



The Case for Earlier Insulin Use in Type 2 Diabetes

What We Know About Diabetes

- ➔ At least 10 in every 100 adult patients in primary care practice have diabetes
- ➔ Injury to the vascular endothelium, the major mechanism underlying diabetes complications, may occur long before diabetes is diagnosed
- ➔ Early use of insulin can help control diabetes and prevent complications

Learning Objectives

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

- ➔ Explain the importance of tight glycemic control for patients with type 2 diabetes
- ➔ Apply the most recent treatment algorithm to identify next steps in the management of patients with type 2 diabetes
- ➔ Select the appropriate short-, intermediate-, and long-acting insulins for the management of type 2 diabetes

Diabetes: A Progressive Disease

Over the lengthy development of type 2 diabetes mellitus (T2DM), normal blood glucose values are usually maintained as a result of the increased insulin secretion that counters the encroachment of insulin resistance. With the inexorable decline of β -cell function, however, the ability to maintain normal blood glucose levels is steadily lost and frank diabetes becomes established. The developmental phase may take 10 years. During that time, subclinical blood glucose elevations cause progressive microvascular damage to the eyes, kidneys, and nervous system, as well as macrovascular damage with atherosclerotic

Insulin is the most effective antiglycemic medication

How often do you need to check sugars in a patient on basal insulin?
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changes in the coronary vessels and injury throughout the vascular endothelium.¹ Thus, by the time many T2DM patients are diagnosed, irreversible changes have occurred.

Value of Tight Control: Significance of A1C

The rationale for tight control of blood glucose has been developed on the basis of a number of studies. Notably, the United Kingdom Prospective Diabetes Study Group (UKPDS)² showed in a large population of patients with T2DM that for every 1% reduction in updated mean glycosylated hemoglobin (A1C), there was a 14% reduction in risk for myocardial infarction (MI) and a 37% reduction in risk for microvascular complications. No threshold of risk was observed for any end point. The UKPDS investigators concluded that complications were least likely to occur in T2DM patients with A1C values in the normal range (<6.0%).² In the Diabetes Control and Complications Trial (DCCT), tight control of type 1 patients (A1C <7%) resulted in similar reductions in both microvascular and macrovascular complications.³

A1C reflects the average blood concentration of glucose over several months and is a strong predictor of diabetic complications. After measurement at the start of therapy, follow-up assessments at approximately 3-month intervals can indicate whether treatment is enabling the patient to achieve and maintain glycemic targets. The frequency of A1C testing depends on the clinical situation, the treatment selected, and the clinician's judgment.⁴

The epidemiologic results of the European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk)⁵ underscored the UKPDS findings with regard to the risk of macrovascular complications in diabetic men. Increasing A1C levels were indicative of all-cause, cardiovascular (CV), and ischemic heart disease mortality throughout the study population, with the lowest rates among patients with A1C <5%. An increase of 1% in A1C was associated with a 28% increase ($P < .002$) in risk of death regardless of age, blood pressure, serum cholesterol, body mass index (BMI), and smoking habit.⁵ A1C seemed to explain the excess mortality risk of diabetes in men and appeared to be a continuous risk factor throughout the population distribution.⁵

The results of DCCT demonstrated the value of intensive control in type 1 diabetes: there was a 50% reduction in MI for patients on multiple daily insulin injections.³ Tight control of A1C in patients with T2DM is supported by the results of a number of studies, including STENO2, a European study targeting the European standard goal of A1C <6.5% as well as intensive control of blood pressure and cholesterol. For patients on intensive treatment compared with patients on standard care during a 13.3-year follow-up period (mean treatment period: 7.8 years; mean observational follow-up: 5.5 years), there was a >50% reduction in the risk of macrovascular complications, including MI, stroke, revascularization, and amputation.⁶

The safety of intensive control strategies⁷⁻¹⁰ has been brought into question by 2 recent publications: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease (ADVANCE) trials. In the intensive treatment arm of ACCORD there was an unexpected increase in CV death. In ADVANCE there was no recognizable CV benefit from intensive A1C reduction, nor was there an increase in adverse CV outcomes. Authors and commentators have suggested that the apparent lack of benefit from tight control seen in ACCORD might stem from hypoglycemia, weight gain,

overly rapid reduction of the A1C, or aggressive treatment of more fragile patients.^{9,10} To date, no specific treatment strategy or drug has been implicated in the poor outcomes. The American Diabetes Association (ADA)/ European Association for the Study of Diabetes (EASD) joint recommendation of a target A1C <7% still stands, with the additional recommendation that for selected individual patients, clinicians should aim for an A1C as close to normal (<6.0%) as possible provided the patient does not experience significant hypoglycemia.¹¹

Good clinical practice mandates control of blood pressure, serum cholesterol, and blood glucose to reduce the risk of death from CV disease and stroke. Treatment goals and guidelines for hypertension are available at www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf. National Cholesterol Education Program Adult Treatment Panel III guidelines are available at www.nhlbi.nih.gov/guidelines/cholesterol/index.htm.

