

# Biphasic Insulin Aspart 30 Three Times Daily Is More Effective Than a Twice-Daily Regimen, Without Increasing Hypoglycemia, in Chinese Subjects With Type 2 Diabetes Inadequately Controlled on Oral Antidiabetes Drugs

WENYING YANG, PHD<sup>1</sup>  
 QIUHE JI, PHD<sup>2</sup>  
 DALONG ZHU, PHD<sup>3</sup>  
 JINKUI YANG, PHD<sup>4</sup>

LULU CHEN, PHD<sup>5</sup>  
 ZHIMIN LIU, MSC<sup>6</sup>  
 DEMIN YU, PHD<sup>7</sup>  
 LI YAN, MSC<sup>8</sup>

**OBJECTIVE** — To assess the efficacy and safety of twice- and thrice-daily biphasic insulin aspart 30 (BIAsp 30) in Chinese subjects with type 2 diabetes inadequately controlled with oral antidiabetes drugs (OADs).

**RESEARCH DESIGN AND METHODS** — In this 24-week, multicenter, parallel-group, randomized, treat-to-target study, 321 Chinese insulin-naïve subjects with poorly controlled type 2 diabetes (fasting blood glucose  $\geq 7.8$  mmol/l and A1C  $\geq 7.5\%$ ) were randomized (1:1) to twice- or thrice-daily (BID and TID groups, respectively) BIAsp 30 without OADs. Initial insulin doses were based on fasting blood glucose at randomization. Insulin dose was adjusted with algorithm-controlled titration to achieve premeal blood glucose of 4.4–6.1 mmol/l.

**RESULTS** — A1C decreased significantly in both groups (BID group  $-2.48 \pm 0.07\%$ ; TID group  $-2.81 \pm 0.07\%$ ). Thrice-daily BIAsp 30 showed superiority in A1C improvement ( $-0.33\%$  [95% CI  $-0.53$  to  $-0.13$ ];  $P < 0.01$ ) and helped more subjects achieve A1C targets  $< 7\%$  (BID group 51.3% vs. TID group 65.8%;  $P < 0.01$ ). Thrice-daily BIAsp 30 was more effective in subjects with baseline A1C  $\geq 9\%$  ( $< 7\%$ : BID group 41.5% vs. TID group 58.3%;  $P < 0.01$ ). There was no significant difference in rates of overall and nocturnal major and minor hypoglycemia per subject year between groups. No significant differences in weight gain (BID group  $3.87 \pm 0.28$  kg; TID group  $4.09 \pm 0.27$  kg) and mean daily insulin doses (BID group  $0.82 \pm 0.28$  units/kg; TID group  $0.86 \pm 0.34$  units/kg) were observed.

**CONCLUSIONS** — Twice- and thrice-daily BIAsp 30 were effective in Chinese insulin-naïve subjects with poorly controlled type 2 diabetes. Thrice-daily BIAsp 30 offered greater reduction in A1C without increasing risk of hypoglycemia, insulin dose, and weight gain, especially in subjects with A1C  $\geq 9\%$ .

*Diabetes Care* 31:852–856, 2008

From the <sup>1</sup>Department of Endocrinology, China-Japan Friendship Hospital, Beijing, China; the <sup>2</sup>Department of Endocrinology, Xijing Hospital, 4th Military Medical University, Xi'an, China; the <sup>3</sup>Department of Endocrinology, Nanjing Drum Tower Hospital, Nanjing, China; the <sup>4</sup>Department of Endocrinology, Beijing Tongren Hospital, Beijing, China; the <sup>5</sup>Department of Endocrinology, Wuhan Union Hospital, Wuhan, China; the <sup>6</sup>Department of Endocrinology, Shanghai Changzheng Hospital, Shanghai, China; the <sup>7</sup>Department of Endocrinology, Metabolic Disease Hospital, Tianjin Medical University, Tianjin, China; and the <sup>8</sup>Department of Endocrinology, Sun Yixian Commemorative Hospital, Zhongshan University, Guangzhou, China.

