Insulin Initiation and Intensification: Insights from New Studies

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Abstract
Tight glycemic control is central to reducing the risk of long-term macrovascular and microvascular complications of type 2 diabetes and the associated morbidity and mortality. However majority of the patients do not achieve glycemic targets (HbA1c < 7%). Once insulin treatment has been initiated, each patient’s regimen must be optimized and intensified to reach the target. In many guidelines, initial insulin therapy comprises a single dose of long-acting insulin or premixed insulin. Basal insulin will help to control fasting plasma glucose (FPG) level, but postprandial glucose excursions make a significant contribution to the overall daily hyperglycemia of type 2 diabetic patients. BIAsp 30 is the most prescribed analog premix and consequently has the largest evidence base in terms of randomized controlled trials (RCTs) and observational data. It follows that BIAsp 30 is therefore the analog premix most likely to be used for insulin intensification, both from basal insulin and from BIAsp 30 regimens: OD to BID and from BID to TID.

Introduction
Many patients with type 2 diabetes will ultimately need insulin therapy to maintain their target for glycemic control. Tight glycemic control is central to reducing the risk of long-term macrovascular and microvascular complications of type 2 diabetes and the associated morbidity and mortality.¹ The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD),² as well as the recent British National Institute of Clinical Excellence (NICE) guidelines on type 2 diabetes³ recommend the addition of insulin for people with poorly controlled type 2 diabetes who are already on maximum tolerated doses of metformin and sulphonylurea. NICE recommends that this is the preferred management plan in those that are markedly hyperglycemic. The Diabetes Control and Complications Trial (DCCT) showed that, in patients with type 1 diabetes, intensive treatment reduced the risk of complications compared with conventional management. When patients originally assigned to conventional management were later switched to standard (presumably more intensive) management, they achieved similar standards of glycemic control, but their risk of microvascular and macrovascular complications remained raised. Similar findings have been reported after 10-year follow-up in UKPDS. The higher risk acquired initially due to poor glycemic control may not be easily overcome in the later improvements in glycemic control. Early control of hyperglycemia reduces the risk factor in developing long-term complication. The oxidative stress production secondary to hyperglycemia is believed to be the reason for this “diabetic memory” or “legacy effect.” This induces the production of superoxides by mitochondria leading to many diabetes-related complications. Therefore, it is very important to have good glycemic control as early as possible. This challenge is especially great for primary care physicians, who are increasingly responsible for the care of persons with diabetes. In many guidelines, initial insulin therapy comprises a single dose of long-acting insulin or premixed insulin. Basal insulin will help to control fasting plasma glucose (FPG) level, but postprandial glucose excursions make a significant contribution to the overall daily hyperglycemia of type 2 diabetic patients⁴ where a single dose of preemixed insulin is insufficient to reach the glycemic targets. Forty-three percent of patients do not achieve glycemic targets (HbA1c <7%).⁵ Once insulin treatment has been initiated, each patient’s regimen must be optimized and intensified to reach the target.

Barriers to Insulin Initiation
Many patients are highly restrained about commencing insulin therapy due to their prior perceptions about injection pain, inherent risks for hypoglycemia, weight gain, and/or treatment complexity.⁶ Other patients regard the need to begin insulin as a sign of impending disability, or as a sign of personal failure in their disease management or coping ability; some even view it as a sign that they have let down their family and healthcare providers.⁷ Many studies have demonstrated resistance by patients to accept insulin treatment. In the UKPDS study, 27% of patients initially declined insulin and a survey of 708 insulin-naïve patients found that 28% said they would be unwilling to take insulin if it was prescribed.⁸ There are several myths, misperceptions, and negative attitude that act as barriers about the use of insulin among people with type 2 diabetes as follows:

- Insulin causes blindness, renal failure, amputations, heart attacks, strokes, or early death,
- Sense of personal failure
- Low self-confidence
- Low confidence in therapy
- Injection phobia
- Hypoglycemia concerns
- Feeling that diabetes is a serious cause of concern
- Negative impact on social life and job
- Inadequate health literacy,
- Health care provider inadequately explaining risks/benefits
- Limited insulin self-management training

Some of the physicians’ barriers to timely initiate insulin are as follows:

