



MANAGEMENT OF TYPE 2 DIABETES: Practical Approaches to Insulin Use

Learning Objectives

After completing this activity, participants should be better able to:

- Identify patients with type 2 diabetes who are candidates for insulin initiation
- Evaluate glycemic patterns in patients with type 2 diabetes to determine the best individualized therapeutic approach
- Use short-, intermediate-, or long-acting insulin or premixed insulin to initiate and advance individualized insulin regimens for the management of type 2 diabetes

A Growing Epidemic

The problem of diabetes in the United States continues to grow steadily, so that today this pernicious disease affects approximately 1 in 10 Americans.¹ In 2006, diagnosed and undiagnosed diabetes (defined as fasting plasma glucose [FPG] ≥ 126 mg/dL) affected 10.2% of the adult population in the United States, up from 8.3% in 1988-1994.¹ African Americans (16%) and Mexican Americans (15.7%) have the highest rates of diabetes.¹ Obesity, a significant risk factor for type 2 diabetes (T2DM) is also on the rise, affecting 34% of adults (up from 15% in 1971-1974)¹ and 15% to 18% of children aged 6 to 19.¹ The American Diabetes Association (ADA) estimates that in 2007, health-care costs for people with diabetes were 2.3 times higher than for a similar population without diabetes and that 284,000 deaths could be attributed to the disease.² Figures from 2007 showed that total diabetes-related expenditures run about \$174 billion annually in the United States, including \$116 billion in direct costs and \$58 billion in indirect costs related to reduced productivity, absenteeism, disability, and premature mortality.²

Complications of diabetes also contribute to healthcare costs, particularly hospitalizations for cardiovascular (CV) complications, which represent the second largest category of diabetes-related expense.² Currently, 1 of every 10 health-care dollars is spent on diabetes and its complications.²

As A1C decreases to levels near 7%, PPG becomes a more important determinant than FPG in reaching goal A1C.

What regimen is most effective in the management of PPG?
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Whether intervention prevents complications in the long term was answered affirmatively by the United Kingdom Prospective Diabetes Study (UKPDS), a prospective, randomized trial that followed patients with T2DM who received either intensive therapy or conventional therapy over a 10-year follow-up period.³ A median glycosylated hemoglobin (A1C) level of 7.0% was achieved in patients in the intensive therapy group, while those in the conventional therapy group had a median A1C level of 7.9%. Researchers found that the risk of myocardial infarction (MI) and microvascular complications strongly correlated with A1C levels.³ Further, for each 1% reduction in A1C, there was an associated rate reduction of 14% in MI ($P < .0001$), 12% in stroke ($P = .035$), 16% in heart failure ($P = .021$), 37% in microvascular complications ($P < .0001$), and 21% in diabetes-related mortality ($P < .0001$).³ Similar findings were also seen in a type 1 diabetes population in the Diabetes Control and Complications Trial (DCCT).⁴ The excess morbidity, mortality, and cost associated with diabetes underscore the importance of early diagnosis and aggressive measures to control glucose.

Natural History of T2DM

Fundamentally, the elevation in blood sugar seen in T2DM is the result of a combination of defects in insulin secretion from pancreatic beta cells on a background of insulin resistance (decreased peripheral glucose uptake),⁵ which is a major feature of T2DM.⁶ Insulin-resistant individuals secrete more insulin than insulin-sensitive individuals when exposed to the same glucose challenge.⁷ Prolonged high demand for insulin cannot be met as beta cells are damaged by influences including hyperglycemia, increased free fatty acids, genetic predisposition, amyloid deposition, decreased incretin effect, age, and insulin resistance, leading to loss of beta cell mass and eventually to beta cell failure. The end result is decreased availability of endogenous insulin.⁶ As discovered in an autopsy study, beta cell loss is accelerated in T2DM, regardless of body mass. In this study, obese nondiabetic individuals actually had greater beta cell volume than lean individuals, an expected normal response to compensate for insulin resistance.⁸ However, obese individuals with impaired fasting glucose and both lean and obese individuals with T2DM had significantly lower beta cell volume than comparable nondiabetic individuals.⁸ Clearly, loss of beta cells is intimately involved with development of diabetes.

Fasting glucose levels play an important role in glucose-stimulated insulin release following a meal. The physiologic response to glucose ingestion includes the first-phase insulin response, which is a short-lived spike in insulin release to suppress the rapid postmeal glucose rise, and a longer second-phase insulin release.⁹ However, even minor elevations in FPG levels have a powerful inhibitory effect on first-phase insulin response. At relatively low FPG levels of 100 to 114 mg/dL, individuals lose about 50% of their ability to secrete first-phase insulin in response to meal challenge.¹⁰ At levels between 115 and 149 mg/dL, first-phase insulin release essentially is suppressed.¹⁰ By the time the average patient receives a diagnosis of T2DM, the processes of abnormal glucose metabolism have been ongoing for a decade or more.¹¹ During this time, progressive loss of glycemic control resulting from increased insulin resistance and declining beta cell function leads to slow but steady damage to blood vessels and other tissues.

