

Using continuous glucose monitoring to measure the frequency of low glucose values when using biphasic insulin aspart 30 compared with biphasic human insulin 30: a double-blind crossover study in individuals with type 2 diabetes

Running title: Low interstitial glucose at night with BIAsp 30

Received for publication 26 June 2006 and accepted in revised form 21 January 2007.

Paul G McNally, MD, FRCP¹; John D Dean, MD²; Andrew D Morris, MD³; Peter D Wilkinson, MA⁴; Gerhard Compion, MD⁵; Simon R Heller, DM, FRCP⁶

¹ Leicester Royal Infirmary NHS Trust, Leicester, UK

² Bolton Diabetes Centre, Bolton PCT/Bolton Hospitals NHS Trust, Bolton, UK

³ Division of Medicine & Therapeutics, Ninewells Hospital, Dundee, Scotland, UK

⁴ Wilkinson Associates, Radnage, Bucks, UK

⁵ Novo Nordisk Ltd, Broadfield Park, Crawley, West Sussex, UK

⁶ **Corresponding author:**

Dr Simon Heller
Reader in Medicine
Academic Unit of Diabetes, Endocrinology and Metabolism
Room OU141
School of Medicine and Biomedical Sciences
Beech Hill Road
Sheffield S10 2RX
UK

Email: s.heller@sheffield.ac.uk

An online appendix is available at <http://dx.doi.org/10.2337/dc06-1328>.

Abstract

Objective: Rapid-acting insulin analogs in basal-bolus regimens can reduce nocturnal hypoglycemia, so it is conceivable that twice-daily biphasic insulin analogs might reduce hypoglycemia in patients with insulin-treated type 2 diabetes. We used continuous glucose monitoring (CGMS) and self-reported episodes to investigate differences in the frequency of low glucose values in patients with type 2 diabetes, using either biphasic insulin aspart (BIAsp 30) or biphasic human insulin (BHI 30).

Research Design and Methods: A double-blind, two-period, cross-over trial involving 160 subjects. After 8-weeks' run-in, subjects were randomized to the first of two 16-week treatment periods.

Results: No differences in overall incidence of low interstitial glucose (LIG) were found. 24-h plots of CGMS showed LIG was more frequent at night as during the day, and unrecognized by patients. At night, subjects spent significantly less time (% of total CGMS recorded) with IG <3.5 and <2.5 mmol/l during BIAsp 30 than during BHI 30 treatment (<3.5 mmol/l: 6.36 vs. 7.93% [mean], 0.67 vs. 2.43% [median], respectively, $P = 0.018$; <2.5 mmol/l: 2.35 vs. 2.86% [mean], 0 vs. 0% [median], $P = 0.0467$). No treatment difference in HbA_{1c} was observed.

Conclusions: Overall rates of low glucose over 24 h were not different, but were twice as frequent at night as during the day in individuals with type 2 diabetes. Compared with BHI 30, BIAsp 30 was associated with similar low IG readings over 24 h, but fewer nocturnal episodes and less self-reported nocturnal hypoglycemia.

Trial registration details- This trial was registered at ISRCTN, registration number: ISRCTN34091554 and at ClinicalStudyResults.org, Unique ID: BIASP-1466.

Introduction

Insulin is being used earlier in the management of type 2 diabetes to achieve tighter glucose targets, but weight gain and in particular, hypoglycemia, remain important barriers to the success of treatment (1). The progression from oral agents to combination therapy involving insulin, or insulin monotherapy, increasingly includes the use of insulin analogs. This is particularly true for premixed biphasic insulin combinations, although the evidence for benefit compared with conventional premixed insulin is relatively limited.

In basal-bolus regimens, the inclusion of rapid acting insulin analogs is associated with reduced nocturnal hypoglycemia relative to soluble human insulin (2). It is possible that similar effects may also be observed with biphasic insulin preparations.

We set out to test this hypothesis in a clinical trial (the REACH study – Randomized Evaluation of premix insulin BIAsp30 in Controlling Hypoglycemia in type 2 diabetes) comparing the newer, more physiological, premix analog, biphasic insulin aspart 30 (BIAsp 30: 30% aspart, 70% protaminated aspart) with the conventional human premix, biphasic human insulin 30 (BHI 30: 30% regular insulin, 70% NPH insulin), using continuous glucose monitoring by CGMS and self-reported episodes to record the incidence of hypoglycemia.

