

Role of Insulin Analogs in Type 2 Diabetes

Supported by an educational grant from Novo Nordisk Inc.

This program is supported by an educational grant from Novo Nordisk Inc. It has been accredited by the American Association of Diabetes Educators (AADE) for pharmacists, nurses, and dietitians.

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The following program is a recorded presentation by Carolyn Robertson.

Ms. Robertson is a certified diabetes educator (CDE) and board certified in Advanced Diabetes Management (BC-ADM). She has more than 30 years of experience in diabetes education in intensive/flexible diabetes management, with an active patient caseload for more than 25 years. Ms. Robertson was a pioneer in the intensive management of diabetic pregnancies with over 400 successful pregnancies, as well as an early pioneer in insulin pump therapy. She also has expertise in both type 1 and type 2 diabetes management, glucose sensors, and in the management of patients with kidney and pancreas transplantation.

At the present time, Ms. Robertson has a private practice (*Customized Diabetes Education*) located in New York, serves as the Associate Director of a nonprofit program, and has a contract with the Gonda Diabetes Center at UCLA in California as director of special projects. She is also on the editorial board of *Diabetes Self-Management*, a patient-oriented magazine. Ms. Robertson remains actively involved in clinical research, consultation, and mentoring. Ms. Robertson has been a local board member of both the Juvenile Diabetes Research Foundation International and the American Diabetes Association (ADA). She has published widely in peer-reviewed journals, trade journals, newsletters, as well as on the Internet. Ms. Robertson lectures frequently to local, national, and international audiences of health care professionals, patients, and the general public.

We'll now join Ms. Robertson.

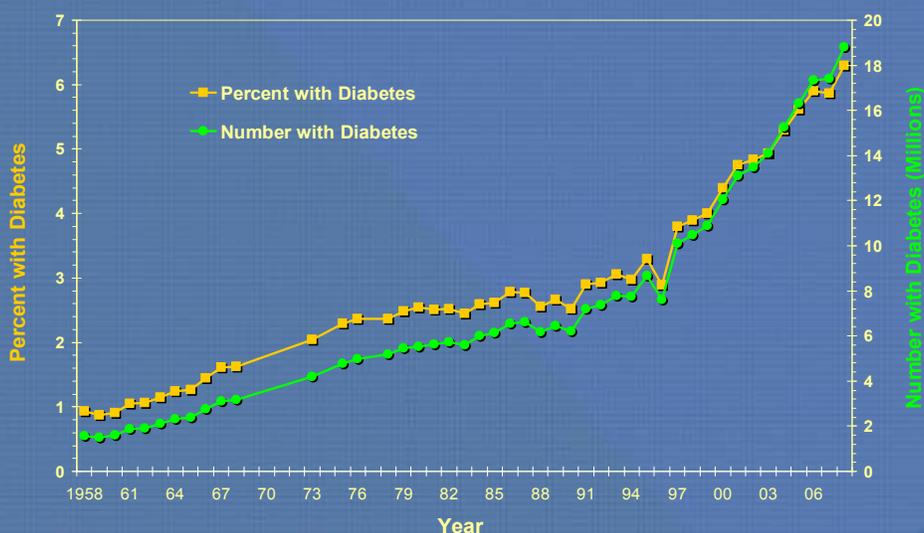
Objectives

- Explain the epidemiology, pathophysiology, and current treatment goals for type 2 diabetes
- Discuss the pharmacokinetics and pharmacodynamics of insulin analogs and their ramifications for glycemic control
- Describe the process for initiating and titrating insulin in patients with type 2 diabetes
- Apply the knowledge gained to initiate and adjust insulin analog therapy

Before we begin this educational activity, I would like to review the objectives. They are to:

- Explain the epidemiology, pathophysiology, and current treatment goals for type 2 diabetes
- Discuss the pharmacokinetics and pharmacodynamics of insulin analogs and their ramifications for glycemic control
- Describe the process for initiating and titrating insulin in patients with type 2 diabetes
- Apply the knowledge gained to initiate and adjust insulin analog therapy

Diabetes Prevalence: 1958–2008

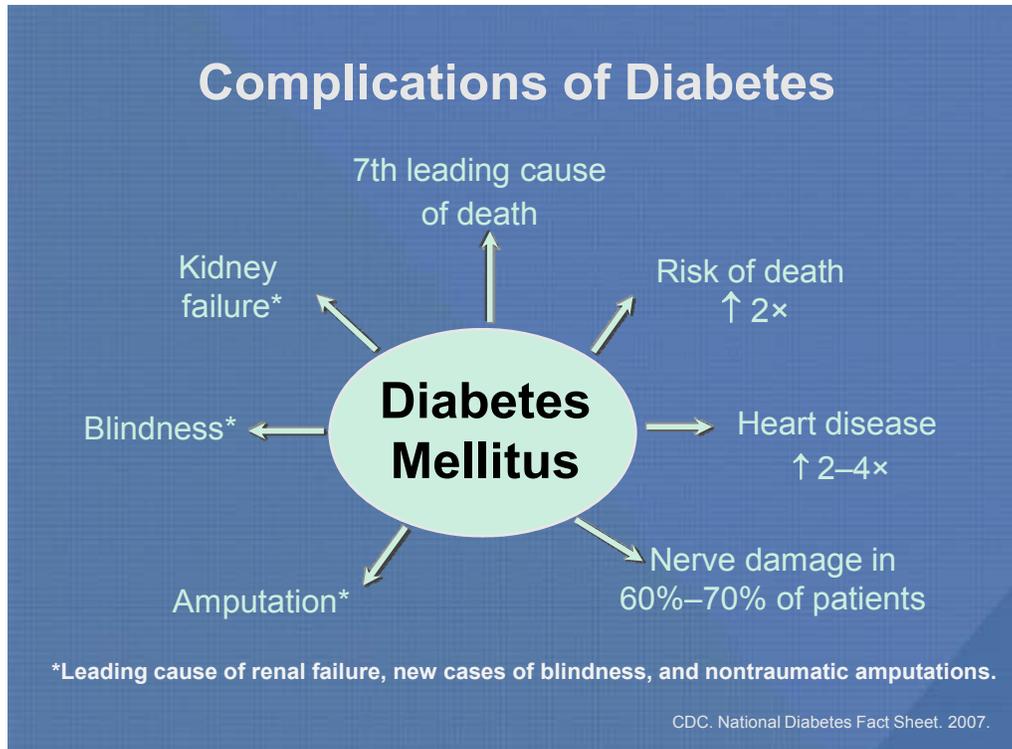


CDC. Division of Diabetes Translation. Available at: <http://www.cdc.gov/diabetes/statistics>. Accessed December 15, 2009.

As this graph shows, the prevalence of diagnosed diabetes in the United States rose dramatically between 1958 and 2008. In 2007 alone, about 1.6 million new cases of diabetes were diagnosed in people aged 20 years or older. Today, about 7.8% of the US population, or approximately 23.6 million people, have diabetes, and in 5.7 million of these people the disease is undiagnosed. In 11 states, the estimated prevalence of diabetes is 10% or greater. The prevalence of diabetes is actually higher in some ethnic groups, including Native Americans, African Americans, and Hispanics.

Type 2 diabetes accounts for at least 90% of diabetes cases in adults. A particularly worrisome trend is the rising prevalence of type 2 diabetes among children and adolescents. According to the Centers for Disease Control and Prevention, type 2 diabetes now accounts for up to 46% of all new cases of diabetes referred to pediatric treatment centers.

Prediabetes is also a health concern. Fifty seven million US residents are estimated to have prediabetes, a condition in which blood glucose (BG) levels are higher than normal, but not high enough to be classified as diabetes. These individuals are at high risk of developing cardiovascular complications, even if they never progress to frank diabetes.



The complications of diabetes have a huge impact on health and well-being. Overall, the risk of death among people with diabetes is twice that among people without diabetes of similar age. Diabetes is currently the seventh leading cause of death. However, many professionals feel that the actual number is higher since it is likely to be underreported as a cause of death.

Mortality in patients with type 2 diabetes is most often due to cardiovascular disease.

- Among people with diagnosed diabetes over the age of 65 years, heart disease contributes to nearly 70% of deaths.
- Adults with diabetes have rates of stroke and heart disease that are 2 to 4 times higher than rates for adults without diabetes.
- Diabetes is the most common cause of new-onset blindness among adults aged 20 to 74 years.
- Diabetic retinopathy causes 12,000 to 24,000 new cases of blindness each year.
- Diabetes is the leading cause of kidney failure.
- Severe forms of diabetes-related nerve damage are a major contributor to lower-extremity amputations.
- More than 60% of nontraumatic lower-limb amputations occur in people with diabetes.

Pathophysiology of Diabetes

Type 1

- Absolute insulin deficiency due to autoimmune or idiopathic destruction of pancreatic beta cells
- Patients require exogenous insulin from the time of diagnosis

Type 2

- Insulin resistance
 - Impaired glucose uptake
 - Hepatic glucose overproduction
 - Compensatory hyperinsulinemia
- Beta-cell dysfunction
 - Glucotoxicity
 - Lipotoxicity
 - Apoptosis

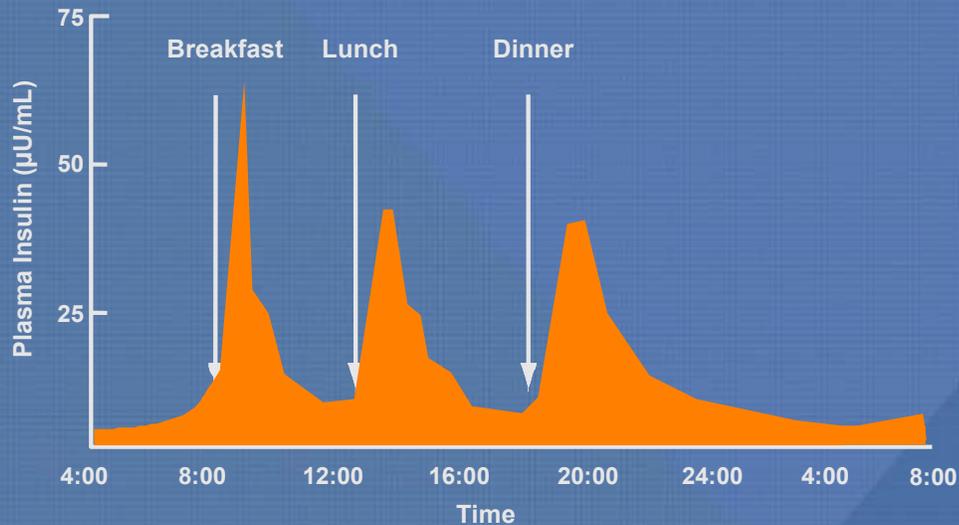
Lebovitz HE. *Therapy for Diabetes Mellitus and Related Disorders*. 2004. Gerich JE. *Eur J Clin Invest*. 2002;32(Suppl 3):46–53. ADA. *Diabetes Care*. 2010;33(Suppl 1):S62–S69. Foulis AK, Clark A. *Joslin's Diabetes Mellitus*. 13th ed. 1994. Bardsley JK, Ratner RE. *The Art and Science of Diabetes Self-Management Education*. 2006.

Type 1 diabetes is characterized by absolute insulin deficiency caused by the destruction of beta cells. Beta-cell destruction usually results from an autoimmune process, but an idiopathic (unknown) process is sometimes involved. The rate of destruction varies widely, but the eventual result is the total loss of insulin production. Persons with type 1 diabetes will usually require exogenous insulin from the time of diagnosis.

Type 2 diabetes is caused by multiple, interrelated pathophysiologic defects involving varying degrees of insulin resistance and insulin deficiency. Insulin resistance occurs when peripheral tissues respond inadequately to insulin, resulting in decreased glucose uptake into muscles and other tissues and increased breakdown of adipocytes (fat cells).

In addition, the liver does not limit glucose production sufficiently in response to insulin. These defects result in elevated concentrations of plasma glucose and free fatty acids even in the absence of food. Insulin secretion is initially increased in response to the insulin resistance. However, beta-cell dysfunction eventually results in a progressive decrease in insulin secretion by the pancreas. In addition, a marked reduction of beta-cell mass often occurs. This reduced mass may be due to an increase in beta-cell apoptosis (programmed cell death). Chronic hyperglycemia causes a further impairment of insulin secretion (glucotoxicity), while increased free fatty acid levels exacerbate peripheral insulin resistance and further impair insulin secretion by beta cells (lipotoxicity).

Physiologic Serum Insulin Secretion Profile

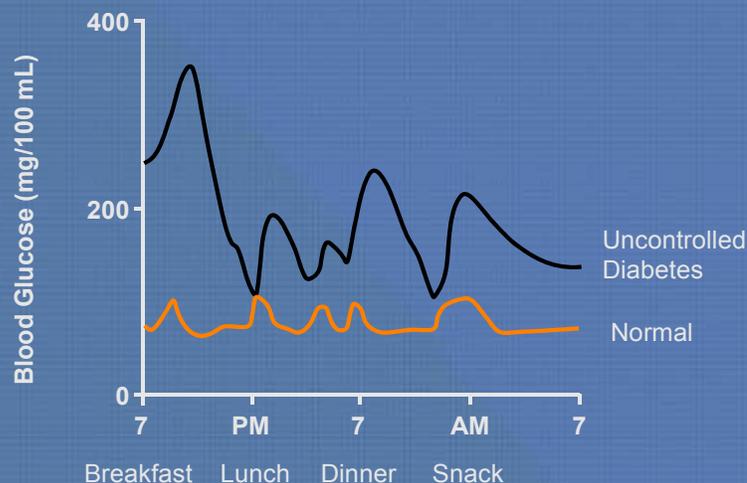


This slide depicts the physiologic profile of insulin secretion in an individual without diabetes. Under normal circumstances, insulin secretion consists of 2 components:

1. Basal secretion: a slow, steady, background level of secretion that regulates hepatic production of glucose and prevents the breakdown of fats and the development of ketoacidosis.
2. Prandial secretion: rapid increases in insulin secretion that occur in response to meals. These prandial insulin peaks help to control and regulate the glucose excursions that occur with meals.

Physiologic insulin secretion is tightly correlated with BG levels, ensuring that these levels do not drop too low between meals or rise too high after carbohydrate ingestion.

Glucose Levels in Uncontrolled Diabetes



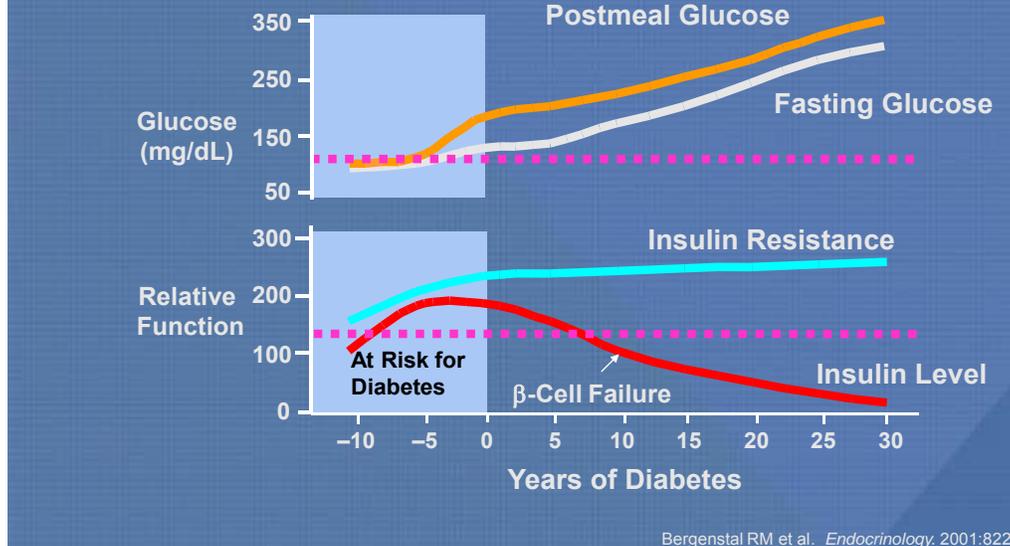
Gavin JR III. *Diabetes Educ.* 2007;33(Suppl 3):66S-73S.

