

## Insulin Initiation During a 20-Minute Office Visit: Part 2: Making It Happen

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***Editor's note.** This article is the second of a two-part series examining the challenge health care professionals face in initiating insulin therapy in patients with type 2 diabetes within the confines of a typical 20-minute office visit. In the first part of this series, the author set the scene with a discussion of patient education from identification of behavioral goals through creation of an individual action plan. Part 1 also explored the key issues that should be covered in initial discussions with patients. These include the concerns patients are likely to have regarding insulin initiation and how to overcome these barriers to early insulin therapy.*

*In this second and final part, the author focuses on how to start insulin therapy. It includes a discussion about tailoring treatment in terms of A1C targets; the various insulin preparations available and their suitability for different patient groups and glucose profiles; initiating and intensifying insulin therapy; and the role of self-monitoring of blood glucose in the successful management of type 2 diabetes.*

*Together, these articles offer real-world strategies for making the best use of limited clinical visit time to prepare patients for starting and intensifying insulin therapy.*

In type 2 diabetes, patient self-management plays an important role in the effective management of the disease. American Diabetes Association (ADA) guidelines recognize that diabetes self-management education is a key component of diabetes care and that care has shifted to place patients with diabetes at the center of the care model.<sup>1</sup> It is therefore help-

ful for health care professionals to adopt a collaborative approach that empowers patients to become actively involved in their care and to play a role in selecting and using their medications, as well as adopting lifestyle and behavioral changes.

Although lifestyle intervention is the initial approach in newly diagnosed type 2 diabetes, it is likely that insulin therapy will ultimately be required to achieve A1C targets. Effective self-management requires patients to understand and use various technologies, medications, and treatment strategies and be able to develop problem-solving skills.<sup>2</sup> Achieving the optimal level of collaboration and patient understanding within the context of a typical 20-minute office visit poses a major challenge to health care providers, especially when discussing the initiation of insulin therapy. This article outlines key issues and offers strategies health care professionals can adopt for the initiation and intensification of insulin therapy in the setting of a standard office visit.

### Target A1C levels

It is now accepted that maintaining A1C levels as close as possible to the normal range (< 6.0%) helps to reduce the incidence of long-term microvascular complications such as nephropathy, neuropathy, and retinopathy in patients with type 2 diabetes.<sup>1,3-6</sup> However, the benefits with respect to macrovascular complications have yet to be clearly established. Findings from two recent large-scale studies—the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and the Action in Diabetes and Vascular Disease:

Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trials—showed that intensive glycemic control did not improve cardiovascular outcomes compared to conventional therapy, although long-term data are awaited.<sup>7–9</sup>

Diabetes management guidelines issued by ADA and the American College of Endocrinology (ACE)/ American Association of Clinical Endocrinologists (AACE) include target A1C levels.<sup>1,10</sup> ADA's A1C target is < 7% (or < 6% in patients not experiencing hypoglycemia),<sup>1</sup> whereas the ACE/AACE target is ≤ 6.5%.<sup>10</sup> However, findings from the ACCORD and ADVANCE studies suggest that clinicians should individualize glycemic targets according to patients' specific profile.

Taking these data into consideration, the ACE/AACE guidelines highlight that the target A1C goal must be customized for individual patients taking into account numerous factors such as comorbidity, duration of diabetes, history of hypoglycemia, patient education, motivation, adherence, age, and concomitant medications.<sup>10</sup> Similarly, ADA guidelines highlight that, for selected individuals, lowering goals beyond the general goal of < 7% may be reasonable if this can be achieved without significant hypoglycemia or other adverse treatment effects (e.g., in patients with recent-onset type 2 diabetes and/or a long life expectancy without cardiovascular disease.)<sup>1</sup> Conversely, less stringent treatment goals than the general goal of < 7% may be appropriate for adults with longstanding type 2 diabetes, limited life expectancy, or advanced vascular disease.<sup>1</sup>

Both sets of guidelines emphasize the need for lifestyle intervention and metformin as a preferred initial pharmacological option. If lifestyle modification and the addition of metformin fail to meet A1C targets, other options for intensification outlined in the guidelines are oral antidiabetic drugs (OADs) and early insulin therapy. Given that OADs typically fail to maintain glycemic control beyond a few years, insulin

will eventually be required in many, if not most, patients.