Research Design and Methods

Setting and patient population

A total of 160 male and female patients with type 2 diabetes (BMI <40 mg/kg², HbA_{1c} <9.5%) pre-treated with insulin for at least 6 months were recruited to this randomized, double-blind, two-period, crossover trial from 18 centers in the UK. All oral antidiabetic drugs were stopped at study entry. Patients with a history of severe hypoglycemia or hypoglycemia unawareness were not specifically excluded. Baseline characteristics are shown in Table 1. The trial was performed in accordance with the Declaration of Helsinki and Good Clinical Practice. Patients gave written informed consent before any trial-related activities began.

Treatment regimens

During an 8-week run-in, existing insulin therapy was optimized to achieve pre-prandial blood glucose (BG) levels of 5–7 mmol/l. Patients with HbA_{1c} 6.5–8.5% were then randomized to receive BIAsp 30 (n=70), 100 U/ml, or BHI 30 (n=75), 100 U/ml, contained in 3 ml Penfill[®] administered using NovoPen[®] 3. Randomization was carried out by allocating the next available randomization number to each patient, and allocating treatment sequence using a computer-generated code with a block size of four. Randomisation was undertaken centrally with the randomisation number containing information about the treatment for each patient sealed throughout the trial. To maintain the double-blinded trial design, both insulins were injected immediately before breakfast and evening meal (it was deemed unsafe to allow any

injection-meal interval for BIAsp 30 due to the rapid action of insulin aspart). After the first 16-week treatment period, patients switched to the alternative insulin for a further 16 weeks, with no washout period. Throughout the trial, participants were free to adjust the dose (in discussion with research staff) according to individual needs once-a week. No specific instructions were given with regard to evening exercise or snacks.

Continuous glucose monitoring system (CGMS)

Interstitial glucose (IG) was recorded with the MiniMed Continuous Glucose Monitoring System (CGMS; Medtronic Diabetes, Northridge, CA, USA) over four 72-hour periods (two for each treatment period, half way through and at the end of each treatment period). CGMS was performed on normal weekdays and patients were advised to not partake in strenuous exercise during the recording period.

The monitor recorded IG levels every 10 seconds then stored a smoothed average over 5 minutes. The range of IG detection was 2.2–22 mmol/l. The primary endpoint was the frequency of readings below 3.5 mmol/l (IG_{3.5}). IG readings <2.5 mmol/l (IG_{2.5}) were also compared since studies suggest that glucose <2.8 mmol/l is likely to reflect clinically relevant hypoglycemia (3,4).

The 24-hour data were categorized into total, daytime (06:00–midnight) and night-time (midnight–06:00). Low IG readings were also grouped into 'episodes', defined as a set of continuous IG readings <3.5 (or <2.5) mmol/l, allowing up

to two consecutive readings above threshold within the same episode. If a following episode started within 1 h of the start of the previous episode, they were combined and recorded as one episode.

Self-monitoring of blood glucose and self-reported episodes of hypoglycemia

Subjects recorded self-monitored blood glucose (SMBG) using a LifeScan One Touch meter (High Wycombe, UK), to allow regular insulin dose titration. Targets for fasting and pre-prandial BG were 5–7 mmol/l. Measurements were recorded in patients' diaries, but only transferred to the case report form (CRF) in the event of hypoglycemia. Episodes of hypoglycemia were classed as minor if the patient was able to self-treat and BG was <2.8 mmol/l (or 'symptoms only' if BG was ≥2.8 mmol/l or not measured), or *major* if patients were unable to self-treat.

Adverse events

Adverse events were defined as any undesirable medical event occurring during the trial period. Events were classed as serious if they resulted in death, were life-threatening or caused (or prolonged) hospitalization.

HbA_{1c}, laboratory tests and safety parameters

HbA_{1c} was assessed at screening, randomization and at the end of the two treatment periods.

Diabetes Treatment Satisfaction

The WHO Diabetes Treatment Satisfaction Questionnaire (WHO DTSQ) was completed by all subjects at visits 3, 7 and 11. The questionnaire consists of six items rated on a 7-point Likert scale,

which can be summarized in an overall treatment satisfaction score from 0 to 36, where a higher score indicates greater satisfaction.

