Self-titration of biphasic insulin aspart 30/70 improves glycaemic control and allows easy intensification in a Dutch clinical practice

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A B S T R A C T

Aims: This 18-month study assessed the improvement in glycaemic control and proportion of patients reaching glycated haemoglobin (HbA1c) targets with biphasic insulin aspart 30/70 (BIAsp 30) in clinical practice.
Methods: Type-2 diabetes patients failing on oral antidiabetic drugs (n = 90) or existing insulin regimens (n = 59) started or switched to BIAsp 30. Thiazolidinediones were stopped, metformin was continued. BIAsp 30 was given once daily (n = 41), twice daily (n = 96), or three times daily (n = 12). Patients were taught self-monitoring and self-titration using an algorithm, adding daily doses of BIAsp 30 when necessary.
Results: Mean baseline HbA1c was 8.4%, weight 85.4 kg, and age 57.9 years. All patients experienced significant reductions in HbA1c (mean 1.9% ± 0.1), fasting plasma glucose (mean 2.8 mmol/l), and post-prandial glycaemia (mean 2.9 mmol/l); 91% of patients achieved HbA1c < 7% and 52% achieved HbA1c ≤ 6.5%. No major or nocturnal hypoglycaemia were reported; 15% of patients reported minor hypoglycaemia. Insulin-naïve patients gained mean 2.7 kg; patients who switched from another insulin lost weight (mean −0.6 kg).
Conclusion: The results from this study from routine care suggest that BIAsp 30 may allow a large proportion of type-2 diabetes patients (90%) to improve glycaemic control and reach target HbA1c < 7%, using self-titration.

1. Introduction

Good glycaemic control is of great clinical importance to health [1], and the progressive nature of type-2 diabetes makes insulin initiation a necessary therapeutic step for many patients. Each 1% rise in glycated haemoglobin (HbA1c) is estimated to increase the risk of mortality related to diabetes by 25% [2]. In order to limit long-term complications, the American Diabetes Association (ADA) has recommended a target HbA1c level of <7% [3], as has the Dutch Association for Family Practice [4]. The International Diabetes Federation (IDF) and the American Association of Clinical Endocrinologists (AACE) both recommend a level of 6.5% or lower [5].

Premixed insulin formulations comprise soluble insulin (to control mealtime glucose excursions) and intermediate-acting protaminated insulin (to address basal glucose levels). Insulin analogue premixes have been reported to achieve more rapid and higher peak insulin levels, faster and higher
maximum serum insulin concentrations, and a greater post-prandial plasma glucose (PPG) lowering effect than human premixes [6,7]. For example, biphasic insulin aspart 30/70 (BIAsp 30; NovoMix® 30, Novo Nordisk A/S, Denmark) reached peak serum concentrations 30–50% faster than biphasic human insulin (BHI) (P < 0.001), and the peak concentrations were 30–50% higher (P < 0.001) [6]. Owing to the improved pharmacokinetic and pharmacodynamic profiles, insulin analogues often achieve superior metabolic control compared with long- or intermediate-acting insulin, and also allow more flexible administration [8]. Furthermore, reported rates of major and nocturnal hypoglycaemia are lower with premixed insulin analogues than with BHI [9–11]. BIAsp 30 had a significantly lower rate of nocturnal hypoglycaemia than BHI (relative risk, 0.50, 95% confidence interval, CI [0.38, 0.67], P < 0.01), and a lower likelihood of major hypoglycaemia (odds ratio, 0.45 [0.22, 0.93], P < 0.05) [11].

In randomised controlled trials (RCTs), the HbA1c-lowering effect of premixed insulin analogues has been reported to be comparable to that of premixed human insulin [12]. Also, like the fast-acting analogues from which they are derived, premixed insulin analogues enable flexible injection timing relative to meals [6,13], thereby improving adherence, compliance, and quality of life compared with premixed human insulin. While treat-to-target studies have reported that the majority (~66–77%) of patients can achieve their treatment targets using biphasic insulin analogues [14,15], only ~25–30% of patients following the recommended guidelines actually achieve those targets in clinical practice settings [16,17].