The Burden of Diabetes

At least 10 of every 100 adult patients who pass through a primary care clinic have diabetes. Only 7 of 10 patients with established T2DM know they have the disease.¹² Diabetes is inescapable in primary care practice.

According to the Centers for Disease Control and Prevention 2007 prevalence estimates (published in June 2008), 24 million Americans have diabetes.¹³ One quarter of these cases are undiagnosed—and therefore untreated. Another 57 million Americans have signs and symptoms of “prediabetes,” a condition that can be largely prevented from progressing if patients make serious efforts to change their lifestyle and behavior.¹⁴ The rate of diabetes will continue to rise with the increasing prevalence of obesity, aging of the population, decreasing mortality, and growth in minority populations among whom the prevalence and incidence of diabetes are increasing.

The costs of diabetes threaten to overwhelm the healthcare budget. In 2007, a total of \$174 billion of healthcare dollars was spent on diabetes: \$116 billion in direct costs and \$58 billion in indirect costs including decreased productivity, disability-related unemployment, and losses due to premature death (Figure 1).¹⁵ Management of diabetes is more than an academic or humanitarian vocation—it is an economic necessity.

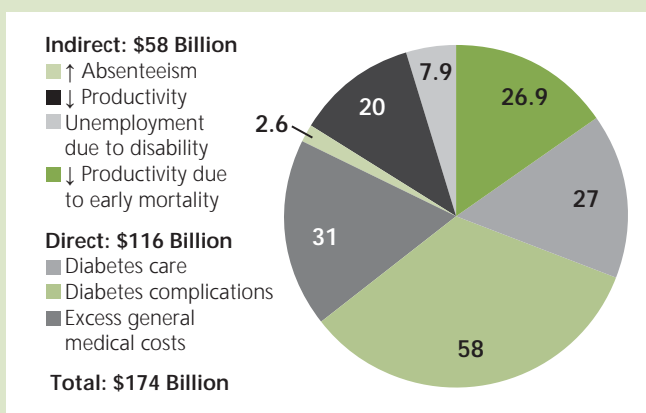


Figure 1. Estimated 2007 direct and indirect costs of diabetes in the United States. Increase of \$42 billion (32%) compared with 2002. One of every 10 healthcare dollars is spent on diabetes. One of every 5 healthcare dollars is spent on a person diagnosed with diabetes. ADA.¹⁵

Advancing Therapy: Not Fast Enough

Despite strong evidence of the advantages of aggressive management, treatment of diabetes remains far from ideal. In the typical initial presentation, the average patient with T2DM has an A1C of 8.6%. In this regard, it is important to recall that an A1C of even 7% is associated with a 2- to 3-fold increase in the risk of MI or stroke. Therefore, delaying adequate therapy can be risky.¹⁶ Although evidence from controlled trials shows the value of tight control of diabetes, clinicians in the United States typically do not initiate insulin until >9 years after diagnosis, when the A1C on average is 9.6%.¹⁷ More commonly, several unsuccessful attempts are made with dietary measures and lifestyle modification, including exercise. During this phase, the A1C may approach 9.0%, at which point, an oral antidiabetic drug (OAD)—metformin or a sulfonylurea (SFU)—often is prescribed. Oral agents may be titrated and/or replaced during the next several years, but have little lasting impact on the disease progression. Rather than following a well-worked out strategy to control the A1C, clinicians may first try one thing, then another until awareness of the A1C elevation is inescapable.

Although a comparison of National Health and Nutrition Examination Surveys (NHANES) III data from 1988 to 1994 with data from 1999 to 2000 shows some improvement in control of A1C, blood pressure, and total cholesterol, good control of all 3 parameters remains elusive. Fully 93% of all patients being treated for T2DM have not achieved a level of control adequate to provide optimal protection against CV or cerebrovascular events.¹⁸