In a person with diabetes, deficits in insulin action and/or insulin secretion result in widely fluctuating BG levels.

In this graph, which shows typical BG levels over a 24-hour period, the bottom curve represents typical levels in an individual without diabetes, whereas the top curve depicts levels in a person with uncontrolled diabetes.

The goal of treatment for persons with diabetes is to bring the upper curve into closer conformity to the lower curve.

Type 2 Diabetes Is a Progressive Disease



This slide depicts the progressive course of type 2 diabetes. Beta-cell deterioration usually occurs over many years, and most patients have had diabetes for at least 10 years by the time the disease is diagnosed.

During this 10-year period, which is represented on the graph by the light blue shading, postprandial glucose (PPG) levels, fasting blood glucose (FBG) levels, and insulin resistance all increase. The pancreas is increasingly unable to synthesize and secrete enough insulin to meet the demands of the insulin-resistant individual, and the initially increased insulin levels begin a gradual progressive decline. Because of the continuous course of pancreatic beta-cell failure, most patients with type 2 diabetes eventually require insulin therapy.

A1C and eAG

A1C (%)	eAG (mg/dL)
6	126
6.5*	140
7	154
7.5	169
8	183
8.5	197
9	212
9.5	226
10	240

Formula: $28.7 \times \text{A1C} - 46.7 = \text{eAG}$.
*American Diabetes Association (ADA) cut point for the diagnosis of diabetes.

- The A1C value reflects glucose control over the previous 3 months
- The A1C-Derived Average Glucose (ADAG) study affirmed the relationship between A1C and estimated average glucose (eAG) levels
- eAG values are expressed in units patients routinely see in their blood glucose measurements

Nathan DM et al. *Diabetes Care*. 2008;31:1473–1478.
ADA. Estimated average glucose, eAG. Available at: <http://professional.diabetes.org/GlucoseCalculator.aspx>.
ADA. *Diabetes Care*. 2010;33(Suppl 1):S11–S61.

The A1C assay, expressed as the percentage of hemoglobin that is glycosylated, measures glycemia over a 3-month period and is used to judge the adequacy of diabetes treatment and adjust therapy. An A1C level $\leq 6\%$ is considered normal. Beginning with the 2010 “Standards of Medical Care in Diabetes,” the American Diabetes Association (ADA) has included the use of A1C for the diagnosis of diabetes, with a cut point of $\geq 6.5\%$.

A1C as an indicator of diabetes control may be difficult to explain to patients. Since A1C is expressed as a percentage, it does not relate directly to the glucose measurements that patients encounter through home glucose monitoring or their laboratory values. This may make A1C targets difficult for patients to translate into action.

The results of the A1C-Derived Average Glucose (ADAG) study have affirmed the existence of a linear relationship between A1C and average BG levels. In light of these study results, the ADA is promoting a new term in diabetes management, estimated average glucose (eAG). Health care providers can now report A1C results to patients using the mg/dL units that they routinely see in their BG measurements. The DiabetesPro section of the ADA Web site (<http://professional.diabetes.org>) provides useful educational materials for health care providers and patients, as well as a calculator that automatically converts A1C levels to eAG values, and vice versa.

Current Treatment Goals

Parameter	ADA	AACE
A1C (%), eAG (mg/dL)	<7, <154	≤6.5, ≤140
Fasting/preprandial glucose (mg/dL)	70–130	<110
Postprandial glucose (mg/dL)	<180*	<140†
Blood pressure (mm Hg)	<130/80	<130/85
LDL cholesterol (mg/dL)	<100‡	<130
HDL cholesterol (mg/dL)	>40 men or >50 women	>35
Triglycerides (mg/dL)	<150	<200

*Peak postprandial capillary plasma glucose; measure 1–2 hours after beginning of meal.

†2-Hour postprandial glucose.

‡The ADA recommends a low-density lipoprotein (LDL) <70 mg/dL in individuals with overt cardiovascular disease.

AACE = American Association of Clinical Endocrinologists;
HDL = high-density lipoprotein.

ADA. *Diabetes Care*. 2010;33(Suppl 1):S11–S61.
AACE/AACE. *Endocr Pract*. 2006;12(Suppl 1):6–12.
AACE. *Endocr Pract*. 2000;6:162–213.

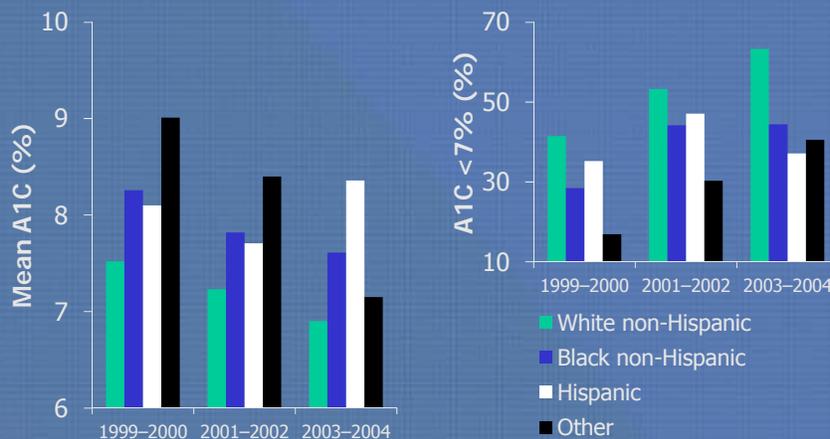
Current treatment goals for diabetes include A1C and fasting plasma glucose (FPG) and PPG levels, as well as target levels for blood pressure and plasma lipids.

Glycemic targets are based on the results of landmark clinical trials which have demonstrated that the risk of developing microvascular and macrovascular complications increases substantially once BG and A1C levels exceed these recommended values. As the table shows, the ADA and the American Association of Clinical Endocrinologists (AACE) have slightly different treatment goals. The ADA favors tighter control of lipids and blood pressure, whereas the AACE favors tighter control of glycemia.

It is important to note that the ADA recommends a low-density lipoprotein level <70 mg/dL in individuals with overt cardiovascular disease.

Regardless of which standard is adopted, patients with diabetes require ongoing medical care and comprehensive self-management to achieve these goals and to prevent complications.

US Glycemic Control Trends: NHANES Data



NHANES = National Health and Nutrition Examination Survey.

Hoerger TJ et al. *Diabetes Care*. 2008;31:81-86.

A study that examined data from the National Health and Nutrition Examination Survey (NHANES) found that overall glycemic control improved in the United States between 1999 and 2004. The investigators attributed this improvement to the adoption of more rigorous clinical guidelines for diabetes care, multifaceted disease management programs by health plans, and national public health awareness programs. In addition during this period, metformin and other new drugs were introduced, the side-effect profiles of the available glucose-lowering medications generally improved, and Medicare increased coverage for diabetes-related supplies during this period.

Although these results are encouraging, they also show that much needs to be done to improve glycemic control, particularly among black non-Hispanic and Hispanic persons. Among Hispanic participants, for example, the mean A1C rose between the beginning and the end of the study, and 63% of this group had an A1C $\geq 7\%$ at the end of the study period. Even in white non-Hispanic people, the group with the highest level of glycemic control, 37% of participants had an A1C $\geq 7\%$ by the end of the study.

Type 2 Diabetes Treatment Options

Intervention	Expected Decrease in A1C (%)	Main Advantage
Lifestyle changes	1.0–2.0	Broad benefits
Metformin	1.0–2.0	Weight neutral
Insulin	1.5–3.5	No dose limit
Sulfonylurea	1.0–2.0	Rapidly effective
Thiazolidinediones	0.5–1.4	Improved lipid profile (PIO)
GLP-1 agonist	0.5–1.0	Weight loss
α-Glucosidase inhibitor	0.5–0.8	Weight neutral
Glinide	0.5–1.5	Rapidly effective
Pramlintide	0.5–1.0	Weight loss
DPP-4 inhibitors	0.5–0.8	Weight neutral
Colesevelam	0.5–0.8	Reduces LDL-cholesterol

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide; PIO = pioglitazone.

Nathan DM et al. *Diabetes Care*. 2009;32:193–203. Welchol (colesevelam). Prescribing information. 2009.

This slide summarizes lifestyle and pharmacologic treatment options for patients with type 2 diabetes. Lifestyle intervention programs that promote weight loss and increase physical activity levels effectively lower glycemia, improve other cardiovascular risk factors, and improve other adverse consequences of excess weight. However, they are insufficient for most patients within 1 year.

Insulin therapy is rapidly effective, and is the most effective intervention for lowering glycemia. When used in adequate doses, insulin can decrease any level of elevated A1C to, or close to, the therapeutic goal. Unlike other BG-lowering medications, there is no maximum dose of insulin beyond which a therapeutic effect will not occur. Insulin therapy also has beneficial effects on triglyceride and high-density lipoprotein cholesterol levels.

Colesevelam, a bile acid sequestrant used primarily to treat hypercholesterolemia, is also indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. Because the major side effect of colesevelam is constipation, it should not be used in patients with gastroparesis or other gastrointestinal motility disorders, in patients after major gastrointestinal surgical procedures, and in others at risk for bowel obstruction.

Currently Available Insulin and Insulin Analogs: Short- and Rapid-Acting

Short-acting insulin (onset of action: 30–60 min)

- Regular human insulin (Humulin® R, Novolin® R)

Rapid-acting insulin analogs (onset of action: 5–15 min)

- Insulin lispro (Humalog®)
- Insulin aspart (NovoLog®)
- Insulin glulisine (Apidra®)

Skyler JS. *Therapy for Diabetes Mellitus and Related Disorders*. 2004.
Apidra® (insulin glulisine). Prescribing information. 2008.

As mentioned, insulin and insulin analogs differ from other pharmacologic treatments for type 2 diabetes in that they can reduce any level of A1C to, or close to, the therapeutic goal. This slide and the next 2 slides show currently available insulin formulations. Short-acting insulin and rapid-acting insulin analogs are used for mealtime coverage of BG levels in multiple daily injection (MDI) therapy to mimic endogenous insulin action. They can be used in insulin pump therapy and can also be administered intravenously.

- Short-acting insulin
 - Novolin® R – human insulin injection (rDNA origin)
 - Humulin® R – human insulin injection (rDNA origin)
- Rapid-acting insulin analogs
 - Insulin lispro injection (rDNA origin) (Humalog®)
 - Insulin aspart (rDNA origin) injection (NovoLog®)
 - Insulin glulisine (rDNA origin) injection (Apidra®)

Regular insulin is usually preferred over an insulin analog for intravenous therapy because it is less expensive. The main pharmacokinetic property that distinguishes the insulin analogs from regular insulin during subcutaneous therapy (dissociation time into dimers and monomers) is not applicable to intravenous therapy.

Currently Available Insulin and Insulin Analogs: Intermediate- and Long-Acting

Intermediate-acting insulin (onset of action: 2–4 hr)

- NPH human insulin (Humulin[®] N, Novolin[®] N)

Long-acting insulin analogs (onset of action: 1–2 hr)

- Insulin glargine (Lantus[®])
- Insulin detemir (Levemir[®])

NPH = neutral protamine Hagedorn.

Humulin[®] N Prescribing Information. 2000.
Lantus[®] (insulin glargine). Prescribing information. 2007.
Levemir[®] (insulin detemir). Prescribing information. 2007.
Novolin[®] N (NPH, human insulin). Prescribing information. 1999.
Skyler JS. *Therapy for Diabetes Mellitus and Related Disorders*. 2004.

Intermediate- and long-acting insulins are used to mimic basal coverage of BG levels.

Intermediate-acting insulin

- NPH (neutral protamine Hagedorn) human insulin (Humulin[®] N, Novolin[®] N)

NPH insulin is a suspension and requires extensive mixing to assure consistent absorption.

Long-acting insulin analogs

- Insulin glargine (Lantus[®])
- Insulin detemir (Levemir[®])

Currently Available Insulin and Insulin Analogs: Premixed Formulations

Premixed insulin (onset of action: 30–60 min)

- Humulin® 70/30
- Humulin® 50/50
- Novolin® 70/30

Premixed insulin analogs (onset of action: 5–15 min)

- Humalog® Mix75/25™
- Humalog® Mix50/50™*
- NovoLog® Mix 70/30

*Onset of action: <0.5 h.

Humalog® (50% insulin lispro protamine suspension and 50% insulin lispro injection). Prescribing information. 2007.
Skyler JS. *Therapy for Diabetes Mellitus and Related Disorders*. 2004.

Premixed formulations were developed for patient convenience by combining short-acting insulin with intermediate-acting insulin. Newer products are combinations of rapid-acting analogs with long-acting analogs. All mixtures are suspensions and require extensive mixing to assure consistent absorption.

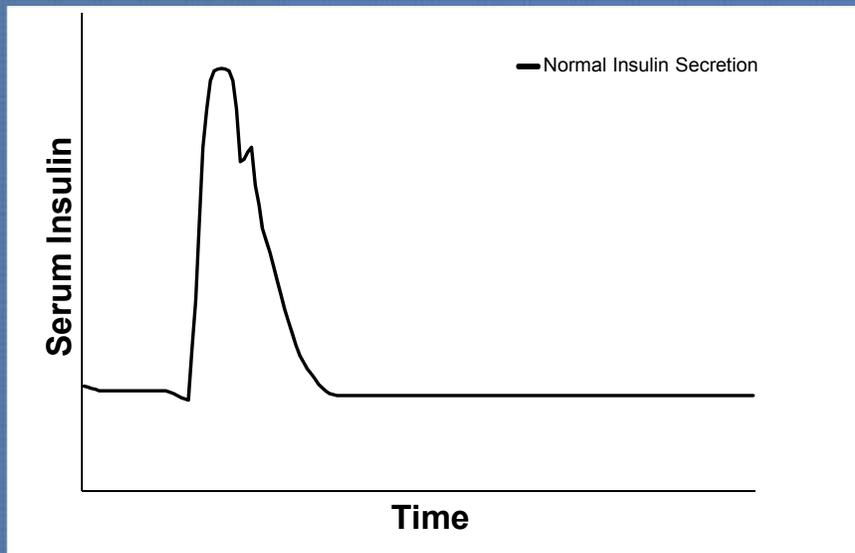
Premixed insulin

- Humulin® 70/30 – 70% NPH human insulin isophane suspension, 30% Regular human insulin injection (rDNA origin)
- Humulin® 50/50 – 50% NPH human insulin isophane suspension, 50% Regular human insulin injection (rDNA origin)
- Novolin® 70/30 – 70% NPH human insulin isophane suspension, 30% Regular human insulin injection (rDNA origin)

Premixed insulin analogs

- Humalog® Mix75/25™ – 75% insulin lispro protamine suspension and 25% insulin lispro injection (rDNA origin)
- Humalog® Mix50/50™ – 50% insulin lispro protamine suspension and 50% insulin lispro injection (rDNA origin)
- NovoLog® Mix 70/30 – 70% insulin aspart (rDNA origin) protamine suspension and 30% insulin aspart (rDNA origin) injection

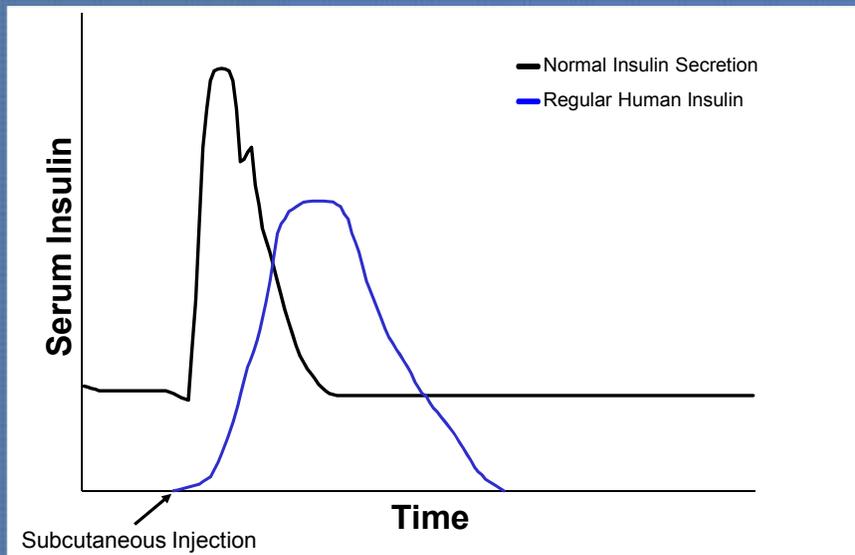
Time–Action Profiles of Insulin and Insulin Analogs: Theoretical Representations



This graph compares the time courses of the various insulin preparations with the profile of normal (physiologic) insulin secretion.

