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Biphasic insulin aspart 30 treatment improves glycaemic control in patients with type 2 diabetes in a clinical practice setting: experience from the PRESENT study

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Aim: The Physicians' Routine Evaluation of Safety and Efficacy of NovoMix® 30 Therapy (PRESENT) study aims to assess the safety and efficacy of biphasic insulin aspart 30 (BIAsp 30) in patients with type 2 diabetes mellitus in routine clinical practice.

Methods: This was a 6-month, prospective, multinational, multiethnic observational study involving 21 977 patients from 13 countries (India, Iraq, Jordan, Kuwait, Lebanon, Qatar, Romania, Russia, Saudi Arabia, South Africa, South Korea, Turkey and the United Arab Emirates). The patients were transferred to BIAsp 30 with or without oral antidiabetic drugs (OADs) from prior treatment with OAD (n = 8583), insulin (n = 5942), OAD + insulin (n = 4673) or diet (i.e. treatment naive) (n = 1707). One thousand and seventy-two patients had incomplete or no information on previous treatment.

Results: At 3 and 6 months, significant reductions from baseline were observed in the mean haemoglobin A_{1c} (HbA_{1c}) (−1.33 and −1.81%), fasting plasma glucose (−3.02 and −3.74 mmol/l) and postprandial plasma glucose (−4.76 and −5.82 mmol/l) ($p < 0.001$). A significantly greater proportion of patients achieved target HbA_{1c} of less than 7% at 3 months (15.3%) and 6 months (27.7%) compared with baseline (4.8%) ($p < 0.001$). Overall, the mean HbA_{1c} at 6 months was lowered in patients regardless of prior treatment: −2.15% (OAD), −1.45% (insulin), −1.47% (OAD + insulin) and −2.35% (treatment naive). In the overall cohort, the rate of total hypoglycaemia was reduced from 5.4 events per patient-year at baseline to 2.2 events per patient-year at study end ($p < 0.001$). Among prior treatment subgroups, the rates of total hypoglycaemia were reduced from 2.5 to 2.1 events per patient-year in the OAD group, from 9.6 to 2.2 events per patient-year in the insulin group and from 7.6 to 2.5 events per patient-year in the OAD + insulin group but were increased from 1.0 to 1.8 events per patient-year in the treatment-naive group ($p < 0.001$). There were 444 adverse drug reactions (ADRs), including 13 serious ADRs: lipodystrophy (three events), symptoms of generalized hypersensitivity (two events), acute painful neuropathy (one event), worsening of diabetic retinopathy (one event), oedema (one event) and unspecified ADRs (five events).

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Conclusion: The use of BIAsp 30 monotherapy or in combination with OADs in clinical practice was effective and safe in patients with poorly controlled type 2 diabetes mellitus.

Keywords: biphasic insulin aspart 30, clinical practice, insulin analogue, observational study, PRESENT study, type 2 diabetes mellitus

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Introduction

While haemoglobin A_{1c} (HbA_{1c}) and fasting plasma glucose (FPG) continue to be routinely used to evaluate glycaemic regulation in type 2 diabetes [1], studies suggest that postprandial plasma glucose (PPPG) concentrations might play a role in the overall glycaemic load, particularly in patients with better glucose control ($HbA_{1c} <$ 7.3%) [2,3]. Studies have shown associations between postprandial hyperglycaemia and increased risks of cardiovascular diseases and death [4–8]. Patients with PPPG greater than 10 mmol/l have shown a 40% higher frequency of myocardial infarction than patients with PPPG concentrations of less than 8 mmol/l [4]. An increase in PPPG by 5.5 mmol/l has been associated with a 20% increase in the risk of cardiovascular diseases [6]. The joint European cardiovascular prevention guideline has acknowledged the importance of PPPG by setting targets in 2004 for self-monitored PPPG levels at 4.0–7.5 mmol/l, much lower than those of the American Diabetes Association (ADA) [9]. Therefore, the goal of therapeutic diabetes care should be to attain a more physiological overall glucose profile by focusing on HbA_{1c}, FPG and PPPG [4,10].

The premixed insulin analogue, biphasic insulin aspart 30 (BIAsp 30), consists of a rapid-acting soluble component (30%) that effectively controls PPPG [10,11] and a long-acting protaminated component (70%) that controls basal glucose between meals [12]. As it closely mimics the physiological insulin profile [13], it provides effective glucose control [14,15] while maintaining a low incidence of hypoglycaemia [16–18]. Further, the rapid action of BIAsp 30 allows for convenient and flexible mealtime dosing, thus improving adherence, compliance and quality of life [14]. Studies have shown that BIAsp 30 could be administered immediately before or up to 15 min after a meal [19,20], thus allowing patients to adjust their dosage according to the amount of food taken.