Corresponding author: Professor Wenying Yang, China-Japan Friendship Hospital, Department of Endocrinology, Beijing, China. E-mail: yangwenying1707@yahoo.com.cn.

Received for publication 15 October 2007 and accepted in revised form 31 January 2008.

Published ahead of print at <http://care.diabetesjournals.org> on 13 February 2008. DOI: 10.2337/dc07-1992. Clinical trial reg. no. NCT00184561, clinicaltrials.gov.

**Abbreviations:** BIAsp 30, biphasic insulin aspart 30; OAD, oral antidiabetes drug; SMBG, self-monitored blood glucose.

© 2008 by the American Diabetes Association.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

In subjects with type 2 diabetes inadequately controlled with oral antidiabetes drugs (OADs), insulin therapy could be used to improve glycemic control (1). The modern premixed insulins, such as biphasic insulin aspart 30 (BIAsp 30), were regularly prescribed twice daily in clinical practice. The Achieving Control Through Insulin plus Oral agents (ACTION) study showed superior A1C improvement in the subjects with the treatment of twice-daily BIAsp 30 plus optimized metformin and pioglitazone than those with OADs only (2). More subjects could achieve A1C targets when the optimized OADs were added with twice-daily BIAsp 30. Furthermore, in the INITIATE study (3), twice-daily BIAsp 30 plus OADs could help the patients with a higher baseline A1C ( $> 9.5\%$ ) significantly improve glycemic levels more than the patients treated with a once-daily basal insulin plus OADs. The 1-2-3 Study is a stepwise comparison among once-, twice-, and thrice-daily BIAsp 30 with OADs treatment in Western patients with type 2 diabetes (4). Patients could achieve more glycemic improvement by increasing BIAsp 30 from twice- to thrice-daily injections. From the studies mentioned above, no results on twice- or thrice-daily BIAsp 30 without OADs were reported.

In this study, we designed a head-to-head comparison to show the efficacy and safety of twice- and thrice-daily BIAsp 30 in Chinese insulin-naïve subjects with type 2 diabetes after at least 6 months of inadequately controlled OAD treatment. We proposed that adding an injection before lunch in twice-daily BIAsp 30 treatment could provide superior A1C improvement to twice-daily BIAsp 30 treatment, especially in those subjects with higher A1C baselines.

## RESEARCH DESIGN AND METHODS

The study protocol was approved by the independent ethics com-

mittees for each participating center and was performed in accordance with the Declaration of Helsinki and the Guidelines on Good Clinical Practice.

This was a 24-week, parallel-group, randomized, treat-to-target study comparing the efficacy and safety of twice- and thrice-daily BIAsp 30. After a 2-week screening period, a total of 321 eligible insulin-naïve subjects from clinics at eight hospitals in China were randomized in 1-to-1 ratio to receive twice-daily (immediately before breakfast and dinner) (BID group) or thrice-daily BIAsp 30 (immediately before breakfast, lunch, and dinner) (TID group) treatment. All subjects discontinued their previous OADs at randomization, and no wash-out period of OADs was used. This study was designed as an open-label trial due to different numbers of daily subcutaneous administration with trial drugs. Randomization codes were stratified by center. Block randomization method was used in this study to minimize bias between the two treatment groups.

Male and female subjects were aged 18–75 years, had BMI  $\leq 32$  kg/m<sup>2</sup>, were poorly controlled on OAD therapy (fasting blood glucose  $\geq 7.8$  mmol/L; A1C  $\geq 7.5\%$ ), and had received one or more OADs for at least 6 months before this research. Subjects had not used insulin therapy preceding the study and were otherwise healthy. No subject was receiving treatments that interfered with glucose metabolism or had any condition that would interfere with study participation or evaluation of results. All subjects were provided with the standard meals on office visits to compare 2-h postbreakfast plasma glucose (PPG) between the treatments. During the trial, the subjects received food intake and lifestyle suggestions from investigators. Female subjects who were pregnant, breastfeeding, or not using adequate contraceptive measures were excluded from the study.