Statistical analyses

HbA_{1c} and CGMS data were analyzed using a mixed model analysis of variance appropriate to the crossover design using the 'PROC MIXED' procedure in SAS[®]. This adjusts for differences in characteristics (such as age and weight) between the groups assigned to each insulin. Where the CGMS data were not normally distributed, data were transformed by adding 1 and using a logarithmic transformation, or alternatively using a rank-based transformation or the Wilcoxon signed rank test. An intention to treat (ITT) analysis was undertaken with the ITT population defined as all randomised patients who took study medication and had at least one follow-up value.

Self-reported hypoglycemia was tested using the Wilcoxon signed rank test; the timing of low IG episodes was tested using the Kruskal-Wallis Test, and proportions were tested using Fishers Exact test.

Missing HbA_{1c} values at visit 2 were replaced by the visit 1 value for the same patient, using the last observation carried forward method. No other missing data were replaced in the study.

Results

The trial profile is shown in Figure 1. HbA_{1c} at follow-up was not obtained for 13 patients, leaving 147 in the ITT population. The CGMS population was based on data collected from 145 patients (CGMS data were incomplete for 15 patients). Some minor

differences in mean height, weight and BMI were seen between the two groups receiving BIAsp 30 or BHI 30 first, due to the higher proportion of males in the latter group (Table 1).

Insulin dose

Mean (\pm SD) total daily insulin doses at the end of the treatment periods were 68.8 \pm 37.8 U for BIAsp 30 [median (range): 59.0 (6.0–238.7)] and 66.6 \pm 34.6 U for BHI 30 [median (range): 58.0 (11.3–240.0)].

Morning doses were larger than evening doses for both treatments - *morning* dose 36.0 \pm 20.2 U for BIAsp 30 [median (range): 32.0 (4–120)] vs. 34.6 \pm 18.9 IU for BHI 30 [median (range): 32.0 (5–130)]; *evening* dose means \pm SD: 33.0 \pm 19.0 U [median (range): 28.0 (2.0–118.7)] vs. 32.0 \pm 17.4 IU [median (range): 28.0 (4.0–110.0)], respectively.

Continuous glucose monitoring system (CGMS)

The mean total number of IG readings recorded per subject was 1477 during BIAsp 30 treatment and 1468 with BHI 30 treatment.

At least one episode of IG_{3.5} was recorded (at any time) by 82% of patients during each treatment period - BIAsp 30 and BHI 30 ($P = 1.0$). For IG_{2.5}, the occurrence was 46% and 54%, respectively ($P = 0.28$). The percentages of patients that recorded at least one low IG episode (IG_{3.5} or IG_{2.5}) during day and night time periods were as follows:

Day time occurrence – IG_{3.5}: 73% with BIAsp 30, 70% with BHI 30 ($P = 0.60$); IG_{2.5} 41% during each treatment ($P = 0.10$).

Night time occurrence – IG_{3.5}: 51% with BIAsp 30, 66% with BHI 30 ($P = 0.015$); IG_{2.5}: 25% and 37%, respectively ($P = 0.039$).

Number of low IG episodes from CGMS

There were no significant differences in the total or daytime number of IG_{3.5} episodes/patient/week between the two treatment arms, but night-time IG_{3.5} episodes were significantly less frequent with BIAsp 30 than with BHI 30.

Total [median (range)]: 3.0 (0–16) vs. 3.0 (0–20), for BIAsp 30 vs. BHI 30, respectively; means (SD): 3.76 (3.60) vs. 3.93 (3.64); $P = 0.62$.

Daytime [median (range)]: 2.0 (0–13) vs. 2.0 (0–18), for BIAsp 30 vs. BHI 30, respectively; means (SD): 2.58 (2.79) vs. 2.36 (2.67); $P = 0.32$.

Night-time [median (range)]: 1.0 (0–8) vs. 1.0 (0–7) respectively; means (SD): 1.18 (1.56) vs. 1.62 (1.71); $P = 0.011$

For IG_{2.5} episodes, there were no statistically significant differences between treatments (total, day or night; data not shown). There were also no significant differences in duration of IG_{3.5} or IG_{2.5} episodes (total, day or night) between BIAsp 30 and BHI 30, although night-time episodes tended to be longer than daytime episodes (data not shown).