Usually, the first clinical sign of beta cell failure is elevated postmeal glucose (impaired glucose tolerance) that is soon followed by abnormalities in FPG as beta cell function declines.⁷

Principles of Diabetes Management: The Lasting Effects of ACCORD

Prior to the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, clinicians believed that lowering A1C as aggressively as possible might result in reduction of diabetes-associated CV complications in patients with T2DM. Previously, UKPDS found no lower threshold of A1C for continued CV benefit.³ ACCORD randomized 10,521 patients with T2DM to receive intensive therapy, which targeted an A1C goal of <6.0%, or standard therapy, which targeted an A1C goal of 7.0% to 7.9%.¹² However, an interim analysis of the study uncovered unexpected higher mortality in the intensive therapy group, which led to early termination of that study arm.¹² ACCORD patients were about 62 years of age at baseline and had a median disease duration of 10 years, median FPG of 175 mg/dL, and median A1C of 8.3%; about one third had a history of previous CV events.¹² Although lower A1C levels were achieved in the intensive therapy group than in the standard therapy group (median, 6.7% vs 7.5%), those in the intensive therapy group experienced more all-cause (5.0% vs 4.0%; $P = .04$) and CV mortality (2.6% vs 1.8%; $P = .02$) than those in the standard therapy group.¹² The difference in mortality is not easily explained, but it may be related to factors such as additional exposure to more drugs from every class, more dose changes, and higher rates of hypoglycemia, weight gain, and fluid retention.¹² It also is possible that for the

Table 1. Results of Steno-2: Intensive Management of Risk Factors

Outcome	Intensive Therapy (n = 67) vs Standard Therapy (n = 63)	P Value
	HR (95% CI)	
All-cause mortality	0.54 (0.32-0.89)	.02
CV mortality	0.43 (0.19-0.94)	.04
CV event	0.41 (0.25-0.67)	<.001
	RR (95% CI)	
Diabetic nephropathy	0.44 (0.25-0.77)	.004
Diabetic retinopathy	0.57 (0.37-0.88)	.01
Autonomic neuropathy	0.53 (0.34-0.81)	.004
Peripheral neuropathy	0.97 (0.62-1.51)	.89

Gaede P, et al.¹³

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ACCORD patients, who already had advanced disease and evidence of CV complications, intensive intervention came too late to provide a significant benefit. This possibility again underscores the importance of early intervention and individualized therapy. More aggressive A1C lowering may be appropriate for the younger patient with no target organ damage, whereas less aggressive targets may be more appropriate for older patients who already have microvascular, macrovascular, and other complications of diabetes.

The importance of managing nonglycemic CV risk factors in addition to targeting blood glucose was made clear by results from the Steno-2 trial.¹³ In this study, patients with T2DM were assigned to intensive therapy, designed to achieve A1C <6.5%, total cholesterol <175 mg/dL, serum triglycerides <150 mg/dL, and blood pressure <130/80 mm Hg, or standard therapy to manage glucose and risk factors. Patients' mean age was in the mid-50s at the beginning of the trial, which had a median 13.3-year follow-up.¹³ Patients receiving intensive therapy derived significant benefit on outcomes of all-cause and CV mortality, CV events, and other diabetes complications (Table 1).¹³ These findings underscore the fact that diabetes evolves in a complex cardiometabolic environment—where various elements overlap and demand monitoring and management—and that as clinicians, the whole person—not a single disease—must be treated.

Initiating Insulin Therapy in T2DM

Clinicians and patients must work closely to develop the most realistic strategy for achieving recommended glucose levels (Table 2). Desirable A1C levels are often not maintained with oral therapy alone in patients who start diabetes treatment on oral antidiabetic agents (OADs).¹⁴

Table 2. National Recommendations for Glycemic Measures

Glycemic Measure	Guideline	
	ADA ^a	AACE/ACE ^b
A1C (%)	<7	≤6.5
Fasting/preprandial (mg/dL)	70-130	<110
2-hour postprandial (mg/dL)	<180 ^a	<140 ^b

Individualize goals for:

- Duration of diabetes, pregnancy status, age, comorbid conditions, hypoglycemic unawareness, individual patient considerations
- PPG may be targeted if A1C goals are not met despite reaching FPG goals

^aThe ADA postprandial target was established in 2001.

^bThe AACE/ACE postprandial target was established in 2004.