The profile of physiologic insulin secretion is plotted on the black line. The prandial or mealtime component is represented by the peak, and the basal component is shown by the relatively flat line at either side of the peak.

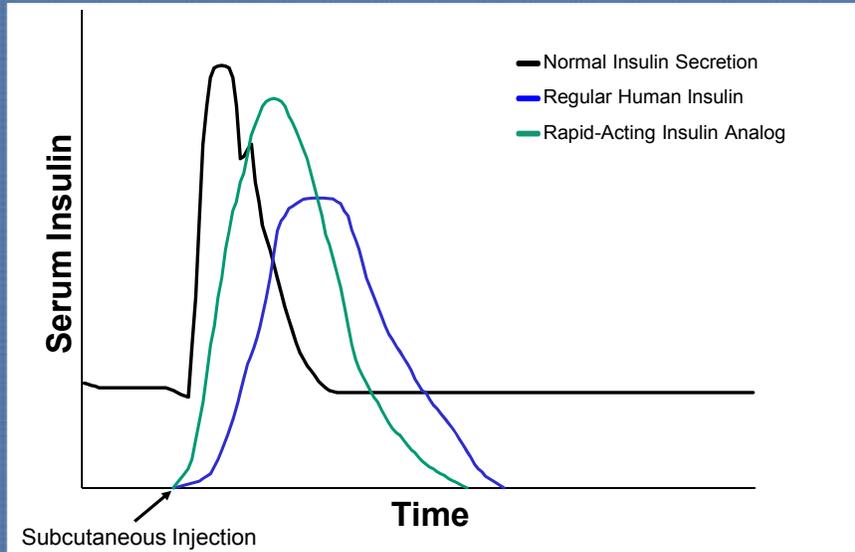
Time–Action Profiles of Insulin and Insulin Analogs: Theoretical Representations



The dark blue line shows the time course of regular human insulin.

As the figure shows, the pharmacokinetic profile of regular human insulin does not reproduce the physiologic insulin profile. Compared with the prandial component of endogenous insulin, regular insulin is absorbed more slowly and declines back to baseline more slowly. Specifically, the onset is delayed for 30 to 60 minutes, the peak occurs after 2 to 4 hours, and the duration can last for up to 8 hours.

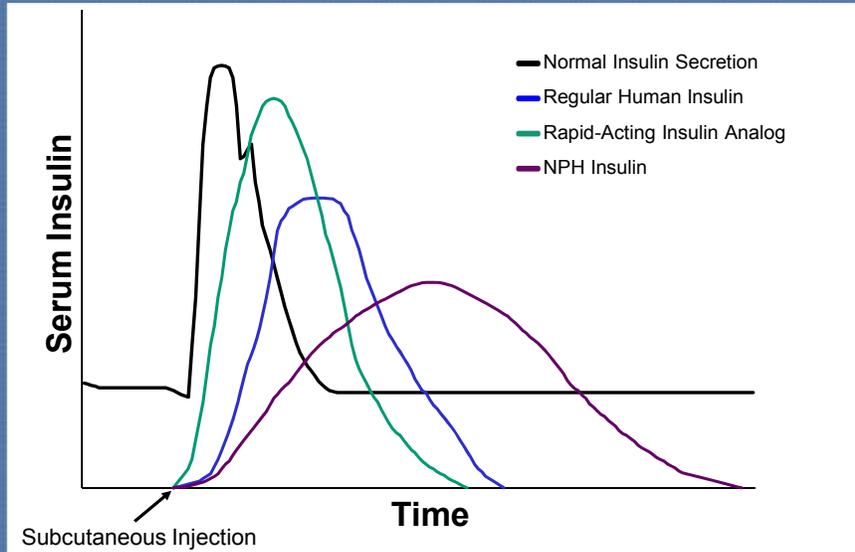
Time–Action Profiles of Insulin and Insulin Analogs: Theoretical Representations



The green line shows the time course of the rapid-acting insulin analogs.

Compared with regular human insulin, the rapid-acting analogs more closely resemble prandial physiologic insulin secretion. Rapid-acting insulin analogs are absorbed and reach peak plasma levels, and also decline back to baseline faster than regular human insulin. The onset of rapid-acting insulin varies from 5 to 15 minutes, its peak occurs in 1 to 2 hours, and the duration is up to 4 hours.

Time–Action Profiles of Insulin and Insulin Analogs: Theoretical Representations

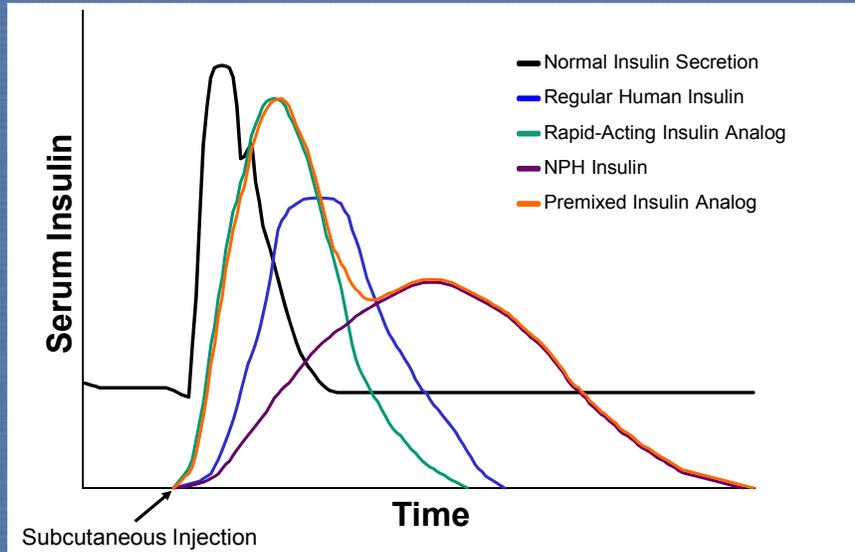


The purple line shows the time course of NPH insulin.

Unlike the basal component of endogenous insulin, which has a flat action profile, NPH insulin peaks at 4 to 10 hours postinjection. The time course of NPH insulin is highly variable.

Notice that NPH insulin does not provide a prandial component until several hours after injection. Patients using NPH should be counseled to have a meal, generally within 4 to 6 hours after injection.

Time–Action Profiles of Insulin and Insulin Analogs: Theoretical Representations

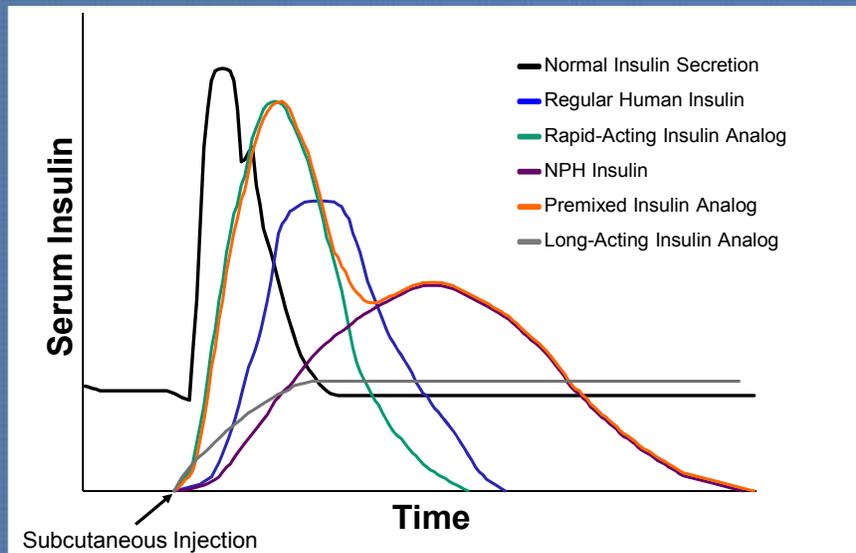


The orange line shows the time course of the premixed insulin analogs.

As the figure shows, the rapid-acting component of the premixed insulin analogs closely reproduces the prandial component of physiologic insulin. However, the long-acting component of premixed insulin analogs has a pronounced peak and therefore differs from the basal component of endogenous insulin.

Patients using premixed insulin analogs need to plan 2 meals—the first occurring within 15 minutes of the injection and the second occurring within 4 to 5 hours of the injection.

Time–Action Profiles of Insulin and Insulin Analogs: Theoretical Representations

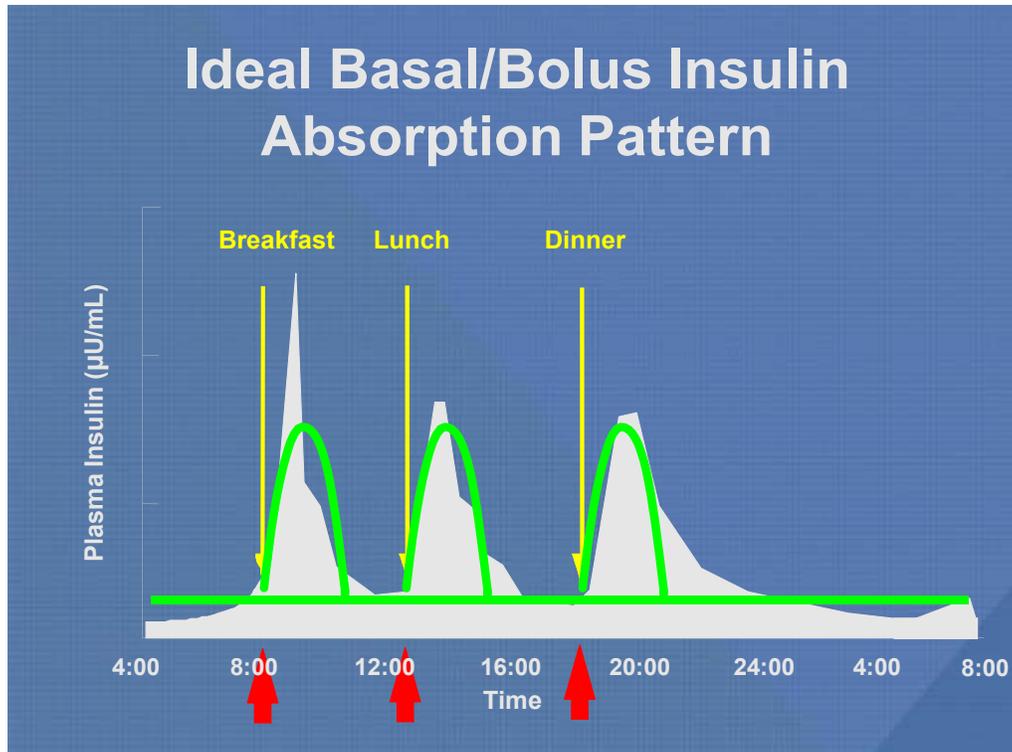


The gray line shows the time course of the long-acting insulin analogs.

Unlike NPH insulin and the long-acting component of the premixed insulin analogs, long-acting insulin analogs are relatively peakless, with flat action profiles. Thus, they more closely reproduce the basal component of physiologic insulin secretion.

The varying time course of each of these insulin products allows the practitioner to work with the patient to develop an insulin plan that fits the individual's unique needs.

Ideal Basal/Bolus Insulin Absorption Pattern



A basal-bolus regimen consisting of a long-acting insulin analog for basal coverage and rapid-acting insulin analogs with meals most closely approximates physiologic insulin secretion.

Despite the benefits of this approach, many patients with type 2 diabetes begin insulin therapy with a less intensive regimen and transition to a basal/bolus regimen later, if necessary. Basal/bolus therapy is the preferred starting regime in patients with type 2 diabetes.

Clinical Trials of Insulin Analogs: Basal Insulin

Study Name	First Author, Year	Regimens
Treat-to-Target	Riddle, 2003	Insulin glargine vs NPH added to oral agents
GWAA	Heine, 2005	Insulin glargine vs exenatide twice daily added to oral agents
Treat-to-Target	Hermansen, 2006	Insulin detemir vs NPH added to oral agents
TITRATE	Blonde, 2009	Insulin detemir with 2 FPG targets
L2T3	Swinnen, 2009	Insulin glargine vs insulin detemir
4-T	Holman, 2009	Insulin detemir vs biphasic insulin aspart 70/30 vs prandial insulin aspart
HEART2D	Raz, 2009	Insulin glargine or NPH vs prandial insulin lispro

FPG = fasting plasma glucose.

Riddle MC et al. *Diabetes Care*. 2003;26:3080–3086. Heine RJ et al. *Ann Intern Med*. 2005;143:559–569.
Hermansen K et al. *Diabetes Care*. 2006;29:1269–1274. Blonde L et al. *Diabetes Obes Metab*. 2009;11:623–631.
Swinnen SG et al. *Diabetes Technol Ther*. 2009;11: 739–743. Holman RR et al. *N Engl J Med*. 2009;361:1736–1747.
Raz I et al. *Diabetes Care*. 2009;32:381–386.

Many clinical trials have assessed the safety and efficacy of basal insulin analog therapy using insulin glargine, insulin detemir, or both. Seven representative trials are summarized in this table and 4 of these are discussed in subsequent slides. I would encourage you to read the full studies if you would like more information.

Two Treat-to-Target studies compared the therapeutic effects of insulin glargine or insulin detemir with those of NPH insulin.

The GWAA study compared treatment with insulin glargine and exenatide twice daily.

The TITRATE Study investigated the use of insulin detemir with the dosage adjusted to achieve 2 different FPG targets.

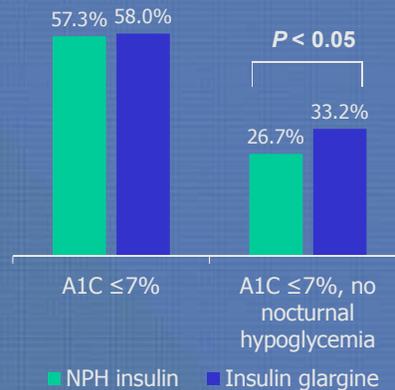
The L2T3 Study was a Treat-to-Target study that directly compared insulin glargine with insulin detemir.

The 4-T Study compared the effects of 3 different regimens: insulin detemir, biphasic insulin aspart 70/30, and prandial insulin aspart.

The HEART2D trial compared basal regimens (using insulin glargine or NPH insulin) with a prandial regimen (using insulin lispro).

Treat-to-Target: Insulin Glargine vs NPH + Oral Therapy

- N = 756
- On stable doses of oral agents
- A1C >7.5%
- Randomized to insulin glargine or NPH at bedtime added to current oral agents for 16 weeks
- Weekly insulin titration to target FPG ≤100 mg/dL



Riddle MC et al. *Diabetes Care*. 2003;26:3080–3086.