The efficacy and safety of BIAsp 30 are well established in the current literature on controlled clinical trials [10–18]. Still, there is little information on its use in routine clinical practice. Well-designed observational studies play an important role in investigating treatment outcomes and supporting the evidence base for drugs and therapies [21]. The few clinical experience observational studies on BIAsp 30 available [22,23] were conducted only within local contexts and did not involve a large number of patients from different countries. The Physicians' Routine Evaluation of Safety and Efficacy of NovoMix® 30 Therapy (PRESENT) study aims to collect these data on BIAsp 30 from a multinational and multiethnic population with type 2 diabetes mellitus. It may also give insights into the treatment patterns and acceptability among physicians and patients in different countries. To our knowledge, this is the largest clinical experience observational study ever conducted on BIAsp 30 treatment and may provide useful complementary data to support the clinical data already existing on BIAsp 30 treatment in type 2 diabetes. In this article, we present the efficacy and safety results of BIAsp 30 treatment in the overall patient cohort and in patients stratified according to their prior diabetes treatments.

Methods

Study Design and Treatment

The objective of this observational study was to collect information on the efficacy and safety of using BIAsp 30, as a monotherapy or in combination with oral antidiabetic drugs (OADs), for type 2 diabetes management in routine clinical practice. This was a 6-month, prospective, uncontrolled, clinical experience evaluation study among medical doctors who used BIAsp 30 for patients with type 2 diabetes in daily clinical practice in several countries and centres. BIAsp 30 treatment (dosage and injection regimen) and discontinuation were entirely at the discretion of the attending physicians. No special investigational procedures other than those routinely used in clinical practice were planned for the patients.

Patient Inclusion and Exclusion Criteria

Only patients with type 2 diabetes who were inadequately controlled on their current therapy and who were prescribed BIAsp 30, as a monotherapy or in combination

with OADs in accordance with the approved labelling, were eligible for the study. As this was an observational study, no inclusion and exclusion criteria were defined. Hence, a small percentage of patients enrolled in the study were identified to have baseline HbA_{1c} of less than 7%, although they may have been considered by their physicians to have poor glycaemic control based on other factors such as hypoglycaemia or poor postprandial glucose control.

Participating Countries

This study was planned in 15 countries: China, India, Iraq, Jordan, Lebanon, Romania, Russia, Saudi Arabia and the Gulf countries (Kuwait, Qatar and the United Arab Emirates), South Africa, South Korea, Sri Lanka and Turkey. However, data from China and Sri Lanka were excluded from this paper, because data were collected from China only at 3 months and from Sri Lanka only at baseline. The data presented here were from the remaining 13 countries.

Data Collection

Patient data were collected during visits at baseline, 3 and 6 months using standardized forms. Patient demographics including weight, relevant concomitant illnesses and medical history were recorded. The medical history included the duration of diabetes, current therapy for diabetes, number of hypoglycaemic episodes and HbA_{1c}, FPG and PPPG measurements. On entering the study, patients were asked to recall the number of hypoglycaemic episodes they had experienced over the last 3 months. This constituted the baseline hypoglycaemia. For the 3- and 6-month datapoints, hypoglycaemia and adverse drug reactions (ADRs) were based on patient recollection and their clinical records from the last visit to the visits at 3 and 6 months. At 3 and 6 months, data were collected on patients' weight, current therapy for diabetes, results of the HbA_{1c} measurements within 1 month prior to the visits and FPG and PPPG measurements within 1 week prior to the visits.

Efficacy and Safety Endpoints

The efficacy and safety endpoints (Box 1) were evaluated at 3 and 6 months of BIAsp 30 treatment. Minor hypoglycaemic episodes were defined as those where the patient was able to treat himself, and major episodes were those where the patient was unable to treat himself. Hypoglycaemic episodes occurring from 00:00 hours to 06:00 hours were classified as nocturnal.

Box 1 Efficacy and safety endpoints

- Efficacy endpoints
  - Change in haemoglobin A_{1c}, fasting plasma glucose and postprandial plasma glucose
- Safety endpoints
  - Incidence of overall, nocturnal, diurnal, minor- and major hypoglycaemic episodes
  - Incidence of serious and non-serious adverse drug reactions (excluding hypoglycaemic episodes)