ADA⁵; ACE/AACE.²⁹

Clinicians need to be both vigilant and proactive, identifying early signs of poor glycemic response and intensifying or changing regimens swiftly to avoid disease progression. The Treat-to-Target Trial demonstrated that the addition of once-daily basal insulin (either neutral protamine Hagedorn [NPH] or glargine) to existing failed OAD therapy substantially decreased FPG and A1C in patients with T2DM after only 18 weeks.¹⁴ At the start of the trial, patients' mean A1C levels were about 8.6% and FPG was nearly 200 mg/dL; 70% were taking metformin plus a sulfonylurea.¹⁴ Both types of basal insulin produced similar reductions in A1C and FPG, but NPH was associated with significantly more hypoglycemia than was glargine ($P < .02$ for symptomatic events).¹⁴

The current ADA/European Association for the Study of Diabetes (EASD) consensus algorithm recognizes insulin as the most effective and cost-efficient way to lower glucose when 1 or 2 oral agents fail to achieve goal A1C and recommends it as a possible second step in treating T2DM for patients who are not controlled with lifestyle modifications and metformin (Figure 1). Therapy should be intensified every 2 to 3 months until A1C goals are met.¹⁵ This algorithm provides a framework for planning initiation and intensification of diabetes care and offers the clinician confidence by providing a tool agreed upon by international diabetes experts and groups.

The body normally produces a fairly constant level of insulin throughout the day that meets the needs for glucose control when not eating (basal secretion), as well as bursts of insulin secreted to control the elevation of glucose after meals (bolus insulin).⁹ Commercially available insulin products seek to mimic these physiologic patterns. Basal insulin provision can be approximated by NPH (usually a human derivative product), an intermediate-acting insulin that lasts about 12 hours and requires multiple injections to truly cover the day. Analog basal insulins, glargine and detemir, have been developed to produce a much more physiologic pattern of basal action. Glargine lasts for 24 hours with very little "peaking" of insulin activity and can be given once daily to approximate physiologic basal insulin replacement.¹⁶ Detemir is not quite as long lasting or as "peakless" as glargine, depending on dose,¹⁷ and is usually given once or twice daily depending on the needs of the individual patient.¹⁸ Rapid-acting analog insulins (glulisine, lispro, aspart) also have been developed and come very close to mimicking the physiologic mealtime needs for insulin. These are often referred to as prandial or bolus insulin. In an attempt to capture the best of both worlds (basal and bolus),

Post-ACCORD/Steno-2 Principles for Managing Patients With T2DM

- **Early diagnosis is key.** Advanced disease is much harder to reverse and manage.
- **Individualize therapy.** Consider disease duration, life expectancy, and comorbid CV disease in establishing treatment targets.
- **Treat aggressively to reach target.** Add to or change failing regimens.
- **Aggressively treat all comorbidities.** Provide robust therapy for all non-glycemic CV risk factors.

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various human derivative and analog premixed products have been devised that combine basal and bolus insulin in the same preparation. Frequently, these are used in 70/30, 75/25, or 50/50 proportions (basal/bolus). The main drawback to premixed insulin is lack of flexibility when titrating (because 2 insulins are involved), and the authors of the ADA/EASD algorithm suggest they be avoided during dose titration. Regular human insulin (RHI), a slower-acting mealtime insulin, is sometimes used for mealtime coverage but has the disadvantage of requiring administration 30 to 45 minutes prior to the meal to attain the best effect. Each insulin type may be effective in different patients at different points in the progression of disease. Analog basal insulin, which has a longer, nonpeaking profile compared to NPH, is less likely to cause hypoglycemia than NPH, particularly during the overnight period.¹⁴ It is often the starting point in initiating insulin therapy. The choice for initiating therapy is generally basal insulin added to oral agents for A1C values <9.5%. A1C levels >9.5% indicate significant glucotoxicity, and therapy would be initiated with multiple daily doses of insulin.¹⁸ Figure 2 illustrates characteristic action profiles of basal and bolus insulin formulations.