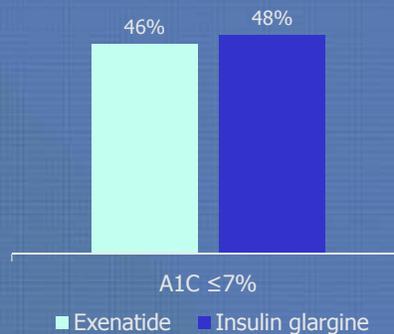
One Treat-to-Target trial compared the efficacy and hypoglycemia risks of insulin glargine versus NPH insulin when added to existing oral therapy. This randomized, open-label, multicenter, 24-week trial enrolled overweight men and women with type 2 diabetes. Participants, who had an A1C of >7.5% on stable doses of 1 or 2 oral agents, were randomized to once-daily insulin glargine or NPH insulin at bedtime. The starting dose of both insulins was 10 units, and the dose was titrated weekly to achieve a target FPG of ≤100 mg/dL. The glycemic target was an A1C of ≤7%.

As the graph shows, nearly 60% of patients in both treatment groups attained the target A1C. However, significantly more patients in the insulin glargine group achieved this target without documented nocturnal hypoglycemia (33.2% vs 26.7%). In addition, the cumulative incidence of hypoglycemic events was lower with insulin glargine than with NPH insulin.

The investigators concluded that this trial offers the basis for a simple, standardized way to initiate basal insulin in routine practice for overweight patients with an A1C between 7.5% and 10% despite the use of 1 or 2 oral agents. The regimen requires just 1 daily injection added to oral therapy and 1 daily FBG measurement to guide dosage adjustment. The lower risk of nocturnal hypoglycemia with insulin glargine relative to NPH insulin reduces a major barrier to starting insulin therapy—fear of hypoglycemia.

GWAA Study: Insulin Glargine vs Exenatide Twice Daily

- N = 551
- Receiving MET + a SU
- A1C 7.0%–10.0%
- Randomized to insulin glargine at bedtime or exenatide before morning and evening meals plus current therapy for 26 weeks
- Insulin titrated to target FBG <100 mg/dL



FBG = fasting blood glucose;
MET = metformin; SU = sulfonylurea.

Heine RJ et al. *Ann Intern Med.* 2005;143:559–569.

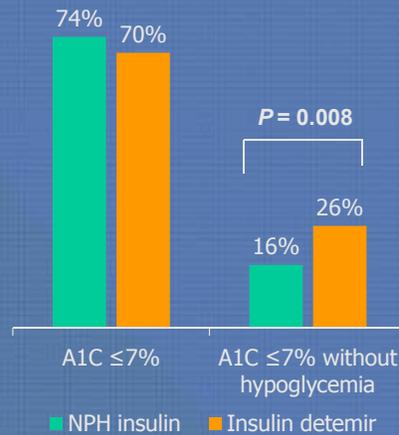
The GWAA study compared the effects of insulin glargine (a basal therapy) with those of exenatide twice daily, a glucagon-like peptide-1 (GLP-1) receptor agonist (a prandial therapy).

This randomized, open-label, multicenter, 26-week trial enrolled overweight men and women with type 2 diabetes. Participants, who had an A1C of 7.0% to 10.0%, were randomized to once-daily insulin glargine at bedtime or to exenatide before morning and evening meals. The starting dose of insulin glargine was 10 units, and patients titrated the dose in 2-unit increments every 3 days to achieve a target FBG of <100 mg/dL. Patients in the exenatide group received fixed doses of 5 µg for the first 4 weeks and 10 µg for the rest of the study. Insulin glargine or exenatide was added to patients' existing therapy, which consisted of metformin and a sulfonylurea.

As the graph shows, nearly 50% of patients in both treatment groups attained the target A1C of ≤7%. At week 26, the A1C reduction from baseline was 1.11% in both groups. Reductions in FPG levels were 51.5 mg/dL with insulin glargine and 25.7 mg/dL with exenatide; this difference was statistically significant in favor of insulin glargine. A FPG level of <100 mg/dL was achieved by 21.6% of patients in the insulin glargine group and by 8.6% of those in the exenatide group. Patients in the insulin glargine group experienced a higher incidence of nocturnal hypoglycemia events and a lower incidence of daytime hypoglycemia events than those in the exenatide group. The investigators concluded that insulin glargine and exenatide twice daily were similarly effective in improving glycemic control in patients with type 2 diabetes that was suboptimally controlled with metformin and a sulfonylurea.

Treat-to-Target: Insulin Detemir vs NPH + Oral Therapy

- N = 476
- On 1 or 2 oral agents for ≥ 4 months
- A1C 7.5%–10.0%
- Randomized to twice-daily insulin detemir or NPH insulin added to existing oral therapy for 26 weeks
- Insulin titrated to achieve prebreakfast and predinner plasma glucose value of ≤ 108 mg/dL



Hermansen K et al. *Diabetes Care*. 2006;29:1269–1274.

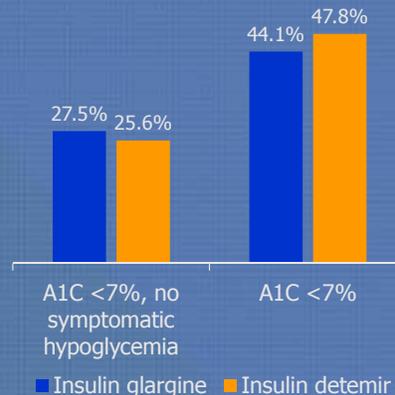
In another Treat-to-Target trial, Hermansen and colleagues compared the efficacy and tolerability of the basal analog insulin detemir versus NPH insulin added to existing therapy to attain an A1C of $\leq 7\%$. In this randomized, open-label, multicenter, 26-week trial, patients who had been receiving 1 or 2 oral agents for ≥ 4 months and whose A1C was 7.5% to 10.0% were randomized to receive twice-daily insulin detemir or NPH insulin. From a starting dose of 10 units twice daily, the insulin dose was titrated every 3 days to achieve prebreakfast and predinner target plasma glucose concentrations of ≤ 108 mg/dL.

As the graph shows, 74% of the NPH insulin group and 70% of the insulin detemir group attained the target A1C of $\leq 7\%$. During the last 12 weeks of the trial, a significantly higher proportion of patients in the insulin detemir group than in the NPH insulin group achieved the target A1C without hypoglycemia (26% vs 16%). Compared with NPH insulin, insulin detemir was associated with a 47% lower risk for any hypoglycemic event and a 55% lower risk for nocturnal hypoglycemic events. Mean weight gain was 1.2 kg with insulin detemir compared with 2.8 kg with NPH insulin.

The investigators concluded that treatment with twice-daily insulin detemir or NPH insulin as an add-on to oral glucose-lowering therapy, using tight dose titration, resulted in clinically important improvements in glycemic control, with most patients attaining an A1C level $< 7.0\%$. At all levels of control, insulin detemir incurred a lower risk of hypoglycemia and reduced weight gain compared with NPH insulin. Insulin detemir therefore appears to represent a significant clinical advance over NPH insulin when used in active dose titration to achieve targeted glycemic control.

L2T3 Study: Insulin Glargine vs Insulin Detemir

- N = 973
- On MET ± other oral agents
- Mean A1C, 8.7%
- Randomized to once-daily insulin glargine or twice-daily insulin detemir for 24 weeks
- Insulin titrated to achieve FPG of <100 mg/dL



Swinnen SG et al. *Diabetes Technol Ther.* 2009;11:739–743. Sanofi-aventis. Clinical trial summary: NCT00405418. 2009.

The L2T3 Study was a direct comparison of the therapeutic effects of insulin glargine and insulin detemir. In this randomized, open-label, multicenter, 24-week trial, patients who had been receiving metformin, with or without other oral agents, for ≥3 months were randomized to receive insulin glargine, given once daily at dinner or at bedtime, or insulin detemir, given twice daily before breakfast and dinner. From a starting dose of 0.2 unit/kg, both insulins were titrated every 2 days to reach an FPG of <100 mg/dL. The primary efficacy endpoint was the percentage of patients in each group who achieved an A1C of <7% without experiencing symptomatic hyperglycemia. A secondary endpoint was the percentage of patients who achieved an A1C of 7%.

As the graph shows, 27.5% of the insulin glargine group and 25.6% of the insulin detemir group attained the target A1C of <7% without symptomatic hypoglycemia. Patients achieving an A1C of <7% included 44.1% of the insulin glargine group and 47.8% of the insulin detemir group. A significantly higher percentage of patients in the insulin detemir group than in the insulin glargine group achieved an A1C value of <6.5% (22.7% vs 16.5%). The proportion of patients experiencing symptomatic hypoglycemia was 55.9% and 56.2% of patients in the insulin glargine and insulin detemir groups, respectively.

Clinical Trials of Insulin Analogs: Biphasic Insulin

Study Name	First Author, Year	Regimens
Lispro-Mixture-Glargine	Malone, 2004	Insulin lispro mix 75/25 vs insulin glargine
DURABLE	Buse, 2009	Insulin lispro mix 75/25 vs insulin glargine
INITIATE	Raskin, 2005	Insulin aspart mix 70/30 vs insulin glargine
Insulin-Based vs Triple Oral Therapy	Lingvay, 2009	Insulin aspart mix 70/30 + MET vs triple oral therapy
1-2-3 Study	Garber, 2006	Insulin aspart mix 70/30, 1–3 daily

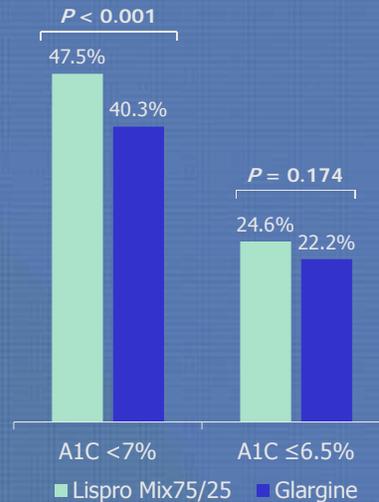
Malone JK et al. *Clin Ther*. 2004;26:2034–2044.
 Buse JB et al. *Diabetes Care*. 2009;32:1007–1013.
 Raskin P et al. *Diabetes Care*. 2005;28:260–265.
 Lingvay I et al. *Diabetes Care*. 2009;32:1789–1795.
 Garber AJ et al. *Diabetes Obes Metab*. 2006;8:58–66.

A number of clinical trials have assessed the safety and efficacy of therapy with a premixed (biphasic) insulin analog formulation. Five representative trials are summarized in this table and 3 of these are more fully described in subsequent slides.

Insulin glargine was used as the active comparator for 2 studies with insulin lispro mix 75/25 and 1 study with insulin aspart mix 70/30. Another study compared the effects of insulin aspart mix 70/30 plus metformin with those of triple oral glucose-lowering therapy. The 1-2-3 Study compared the effects of insulin aspart mix 70/30 when administered once, twice, or three times daily.

DURABLE: Insulin Lispro Mix 75/25 vs Insulin Glargine

- N = 2091
- Insulin-naive
- A1C >7.0% on ≥2 oral medications
- For 24-week initiation phase, patients randomized to insulin lispro mix 75/25 twice daily or insulin glargine, plus oral medications
- Insulin titrated to achieve target A1C of ≤6.5%



Buse JB et al. *Diabetes Care*. 2009;32:1007–1013.

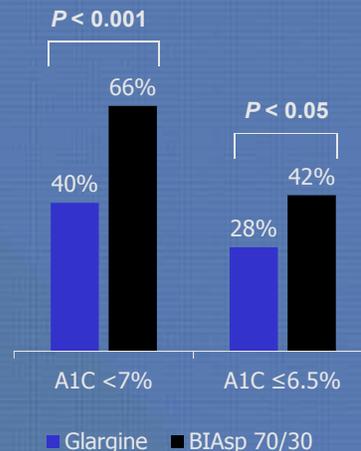
The DURABLE study is a comparative trial of insulin lispro mix 75/25 versus insulin glargine, with a total of 2091 patients. This is a basal/bolus regime compared with a basal regime.

Results of the 24-week initiation phase of DURABLE are summarized here; the 2-year maintenance phase is in progress. In this open-label, parallel-group trial conducted at 242 centers in 11 countries, insulin-naive patients with inadequate control during treatment with at least 2 oral medications were randomized to receive insulin lispro mix 75/25 twice daily before the morning and evening meal or insulin glargine once daily before the morning or evening meal or at bedtime. Patients maintained their oral glucose-lowering drugs at stable doses. The minimum starting dose was 10 units twice daily for insulin lispro mix 75/25 and 10 units once daily for insulin glargine. Insulin dose adjustments were made to achieve a target A1C goal ≤6.5%, using regimen-specific titration algorithms.

As the graph shows, 47.5% of patients in the insulin lispro mix 75/25 group and 40.3% of those in the insulin glargine group achieved an A1C <7.0%; this difference was statistically significant. However, there was no difference between the groups in the percentage of patients who achieved an A1C ≤6.5%: 24.6% in the mix 75/25 group and 22.2% in the insulin glargine group. Compared with patients in the insulin glargine group, patients in the mix 75/25 group experienced more weight gain and higher rates of overall hypoglycemia but lower rates of nocturnal hypoglycemia.

INITIATE: Biphasic Insulin Aspart (BIAsp 70/30) vs Insulin Glargine

- N = 233
- Currently on >1000 mg/d MET alone or in combination with other OADs
- A1C ≥8.0%
- MET dose optimized before initiating insulin
- Patients randomized to twice-daily BIAsp 70/30 or once-daily insulin glargine for 28 weeks
- Insulin titrated to attain FPG of 80–110 mg/dL



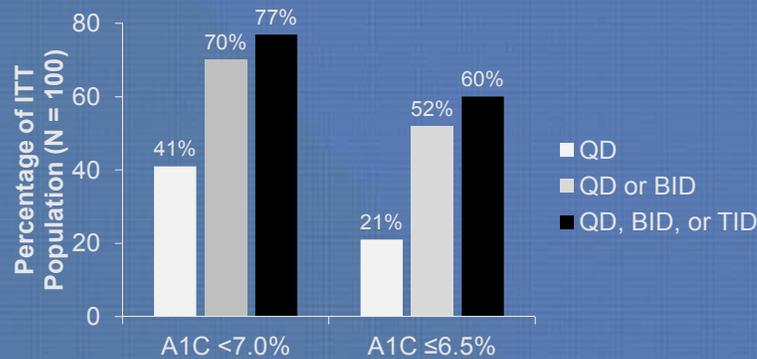
OADs = oral antidiabetes drugs.

Raskin P et al. *Diabetes Care*. 2005;28:260–265.

The INITIATE trial compared twice-daily biphasic insulin aspart 70/30 (BIAsp 70/30) with once-daily insulin glargine for patients with type 2 diabetes inadequately controlled on oral agents. A total of 233 insulin-naïve patients treated with >1000 mg/d of metformin alone or in combination with other glucose-lowering drugs were randomized to either BIAsp 70/30 prebreakfast and predinner or insulin glargine at bedtime for 28 weeks. The metformin dose was titrated up to 2550 mg/d before insulin was initiated. BIAsp 70/30 was started at 5 to 6 units twice daily and insulin glargine was started at 10 to 12 units once daily. Insulin doses were titrated to a target FPG of 80 to 110 mg/dL.