Statistical Analyses

All enrolled patients with baseline data were included in the safety analysis set, which was used for the efficacy and safety analyses. Patient baseline demographic information, current diabetes therapy and efficacy and safety outcomes were presented as descriptive statistics (%, mean $\pm$ s.d. and 95% CI). Changes from baseline in HbA_{1c}, FPG and PPPG were tested using the paired *t*-test. One-way ANOVA modelling of baseline demographics, dosage of BIAsp 30 and changes in glycaemic parameters were performed for the subgroups. Differences in the proportions of patients achieving HbA_{1c} of less than 7% among the groups were compared using the chi-squared test. Changes from baseline in the proportion of patients with HbA_{1c} of less than 7% (ADA guidelines) and the proportion of patients reporting hypoglycaemic episodes were compared using the McNemar's test. Hypoglycaemic episodes and ADRs were presented according to category and severity using summary statistics and event rates. Changes from baseline in the rates of hypoglycaemic episodes per patient-year were compared using the Wilcoxon sign-rank test. A simple regression model was used to analyse the change in mean body weight in relation to the final dose of BIAsp 30. The data were presented for the overall cohort and the subgroups based on patients' prior diabetes treatments. All the statistical analyses were performed using SAS® version 9.1.3 (SAS Institute, Cary, NC, USA).

Results

Baseline Characteristics

Of the 22 857 patients initially enrolled, 21 977 patients had baseline data and hence were eligible for the study and constituted the overall safety analysis cohort. The majority (81.7%, n = 17 946) completed the 6-month study, but 10.9% of the patients (n = 2395) provided only

baseline data and 7.4% (n = 1636) completed only 3 months of the study. The country and ethnic distribution are summarized in table 1. Among the patients, 87% had previously received insulin or OAD treatment for diabetes, whereas 8% of the patients had not received either treatment and 5% had provided incomplete or no information on previous treatment. Among the patients who received prior treatment (n = 19 198), the largest group (45%) was previously treated with OAD only, whereas 31% were treated with insulin only and 24% were treated with insulin + OAD (table 2). Baseline demographics and glycaemic control were significantly different among the subgroups ($p < 0.001$; tables 2 and 4). Patients on prior insulin treatment, either alone or in combination with OADs, had a longer duration of diabetes compared with the OAD-only and treatment-naive groups. These groups had a slightly better baseline HbA_{1c} compared with the OAD-only and treatment-naive groups.

BIAsp 30 Dosing and Patient Body Weight

The majority of the overall cohort followed a twice-daily injection regimen (80.0% at treatment initiation, 80.1% at 3 months and 78.5% at 6 months), while the remaining patients followed a once-daily regimen (16.8% at treatment initiation, 15.2% at 3 months and 14.6% at 6 months) or a thrice-daily regimen (3.2% at treatment initiation, 4.7% at 3 months and 6.9% at 6 months). Of the overall cohort, only a small number of patients (n = 884) increased their number of daily injections, and this practice varied across the countries. For example, Korea had the highest number of patients who increased injections (n = 464), whereas Turkey had the lowest number (n = 6). A future study investigating the effects of insulin intensification in terms of frequency of injection can be explored. The dosage of BIAsp 30 at 3 and 6 months was slightly higher compared with treatment initiation (table 3). As expected, the OAD-only and treatment-naive groups, having had no experience with insulin use, were prescribed the lowest doses of BIAsp 30. The mean body weight of the patients was unchanged throughout the study (table 3). Dosage of BIAsp 30 and body weight were significantly different among the subgroups ($p < 0.001$). No significant relationship was found between the change in mean body weight at 6 months and final dose of BIAsp 30.

Table 1 Country and ethnic distribution of the study population

	n	%*
Safety population	21 977	
Country		
South Korea	5828	26.5
India	3559	16.2
Turkey	3041	13.8
Saudi Arabia and Gulf countries (Kuwait, Qatar and the United Arab Emirates)	2226	10.1
Russia	2150	9.8
Iraq	1888	8.6
South Africa	1473	6.7
Romania	912	4.1
Lebanon	551	2.5
Jordan	349	1.6
Ethnic group		
Asian/Pacific Islander	9816	45.4
White	6713	31.1
Middle Eastern/Arabic	4117	19.1
Black	651	3.0
Others/unknown	476	0.5
Coloured	196	0.9
American Indian–Alaskan Native	8	<0.1

*Percentages may not total 100 because of rounding up.

Glycaemic Control

The mean HbA_{1c} in the overall cohort and the prior treatment subgroups was significantly improved from baseline at the end of 3 and 6 months of treatment ($p < 0.001$) (table 4). At the end of 6 months, the mean HbA_{1c} in the overall cohort was improved by $1.81 \pm 1.84\%$. The changes in mean HbA_{1c} at 3 and 6 months were significantly different among the subgroups ($p < 0.001$; table 4). Patients in the treatment-naive and OAD-only prior treatment groups showed a greater improvement compared with the insulin-only and the insulin + OAD groups. The proportion of patients achieving target HbA_{1c} increased significantly from baseline in overall cohort and the subgroups ($p < 0.001$; figure 1). The proportions of patients achieving HbA_{1c} of less than 7% were significantly different among the subgroups at 3 months ($p < 0.001$), but not at 6 months ($p = 0.06$). The largest proportion of patients achieved this target in the treatment-naive subgroup. Among the patients in the overall cohort who achieved target HbA_{1c} at 3 and 6 months, 68.3 and 69.3% did not report hypoglycaemia respectively.