ADA/EASD Guidelines Promote Early, Effective Treatment

A number of critical points emerge from the ADA/EASD consensus statement for the initiation and adjustment of diabetes therapy (Figure 2).¹¹ First, provided patients have no evidence of renal impairment, the appropriate initial therapy for T2DM is initiation of metformin and lifestyle changes. Lifestyle intervention is important, but such behavioral changes are difficult to sustain and rarely are effective long term. Therefore, lifestyle change should initially be instituted in tandem with oral therapy. Second, at 3-month follow-up, an A1C <7% indicates adequate control of glycemia, whereas an A1C \geq 7% is a signal to advance therapy. Based on the most current revision of the ADA/EASD consensus treatment algorithm,¹¹ the clinician at this stage is faced with a “tier 1” or “tier 2” decision. A tier 1 pathway allows selection of therapies that are well-proven clinically and that are proven to be cost-effective. A tier 1 approach would lead the provider to add basal insulin or SFU to metformin to better control A1C. Cautions are issued about the possibility of hypoglycemia with SFUs. The tier 2 choices reflect less robust clinical outcomes evidence and are more costly than tier 1 options. However, this route may be more appropriate for patients employed in high-risk jobs where hypoglycemia is particularly dangerous, such as truck drivers who require a commercial driver’s license, or those for whom weight loss is a major objective. A tier 2 strategy offers 2 options allowing treatment based on patient characteristics. Pioglitazone can be added to metformin if weight gain or fluid retention are not potential concerns or an incretin mimetic can be added to metformin if weight loss is a desired goal.

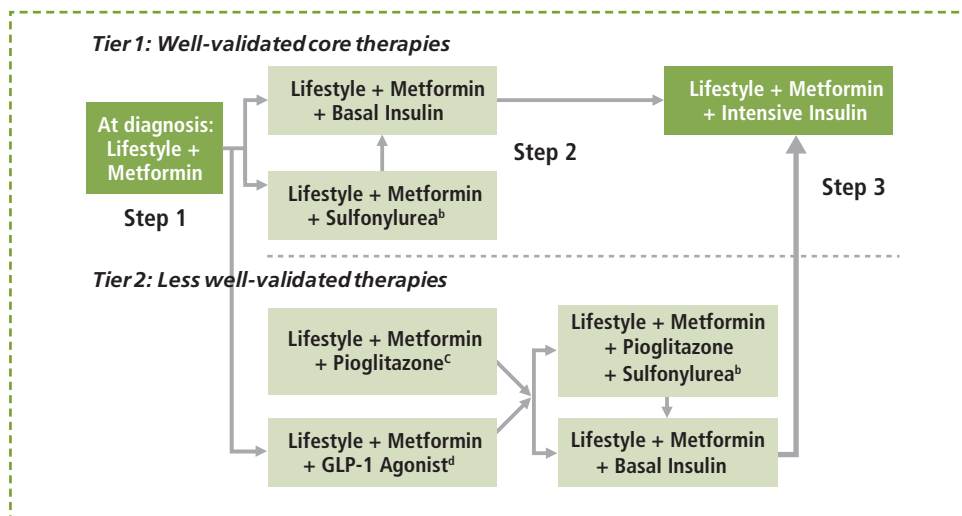


Figure 2. ADA/EASD: Consensus algorithm for initiation and adjustment of therapy for T2DM.^a

^aReinforce lifestyle interventions at every visit. Check A1C every 3 months until <7% and then at least every 6 months; ^bOther than glyburide or chlorpropamide; ^cOption if hypoglycemia is particularly undesirable. Associated with increased risks of edema, congestive heart failure, and fracture; ^dOption 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. Nathan DM et al.¹¹

The use of more than 2 OADs is unlikely to be an effective strategy for diabetes control and should be discouraged. Only about 14% of patients achieve and maintain an A1C goal of <7% when adding a third OAD to 2 previously ineffective OADs.¹⁹

The ADA/EASD algorithm endorses the addition of basal insulin to the metformin + lifestyle regimen as the most effective and cost-efficient second step.¹¹ In the UKPDS study, which underscored the importance of tight glycemic control to prevent micro- and macrovascular complications, the investigators found that the combination of an OAD with insulin ensured more durable maintenance of target A1C (<7%) than conventional oral therapy or insulin alone.²⁰ Usually, OADs are continued on initiation of basal insulin.

