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Biphasic insulin aspart 30 plus metformin: an effective combination in type 2 diabetes

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Aim: This study compared glycaemic control achieved with biphasic insulin aspart 30 (BIAsp 30) monotherapy, BIAsp 30 plus metformin and glibenclamide plus metformin in patients with type 2 diabetes not adequately controlled with metformin.

Methods: In this multinational, open-labelled, parallel group, 16-week trial, 341 patients (patients not adequately controlled with metformin for at least 1 month) with type 2 diabetes were studied. Patients were randomized to receive BIAsp 30, twice daily (n = 107 exposed to treatment), or BIAsp 30, twice daily, plus metformin (n = 108) or glibenclamide plus metformin (n = 114). The primary endpoint was HbA_{1c} at end of trial; adverse events, hypoglycaemia episodes, blood lipids and weight were also monitored.

Results: In the total population (HbA_{1c} 7.5–13.0% at screening), end-of-trial HbA_{1c} levels were lower in patients receiving BIAsp 30 plus metformin compared with those receiving BIAsp 30 only [mean treatment difference (±s.e.m), $0.39 \pm 0.15\%$, $p = 0.007$]. In a subpopulation ($HbA_{1c} \geq 9.0\%$ at baseline, n = 193), patients receiving BIAsp 30 plus metformin had significantly lower HbA_{1c} levels at the end of the trial compared with those receiving glibenclamide plus metformin (treatment difference, $0.46 \pm 0.21\%$, $p = 0.027$). Mean body weight (±s.d) at the end of the trial was significantly lower in patients receiving glibenclamide plus metformin compared with those receiving BIAsp 30 only (84.3 ± 13.3 kg vs. 88.9 ± 16.9 kg, $p < 0.001$). No major hypoglycaemic episodes were recorded during the trial, and incidence rates for minor and symptoms-only hypoglycaemia were low and similar between treatment groups (0.03–0.04 events/patient/week).

Conclusion: BIAsp 30 added to metformin could be an appropriate therapeutic option for achieving good glycaemic control, compared with the addition of a second oral agent, particularly where $HbA_{1c} \geq 9\%$.

Keywords: BIAsp 30, glibenclamide, glycaemic control, metformin, type 2 diabetes
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Introduction

As was demonstrated in the UK Prospective Diabetes Study (UKPDS), tight glycaemic control is essential in reducing the risk of diabetes complications and cardiovascular disease [1]. The major benefit observed was a reduction in microvascular endpoints, although myocardial infarction also was reduced by 16%. However, due to the progressive nature of type 2 diabetes, as the UKPDS results indicate, it becomes increasingly difficult to maintain glycaemic targets using a single oral anti-diabetic drug (OAD) [2]. When OAD monotherapy becomes insufficient, glycaemic control can be enhanced by combining two OADs having different mechanisms of action [3]. However, most OADs require some residual β-cell function, and due to the reduction in β-cell mass and

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insulin release, which typically occurs as type 2 diabetes progresses, even multiple oral therapies become ineffective. Indeed, in the UKPDS, after 3 years' therapy, only 44% of obese patients who received metformin as monotherapy managed to achieve their glycaemic targets ($HbA_{1c} < 7.0\%$); after 9 years' treatment, this had reduced further to 13% [2]. Although the addition of a second oral agent can improve glycaemic control, the need for insulin therapy is only delayed for a few years [2].

Metformin is a biguanide that has proven efficacy and safety as an OAD, which has gained worldwide acceptance over the past 20 years [4]. It is often considered a first-line therapy in obese diabetes patients due to its beneficial effects on weight [5]. Biphasic insulin aspart 30 (BIAsp 30) is a premixed insulin analogue consisting of 30% soluble rapid-acting insulin aspart and 70% protamine-crystallised insulin aspart (BIAsp 30, NovoMix® 30, Novo Nordisk A/S, Bagsvaerd, Denmark). Pharmacodynamic studies in patients with type 2 diabetes have demonstrated that the faster onset and greater peak action of rapid-acting insulin aspart is retained with BIAsp 30 [6,7]. BIAsp 30 therefore has the potential to improve post-prandial glucose control compared with equivalent premixed human insulin preparations, while maintaining glycaemic control between meals [8,9].