The mean fasting and postprandial glucose concentrations also showed improvements in the overall cohort and the subgroups ($p < 0.001$) (table 4). At the end of 6 months, the FPG concentration in the overall cohort was improved by 3.74 ± 3.91 mmol/l and the PPPG concentration was improved by 5.82 ± 5.10 mmol/l. The changes in FPG and PPPG were significantly different

Table 2 Baseline characteristics of the study population

Characteristics	Treatment naive	OAD* only	Insulin† only	Insulin† + OAD*	Overall	p value‡
Safety population§	1707	8583	5942	4673	21 977	
Gender (male/female) (%)	56.5/43.5	51.5/48.5	48.3/51.7	47.0/53.0	49.9/50.1	N.A.
Mean age (years) ± s.d.	52.2 ± 13.7	55.2 ± 11.2	55.3 ± 13.4	56.7 ± 11.0	55.3 ± 12.2	<0.001
Mean diabetes duration (years) ± s.d.	5.6 ± 6.0	8.9 ± 6.1	11.0 ± 7.3	11.0 ± 7.0	9.7 ± 6.8	<0.001
Mean BMI (kg/m^2) ± s.d.	25.6 ± 4.9	27.3 ± 5.1	26.6 ± 4.9	27.7 ± 5.3	27.1 ± 5.1	<0.001
Mean HbA_{1c} (%) ± s.d.	10.0 ± 2.3	9.8 ± 1.9	9.2 ± 1.8	9.3 ± 1.8	9.5 ± 1.9	<0.001

BMI, body mass index; HbA_{1c}, haemoglobin A_{1c}; OAD, oral antidiabetic drug.
*The most commonly used OADs were sulphonylureas (72%) and biguanides (22%).
†The most commonly used insulin was human insulin (89%); less commonly used were animal insulin (3.0%) and analogue insulin (9.2%).
‡Results from the ANOVA model included previous treatment (treatment naive, OAD only, insulin only and insulin + OAD) as factor.
§One thousand and seventy-two patients had incomplete or no information on previous treatment.

among the subgroups ($p < 0.001$). Again, the OAD-only and treatment-naive groups showed a greater improvement compared with the insulin-only and the insulin + OAD groups.

Hypoglycaemia

The overall percentages of patients reporting hypoglycaemic episodes were lower at 3 months (19.9%) and at 6 months (17.8%) compared with baseline (22.3%) (baseline here refers to the period of 3 months before the start of the study when the patients were using their previous diabetes treatment.) ($p < 0.001$). The rates of hypoglycaemic episodes were lower at the end of the study in the overall cohort, the insulin-only subgroup and the insulin + OAD subgroup ($p < 0.001$; figure 2). The insulin-only subgroup reported the biggest reductions in hypoglycaemic rates. In the OAD-only subgroup, nocturnal, major and minor episodes decreased, whereas diurnal episodes increased ($p < 0.001$). In the treatment-naive subgroup, the rates of nocturnal, diurnal and minor hypoglycaemic episodes increased ($p < 0.001$), whereas the rate of major episodes remained low at baseline and end of study ($p = 1.000$).

Adverse Drug Reactions

During the 6-month study period, 444 ADRs were reported at an event rate of 0.05 events per patient-year. The majority of the events were reported in the first 3 months (342 events), and fewer events were reported in the last 3 months (102 events). The most commonly reported ADRs were refraction disorders (81 events), symptoms of local hypersensitivity (74 events) and unspecified ADRs (83 events). Of these, 13 were serious ADRs, including three reports of lipodystrophy, two symptoms of generalized hypersensitivity and one each of acute painful neuropathy, worsening of diabetic retinopathy and oedema. There were five reports of unspecified serious ADRs.

Discussion

One of the main goals of treating patients with type 2 diabetes is to produce near-normal glucose levels to