At the end of the study, 66% of patients in the BIAsp group and 40% of those in the insulin glargine group attained an A1C <7%, and 42% of patients in the BIAsp group and 28% of those in the insulin glargine group attained an A1C ≤6.5%. Mean A1C values were 6.91% for the BIAsp group compared with 7.41% for the insulin glargine group. Mean A1C reductions were especially pronounced in patients whose baseline A1C was >8.5% (3.13% with BIAsp 70/30 vs 2.60% with insulin glargine). Both the incidence of minor hypoglycemic episodes and the incidence of weight gain was higher in BIAsp-treated patients. The investigators concluded that BIAsp 70/30 appears to be more effective than insulin glargine and a reasonable choice for initiating insulin therapy in insulin-naïve subjects with type 2 diabetes that is not optimally controlled on oral therapy. This approach seems to be particularly effective for patients whose A1C before insulin initiation is >8.5%.

1-2-3 Study: Optimal Dosing of Biphasic Insulin Aspart 70/30



Among completers (n = 74) at the end of the study:

- 88% achieved A1C <7.0%
- 77% achieved A1C ≤6.5%

ITT = intent to treat.

Garber AJ et al. *Diabetes Obes Metab.* 2006;8:58–66.

The 1-2-3 Study assessed whether addition and self-titration of biphasic insulin aspart 70/30 (BIAsp 30) could achieve AACE and ADA glycemic targets in patients who were not at goal with oral therapy, with or without basal insulin.

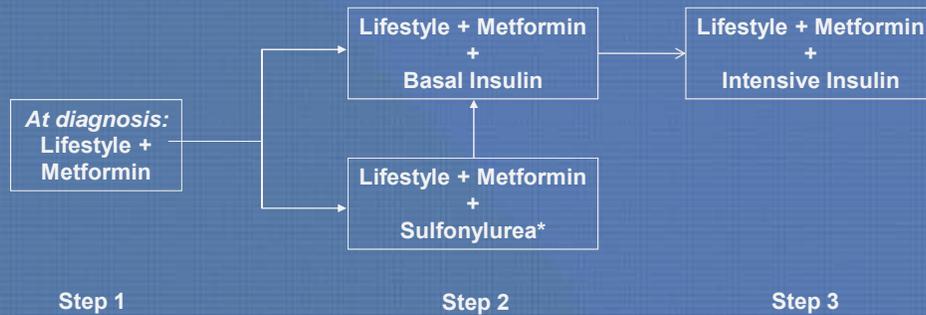
Participants discontinued basal insulin and added one 12-unit predinner injection of BIAsp 30. The dose was then titrated to achieve an FBG level of 80 to 110 mg/dL. At 16 weeks, patients completed the study if their A1C was ≤6.5%; otherwise, they remained in the study and added a prebreakfast injection of 6 units of BIAsp 30. This dose was titrated to achieve a predinner BG level of 80 to 100 mg/dL. At 32 weeks, patients completed the study if their A1C was at goal; otherwise, they added a prelunch injection of 3 units of BIAsp 30. This dose was titrated based on 2-hour postlunch BG to achieve a PPG level of 100 to 140 mg/dL.

The intent-to-treat population included 100 patients. As shown on the graph, the addition of up to 3 doses of BIAsp 30 enabled 60% of patients to reach the A1C target of ≤6.5% and 77% of patients to reach the target of <7%. An analysis of the 74 patients who completed the study found that 77% of patients achieved an A1C of ≤6.5% and 88% achieved an A1C of <7%.

The investigators concluded that the addition of once-daily BIAsp 30 to prior oral therapy is a viable treatment approach for many patients and can be safely intensified to achieve glycemic control in most patients who are not attaining their glycemic goals with oral therapy alone.

2009 ADA/EASD Algorithm: Tier 1 Interventions

Well-Validated Core Therapies



*Sulfonylurea therapy should consist of treatment with 1 of 3 second-generation agents: gliclazide, glimepiride, or glipizide. The second-generation agents glyburide (glibenclamide) or chlorpropamide should be avoided because they are associated with an increased risk for hypoglycemia.

EASD = European Association for the Study of Diabetes.

Nathan DM et al. *Diabetes Care*. 2009;32:193–203.

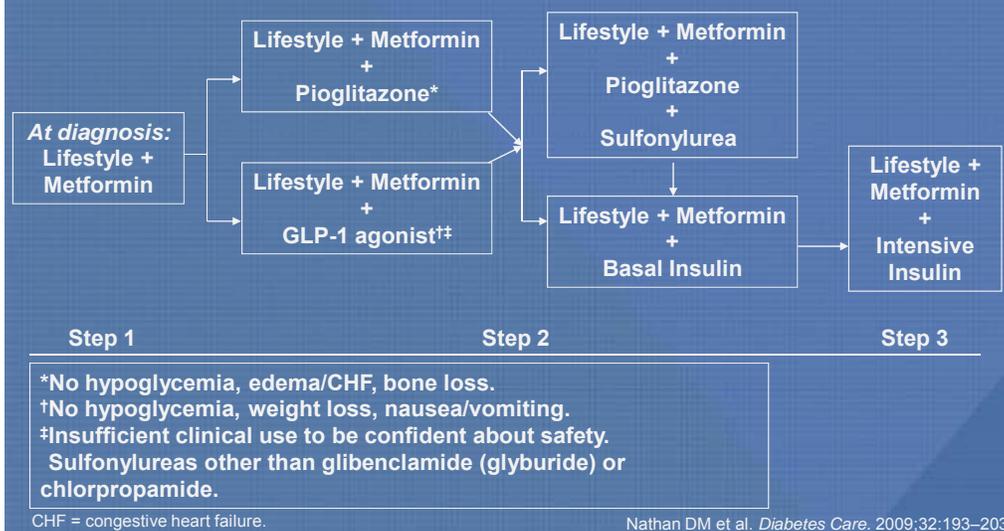
Early in 2009, the ADA and the European Association for the Study of Diabetes (EASD) published a consensus algorithm for the initiation and adjustment of therapy in type 2 diabetes. This revision of an algorithm previously published in 2006 includes glucose-lowering medications that have recently been developed. The algorithm has 2 tiers, the first includes well-validated core therapies and the second includes newer, less well-validated therapies.

The principles underlying the algorithm are that health care providers should reinforce lifestyle interventions at every visit and check A1C every 3 months until the A1C is <7% and then at least every 6 months. Interventions should be changed if the A1C is $\geq 7\%$.

As shown in this slide, which depicts Tier 1 interventions, Step 1 consists of lifestyle modifications and metformin therapy at diagnosis. Insulin initiation at the time of diagnosis is recommended for individuals presenting with weight loss or other severe symptoms or signs of hyperglycemia. If Step 1 treatments do not achieve the patient's glycemic goals, another medication should be added within 2 to 3 months of the initiation of therapy or at any time when the target A1C level is not reached. At Step 2, basal insulin (a long-acting insulin analog or NPH insulin) should be added for a patient with an A1C level $>8.5\%$ or with symptoms secondary to hyperglycemia. Other patients should receive a sulfonylurea (other than glyburide [glibenclamide] or chlorpropamide, which are associated with an elevated risk for hypoglycemia). Step 3 interventions consist of the initiation or the intensification of insulin therapy. Intensifying insulin therapy usually consists of additional injections, such as giving a rapid-acting insulin analog or a short-acting regular insulin before selected meals to reduce PPG excursions.

2009 ADA/EASD Algorithm: Tier 2 Interventions

Less Well-Validated Therapies



Tier 2 of the ADA/EASD algorithm presents less well-validated therapies that can be considered as Step 2 options in selected clinical settings. Specifically, when hypoglycemia is particularly undesirable (eg, in patients who have hazardous jobs), the addition of pioglitazone or a GLP-1 agonist may be considered.

An important advantage of pioglitazone is that it does not cause hypoglycemia. Peripheral edema is a frequent adverse effect, and pioglitazone-treated patients in clinical trials had a 2-fold increased risk for congestive heart failure. Bone loss may also occur. Although rosiglitazone, another thiazolidinedione (TZD), has also been approved for the treatment of type 2 diabetes, the consensus group unanimously advised against its use because of the possible increased risk for myocardial infarction.

Like pioglitazone, the GLP-1 agonists (exenatide, liraglutide) do not cause hypoglycemia. They also cause moderate weight loss (eg, 2–3 kg over 6 months). Gastrointestinal disturbances, such as nausea, vomiting, and diarrhea, occur commonly, especially at the start of treatment. Use of a GLP-1 agonist is preferable to treatment with pioglitazone when promotion of weight loss is a major consideration and the A1C level is close to target (<8.0%).

If these interventions are not effective in achieving the target A1C level or are not tolerated, the addition of a sulfonylurea other than glyburide or chlorpropamide could be considered. Alternatively, Tier 2 interventions could be stopped and basal insulin started.

2009 AACE/ACE Algorithm: Basic Principles

- Conforms to consensus for current standards of care by expert endocrinologists
- Therapy should be monitored every 2–3 months
- Treatment should be intensified until A1C goal is achieved
- Progresses from monotherapy, to dual therapy, to triple therapy, to insulin therapy ± additional agents
- Stratifies treatment approach based on current A1C level: 6.5%–7.5%, 7.6%–9.0%, or >9.0%

ACE = American College of Endocrinology.

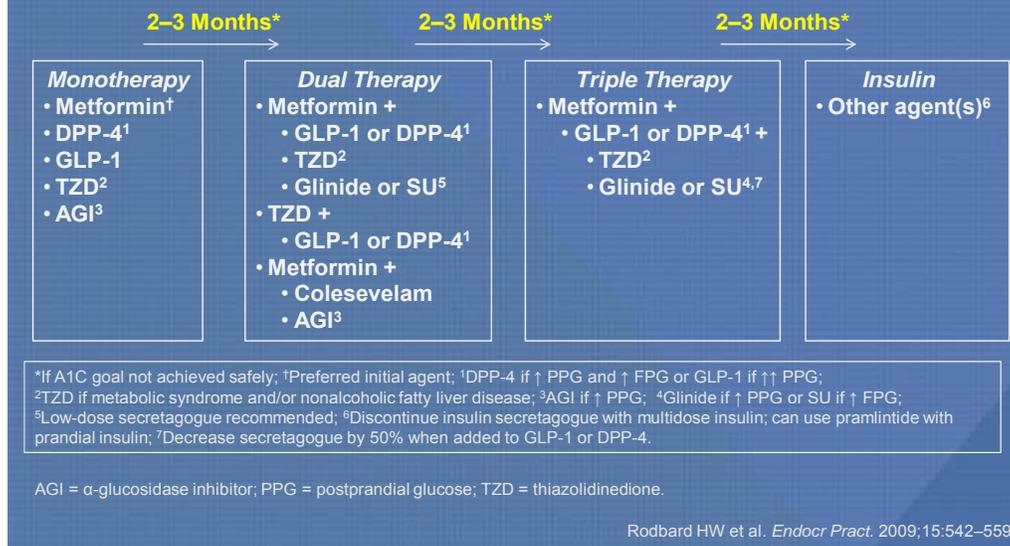
Rodbard HW et al. *Endocr Pract.* 2009;15:542–559.

Another important treatment algorithm was developed by the AACE and the American College of Endocrinology and published in September 2009. The intent of the authors was to conform as nearly as possible to a consensus for current standards of care by expert endocrinologists who specialize in the management of patients with type 2 diabetes and have the broadest experience in outpatient clinical practice. Core principles are that therapy should be monitored every 2 to 3 months and that therapy should be intensified until the A1C goal has been reached.

The algorithm progresses from monotherapy to dual therapy, to triple therapy, and then to insulin therapy with or without additional agents. In addition to insulin, the algorithm includes 8 major classes of medications: biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors, GLP-1 receptor agonists, TZDs, α -glucosidase inhibitors, sulfonylureas, meglitinides, and bile acid sequestrants. Choices of medications are prioritized according to their safety, risk of hypoglycemia, efficacy, simplicity, anticipated degree of patient adherence, and cost.

Unique to this algorithm is a therapeutic approach stratified on the basis of the current level of glycemic control, with different treatment strategies recommended for patients whose A1C level is 6.5%–7.5%, 7.6%–9%, and >9%.

2009 AACE/ACE Algorithm: A1C 6.5%–7.5%



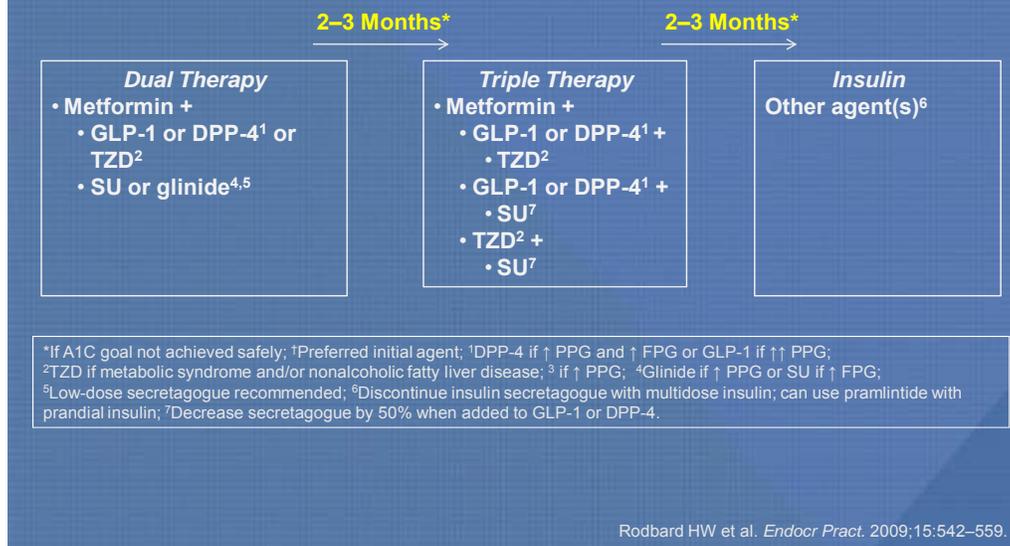
If a patient has an A1C $\leq 7.5\%$, it may be possible to achieve the A1C goal of $\leq 6.5\%$ with monotherapy. Because of its safety and efficacy, metformin is the cornerstone of monotherapy and is usually the most appropriate initial choice for monotherapy unless there is a contraindication. Alternatively, a DPP-4 inhibitor, GLP-1 agonist, TZD, or α -glucosidase inhibitor may be used.

Metformin should remain the cornerstone of treatment for most patients who progress to dual therapy. When metformin is contraindicated, a TZD may be used as the therapeutic foundation. Because metformin or a TZD are insulin sensitizers, the second component of dual therapy is usually an insulin secretagogue, a GLP-1 analog, DPP-4 inhibitor, glinide, or sulfonylurea.

For patients who advance to triple therapy, metformin generally remains the cornerstone of treatment. A GLP-1 agonist is the second preferred component because of the safety of this therapeutic class and its association with moderate weight loss. The third member of the triple-therapy combination might be a TZD, glinide, or sulfonylurea. These agents are recommended because they minimize the risk of hypoglycemia. The combination with metformin, especially when coupled with a GLP-1 agonist, may partially help to counteract the weight gain often associated with glinides, sulfonylureas, and TZDs.

When triple therapy fails to achieve glycemic control, insulin therapy, with or without adjuvant therapy, is required. AACE/ACE guidelines for insulin therapy are discussed in subsequent slides.