- Concerns over patients with comorbidities
- Excess weight gain in already overweight patients
- Concerns about patient non-compliance
- Risk of severe hypoglycemia/adverse effects on QoL

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Initiating Insulin therapy

After deciding to initiate insulin therapy, choices must be made about the insulin regimen to be prescribed and the exact goals of treatment. These decisions depend greatly on individual patients' situations and aspirations. There are various choices of regimen when it comes to initiating insulin in type 2 diabetes. Each has its pros and cons. The simplest option is to add a once-daily injection of a basal insulin formulation to the patient's existing oral antidiabetic drug regimen. At the other extreme is basal-bolus therapy where, in addition to basal insulin, the patient injects a rapid-acting bolus insulin before each meal, with each dose tailored to the anticipated carbohydrate intake. Basal-bolus therapy is the most sophisticated and physiologic approach, but it may be considered unnecessarily complicated and taxing for the patient with type 2 diabetes initiating insulin. A more popular choice is to use a premixed insulin formulation in which rapid- and long-acting components are included in the same vial or pen. Premixed insulins address the endogenous deficits in prandial as well as basal insulin secretion while minimizing injections and blood glucose monitoring.

Initiating Insulin with Basal Analogs or Intensification with Basal-bolus

The basal-bolus insulin strategy, which can be used in patients with either type 1 or type 2 diabetes, incorporates the concept of providing continuous basal insulin secretion throughout the day and night with brief increases in insulin levels at the time of meal ingestion through the administration of bolus doses.

The use of preprandial regular insulin with bedtime NPH insulin as the basal insulin has been a common strategy for intensive insulin therapy in India. However, since regular insulin should be administered 20 to 40 min before a meal, a risk of hypoglycemia exists if the meal is delayed. If regular insulin is given just before a meal, high postprandial glucose levels and delayed hypoglycemia may result. A strategy that provides flexibility in the mealtime administration of insulin is the use of the rapid-acting insulin analogs like insulin aspart, administered immediately before meals, and a long-acting insulin, such as insulin detemir or glargine, as the basal insulin. NPH insulin, which exhibits peak action 5 to 7 h after administration, has also been used in combination with rapid-acting insulin analogs, commonly given twice daily.

In patients with type 2 diabetes, twice-daily regimens of insulin mixtures provide similar glycemic control as an intense regimen of multiple daily injections. Split self-mixed insulin regimens are effective for helping patients achieve glycemic control, yet an inherent risk of error exists. By combining the insulins themselves, patients can encounter problems with mixing technique and inaccurate dosing ratios, potentially reducing the effectiveness of the short-acting insulin. The benefits of premixed insulin formulations, such as a human insulin 70/30 mixed suspension (70% NPH insulin and 30% regular insulin), or NovoMix\textsuperscript{R} 30 (BIAsp 30) include reduced errors and improved dosing accuracy as well as the convenience of using a single vial.

Initiation and Intensification of Insulin Therapy using Premix Insulins

At present, international recommendations for intensification of insulin therapy using premix analogues are limited. The American Association of Clinical Endocrinologists' (AACE 2007) guidelines cover the following:

- Transition from a long-acting insulin analogue to a premixed insulin analogue BID.
- Transition from an OD premixed insulin analog to a BID premixed insulin analog.

In both scenarios, the recommendations are as follows:

- Divide the total daily dose into 2 equal doses (following 1:1 dose transfer from basal insulin)
- Give half before breakfast, the other half before dinner
- Titrate to goal based on self-monitored blood glucose data and diet history
- The largest meal will require a larger proportion of insulin
- Reduce the total dose by 20% if the patient experiences recurrent hypoglycemia.

The AACE guidelines do not cover the possible intensification from BID premix analog to TID premix analog. The International Diabetes Federation (IDF 2009) guidelines mention premixes as viable intensification options but offer no specific guidance. The BIAsp 30 EU label has the indication for progressing from OD to BID and from BID to TID, but again no specific dosing guidelines are given for intensification. A recent consensus statement from the UK recommended premix analogs BID (intensifying to TID as required) as a treatment option for patients with type 2 diabetes switching from basal insulin.\textsuperscript{10} The initial dose was recommended to be 80% of the final basal dose with titration to target over 14 days. However, these guidelines fail to include guidance on how the dose should be split and titrated.\textsuperscript{10} New international guidelines that cover all appropriate scenarios for insulin intensification with premixed analogs are therefore needed. BIAsp 30 is the most prescribed analog premix and consequently has the largest evidence base in terms of randomized controlled trials (RCTs) and observational data. It follows that BIAsp 30 is therefore the analog premix most likely to be used for insulin intensification, both from basal insulin and from BIAsp 30 regimens: OD to BID and from BID to TID.

