

Five Simple Steps to Optimize Bolus Insulin Therapy in Type 2 Diabetes

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The chronic consequences of hyperglycemia in diabetes are well documented. There is evidence that aggressive glycemic control is beneficial in certain populations. Therapy optimization occurs when ineffective medications are adjusted or new medications are added to achieve target glucose levels with minimal adverse events, specifically, hypoglycemia. Therapy selection and glycemic goals vary depending on diabetes type, duration, and comorbidities.

Insulin is paramount in reaching A1C goals for many patients with type 2 diabetes. Relying on sliding-scale insulin, a method in which the patient reactively takes a predetermined number of units of bolus insulin per blood glucose level in response to hyperglycemic self-monitored blood glucose readings, as an effective means of controlling blood glucose is not supported by evidence-based medicine. Often, basal insulin alone is not sufficient because of declining β -cell function. Establishing a basal-bolus insulin regimen can achieve glycemic control even with daily fluctuations in carbohydrate intake.

There are numerous anecdotal methods for initiating such therapy, but no consensus has developed. Health care providers must review recent literature on methods of optimizing bolus insulin to assist their patients in reaching glycemic targets and reducing the risk of hypoglycemia. Five simple steps to optimize bolus insulin therapy, as discussed below and summarized in Table 1,

may provide people with diabetes and their health care teams with a guide for success.

Rationale for Individualized Insulin Optimization

In the landmark U.K. Prospective Diabetes Study (UKPDS), people with newly diagnosed type 2 diabetes in the intensive therapy arm were treated with sulfonylurea, metformin, or insulin and attained an A1C of 7% compared to 7.9% with standard therapy. Obtaining a lower A1C reduced microvascular complications by 25% over a median period of 11 years (1). Additionally, a long-term cohort follow-up demonstrated reduced cardiovascular events in the intensive therapy group (2).

Results from the UKPDS and its 10-year follow-up led researchers to explore the question of whether more intensive glucose control was warranted in everyone. Regrettably, recent subsequent trials showed otherwise. Three trials (ACCORD [Action to Control Cardiovascular Risk in Diabetes], ADVANCE [Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation], and VADT [Veterans Affairs Diabetes Trial]) resulted in A1C values of ~6.4–6.9% with intensive therapy versus 7.3–8.4% with standard therapy over 3.0–5.6 years in individuals at high risk for cardiovascular events (3–5). These trials demonstrated no reduction in macrovascular events, and only one—ADVANCE—demon-

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TABLE 1. Five Steps of Bolus Insulin Optimization

Step 1. Form a multidisciplinary team	The team should include clinical pharmacists, certified diabetes educators, registered nurses, dietitians, health coaches, and care coordinators.
Step 2. Determine glucose goals	Based on patient-specific factors, set targets for A1C, FPG, and preprandial glucose levels.
Step 3. Optimize basal insulin	Titrate the basal dose until FPG is at goal.
Step 4. Choose an optimization method	Use guidelines or evidence-based literature to choose an optimization method to meet the individualized goals of patients and care providers.
Step 5. Schedule follow-up	Review patients' glucose readings and doses every 1–2 weeks initially, and then space out follow-up over time. For the long-term, follow up every 3–6 months based on A1C goal achievement.

strated reductions in microvascular disease. The ACCORD trial showed increased total mortality in the intensive therapy group. These studies led experts to challenge the need for intensive therapy in individuals with type 2 diabetes with moderate to high cardiovascular risk and comorbidities. The variance in the results of these and other trials provides a rationale for setting patient-specific glucose goals and developing individualized therapy regimens.

Five Steps of Bolus Insulin Optimization

Step 1. Form a Multidisciplinary Care Team

Patients and providers form a partnership for effective diabetes management. In addition, a multidisciplinary team that includes clinical pharmacists, certified diabetes educators, registered nurses, dietitians, health coaches, and care coordinators can aid in the optimization process. The team takes into account patient-specific characteristics to develop a successful, individualized plan. Teaching individuals with diabetes about the different aspects of bolus insulin optimization and the importance of communicating their results with their care team ensures prompt follow-up will occur. The American Diabetes Association (ADA) recommends comprehensive education about self-monitoring of blood glucose (SMBG), diet, exercise, and the avoidance and treatment of hypoglycemia (6). Providing such education helps ensure patients under-

stand how each of these topics factor into blood glucose regulation and hypoglycemia prevention. Having a multidisciplinary team available will facilitate the success of the next four steps in the bolus optimization process.