2009 AACE/ACE Algorithm: A1C 7.6%–9.0%

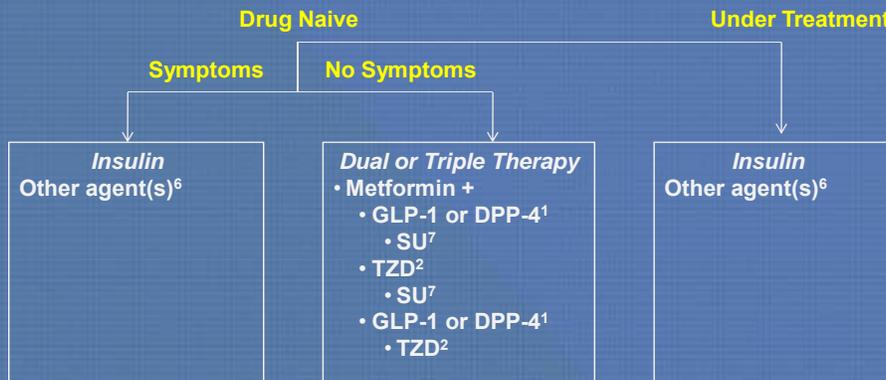


In the AACE algorithm, the use of monotherapy is bypassed for patients with an A1C of 7.6%–9%, and treatment begins with dual therapy. Again, metformin is a cornerstone of the dual therapy. A GLP-1 agonist or DPP-4 inhibitor is generally the preferred second component, with a GLP-1 agonist given higher priority due to its somewhat greater effect on reducing PPG excursions and its potential for inducing substantial weight loss. The lower position of the TZDs is attributable to their associated risks of weight gain, fluid retention, congestive heart failure, and fractures. Sulfonylureas and glinides are placed lower on the decision tree because of their greater risk of inducing hypoglycemia.

As shown on the slide, there are 5 options for patients in this A1C range who advance to triple therapy. The combination of metformin, TZD, and a sulfonylurea has the lowest priority because of its increased risk of weight gain and the risk of hypoglycemia. Glinides, α -glucosidase inhibitors, and colesevelam are not considered in this A1C range because of their limited A1C-lowering potential.

Considerations for insulin therapy for patients with a current A1C of 7.6% to 9% are similar to those for patients at the lower A1C range and are discussed in subsequent slides.

2009 AACE/ACE Algorithm: A1C >9.0%



^{*}If A1C goal not achieved safely; ¹Preferred initial agent; ¹DPP-4 if ↑ PPG and ↑ FPG or GLP-1 if ↑↑ PPG; ²TZD if metabolic syndrome and/or nonalcoholic fatty liver disease; ³AGI if ↑ PPG; ⁴Glinide if ↑ PPG or SU if ↑ FPG; ⁵Low-dose secretagogue recommended; ⁶Discontinue insulin secretagogue with multidose insulin; can use pramlintide with prandial insulin; ⁷Decrease secretagogue by 50% when added to GLP-1 or DPP-4.

Rodbard HW et al. *Endocr Pract.* 2009;15:542–559.

For drug-naive patients with A1C levels >9%, it is unlikely that the use of 1, 2, or even 3 agents—other than insulin—will achieve the A1C goal of ≤6.5%. If the patient is asymptomatic, particularly with a relatively recent onset of diabetes, a good probability exists for preservation of some beta-cell function, implying that dual or triple therapy may be sufficient. The slide shows the 8 possible options for these patients.

In contrast, prompt initiation of insulin therapy is appropriate for symptomatic patients who are experiencing polydipsia, polyuria, and weight loss, or for patients who have already been treated with regimens of dual or triple therapy similar to the ones shown on this slide.

2009 AACE/ACE Algorithm Insulin Selection

Type of Insulin	Comments
Rapid-acting insulin analogs (insulins lispro, aspart, and glulisine)	Have time course of action that closely mimics features of endogenous insulin
Long-acting insulin analogs (insulins glargine and detemir)	Both can be used with 1 injection per day; insulin detemir has excellent reproducibility of absorption profile within individuals and may cause less weight gain than other insulins
Premixed insulins (insulins lispro or aspart with protamine)	Suitable for coverage for breakfast and lunch or for dinner and overnight; less effective than a fully optimized basal/bolus regimen
Regular human insulin	Not recommended
NPH insulin	Not recommended

Rodbard HW et al. *Endocr Pract.* 2009;15:542–559.

The 2009 AACE/ACE (American College of Endocrinology) algorithm recommends the use of rapid-acting insulin analogs rather than regular human insulin. With regular human insulin, the onset of action is too slow and the persistence of effect is too long to mimic a normal prandial physiologic profile. The result is impaired efficacy and an increased risk of delayed hypoglycemia.

The algorithm also recommends that a long-acting insulin analog be used in preference to NPH insulin. NPH insulin shows wide variability in its absorption rate from day to day, even within individuals, and does not have a sufficiently long time course to provide basal insulinization for a 24-hour period. Furthermore, it has a pronounced peak. Compared with long-acting insulin analogs, there is an increased risk of hypoglycemia with NPH insulin.

The algorithm gives a qualified endorsement to the use of insulin aspart premixed with aspart-protamine and insulin lispro premixed with lispro-protamine. These products provide a time course that is suitable for coverage for breakfast and lunch or for dinner and the overnight period. Rather than resulting in 2 discrete peaks, these premixed insulins have a single peak at about 1.5 hours, followed by a slow decline. Accordingly, they do not mimic normal physiologic processes. They are neither as flexible nor as effective as a fully optimized basal/bolus regimen that includes a rapid-acting insulin analog and a long-acting insulin analog. Premixed products containing regular human insulin and NPH insulin are not recommended because maximal activity does not occur until approximately 2 to 2.5 hours postinjection.

2009 AACE/ACE Algorithm Insulin and Adjuvant Therapy

Agent	Comments
Metformin	Most commonly used and safest adjuvant medication
Pramlintide	Can help to control PPG
GLP-1 agonists, DPP-4 inhibitors	Not currently approved for use with insulin
Sulfonylureas, glinides	Should be discontinued when prandial insulin is introduced
Thiazolidinediones	Use with insulin associated with weight gain, fluid retention, CHF, bone fractures
α -Glucosidase inhibitors, colesevelam	Unlikely to contribute materially to effectiveness

Rodbard HW et al. *Endocr Pract.* 2009;15:542–559.

What about using insulin with other hypoglycemic therapies?

According to the 2009 AACE/ACE algorithm, metformin is the most commonly used and safest medication to combine with insulin. Pramlintide, an analog of pancreatic amylin, can be helpful for controlling PPG when administered immediately before meals.

GLP-1 agonists and DPP-4 inhibitors have not been approved for use with insulin.

Sulfonylureas and glinides should be discontinued when prandial insulin is introduced, because postprandial excursions can usually be managed better with a rapid-acting insulin analog or premixed insulin preparation.

Use of TZDs in combination with insulin is associated with a high probability of weight gain, fluid retention, increased risk of congestive heart failure, and a significantly increased risk of fractures in both men and women.

Both the α -glucosidase inhibitors and colesevelam are unlikely to contribute materially to the effectiveness of insulin.

SMBG: ADA and AACE/ACE Recommendations

- SMBG frequency should be increased when a patient begins insulin therapy
- Patients receiving basal insulin therapy at bedtime or premixed insulin therapy before dinner should determine their FBG level each morning
- Patients using MDIs of insulin should perform SMBG ≥ 3 times daily
- To achieve PPG targets, postprandial SMBG may be appropriate

MDI = multiple daily injections;
SMBG = self-monitoring of blood glucose.

ADA. *Diabetes Care*. 2010;33(Suppl 1):S11–S61.
Rodbard HW et al. *Endocr Pract*. 2009;15:542–559.

This slide lists ADA and AACE/ACE recommendations for self-monitoring of blood glucose (SMBG) in persons with type 2 diabetes. SMBG frequency should be increased when a patient begins insulin therapy. Patients receiving basal insulin at bedtime or premixed insulin before dinner should determine their FBG level each morning. Patients using MDIs of insulin should perform SMBG 3 or more times daily, usually prior to injection to determine if changes to the dose need to be made to assure safety. To achieve PPG targets, postprandial SMBG may also be appropriate.

Because the accuracy of SMBG is both user and instrument dependent, it is important to evaluate each patient's monitoring technique, both initially and at regular intervals thereafter. Optimal use of SMBG requires proper interpretation of the data. Therefore, patients should be taught how to use SMBG data to adjust food intake, exercise, and pharmacological therapy to achieve their glycemic goals. Health care providers should reevaluate these skills periodically.

Which Patients Should Receive Insulin as First-Line Therapy?

- Clinical situations
 - Severely uncontrolled diabetes with catabolism (FPG >250 mg/dL)
 - Random glucose levels consistently >300 mg/dL
 - A1C >10%
 - Ketonuria
 - Symptomatic diabetes with polyuria, polydipsia, and weight loss
- After symptoms are relieved and glucose levels decreased, oral agents can often be added and it may be possible to withdraw insulin, if preferred

Nathan DM et al. *Diabetes Care*. 2009;32:193–203.

In certain clinical situations, patients should receive insulin as first-line therapy. These include severely uncontrolled diabetes with catabolism (defined as FPG levels >250 mg/dL), random glucose levels consistently above 300 mg/dL, A1C >10%, the presence of ketonuria, or symptomatic diabetes with polyuria, polydipsia, and weight loss.

Insulin is the treatment of choice in these settings because it can be titrated rapidly and is associated with the greatest likelihood of rapidly returning glucose levels to target levels.

Once symptoms have been relieved and glucose levels decreased, oral agents can often be added and it may be possible to withdraw insulin, if preferred.

Considerations in Choosing an Insulin Regimen

- **Flexibility, lifestyle needs**
 - Meal/snack schedules
 - Activity patterns
- **Capability and willingness of patient**
 - Manual dexterity and visual acuity
 - Ability to follow basic meal plan
 - Problem-solving and basic math skills
- **Degree of hyperglycemia**
- **Glycemic pattern: need to improve FPG or PPG**
- **Cost issues**

Hirsch IB et al. *Clin Diabetes*. 2005;23:78–86.
Gavin JR III. *Diabetes Educ*. 2007;33:66S–73S.

In selecting an insulin regimen, it is essential to consider the patient's needs, concerns, capabilities, and resources. Patients have varying needs for flexibility. While some have relatively consistent mealtimes and activity patterns, others may vary the number and timing of meals and engage in sporadic exercise. The insulin regimen must be tailored to the individual's lifestyle and may need to be changed frequently for some patients.

Many patients are reluctant to accept MDIs of insulin when they start insulin therapy, so beginning with a basal/bolus regimen may not be feasible. Patients may also have concerns about insulin storage or handling. A discussion of insulin pens might alleviate some of their concerns.

The patient's degree of hyperglycemia will also impact regimen selection. Extreme hyperglycemia (FPG >250 mg/dL) will require basal/bolus therapy that may be continued or modified once glucose levels return to near-normal levels.

The closer A1C levels are to the normal range, the greater is the contribution of PPG to the patient's overall glycemic status. Thus, basal insulins targeting FPG may be used in patients with higher A1C, while rapid-acting insulins that target PPG may be more appropriate for patients whose A1C is closer to the normal range.

A regimen's safety and efficacy should be higher priorities than the cost of glucose-lowering therapy, since the cost of medications is only a small part of the cost of diabetes care. Nevertheless, patients with limited means and without prescription drug insurance coverage often consider the lower priced NPH insulin or premixed regular and NPH insulin to be their best treatment choices.

Insulin Regimen Options

Regimen	Advantages	Disadvantages
Once-daily basal	Single daily injection; covers FBG	Other therapy needed to control PPG excursions
Once-daily premixed	Single daily injection, covers FBG and 1 PPG excursion	Requires consistent daily routine; all PPG excursions not covered
Twice-daily premixed	Covers FBG and 2 PPG excursions	Requires consistent daily routine
Prandial	Covers PPG excursions	Does not cover FBG; usually requires 3 daily insulin injections and insulin-sensitizer therapy
Basal/bolus	Approximates physiologic insulin secretion; allows for maximum lifestyle flexibility	Requires MDIs and frequent SMBG

Hirsch IB et al. *Clin Diabetes*. 2005;23:78–86. Gavin JR III. *Diabetes Educ*. 2007;33:66S–73S. Robertson C. *Diabetes Educ*. 2006;32:423–432. Rodbard HW et al. *Endocr Pract*. 2009;15:542–559.

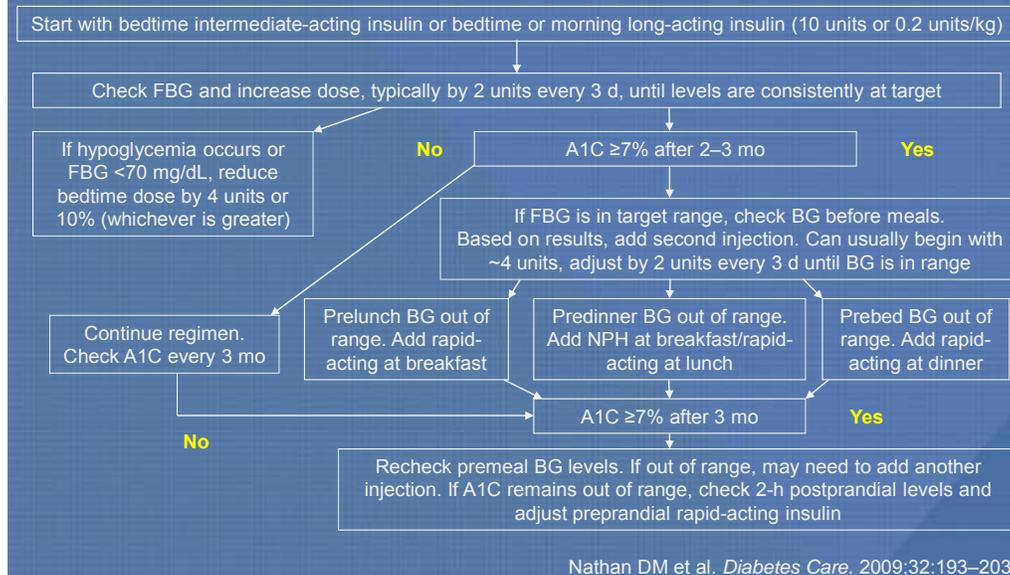
This slide summarizes the most frequently used treatment options for patients with type 2 diabetes. Once-daily basal insulin minimizes injections and covers FBG levels, but requires oral therapy (or the patient’s endogenous insulin) to cover PPG excursions.

A regimen of once-daily premixed insulin covers FBG and 1 PPG excursion. Although it entails only 1 insulin injection, it requires a consistent daily mealtime and exercise routine and does not allow for correction of out-of-range glucose levels. Use of twice-daily premixed insulin covers FBG and overnight as well as 2 PPG excursions, but also necessitates a consistent daily mealtime routine.

Prandial regimens cover PPG excursions. However, this approach necessitates treatment with an insulin sensitizer (usually metformin) to cover FBG and generally requires 3 daily insulin injections.

Basal/bolus regimens allow for dose modifications in response to the patient’s glucose levels. This is the most flexible regimen, it allows changes in meal amount and meal timing and it most closely approximates physiologic insulin secretion. However, it requires MDIs of insulin and frequent SMBG.

2009 ADA/EASD Algorithm for Initiating and Titrating Insulin



The 2009 ADA/EASD algorithm for the management of hyperglycemia in type 2 diabetes includes a separate algorithm for the initiation and adjustment of insulin regimens. This is based on an algorithm published by Hirsch and associates in 2005.

According to the ADA/EASD algorithm, insulin therapy can begin either with intermediate-acting insulin at bedtime or with a long-acting insulin analog at bedtime or in the morning. The suggested starting dose is either 10 units or 0.2 unit/kg. Based on SMBG results, the dosage can be increased every 3 days.

Patients whose A1C is $\geq 7\%$ after 2 to 3 months can add a second injection, based on which of their values is out of range. Patients whose prelunch BG is out of range can add a rapid-acting insulin analog at breakfast. Those whose predinner BG is out of range can add NPH insulin at breakfast or a rapid-acting insulin analog at lunch. Those whose bedtime BG is out of range can add a rapid-acting insulin analog at dinner.

For patients whose A1C remains $\geq 7\%$ after 3 months and whose premeal BG levels are out of range, it may be necessary to add a third injection in the evening. If the A1C is still out of range, the health care provider should check 2-hour PPG levels and adjust the dose of the patient's preprandial rapid-acting insulin analog.