Prompt Use of Basal Insulin Improves Glycemic Control

Nondiabetic persons exhibit “basal-bolus” insulin secretion, with a basal level of insulin secreted throughout the day and a pulsatile increase in insulin secretion (bolus) after each meal followed by return to baseline. In a key study of the pulsatile patterns of insulin secretion, incremental insulin responses to meals were significantly ($P < .005$) lower in patients with T2DM, who had “more sluggish” increases and decreases after meals than healthy control subjects.²¹ In addition, disruptions to insulin secretion became more severe as the day progressed; investigators frequently could not identify a clear secretory response to the evening meal in patients with T2DM.²¹ The goal of initial basal insulin therapy is to increase the basal insulin supply. Intermediate- or long-acting

insulin usually is selected to initiate insulin therapy.¹¹ Insulin is the most effective antiglycemic medication, based on capacity to lower the A1C. Currently available insulins are all effective in controlling hyperglycemia, but have markedly different side effect profiles, particularly with regard to hypoglycemia.^{11,22,23}

Basal insulin is available in long-acting formulations that can provide “background” coverage for up to 24 hours, compensating for the failure to meet resting insulin needs that differentiates patients with T2DM from healthy persons.²¹ Clinicians may choose from neutral protamine Hagedorn (NPH) insulin, insulin detemir, insulin glargine, or a premixed insulin product that combines long-acting and short-acting components.

These basal insulins differ in duration of effect, dosage, and administration. NPH is given once daily at bedtime or twice a day for full 24-hour coverage; detemir once or twice daily; and glargine once daily. NPH has a peak effect and its action lasts approximately 12 hours. Thus, NPH does not provide peakless 24-hour coverage to mimic normal physiology. The mode of action of NPH is highly variable.²⁴ Detemir exhibits a dose-dependent duration of action that can be prolonged for up to 24 hours with higher dose levels. As higher dose levels are administered, detemir exhibits more peaking in its action curve, a property that can increase the likelihood of hypoglycemia.²⁵ Consequently, approximately 50% of patients require detemir dosing twice a day for an optimal 24-hour basal replacement pattern.²⁶ With a peakless, 24-hour course of action, glargine most closely approaches human physiology.^{27,28} Glargine is given once daily at the same time of day to achieve 24-hour coverage.

Several premixed insulin preparations that combine rapid-acting with long-acting components are available, but should not be used during the dose adjustment phase of insulin initiation according to the ADA/EASD basic guidelines.²⁹ When premixed insulin is administered, the rapid-acting component approximates the physiologic pattern of a rapid increase in insulin action with a fairly quick return to baseline during about 4 hours. The longer acting component remains active for 8 to 12 hours, sometimes leading to the presence of unnecessary amounts of insulin between meals or overnight. Unless the patient eats to prevent a precipitous fall in blood glucose, a hypoglycemic episode is likely to occur during these periods of excess insulin activity.

Dosing Basal Insulin: Choose Your Algorithm

The usual approach in initiating basal insulin is to start with a low dose and gradually titrate upward, aiming to ensure efficacy while avoiding hypoglycemia. A number of algorithms based on results of clinical trials can be used safely to achieve optimal control (Figure 3).^{22,28,30,31}

In the Canadian Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment (INSIGHT) study,²⁸ Gerstein et al demonstrated the safety and efficacy of the patient-directed “1-1-100” algorithm, in which an initial dose of glargine 10 U is increased by 1 U daily until a fasting plasma glucose (FPG) of 100 mg/dL is achieved. At the 24-week visit, a higher proportion of patients assigned to insulin glargine in the 1-1-100 algorithm had achieved the primary end point of 2 consecutive

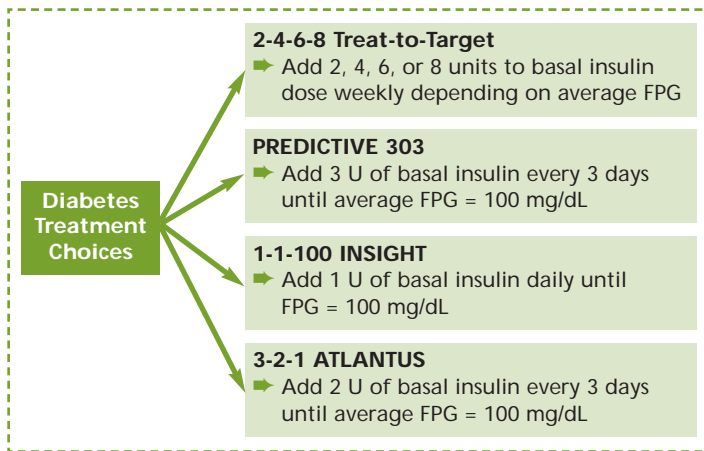


Figure 3. Choice of algorithms for self-titration of antiglycemic therapy in type 2 diabetes. Riddle MC et al²²; Gerstein HC et al²⁸; Meneghini L et al³⁰; Davies M et al.³¹