24-hour distribution of low IG episodes from CGMS

The hourly frequency of IG_{3.5} over 24 h is shown in Fig 2A. The nocturnal frequency was higher than the daytime frequency for both treatments. BHI 30 treatment resulted in a peak frequency of

IG_{3.5} at 0500–0600 h compared with 0200–0300 h for BIAsp 30. Both treatments showed a small peak at lunchtime. The overall difference in timing of IG_{3.5} was statistically significant ($P < 0.001$). A similar pattern was seen for IG_{2.5}, but data were 70% less frequent.

Percentage of time spent with IG <3.5 and <2.5 mmol/l

Total: the percentage of time spent with IG <3.5 or <2.5 mmol/l tended to be lower for BIAsp 30 than with BHI 30, but differences were not statistically significant.

Daytime: there were no significant differences between treatments for IG_{3.5} or IG_{2.5}.

Night-time: the percentage of time spent with IG_{3.5} or IG_{2.5} was significantly lower for BIAsp 30 than for BHI 30.

Self-reported hypoglycemia

The percentage of patients that reported any episodes of minor hypoglycemia was 90% and 84%, for BIAsp 30 and BHI 30 therapy, respectively. Two episodes of major hypoglycemia were reported during BIAsp 30 treatment (one each for two patients), compared with seven episodes (from five patients) during BHI 30 treatment (too few episodes to allow statistical analysis).

Rates of self-reported hypoglycemia

Mean total and daytime rates of hypoglycemia were similar for BIAsp 30 and BHI 30. Rates of nocturnal hypoglycemia were significantly lower with BIAsp 30 1.5 (4.54) compared to BHI 30 treatment 3.8 (8.0) episodes per patient per year, ($P = 0.002$).

24-hour timing of hypoglycemic episodes from CRF

The hourly frequency of self-reported hypoglycemia over 24 h is shown in Fig 2B. The highest peak for both treatments occurred at lunchtime, with a second peak observed later in the day, although this tended to be earlier with BHI 30 than with BIAsp 30. Most symptomatic night-time episodes during treatment with BHI 30 occurred between the hours of 3–7am and were more frequent than those experienced during treatment with BIAsp 30, which tended to occur slightly earlier.

Adverse events

While receiving BIAsp 30, 58% of patients reported a total of 189 adverse events, while 56% of patients reported 217 events while receiving BHI 30. Only 4% and 6% of these were serious for BIAsp 30 and BHI 30 treatment, respectively.

HbA_{1c}, laboratory tests

Following the run-in period, the overall mean HbA_{1c} was 7.46%. After BIAsp 30 treatment, patients achieved a mean HbA_{1c} of 7.28%, compared with 7.22% after BHI 30. The treatment difference of 0.06% (BIAsp 30 - BHI 30) was not statistically significant (95% CI [-0.04; 0.17]%, $P = 0.21$).

Diabetes Treatment Satisfaction

There were no between-treatment differences in overall DTSQ score (mean \pm SD: 30.60 \pm 5.84 vs. 30.95 \pm 5.01, for BIAsp 30 and BHI 30, respectively; treatment difference: -0.46, $P = 0.25$).

Conclusions

CGMS is a useful tool for assessing daily glucose fluctuations (5) but has certain limitations: it measures glucose concentrations in the extracellular interstitium rather than in the intravascular space. The relationship between glucose concentrations in these two compartments is not straightforward and may alter according to physiological variation in insulin concentration, and glucose uptake, utilization and elimination (6,7). These limitations are countered by the ability to record continuous glucose data and detect unrecognized hypoglycemic episodes (8–13). Most studies to date have involved patients with type 1 diabetes, and there is relatively little information describing CGMS in type 2 diabetes.