The advantages of combining insulin and metformin in patients with type 2 diabetes are becoming apparent. The use of an OAD such as metformin often permits a reduction in insulin dose, and therefore of side effects, compared with when insulin is used alone [4,10]. This makes combination therapy particularly attractive for patients transitioning to insulin. Studies have shown that this treatment combination is both safe and effective, being able to decrease HbA_{1c} by at least 2% without increased risk of hypoglycaemia and weight gain [11–13]. Metformin offers the additional advantage of being able to reduce plasma triglyceride concentrations by approximately 30% and low-density lipoprotein cholesterol by 5–10%, as well as to lower plasminogen activator inhibitor 1, which has beneficial effects on the hypercoagulable state common in type 2 diabetes [4]. These metabolic and clinical advantages could encourage earlier initiation of insulin therapy, which may reduce the adverse effects of chronic glucotoxicity and lipotoxicity, thereby decreasing secretory demands on β cells and prolonging endogenous insulin secretion [14]. This is in contrast to other OADs such as sulfonylureas, which may exert negative effects by overstimulating β cells [14].

The aim of this study was to compare the glycaemic control achieved by using BIAsp 30 alone and in combination with metformin, vs. the sulfonylurea glibenclamide in combination with metformin, in patients with type 2 diabetes who were not satisfactorily controlled on metformin monotherapy. *Post-hoc* analyses were conducted to examine efficacy in a subgroup with poor glycaemic control at baseline.

Methods

The trial was carried out in accordance with the Declaration of Helsinki, Good Clinical Practice and was approved by the local ethics committees. All participants gave informed, written consent before starting the trial. Exclusion criteria included significant medical problems, such as proliferative retinopathy, impaired hepatic or renal function, recurrent severe hypoglycaemia, cardiac disease, anaemia or change in dose of medications known to interfere with glucose metabolism.

Trial Design, Dosing and Titration Regimens

This multinational, open-label, parallel group trial was conducted in 11 countries (Croatia, Czech Republic, Denmark, France, Greece, Hungary, Norway, Poland, Portugal, Russia, Spain). A total of 341 patients with type 2 diabetes were randomized to one of three treatments: BIAsp 30 alone; metformin plus BIAsp 30 in combination; or metformin plus a sulphonylurea (glibenclamide). Randomization was carried out using a telephone randomization system (Interactive Voice Response System), which automatically assigned treatment according to a pre-defined randomization list. At the time of recruitment, patients had been receiving at least 850 mg metformin per day for at least 1 month.

The initial daily dose of BIAsp 30 was 0.2 U/kg body weight per day in the BIAsp plus metformin group and 0.3 U/kg body weight per day in the BIAsp 30 only group. Half the dose was injected immediately (0–5 min) before breakfast and the other was injected immediately before the main evening meal. Total daily doses were individually titrated every 1–7 days in steps of 2–4 U per injection. The breakfast insulin dose was adjusted on the basis of post-breakfast and pre-dinner blood glucose values (target range 5–8 mmol/l), whereas the evening meal dose was adjusted according to post-dinner, night time and pre-breakfast blood glucose values (target range 5–8 mmol/l). In the sulphonylurea group, it was recommended that glibenclamide treatment be started at 1.75 mg once daily in the morning and gradually increased every 3–7 days in 1.75 mg increments up to a maximum daily dose of 10.5 mg [15]. Where the daily dose exceeded this amount, 7 mg

were given in the morning while the remainder was administered with the evening meal.

After randomization, all patients were transferred from their usual metformin to metformin supplied by the trial co-ordinators (Glucophage®, Lipha, France). The mean total daily metformin dose was maintained at pretrial dosing levels throughout the trial, approximately 1660 (range 500–3000) mg per day in both combination-treatment groups. Metformin was supplied in tablet form, containing 500 or 850 mg metformin hydrochloride, and when a combination of the 500 and/or 850 mg tablets could not match the exact pretrial dose, the combination that gave the closest match was used. Metformin is usually titrated on the basis of individual maximum tolerated or maximum effective doses; the mean doses used in this trial were within the typically prescribed range.

Endpoints

The primary endpoint was HbA_{1c} at the end of the trial with baseline HbA_{1c} used as a covariate, and secondary endpoints included eight-point blood glucose profiles (measured before and 90 min after breakfast, lunch and dinner, at bedtime and at 2 a.m), weight, triglycerides and high-density lipoprotein (HDL)-cholesterol. HbA_{1c} was assayed using HPLC on a Bio-Rad Diagnostic. Blood glucose profiles were measured by the patients with a blood glucose meter (One Touch® Profile™, LifeScan, USA), provided by Novo Nordisk A/S. Fasting lipid concentrations were assessed using standard laboratory methods. Blood lipids were determined and weight was recorded at baseline and at weeks 4, 8, 12 and 16. Blood glucose profiles were obtained at weeks 1, 2, 4, 8, 12 and 16, and at baseline.