Clinical Evidence for Intensification with BIAsp 30

Patients who need insulin intensification can be classified as the following 2 categories.

1. Those who fail to maintain good glycemic control even after using basal insulin±OADs
2. Those who fail to maintain good glycemic control even after using BIAsp 30 OD or BID

Clinical Evidence for Patients Failing on Basal Insulin

Twice-daily regimen of BIAsp 30 has been shown to provide greater postprandial glycemic control than twice-daily NPH or BHI 30, 30–32 or once-daily IGlarg. In a randomized double blind trial by Christiansen et al.,\textsuperscript{11} comparing 403 patients with type 2 diabetes, insufficiently controlled on OADs or NPH insulin, the mean prandial glucose in patients previously treated with NPH monotherapy was 1.05 mmol/L lower for the BIAsp 30 group, compared with those on NPH (p < 0.0001). These patients (coming from NPH monotherapy) also achieved a greater reduction in HbA1c when treated with twice-daily BIAsp 30, than when given...
twice-daily NPH (-0.78% vs -0.58%, respectively; p = 0.03).

Boehm et al. compared postprandial and overall glycemic control in a population of patients with type I or type II diabetes (n = 294) treated with BIAsp 30 or human insulin 30 in a randomized, open label parallel group study. The study was initially planned for 12 weeks then serially extended for 1, 2, and 4 years. The HbA1c-lowering effect of BIAsp 30 is equal to that of BHI 30 (twice-daily in patients with type 1 or type 2 diabetes) but treatment with BIAsp 30 resulted in a more favourable degree of postprandial blood glucose control than BHI 30. After completion of a 3-month trial, the study patients with type 2 diabetes (n = 125) were allowed to continue treatment in an open-label fashion for an additional 21 months. There was no significant difference in HbA1c values between the two treatment groups but increment in body weight was only 0.5 kg in patients treated with BIAsp 30 as compared to 2 kg in BHI 30 (p = 0.07).

Raskin et al. (INITIATE study) compared twice-daily BIAsp 30 with once-daily IGLarg in insulin-naïve patients with type 2 diabetes who were poorly controlled on OADs (only continuation with pioglitazone was allowed during the treatment phase). At the 28-week endpoint, the BIAsp 30 group had a lower mean HbA1C value than the IGLarg group (6.91% ± 1.17 vs. 7.41% ± 1.24; p < 0.01), and 66% of patients using BIAsp 30 reached the target HbA1c of <7% (from -9.8% at the start of the study) compared with 40% of patients on IGLarg (p < 0.001).

Kilo et al. evaluated the clinical effectiveness of starting patients on a relatively simple regimen of once-daily injections of either biphasic insulin aspart 70/30 (10 min before dinner), NPH insulin (at 10 p.m.), or biphasic human insulin 70/30 (30 min before dinner) in combination with metformin. HbA1C was decreased by 2.3%, 1.9%, and 1.8% from baseline after treatment with BIAsp 70/30, NPH insulin, or human insulin 70/30, respectively.

One RCT, the PREFER study, randomized 719 patients previously treated with 2 OADs with, or 1 without, basal insulin to either BIAsp 30 BID or basal-bolus therapy (insulin detemir and insulin aspart). After 26 weeks of therapy, patients previously treated with basal insulin showed a reduction in HbA1C of 0.75% (baseline level for the BIAsp 30 group was previously treated with basal insulin showed a reduction in NPH insulin (at 10 p.m.), or biphasic human insulin 70/30 (30 min before dinner), either 1:1 (if human basal) or 1:1.3 (if analog basal), without basal insulin therapy in routine care, the dose was transferred, on average, approximately 1:1 for those previously on human basal (mean total baseline BIAsp 30 dose: 0.50 U/kg) and 1:1.3 for those coming from analog basal (mean total baseline BIAsp 30 dose: 0.45 U/kg). During the 6-month observation period, doses underwent very little titration, final doses were 0.56 and 0.48 U/kg, respectively.