In the present study, CGMS demonstrated that rates of IG <3.5 and <2.5 mmol/l at night were around double those during the day in patients with type 2 diabetes treated with premixed insulins BIAsp 30 and BHI 30. This is contrary to the general perception – based on self-reported data (14,15) – that nocturnal hypoglycemia is uncommon in type 2 diabetes. Indeed, we also found that in contrast to the CGMS data, self-reported episodes were highest during the day. The majority of nocturnal episodes were therefore unrecognized, although it is unsurprising that patients fail to wake when mildly hypoglycemic at night. There is evidence in type 1 diabetes that asymptomatic nocturnal hypoglycemia may induce hypoglycemia unawareness (16), but the clinical relevance of our

findings in type 2 subjects is uncertain.

Generally, the distribution of self-reported episodes of hypoglycemia corroborates the CGMS data, increasing our confidence that these findings are robust. The shapes of the two frequency profiles were similar, with both identifying a peak in occurrence of low glucose at lunchtime. However, self-reported episodes at lunchtime were higher during BIAsp 30 treatment than during BHI 30 treatment (opposite to the pattern at night). Thus, there was no overall difference in the frequency of self-reported hypoglycemia.

Our CGMS data show that BIAsp 30 twice-daily led to significantly fewer nocturnal episodes of IG <3.5 mmol/l than twice-daily BHI 30. Furthermore, the percentage of time patients spent with IG below 3.5 and 2.5 mmol/l at night was lower during treatment with BIAsp 30. Since total daily insulin doses were similar for both insulins, differences in the frequencies of low IG readings may reflect differences in insulin kinetics. The faster onset and shorter duration of the rapid-acting analog, insulin aspart, contained in BIAsp 30 (17,18) may explain the difference in the time of the peak frequency of nocturnal low IG readings, which occurred at 3 am with BIAsp 30 compared with 6 am for BHI 30. Self-reported, symptomatic nocturnal hypoglycemia was also significantly lower with BIAsp 30 than with BHI 30, suggesting these differences are clinically relevant.

The data on the timing of low glucose values in this study may

help to guide the dose of premixed insulins containing rapid acting insulin analogs. Our data suggest that when moving from BHI 30 to BIAsp 30, the pre-breakfast dose should be reduced to lower the risk of pre-lunch hypoglycemia, and the pre-dinner dose increased (keeping the overall total insulin dose the same). This should effectively move the ratio of doses towards a ½ – ½ split, as observed in other recent studies (19–21). Furthermore, because of the observed peak in low glucose values at lunchtime, pre-lunch rather than pre-dinner blood glucose levels may be a safer target for adjusting the pre-breakfast dose of a premixed insulin.

In conclusion, nocturnal low glucose levels in patients with type 2 diabetes using twice daily insulin may be more frequent than supposed. The use of BIAsp 30 was associated with similar overall rates of low IG and symptomatic hypoglycemia than BHI 30, but fewer episodes at night, probably reflecting the longer duration of action of regular human insulin relative to insulin aspart. These data suggest that a more aggressive approach to achieving glucose targets, particularly lower fasting glucose may be safer when using preparations containing fast-acting insulin analogs.

Acknowledgements

The following investigators participated in the REACH study: Dr. J. Alcolado, University Hospital of Wales; Dr. J. Dean, Bolton PCT/Bolton Hospital NHS Trust; Dr. M. Fisher, Glasgow Royal Infirmary; Prof. A. Hattersley,

University of Exeter; Dr. S. Heller, Northern General Hospital; Prof. P. Home, University of Newcastle; Dr. D. Hopkins, Central Middlesex Hospital; Dr. R. Jones, St. Thomas's Hospital; Dr. J. Lorains, Clatterbridge Hospital; Dr. P. McNally, Leicester Royal Infirmary; Prof. A. Morris, Ninewells Hospital & Medical School; Prof. T. O'Brien, University College Hospital, Galway;

Dr. S. Page, QMC, Nottingham; Prof. R. Donnelly and Dr. A. Scott, Derby City General Hospital; Dr. J. Thow, York District Hospital; Dr. J. Vora, Royal Liverpool University Hospital; Dr. S. Gray, St. John's Hospital; and Dr. D. Bowen-Jones, Arrowe Park Hospital.

For editorial assistance, the authors wish to thank Scott Gouveia.