All OADs were discontinued upon initiation of BIAsp 30, and BIAsp 30 was administered subcutaneously using NovoMix 30 FlexPen, a prefilled disposable pen device provided by Novo Nordisk (China) Pharmaceuticals. The starting doses for BIAsp 30 were based on fasting blood glucose at randomization. In the BID BIAsp 30 group, the initial total daily dose was equally divided into the prebreakfast and predinner dose. In the TID BIAsp 30 group, the initial dose distribution ratio for breakfast, lunch, and dinner doses was 25:25:50%. Insulin

dose was adjusted based on the mean premeal self-monitored blood glucose (SMBG) to achieve premeal blood glucose targets of 4.4–6.1 mmol/L. All subjects performed premeal self-monitoring of blood glucose on 3 consecutive days before each of the 19 patient contacts during the 24-week trial. For the BID BIAsp 30 group, the prebreakfast SMBG was used to adjust the dose at the next dinner, and the predinner SMBG was used to adjust the dose at the next day's breakfast. For the TID BIAsp 30 group, the prebreakfast SMBG was used to adjust the dose at the next dinner, prelunch SMBG was used to adjust the dose at the next day's breakfast, and predinner SMBG was used to adjust the dose at the next day's lunch. The extent of the dose titration was based on the following guidelines: decrease by 2 units if premeal blood glucose is  $< 4.4$  mmol/L, no change if blood glucose is 4.4–6.1 mmol/L, increase by 2 units if blood glucose is 6.2–7.7 mmol/L, increase by 4 units if blood glucose is 7.8–10.0 mmol/L, and increase by 6 units if blood glucose is  $> 10.0$  mmol/L (5). Dose adjustment was only performed at visits and no more than two daily doses were adjusted at the same visit. At each lab visit, prebreakfast plasma glucose and 2-h postbreakfast plasma glucose testing was performed. Patients were required to fast before each lab visit.

### Efficacy parameters

The change in A1C after 24 weeks' treatment was the primary end point. Change in A1C after 12 weeks, prebreakfast plasma glucose, 2-h postbreakfast plasma glucose, and percentages of subjects who achieved A1C targets (American Diabetes Association standard =  $< 7\%$  [6]; International Diabetes Federation standard =  $\leq 6.5\%$  [7]) at the end of treatment were also recorded in the two treatment groups.

### Safety parameters

Episodes of hypoglycemia (including major, minor, and nocturnal hypoglycemia) were recorded during the study. Major hypoglycemia was defined as an episode with neurological symptoms consistent with hypoglycemia that could not be self-treated by the patient. Minor hypoglycemia were episodes that were self-treated and with a confirmed blood glucose reading  $< 2.8$  mmol/L. Adverse events were reported throughout the whole study. Standard laboratory parameters, weight,

and vital signs were assessed at the beginning and the end of the study.

### Statistical analyses

A total of 321 subjects were randomized assuming a drop-out rate of 20%, allowing a power of 80% to detect that thrice-daily BIAsp 30 was noninferior to twice-daily BIAsp 30 ( $\alpha = 0.025$ ,  $\beta = 0.2$ ). Analyses for primary and secondary end points were performed on the intent-to-treat population.

The estimated treatment difference (TID group minus BID group) in A1C, the 95% CI, and the *P* value were obtained from an ANCOVA model, with treatment and center as factors and A1C at baseline (visit 1) as a covariate. If noninferiority could be demonstrated, the superiority of thrice-daily BIAsp 30 would be assessed. Percentages of subjects who achieved A1C targets at the end of the study were analyzed by a logistic regression approach with treatment, center, and baseline A1C as explanatory variables. The changes in 2-h postbreakfast blood glucose and prebreakfast blood glucose were analyzed for treatment difference using the ANCOVA model, with treatment and center as factors and the value of A1C at baseline (visit 1) as a covariate. The Poisson regression model was used for the analysis of hypoglycemia. Effects for sex and ethnicity were also investigated.