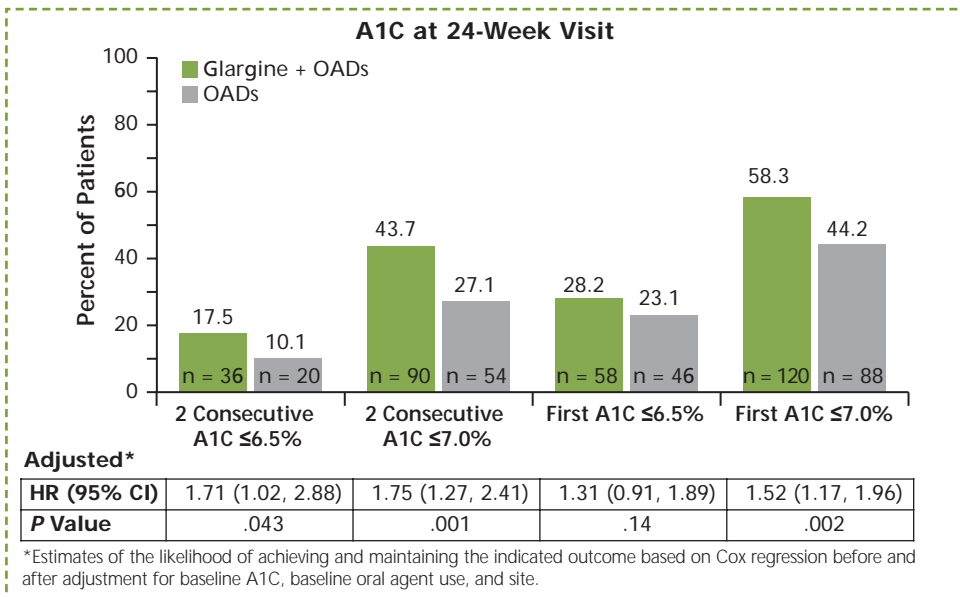


Figure 4. 1-1-100 INSIGHT: Achievement of 2 consecutive A1Cs ≤6.5%. Gerstein HC et al.²⁸

A1C levels ≤6.5% than control participants (17.5% n = 36 vs 10.1% n = 20; $P = .032$). Over the course of the 24-week trial, patients on glargine using the 1-1-100 algorithm had a greater decrease in A1C and FPG than controls and expressed greater satisfaction with diabetes treatment (Figure 4).²⁸

The “2-4-6-8 treat-to-target” algorithm was based on a study comparing the effects of bedtime glargine (n = 367) and NPH (n = 389) insulin added to OAD therapy in overweight men and women with T2DM. Riddle et al found that systematic titration with

both types of insulin achieved the target A1C of 7% in approximately 60% of patients.²² However, although the 2 insulins produced similar FPG and A1C levels, there was considerably less symptomatic hypoglycemia with the use of glargine, especially during the night. Investigators achieved optimum effect with titration to 45-U glargine on average. Patient adherence to the protocol exceeded 90%.²² In the 2-4-6-8 treat-to-target algorithm based on these results, 2, 4, 6, or 8 U are added to the basal insulin dose weekly according to the average FPG until a morning fasting glucose of 100 mg/dL is achieved.²² Other current algorithms follow similar titration patterns. The “Predictive 303” protocol adds 3 U basal insulin every 3 days to reach a morning fasting target of 100 mg/dL,³⁰ and the “3-2-1” algorithm from A Trial Comparing Lantus Algorithms to Achieve Normal Blood Glucose Targets in Patients With Uncontrolled Blood Sugar (ATLANTUS) adds 2 U basal insulin every 3 days until the average FPG is 100 mg/dL.³¹

Taking the Next Steps in Postprandial Glycemic Control: Rapid-Acting Insulin Analogs

For patients who experience postprandial excursions despite good adherence to an optimal basal insulin protocol, transition from a basal to a basal-bolus insulin regimen may be indicated. Monnier et al determined that postprandial glucose excursions have a greater impact than FBG on A1C elevation at A1C levels that are close to the national goal of 7%.³² Thus, the Monnier data suggest that use of rapid-acting mealtime insulin to address postprandial control may be a logical addition to basal insulin as part of a strategy to achieve A1C levels at or below the national goal of 7%. Whereas human Regular insulin is the gold standard for glycemic control, flexible dosing with a rapid-acting analog insulin offers important advantages in meeting mealtime requirements with minimal risk of hypoglycemia.³³ The available agents—insulin lispro, aspart, and glulisine—offer a shorter duration of action than Regular insulin and more consistent kinetics irrespective of the site of injection and with large doses. A significant advantage of the rapid-acting analogs over human Regular insulin is that the analogs can be given at the time of the meal, eliminating the inconvenience of having to plan an injection of Regular insulin 30 to 45 minutes before the meal to achieve the desired effect. Although rapid-acting insulins in general are absorbed more slowly in obese patients, glulisine has a somewhat faster onset of action than lispro in obese patients independent of BMI.³⁴⁻³⁶