References

1. Leese PG, Wang J, Broomhall J, Kelly P, Marsden A, Morrison W, Frier BM, Morris AD, for the DARTS/MEMO Collaboration: Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes. *Diabetes Care* 26:1176–1180, 2003
2. Heller SR, Colagiuri S, Vaaler S, Wolffenbuttel BH, Koelendorf K, Friberg HH, Windfeld K, Lindholm A: Hypoglycemia with insulin aspart: a double-blind, randomized, crossover trial in subjects with Type 1 diabetes. *Diabet Med* 21(7):769–775, 2004
3. Høi-Hansen T, Pedersen-Bjergaard U, Thorsteinsson B: Reproducibility and reliability of hypoglycemic episodes recorded with Continuous Glucose Monitoring System (CGMS) in daily life. *Diabet Med* 22(7):858–862, 2005
4. Monsod TP, Flanagan DE, Rife F, Saenz R, Caprio S, Sherwin RS, Tamborlane WV: Do sensor glucose levels accurately predict plasma glucose concentrations during hypoglycemia and hyperinsulinemia? *Diabetes Care* 25(5):889–893, 2002
5. Brynes AE, Lee JL, Brighton RE, Leeds AR, Dornhorst A, Frost GS: A low glycemic diet significantly improves the 24-h blood glucose profile in people with type 2 diabetes, as assessed using the continuous glucose MiniMed monitor. *Diabetes Care* 26(2):548–549, 2003
6. Aussedat B, Dupire-Angel M, Gifford R, Klein JC, Wilson GS, Reach G: Interstitial glucose concentration and glycemia: implications for continuous subcutaneous glucose monitoring. *Am J Physiol Endocrinol Metab* 278(4):E716–728, 2000
7. Kulcu E, Tamada JA, Reach G, Potts RO, Lesho MJ: Physiological differences between interstitial glucose and blood glucose measured in human subjects. *Diabetes Care* 26(8):2405–2409, 2003
8. Chico A, Vidal-Rios P, Subirà M, Novials A: The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemia in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control. *Diabetes Care* 26(4):1153–1157, 2003
9. Kapitza C, Ludwig V, Obermaier K, Wientjes KJ, Hoogenberg K, Jungheim K, Heineman L, Glucose Monitoring Study Group: Continuous glucose monitoring: reliable measurements for up to 4 days with the SCGM1 system. *Diabetes Technol Ther* 5(4):609–614, 2003
10. Sachedina N, Pickup JC: Performance assessment of the Medtronic-MiniMed Continuous Glucose Monitoring System and its use for measurement of glycemic control in type 1 diabetic subjects. *Diabet Med* 20(12):1012–1015, 2003
11. Conrad SC, Mastrototaro JJ, Gitelman SE: The use of a continuous glucose monitoring system in hypoglycemic disorders. *J Pediatr Endocrinol Metab* 17(3):281–288, 2004
12. Goldberg PA, Siegel MD, Russel RR, Sherwin RS, Halickman JI, Cooper DA, Dziura JD, Inzucchi SE: Experience with continuous

- blood glucose monitoring system in a medical intensive care unit. *Diabetes Technol Ther* 6(3):339–347, 2004
13. Weintrob N, Schechter A, Benzaquen H, Shalitin S, Lilos P, Galatzer A, Phillip M: Glycemic patterns detected by continuous subcutaneous glucose sensing in children and adolescents with type 1 diabetes mellitus treated by multiple daily injections vs continuous subcutaneous insulin infusion. *Arch Pediatr Adolesc Med* 158(7):677–684, 2004
 14. 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
 15. Miller CD, Phillips LS, Ziemer DC, Gallina DL, Cook CB, El-Kebbi IM: Hypoglycemia in patients with type 2 diabetes mellitus. *Arch Intern Med* 161(13):1653–1659, 2001
 16. Veneman T, Mitrakou A, Mokan M, Cryer P, Gerich J: Induction of hypoglycemia unawareness by asymptomatic nocturnal hypoglycemia. *Diabetes* 42(9):1233–1237, 1993.
 17. Home PD, Barriocanal L, Lindholm A: Comparative pharmacokinetics and pharmacodynamics of the novel rapid-acting insulin analog, insulin aspart, in healthy volunteers. *Eur J Clin Pharmacol* 55(3):199–203, 1999
 18. Mudaliar SR, Lindberg FA, Joyce M, Beerdsen P, Strange P, Lin A, Henry RR: Insulin aspart (B28 asp-insulin): a fast-acting analog of human insulin: absorption kinetics and action profile compared with regular human insulin in healthy nondiabetic subjects. *Diabetes Care* 22(9):1501–1506, 1999
 19. Raskin P, Allen E, Hollander P, Lewin A, Gabbay RA, Hu P, Bode B, Garber A; INITIATE Study Group: Initiating insulin therapy in type 2 Diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care* 28(2):260–265, 2005
 20. Kann P, Regulski M, Medding J: Twice-daily biphasic insulin aspart 30 plus metformin compared with once-daily insulin glargine in combination with glimepiride in type 2 diabetes. *Endocrine Abstracts* 10:OC8, 2005
 21. Garber AJ, Wahlen J, Wahl T, Bressler P, Braceras R, Allen E, Jain R: Attainment of glycemic 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(1):58–66, 2006