Table 3 Patient body weight and BIAsp 30 dosage at baseline, 3 and 6 months

	Treatment naive	OAD only	Insulin only	OAD + insulin	Overall	p value*
Safety population	1707	8583	5942	4673	21 977	
Mean total daily BIAsp 30 dose (U/kg body weight)						
At treatment initiation	0.44 ± 0.20	0.41 ± 0.19	0.57 ± 0.23	0.51 ± 0.22	0.48 ± 0.22	<0.001
At 3 months	0.47 ± 0.21	0.48 ± 0.21	0.61 ± 0.23	0.54 ± 0.23	0.53 ± 0.23	<0.001
At 6 months	0.49 ± 0.22	0.50 ± 0.22	0.62 ± 0.24	0.56 ± 0.24	0.55 ± 0.24	<0.001
Mean body weight (kg)						
At treatment initiation	69.28 ± 15.42	74.22 ± 15.85	72.21 ± 14.95	74.67 ± 16.20	73.58 ± 15.97	<0.001
At 3 months	68.38 ± 14.53	73.87 ± 14.91	71.68 ± 14.20	74.22 ± 15.66	73.10 ± 15.01	<0.001
At 6 months	68.22 ± 14.29	74.03 ± 14.55	71.89 ± 13.90	74.31 ± 15.27	73.26 ± 14.73	<0.001

BIAsp 30, biphasic insulin aspart 30; OAD, oral antidiabetic drug. Data are presented as mean ± s.d.
*Results from the ANOVA model included previous treatment (treatment naive, OAD only, insulin only and insulin + OAD) as factor.

Table 4 Change in glucose parameters from baseline

	Treatment naive	OAD only	Insulin only	OAD + insulin	Overall	p value†
Safety population	1707	8583	5942	4673	21 977	
HbA_{1c} (%) ± s.d. (95% CI)						
At baseline	9.98 ± 2.32	9.77 ± 1.85	9.18 ± 1.83	9.25 ± 1.76	9.52 ± 1.90	<0.001
Change at 3 months	−1.79 ± 2.02* (−1.91; −1.67)	−1.63 ± 1.63* (−1.68;−1.59)	−1.01 ± 1.58* (−1.06;−0.96)	−1.04 ± 1.47* (−1.09;−0.99)	−1.33 ± 1.66* (−1.36;−1.30)	<0.001
Change at 6 months	−2.35 ± 2.23* (−2.48; −2.23)	−2.15 ± 1.80* (−2.19; −2.11)	−1.45 ± 1.76* (−1.50;−1.40)	−1.47 ± 1.70* (−1.52;−1.42)	−1.81 ± 1.84* (−1.84;−1.78)	<0.001
FPG (mmol/l) ± s.d. (95% CI)						
At baseline	13.48 ± 5.38	12.38 ± 3.97	11.13 ± 3.85	10.95 ± 3.61	11.84 ± 4.12	<0.001
Change at 3 months	−4.52 ± 4.96* (−4.79; −4.25)	−3.66 ± 3.65* (−3.75;−3.57)	−2.28 ± 3.68* (−2.39;−2.18)	−2.18 ± 3.36* (−2.29;−2.07)	−3.02 ± 3.84* (−3.07;−2.96)	<0.001
Change at 6 months	−5.16 ± 5.11* (−5.45; −4.87)	−4.47 ± 3.68* (−4.56;−4.38)	−2.97 ± 3.71* (−3.07;−2.86)	−2.89 ± 3.57* (−3.01;−2.78)	−3.74 ± 3.91* (−3.80;−3.68)	<0.001
PPPG (mmol/l) ± s.d. (95% CI)						
At baseline	18.88 ± 6.44	17.10 ± 4.79	15.28 ± 5.10	15.53 ± 4.92	16.39 ± 5.19	<0.001
Change at 3 months	−6.59 ± 6.17* (−6.93; −6.25)	−5.63 ± 4.73* (−5.75;−5.52)	−3.81 ± 4.81* (−3.95;−3.67)	−3.74 ± 4.50* (−3.89;−3.60)	−4.76 ± 4.95* (−4.83;−4.68)	<0.001
Change at 6 months	−7.87 ± 6.25* (−8.23; −7.52)	−6.76 ± 4.77* (−6.87;−6.64)	−4.79 ± 4.96* (−4.94;−4.65)	−4.84 ± 4.85* (−5.00;−4.69)	−5.82 ± 5.10* (−5.90;−5.74)	<0.001

CI, confidence interval; FPG, fasting plasma glucose; HbA_{1c}, haemoglobin A_{1c}; OAD, oral antidiabetic drug; PPPG, postprandial plasma glucose.
*$p < 0.001$ (change from baseline).
†Results from the ANOVA model included previous treatment (treatment naive, OAD only, insulin only and insulin + OAD) as factor.

prevent the development of diabetic complications [24]. Treatments with diet, insulin or oral agents are known to improve glycaemia [25], but how often these therapies can attain glycaemic target levels set by the ADA has not been formally studied [24]. Strict treatment with human insulin in patients with microvascular and macrovascular complications has shown that a reduction in HbA_{1c} could be achieved, but at a higher risk of hypoglycaemia [26]. In treat-to-target studies with insulin analogues, however, it has been shown that treatment with premixed biphasic insulin analogues can achieve targets at a lower price of hypoglycaemia and with acceptable weight gain [12,27]. The question remains whether this can be validated in a normal clinical setting. Our study of over 20 000 patients with poor glucose control showed that BIAsp 30 treatment was efficacious in improving parameters of glycaemic control without increasing body weight or the incidence of hypoglycaemia and other ADRs over previous therapy. These results support the findings from clinical trials and clinical experience studies, which consistently show that BIAsp 30 is safe and efficacious [12,17,18,22,23,28].