### Initiating and Intensifying Insulin Therapy

It is important that insulin therapy be tailored to meet individual patients' needs (i.e., considering patient-oriented issues such as preferences, lifestyle, motivation, and risks, as well as their glucose profile). A summary of which insulins are suitable for different patient groups and glucose profiles is given in Table 1.<sup>11–17</sup>

The simplest way to start insulin therapy is to add a basal insulin analog (detemir or glargine) to oral therapy while reducing doses of oral agents.<sup>1</sup> Long-acting insulin analogs provide up to 24-hour fasting plasma glucose (FPG) control and have the flexibility of being administered once or twice daily.

Compared to intermediate-acting human insulins such as NPH, these agents have relatively flat time-action profiles. Clinical trials comparing basal insulin analogs to human insulins have been designed to demonstrate noninferiority in terms of A1C reduction. However, reduced complications of hypoglycemia have been observed with basal insulin analogs compared to NPH insulins,<sup>18–22</sup> and insulin detemir is associated with significantly lower weight gain than NPH or insulin glargine.<sup>22–25</sup>

The benefits of basal insulin analogs compared to human insulins are reflected in the recent ACE/AACE consensus algorithm,<sup>10</sup> which highlights that human insulins are a less desirable option than basal insulin analogs because of their higher risk of hypoglycemia and less predictability in effect.

Several dosing algorithms have been developed to provide standardized methods of achieving glycemic control with basal analogs.<sup>8,20,21,26,27</sup> In the real world, however, patients need to be able to adjust their own insulin doses. Two key observational trials, GOAL A1C<sup>25</sup> and PREDICTIVE 303<sup>28</sup> have demonstrated this principle with basal insulins (Table 2).

In the GOAL A1C trial,<sup>25</sup> glargine was added to oral therapy

in 7,893 patients with type 2 diabetes. Greater A1C reductions were achieved in patients receiving active titration advice and guidance through weekly contact via telephone, e-mail, or fax, compared to dose titration changes left to the physician's discretion (i.e., standard titration) with no unsolicited contact between visits (change in A1C 1.5 vs. 1.3%, respectively;  $P < 0.0001$ ). Furthermore, a significantly higher proportion of patients who were actively self-titrating and receiving point-of-care testing achieved an A1C of < 7% compared to those actively titrating and receiving laboratory A1C testing (41 vs. 36%;  $P < 0.0001$ ).

The PREDICTIVE 303 study<sup>28</sup> involving 5,604 patients with type 2 diabetes compared patient-driven adjustment of an add-on dose of detemir using a simple 303 algorithm (see Table 2) against standard-of-care physician-driven dose adjustment. Although reductions in A1C were similar between the two groups (–1.1% for the algorithm group and –1.0% for the standard-of-care group;  $P = 0.0933$ ), the self-titrated group achieved greater reductions in FPG than the standard-of-care group (–55.4 vs. –44.5 mg/dl;  $P = 0.0001$ ).

Also, in the TITRATE study,<sup>29</sup> patients successfully self-titrated to very aggressive FPG levels of either 80–110 or 70–90 mg/dl with low rates of hypoglycemia episodes using the PREDICTIVE 303 algorithm. The majority of patients in both titration groups at the end of the study achieved the ADA-recommended A1C level of < 7% (64.3% of those in the 70–90 mg/dl FPG target group and 54.5% of those in the 80–110 mg/dl FPG target group).

These data suggest that patient-driven dose adjustments may be a safe and effective alternative to physician-directed dose adjustments in the primary care setting.

