What to Do After Basal Insulin: 3 Tx Strategies for Type 2 Diabetes

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What to do after basal insulin: 3 Tx strategies for type 2 diabetes

These strategies can help you optimize glucose control in your patient with type 2 diabetes when basal insulin alone isn’t sufficient.

Diabetes mellitus is a complex, progressive disease that affects every family physician’s practice. Major diabetes organizations recommend that treatment be ongoing and progressive in order to control the disease. The American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and the American Association of Clinical Endocrinologists recommend that patients be assessed every 2 to 3 months after diagnosis and that treatment should be intensified if the patient is not meeting treatment goals. Using this approach, all people with type 2 diabetes could be on insulin one year after diagnosis.

While many family physicians have become comfortable with using once-daily basal insulin such as glargine or detemir, what to do after basal insulin is much more complex. This review builds upon an earlier article in this journal, “Insulin for type 2 diabetes: How and when to get started,” by explaining 3 strategies to consider when basal insulin alone isn’t enough.

### 3 main strategies for intensifying treatment

Basal insulin is indicated for patients who have glucose toxicity and persistently elevated hemoglobin A1c (HbA1c) despite using 2 or more oral agents, or for those who have not achieved glucose goals one year into treatment. ADA/EASD recommends initiating a weight-based approach for basal insulin therapy based on initial HbA1c levels >7% or >8%. Instructing and encouraging patients to titrate their own insulin dose based on fasting glucose readings provides greater and faster glucose control.

Despite these attempts, some patients will not reach their glucose goals with basal insulin. When intensifying treatment beyond basal insulin therapy, patient preference, cost-effectiveness, safety, tolerability, glycemic efficacy, risk of hypogly-
cemia, effects on cardiovascular risk factors, and other non-glycemic effects should be considered in the shared decision-making process. There are 3 main strategies for intensifying treatment:

1. **Basal plus incretin therapy.** Add a newer injectable agent such as a glucagon-like peptide 1 receptor agonist (GLP-1RA).
2. **Basal plus one strategy.** Add prandial insulin prior to the largest meal of the day.
3. **Basal-bolus combination.** Add insulin prior to all meals.

**Table 1** provides details of several studies that have documented the efficacy of these 3 strategies.

**Monitoring blood glucose to guide the way**
Blood glucose monitoring using either a 7-point glucose monitoring technique or staggered glucose checks should guide insulin intensification. A 7-point glucose profile includes pre-meal and post-meal readings for 3 meals a day and an additional bedtime reading. This is typically performed for 3 to 7 days prior to an appointment and provides an estimate of a typical full day’s glucose pattern.

Staggered monitoring includes a pair of glucose checks taken immediately before and typically 90 minutes after a meal. This is assigned to a different meal each day in order to obtain the same information as is achieved with 7-point monitoring, but with fewer checks on any given day. It may take up to 2 to 3 weeks to gather the necessary information using the staggered monitoring technique.

In order to optimize insulin strategies for tighter glycemic control, it is important to review blood glucose logs at each office visit with either of the above techniques.

**Basal plus incretin therapy**
GLP-1RAs are subcutaneously administered injectable incretin agents. They mimic the action of endogenous GLP-1 hormones, which are normally secreted in response to meals by the cells of the small intestine. GLP-1 stimulates glucose-dependent insulin secretion, suppresses postprandial glucagon release from pancreatic alpha cells, signals satiety, and slows gastric emptying. In other words, GLP-1 appears to be a physiologic regulator of appetite and food intake. GLP-1 is rapidly metabolized and inactivated by dipeptidyl peptidase-4 (DPP-4) enzymes. The amplification of insulin secretion elicited by hormones secreted from the gastrointestinal (GI) tract is called the “incretin effect.” Obesity, insulin resistance, and type 2 diabetes greatly reduce the incretin effect.

GLP-1RAs mimic the incretin effect and are not degraded by endogenous DPP-4 enzymes. They provide a pharmacologic level of GLP-1 activity, including beneficial glucose effects (via insulin secretion and glucagon suppression), but they also increase GI adverse effects, such as nausea and vomiting. Further, they can suppress appetite and contribute to weight loss.