Step 2. Determine Glucose Goals

The second step in optimizing bolus insulin is to determine patient-specific glucose goals. Long-term glucose goals focus on A1C results. A1C represents a composite of glycemic control over the previous 2–3 months and is a product of fasting and daytime pre- and postprandial glucose levels. ADA recommends a target A1C of <7% for the majority of patients to reduce the risk of microvascular complications and long-term macrovascular disease if implemented soon after diagnosis (6). ADA also advocates individualizing therapy and glucose goals based on duration of diabetes and existing comorbidities.

Individualized glycemic targets will vary depending on individual patients' goals, comorbidities, risk of hypoglycemia, duration of diabetes, and diabetes type. A more stringent A1C goal of <6.5% might be considered for those who can safely achieve it without significant hypoglycemia or other adverse events; a less aggressive A1C goal of <8.5% may be appropriate for older adults with poor health and a limited life expectancy.

Because A1C is a long-term average, achieving the A1C goal is accom-

plished by meeting daily glucose goals. ADA recommends a preprandial glucose goal of 80–130 mg/dL and a peak postprandial glucose of <180 mg/dL. Because fasting plasma glucose (FPG) is generally measured before breakfast, it is considered preprandial and has the same goal of 80–130 mg/dL. Again, glucose target ranges should be adjusted based on individual requirements.

Step 3. Optimize Basal Insulin

Because basal insulin is usually the initial insulin therapy for people with type 2 diabetes, optimizing this component of the insulin regimen should occur before adding bolus insulin. Basal insulin will lower glucose levels over a 24-hour period but has less effect on postprandial hyperglycemia. The goal of basal insulin therapy is to suppress the liver from releasing excess glucose, and it is titrated based on FPG. If FPG is at goal but A1C still is not, premeal bolus insulin should be considered (6).

Often, providers continue to increase a patient's total basal insulin dose instead of initiating bolus insulin with meals. "Overbasalization" occurs when the basal dose is increased, but glycemic targets are not achieved (7). One reason the A1C target in such cases is not reached with continued titration of basal insulin is, at an A1C of 7.3%, 70% of the glucose average is the result of postprandial hyperglycemia, whereas fasting hyperglycemia accounts for only 30% of the A1C (8). Thus, get-

TABLE 2. Bolus Insulin Optimization Methods

Method	Initiation	Titration (based on SMBG)	Titration Frequency
ADA (6)	4 units, 0.1 units/kg, or 10% basal dose	Add 1–2 units or 10–15% if >131 mg/dL No change if 80–130 mg/dL Reduce by 2–4 units or 10–20% if <80 mg/dL Individualize goals if necessary	Once to twice weekly until glucose target is reached
AUTONOMY Q1D (9)	10% of total glargine dose with first meal of the day	Add 1 unit if >114 mg/dL No change if 85–114 mg/dL Reduce by 1 unit if 56–84 mg/dL Reduce by 2 units if <56 mg/dL	Self-titrate daily until target is achieved based on the previous day’s premeal glucose for the meal after the injection (e.g., if injected with breakfast, use previous day’s prelaunch reading)
AUTONOMY Q3D (9)	10% of total glargine dose with first meal of the day	Add 4 units if >144 mg/dL Add 2 units if 115–144 mg/dL No change if 85–114 mg/dL Reduce by 2 units if 56–84 mg/dL Reduce by 4 units if <56 mg/dL	Self-titrate every 3 days until target is achieved based on the median premeal blood glucose from the previous 3 days for the meal after the injection (e.g., if injected with breakfast, use median of previous 3 days’ prelaunch readings)
FullSTEP stepwise (10)	4 units before meal with greatest carbohydrate content	Add 1 unit if >130 mg/dL No change if 70–130 mg/dL Reduce by 1 unit if <70 mg/dL	Self-titrate daily until target is achieved based on subsequent premeal glucose, at one, two, or three meals, depending on the number of boluses administered; patients were advised to self-adjust their bolus insulin on the basis of the previous day’s glucose readings
FullSTEP basal-bolus (10)	2 units before meals 3 times/day	Add 1 unit if >130 mg/dL No change if 70–130 mg/dL Reduce by 1 unit if <70 mg/dL	Self-titrate daily until target is achieved based on the previous day’s glucose readings before each meal and at bedtime

ting A1C to <7% for patients who are already on optimized basal insulin requires targeting postprandial hyperglycemia by instituting a bolus insulin optimization method.