A large observational study (1-2-3 study), in patients with type 2 diabetes failing oral agent therapy with or without basal insulin was conducted to assess whether addition and self-titration of biphasic insulin aspart 70/30 (BIAsp 30) could achieve American Association of Clinical Endocrinologists (AACE)/International Diabetes Federation (IDF) and American Diabetes Association (ADA) glycemic targets (HbA1C <6.5 and <7%). Enrolled patients (N = 100, HbA1c 7.5 and ≤10%) were >18 years of age, had diabetes >12 months and had received a stable antidiabetic regimen for at least 3 months [minimum of 2 oral antidiabetic drugs (OADs) or at least 1 OAD plus once-daily basal insulin ≤60 U]. Patients discontinued prior basal insulin and added one injection of BIAsp. Patients self titrated their BIAsp 30 dose with investigator guidance every 3 or 4 days to achieve pre-breakfast fasting blood glucose (FBG) of 80–110 mg/dL. At >16 weeks, a pre-breakfast injection of 6 U of BIAsp 30 was added if week 15 HbA1C exceeded 6.5%; the added dose was titrated to achieve pre-dinner BG of 80–110 mg/dL. After an additional 16 weeks, 3 U of pre-lunch BIAsp 30 was added if HbA1C exceeded 6.5%. This added dose was adjusted based on 2-h post lunch BG to achieve postprandial glucose of 100–140 mg/dL. Subjects achieving an HbA1C ≤6.5% at 15 and 31 weeks completed the study at weeks 16 and 32 respectively. At the end of the study period, in poorly-controlled type 2 diabetic patients the addition of once-daily BIAsp 30 at dinnertime resulted in 41% of the patient reaching HbA1C 7.0%. Addition of a 2nd and 3rd injection of BIAsp 30 resulted in a total of 70% and 77% of patients achieving an HbA1C of 7.0% respectively. This stepwise approach to insulin initiation and intensification achieved significant reductions in HbA1C, FBG, and PPG with no nocturnal hypoglycaemia and very few major hypoglycemic episodes.

In another 26 weeks, open-labeled, randomized parallel group, multinational treat-to-target RCT (Once Mix Study), 480 insulin naïve subjects were randomized to receive either BIAsp 30 before dinner or insulin glargine at bedtime, both in the study. The HbA1c-lowering effect of BIAsp 30 is equal to that of BHI 30 (twice-daily in patients with type 1 or type 2 diabetes) but treatment with BIAsp 30 resulted in a more favourable degree of postprandial blood glucose control than BHI 30. After completion of a 3-month trial, the study patients with type 2 diabetes (n = 125) were allowed to continue treatment in an open-label fashion for an additional 21 months. There was no significant difference in HbA1c values between the two treatment groups but increment in body weight was only 0.5 kg in patients treated with BIAsp 30 as compared to 2 kg in BHI 30 (p = 0.07).
combination with metformin and glimepiride. Estimated mean reduction in HbA1C from baseline to end of treatment was -1.41% with BIAsp 30 and -1.25% with insulin glargine (BIAsp 30–insulin glargine = -0.16%, 95% CI [0.30; -0.02], p = 0.029). At the end of treatment, mean HbA1C was 7.1% and 7.3% for BIAsp 30 and insulin glargine, respectively. Significantly lower plasma glucose levels were observed with BIAsp 30 post-dinner (BIAsp 30–insulin glargine = -0.52 mmol/L, 95% CI [-1.02; -0.03], p = 0.04) and at bedtime (BIAsp 30–insulin glargine = -0.78 mmol/L, 95% CI [-1.25; -0.31], p < 0.001). The relative risk (RR) of experiencing a nocturnal hypoglycemic episode (00:00–06:00 a.m.) was significantly higher with BIAsp 30 than with insulin glargine (1.1 versus 0.5 episodes/year, RR = 2.41, 95% CI [1.34; 4.34], p = 0.003), but overall hypoglycemia rates were low.