PCE Takeaways

- ➔ For patients who cannot achieve A1C targets with 1 or 2 OADs plus lifestyle measures, OADs should be continued and basal insulin initiated and titrated according to a proven algorithm until FPG \leq 100 mg/dL is achieved
- ➔ Several simple algorithms can be used to achieve optimal glycemic control with insulin
- ➔ If A1C or FPG remains above target despite adequate basal insulin dosing, consider a bolus dose of rapid-acting insulin analog before the main meal to prevent postprandial excursions, then in succession before the remaining meals, depending on therapeutic response

CASE STUDY

All in the Family: Type 2 Diabetes

Presentation

A 58-year-old man presents with a complaint of recent fatigue and unusual hunger. The patient has a history of hypertension, for which he takes an angiotensin-converting enzyme (ACE) inhibitor. He is somewhat overweight, but otherwise in generally good health. The underlying reason for the visit emerges in the course of conversation with his physician. After meeting a cousin for lunch, the patient “tried out” the cousin’s glucometer. On seeing that the patient’s postprandial blood glucose was 143 mg/dL, the cousin insisted the patient seek medical attention.

Physical Examination

- A1C (point-of-care): 6.1%
- Blood pressure: 126/72 mm Hg
- BMI: 31 kg/m²
- Height: 5 ft 9 in
- Waist: 41 in
- Weight: 210 lb

Laboratory Values

- BUN: 29 mg/dL
- Creatinine: 0.9 mg/dL
- HDL: 23 mg/dL
- LDL: 106 mg/dL
- Plasma glucose: 136 mg/dL (nonfasting)
- Total cholesterol: 234 mg/dL
- Triglycerides: 287 mg/dL
- Urinalysis: negative

Clinical Decision Point

What is your diagnosis for this patient?

- T2DM
- Prediabetes
- Impaired fasting glucose
- Unsure at this point

Comment

While this patient’s postprandial blood glucose level is abnormal, the point-of-care A1C does not confirm a diagnosis of T2DM because A1C is not a diagnostic tool. The laboratory values indicate impaired glucose tolerance and possibly a prediabetic state. The next step for this patient is a confirmatory 2-hour oral glucose tolerance test (OGTT).

OGTT results are as follows:

- Prescreen: 103 mg/dL
- Fasting: 106 mg/dL
- 2-hour: 236 mg/dL

The patient presents 2 hours after eating for a follow-up appointment, as instructed, and is found to have a glucometer reading of 213 mg/dL.

The patient’s blood glucose values meet the ADA criteria for T2DM (FPG \geq 126 mg/dL [7.0 mmol/L] or casual blood glucose \geq 200 mg/dL [11.1 mmol/L] with symptoms).

Clinical Decision Point

What is the first step in managing this patient’s condition?

- Institute lifestyle changes
- Re-evaluate the patient in 3 months
- Refer the patient for comprehensive diabetes education
- Start an oral antihyperglycemic agent

Comment

The ADA/EASD algorithm indicates that the first treatment step after diagnosis of diabetes is initiation of metformin (if there are no kidney problems) plus lifestyle changes. The patient should be followed up at 3 months and agents added if A1C is not <7%.

The ADA Standards of Care also emphasize the importance of using a variety of educational strategies and techniques to help patients understand diabetes and develop problem-solving skills in managing the disease.⁴ Education helps people with diabetes take on the responsibility for self-care, maintaining effective self-management as the disease presents new challenges and as new treatments become available.⁴ The ADA recognizes diabetes self-management education tailored to each patient's needs as an integral component of any treatment plan.⁴

Metformin is initiated and titrated over several weeks to 1000 mg twice daily, which the patient tolerates well. He attends regular appointments with the certified diabetes educator (CDE) as part of his comprehensive program of lifestyle change and nutrition, in addition to pharmacologic management.

After an early weight loss of 12 lb and achievement of A1C of 5.8%, the patient fails to keep scheduled appointments because he feels he is doing well. He misses several CDE visits, and then stops altogether. At a clinic visit 1 year later, physical findings are as follows:

- A1C: 8.1%
- Blood pressure: 134/82 mm Hg
- HDL: 32 mg/dL
- LDL: 79 mg/dL
- Total cholesterol: 156 mg/dL
- Triglyceride: 143 mg/dL
- Weight: 225 lb (gain of 23 lb)

Because the patient is reluctant to start insulin and has concerns about cost, glyburide 5 mg daily is added to the metformin regimen. The patient is also taking ramipril and amlodipine to control hypertension,

atorvastatin and niacin to manage dyslipidemia, and aspirin to reduce CV risk. At 3-month follow-up, his A1C is 6.8%. Adherence to the antidiabetic regimen is improved and the patient regularly attends scheduled visits. After about 18 months, however, his A1C has risen to 7.6%.