Table 1. Baseline characteristics of patients randomized to the study, split by treatment sequence.

	BIAsp 30 first	BHI 30 first	Both treatment sequences
<i>n</i>	80	80	160
Age (yrs)	61.8 ±9.5	62.7 ±8.7	62.3 ±9.1
Gender (M/F)	49/31	63/17	112/48
Height (m)	1.67 ±0.09	1.71 ±0.08	1.69 ±0.09
Body weight (kg)	83.3 ±14.5	89.1 ±14.0	86.2 ±14.5
BMI (kg/m ²)	29.7 ±4.5	30.5 ±4.8	30.1 ±4.7
HbA _{1c} (%)	7.5 ±0.7	7.5 ±0.7	7.5 ±0.7
Time since diagnosis (yrs)	11.5 ±7.6	12.1 ±8.5	11.8 ±8.0

Mean ±SD, number or percentage
 BIAsp 30: biphasic insulin aspart 30
 BHI 30: biphasic human insulin 30

Figure 1. Trial profile of subject flow. CGMS: continuous glucose monitoring system.

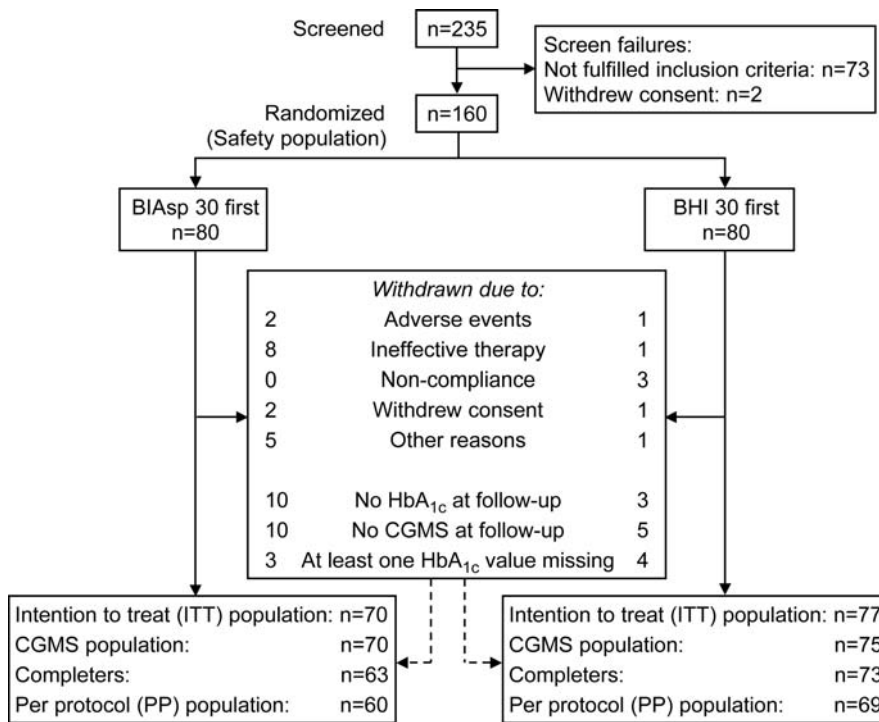


Figure 2. Twenty four-hour frequencies of: interstitial glucose readings <3.5 mmol/l measured by CGMS (A) and self-reported episodes of hypoglycemia (B), during treatment with twice-daily BIAsp 30 or BHI 30.