**Clinical Evidence for Patients Failing on BIAsp 30 OD or BID**

Velojic-Golubovic et al.21 in a 3-month study, compared the effect of adding biphasic insulin aspart 30 (BIAsp30) and premixed human insulin 30/70 (BIH30) along with metformin (met) on overall glycemic control in insulin-naive, obese patients (30 males/20 females) with Type 2 diabetes (T2DM). The patients received either twice-daily BIAsp30 (N = 20) or twice-daily BIH30 (N = 30), and continued to receive maximal doses (2000 mg) of met for the duration of the study. Sulphonylureas were not administered as oral form of therapy. The primary efficacy endpoint was the change in HbA1C in both groups at the end of the study. The endpoints for safety were hypoglycemic episodes and weight gain. There was reduction in HbA1C in both the treatment groups at the end of the study (BIAsp30+MET by 2.5% [2.16-2.86%; 95% CI]; BIH30+MET by 1.18% [0.98–1.39%; 95% CI]). Significantly better HbA1c reduction was seen with BIAsp30+MET (1.33%; p < 0.05) when compared to the BIH30+MET treatment arm. Better reduction in postprandial glucose and the fasting plasma glucose levels were also seen in the BIAsp30+MET. Similarly, weight gain was also lower in the BIAsp30+MET group. No significant difference in the frequency or number of hypoglycemic episodes was observed between the two groups. It was therefore concluded that adding BIAsp30 to met in obese patients with T2DM results in better glycemic control and less weight gain than adding BIH30.

Yang et al.22 conducted a study 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 antidiabetic drugs (OADs). 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, 7.8 mmol/L and A1C, 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. A1C decreased significantly in both groups (BID group -2.48 to -0.07%; TID group -2.81 to -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 < 0.001). Thrice-daily BIAsp 30 was more effective in subjects with baseline A1C ≥ 9% (<7%: BID group 41.5% vs. TID group 58.3%; P < 0.001). There was no significant difference in rates of overall and nocturnal major and minor hypoglycemia per subject year between groups.

Roth et al.23 conducted a study to determine whether the addition of a third injection of biphasic insulin aspart 70/30 (BIAsp 30) just before lunch in older patients with type 2 diabetes who did not achieve goals with a twice-daily (BID) regimen would optimize glycemic control in a clinical practice setting. A retrospective chart analysis was conducted. In 12 patients aged 52–80 years with type 2 diabetes who had been diagnosed between 5 and 24 years earlier and who remained on oral antidiabetes agents, a third injection of BIAsp 30 was added because optimal glycemic control (glycosylated hemoglobin [HbA1c] <7%) was not achieved on a BID regimen. Changes in HbA1c, body weight, total insulin dose, and frequency of hypoglycemia were analyzed after 6 months of three times daily (TID) treatment. Mean HbA1c decreased from 8.4% to 7.2%. An HbA1c goal of <7% was attained by 58% of patients. Although the total insulin dose increased by 11% with the TID regimen, pre-breakfast and predinner doses decreased by 15%.

Khan et al.24 conducted a study to determine whether the addition of a third injection of biphasic insulin aspart 70/30 (BIAsp 30) just before lunch in older patients with type 2 diabetes who did not achieve goals with a twice-daily (BID) regimen would optimize glycemic control in a clinical practice setting. A retrospective chart analysis was conducted. In 12 patients aged 52–80 years with type 2 diabetes who had been diagnosed between 5 and 24 years earlier and who remained on oral antidiabetes agents, a third injection of BIAsp 30 was added because optimal glycemic control (glycosylated hemoglobin [HbA1c] <7%) was not achieved on a BID regimen. Changes in HbA1c, body weight, total insulin dose, and frequency of hypoglycemia were analyzed after 6 months of three times daily (TID) treatment. Mean HbA1c decreased from 8.4% to 7.2%. An HbA1c goal of <7% was attained by 58% of patients. Although the total insulin dose increased by 11% with the TID regimen, pre-breakfast and predinner doses decreased by 15%.