Basal insulin analogs are less effective at normalizing postprandial glucose than FPG; eventually, most patients require intensification of insulin therapy by adding prandial insulin such as a rapid-acting analog. Three rapid-acting insulin analogs—lispro, aspart, and gluli-

Table 1. Tailoring Insulin Requirements to Patient Needs<sup>11-17</sup>

Insulin Regimen	Patient Profile	Glucose Profile	Treatment Options <sup>a</sup>
Basal or prandial only	<ul style="list-style-type: none"> <li>Does not want multiple injections</li> <li>Still receiving oral therapy</li> <li>Less stringent treatment goals recommended (e.g., elderly)</li> </ul>	<ul style="list-style-type: none"> <li>Fasting and postprandial hyperglycemia with significant insulinopenia</li> </ul>	1) Insulin glargine or insulin detemir <sup>b</sup> at night, <sup>c</sup> 2) NPH twice daily, <sup>b</sup> or 3) premixed insulin before breakfast and evening meal; for older/frail patients: 1) insulin glargine in the morning or 2) insulin detemir or NPH at night
		<ul style="list-style-type: none"> <li>Fasting hyperglycemia and daytime euglycemia</li> </ul>	Continue OADs 1) Insulin glargine, detemir, or NPH at night or 2) prandial insulin at the evening meal if bedtime blood glucose is > 140 mg/dl
		<ul style="list-style-type: none"> <li>Postprandial hyperglycemia and fasting euglycemia</li> </ul>	1) Insulin glargine, detemir, or NPH in the morning or 2) prandial insulin before one or more meals
Basal-bolus	<ul style="list-style-type: none"> <li>Unpredictable lifestyle</li> <li>High level of motivation</li> <li>Failure of previous therapy</li> <li>High risk of complications</li> </ul>	<ul style="list-style-type: none"> <li>Fasting hyperglycemia and postprandial euglycemia in patients on prandial insulin</li> </ul>	Introduce basal insulin, usually at night; initial dose of insulin detemir or insulin glargine, typically 10 units
		<ul style="list-style-type: none"> <li>Postprandial hyperglycemia and fasting euglycemia in patients on basal insulin</li> </ul>	Add prandial insulin at largest meal of the day initially, followed by second largest and then smallest; titrate dose according to results of blood glucose testing 2 hours after the start of the meal, before the next meal, or at bedtime if the injection is administered before the evening meal; lower the basal insulin dose by amount of prandial insulin given
Premixed	<ul style="list-style-type: none"> <li>Preference for fewer injections</li> <li>Preference for simple basal-bolus regimen</li> <li>Regular mealtime schedule</li> </ul>	<ul style="list-style-type: none"> <li>Fasting and postprandial hyperglycemia with significant insulinopenia</li> </ul>	An alternative to basal insulin, given before morning and evening meals

<sup>a</sup>The 2009 AACE/ACE guidelines recommend the use of insulin detemir and insulin glargine over NPH insulin.<sup>9</sup>

<sup>b</sup>Insulin detemir is approved as a once- or twice-daily insulin in the United States. The AACE/ACE 2009 guidelines<sup>10</sup> and current labeling recommendations in Europe and Canada are for once-daily administration.<sup>15,16</sup> The detemir prescribing information highlights that the dose of insulin detemir should be individualized based on the physician's advice in accordance with the needs of the patient.<sup>17</sup> For patients treated with once-daily detemir, the dose should be administered with the evening meal or at bedtime. For patients requiring twice-daily dosing for effective blood glucose control, the evening dose can be administered either with the evening meal, at bedtime, or 12 hours after the morning dose.

<sup>c</sup>Continue OAD and add prandial insulin as necessary.

sine—are currently available in the United States. Compared to regular human insulin, rapid-acting insulin analogs show faster absorption, a more rapid onset of activity, and a

shorter duration of action, resulting in improved postprandial glucose control. Moreover, rapid-acting analogs can be given within 15 minutes before or after meals, unlike conven-

tional human insulin preparations, which must be given 30–45 minutes preprandially.

