differentiating among the treatment groups. The statistical software package SAS version 6.12 (Cary, NC) was used.

RESULTS — A total of 275 type 2 diabetic patients were screened at 30 trial sites in Germany. Forty-four patients failed screening because of nonfulfillment of inclusion/exclusion criteria. Of the remaining 231 subjects, 75 received insulin aspart, 80 received HI, and 76 received MIX. Twenty-seven randomized patients (11 insulin aspart, 9 HI, and 7 MIX) were prematurely withdrawn from the trial. They either had not met the selection criteria or withdrew their consent. A total of 204 patients completed the trial according to the protocol. The patient disposition is shown in Fig. 1.

Efficacy results

Insulin aspart was not equivalent to another treatment group in terms of reduction of HbA_{1c}. However, treatment with insulin aspart resulted in more pronounced improvement of HbA_{1c} levels in the course of the trial when compared with HI or human MIX. During the 12-week maintenance period, HbA_{1c} decreased by 0.91 ± 1.00% in the insulin aspart group, by 0.73 ± 0.87% in the HI group, and by 0.65 ± 1.10% in the MIX group. The results for the primary efficacy end point (change of HbA_{1c}) are summarized in Table 2.

The decrease of the mean postprandial blood glucose levels was most pronounced in patients treated with insulin

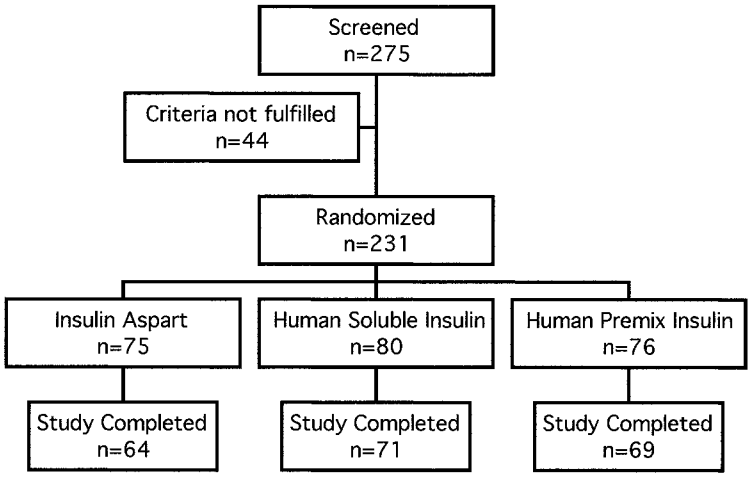

Figure 1—*Patient disposition chart.*

aspart. At the end of the maintenance period, mean postprandial blood glucose levels in the insulin aspart group were lower by 8 mg/dl (0.44 mmol/l) to >30 mg/dl (1.67 mmol/l) when compared with the respective blood glucose levels for the HI group and 20 mg/dl (1.11 mmol/l) to >30 mg/dl (1.67 mmol/l) when compared with the MIX group (Fig. 2). The preprandial blood glucose levels at the end of the trial were comparable among the treatment groups. The percentage of patients with overall postprandial blood glucose levels >180 mg/dl (10.0 mmol/l) also was lowest in the insulin aspart group at the end of the trial: 26.7% of the insulin aspart patients had blood glucose values >180 mg/dl after breakfast (vs. 29.0% of the HI patients and 40.0% of the MIX patients), 14.3% of the insulin aspart patients with blood glucose >180 mg/dl after lunch (vs. 30.0% of the HI patients and 23.5% of the MIX patients), and 13.3% of the insulin aspart patients with blood glucose >180 mg/dl after dinner (vs. 35.5% of the HI patients and 25.0% of the MIX patients).

The mean preprandial insulin doses per injection were similar in the insulin aspart (10–13 units) and the HI group (10–14.5 units). At the end of the trial, the proportion of patients taking NPH insulin in addition to the preprandial short-acting insulin preparations was 72% in the insulin aspart group and 81% in the HI group. The mean doses of NPH insulin additionally injected at bedtime tended to be slightly higher in the insulin aspart group (17 IU) than in the HI group (14 IU) at the end of the trial. When comparing the preprandial doses of insulin aspart in the patients with additional NPH insulin with those in patients without additional NPH insulin, no clinically relevant difference was observed. The mean insulin doses in the MIX group slightly increased during the course of the trial.