As observational study methods continue to improve, their results have become an essential source of “real-life” clinical data [18,19]. In patients with diabetes, observational studies can indicate whether the improved glycaemic control associated with particular treatments in RCTs carries over into clinical practice. For instance, previous observational studies have reported that glycaemic control remains above recommended targets in many patients despite the use of insulin: only 34% of type-2 diabetes patients in the USA achieved HbA1c < 7% between 1999 and 2000 [17], and a large, longitudinal, population-based study in Germany and the UK reported that only 24% of 3600 patients achieved an HbA1c target of <7%, while 32% maintained HbA1c levels ≥9% [20].

The current open-label, non-randomised, prospective, observational study, which follows patients in an everyday clinical practice setting, aimed to: (1) assess the proportion of patients who could achieve a target HbA1c level of <7% using BIAsp 30, as has been reported in treat-to-target studies [14]; (2) examine the rates of hypoglycaemia among patients using BIAsp 30; (3) assess whether it is feasible to teach patients with type-2 diabetes to self-titrator on the basis of self-monitoring in routine care.

### 2. Methods

This was a study of patients with type-2 diabetes from a Dutch clinical practice, conducted during the 12 months beginning 1 January 2004. All patients with type-2 diabetes who were aged 21 years or more, and who were starting or switching to BIAsp 30, were eligible for inclusion. Patients who had reached a maximum dose of oral therapy and were not achieving glycaemic targets were started on BIAsp 30 according to their physician’s decision. Dutch guidelines for targets were closely followed [4], therefore, for example, two HbA1c measurements of 7.1%, with a 3-month interval, on maximum dose of oral therapy would lead to the physician’s recommendation of insulin initiation. The study was approved by the regional Ethics Committee, and an informed consent was obtained from each patient before the start of the study. Patients who needed to change from their existing insulin regimen (BHI, neutral protamine Hagedorn [NPH] insulin, insulin glargine), because of not reaching glycaemic control targets, were also entered into the study if their physician considered BIAsp 30 an appropriate new insulin option. Patients were excluded if they were unwilling to learn to self-titrator, or stated at the onset of the study that they were not willing to inject more than once a day. There were no other exclusion criteria.

#### 2.1. Treatment allocation

The starting treatment regimen of BIAsp 30 was determined according to HbA1c values at baseline and pre-study treatment; patients could start BIAsp 30 once (OD), twice (BD) or three times (TD) daily (Table 1). Insulin-naive patients were initiated with 6–24 U of BIAsp 30, while patients changing from an existing insulin regimen received the same dose of BIAsp 30 at baseline as their previous insulin but if HbA1c was < 8.5% the dose would be split over more injections. All patients were taught to self-monitor and self-titrator over a maximum period of 10 weeks at the start of insulin therapy, using a titration algorithm similar to that used in treat-to-target studies [15]. The dose titration schedule is shown in Table 2. Two algorithms were developed: one for pre-meal titration, another for post-meal titration. When patients had learned to use the pre-meal titration algorithm, the post-meal algorithm was introduced. Patients were instructed to titrate up their dose no more than twice a week with three days between changes, and if injecting twice or three times a day preferably only one dose change at a time; titrating down could be done whenever necessary. Diabetes nurses were available to assist patients at any time, as is standard in Dutch diabetes care. Patients were in telephone contact with the nurses after every series of blood glucose (BG) measurements, until they managed the titration comfortably. The nurses subjectively assessed each patient after every telephone call, and the dia-

<table>
<thead>
<tr>
<th>Table 1: Treatment initiation of biphasic insulin aspart 30 (BIAsp 30).</th>
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<tbody>
<tr>
<td>HbA1c at baseline (%)</td>
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<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>&lt;8.5</td>
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<tr>
<td>&lt;8.5</td>
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<tr>
<td>&lt;8.5</td>
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<tr>
<td>&gt;8.5</td>
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<tr>
<td>&gt;8.5</td>
</tr>
<tr>
<td>&gt;8.5</td>
</tr>
</tbody>
</table>

OD, once daily; BD, twice daily; TD, three times daily.
Table 2 – Dosing titration schedule used with biphasic insulin aspart 30 (BIAsp 30).