Clinical Decision Point

What is your next treatment recommendation?

- Increase lifestyle measures
- Add a third OAD
- Initiate insulin
- Discuss gastric bypass

Comment

The ADA/EASD treatment guidelines call for a third OAD or insulin at this point; noting that at this stage insulin is preferable based on effectiveness and expense.¹¹ Although the patient is overweight, he is not a candidate for gastric bypass because his BMI is <40 kg/m². The results of studies, however, have shown resolution of diabetes in more than 75% of patients after bariatric surgery.³⁷

As a result of his comprehensive diabetes education, the patient is aware of the possibility of using insulin early in the course of treatment and realizes that this is the natural progression of his condition. He is somewhat apprehensive, but accepts the recommendation of insulin.

Clinical Decision Point

How will you initiate insulin therapy?

- Calculate an initial dose based on weight
- Start 10 U glargine every day and patient adjusts daily
- Start 10 U glargine every day and patient adjusts every 3 days
- Start 10 U detemir every day and patient adjusts every 3 days, possibly switching to twice a day as dose increases
- Start 10 U glargine every day and patient makes weekly adjustments

Comment

Insulin therapy should be initiated at a low starting dose to avoid hypoglycemia and then self-titrated by the patient according to a clinically proven dosing algorithm (Figure 3). Weight-based dosing is rarely used. Oral agents should be continued during insulin use.

The 2-OAD regimen is continued and basal insulin therapy with glargine is initiated according to the 1-1-100 algorithm.²⁸ Glargine is selected because it causes significantly less nocturnal hypoglycemia than NPH, thus minimizing a prominent barrier to insulin initiation.²² Experience in the INSIGHT and other trials confirms that glargine can be used in both primary and specialty care for diabetic patients with a wide range of characteristics.²⁸ An initial dose of 10 U is increased by 1 U daily. During 6 months of follow-up the dose advances to

glargine 49 U/day; the average FPG is 130 mg/dL and A1C is 7.6%.

On the clinician's advice, the patient continues titrating the glargine dose to 70 U daily, which produces an average FPG of 102 mg/dL. His A1C declines to 6.4%. After 2 years, average FPG is 104 mg/dL, but the A1C is now 7.2%. To control postprandial excursions, mealtime dosing with glulisine, a short-acting insulin analog, is added at doses ranging from 10 U to 17 U daily, depending on the carbohydrate content of the meal and the patient's level of activity. Supplemental insulin is prescribed at a dose of 1 U for every 25 mg/dL above 130 mg/dL in addition to the planned mealtime dose, according to the premeal self-monitored blood glucose.

Six months later, the patient's A1C is 6.3%. He feels well, seldom experiences hypoglycemia, and is satisfied with his blood glucose control.

Questions From Symposium Participants



➔ **Q:** At what time of day should glargine be given, and how frequently should the blood sugar be checked?

A: Glargine is given once a day at a consistent time. Initially in diabetic management, FPG must be checked because dosing in all basal self-titration algorithms is based on the FPG. It's not necessary to regularly check blood sugars beyond that; however, it is usual to spot check both fasting and postprandial sugars occasionally to monitor overall control.

➔ **Q:** Should oral agents be discontinued in the patient taking insulin once the A1C is under control?

A: Patients should remain on oral agents, except as previously noted. In diabetes the pancreas is progressively failing. There's never a point at which a final goal has been reached and treatment can be stopped; diabetes treatment is always maintenance therapy.

➔ **Q:** Why initiate therapy with metformin only and not a glitazone?

A: The ADA/EASD algorithm was developed to be efficient and cost-effective. Metformin, at a cost of \$4 a month, is the most potent oral agent. It can lower A1C by 1.5 to 2 percentage points. That is more potent than the TZDs. Glitazones cost between \$150 and \$200 a month. Additionally, metformin generally is well tolerated and suitable for a wide spectrum of patients except those with renal insufficiency or the very elderly.

➔ **Q:** How does the incretin mimetic exenatide work?

A: Exenatide is a protein that simulates the glucoregulatory effects of incretin hormones. It slows gastric emptying, turns off the satiety center, decreases hepatic production of glucose, and stimulates first-phase insulin secretion from the pancreas. It has to be given twice a day by injection and, in general, will lower the A1C about 0.4% to 0.8%, although with prolonged use the A1C drop may approximate 1.2%. This may not be appropriate for a patient who starts out with a very elevated initial A1C because it may not drop to an acceptable target range. Exenatide's main effect in improving A1C is to suppress postprandial excursions.