Safety Assessments

Any adverse events, defined as an undesirable event occurring during the trial, were recorded for all exposed patients (safety population). Serious adverse events were defined as events causing or threatening to cause death or resulting in significant hospitalization or incapacity. Hypoglycaemia episodes were classed as either major (requiring assistance, blood glucose < 2.8 mmol/l and requiring food intake or IV glucose) or minor (symptoms consistent with hypoglycaemia, confirmed with blood glucose measurement of < 2.8 mmol/l and handled by the patient, or any asymptomatic blood glucose measurement < 2.8 mmol/l). Symptoms judged related to hypoglycaemia, but not confirmed by blood glucose measurement, were also reported.

Statistical Methods

A power calculation was performed for the primary endpoint (HbA_{1c} at end of trial) using the standard deviation of the within-patient difference (0.85% units), as estimated by a previous trial in patients with type 2 diabetes [16]. It was expected that 10–15% of patients would withdraw from the trial and therefore 450 patients (150 in each treatment group) would yield a sufficient power (>90%) to detect a difference of 0.35% in the long-term glycaemic level between any of the three treatment groups.

End-of-trial HbA_{1c} was analysed using ANOVA, with treatment regimen and country as fixed effects, and with HbA_{1c} value at baseline as a covariate. Each of the eight-point glucose measurements was analysed individually, using the same model as used in the analysis of the primary endpoint. Weight, triglycerides and HDL cholesterol were analyzed using a repeated measures analysis of variance including treatment regimen, visit, country and visit-by-treatment interaction as fixed effects and baseline value as a covariate. The number of minor hypoglycaemia episodes and total number of episodes (minor, major and symptoms-only) were analysed using a log linear Poisson regression model, with treatment and country as factors. Because few major hypoglycaemic episodes occurred, no formal statistical analyses were performed. All analyses were either based on the intention-to-treat (ITT) dataset ($n = 329$) or subgroups of the ITT population. Adverse events were reported for exposed subjects (safety population, $n = 329$), which was the same as the ITT population. Differences between treatment groups for all primary and secondary efficacy endpoints were analysed according to EMEA guidelines for adjustment of baseline covariates [17]. Unless otherwise indicated, endpoints are provided as mean ± standard error [Mean (s.e.m)].

Because it was thought that patients who were less well controlled at baseline might represent a population that could respond differently to treatment, *post-hoc* analyses of the primary endpoint, HbA_{1c}, and several secondary endpoints were performed in subpopulations, based on level of glycaemic control at enrollment. Patients with a baseline $HbA_{1c} \geq 9.0\%$, corresponding to an average plasma glucose level of approximately 13.5 mmol/l [18], were defined as being poorly controlled with metformin monotherapy, and those with $HbA_{1c} < 9.0\%$ were defined as well controlled. This arbitrary classification was based on generally accepted definitions for the degree of glycaemic control [19]. *Post-hoc* analysis based on degree of glycaemic control was considered appropriate due to the number

of patients in these subpopulations (baseline $HbA_{1c} \geq 9.0\%$, 193 patients exposed or baseline HbA1c $< 9.0\%$, 136 patients exposed) and the fact that the subpopulations were approximately equally distributed among treatment groups and were otherwise comparable at baseline.

Results

Patient characteristics at enrollment for the total population are shown in table 1 and the disposition of randomized patients is shown in figure 1. At least 96% of patients allocated to each treatment group completed trial treatment. A total of 12 patients withdrew from the study before exposure to the trial products, leaving 329 patients in the safety population. Reasons for withdrawal included unwillingness to use insulin, personal/family circumstances, non-compliance and patient refusal.

The number of exposed patients in the subpopulation with $HbA_{1c} \geq 9\%$ was 64, 58 and 71 for BIAsp 30 only, BIAsp 30 plus metformin and glibenclamide plus metformin, respectively; in the subpopulation with $HbA_{1c} < 9\%$, the number of exposed patients was 43, 50 and 43, for BIAsp 30 only, BIAsp 30 plus metformin, and glibenclamide plus metformin, respectively. There were no pronounced differences between the two subpopulations with respect to baseline demographic characteristics (table 1).

Efficacy

In the total population, there was a reduction in mean HbA_{1c} in all three treatment groups; HbA_{1c} was reduced by 1.6% in the BIAsp only group, 1.7% in the BIAsp plus metformin group and 1.7% in the glibenclamide plus metformin group (figure 2). At the end of the trial, patients who received a combination of BIAsp 30 plus metformin had statistically lower HbA_{1c} levels compared with those who received BIAsp 30 alone [treatment difference, 0.39% (0.15), $p = 0.007$] (table 2). HbA_{1c} levels in patients who received metformin in combination with BIAsp 30 were numerically lower than the levels of those who had glibenclamide plus metformin, but this difference [0.20% (0.15)] was not statistically significant.