**RESULTS** — Of 321 randomized subjects, 160 subjects received twice-daily BIAsp 30 (BID group) and 161 received thrice-daily BIAsp 30 (TID group). A total of 12 and 4 individuals withdrew from the study in the BID and TID BIAsp 30 groups, respectively. In the BID group, eight subjects withdrew due to noncompliance with the protocol, three due to adverse events, and one due to ineffective therapy. In the TID group, two subjects withdrew due to adverse events, one for noncompliance and one for not wanting to inject insulin. Baseline characteristics were comparable between two treatment groups (Table 1), with the mean baseline A1C being  $\sim 9.5\%$  in both groups. Around half of subjects in the two groups received three or more OADs before the study. No effect of sex or ethnicity was found in this trial. The relatively low BMI at baseline is reflective of a typical patient with type 2 diabetes in China (8,9).

### Efficacy

**A1C.** A1C was significantly reduced by (mean  $\pm$  SE)  $2.48 \pm 0.07\%$  and  $2.81 \pm$

Table 1—Subject baseline characteristics of the intent-to-treat population

	Twice-daily BIAsp 30	Thrice-daily BIAsp 30
n	160	161
Completers (n)	148	157
Age (years)	54.4 ± 9.1	55.3 ± 8.8
Sex (male/female)	88/72	79/82
BMI (kg/m <sup>2</sup> )	24.3 ± 3.2	24.3 ± 3.1
Duration of diagnosed diabetes (years)	7.7 ± 5.1	8.0 ± 4.8
Diabetes complications		
Retinopathy	11.3	9.9
Nephropathy	5.0	1.9
Neuropathy	10.0	3.1
Macroangiopathy	3.8	9.3
Baseline A1C	9.52 ± 1.4	9.55 ± 1.5
Prior treatments with OADs		
One OAD	11.9	18.0
Two OADs	35.0	36.6
Three or more OADs	53.1	45.3
Discontinuation from study*		
For adverse event	3 (2)	2 (1)
For noncompliance	8 (5)	1 (1)
For ineffective therapy	1 (1)	0
For other reasons	0	1 (1)

Data are means ± SD, percent, or n (%), unless otherwise indicated. \*Adverse event withdrawals in the twice-daily treatment were anaphylaxis appendicitis and pain of waist; adverse event withdrawals in the thrice-daily treatment were nausea and acute myocardial infarction. The one “other” referred to refusal to inject insulin.

0.07% in the BID and TID BIAsp 30 groups, respectively, after 24 weeks’ treatment (Fig. 1). End-of-trial A1C values were 7.01 and 6.68% in the BID and TID groups, respectively. Subjects receiving thrice-daily BIAsp 30 achieved a greater reduction in A1C compared with twice-

daily BIAsp 30–treated subjects (difference: −0.33% [95% CI −0.53 to −0.13]; *P* < 0.01). After only 12 weeks of treatment, subjects receiving thrice-daily BIAsp 30 achieved superior reduction in A1C to the order of 0.3% (*P* < 0.01) compared with those receiving twice-daily BI-

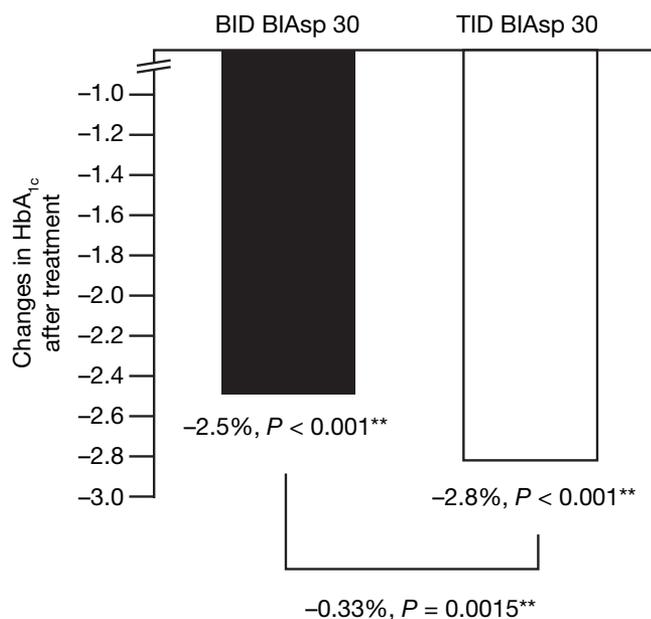


Figure 1—The changes in A1C after treatment with twice- or thrice-daily BIAsp30. \*\**P* value < 0.01. ■, twice-daily BIAsp 30; □, thrice-daily BIAsp 30.