Our study showed a mean reduction in HbA_{1c} of 1.3% at the end of 3 months and of 1.8% at the end of 6 months in the overall cohort. In a 16-week trial on BIAsp 30 treatment [28], there was an improvement in HbA_{1c} of 1.6% among patients treated with twice-daily BIAsp 30 monotherapy and of 1.7% in patients using twice-daily BIAsp 30 + metformin. In a separate 12-week trial [18], patients treated with once-daily BIAsp 30 + metformin had a reduction in HbA_{1c} of 1.3% and a reduction in fasting glucose of 4.2 mmol/l, which was slightly better than the improvement in our cohort after 3 months (by 3.02 ± 3.84 mmol/l). Similar improvements in HbA_{1c}, fasting glucose and postprandial glucose were reported in clinical experience studies of BIAsp 30 treatment [22,23]. Although it appeared that the mean reduction in HbA_{1c} was comparable among these studies and ours, the proportion of patients achieving target HbA_{1c} of less than 7% was lower in our overall cohort (27.7% after 6 months) compared with some of these studies, such as Joshi *et al.* [22], in which the proportion of patients achieving target HbA_{1c} increased to 45.6% after 12 weeks. This could be because the baseline HbA_{1c} was lower for patients in Joshi's study (8.8%), compared with our study.

The BIAsp 30 dosage prescribed in our study was low compared with studies such as the 1-2-3 study [27] and the treat-to-target INITiation of Insulin to reach AIC TargEt (INITIATE) study [12], which used more aggressive treat-to-target regimens. In the INITIATE study,

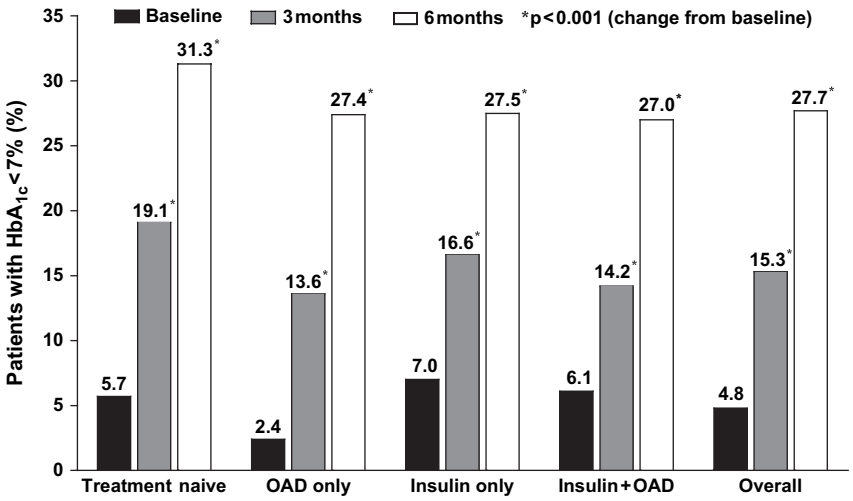

Fig. 1 Proportion of patients with an HbA_{1c} of less than 7% before and after treatment. *$p < 0.001$ (McNemar's test for change from baseline). HbA_{1c}, haemoglobin A_{1c}; OAD, oral antidiabetic drug.

insulin-naive patients with type 2 diabetes with prior OAD treatment were treated with twice-daily BIAsp 30 + OADs. BIAsp 30 dosage increased from a baseline of 0.1 U/kg body weight per day to 0.8 U/kg body weight per day at the end of 28 weeks. The mean HbA_{1c} was reduced by 2.8% and FPG was reduced from a baseline of 14.0 to 7.1 mmol/l. The proportion of patients achieving target HbA_{1c} of <7% was 66% and ≤6.5% was 42%. This was a much greater improvement in glycaemic control than in our study and it suggested that a more aggressive titration regimen of BIAsp 30 could result in better glycaemic control. However, one should consider that in many of the countries participating in our study, self-monitoring is still very much a novelty or may be unavailable because of healthcare budget constraints. Even in industrialized countries, where self-titration is practiced, there is still much to learn regarding the optimal method for initiating and titrating insulins [29]. Nevertheless, several studies have shown that titration can improve glucose control. In an observational study of Dutch patients with type 2 diabetes failing OADs, 91% of patients achieved an HbA_{1c} of ≤7% after 18 months of self-titration of BIAsp 30, with no occurrence of major hypoglycaemia [30]. Another study comparing a physician-led titration treatment algorithm with a self-titration algorithm using an insulin analogue found that both algorithms resulted in improved glycaemic control with low incidences of severe hypoglycaemia and concluded that any titration regimen successfully undertaken by patients themselves would be beneficial [29].