In the subpopulation with $HbA_{1c} \geq 9\%$ at baseline, end-of-trial HbA_{1c} was lower in the BIAsp 30 plus metformin group compared with the glibenclamide plus metformin group [treatment difference, 0.46% (0.21), $p = 0.027$]. No other statistically significant between-treatment differences were shown in this subpopulation for HbA_{1c} (table 2). For the subpopulation with $HbA_{1c} < 9\%$ at baseline, end-of-trial HbA_{1c} was lower for both the BIAsp 30 plus metformin compared with BIAsp 30 alone [treatment difference, -0.42% (0.20), $p = 0.04$] and for glibenclamide plus metformin compared with BIAsp 30 alone [treatment difference, -0.65% (0.21), $p = 0.003$].

Eight-point blood glucose measurements were taken before the randomization visit and at the end of the trial by each patient (figure 3). At each of the profile measurement points, the mean blood glucose values in the total population decreased during the trial in all three-treatment groups. At the 90-min post-lunch time point, blood glucose in the glibenclamide plus metformin group was statistically lower than the BIAsp 30 only group [treatment difference, -0.74 (0.36) mmol/l, $p = 0.038$]. There were no differences between treatment groups in the other seven blood glucose points, and no difference in the mean prandial blood glucose increment (defined as the average blood glucose increment following breakfast, lunch and dinner) between the three treatment groups (table 2). However, at the end of the trial, the lunch time prandial blood glucose increment was lower in the glibenclamide plus metformin group than in the BIAsp 30 only

Table 1 Patient demographics for the total population

		Treatment group	
	BIAsp 30	BIAsp 30 + metformin	Glibenclamide + metformin
Number of patients	107	108	114
Mean age, years (s.d)	55.2 (10.3)	56.4 (9.0)	58.1 (8.8)
Men/women	50/57	53/55	52/62
Mean weight, kg (s.d)	87.3 (16.5)	85.1 (15.1)	84.0 (13.4)
BMI kg/m^2 (s.d)	30.9 (4.5)	30.4 (4.0)	30.5 (4.4)
Mean duration of diabetes, years (s.d)	8.2 (7.1)	6.7 (5.7)	8.1 (6.2)
Mean HbA1c percentage (s.d)	9.6 (1.5)	9.3 (1.3)	9.4 (1.4)
Mean HDL cholesterol, mmol/l (s.d)	1.2 (0.3)	1.2 (0.3)	1.2 (0.2)
Mean triglycerides, mmol/l (s.d)	2.6 (2.5)	2.8 (2.4)	2.2 (2.0)

BIAsp 30, biphasic insulin aspart 30; HDL, high-density lipoprotein.

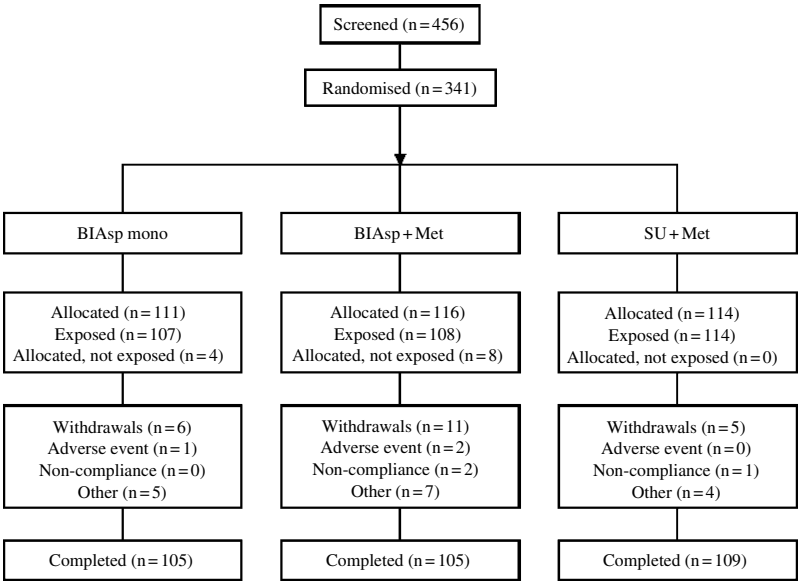

Fig. 1 Disposition of patients allocated to each treatment arm of the trial.

group [−1.12 (0.33) mmol/l, $p < 0.001$] and the BIAsp 30 plus metformin group [−0.70 (0.33) mmol/l, $p = 0.036$].