Asp 30, and this was maintained until the end of the trial. In a subanalysis, subjects with baseline A1C ≥9% achieved greater reductions in A1C than was observed in the main cohort (BID group −3.16 ± 1.50% and TID group −3.61 ± 1.46%; the A1C difference −0.45% [95% CI −0.76 to −0.14]; *P* < 0.01).

**Achieving A1C targets**

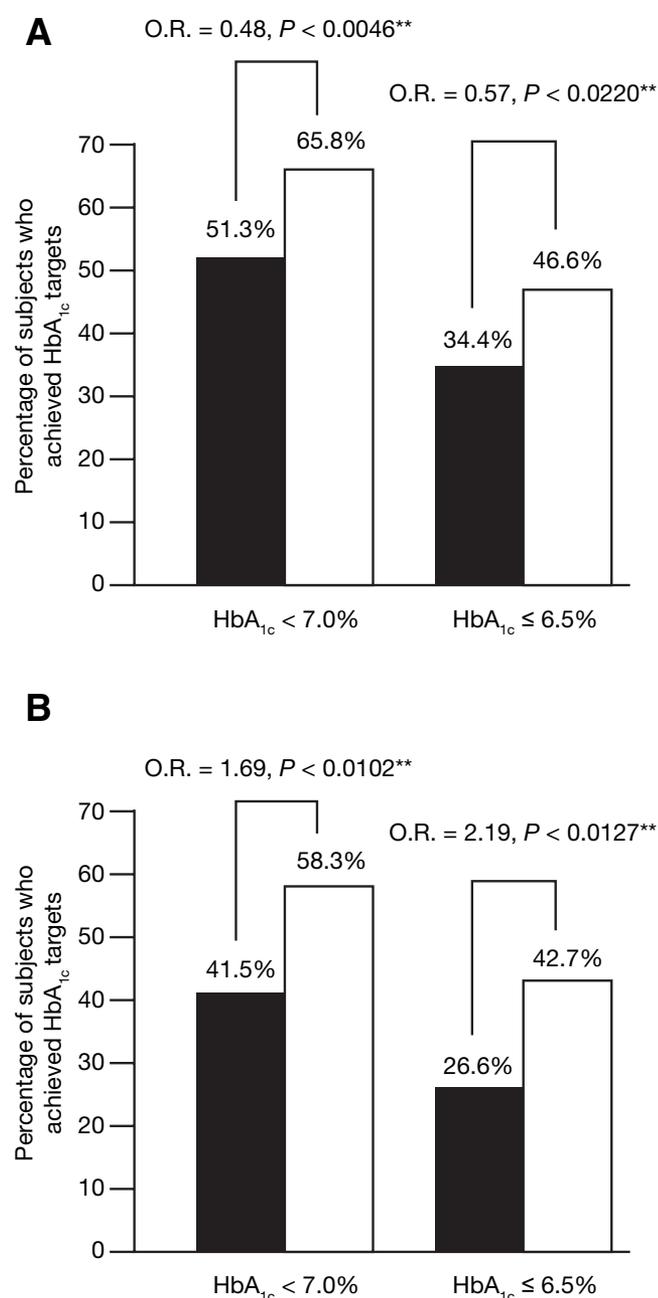
At the end of treatment, significantly more subjects in the TID BIAsp 30 group reached A1C targets than in the BID BIAsp 30 group (Fig. 2). In particular, in subjects with baseline A1C ≥9%, the percentages of subjects achieving an A1C target ≤6.5% with thrice-daily BIAsp 30 was 1.6-fold greater compared with those in the BID BIAsp 30 group (BID group 42.7% vs. TID group 26.6%; *P* < 0.05). No significant difference was observed in prebreakfast plasma glucose and 2-h postbreakfast plasma glucose between the groups.