GLP-1RAs can be considered as an add-on therapy for patients whose HbA1c exceeds 7% and whose fasting blood glucose ranges from 80 to 130 mg/dL, or for patients with a basal insulin dose >0.5 unit/kg/d. The 5 currently available GLP-1RAs (exenatide,
**TABLE 1**

3 ways to intensify type 2 diabetes treatment: A look at the evidence

<table>
<thead>
<tr>
<th>Study (date)</th>
<th>Patients (N)</th>
<th>Treatment groups</th>
<th>Trial duration</th>
<th>HbA1c</th>
<th>Fasting plasma glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basal plus GLP-1RA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosenstock J, et al (2014)</td>
<td>586; average DM duration 11 years</td>
<td>1. Albiglutide, 30 mg weekly titrated to 50 mg if necessary, plus once-daily titrated glargine 2. Titrated preprandial insulin lispro 3 times/d plus once-daily titrated glargine</td>
<td>52 weeks (26-week results)</td>
<td>Overall baseline: 8.5%. Decreased by 0.82% with albiglutide, 0.66% with insulin lispro. Treatment difference 0.16% (P&lt;.0001), which met the non-inferiority endpoint</td>
<td>Similar at baseline (data not published). Mean was lower in albiglutide group (P=.236)</td>
</tr>
<tr>
<td><strong>Basal plus one</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Owens DR, et al (2011)</td>
<td>106; average DM duration 11.5±7 years</td>
<td>1. Glargine daily with OHA (control group) 2. Addition of glulisine to the main meal with glargine and OHA (glulisine group)</td>
<td>6 months (3-month run-in period and 3-month randomized period)</td>
<td>Overall baseline: 8.5±0.6%. Decreased by 0.11±0.08% in control group, 0.37±0.09% in glulisine group (P=.029)</td>
<td>Overall baseline: 143±40 mg/dL Decreased to 110±22 mg/dL (control group) vs 111±22 mg/dL (glulisine group)</td>
</tr>
<tr>
<td>Lankisch MR, et al (2008)</td>
<td>393; average DM duration 10 years</td>
<td>1. Addition of glulisine at breakfast to existing glargine regimen 2. Addition of glulisine at main mealtime to existing glargine regimen</td>
<td>24 weeks</td>
<td>Overall baseline: 7.3±0.7%. Decreased by 0.5% in glulisine group, 0.6% in main mealtime glulisine group (P&lt;.001)</td>
<td>Overall baseline increased from 6.0±0.8 mmol/L (108±14 mg/dL) to 6.7±1.4 mmol/L (121±25 mg/dL) in breakfast group, and from 5.9±0.8 mmol/L (106±14 mg/dL) to 6.3±1.4 mmol/L (113±25 mg/dL) in main mealtime group</td>
</tr>
<tr>
<td><strong>Basal-bolus combination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Davidson MB, et al (2011)</td>
<td>341; average DM duration 10 years</td>
<td>1. One insulin glulisine injection with the largest meal of the day (1X group) 2. One glulisine injection prior to 2 meals/d (2X group) 3. One glulisine injection prior to 3 meals/d (3X group)</td>
<td>24 weeks</td>
<td>Overall baseline: 7.8%. Decreased by 0.44% in 1X group, 0.36% in 2X group, 0.43% in 3X group (NS)</td>
<td>Overall baseline: 131 mg/dL. Data (not published) was reported as comparable in all groups at the end of study</td>
</tr>
</tbody>
</table>

BG, blood glucose; DM, diabetes mellitus; HbA1c, hemoglobin A1c; NS, not significant; OHA, oral hypoglycemic agent.

Dosing varies with each agent and includes twice daily before meals for exenatide, once daily (independent of meals) for liraglutide, and once weekly for exenatide extended-release, albiglutide, and dulaglutide. These agents should not be used for patients with a history of pancreatitis or a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2. Because exenatide is cleared through the kidneys, its use is contraindicated in patients with a creatinine clearance <30 mL/min or end-stage renal disease. Caution is advised for its use in patients with a creatinine clearance of 30 to 50 mL/min.
Conclusions

After 26 weeks, HbA1c reduction, goal HbA1c <7%, and goal HbA1c <6.5% was comparable and noninferior in both treatment groups. Weight was significantly lower in the albiglutide group. Adverse reactions were comparable. Findings support noninferiority between albiglutide and insulin lispro and a weight-loss benefit with albiglutide.