In the subpopulation with baseline $HbA_{1c} < 9\%$, the pattern differed from that of the overall population: the average blood glucose level was found to be lower for BIAsp 30 plus metformin than for BIAsp 30 alone [treatment difference, −0.82 (0.30) mmol/l, $p = 0.008$], and for glibenclamide plus metformin relative to BIAsp 30 alone [treatment difference, −0.88% (0.31) mmol/l, $p = 0.005$]. Furthermore, the after lunch, bedtime, and 2 a.m mean blood glucose levels were found to be statistically significantly lower for BIAsp30 plus metformin than for BIAsp 30 alone (table 2). In addition, the after lunch and before dinner mean blood glucose was found to be lower in the glibenclamide plus metformin group than in the BIAsp 30 group (table 2). No statistically significant differences were found between BIAsp 30 plus metformin and glibenclamide plus metformin groups (table 2). In the $HbA_{1c} \geq 9\%$ subpopulation, before-lunch blood glucose was lower for patients who received BIAsp 30 than for those in the glibenclamide plus metformin group [treatment difference, 1.07 (0.45) mmol/l, $p = 0.02$].

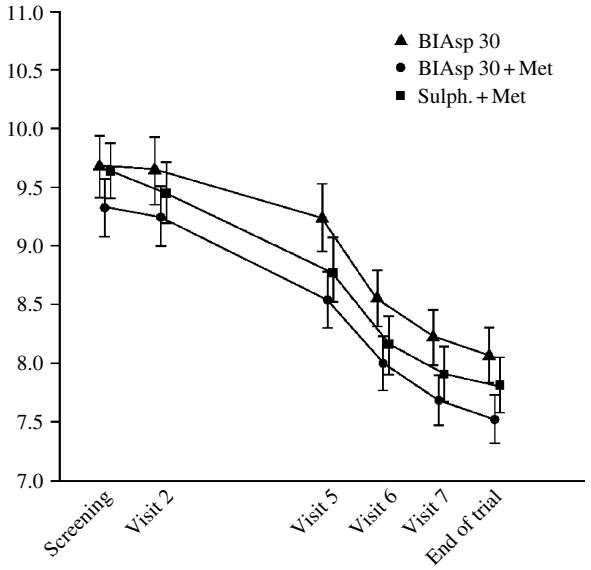

Fig. 2 Comparison of the reduction in mean HbA_{1c}, throughout the trial period in the total population for 316 patients with measurements both at baseline and at the end of the trial, amongst treatment with biphasic insulin aspart 30 (BIAsp 30) alone, BIAsp 30 with metformin, and glibenclamide plus metformin. HbA_{1c} achieved by patients who received BIAsp 30 plus metformin was significantly lower ($p = 0.007$) than patients who had BIAsp 30 only at the end of the treatment period.

During the trial period, for the ITT population, small increases in body weight occurred in all three treatment groups: 1.6 kg in the BIAsp 30 only group, 0.8 kg in the BIAsp 30 plus metformin group and 0.1 kg in the glibenclamide plus metformin group. End-of-trial weights did not differ significantly between the BIAsp 30 plus metformin group and the glibenclamide plus metformin group [treatment difference, −0.66 (0.41) kg, $p = 0.10$] and there was borderline significance in BIAsp 30 plus metformin vs. the BIAsp 30 only group [treatment difference, −0.80 (0.41) kg, $p = 0.051$] (table 2). Mean body weight of the glibenclamide plus metformin group was, however, lower than that of the BIAsp 30 only group after the trial [treatment difference, −1.46 (0.41) kg, $p < 0.001$].

Table 2 Treatment group differences, at end of the trial, for all endpoints, for the total population and for subpopulations with $HbA_{1c} < 9$ and $\geq 9\%$ at baseline