**Hypoglycemia**

Major hypoglycemic episodes were experienced by one person (one event) in the BID BIAsp 30 group and three people (five events, one of which was nocturnal) in the TID BIAsp 30 group. Minor episodes were experienced by 23% of the BID group (a total of 91 events) and 19% of the TID group (65 events). The rates (episodes per subject-year) of overall major and minor hypoglycemia were 1.28 in the BID group and 0.96 in the TID group. For minor hypoglycemia, rates of 1.27 episodes per subject year in the BID BIAsp 30 group and 0.89 episodes per subject year in the TID BIAsp 30 group were recorded. There was no significant difference in the rate of overall (relative risk = 0.75, *P* = 0.32) and nocturnal (0.98, *P* = 0.97) major and minor hypoglycemia between treatments. In subjects who achieved an A1C target <7.0%, 43.9% of subjects in the BID group and 47.2% of subjects in the TID group had no hypoglycemia. Furthermore, the TID BIAsp 30 group showed a significantly lower risk of major and minor hypoglycemia compared with the BID BIAsp 30 group in this subpopulation (0.41, *P* < 0.05).

**Insulin doses and weight gain**

There was no significant difference in the total daily insulin dose between the two treatments (0.82 ± 0.28 units/kg for the BID and 0.86 ± 0.34 units/kg for TID groups; *P* = 0.19). In the BID BIAsp 30 group, the 50:50 split of the total insulin



**Figure 2**—The percentages of subjects who achieved A1C targets ( $\leq 6.5$  and  $< 7\%$ ). A: The percentages of subjects who achieved A1C targets in the main cohort. ■, twice-daily BIAsp 30; □, thrice-daily BIAsp 30. B: The percentages of subjects who achieved A1C targets in subjects with A1C baseline  $\geq 9\%$ . ■, twice-daily BIAsp 30; □, thrice-daily BIAsp 30.

daily dose initiated at the start of the trial was maintained by the end of the trial (prebreakfast and predinnertime doses were  $0.40 \pm 0.15$  and  $0.41 \pm 0.15$  units/kg, respectively), while those in the TID BIAsp 30 group were  $0.29 \pm 0.15$ ,  $0.22 \pm 0.11$ , and  $0.36 \pm 0.14$  units/kg (prebreakfast, prelunch, and predinner doses, respectively). The dose ratio at the end of trial in the thrice-daily treatment was similar to that at the start of trial.

Weight increased significantly in

both treatment groups. In the BID group, the increase was  $3.87 \pm 0.28$  kg (95% CI 3.323–4.417); for the TID group, the increase was  $4.09 \pm 0.27$  kg (3.549–4.626). There was no difference in weight gain between treatment groups.

#### Other safety parameters

All serious adverse events (BID group: three cases by three subjects; TID group: one case by one subject) were assessed as unlikely to be related to the treatment.

The end-of-treatment laboratory results in blood chemistry or hematology and the mean values for vital signs were similar to those at baseline in both groups.

**CONCLUSIONS**— As type 2 diabetes progresses, the need for insulin also increases and patients should receive adequate insulin therapy in order to improve glycemic control. But the consensus on how or when to initiate insulin treatment in type 2 diabetes is lacking, and insulin regimens are known to vary among countries (6,10). In China, diagnosis of diabetes and initiation of insulin therapy in patients with type 2 diabetes may be late due to lack of awareness. The UK Prospective Diabetes Study results showed that  $\beta$ -cell function was reduced by 50% at the time of diagnosis of fasting hyperglycemia (5). In our study, subjects had a long duration of diabetes ( $\sim 8$  years) and were in poor control (mean A1C at baseline was 9.5%), suggesting that the subjects in our trial would have very little  $\beta$ -cell function remaining. In addition, patients in China have relatively low BMI, so Chinese patients may have worse  $\beta$ -cell function compared with Caucasians when initiating insulin therapy, especially in those with a high A1C baseline. In this study, we aimed to compare, for the first time, the efficacy and safety of a twice- and thrice-daily regimen of BIAsp 30 (without OADs) in a group of patients whose baseline characteristics were similar to those seen in day-to-day practice in our clinics.