In patients requiring prandial coverage, addition of a rapid-acting

Table 2. Algorithms for Initiation of Insulin in Patients with Type 2 Diabetes

Initiation of Basal Insulin in Patients with Type 2 Diabetes in Real-World Observational Studies			
Study	Initial Dose (Units/Day)	Interval	Dose Change (Units)
PREDICTIVE 303 <sup>28a</sup>	Determined by physician based on package insert for insulin-naïve patients <sup>c</sup>	Every 3 days	FPG values: <sup>b</sup> > 110 mg/dl: ↑3 80–110 mg/dl: 0 < 80 mg/dl: ↓3
GOAL A1C <sup>25</sup>	10	Weekly	FPG values: <sup>d</sup> ≥ 180 mg/dl: 8 ≥ 160 to < 180 mg/dl: 6 ≥ 140 to < 160 mg/dl: 4 ≥ 120 to < 140 mg/dl: 2 ≥ 100 to < 120 mg/dl: 0–2 ≤ 100 to ≥ 70 mg/dl: 0 < 70 mg/dl: previous lower dose < 36 mg/dl: upward titration stopped for 1 week
Initiation of Bolus Insulin in Basal-Bolus Regimen			
Algorithm	Dosage	Interval	Prandial Insulin Dose Change (Units)
Simple prandial insulin <sup>e</sup> algorithm in addition to standard basal insulin algorithm <sup>31</sup>	50% of the total daily insulin dose was used for mealtime insulin <sup>f</sup>	Adjusted weekly based on blood glucose testing results from previous week	If the mealtime dose is ≤ 10 units, this should be decreased or increased by 1 unit for blood glucose values below or above target, respectively. For insulin doses between 11 and 19 units, the dose should be adjusted up or down by 2 units, and for doses ≥ 20 units, the dose should be adjusted up or down by 3 units.

<sup>a</sup>PREDICTIVE 303 algorithm included patients on basal and basal-bolus insulin regimens.

<sup>b</sup>Every 3 days based on mean of three self-monitored FPG tests.

<sup>c</sup>0.1–0.2 units/kg once daily in the evening or 10 units once or twice daily.

<sup>d</sup>Mean of last 2–4 days of morning fasting FPG test results.

<sup>e</sup>Insulin glulisine was used as prandial insulin.

<sup>f</sup>Initial basal insulin (glargine) dose was calculated as 50% of the pre-randomization total daily insulin dose; subsequently, dosing was titrated weekly according to the mean of the last 3 days of fasting blood glucose testing and according to a standard algorithm for adjusting background insulin.

insulin analog before the largest meal of the day may be sufficient.<sup>30</sup> If A1C goals are still not achieved, an injection before the second-largest meal can be added. However, basal-bolus therapy is usually required; this involves adding to a basal insulin regimen (in which patients may be taking an OAD to control postprandial glucose elevations) a rapid-acting prandial insulin analog to replace oral therapy for all meals.<sup>3</sup>

Many health care providers without access to a diabetes team find the prospect of initiating bolus insulin particularly daunting. The treatment algorithm described by Bergenstal

et al.<sup>31</sup> provides one approach for intensifying treatments with a prandial insulin in the context of a basal-bolus regimen. According to this algorithm, prandial insulin can be administered so that it constitutes 50% of the total daily insulin dose (the other 50% being basal insulin) and should be given in three divided doses to cover daily meals: 50% for the meal containing the most carbohydrate, 33% for the middle-sized meal, and 17% for the smallest meal. Dosage can be titrated according to the algorithm shown in Table 2.

Rather than adding a prandial insulin, some patients may prefer to

switch from a basal insulin analog to a premixed insulin analog formulation, which involves giving a fixed-dose combination of both long- and rapid-acting insulin analogs in a stable mixture up to three times daily.<sup>30</sup> Patients may prefer this option because it only requires them to keep track of one insulin formulation.