	Total population			Subpopulation (HbA1c < 9%)			Subpopulation (HbA1c ≥ 9%)		
	(BIAsp 30 + Met) − BIAsp 30	(Glib + Met) − BIAsp 30	(Glib + Met) − (BIAsp 30 + Met)	(BIAsp 30 + Met) − BIAsp 30	(Glib + Met) − (BIAsp 30)	(Glib + Met) − (BIAsp 30 + Met)	(BIAsp 30 + Met) − BIAsp 30	(Glib + Met) − (BIAsp30	(Glib + Met) − (BIAsp 30 + Met)
HbA_{1c} (%)	−0.39 (0.15)†	−0.20 (0.15)	0.20 (0.15)	−0.42 (0.20)*	−0.65 (0.21)†	−0.23 (0.20)	−0.39 (0.21)	0.07 (0.20)	0.46 (0.21)*
Body weight (kg)	−0.80 (0.41)	−1.46 (0.41)‡	−0.66 (0.41)	0.31 (0.59)	−0.74 (0.61)	−1.05 (0.59)	−1.54 (0.57)†	−1.96 (0.55)‡	−0.43 (0.56)
Triglycerides (mmol/l)	0.23 (0.14)	0.08 (0.14)	−0.15 (0.14)	0.09 (0.20)	−0.02 (0.21)	−0.11 (0.20)	0.22 (0.20)	0.09 (0.18)	−0.13 (0.19)
HDL cholesterol (mmol/l)	0.01 (0.03)	−0.04 (0.03)	−0.05 (0.03)	0.00 (0.05)	−0.06 (0.05)	−0.06 (0.05)	0.00 (0.03)	−0.03 (0.03)	−0.03 (0.03)
Glucose (mmol/l)									
Before breakfast	−0.05 (0.27)	0.01 (0.27)	0.07 (0.27)	−0.41 (0.31)	−0.53 (0.31)	−0.11 (0.31)	0.11 (0.42)	0.18 (0.39)	0.08 (0.40)
After breakfast§	0.00 (0.41)	0.29 (0.40)	0.29 (0.40)	−0.36 (0.56)	−0.42 (0.58)	−0.06 (0.57)	0.19 (0.59)	0.43 (0.56)	0.24 (0.56)
Before lunch	0.11 (0.30)	0.43 (0.30)	0.33 (0.30)	−0.41 (0.35)	−0.54 (0.35)	−0.14 (0.35)	0.57 (0.48)	1.07 (0.45)*	0.50 (0.46)
After lunch§	−0.33 (0.36)	−0.74 (0.36)*	−0.41 (0.36)	−1.46 (0.51)†	−2.08 (0.52)‡	−0.62 (0.51)	0.24 (0.51)	−0.22 (0.49)	−0.46 (0.50)
Before dinner	−0.06 (0.35)	−0.57 (0.34)	−0.51 (0.34)	−0.76 (0.47)	−1.09 (0.48)*	−0.33 (0.47)	0.60 (0.50)	−0.22 (0.48)	−0.82 (0.48)
After dinner§	−0.17 (0.37)	−0.15 (0.37)	0.02 (0.37)	−0.76 (0.46)	−0.65 (0.47)	−0.11 (0.47)	0.31 (0.55)	−0.18 (0.53)	−0.49 (0.54)
Bedtime	−0.41 (0.34)	−0.02 (0.34)	0.39 (0.33)	−1.05 (0.47)*	−0.42 (0.47)	0.63 (0.46)	0.15 (0.51)	0.18 (0.48)	0.03 (0.48)
02:00	−0.31 (0.30)	−0.36 (0.30)	−0.06 (0.30)	−0.75 (0.34)*	−0.62 (0.36)	0.13 (0.36)	−0.01 (0.47)	−0.31 (0.44)	−0.30 (0.44)
Average prandial increment¶	−0.15 (0.21)	−0.14 (0.21)	0.01 (0.21)	−0.32 (0.29)	−0.35 (0.29)	−0.03 (0.29)	−0.11 (0.31)	−0.17 (0.29)	−0.06 (0.30)
Average BG**	−0.10 (0.25)	−0.16 (0.25)	−0.06 (0.25)	−0.82 (0.30)†	−0.88 (0.31)†	−0.06 (0.30)	0.40 (0.39)	0.12 (0.37)	−0.28 (0.38)

All values are mean (s.e.m). Triglyceride reference range: 0–2.25 mmol/l; HDL cholesterol reference range: 0.91–2.5 mmol/l.

*$p < 0.05$.

†$p < 0.01$.

‡$p < 0.001$.

§90 min afterwards.

¶Average prandial increment taken over three meals.