In our study, both the twice- and thrice-daily regimens were effective for insulin-naïve patients and resulted in significant A1C improvements. Insulin therapy with thrice-daily BIAsp 30 mediated a significantly greater reduction in A1C than twice-daily BIAsp 30 (A1C difference of 0.33%). The mean A1C at the end of the trial in the TID group was  $\sim 6.68\%$  lower than the A1C target ( $< 7\%$ ). Clinically, more subjects achieved the American Diabetes Association and International Diabetes Federation A1C targets with a thrice-daily BIAsp 30 regimen than with a twice-daily regimen. In subjects with baseline A1C  $\geq 9\%$ , the advantage of thrice-daily BIAsp 30 was more notable than twice-daily treatment; A1C achieved greater reductions with thrice-daily BIAsp 30 compared with subjects in the main cohort. These improvements with a thrice-daily regimen were seen despite no significant difference in total daily dose. By spreading the dose equally between three meals rather

than just two, the additional BIAsp 30 injection may be more suitable for Chinese patients who have a heavy lunch. The thrice-daily regimen provided prandial insulin coverage at lunch, in addition to breakfast and dinner, compared with twice-daily BIAsp 30. Thrice-daily BIAsp30 may be more physiological for Chinese patients with poor  $\beta$ -cell function and a heavy lunch. Both fasting plasma glucose and postbreakfast plasma glucose contribute to A1C (11), though our study showed that there was no difference between treatment groups in fasting plasma glucose or post-breakfast plasma glucose after breakfast. We propose, therefore, that the third lunch-time injection lowered postbreakfast plasma glucose after lunch to such an extent that overall glycemia, as measured by A1C, was significantly reduced, though we do not have the data to verify this.

The extent of the improvement in glycemia was similar to that reported in the INITIATE study (3). In the INITIATE study, where a similar titration algorithm was used, A1C was reduced by 2.8% with twice-daily BIAsp 30. Twice-daily BIAsp 30 allowed 42 and 66% of subjects achieve the A1C targets  $\leq 6.5\%$  and  $< 7\%$ , respectively, after 28 weeks of treatment. It is worthy to note that the extent of glycemia achieved with our study was through insulin alone, since all OADs were discontinued at the start of the trial. A number of trials have shown that when used in combination with metformin, the effects of BIAsp 30 are far greater than when used alone (11,12). One may wonder, therefore, if greater improvements in glycemia may have been achieved had metformin been used? A study investigating the most optimal treatment regimen using BIAsp 30 initiated in type 2 diabetic patients is still called for.

There was no difference in overall major and minor hypoglycemia between treatments. In subjects who achieved A1C  $< 7\%$ , the rate of major and minor hypoglycemia was significantly lower in the TID BIAsp 30 group than the BID BIAsp 30 group ( $P < 0.05$ ). This suggests that by spreading the dose more evenly throughout the day, with lower doses at each injection, there is less risk of hypoglycemia, without compromising glycemia. In addition, the rates of minor hypoglycemia observed in our study are lower than those reported for the twice-daily BIAsp 30 regimen in the INITIATE study (3.4 episodes per patient per year), where similar reductions in A1C

were achieved (3). However, there were different blood glucose hypoglycemia definitions between the two studies; for INITIATE, the blood glucose level was  $< 3.1$  mmol/L, whereas our study was lower at 2.8 mmol/L. This may explain the apparent lower rate of hypoglycemia seen in our study. Moreover, the treatment of insulin combined with OADs may explain the higher rate of hypoglycemia in the INITIATE study compared with the use of insulin only in our study.