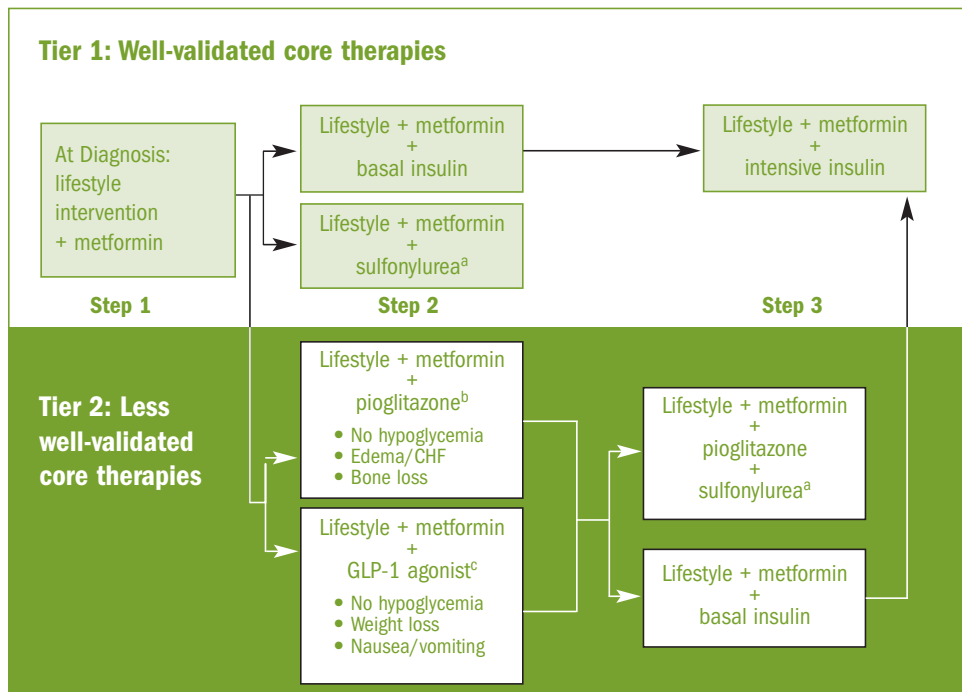


Figure 1. ADA/EASD consensus algorithm for initiation and adjustment of therapy for T2DM. Reinforce lifestyle interventions at every visit. Check A1C every 3 months until <7% and then at least every 6 months. ^aOther than glyburide or chlorpropamide; ^bOption if hypoglycemia is particularly undesirable. Associated with increased risks of edema, congestive heart failure, and fracture; ^cOption if hypoglycemia is particularly undesirable or weight loss is a major consideration and A1C is <8%. Associated with relatively high frequency of nausea, vomiting, and diarrhea. Insufficient clinical use for confidence regarding safety. Used with permission of *Diabetes Care*, from Nathan DM, et al¹⁵; permission conveyed through Copyright Clearance Center, Inc.

Initiating Basal Insulin Therapy for T2DM

In patients with T2DM, elevated FPG blunts insulin release normally triggered by meals and snacks. The result is that these patients have higher blood glucose levels throughout the day due to weakened first-phase response to mealtime glucose influx.⁹ The goal of insulin treatment is to return the system to a state that more closely resembles the nondiabetic state. Basal insulin helps to restore background FPG to normal levels, since it is largely the overnight basal production of glucose by the liver that determines the FPG value. To achieve the proper dosing, basal insulin is commonly started at a dose of 10 U, which is unlikely to cause hypoglycemia, and titrated upward according to one of several titration algorithms. These algorithms have been shown to be both safe and effective in identifying the basal insulin dose required to achieve FPG control (100-110 mg/dL) and are simple for patients to learn and administer (Table 3).^{14,19-21}

Role of Premixed Insulin

Premixed insulin combines a short-acting prandial component that effectively manages postprandial hyperglycemia with a longer acting basal-like component (Figure 3).^{22,23} Most patients treated with premixed insulin will require morning and evening doses, and some require 3 daily doses for A1C and FPG goals to be achieved.²⁴ A study that compared a basal insulin analog (glargine) with premixed insulin found the latter associated with more than twice as much hypoglycemia as glargine plus OADs (9.87 vs 4.07 events; $P < .0001$).²⁵ A recently published meta-analysis found that evidence favors premixed insulin analogs for control of postprandial glucose (PPG) and reducing A1C, but basal insulin analogs are more effective for reducing FPG and are associated with less weight gain and hypoglycemia.²⁶

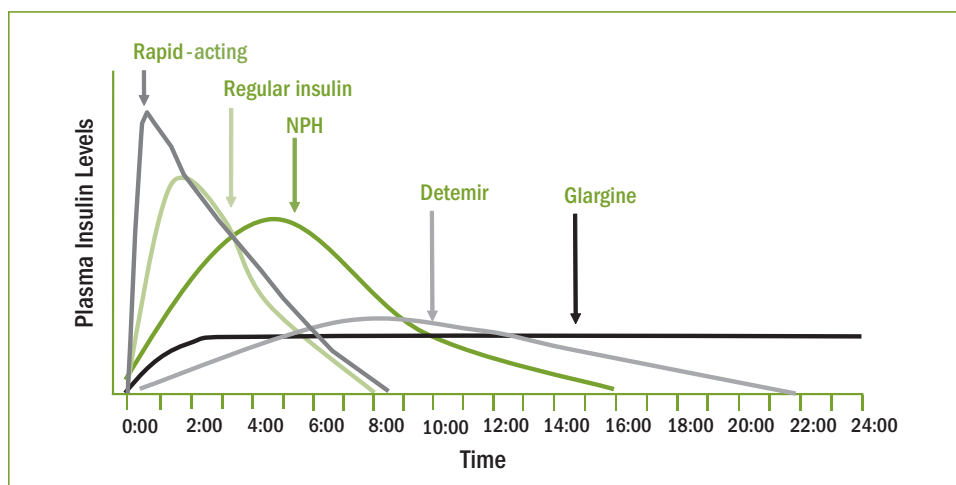


Figure 2. Characteristic action profiles of different insulin types. From left: rapid-acting analogs (eg, aspart, glulisine, lispro); regular human insulin; intermediate-acting NPH; long-acting basal insulin analogs detemir and glargine. Plank J, et al¹⁷; Rosenstock J, et al³⁵; Rave K, et al.³⁶