Step 4. Choose an Optimization Method

Just as glucose goals are not “one size fits all,” neither are all bolus insulin optimization algorithms. Three methods described in recent medical literature include one recommended in the ADA’s *Standards of Medical Care*, another used in the AUTONOMY trial, and a third employed in the FullSTEP trial (Table 2) (6,9,10). Each method has a different initi-

ation dose, titration process, blood glucose goal, and titration frequency schedule. Understanding each method, as well as patient-specific factors, will allow the team to choose the correct regimen for each patient. Using guidelines or clinical trial-based algorithms may increase the likelihood of success because these methods have been shown to be safe and effective.

ADA Method

The ADA approach, as discussed in the *Standards of Medical Care in Diabetes—2017*, offers options to initiate, titrate, and optimize bolus insulin (6). This regimen can be adjusted by care team members, or

the team may develop a self-titration algorithm for patients. Because this algorithm provides different options, the team must decide which to use when developing the optimization plan. Bolus insulin is initiated before the largest meal of the day at 4 units, 0.1 units/kg, or 10% of the basal dose. The dose is increased by 1–2 units or 10–15% once or twice weekly until the SMBG target is reached. If the SMBG target is achieved and the A1C is still not at goal, a second injection may be added, followed by a third injection, if necessary.

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AUTONOMY Trial Method

The AUTONOMY trial studied the effectiveness in lowering A1C of two patient-driven approaches to titrating prandial insulin lispro in patients with type 2 diabetes (9). After a participant's FPG was at goal with the use of insulin glargine, insulin lispro was initiated with one injection before breakfast. One algorithm had the patient titrate daily, and another called for patient titration every 3 days. Insulin lispro was progressively added to the other meals when blood glucose targets were not achieved. At the end of 24 weeks, the two approaches were shown to be clinically equivalent.

FullSTEP Trial Method

The FullSTEP trial studied the initiation of insulin aspart once daily before the largest carbohydrate meal (stepwise) or three times per day (basal-bolus) in patients on optimized insulin detemir therapy (10). In both groups, patients self-titrated the insulin aspart daily. If individuals who initiated one injection per day did not have an A1C <7% at 11 weeks, they added an additional injection of insulin aspart with their next largest carbohydrate meal. If after 22 weeks the A1C was not <7%, an additional injection was added before the third meal. Over 32 weeks, participants initiated with the stepwise plan had a similar A1C with significantly lower hypoglycemia and better patient satisfaction compared to the group who initiated three bolus injections per day.

Step 5. Schedule Follow-Up

The ADA algorithm adjusts bolus doses once or twice per week. The AUTONOMY algorithms adjust the doses either daily or every 3 days. The FullSTEP algorithm adjusts the

dose daily. Following up with patients within the first week of initiation will ensure they understand how to titrate their doses. This follow-up can be done by one of the team members and does not necessitate an in-person visit. Telephone or secure electronic means will allow patients to share glucose results with less disruption to their normal routine. Establishing real-time result-sharing and feedback should improve the likelihood of continuous interaction over time.

During each follow-up visit, patients should be asked about hypoglycemia. If hypoglycemia occurs, determination of the cause and appropriate adjustments should occur. All three methods start with a low dose of bolus insulin to decrease the risk of hypoglycemia. As therapy is titrated, hypoglycemia is more common but can be minimized with frequent follow-up.

Conclusion

This article describes a simple five-step process for optimizing bolus insulin therapy based on recent literature. Forming a multidisciplinary care team, determining individual glucose goals, optimizing basal insulin, choosing and following a bolus insulin optimization algorithm, and scheduling appropriate follow-up will allow patients and providers to work as a team to reach individualized glucose goals. No single optimization method will provide success for every person with type 2 diabetes, but passively monitoring blood glucose without making adjustments may prevent patients from getting to goal and benefiting from reductions in the long-term consequences of diabetes. Although there are differences of opinion in the literature about how best to optimize bolus insulin therapy, now is the time

to institute a plan and take action for each patient.

Duality of Interest

The authors are employed by Novo Nordisk, Inc., which manufactures and markets insulin for the treatment of diabetes.

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