No patient experienced major hypoglycemia on BID or TID dosing. With the TID regimen, no minor hypoglycemic events were reported by patients and mean body weight decreased by 2.25 lb. The addition of a third injection of BIAsp 30 substantially improved HbA1c and decreased body weight and the incidence of hypoglycemia in 12 patients with type 2 diabetes who did not achieve optimal glycemic control on a BID regimen.
Conclusion from Clinical Data Regarding Intensification with BIAsp 30

- In treat-to-target intensification studies the total dose of BIAsp 30 increased considerably in the consecutive intensification (OD-BID-TID) phases
- When BIAsp 30 BID was compared with BIAsp 30 TID in parallel-group studies, total dose did not differ that much
- Dose distribution of twice-daily administration was close to 50:50
- In the majority of studies, the highest dose of BIAsp 30 TID was given at dinner followed by the doses at breakfast and lunch

Practical Guidelines for Intensification of Insulin with BIAsp 30

Switching from basal insulin to OD or BID BIAsp 30

Unnikrishnan et al.25 has provided an algorithm to switch from basal to premix insulin (BIAsp 30) (Fig. 1). If the patient has HbA1c higher than 8%, they should be transferred to BIAsp 30 BID. If HbA1c is moderately elevated (between 7.0% and 8.0%) but FPG is within the normal range (4–6 mmol/L), the suboptimal overall glycemia is probably caused by elevated PPG; thus, the patient should be transferred to BIAsp 30 BID as it provides prandial coverage as well. If, however, HbA1c is between 7.0% and 8.0%, and FPG is higher than 6 mmol/L, the existing basal insulin dose(s) can be titrated further until the patient achieves FPG below 6 mmol/L. If recurrent hypoglycaemia limits uptitration of the basal dose, or the daily dose reaches 0.5 U/kg (insulin units per kg body weight), switching to BIAsp 30 BID can be considered.

Intensification with Premix Insulin

The following recommendations can be followed when intensifying premix insulin therapy.

OD to BID

- Split the OD dose into equal breakfast and dinner doses (50:50)
- Titrate the doses preferably once a week according to the algorithm below
- Discontinue SUs
- Continue metformin
- Consider discontinuing thiazolidinediones (TZDs) as per local guidelines and practice

BID to TID

- Add 2–6 U or 10% of total daily BIAsp 30 dose before lunch
- Down titration of morning dose (-2 to 4 U) may be needed after adding the lunch dose
- Titrate the doses preferably once a week according to the algorithm below
- Continue metformin
- Consider discontinuing thiazolidinediones (TZDs) as per local guidelines and practice
- Administer BIAsp 30 just before meals

Titration Algorithm for Implementing the Above Guidelines

<table>
<thead>
<tr>
<th>Pre-prandial BG value</th>
<th>Dose change</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4.4 mmol/L</td>
<td>&lt;80 mg/dL</td>
</tr>
<tr>
<td>4.4–6.1 mmol/L</td>
<td>80–110 mg/dL</td>
</tr>
<tr>
<td>6.2–7.8 mmol/L</td>
<td>111–140 mg/dL</td>
</tr>
<tr>
<td>7.9–10.0 mmol/L</td>
<td>141–180 mg/dL</td>
</tr>
<tr>
<td>&gt;10.0 mmol/L</td>
<td>&gt;180 mg/dL</td>
</tr>
</tbody>
</table>

Ref: Unnikrishnan et al. 2009 (25)

When using this titration algorithm to adjust BIAsp 30 doses after intensifying basal insulin therapy to BIAsp 30 BID, or intensifying BIAsp 30 OD or BID to BIAsp 30 BID or TID, the following guidance should be noted:

- The lowest of 3 previous days’ premeal levels should be used.
- Always change the mealtime dose preceding the measurement.
- The dose should not be increased if hypoglycemia occurs during these days.
- Dose adjustments can be made once a week until target is reached.
- Only one dose at a time should be changed: the evening dose should be titrated first, followed by the breakfast dose and finally the lunch dose as appropriate.
Clinical Insights to be Considered During BIAsp 30 Dosing and Titration

- Patients with high BMI likely to require higher doses
- More care when titrating thin/elderly (more insulin sensitive) patients
- Multiple doses of insulin easier to administer using pens
- Give some dosing expectations (use examples of typical insulin dose ranges in the text but not in the algorithm)
- Explaining the rationale behind using more insulin injections is a safer way of administering a higher insulin dose.

References

23. Tibaldi JT. Biphasic insulin aspart 70/30 three times a day in older patients with type 2 diabetes not achieving optimal glycaemic control on a twice-daily regimen: A retrospective case series analysis from clinical practice. Advances in Therapies 2007;24:1348-1356.