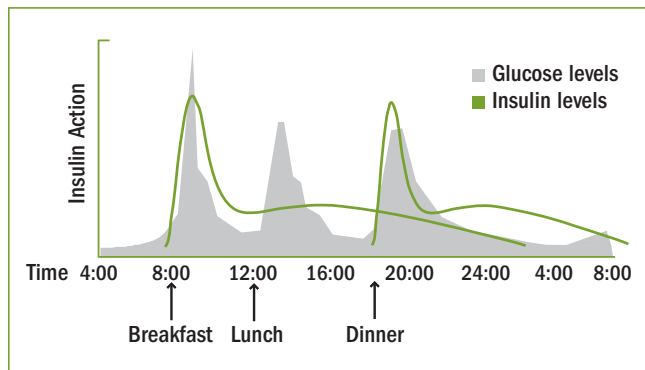


Figure 3. Profile of twice-daily premixed insulin analogs (lispro 75/25 or aspart 70/30). Usually dosed before the evening (largest) and morning meals, premixed insulin analogs provide a prandial peak to control PPG and a longer lasting insulin level that is similar to basal insulin. Note that no prandial insulin response accompanies lunch. Leahy J²²; Nathan DM.²³

The Problem of PPG in Glucose Control

Monnier and colleagues demonstrated that as A1C decreases to levels near 7%, PPG becomes the predominant focus in further improving glucose control and not FPG, which plays the predominant role at higher A1C levels.²⁷ Practically speaking, this means that as a patient’s A1C level gets closer to goal, uncontrolled PPG will keep it from reaching that target even when the FPG value is well within accepted limits.

Further, the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study, which analyzed data from 22,514 individuals, found that elevated PPG correlated with all-cause mortality independent of FPG levels.²⁸ National glycemic recommendations include 2-hour PPG goals as well as fasting/preprandial goals

Table 3. Titration Algorithms for Basal Insulin

Algorithm	Method
2-4-6-8 Treat to Target ¹⁴	Add 2, 4, 6, or 8 U to basal insulin weekly depending on average FPG
PREDICTIVE 303 ¹⁹	Add 3 U basal insulin every 3 days until average FPG = 100 mg/dL
1-1-100 INSIGHT ²⁰	Add 1 U basal insulin daily until FPG = 100 mg/dL
3-2-1 ATLANTUS ²¹	Add 2 U basal insulin every 3 days until average FPG = 100 mg/dL

INSIGHT = Implementing New Strategies With Insulin Glargine for Hyperglycemia Therapy; PREDICTIVE = Predictable Results and Experience in Diabetes Through Intensification and Control to Target: an International Variability Evaluation. Riddle M, et al¹⁴; Meneghini L, et al¹⁹; Gerstein HC, et al²⁰; Davies M, et al.²¹

(Table 2).^{5,29} Given the timing of meals, PPG phases tend to overlap and individuals may spend 12 or more hours a day in postprandial states.³⁰ Clinically, this means that patients with poor PPG control are spending most of their waking day in a hyperglycemic state. Unfortunately, PPG is poorly controlled in many patients with T2DM, including 39% of those with A1C levels <7% and essentially all of those with A1C levels >7%.³¹ Even in patients with an A1C value >7% on OADs, essentially all experience postprandial hyperglycemia with glucose values >200 mg/dL at some point in the day.³¹

There are 2 options for adding prandial insulin: RHI and rapid-acting insulin analogs.³² Looking at the action profiles of the different types of insulin (Figure 2), it is clear that rapid-acting insulin analogs produce a very fast insulin spike, with onset of action within 15 minutes and a peak concentration within 1 hour.^{17,33-36} They can be given immediately before a meal³² and up to 20 minutes after a meal is begun and still be effective. With RHI, the onset of action is 30 minutes to an hour, meaning the injection must be given 30 to 45 minutes prior to the meal.³² For some patients, this can be difficult to manage, particularly patients at work, adult patients with active families, or any patient who is eating away from home.

In physiologic terms, a basal/bolus regimen closely mimics the natural insulin release in response to meals.²² When a patient becomes a candidate for mealtime insulin, transitioning from a basal regimen to a basal/bolus regimen is a fairly simple stepped process (Figure 4). Patients start by adding bolus insulin at their biggest meal, which is usually the evening meal, and then adding additional doses as necessary with other meals to maintain PPG goals and get A1C to target. At the outset, the basal insulin dose is decreased by the same amount as the bolus insulin dose, and it is later adjusted to maintain FPG and A1C values. The bolus insulin dose can be adjusted individually and daily depending on the expected carbohydrate content of a meal (higher carbohydrate content, more bolus insulin) or patient's activity level that day (less bolus insulin if highly active).³² It should be noted that metformin, and possibly thiazolidinediones, should be continued when bolus insulin is initiated, but it is appropriate at that point to discontinue sulfonylureas.³²