**Average taken from eight points of BG profile.

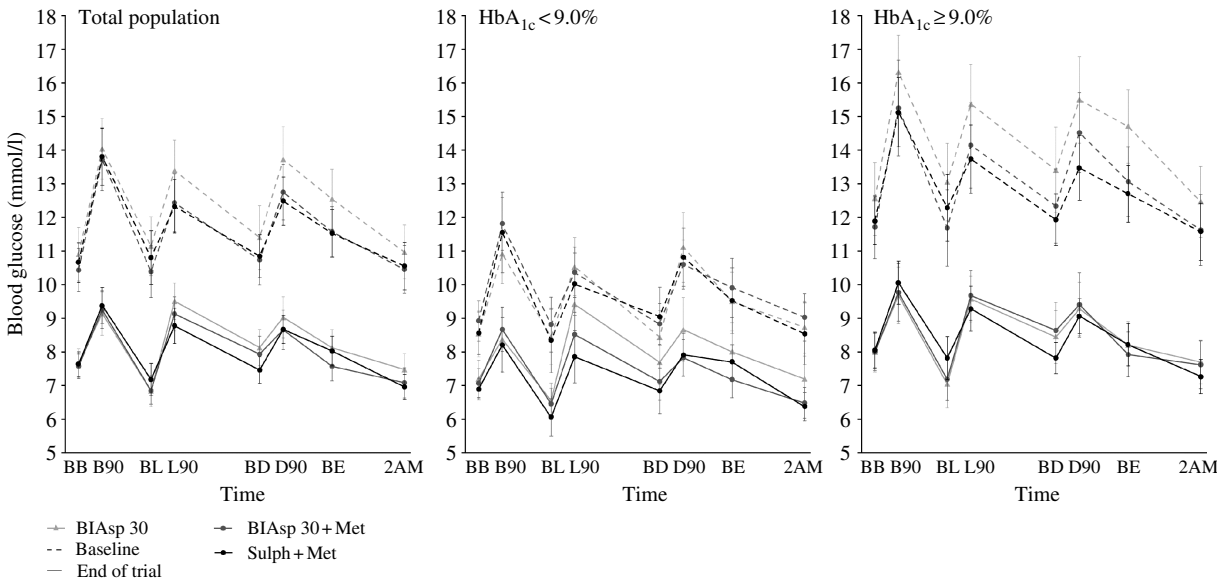

Fig. 3 Mean eight-point glucose profiles (±2 s.e.m) at baseline and end-of-trial by treatment group, for all patients, and patients with good ($HbA_{1c} < 9.0\%$) and poor ($HbA_{1c} \geq 9.0\%$) glycaemic control at baseline.

By the end of the trial, triglycerides had decreased in all three treatment groups: by 0.5–0.6 mmol/l in both BIAsp 30 groups and by 0.2 mmol/l in the glibenclamide plus metformin group. There were no statistical differences, however, between the three treatment groups at the end of the trial [2.0 (1.2) mmol/l, 2.3 (1.5) mmol/l and 2.0 (1.1) mmol/l], for BIAsp 30 only, BIAsp 30 plus metformin and glibenclamide plus metformin groups, respectively. HDL-cholesterol increased marginally in all three treatment groups (0.1–0.2 mmol/l) but these changes were not statistically significant. Similar effects were seen for patients in the subpopulations.

Doses of BIAsp 30 and glibenclamide were gradually increased during the trial. During the 16-week trial period, mean (s.d) doses for BIAsp 30 were increased from 0.3 to 0.51 (0.25) U/kg/day in the monotherapy group and from 0.2 rising to 0.30 (0.12) U/kg/day for the BIAsp 30 plus metformin combination group. The mean starting dose of glibenclamide was 2.33 (1.38) rising to 6.58 (4.18) mg by the end of the trial. The dose of metformin received throughout the trial remained unchanged and was similar (approximately 1660 mg per day) between the two groups receiving metformin.

Safety and Hypoglycaemia

During the trial, 201 adverse events were reported. The proportions of patients who had at least one adverse event were: 42% in the BIAsp 30 only group, 31% in the BIAsp 30 plus metformin group and 24% in the glibenclamide plus metformin group. All but one of these events was classed as mild or moderate, and the majority (95%) were deemed to be unrelated to the trial products. Neither single type of adverse event predominated nor was any single organ system disproportionately affected. The most frequent events in each of the treatment groups were upper respiratory infection (6–7%), back pain (3–6%) and headache (4–7%). Five serious adverse events were recorded during the trial, but deemed unlikely to be treatment-related. These included one death of a patient at home following a myocardial infarction, which the local investigator also judged unlikely to be related to the trial products (BIAsp 30 plus metformin for 44 days).

There were no major hypoglycaemic episodes during the trial. For symptoms-only and minor hypoglycaemia, the number of patients experiencing episodes, and the number of events were similar amongst the treatment groups (Table 3). Furthermore, the incidence rates (events per patient per week) were also similar amongst treatment groups and no significant differences were found in the safety population.