Important messages of the ADA/EASD algorithm are that there are multiple ways to initiate insulin therapy and that meeting the patient's glycemic targets is likely to require multiple adjustments of the doses and types of insulin administered.

2009 ADA/EASD Insulin Algorithm: Example

Ian weighs 91 kg and has an A1C of 10.3%

Initial dosing	0.2 unit × 91 kg = 18.2, rounded to 18 units of long-acting insulin analog at bedtime
Dose adjustment based on FBG	Long-acting insulin analog dose increased by 2 units every 3 days to 26 units
Dose adjustment based on A1C of 8.6% after 3 months	FBG at target, but bedtime BG out of range. Rapid-acting insulin analog added at dinner. Starting dose of 4 units, adjusted by 2 units every 3 days to 10 units
Dose adjustment based on A1C of 7.4% after 3 more months	Predinner BG out of range. Rapid-acting insulin analog added at lunch, titrated to 6 units
A1C 6.8% after 3 more months	Continue regimen and check A1C every 3 months

Nathan DM et al. *Diabetes Care*. 2009;32:193–203.

This slide gives an example of the use of the 2009 ADA/EASD algorithm for initiating and titrating insulin. Ian weighs 91 kg and has an A1C of 10.3%. He begins insulin therapy with a bedtime dose of a long-acting insulin analog. His initial dose is calculated by multiplying 0.2 unit × 91 kg. The result, 18.2 units, is rounded to 18 units.

Ian checks his FBG daily and increases his dose of long-acting insulin analog by 2 units every 3 days until his FBG level is consistently at target. His dose is titrated to 26 units. After 3 months, Ian's A1C is now lowered to 8.6%. Review of his BG logs shows that his FBG remains at target, but his bedtime BG is out of range. Therefore, he adds a rapid-acting insulin analog at dinner. From a starting dose of 4 units, he increases his dose by 2 units every 3 days until his bedtime BG is consistently at target. His titrated dinnertime dose is 10 units.

After 3 more months, Ian's A1C has improved but is still above goal at 7.4%. Review of his BG logs shows that his predinner BG is out of range. He adds a rapid-acting insulin analog at lunch. From a starting dose of 4 units, he increases his dose to a total of 6 units. After 3 additional months, Ian's A1C is 6.8% and is thus at goal. He will continue his current regimen and his A1C will be checked every 3 months to determine whether further regimen adjustments are needed.

Staged Diabetes Management: Basal Insulin

Initial dosing	A1C <9%: 0.1 unit/kg A1C ≥9%: 0.2 unit/kg
Timing	Morning or evening, to fit patient's schedule
Adjustment frequency	Weekly, based on FBG
Adjustment criteria	FBG <70 mg/dL: decrease by 1–2 units FBG 140–250 mg/dL: increase by 2–4 units FBG >250 mg/dL: increase by 4–8 units
Other agents	Continue

Example: John weighs 88 kg, has an A1C of 9.5%, and is taking metformin and glipizide. His initial basal insulin dose is 18 units ($88 \times 0.2 = 17.6$ units, rounded up to 18 units). One week later, his FBG level is 146 mg/dL, and he increases his insulin dose to 20 units. He continues his oral glucose-lowering medications.

Pearson J, Powers MA. *Diabetes Educ.* 2006;32:19S–28S.

Staged diabetes management is yet another approach to the treatment of diabetes. It was developed by the International Diabetes Center. A major advantage of this approach is that both the patient's weight and A1C are used in calculating the initial dose and in making subsequent dose adjustments.

As shown in this table, the recommended initial dose of basal insulin is 0.1 unit/kg if the patient has an A1C <9% and 0.2 unit/kg if the patient has an A1C ≥9%. After the patient begins therapy, the basal insulin dose should be adjusted weekly, based on the FBG level. If the FBG level is <70 mg/dL, the insulin dose should be decreased by 1 to 2 units. If the FBG level is 140 to 250 mg/dL, the insulin dose should be increased by 2 to 4 units. If the FBG level is >250 mg/dL, the insulin dose should be increased by 4 to 8 units. Patients should continue their current oral therapy when they begin insulin therapy.

As an example, John weighs 88 kg, has an A1C of 9.5%, and is taking metformin and glipizide when he begins insulin therapy. His initial basal insulin dose is 18 units ($88 \times 0.2 = 17.6$ units, rounded up to 18 units). One week later, his FBG level is 146 mg/dL, and he increases his insulin dose to 20 units. He continues to take his oral glucose-lowering medications.

Staged Diabetes Management: Premixed Insulin Analogs

Initial dosing	A1C <9%: 0.1 unit/kg in morning and evening A1C ≥9%: 0.2 unit/kg in morning and evening
Total daily units	0.2–0.4 unit/kg
Adjustment frequency	Weekly, based on AM or PM blood glucose
Adjustment criteria	Prebreakfast FBG <70 mg/dL: decrease PM by 1–2 units FBG 140–250 mg/dL: increase PM by 1–2 units FBG >250 mg/dL: increase PM by 2–4 units Presupper BG <70 mg/dL: decrease AM by 1–2 units BG 140–250 mg/dL: increase AM by 1–2 units BG >250 mg/dL: increase PM by 2–4 units
Other agents	Discontinue secretagogue, consider continuing insulin sensitizer(s)

Pearson J, Powers MA. *Diabetes Educ.* 2006;32:19S–28S.

This table summarizes the Staged Diabetes Management approach to treatment with a premixed insulin analog.

The recommended initial dose of premixed insulin analog is 0.1 unit/kg in the morning and evening if the patient has an A1C <9% and 0.2 unit/kg in the morning and evening if the patient has an A1C ≥9%. After the patient begins therapy, the insulin dose should be adjusted weekly, based on the morning or evening BG level. If the prebreakfast BG level is <70 mg/dL, the evening insulin dose should be decreased by 1 to 2 units. If the prebreakfast BG level is 140 to 250 mg/dL, the evening insulin dose should be increased by 1 to 2 units. If the prebreakfast level is >250 mg/dL, the evening insulin dose should be increased by 2 to 4 units. Similarly, if the predinner BG level is <70 mg/dL, the morning insulin dose should be decreased by 1 to 2 units. If the predinner BG level is 140 to 250 mg/dL, the morning insulin dose should be increased by 1 to 2 units. If the predinner level is >250 mg/dL, the morning insulin dose should be increased by 2 to 4 units. Patients should discontinue secretagogue therapy but consider continuing 1 or more insulin sensitizers.

Staged Diabetes Management: Premixed Insulin Analogs—Example

Marie weighs 70 kg and has an A1C of 8.5%.
Her current glucose-lowering medications are
metformin, glyburide, and pioglitazone.

Initial dosing	0.1 unit 70 kg = 7 units in morning and evening
Adjustment after 1 week based on prebreakfast FBG of 220 mg/dL	7 units + 2 additional units = 9 units in evening
Adjustment after 1 week based on presupper FBG of 160 mg/dL	7 units + 1 additional unit = 8 units in morning
Concomitant glucose-lowering drugs	Discontinue glyburide, continue metformin and pioglitazone

Pearson J, Powers MA. *Diabetes Educ.* 2006;32:19S–28S.

This slide gives an example of the use of the Staged Diabetes Management approach for a patient who is initiating insulin therapy with a premixed insulin analog regimen.

Marie has an A1C of 8.5% and weighs 70 kg. She is taking metformin, glyburide, and pioglitazone.

On the basis of Marie's A1C level and weight, her initial dose of premixed insulin analog is $70 \text{ kg} \times 0.1 \text{ unit}$, or 7 units in the morning and evening. She discontinues glyburide and continues to take metformin and pioglitazone.

One week after beginning this regimen, Marie's prebreakfast FBG level is 220 mg/dL. Therefore, she increases her evening dose of premixed insulin analog by 2 units, to a total of 9 units. Marie's presupper BG level is 160 mg/dL. Therefore, she increases her morning dose of premixed insulin analog by 1 unit, to a total of 8 units.

Staged Diabetes Management: Basal/Bolus Regimen

Initial dosing	A1C <9%: 0.1 unit/kg long-acting insulin analog AND 0.1 unit/kg rapid-acting insulin analog divided between meals A1C ≥9%: 0.2 unit/kg long-acting insulin analog AND 0.2 unit/kg rapid-acting insulin analog divided between meals
Total daily units	0.2–0.4 unit/kg
Adjustment frequency	Weekly (at a minimum)
Adjustment criteria	Once most daily BG levels are <200 mg/dL, check BG levels 2 h after the start of the meal to ensure that postmeal BG goal of <160 mg/dL is met. If 2-h postmeal BG is ≥160 mg/dL, increase mealtime insulin by 1–2 units if BG is 160–240 mg/dL, and 2–4 units if BG is >250 mg/dL
Other agents	Discontinue secretagogue, consider continuing insulin sensitizer(s)

Pearson J, Powers MA. *Diabetes Educ.* 2006;32:19S–28S.

This table summarizes the Staged Diabetes Management approach to basal/bolus insulin therapy. For patients with an A1C <9%, recommended initial doses are 0.1 unit/kg of long-acting insulin and 0.1 unit/kg of rapid-acting insulin divided between meals. For patients with an A1C ≥9%, recommended initial doses are 0.2 unit/kg of long-acting insulin and 0.2 unit/kg of rapid-acting insulin divided between meals.

Once most daily BG levels are <200 mg/dL, patients should check their BG levels 2 hours after the start of the meal to ensure that the PPG goal of <160 mg/dL is met. If the 2-hour PPG level exceeds this target, the amount of mealtime insulin should be increased by 1 to 2 units if the BG level is 160 to 240 mg/dL or by 2 to 4 units if the BG level is >250 mg/dL. The aim for patients who take a mealtime insulin is to see no more than a 40 mg/dL difference between the premeal and postmeal BG values. For example, if the premeal BG level is 100 mg/dL, the 2-hour postmeal goal should be <140 mg/dL. The goal of diabetes therapy is to achieve near-normal glycemia without wide fluctuations in BG values. At the same time that they are adjusting their insulin doses, patients should review their insulin-to-carbohydrate ratios (ICRs) and patterns of physical activity.

Patients taking a secretagogue should discontinue it, but they should consider continuing therapy with 1 or more insulin sensitizers.

Staged Diabetes Management: Basal/Bolus Regimen: Example

Roberto weighs 91 kg and has an A1C of 10.1%.
Current glucose-lowering drugs are metformin,
glipizide, and exenatide.

Initial dosing	Long-acting insulin analog: 0.2 unit \times 91 kg = 18.2, or 18 units Rapid-acting insulin analog: 0.2 unit \times 91 kg = 18.2, or 18 units; divided as 5 units at breakfast, 6 units at lunch, and 7 units at dinner
Adjustment (after 4 days [Friday])	Most BG values are <200 mg/dL. Two hours after starting breakfast, BG level is 255 mg/dL. Saturday prebreakfast dose of rapid-acting insulin analog will be increased by 2 units, to 7 units. Other premeal doses will also be increased, based on 2-hour PPG levels.
Concomitant glucose-lowering drugs	Discontinue glipizide and exenatide, continue metformin

Pearson J, Powers MA. *Diabetes Educ.* 2006;32:19S–28S.

This slide gives an example of the use of the Staged Diabetes Management approach for a patient who is initiating insulin therapy with a basal/bolus insulin analog regimen.

Roberto weighs 91 kg and has an A1C of 10.1%. His current glucose-lowering drugs are metformin, glipizide, and exenatide.

Because Roberto's A1C is greater than 9%, his initial dose of long-acting insulin analog is calculated by multiplying his body weight, 91 kg, by 0.2 unit. The result, 18.2, is rounded to 18 units of long-acting insulin analog.

Roberto's initial total dose of rapid-acting insulin analog is also calculated by multiplying 91 kg by 0.2 unit. The result, 18.2, is rounded down to 18 units. Based on his anticipated carbohydrate intake and activity levels, Roberto's total dose of rapid-acting insulin analog is divided among his meals. The initial allocation is 5 units at breakfast, 6 units at lunch, and 7 units at dinner. Roberto discontinues glipizide and exenatide and continues taking metformin.

On Friday, after 4 days of insulin therapy, most of Roberto's BG levels are less than 200 mg/dL. Two hours after starting breakfast, his PPG level is 255 mg/dL. Based on this reading, Roberto will increase his prebreakfast insulin dose by 2 units, to 7 units, on Saturday. If warranted by his BG levels 2 hours after beginning lunch and dinner, Roberto will also increase the amount of rapid-acting insulin analog taken before those meals.

Carbohydrate Counting

- Carbohydrate counting is a meal-planning approach for patients using basal/bolus insulin regimens
- Patients perform premeal SMBG and adjust mealtime insulin dose based on anticipated carbohydrate content of meal
- Calculation of the patient's insulin-to-carbohydrate ratio (ICR) is a prerequisite
 - ICR is based on individual's sensitivity to insulin
 - For an individual with an ICR of 1:12, 1 unit of insulin is needed to match 12 g of carbohydrate
 - Typical ICRs are 1:10 to 1:15 for nonobese adults and 1:5 for obese adults
 - ICRs may vary during the day

Tomky DM, Kulkarni K. *The Art and Science of Diabetes Self-Management Education*. 2006:371–398.

Carbohydrate counting is a valuable meal-planning approach for patients using basal/bolus insulin regimens. It permits a more flexible eating schedule and more dietary freedom while maintaining glycemic control. With carbohydrate counting, patients perform SMBG before meals and adjust their mealtime insulin dose on the basis of the carbohydrate content of the anticipated meal.

A prerequisite to carbohydrate counting is the calculation of the patient's insulin to carbohydrate ratio (ICR). The ICR is based on the principle that 1 unit of rapid-acting insulin is needed to match a specified amount of carbohydrate, and the ratio is determined by the individual's sensitivity to insulin. For example, in a patient with an ICR of 1:12, 1 unit of insulin is needed to match 12 grams of carbohydrate. An adult who is not obese might have an ICR ranging from 1:10 to 1:15. In contrast, an adult who is obese might have an ICR of 1:5. Initially, an individual's ICR is usually calculated by a diabetes educator or dietitian, but it can subsequently be recalculated by the patient to reflect changes in insulin sensitivity.

ICRs can vary throughout the day. For example, a patient's ICR may be 1:10 at breakfast, 1:12 at lunch, and 1:8 at dinner.

Carbohydrate Counting: Example

Marlene works in an office and has an ICR of 1:8. She anticipates that her lunch will have a higher carbohydrate content on Tuesday, when she goes out for pizza with friends, than on Monday, when she brings her lunch from home.

Day	Anticipated Carbohydrate Content of Meal	Calculation of Rapid-Acting Insulin Analog Dose
Monday	65 g	$65 \div 8 = 8.1$, or 8 units
Tuesday	70+ g	$70 \div 8 = 8.75$, or 9 units

Tomky DM, Kulkarni K. *The Art and Science of Diabetes Self-Management Education*. 2006:371–398.

This slide shows an example of the way in which carbohydrate counting is used to determine the mealtime dose of a rapid-acting insulin analog.

Marlene, who works in an office, uses a basal/bolus insulin regimen and has an ICR of 1:8. On Monday she brings her lunch from home. Anticipating that her lunch will contain about 65 grams of carbohydrate, she takes 8 units of her rapid-acting insulin analog.

On Tuesday, on the other hand, she is going out with her friends for pizza. She anticipates that her lunch will contain at least 70 grams of carbohydrate and therefore takes 9 units of rapid-acting insulin analog.

Using a Correction Bolus

- In addition to taking their regular premeal insulin dose, patients can administer a correction bolus dose when their premeal BG level is too high
- The size of the correction bolus is calculated using the patient's insulin sensitivity factor (ISF)
 - The ISF is the value in mg/dL by which 1 unit of insulin lowers BG
 - A patient using a rapid-acting insulin analog would calculate the ISF by dividing 1700 by the total daily insulin dose
 - A patient using regular human insulin would divide 1500 by the total daily insulin dose
- To determine the size of the correction bolus, the patient would calculate the difference between the actual premeal BG value and the target BG value
- This difference, divided by the ISF, is the correction bolus to be administered

Tomky DM, Kulkarni K. *The Art and Science of Diabetes Self-Management Education*. 2006:371–398.