<table>
<thead>
<tr>
<th>Titration instruction</th>
<th>Pre-meal</th>
<th>Post-meal</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;8 mmol/lᵃ</td>
<td>+4 U until goal reached</td>
<td>&gt;12 mmol/l for 3 daysᵇ</td>
</tr>
<tr>
<td>6–8 mmol/lᵇ</td>
<td>+2 U until goal reached</td>
<td>9–12 mmol/l for 3 daysᵇ</td>
</tr>
<tr>
<td>4–6 mmol/l</td>
<td>No change</td>
<td>5–9 mmol/l</td>
</tr>
<tr>
<td>&lt;4 mmol/lᵇ</td>
<td>–2 U until goal reached</td>
<td>&lt;5 mmolᵇ</td>
</tr>
</tbody>
</table>

ᵃ If the mean glucose at three consecutive readings was in this range.
ᵇ One occasion.
ᶜ If HbA₁c >7% after 3 months, add 4 U BIAsp 30 at breakfast or lunch.

The therapy team decided on a weekly basis whether the patient had managed the titration and could stop the telephone contact.

2.2. Assessments

Patients were assessed at baseline and followed for 18 months, with follow-up appointments scheduled at 3-month intervals (standard practice at the clinic). Patients recorded all data in a diary. At each visit, a blood sample was taken for HbA₁c measurement, and analyses were carried out by the Havenziekenhuis laboratory, Rotterdam, The Netherlands.

Fasting plasma glucose (FPG) and PPG were self-measured, with PPG being measured 90–120 min after meals. At each visit, patient diaries were examined and FPG and PPG self-measurements noted in medical records. Patients were initially asked to perform measurements and provide one 7-point profile per week, consisting of three pre-prandial, three post-prandial, and one bedtime measurement. When titration had reached a stable state, this was changed to either a 4-point profile (pre-prandial and bedtime) or a 3-point post-prandial profile, once every 1 or 2 weeks in alternative order. Hypoglycaemic events were considered minor when the patient was able to treat the event without assistance; events were considered major when the patient needed help. Hypoglycaemic events were noted in a diary that patients handed in at their follow-up visits.

Therapy decisions were made by the physician according to standard clinical practice; treatment could be intensified to more injections if HbA₁c did not reach the target of 7%. BIAsp 30 was injected directly prior to meals: if OD, then before the evening meal, and if BD, before breakfast and the evening meal, plus before lunch if a third injection was needed.

Metformin was continued throughout the study, as were insulin secretagogues, but only if patients were using OD BIAsp 30. Thiazolidinediones were discontinued in all insulin-naive patients. Sulphonylurea preparations were continued while the patient was on one injection of BIAsp 30, but discontinued on the intensification to two injections daily.

The reasons why patients changed from existing insulin regimens to BIAsp 30 included: inadequate glycaemic control (including post-prandial control), problems injecting 30 min before meals, and problems with insulin pens.

2.2.1. Outcome measures

The primary outcome measure was HbA₁c level; secondary outcome measures included FPG level, PPG level, hypoglycaemic events, and weight.

2.2.2. Statistical analyses

Data were analysed according to prior insulin therapy and overall. Within-group changes from baseline were tested for statistical significance using a paired t-test, and changes from baseline between previous treatment groups were tested for differences using ANCOVA (analysis of covariance), with the baseline value of the parameter as the covariate. Episodes of hypoglycaemia were summarised using frequency tables. Within-group changes from baseline were tested for statistical significance using the Wilcoxon signed rank test.