Overall, these studies showed that treatment with BIAsp 30 improved glycaemic control in patients previously receiving different types of therapy. In our study, treatment-naive and insulin-naive patients previously treated with only OADs showed the greatest improvements. At the same time, the groups previously receiving insulin treatment also showed improvements in glycaemic control with BIAsp 30 therapy. One reason for this could be the improved PPPG control, which is considered to be a significant component of overall glycaemic control, especially when HbA_{1c} is approaching target.

Very few major hypoglycaemic episodes have been reported in the literature on BIAsp 30 treatment [12,16,18,22,23,28]. The proportion of patients in our study who reported minor hypoglycaemic episodes was comparable to those of the other studies, which varied from 10 to 43% [12,18,23,28]. However, the event rates were higher in our study compared with these studies (ranging from 0.04 to 3.4 events per patient-year) [12,28]. Nevertheless, there was an overall decrease in the event rates and the proportion of patients reporting hypoglycaemic episodes at the end of the study. The biggest reduction in hypoglycaemic episodes was seen in the insulin-only group. This suggested that BIAsp 30 was safer and associated with a lower incidence of hypoglycaemia compared with other insulins, notably the human insulin, as the majority of the patients were previously treated with human insulin. The group previously treated with only OAD reported a slight increase in diurnal minor episodes at the end of the study, while the treatment-naive group reported a slight increase in all the hypoglycaemia categories except the major episodes. It was possible that these patients, being new to insulin treatment, lacked the experience with insulin