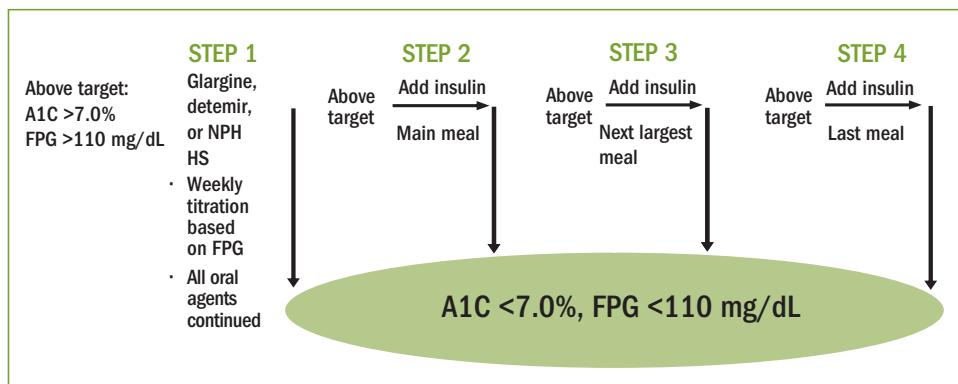


Figure 4. Stepwise approach to transition from basal to basal/bolus insulin therapy in patients with T2DM. At each step, addition of a rapid-acting prandial insulin may help to control PPG and improve glycemic control. Adapted from Karl DM.³²

CASE
STUDYA 38-Year-Old Woman With a 3-Year History of
T2DM on Premixed Insulin

Presentation

A 38-year-old Caucasian woman who has just relocated presents to a new clinician's office with complaints of night sweats and shivers that awaken her and leave her feeling "dreadful" and exhausted in the morning. She has 3 children at home, works part-time, and has limited pharmacy benefits. Her relevant medical history includes a diagnosis of T2DM 3 years prior that was treated with metformin and a sulfonylurea. When her A1C level reached 9.3%, her clinician initiated a premixed insulin analog (70/30 aspart) 18 U twice daily along with her existing OAD therapy.



Physical Examination

- Height: 5 ft 8 in
- Weight: 162 lb
- Body mass index: 24.6 kg/m²
- Blood pressure: 135/85 mm Hg

Laboratory Results

- Lipids
 - Total cholesterol: 225 mg/dL
 - Low-density lipoprotein cholesterol: 132 mg/dL
 - High-density lipoprotein cholesterol: 40 mg/dL
 - Triglycerides: 210 mg/dL
 - Non-high-density lipoprotein cholesterol: 185 mg/dL
- A1C: 7.6%
- FPG: 182 mg/dL

Clinical Decision Point

How should the new clinician proceed at this point?

- Treat nonglycemic risk factors
- Intensify lifestyle management: diet, exercise, weight management

- Refer for diabetes education
- Ask patient to self-monitor glucose to establish baseline glycemic values
- All of the above

Comment

In line with findings from Steno-2,¹³ her clinician adds a statin and an angiotensin-converting enzyme inhibitor to the patient's regimen to control her lipid and blood pressure values while efforts continue to improve her glucose levels. She meets with a diabetes educator and works out a modified diet and exercise plan, including 30 minutes of exercise 5 times a week. She agrees to keep a self-monitored blood glucose (SMBG) diary, measuring glucose before breakfast, before each meal, before bedtime, and during night sweats for 1 week.

The diary shows that her FPG and predinner glucose levels are high, but they are close to target at lunch and then, unfortunately, hypoglycemia develops overnight (Figure 5).

Daily Blood Glucose Diary						Week Starting _____			
	BREAKFAST		LUNCH		DINNER		HS	Middle of night	
	Dose	Blood Sugar	Dose	Blood Sugar	Dose	Blood Sugar	Dose		
Monday		147		110		153		185	57
Tuesday		138		112		170		164	48
Wednesday		140		90		155		205	-
Thursday		166		105		134		213	60
Friday									
Saturday									
Sunday									

Figure 5. Glucose diary: first week.

Clinical Decision Point

What changes should be made in this patient's regimen?

- Change her oral medications, continue premixed insulin
- Continue oral medications, stop premixed insulin, and initiate a long-acting basal insulin analog
- Lower the dose of premixed insulin
- Discontinue oral medications, continue premixed insulin

Comment

The dilemma for this patient is that she needs both more insulin and less insulin at the same time, which cannot be achieved with a fixed-dose, premixed insulin. While the case can be made to drop the sulfonylurea, it is very unlikely that this agent is the cause of the nocturnal hypoglycemia. The clinician discontinues the premixed insulin and prescribes a basal insulin analog at a starting dose roughly equivalent to the basal dose she is

Daily Blood Glucose Diary						Week Starting _____			
	BREAKFAST		LUNCH		DINNER		HS	Middle of night	
	Dose	Blood Sugar	Dose	Blood Sugar	Dose	Blood Sugar	Dose		
Monday		107		126		133		185	—
Tuesday		116		123		120		164	118
Wednesday		102		121		105		205	112
Thursday		94		132		120		213	—
Friday									
Saturday									
Sunday									

Figure 6. Glucose diary: 3-month follow-up.

currently receiving daily in her premixed insulin. The basal insulin analog is started at 25 U and self-titrated to 45 U over the next 3 weeks, and the OADs are continued.