The total daily insulin dose in the two treatment groups was similar by the end of the study, suggesting that greater glycemic control can be achieved if the total daily dose is spread more evenly throughout the day. Once again, the BID BIAsp 30 group of the INITIATE study reported almost identical total daily insulin doses ( $0.82 \pm 0.40$  units/kg). The proportion of total daily insulin doses of each injection (1:1 for twice-daily BIAsp 30; 1:1:2 for thrice-daily BIAsp 30) is a recommendable regimen but still needs further exploration.

Weight gain was similar between the two groups and indeed similar to that seen in patients receiving twice-daily BIAsp 30 in the INITIATE study (3). Patients coming from such poor glycemic control often experience some weight gain when they achieve good control (12). We may expect greater improvements in glycemia and less weight gain if metformin had been added. Of course, it is still essential, therefore, to reinforce diet and lifestyle advice when starting insulin to limit any weight gain.

In conclusion, as an insulin initiation regimen, both twice- and thrice-daily BIAsp 30 regimens were efficacious and well tolerated in the treatment of insulin-naïve subjects with type 2 diabetes. Patients with very poor glycemic control ( $\geq 9\%$  A1C) can achieve greater reductions in A1C, and more patients achieved A1C targets with a thrice- versus twice-daily BIAsp 30 regimen. Furthermore, by spreading the dose more evenly throughout the day with thrice-daily BIAsp 30, the risk of hypoglycemia was not increased with better glycemic control.

**Acknowledgments**— This trial was financially supported by Novo Nordisk (China).

The authors thank and acknowledge the work of the staff at all participating hospitals and clinical laboratories. Thanks to Novo Nordisk CRO, Hong Rao, Xiaosun Lu, and Yan Zhou for their technical support.

## References

- Nathan DM: Finding new treatments for diabetes: how many, how fast. . . how good? *N Eng J Med* 356:437–440, 2007
- Raskin P, Matfin G, Schwartz SL, Chaykin L, Chu PL, Braceras R, Wynne A: Addition of biphasic insulin aspart 30 to optimized metformin and pioglitazone treatment of type 2 diabetes mellitus: the ACTION study (Achieving Control Through Insulin plus Oral ageNts) *Diabetes Obes Metab*, 2007 (Epub ahead of print)
- Raskin P, Allen E, Hollander P, Lewin A, Gabbay RA, Hu P, Bode B, Garber A, the INITIATE Study Group: Initiation insulin therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care* 28:260–265, 2005
- Garber A, Wahlen J, Wahl T, Bressler P, Braceras R, Allen E, Jain R, the 1–2–3 Study Group: Attainment of glycaemic goals in type 2 diabetes with once-, twice-, or thrice-daily dosing with biphasic insulin aspart 70/30 (the 1–2–3 study). *Diabetes Obes Metab* 8:58–66, 2006
- Matthews DR, Cull CA, Stratton IM, Holman RR, Turner RC: UKPDS 26: sulphonylurea failure in noninsulin-dependent diabetic patients over six years. UK Prospective Diabetes Study (UKPDS) Group. *Diabetes Med* 15:297–303, 1998
- American Diabetes Association: Standard of medical care in diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1):S15–S35, 2004
- IDF Clinical Guidelines Task Force: Global guideline for type 2 diabetes: recommendations for standard, comprehensive, and minimal care. *Diabet Med* 23: 579–593, 2006
- Pan C, Yang W, Jia W, Weng J, Tian H: Current diabetes care status in China: an observational survey study (DIABCARE 2006) (EASD abstract 1021).
- Pan XR, Yang WY, Li GW, et al. Prevalence of diabetes and its risk factors in China, 1994. National Diabetes Prevention and Control Cooperative Group. *Diabetes Care* 20(11):1664–1669, 1997
- Wright A, Burden AC, Paisey RB, Cull CA, Holman RR Sulphonylurea Inadequacy: Efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective diabetes Study (UKPDS 57). *Diabetes Care* 25:330–336, 2002
- Monnier L, Lapinski H, Colette C: Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 patients: variations with increasing levels of HbA<sub>1c</sub>. *Diabetes Care* 26:881–885, 2003
- UK Prospective Diabetes Study (UKPDS) Group: Intensive, blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998