3. Results

A total of 150 patients were included in the study, and seven were excluded (four did not want to learn to self-titrate, and three refused the possibility of multiple injections).

Over the first 4 weeks, patients approached the diabetes nurses on average twice a week; 21 of 149 patients kept up this frequency for longer periods. After 18 months, one elderly patient still needed regular advice on insulin dose adjustment, and five patients frequently made incorrect decisions when adjusting their insulin dose (three of these five patients did not get to the stage of the post-prandial self-titration).

Table 3 – Baseline characteristics of patients by previous treatment (mean values).

<table>
<thead>
<tr>
<th>Insulin-naive</th>
<th>Prior insulin treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>91</td>
</tr>
<tr>
<td>Age, years (range)</td>
<td>56.7 (34–79)</td>
</tr>
<tr>
<td>Male/female</td>
<td>41/50</td>
</tr>
<tr>
<td>Weight, kg (range)</td>
<td>83.5 (56.1–124.2)</td>
</tr>
<tr>
<td>Diabetes duration, years (range)</td>
<td>6.7 (4.2–9.7)</td>
</tr>
<tr>
<td>HbA₁c, % (range)</td>
<td>8.5 (7.1–12.7)</td>
</tr>
</tbody>
</table>

NPH, neutral protamine Hagedorn; BHI, biphasic human insulin.
For example, one patient never adjusted his insulin dose to the high glucose readings he was getting because he blamed them on stress, not considering that he was actually out of metabolic control, and perhaps even stressed because of that. Two patients measured their glucose levels irregularly but did generally make the correct titration decisions. The majority of patients (144/149) managed to learn how to self-titrate; just four patients continued to make errors, and only one patient needed frequent reassuring about the decisions she was making.

Patient baseline characteristics by pre-study therapy are shown in Table 3. The majority of patients were insulin-naïve \((n = 90)\), while 59 changed from an existing insulin regimen. The maximum daily dose of insulin at baseline was 12 U, and the mean dose of metformin at the beginning and end of the study was 1750 mg/day.

During the 18 months of the study, one patient who was admitted to hospital with a cerebral vascular accident switched from BIAsp 30 to basal–bolus therapy, though BIAsp 30 was reinstated at the patient’s request after 3 months. This patient was excluded from analysis.

Of 41 patients who started the study on OD injections of BIAsp 30, 19 were still injecting once daily at the end of the study. A total of 96 patients started on BD BIAsp 30 injections, while 90 patients were injecting BD after 18 months. Twelve patients started on three injections per day and at end of the study, 40 were injecting TD. Patients took BG measurements at least once a week during the first weeks of therapy (76% assessed their glucose twice a week).

### 3.1. Glycaemic control

After 18 months, all patients experienced significant reductions in all three measurements of glycaemic control, regardless of pre-study regimen: there was a mean (SEM) reduction of 1.9% (0.1) in HbA1c, 2.8 mmol/l (0.2) in FPG, and 2.9 mmol/l (0.2) in PPG (all \(P < 0.001\); Fig. 1a–c). A total of 91% of patients achieved the target HbA1c of <7%, and 52% achieved HbA1c \(\leq 6.5\%\). Previous treatment regimen had a significant effect on HbA1c at 18 months (\(P < 0.01\)).

### 3.2. Safety

No major or nocturnal hypoglycaemic events were reported during the study. A total of 15% of patients reported minor hypoglycaemic episodes during the study (13% reported one episode, 1% reported two episodes, and 1% reported three episodes). Patients who had previously used BHI, NPH insulin, or insulin glargine reported fewer minor hypoglycaemic events after switching to BIAsp 30 (Table 4). None of the patients gave a history of needing outside assistance for treating hypoglycaemia, and no patients were treated for hypoglycaemia in the emergency room at the hospital, the University Clinic, or their GP practice.