Safety results

The proportion of patients with adverse events was comparable in all three treatment groups and ranged from 43 to 47%. Bronchitis and upper respiratory tract infections affected >20% of the insulin aspart and HI patients and 10% of the MIX patients. Two patients (3%) in each treatment group experienced adverse events related to the trial medication. The proportions of patients with hypoglycemic episodes during the trial period (41% insulin aspart and HI each, 30% MIX) were not statistically different. In the insulin aspart group, each patient experienced 0.40 hypoglycemic episodes per month of exposure, whereas this ratio was 0.56 hypoglycemic episodes per month in the HI group and 0.19 episodes in the MIX group (insulin aspart HI, $P = 0.827$; insulin aspart MIX, $P = 0.122$; HI-MIX, $P = 0.090$). No drug-related allergic reactions were observed during the trial.

Body weight

The change of body weight throughout the trial was found to be most advantageous in the insulin aspart group, with a median change of 0 kg, whereas there was a median increase of body weight of 0.5 kg in the HI group and 1.0 kg in the MIX group.

CONCLUSIONS — Short-acting insulin analogs were introduced to achieve insulin profiles as close to physiological levels as possible. The reduced tendency for self-association of insulin aspart leads to faster absorption and higher peak insulin levels in both type 1 and type 2 diabetic patients (16,27). All trials comparing short-acting analogs to unmodified human insulin showed reduced postprandial excursions in clinical use (15,16,18–20). For type 2 diabetic patients, however, so far there have been no data comparing the three therapeutic options: conventional insulin therapy with MIX versus preprandial insulin therapy with HI (with/without NPH insulin) versus preprandial insulin therapy with a short-acting insulin analog, insulin aspart (with/without NPH insulin).

At the end of the trial, HbA_{1c} had decreased in all three treatment groups, with the most pronounced reduction in the insulin aspart group. Whereas the mean preprandial blood glucose levels were found to be comparable among the three groups, a clear difference among the treatment groups was established with regard to postprandial blood glucose levels at the

Table 2—*Statistical equivalence test of changes in HbA_{1c} (%)*

	Soluble insulin		Premix insulin	
	95% CI	*P*	95% CI	*P*
Intention-to-treat				
Insulin aspart	−0.21 to 0.57	0.025	−0.17 to 0.69	0.092
Soluble insulin	—		−0.33 to 0.43	0.006*
Per protocol				
Insulin aspart	−0.24 to 0.58	0.027	−0.14 to 0.7	0.176
Soluble insulin	—		−0.28 to 0.58	0.026

End of trial versus baseline 95% confidence intervals and *P* values are given for the intention-to-treat and the per-protocol analysis. The significance level for *P* is 0.0083. *$P < 0.0083$.