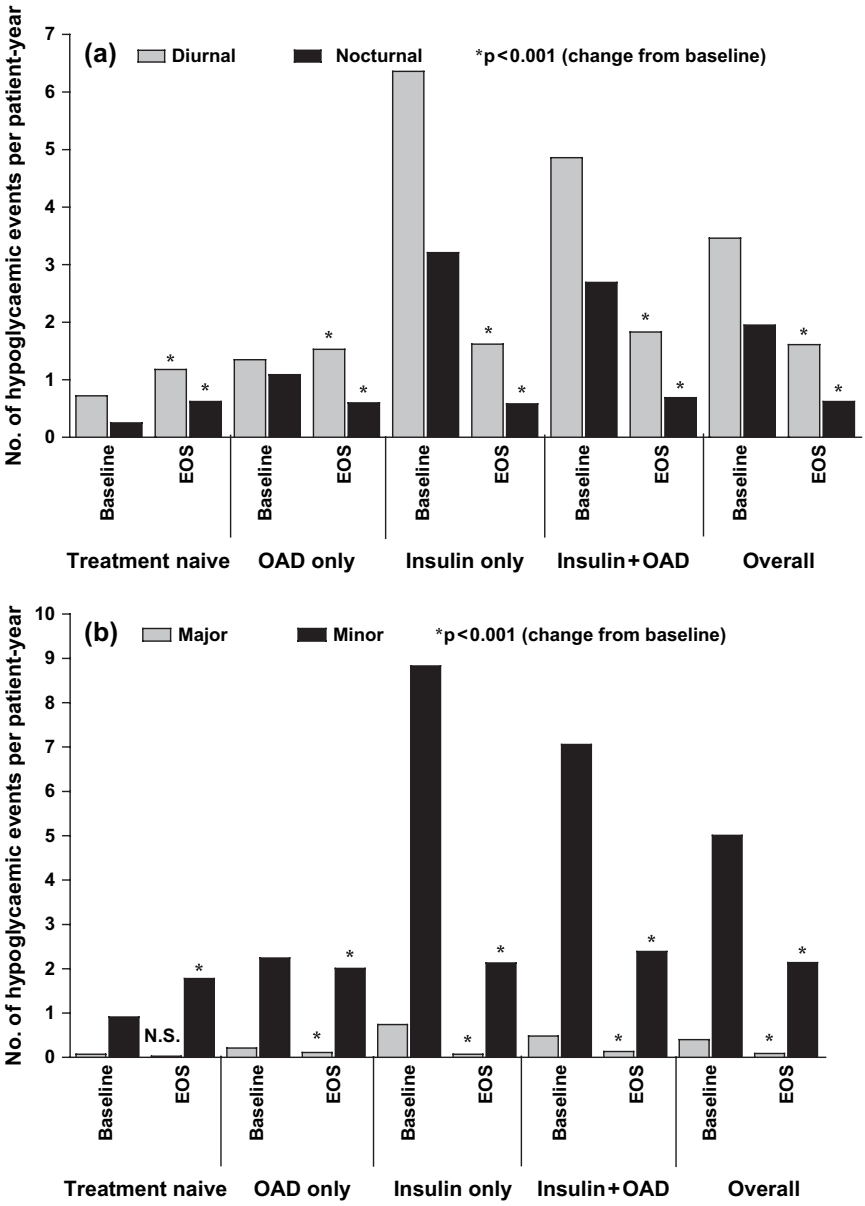

Fig. 2 Hypoglycaemia at baseline and EOS classified according to (a) time of day and (b) severity. *p < 0.001 (Wilcoxon sign-rank test for change from baseline). EOS, end of study; N.S., not significant; OAD, oral antidiabetic drug.

use. It has been shown in a 24-month study [17] that hypoglycaemia with BIAsp 30 treatment was a transient effect that decreased over time with no detrimental effects on its efficacy. Given that most of the hypoglycaemic episodes reported were minor in severity, this suggested that BIAsp 30 could be safely administered even to insulin-naive patients with few major hypoglycaemic episodes. One interesting point to note was the occurrence of hypoglycaemic episodes at baseline in the treatment-naive subgroup. Some of these patients were identified to have concomitant complications such as neuropathy and were taking concomitant medications, both of which could have had an effect on blood glucose. Another reason could be factors (e.g. patients being elderly) leading to requirement of third party assistance, as defined for major hypoglycaemia. Other factors contributing to symptomatic hypoglycaemia could be related to malnutrition, missing of meals, alcohol consumption and reactive hypoglycaemia [31–33]. However, these informations were

not captured in the data collection forms, and it was not possible to determine the precise cause of these hypoglycaemic episodes. Nevertheless, the number of all hypoglycaemic events at baseline in this subgroup was small (1.0 events per patient-year).

Two thirds of the patients who achieved target HbA_{1c} of less than 7% did not experience any hypoglycaemic episodes throughout the study period. This observation is an encouraging result and an important factor in addressing one of the barriers to insulin treatment – namely, the fear of experiencing hypoglycaemia.

The low incidence of ADRs in this study was consistent with the good safety profile of BIAsp 30 reported in the literature [34]. In our study, the most common ADRs were refraction disorders, acute painful neuropathy, symptoms of local hypersensitivity and other ADRs not specified. Common serious ADRs were symptoms of generalized hypersensitivity, lipodystrophy and others not specified. Acute painful neuropathy and retinopathy are known to be transient effects caused by strict glycaemic control [35–38]. It was possible that the improvement in glycaemic control led to some of the ADRs observed in this study.

Weight gain was negligible in our study. This was consistent with small weight increases seen in both a short-term study [22] and a long-term study [17], which recorded an increase of only 0.05 kg at the end of 24 months. Other studies have reported slightly higher weight increases of 0.7–5.4 kg [12,18,28]. In these studies, treatment was more aggressive and the insulin dosage was higher. It appears that weight increase could be dependent on BIAsp 30 dosage. However, in our study, weight gain and insulin dosage were not found to have a significant relationship. The study period of 6 months in our study was short, and the dosage of BIAsp 30 was based on routine clinical practice and not treat-to-target algorithms. It is possible that a study of longer duration (such as 2 years of observation) and higher doses of insulin are necessary to estimate the weight-gain effect of insulin therapy.

Study Limitations

As this was an observational study, there were no strict inclusion and exclusion criteria. Hence, a small percentage of patients enrolled in the study were identified to have baseline HbA_{1c} of less than 7%, although they may have been considered by their physicians to have poor glycaemic control. Second, as there was no control group treated with other premixed insulins, the improvements in glycaemic control could potentially be explained as a study effect. However, this study effect should be minimal in an observational study compared with closely monitored clinical trials in which participating patients make an extra effort to control their diabetes condition. The method of data collection for hypoglycaemic episodes and ADRs was based on patient recollection, which could have resulted in under-reporting. Further, blood glucose measurements were not recorded during hypoglycaemic episodes that occurred prior to the start of the study. Lastly, the study was conducted over a short period and therefore was inadequate for capturing long-term trends and observations. Because of these above-stated limitations, the results should be taken with some caution. However, the large number of patients enrolled in this study does serve as a counterbalance to the traditional shortcomings of an observational study, and the positive results from this study do confirm the results of randomized controlled trials.

Conclusions

The findings from this large observational study involving more than 20 000 patients concurred with findings from clinical trials, and showed that the use of BIAsp 30 treatment in clinical practice was both effective and safe in patients with type 2 diabetes mellitus who were considered to be poorly controlled on prior diabetes therapy.

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