Insulin-naïve patients gained an average of 2.7 kg over 18 months (\(P < 0.001\)), but patients who had changed from another insulin regimen actually lost weight (mean weight loss was 0.6 kg). Patients who switched from BHI lost 0.5 kg, those who switched from NPH insulin lost 0.6 kg, and those who switched from insulin glargine lost 0.7 kg (all NS).

### 3.3. Dose

As expected, the insulin dose increased significantly for all patients from baseline (0.31 U/kg) to 18 months (0.61 U/kg;
reach HbA1c TargEt study [15], mean HbA1c improved by insulin-naïve patients initiated on BIAsp 30 reached the HbA1c 2.8% and FPG improved by 6.9 mmol/l in 28 weeks; 66% of practice – achieved very good results: mean HbA1c improved by 1.9%, FPG by 2.8 mmol/l, and 90% of patients achieved the treatment target of <7%. Both of these studies employed a pre-defined dose-adjustment algorithm to help patients reach treatment targets. In the context of these trials with strict selection criteria, the present study – which was conducted in a real clinical practice setting. The majority (90%) of patients included in this study, who started BIAsp 30 or switched from a previous insulin regimen, were able to achieve the treatment target of HbA1c < 7% by self-titrating. At the end of the study period, 19 patients using BIAsp 30 OD, 90 were using it BD, and 40 were using it TD.

In an open-label study involving OD, BD or TD BIAsp 30 treatment with an aggressive titration algorithm, Garber and colleagues reported an improvement of 1.4% in HbA1c levels and of 2.7 mmol/l in FPG in 48 weeks in patients with type-2 diabetes [14]. Of patients who switched to BIAsp 30 from oral agents, with or without basal insulin, 77% achieved the HbA1c target of <7%. In the INITIATE (INITIATion of Insulin to reach Hba1c Target) study [15], mean HbA1c improved by 2.8% and FPG improved by 6.9 mmol/l in 28 weeks; 66% of insulin-naïve patients initiated on BIAsp 30 reached the HbA1c target of <7%. Both of these studies employed a pre-defined dose-adjustment algorithm to help patients reach treatment targets. In the context of these trials with strict selection criteria, the present study – which was conducted in a real clinical practice – achieved very good results: mean HbA1c improved by 1.9%, FPG by 2.8 mmol/l, and 90% of patients achieved the treatment target of HbA1c <7%, despite poor control at the start.

P < 0.01), particularly for patients initiating insulin therapy (Table 5).

### Table 4 – Rate of minor hypoglycaemic episodes at baseline and at 18 months by pre-study therapy.

Hypoglycaemic episodes were assessed for 12 weeks prior to baseline and for all 18 months of the study.

<table>
<thead>
<tr>
<th>Pre-study therapy</th>
<th>Baseline (events/patient-year)</th>
<th>18 months (events/patient-year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin-naïve (n = 90)</td>
<td>0.0</td>
<td>0.1</td>
</tr>
<tr>
<td>BHI 30 (n = 21)</td>
<td>8.1</td>
<td>0.3</td>
</tr>
<tr>
<td>NPH insulin (n = 18)</td>
<td>5.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Insulin glargine (n = 20)</td>
<td>0.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

NPH, neutral protamine Hagedorn; BHI, biphasic human insulin.

### Table 5 – Insulin dose over 18 months by pre-study therapy.

<table>
<thead>
<tr>
<th>Pre-study therapy</th>
<th>Baseline (U/kg)</th>
<th>18 months (U/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin-naïve (n = 90)</td>
<td>0.17</td>
<td>0.57</td>
</tr>
<tr>
<td>BHI 30 (n = 21)</td>
<td>0.63</td>
<td>0.74</td>
</tr>
<tr>
<td>NPH insulin (n = 18)</td>
<td>0.47</td>
<td>0.68</td>
</tr>
<tr>
<td>Insulin glargine (n = 20)</td>
<td>0.41</td>
<td>0.58</td>
</tr>
</tbody>
</table>

NPH, neutral protamine Hagedorn; BHI, biphasic human insulin.