<table>
<thead>
<tr>
<th>Study (date)</th>
<th>Patients (n)</th>
<th>Treatment groups</th>
<th>Trial duration</th>
<th>hba1c</th>
<th>fasting plasma glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 years</td>
<td>341; average</td>
<td>1. one glulisine</td>
<td>24 weeks</td>
<td>6.8</td>
<td>7.8% ±0.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>injection</td>
<td>overall baseline:</td>
<td></td>
<td>(control group) vs 111±22 mg/dl</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. addition of</td>
<td>0.37±0.09% in</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>glulisine at</td>
<td>main mealtime</td>
<td>6.0</td>
<td>(glulisine group)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>largest meal of</td>
<td>group</td>
<td>±0.8</td>
<td>108±14 mg/dl</td>
</tr>
<tr>
<td></td>
<td></td>
<td>the day</td>
<td>(3X group)</td>
<td></td>
<td>113±25 mg/dl</td>
</tr>
<tr>
<td>10 years</td>
<td>393; average</td>
<td>1. addition of</td>
<td>0.37±0.09% in</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>glulisine</td>
<td>main mealtime</td>
<td>6.7</td>
<td>(121±25 mg/dl)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>at breakfast</td>
<td>group</td>
<td>±1.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2X group)</td>
<td>(1X group)</td>
<td></td>
<td>110±22 mg/dl</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2X group)</td>
<td></td>
<td>111±22 mg/dl</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.44% in 1X group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.43% in 3X group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.36% in 2X group</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Glulisine given at breakfast was equally effective in controlling HbA1c as glulisine given at the main mealtime. Significantly more patients achieved target HbA1c ≤7% in the main mealtime group. Changes in weight (NS) and rates of hypoglycemia (NS) were comparable in both groups.

At 24 weeks, HbA1c reductions was noninferior among 1X or 2X groups compared to 3X group. However, a greater number of patients achieved HbA1c <7% in the 3X group (46%) vs the 1X (34%) and 2X (30%) groups (P=.17 and P=.045, respectively). Findings confirm that a regimen with multiple daily injections is more likely to reach target HbA1c levels without a significant impact on weight or hypoglycemia.

**Basal plus one strategy**

To best utilize prandial insulin, it is important to know what the patient’s glucose readings are before and after meals as assessed by the 7-point or staggered blood glucose monitoring techniques described earlier. Once you have clarified which meal(s) are raising the patient’s glucose levels, selecting appropriate treatment becomes easier. To reduce the glucose-monitoring burden for the patient, it may be acceptable to allow the patient to omit the fasting glucose measurement (if stable).

The first major decision is whether to treat one meal per day (basal plus one) or all meals (basal-bolus). Adding a rapid-acting insulin prior to one meal a day (usually the largest meal) is a reasonable starting point.16

The meal that produces the highest post-prandial glucose readings can be considered the meal of greatest glycemic impact. The “delta” value—the difference between pre-meal glucose and 2-hour postprandial glucose readings—also helps to determine the largest meal of the day.17 The average physiologic delta is ≤50 mg/dL.17 If the delta for a meal is >75 mg/dL, consider initiating prandial insulin prior to that meal and titrating the dose to achieve a target glucose level of <130 mg/dL before the next meal.

Using 4 to 6 units of a rapid-acting insulin per meal is a good initial regimen for a basal plus one (as well as for a basal-bolus) approach.16 If the patient experiences significantly increased insulin demands as indicated by glucose patterns where the post-meal glucose is still consistently above 180 mg/dL, the initial regimen may be modified to 0.1 unit per kg per meal,17-19 and then titrated up to a maximum of 50% of the total daily insulin dose (TDD) for basal plus one16 (or 10%-20% of TDD per meal for basal-bolus).

**Consider the timing of administration.** Rapid-acting insulin analogs exhibit peak pharmacodynamic activity 60 minutes after injection (TABLE 3).20

Peak carbohydrate absorption following a meal occurs approximately 75 to 90 minutes after eating begins.17,21 Thus, to synchronize the action of insulin with carbohydrate digestion, the analog should be injected 15 minutes before meals. This can be increased by titrating prandial insulin by 1 unit/d to a goal of either a 90-minute to 2-hour postprandial glucose of <140 to 180 mg/dL or the next pre-prandial glucose of <130 mg/dL.16 The goal is to obtain a near-normal physiologic delta of ≤50 mg/dL. The drop in delta noted with every unit of insulin added to the current dose can provide a rough approximation of how many additional insulin titrations will be needed to achieve a delta of ≤50 mg/dL.

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**TABLE 3**

<table>
<thead>
<tr>
<th>WHAT TO DO AFTER BASAL INSULIN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>4-6 units</td>
</tr>
</tbody>
</table>

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A GLP-1RA can be considered for patients with an HbA1c >7% and a fasting glucose ranging from 80 to 130 mg/dL.
Basal-bolus combination

A gradual increase from one injection before a single meal each day to as-needed multiple daily injections (MDIs) is the next step in hyperglycemia management. Starting slow and building up to insulin therapy prior to each meal offers structure, simplicity, and physician-patient confidence in diabetes management. The slow progression from basal plus one to basal-bolus combination allows the patient ease into a complex, labor-intensive regimen of MDIs. Additionally, the stepwise reduction of postprandial hyperglycemia with this slow approach often reduces the incidence of hypoglycemia (more on this in a moment).8

Advanced insulin users can calculate an “insulin-to-carbohydrate ratio” (ICR) to estimate the amount of insulin they need to accommodate the amount of carbohydrates they ingest per meal. An ICR of 1:10 implies that the patient administers 1 unit of insulin for every 10 grams of carbohydrates ingested. For example, if a patient with an ICR of 1:10 concludes that his meal contains a total of 60 grams of carbohydrates, then he would administer 6 units of insulin prior to this meal to address the anticipated post-meal hyperglycemia.