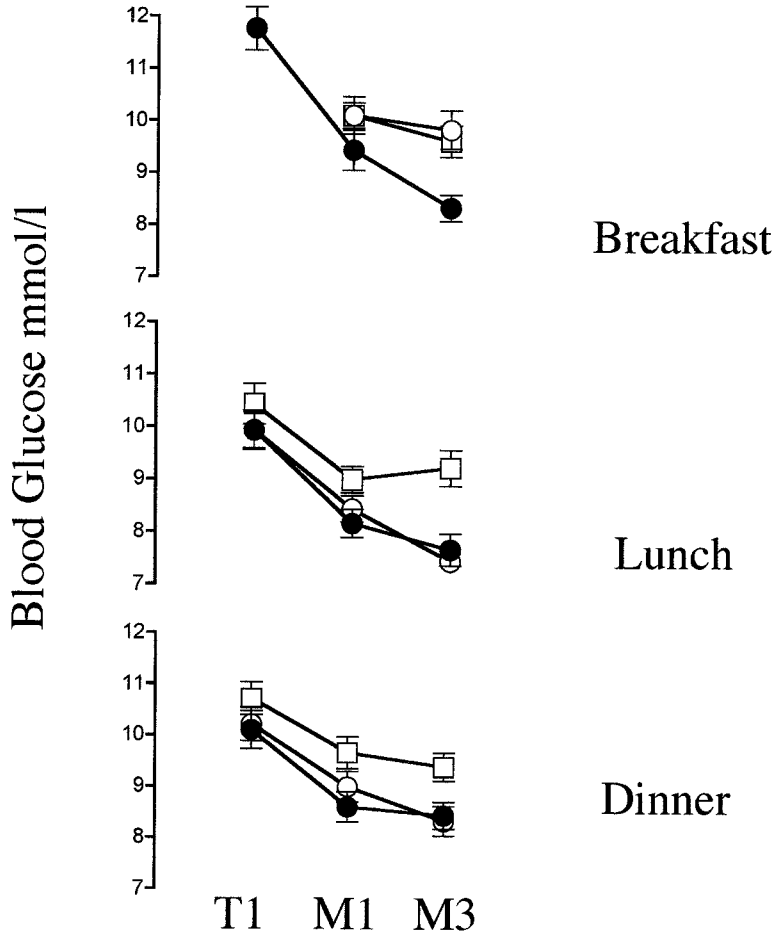

Figure 2—*Mean postprandial blood glucose levels ± SD (mmol/l) 90 min after breakfast, lunch, or dinner at the randomization visit (T1) and 1- or 2-month maintenance period (M1, M2) following a 1- to 3-week titration period. Insulin aspart (●), soluble insulin (○), and premix insulin (□). Postprandial breakfast blood glucose was reduced most efficiently in the aspart group in the maintenance period. After lunch or dinner, the aspart and soluble insulin groups both had similar blood glucose levels but were obviously lower compared with the premix group.*

end of the 3-month maintenance period, showing the lowest values for insulin aspart (between 8 and 30 mg/dl lower [0.44–1.67 mmol/l]). Furthermore, the insulin aspart group showed the lowest percentage of patients with postprandial blood glucose levels >180 mg/dl (10.00 mmol/l) at the end of the maintenance period compared with the HI and MIX groups. The mean blood glucose values in the subgroup of patients who used NPH insulin in addition to insulin aspart or HI did not relevantly differ from the results described above.

The proportion of patients who experienced hypoglycemic episodes during the trial was not statistically different comparing the three treatment groups. The average number of hypoglycemic episodes per patient treated with insulin aspart (1.4 episodes) was lower than in patients treated with HI (2.0 episodes) but higher than in patients treated with premix insulin (0.7 episodes). The insulin aspart group revealed a lower risk for hypoglycemic events than the HI group: 3.2 episodes in the insulin aspart group on average vs. 4.8 episodes in the HI group and 2.4 episodes in the MIX group. Thus, it may be concluded that the administration of MIX is associated with a lower risk of hypoglycemic events when compared with insulin aspart and human soluble insulin. However, this lower hypoglycemic risk is achieved at the expense of a higher HbA_{1c}.

In a 12-week randomized open-label trial with 294 type 1 and type 2 diabetic patients, Boehm et al. (28) compared MIX (70 NPH/30 regular) and premixed insulin aspart (70 NPH/30 aspart) in a twice daily, immediately preprandial regimen. Postprandial glycemic control was significantly improved in the group with premixed insulin aspart, and overall glycemic control in terms of HbA_{1c} was similar in both groups. The number of major hypoglycemic episodes with aspart was one-half that with MIX; however, the overall risk of both minor and major hypoglycemia did not differ significantly between treatments. In contrast to our study, the Boehm et al. (28) study included both type 1 and type 2 diabetic patients and did not include any intensified therapeutic regimen as a third arm.

In a randomized, double-blind, double-dummy crossover trial with 25 insulin-requiring type 2 diabetic patients, Rosenfalck et al. (27) compared HI immediately before and 30 min before, and insulin aspart immediately before a test meal. Postprandial blood glucose excursion as well as maximum serum glucose concentration up to 360 min after dosing were significantly smaller/lower in the aspart group versus HI immediately before a meal group. No difference in glycemic control was shown against HI 30 min before a meal group. In comparison with our study, this trial included fewer type 2 diabetic patients. Besides, it was a one-meal study and not a 3-month comparison.

In conclusion, although the present study did not show insulin aspart to be statistically equivalent to HI and MIX (70/30) with regard to glycemic control, our data demonstrate that treatment with insulin aspart is followed by improved glycemic control in terms of HbA_{1c} and postprandial glucose levels when compared with HI and MIX (70 NPH/30 regular). Insulin aspart was safe and well tolerated in terms of hypoglycemia. Not of primary focus but of clinical relevance, body weight remained unchanged in the insulin aspart group, whereas an increase of body weight was observed in the other groups.

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