Premixed insulin analogs (biphasic insulin aspart 70/30, insulin lispro 75/25, and insulin lispro 50/50) are suitable for people with fairly regular eating patterns who consume relatively small lunches because the rapid-acting analog

peaks within 1–2 hours after injection. Both insulin lispro 75/25 and biphasic insulin aspart 70/30 have been shown to provide more effective control of postprandial blood glucose than premixed human insulin 70/30 or NPH insulin, with a reduced risk of hypoglycemia.<sup>32–36</sup>

Referral to a registered dietitian (RD) for instruction on an individualized insulin-to-carbohydrate plan may be beneficial for patients during initiation or intensification of an insulin regimen. ADA recommends that an RD should play a leading role in providing nutrition care,<sup>37</sup> and the Dose Adjustment for Normal Eating (DAFNE) study<sup>38</sup> showed that patients with type 1 diabetes and moderate to poor glycemic control achieved significantly better A1C results when allocated to immediate DAFNE training than did those whose training was deferred for 6 months (8.4 vs. 9.4%;  $P < 0.0001$ ).

### Self-Monitoring of Blood Glucose (SMBG)

The successful management of type 2 diabetes hinges on the extent to which patients are motivated and confident enough to keep regular and accurate records of their blood glucose levels, a step that can be reinforced through the “monitoring” goal included in the American Association of Diabetes Educators’ AADE7 self-care behaviors framework.<sup>39</sup> Most experts agree that insulin-requiring patients should monitor their blood glucose when fasting, before meals, and before bed, and that additional postprandial SMBG would further facilitate insulin dose adjustment.<sup>1,10,40</sup> Assessment of fasting glucose will assist patients with evaluating their basal dose of insulin, and pre- and postprandial SMBG will facilitate mealtime dose assessment. For patients new to basal insulin who are checking their fasting glucose levels only, a late-afternoon blood glucose test can be helpful in evaluating rising glucose levels throughout the day resulting from mealtime excursions.

Ensuring that patients understand the relationship between carbohydrate counting and insulin requirements, the need for regular monitoring, and the connection

between poor glycemic control and the development of complications is crucial to achieving this end. Karter et al.<sup>41</sup> demonstrated that more frequent SMBG produced significantly better glycemic control, irrespective of diabetes type or regimen used.

Patients require thorough training about how to use blood glucose meters, including operating and calibrating the meter, obtaining an adequate blood sample, using control solutions, caring for and storing the device, safely disposing of sharps, and documenting and interpreting results.<sup>42</sup>

Once measured, levels should be recorded in a logbook (paper or electronic). Although most meters currently on the market have a memory feature, these are limited by the accuracy of the date and time setting. If properly instructed, patients should be able to correct suboptimal levels by adjusting their insulin dose, changing their carbohydrate intake, or exercising.<sup>38</sup>

Using logbooks to record glucose levels, carbohydrate intake, activity levels, and dose changes helps to promote interaction between patients and their health care provider. The provider can regularly review patients’ treatment patterns and have meaningful discussions about the quality of glycemic control, actively involving patients in the decision-making process. Technological advances in the form of telemedicine (e.g., video-conferencing, remote glucose monitoring, and Web-based communication with nurses and education resources) can enhance patient-provider interactions. Electronic sharing of glucose values and other data between providers and patients has been shown to improve glycemic control compared to standard care.<sup>43</sup>

### Conclusion

Because of the progressive nature of type 2 diabetes, most patients will ultimately require insulin therapy to achieve A1C targets. Health care providers therefore need to be able to educate patients about the most effective approaches to insulin implementation and intensification. This involves being able to advise patients regarding the most appropriate insu-

lin therapy for their individual needs. The introduction of insulin analogs, the availability of modern insulin devices, and access to treatment algorithms can all help providers reassure patients about the benefits of insulin treatment and devise action plans to achieve optimum glycemic control.

A recent ACE/AACE consensus statement<sup>10</sup> indicated that basal insulin analogs are preferred over human insulin because they offer a more consistent effect with a lower risk of hypoglycemia. Moreover, intensification of insulin therapy can be achieved by adding prandial insulin or switching to premixed insulin analogs. Finally, providers need to encourage effective SMBG and assist patients with the use of blood glucose meters.

It is incumbent on all of us as health care providers to gain an understanding of what patients most want to achieve out of life, to show them that optimal diabetes control will help them reach their hopes and dreams, and—last but not least—to demonstrate that we will support them in attaining these goals.

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