In order to use the ICR regimen, a patient would need to be able to accurately determine the nutritional content of his meals (starch, protein, carbohydrates, and fat) and calculate the appropriate insulin dosage. For successful diabetes management, it is essential to evaluate the patient’s skills in these areas before starting an ICR regimen, and to routinely assess hypoglycemic episodes at follow-up visits.

An ICR approach is usually reserved for patients who require tighter glucose control than that obtained from fixed prandial insulin doses, such as patients with type 1 diabetes, those with variable meal schedules and content, those with a malabsorption syndrome that requires consuming meals with a specific amount of carbohydrates, athletes on a structured diet with specific carbohydrate content, and patients who want flexibility with carbohydrate intake with meals.

The risk of hypoglycemia is a major barrier to initiating basal-bolus insulin therapy. Hypoglycemia is classified as a blood glucose level of <70 mg/dL, and severe hypoglycemia as <50 mg/dL, regardless of whether the patient develops symptoms.22 Symptoms of hypoglycemia include dizziness, difficulty speaking, anxiety, confusion, and lethargy. Hypoglycemia can result in loss of consciousness or even death.22

A patient who has frequent hypoglycemic episodes may lose the protective physiologic response and may not recognize that he is experiencing a hypoglycemic episode ("hypo-

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**TABLE 2**

GLP-1 receptor agonists used to treat type 2 diabetes*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing frequency</th>
<th>Renal dosing</th>
<th>Relation to meals</th>
<th>Warnings/precautions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide11</td>
<td>Twice daily</td>
<td>Caution for Cr Clr of 30-50 mL/min</td>
<td>30-60 minutes before am and pm meals</td>
<td>Pancreatitis; thyroid C-cell cancer; avoid use with Cr Clr &lt;30 mL/min</td>
</tr>
<tr>
<td>Exenatide extended-release12</td>
<td>Once weekly</td>
<td>Caution for Cr Clr of 30-50 mL/min</td>
<td>Not related to meals</td>
<td>Pancreatitis; thyroid C-cell cancer; avoid use with Cr Clr &lt;30 mL/min or ESRD</td>
</tr>
<tr>
<td>Liraglutide13</td>
<td>Once daily</td>
<td>Caution for Cr Clr of 30-50 mL/min</td>
<td>Not related to meals</td>
<td>Pancreatitis; thyroid C-cell cancer; MEN type 2</td>
</tr>
<tr>
<td>Albiglutide14</td>
<td>Once weekly</td>
<td>No dosage adjustment</td>
<td>Not related to meals</td>
<td>Medullary thyroid cancer</td>
</tr>
<tr>
<td>Dulaglutide15</td>
<td>Once weekly</td>
<td>No dosage adjustment</td>
<td>Not related to meals</td>
<td>Thyroid C-cell tumors. Not studied with pancreatitis</td>
</tr>
</tbody>
</table>

Cr Clr, creatinine clearance; ESRD, end-stage renal disease; GLP-1, glucagon-like peptide 1; MEN, multiple endocrine neoplasia.

* Nausea is a common adverse effect of all GLP-1 receptor agonists; for some of these agents, weight loss and vomiting also are common. All GLP-1 receptor agonists are pregnancy category C.
**TABLE 3**

<table>
<thead>
<tr>
<th>Insulin type</th>
<th>Onset (h)</th>
<th>Peak (h)</th>
<th>Duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular (short-acting)</td>
<td>0.5</td>
<td>2-4</td>
<td>6-8</td>
</tr>
<tr>
<td>Aspart (rapid-acting)</td>
<td>≤0.25</td>
<td>1-3</td>
<td>3-5</td>
</tr>
<tr>
<td>Lispro (rapid-acting)</td>
<td>≤0.25</td>
<td>1</td>
<td>2-4</td>
</tr>
<tr>
<td>Glulisine (rapid-acting)</td>
<td>≤0.25</td>
<td>1</td>
<td>3.5-4.5</td>
</tr>
</tbody>
</table>

**References**

16. Vaidya A, McMahon GT. Initiating insulin for type 2 diabetes:


18. Sharma MD, Garber AJ. Progression from basal to pre-mixed or rapid-acting insulin – Options for intensification and the use of pumps. US Endocrinology. 2009;5:40-44.