Discussion

In recent years, there has been growing evidence of the advantages in combining metformin with insulin in patients with type 2 diabetes [11,12]. The clinical benefits of BIAsp 30 on post-prandial blood glucose [8,9] together with the positive clinical outcomes of

Table 3 Comparison of symptoms-only and minor hypoglycaemia that occurred in patients, in the total population, who received biphasic Insulin aspart 30 (BIAsp 30) only, BIAsp 30 plus metformin or glibenclamide plus metformin during the 16-week trial period

	Treatment group		
	BIAsp 30	**BIAsp 30 + metformin**	**Glibenclamide + metformin**
Number of patients in safety population (exposed subjects)	107	108	114
Number of patients with at least one minor episode (number of minor episodes)	10 (20)	13 (23)	9(28)
Number of patients with symptoms-only events (number of symptoms-only events)	22 (44)	22 (44)	23(43)
Incidence rate*	0.037	0.039	0.04

*Number of hypoglycaemic events, including minor hypoglycaemia and symptoms only, per patient per week. Safety and intention-to-treat (ITT) populations were the same in this trial.

therapy with metformin support the use of this two-agent combination. In the current study, the use of BIAsp 30 as an add-on therapy to metformin led to improvements in glycaemic control, with no episodes of major hypoglycaemia, and without an increase in the risk of minor or symptoms-only hypoglycaemia, and with positive trends in the development of cardiovascular risk factors (improvements in the lipid profile).

In the subpopulation with baseline $HbA_{1c} \geq 9\%$, patients allocated to BIAsp 30 plus metformin had significantly lower HbA_{1c} levels compared with the glibenclamide plus metformin treatment group. These results are in line with what would be expected: increased hyperglycaemia is consistent with decreasing β-cell function [20], and because both of these oral agents exploit endogenous insulin secretion, it is unlikely that patients with poorly controlled diabetes, and therefore more advanced β-cell loss would benefit more from two OADs than from insulin in combination with an OAD.

A recent study investigated the effect of removing metformin from insulin plus metformin combination regimen in subjects with type 2 diabetes [21]. Glycaemic control significantly deteriorated with metformin removal suggesting that metformin may play an important role in the success of insulin plus metformin combination therapy. This supports the current findings, where BIAsp 30 plus metformin was shown to be superior to BIAsp 30 alone at controlling glycaemia. By the end of the trial, despite achieving superior glycaemic control compared with patients receiving BIAsp 30 only, the BIAsp 30 plus metformin group received a lower dose of insulin. This demonstrates an 'insulin-sparing' effect of metformin, which has been reported elsewhere [11,21]. Inevitably, lower insulin doses have implications for less weight gain.

Weight gain is a common problem associated with intensive insulin treatment [9]. For example, in the UKPDS study [1], patients receiving insulin gained an average of 4.0 kg over the 10-year study period compared with 1.7 kg in glibenclamide-treated patients. It is encouraging to note therefore that in the current study, a combination of BIAsp 30 with metformin had a more favourable effect on weight gain, compared with BIAsp 30 monotherapy. Furthermore, adding BIAsp 30 to metformin enhanced glycaemic control without resulting in any adverse effect on weight, compared to adding glibenclamide to existing metformin therapy.

There is concern that the use of insulin treatment may lead to an increased risk of hypoglycaemia [1]. However, the results in the current study show that there was no difference in the incidence of minor hypoglycaemia episodes between treatment groups. Indeed, in a randomized controlled trial in type 1 and type 2 patients, BIAsp 30 was associated with fewer minor episodes compared with biphasic human insulin and fewer nocturnal events [9]. This claim is supported by an additional study that reported improved glycaemic control, but no increase in hypoglycaemia, when once-daily BIAsp 30 was added to metformin [12].

End-of-trial values for HbA_{1c}, as well as the eight-point blood glucose values suggest that BIAsp 30 titration could have been more intensive, which might have brought more patients closer to recommended glycaemic targets (e.g. $HbA_{1c} \leq 6.5\%$) [22]. However, the potential for increased hypoglycaemia would need to be considered with intensified treatment. For example, in the intensified treatment arm of the DCCT, the incidence of severe hypoglycaemia was approximately triple the rate seen in the conventional treatment arm [23,24]. Nevertheless, there is a growing body of evidence that

intensification with insulin analogues may not be associated with the same degree of increased risk of hypoglycaemia [25]. Whether further titration of glibenclamide would have improved glycaemic control is unknown. However, the metformin dosage was already near maximum, and there is evidence that tolerance to long-acting sulphonylureas can develop if maximum doses are administered [26].

In summary, the addition of BIAsp 30 to metformin is effective and well tolerated, particularly in patients with poor glycaemic control. In the overall population, no significant difference was found in glycaemic control comparing BIAsp 30 with or without metformin, with metformin plus glibenclamide. The combination of insulin and metformin offers good glycaemic control and should therefore be considered as a therapeutic option in the step-wise efforts towards achieving tight glycaemic control in patients with type 2 diabetes.

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