3-Month Follow-Up Visit

Three months later, on a regimen of metformin, a sulfonylurea, and 45 U glargine, the patient's A1C value is down to 7.2%. Her SMBG diary shows that her FPG and pre-meal and nocturnal glucose values are all within acceptable ranges (Figure 6). However, her PPG, which should be <180 mg/dL, consistently is high after the evening meal (185-213 mg/dL).

Clinical Decision Point

How could this patient's therapy be modified to reach A1C goal?

- Continue to titrate long-acting insulin glargine
- Switch to another long-acting insulin analog

Correction Factor for Dosing Rapid-Acting Insulin When Premeal Blood Sugar Is >130 mg/dL

The purpose of mealtime insulin is to provide necessary insulin to cover the glycemic load of the meal to be consumed (by carbohydrate counting or estimation) and to reduce the ambient premeal sugar back to the premeal goal of 130 mg/dL (stated ADA premeal target), if necessary. As a general rule, 1 unit of rapid-acting analog insulin should lower the ambient sugar by 25 mg/dL. An easy-to-use equation is as follows: $(\text{patient sugar} - 130)/25 = \text{correction factor units}$. For example, if the premeal sugar is 205, $(205 - 130)/25 = 3$ units. The 3 units of “correction factor” insulin are added to the number of units estimated to cover the meal. This is very different from the older concept of a “sliding scale,” which adds insulin only if the patient’s sugar reaches unacceptably elevated levels.

- Add mealtime (prandial) insulin
- Intensify dietary and other lifestyle measures

Comment

PPG plays a proportionally larger role than FPG as the A1C level gets closer to 7%. Achieving PPG control is important to overall glucose control, because patients may spend 12 or more hours a day in a postprandial state. Adding rapid-acting prandial insulin at the evening meal should help control PPG without increasing the patient’s risk of nocturnal hypoglycemia. A combined basal-prandial insulin regimen most closely reproduces physiologic insulin. In this case, the clinician adds prandial insulin to the basal insulin and metformin and discontinues the sulfonylurea.

6-Month Follow-Up Visit

The patient remains on metformin, 45 U glargine once daily, and 5 to 10 U of glulisine at the evening meal. She adjusts the glulisine dose daily according to meal carbohydrate content, daily activity, and premeal glucose level using the correction factor equation (see Box, page 95). Her A1C and FPG levels are down to 6.5% and 110 mg/dL, respectively. Her weight is down to 154 lb and blood pressure is 122/74 mm Hg. She reports feeling better and says she rarely has nocturnal hypoglycemia. She is pleased with the control she has over her glucose and feels she has regained the energy to deal with her busy life.

Read Q&A from the live symposia at www.practicingclinicians.com/H2_2009/insqa.pdf

References

1. National Center for Health Statistics. *Health, United States, 2008, With Chartbook*. Hyattsville, MD: 2009.
2. American Diabetes Association. Economic costs of diabetes in the U.S. in 2007. *Diabetes Care*. 2008;31:596-615.
3. Stratton IM, Adler AT, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321:405-412.
4. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:977-986.
5. American Diabetes Association. Standards of medical care in diabetes—2008. *Diabetes Care*. 2008;31:S12-S54.
6. Centers for Disease Control and Prevention. National diabetes fact sheet. <http://www.cdc.gov/diabetes/pubs/general.htm#what>. Accessed June 4, 2009.
7. Leahy JL. Natural history of beta-cell dysfunction in NIDDM. *Diabetes Care*. 1990;13:992-1010.
8. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. *Diabetes*. 2003;52:102-110.
9. Polonsky KS, Given BD, Hirsch LJ, et al. Abnormal patterns of insulin secretion in non-insulin-dependent diabetes mellitus. *N Engl J Med*. 1988;318:1231-1239.
10. Brunzell JD, Robertson RP, Lerner RL, et al. Relationships between fasting plasma glucose levels and insulin secretion during intravenous glucose tolerance tests. *J Clin Endocrinol Metab*. 1976;42:222-229.
11. Harris MI, Klein R, Welborn TA, Knudman MW. Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. *Diabetes Care*. 1992;15:815-819.
12. Action to Control Cardiovascular Risk in Diabetes Study Group; Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358:2545-2559.
13. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med*. 2008;358:580-591.
14. Riddle MC, Rosenstock J, Gerich J; Insulin Glargine 4002 Study Investigators. The Treat-to-Target Trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care*. 2003;26:3080-3086.
15. Nathan DM, Buse JB, Davidson MB, et al; American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2008;31:1-11.
16. Rossetti P, Porcellati F, Bolli GB, Fanelli CG. Prevention of hypoglycemia while achieving good glycemic control in type 1 diabetes. *Diabetes Care*. 2008;31(suppl 2):S113-S120.
17. Plank J, Bodenlenz M, Sinner F, et al. A double-blind, randomized, dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting insulin analog detemir. *Diabetes Care*. 2005;28:1107-1112.
18. Holman RR, Thorne KI, Farmer AJ, Davies MJ, Keenan JF, Levy JC; for the 4-T Study Group. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med*. 2007;357:1716-1730.
19. Meneghini L, Koenen C, Weng W, Selam JL. The usage of a simplified self-titration dosing guideline (303 Algorithm) for insulin detemir in patients with type 2 diabetes—results of the randomized, controlled PREDICTIVE 303 Study. *Diabetes Obes Metab*. 2007;9:902-913.
20. Gerstein HC, Yale JF, Harris SB, Issa M, Stewart JA, Dempsey E. A randomized trial of adding insulin glargine vs. avoidance of insulin in people with type 2 diabetes on either no oral glucose-lowering agents or submaximal doses of metformin and/or sulphonylureas. The Canadian INSIGHT (Implementing New Strategies With Insulin Glargine for