➔ **Q:** If a woman has a history of gestational diabetes and has completed her family, how frequently would you check her glucose levels?

A: This patient should be checked annually. Women with gestational diabetes have a 30% to 40% risk for the subsequent development of diabetes.

➔ **Q:** How can weight gain after starting insulin be controlled?

A: With insulin, an estimated weight gain of 2 kg for every lowering of 1 percentage point in A1C should be expected. That is true for most diabetes therapies. Weight gain may be more than expected with TZDs, but it appears that metformin is weight-neutral or may cause some reduction. Patients can also lose a little weight with diet and exercise if they remain committed. Starting therapy with metformin and adding basal insulin is a strategy that mitigates the tendency to gain weight. Using analog insulins that are associated with less hypoglycemia (because of their more physiologic action profiles) in the appropriate dose will mitigate the weight gain associated with insulin use.

➔ **Q:** What type of insulin is best for patients with A1C in the 11% to 12% range?

A: Every insulin lowers A1C, but the side effect profiles vary. The analog insulins are easier to use than NPH, Regular, or premixed preparations because they are closer to human physiology and less likely to induce hypoglycemia. Often, when the A1C is very high at the start, clinicians will use a multiple daily injection (MDI) regimen that includes both basal and mealtime rapid-acting insulin. What matters is that the insulin regimen is used effectively with a glucose end point in mind. The higher the A1C, the more important it is to target control of the FPG as this is the main contributor to A1C at higher A1C values. Basal insulin is the primary contributor to control of FPG. Once A1C is in the lower range, the regimen can be fine-tuned at mealtime with a rapid-acting insulin. Frequently, once the initial glucose (and free fatty acid) toxicity is overcome by aggressively administering insulin, patients can be controlled on an oral or oral + basal regimen.

➔ **Q:** How is a patient on premixed insulin converted to basal insulin?

A: If the patient is on 70/30 premixed insulin, 70% of that insulin is long-acting (basal), and 30% is fast-acting (mealtime). If the patient is taking 40 U of premixed insulin twice a day, that means he's on 80 U total of insulin a day. Seventy percent is long-acting, so the pre-mixed regimen would deliver 56 U of long-acting basal insulin daily. However, to ensure that the switch to basal insulin doesn't precipitate hypoglycemia, many clinicians start with 80% of the calculated basal dose and titrate with the 1-1-100 algorithm to a final dose, with average FPG of about 100 mg/dL. That would put the initial basal dose at around 45 to 50 U.

➔ **Q:** What type of insulin can be used in the frail elderly in nursing homes?

A: Glargine, which is taken once daily, is a good option. It is long-acting, doesn't have a pronounced action peak, and can be gradually titrated. Once-daily dosing makes administration easy. For such patients, an A1C in the 7% range is acceptable.

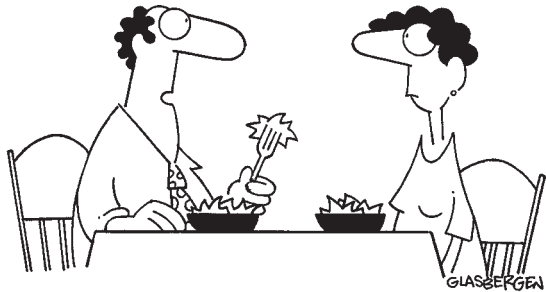
➔ **Q:** How do you determine when to split the detemir and what should the baseline dose be?

A: With the Predictive 303 self-titration algorithm, dosing starts with 10 U detemir daily and increases by 2 U every third day according to the average FPG during the previous 3 days. The desired end point is an average FPG of 100 mg/dL. The detemir dose may need to be split into twice-daily dosing if the patient develops hypoglycemia while aiming for the FPG target of 100 mg/dL. Changing to twice-daily dosing may also be desirable if the FPG reaches 100 mg/dL, but the blood sugar at dinner time remains elevated.

➔ **Q:** Is it okay if the fasting glucose stays between 90 and 100 mg/dL?

A: lowered from very high to near normal ranges, the improvement in A1C usually is significant. However, when the fasting glucose is driven much below 100 mg/dL, the incremental drop in A1C is minimal and the likelihood of hypoglycemic side effects increases substantially. An FPG target range of 90 to 110 mg/dL is satisfactory and lower numbers should not be forced.

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"My doctor says I'm a Type 8 diabetic...that's a Type 2 with four times more excuses for not exercising."

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