As might be expected, patients who were previously insulin-naïve or switched from a basal insulin regimen achieved the greatest improvements in glycaemic control (mean HbA1c reduction 2.1% and 1.9%, respectively, P < 0.001). Nevertheless, patients previously using human premixed insulin also improved their glycaemic control after switching to BIAsp 30: mean HbA1c reduction was 1.2%, mean FPG reduction was 1.3 mmol/l, and PPG improved by 1.7 mmol/l from baseline (this may be due to the improved pharmacokinetic profile of BIAsp 30, which allows more precise targeting of FPG). Patients who previously used insulin glargine saw a considerable improvement of 3.8 mmol/l in their PPG control. This implies that PPG control plays a significant role in overall glycaemic control, becoming even more important than PPG when better control (lower HbA1c level) is achieved [16]. Mean HbA1c and FPG of patients who switched from insulin glargine were also significantly reduced by 1.9% mmol/l and 1.7 mmol/l, respectively.

The present study suggests that a large majority of patients in clinical practice can reach their treatment targets using BIAsp 30 OD, BD, or TD. It is thought that the high treatment adherence may have been due to the low rate of minor hypoglycaemia and the absence of major or nocturnal hypoglycaemic episodes. However, as nocturnal hypoglycaemic events were taken from patients’ histories and diaries, it is possible that they could have slept through hypoglycaemic events, which would not have been recorded. Patients were not routinely asked to take nocturnal readings of their glucose levels. Also, involvement of patients in the management of their diabetes may have contributed to the encouraging results of this study. In RCTs, self-titration has been shown to help the improvement of glycaemic control [21]; thus self-titration in this non-randomised study may have encouraged patients to aim for better glycaemic control and contributed to the benefits achieved.

The safety profile during the present study appeared to be very good; no major hypoglycaemic episodes occurred and the rate of minor hypoglycaemic episodes improved during the study, with only 15% of patients experiencing minor hypoglycaemia. Improved glycaemic control in insulin therapy is usually associated with weight gain, but only insulin-naïve patients gained weight upon initiation of BIAsp 30 in this study (mean 2.7 kg). Patients who switched from a previous insulin regimen actually lost an average of 0.6 kg.

Patients using human mixed insulins are advised to snack between meals to prevent hypoglycaemia, as human insulins do not match glucose excursions accurately. However, with the more physiological profile of BIAsp 30, there is no need for snacking between meals. This may explain the weight loss experienced by patients previously treated with insulin. These results imply that some patients with type-2 diabetes can switch to BIAsp 30 from other insulin regimens without worrying about further weight gain, despite an increased daily dose.

Some of the limitations of this study include generalisability of the results, as patients who were not willing to learn self-titration would have been excluded. Also, some methodological shortcomings should be pointed out, such as the non-randomised and non-blinded design, which may present a potential bias. However, in view of the long-term follow-up...
in this study (18 months), it would have been difficult to carry out the study in a blinded fashion.

5. Conclusions

In this study, 90% of patients with type-2 diabetes who started insulin treatment with BIAsp 30, or switched to BIAsp 30 from another insulin regimen, reached an HbA1c target of <7%. This result was achieved in combination with teaching patients self-titration, which proved to be easy to learn and perform for the majority of patients.

BIAsp 30 is an effective and well-tolerated treatment option for a significant proportion of patients with type-2 diabetes, and can be administered OD to TD.

Conflict of interest statement

This study was unsponsored. Dr Ligthelm has received honoria and is a member of an International Advisory Board for Novo Nordisk.

Acknowledgements

The author would like to thank Melissa Sharif Nassir for her invaluable assistance in collecting the study data, and the diabetes team at the Havenziekenhuis in Rotterdam for their help with data collection. Writing assistance for this article was provided by Dr Eva Cyhlarova, Watermeadow Medical, Witney, UK.

References