Management of Type 2 Diabetes: Practical Approaches to Insulin Use

- Hyperglycaemia Treatment) Study. *Diabetes Med.* 2006;23:736-742.
21. Davies M, Storms F, Shuter F, Bianchi-Biscay M, Gomis R; ATLANTUS Study Group. Improvement of glycemic control in subjects with poorly controlled type 2 diabetes: comparison of two treatment algorithms using insulin glargine. *Diabetes Care.* 2005;28:1282-1288.
 22. Leahy J. Intensive insulin therapy in type 1 diabetes mellitus. In: Leahy J, Cefalu W, eds. *Insulin Therapy.* New York, NY: Marcel Dekker; 2002:87-112.
 23. Nathan DM. Clinical practice. Initial management of glycemia in type 2 diabetes mellitus. *N Engl J Med.* 2002;347:1342-1349.
 24. Garber AJ, Wahlen J, Wahl T, et al. Attainment of glycaemic goals in type 2 diabetes with once-, twice-, or thrice-daily dosing with biphasic insulin aspart 70/30 (The 1-2-3 Study). *Diabetes Obes Metab.* 2006;8:58-66.
 25. Janka HU, Plewe G, Riddle MC, Kliebe-Frisch C, Schweitzer MA, Yki-Järvinen H. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. *Diabetes Care.* 2005;28:254-259.
 26. Qayyum R, Bolen S, Maruthur N, et al. Systematic review: comparative effectiveness and safety of premixed insulin analogues in type 2 diabetes. *Ann Intern Med.* 2008;149:549-559.
 27. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). *Diabetes Care.* 2003;26:881-885.
 28. The DECODE Study Group on behalf of the European Diabetes Epidemiology Group. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases? *Diabetes Care.* 2003;26:688-696.
 29. Jellinger PS, Davidson JA, Blonde L, et al. Road maps to achieve glycemic control in type 2 diabetes mellitus: ACE/AACE Diabetes Road Map Task Force. *Endocr Pract.* 2007;13:260-268.
 30. Monnier L. Is postprandial glucose a neglected cardiovascular risk factor in type 2 diabetes? *Eur J Clin Invest.* 2000;30(suppl 2):3-11.
 31. Erlinger TP, Brancati FL. Postchallenge hyperglycemia in a national sample of U.S. adults with type 2 diabetes. *Diabetes Care.* 2001;24:1734-1738.
 32. Karl DM. The use of bolus insulin and advancing insulin therapy in type 2 diabetes. *Curr Diab Rep.* 2004;4:352-357.
 33. Hirsch IB. Insulin analogues. *N Engl J Med.* 2005;352:174-183.
 34. Howey DC, Bowsher RR, Brunelle RL, Woodworth JR. [Lys(B28), Pro(B29)]-human insulin. A rapidly absorbed analogue of human insulin. *Diabetes.* 1994;43:396-402.
 35. Rosenstock J, Wyne K. Insulin treatment in type 2 diabetes. In: Rosenstock J, Goldstein BJ, et al, eds. *Textbook of Type 2 Diabetes.* London, UK, and New York, NY: Martin Dunitz; 2003:131-154.
 36. Rave K, Bott S, Heinemann L, et al. Time-action profile of inhaled insulin in comparison with subcutaneously injected insulin lispro and regular human insulin. *Diabetes Care.* 2005;28:1077-1082.

PCEFORUM

It's your turn. Post your comments
to this clinical question:



The ADA recommends that most patients with type 2 diabetes take certain "guardian medications" for cardioprotection. Do you follow this in your practice, and if so, which medications do you regularly prescribe?

Post your answer to this question and more on the PCE Forum www.practicingclinicians.com/forumhomestudy