In addition to taking their regular mealtime dose of insulin, patients receiving basal/bolus insulin therapy can administer a correction bolus dose when their premeal BG level is too high. The size of the correction bolus dose can be calculated once an individual's insulin sensitivity factor (ISF) has been determined.

The ISF is the value in mg/dL by which 1 unit of insulin lowers BG. A patient using a rapid-acting insulin analog would calculate the ISF by dividing 1700 by the total daily insulin dose. A patient using regular human insulin would calculate the ISF by dividing 1500 by the total daily insulin dose.

To determine the size of the correction bolus, the patient would calculate the difference between the actual premeal BG value and the target premeal BG value. This difference, divided by the ISF, is the correction bolus to be administered.

Patients using this approach to insulin management need to be evaluated for numeracy skills. The use of a calculator or written examples of the calculated dose for favorite meals may be helpful to prevent calculation errors.

Correction Bolus: Example

- Insulin sensitivity factor (ISF)
 - Brian has a total daily insulin dose of 80 units
 - He uses a rapid-acting insulin analog as his mealtime insulin
 - His ISF is $1700 \div 80 = 21.25$
- Correction bolus dose
 - Brian's preprandial BG target is ≤ 130 mg/dL
 - His prelunch BG level is 170 mg/dL
 - The difference between his target and actual BG value is $170 - 130 = 40$ mg/dL
 - His correction bolus dose is: $40 \div 21.25 = 1.9$, or 2 units of his rapid-acting insulin analog

Tomky DM, Kulkarni K. *The Art and Science of Diabetes Self-Management Education*. 2006:371–398.

Here is an example of how the ISF and the correction bolus dose are calculated.

Brian's total daily insulin dose is 80 units. He uses a rapid-acting insulin analog as his mealtime insulin. His ISF is $1700 \div 80$, or 21.25. (On the other hand, if he used regular human insulin at mealtimes, his ISF would be $1500 \div 80$, or 18.75.)

Now that Brian's ISF has been calculated, it is possible to determine his correction bolus dose. Brian's premeal BG target is ≤ 130 mg/dL, but his actual prelunch level is 170 mg/dL. Therefore, the difference between his target and actual BG values is $170 - 130$, or 40 mg/dL. Dividing 40 by Brian's ISF of 21.25 equals 1.9. Therefore, Brian's correction bolus dose is 2 units, and he would add these 2 units to his prelunch dose of rapid-acting insulin analog.

Psychological Resistance to Insulin

- Nearly one third of patients not taking insulin would be unwilling to begin insulin therapy even if it were prescribed
- Patients have many negative perceptions about insulin
 - Indication of personal failure
 - Sign that diabetes has become more serious
 - Anticipation that injections will be painful
 - Fear of developing hypoglycemia
 - Worry about weight gain

Polonsky WH et al. *Diabetes Care*. 2005;28:2543–2545. Peragallo-Dittko V. *Diabetes Educ*. 2007;33:60S–65S. Peyrot M et al. *Diabetes Care*. 2005;28:2673–2679. Peyrot M et al. *Diabetologia*. 2003;46(Suppl 2):A89.

Psychological resistance to insulin is reluctance on the part of patients to start insulin therapy when it would be beneficial. In a recent survey of patients with type 2 diabetes who were not receiving insulin, 28.2% said that they would be unwilling to take insulin even if it were prescribed for them. Another study showed that 57% of patients were worried about starting insulin therapy, and that 48% of those patients believed that starting insulin meant that they had not followed treatment recommendations correctly.

Patients resist starting insulin therapy for many reasons, including a sense of personal failure and concern that it means their diabetes has become more serious. Patients are often fearful about injection-related pain, developing hypoglycemia, or gaining weight.

Overcoming Psychological Resistance to Insulin

- Provide comprehensive patient education
 - Stress the progressive nature of beta-cell decline
 - Describe insulin as one step in the management process, not a last resort
 - Explain that the insulin regimen will be matched to the patient's needs and lifestyle
 - Teach management of hypoglycemia and weight gain
 - Introduce various insulin delivery options
 - Explain advantages of insulin analogs (eg, increased mealtime flexibility)
- Develop a diabetes care team that includes nurses, dietitians, and psychologists

Funnell MM et al. *Diabetes Educ.* 2004;30:274–280.
Peragallo-Dittko V. *Diabetes Educ.* 2007;33:60S–65S.
Korytkowski M. *Int J Obes Relat Metab Disord.* 2002;26(Suppl 3):S18–S24.
Ratner R. *Pract Diabetol.* 2004;23:14–24.

Patient education is essential for overcoming psychological resistance to insulin. Patients should understand the progressive beta-cell destruction that occurs in type 2 diabetes. Treatment should emphasize glycemic control rather than alternatives to insulin or insulin avoidance. Beginning a dialog about insulin at the time of diagnosis and emphasizing the ways in which insulin regimens can be individualized may encourage patient acceptance when insulin actually becomes necessary. To reduce fears about weight gain and hypoglycemia, patients should be taught strategies for preventing and treating these side effects.

Introducing a variety of insulin delivery devices may make the idea of insulin therapy more palatable. Health care providers should also emphasize that currently available needles are very small and thin, minimizing injection-related discomfort. Patients should understand the difference between insulin and insulin analogs, and the many benefits, such as increased mealtime flexibility, associated with insulin therapy.

Use of a diabetes care team—including physicians, nurses, dietitians, and psychologists—helps to ensure that patients receive comprehensive, up-to-date education about their disease and its management.

Clinical Inertia

- Over 50% of nurses and primary care physicians report delaying insulin therapy until it is absolutely necessary
- Delaying insulin therapy is more common
 - In US physicians vs physicians in most other countries
 - In primary care physicians vs specialists
 - In practitioners who underestimate the efficacy of insulin therapy
- Widespread perceptions
 - Managing treatment regimens will require extra time
 - More office resources will be needed
 - Patients will be at increased risk for weight gain and hypoglycemia
 - Patients will feel angry and alienated

Polonsky WH et al. *Clin Diabetes*. 2004;22:147–150.
Peragallo-Dittko V. *Diabetes Educ*. 2007;33:60S–65S.
Peyrot M et al. *Diabetes Care*. 2005;28:2673–2679.
Phillips P. *Rev Diabet Stud*. 2005;2:35–39.

In treating patients with type 2 diabetes, many health care providers demonstrate clinical inertia, delaying the transition to insulin therapy for as long as possible. In the Diabetes Attitudes, Wishes, and Needs (DAWN) study, more than 50% of the primary care physicians and nurses who were surveyed said that insulin should be delayed until absolutely necessary. Delaying insulin therapy was more common in US physicians than in physicians in most other countries and in primary care physicians compared with specialist physicians. Practitioners who underestimate the efficacy of insulin therapy are also likely to delay the transition to insulin. As shown on the slide, health care providers have various negative perceptions of insulin.

Because of their concerns, providers may amplify patients' own fears about starting insulin, leading to an unspoken collusion between providers and patients to defer insulin therapy for as long as possible. For example, a clinician may use insulin as a potential punishment, threatening to prescribe it if a patient fails to lose weight. Replacing clinicians' negative attitudes and perceptions with a more positive view of insulin is an essential step toward achieving more effective diabetes management.

Hypoglycemia Causes and Prevention

- Less common in type 2 than in type 1 diabetes
- Causes
 - Insulin dosing errors
 - Missed or delayed meals, inadequate carbohydrate intake
 - Unplanned physical activity
 - Illness
- Prevention
 - Adjusting insulin regimen based on past experience, mealtimes, expected physical activity
 - Using rapid-acting insulin analogs
 - Dose can be adjusted with each meal based on carbohydrate counting
 - Insulin level declines rapidly back to baseline levels

Steil CF. *The Art and Science of Diabetes Self-Management Education*. 2006:321–355.
Cryer PE et al. *Diabetes Care*. 2003;26:1902–1912.

Although hypoglycemia is a risk associated with insulin therapy, it occurs less frequently in patients with type 2 diabetes than in those with type 1 diabetes. Hypoglycemia is best defined based on its symptoms. Mild hypoglycemia is characterized by adrenergic symptoms, such as sweating, trembling, lightheadedness, and lack of coordination. Severe hypoglycemia is marked by the inability to self-treat due to mental confusion, lethargy, or unconsciousness. Glycemic thresholds for the onset of hypoglycemia symptoms differ among individuals, but a lower limit of 70 mg/dL has been suggested. Causes of hypoglycemia include errors in insulin dosing, missed or delayed meals, inadequate carbohydrate consumption, unplanned physical activity, or illness. Adrenergic symptoms of low blood sugar may be absent due to use of concomitant medications, such as beta blockers, or the condition of hypoglycemia unawareness.

To prevent hypoglycemia, insulin regimens should be adjusted based on past experience, expected timing and size of meals, and anticipated physical activity. Ideally, insulin regimens should be as flexible as possible, enabling patients to adjust doses to meal size and schedule changes. The use of rapid-acting insulin analogs encourages such flexibility. Their onset of action, ranging from 5 to 15 minutes, means that patients do not have to wait for 30 minutes postinjection to begin eating. Rapid decline of insulin levels back to the baseline value helps patients to avoid the postprandial hypoglycemia that can be associated with the use of regular insulin.

Hypoglycemia Treatment

- “Rule of 15”
 - 15 to 20 grams carbohydrate, then retest blood in 15 minutes
 - 1/2 cup juice or soda
 - 1 cup fat-free milk
 - 1 tbsp honey, jam, or sugar
 - 1 tube glucose gel or 3 glucose tablets
 - Follow with meal or snack
- If unable to swallow, give glucagon followed by carbohydrates as soon as possible
- If unconscious, give glucagon and summon emergency assistance
- Severe or prolonged hypoglycemia may require IV glucose and professional assistance

Glucagon Kits



Steil CF. *The Art and Science of Diabetes Self-Management Education*. 2006:321–355.
Cryer PE et al. *Diabetes Care*. 2003;26:1902–1912.

Asymptomatic hypoglycemia detected by SMBG and episodes of symptomatic hypoglycemia in which the patient can swallow should usually be treated by following the “rule of 15.” The patient should consume 15 to 20 grams of carbohydrate, wait 15 minutes and then recheck BG. Examples of substances containing 15 g of carbohydrate are 1/2 cup of juice or soda; 1 cup of fat-free milk; 1 tablespoon of honey, jam, or sugar; 1 tube of glucose gel; or 3 glucose tablets. If the BG remains below 70 mg/dL upon recheck, treatment should be repeated even if the symptoms have disappeared. To prevent the recurrence of hypoglycemia, patients should eat a meal or snack within the next hour. High-fat foods should not be used to treat hypoglycemia because they take longer to raise BG levels.

A patient experiencing a severe episode of hypoglycemia who is still able to swallow may be coaxed into drinking juice. If the patient is unable to swallow, a glucagon injection can be given to stimulate hepatic glucose production. A family member or friend of the patient should know how and when to inject glucagon. Liquid carbohydrates should follow as soon as the patient is able, since the effects of glucagon are short-lived. If the patient is unconscious, glucagon should be given and emergency assistance summoned, since glucagon may not be effective, especially in cases of frequent hypoglycemia or glycogen depletion. Intravenous glucose is the preferred treatment for severe hypoglycemia. Severe hypoglycemia caused by a sulfonylurea may be prolonged and require treatment with glucose infusions and hospitalization. Under these circumstances, the risk for recurrent hypoglycemia needs to be evaluated before the patient is discharged.

Insulin and Weight Gain

- Modest weight gain is a consequence of insulin therapy
 - Average weight gain is about 2 to 4 kg
 - Weight gain is mainly due to correction of glycemia and reduction in glycosuria
- Guidelines
 - Educators should be honest about the potential for weight gain
 - Establishing a meal and exercise plan can help minimize weight gain
 - Patients should be reminded that exercise also improves insulin sensitivity

Nathan DN et al. *Diabetes Care*. 2009;32:193–203. Kazlauskaitė R, Fogelfeld L. *Dis Mon*. 2003;49:377–420. Peragallo-Dittko V. *Diabetes Educ*. 2007;33:60S–65S.

Concern about weight gain is one reason why patients resist insulin therapy.

Modest weight gain is a consequence of treatment with insulin. Insulin is typically associated with weight gain of about 2 to 4 kg. The main reason for this increase is the improved glucose metabolism (anabolism) that results from insulin therapy. Insulin both corrects the patient's glycemia and reduces glycosuria.

Diabetes educators and other health care providers should address patients' concerns by being truthful about the potential for weight gain when starting insulin.

Establishing a meal and exercise plan may help to minimize weight gain. It is also helpful to remind patients that exercise not only promotes weight loss, but also improves insulin sensitivity (ie, reduces insulin resistance) by promoting glucose uptake into muscle.

Initiating Insulin Therapy: Case 1 – Barbara

Description	46-year-old African American woman Weight: 73 kg (162 lb); height: 165 cm (65 in); BMI: 27 kg/m ²
Lab values	Current A1C: 9.0% (eAG, 212 mg/dL) Previous A1C (6 months ago): 8.8% (eAG, 206 mg/dL) Last FBG (3 days ago): 170 mg/dL
Lifestyle	Married, 2 children in college Works full-time as accountant 60-minute commute each way Erratic SMBG and mealtimes; dinner always largest meal
Diabetes history, symptoms	Diagnosed with type 2 diabetes 6 years ago Reports increasing fatigue over last month No polydipsia, polyuria, or weight changes No vision changes or numbness/burning in extremities
Medications	Metformin, 1000 mg BID; glyburide, 10 mg BID Reluctant to start insulin therapy due to fear of injections

BMI = body mass index.

Barbara is a 46-year-old African American woman who has a body mass index (BMI) of 27 kg/m². Her current A1C is 9.0% and her previous A1C, 6 months earlier, was 8.8%. Her most recent FBG value, obtained 3 days earlier, is 170 mg/dL.

Barbara is married and has 2 children, who are college students. She works full-time as an accountant and has a 60-minute commute to and from work. Both her BG monitoring schedule and her mealtimes are erratic. Dinner is consistently her largest meal.

Barbara was diagnosed with type 2 diabetes 6 years ago. She reports steadily increasing fatigue over the past month. She has not experienced polydipsia, polyuria, or weight changes. She does not have a history of vision changes or of numbness or burning in the extremities.

Currently, Barbara takes metformin 1000 mg twice daily and glyburide 10 mg twice daily. She says that she is reluctant to start insulin therapy due to fear of injections.

Initiating Insulin Therapy: Case 1 – Barbara

- What are Barbara's BG goals?
 - FBG: 70–130 mg/dL
 - PPG: <180 mg/dL
- What management options might help Barbara achieve her glycemic targets?
 - Adding a third oral agent
 - Adding a GLP-1 receptor agonist
 - Adding a long-acting insulin analog once daily and continuing oral agents
 - Starting a premixed insulin analog given once daily at dinner and discontinuing oral agents
 - Starting a premixed insulin analog given twice daily and discontinuing oral agents
 - Starting a basal-bolus insulin analog regimen and discontinuing oral agents

Barbara's BG goals are consistent with ADA guidelines for FBG and PPG.

Management options that might help Barbara reach her targets include:

- Adding a third oral agent, such as a TZD or a DPP-4 inhibitor
- Adding a GLP-1 receptor agonist
- Adding a long-acting insulin analog once daily and continuing oral agents
- Starting a premixed insulin analog once daily at dinner and discontinuing oral agents
- Starting a premixed insulin analog twice daily and discontinuing oral agents
- Starting a basal/bolus insulin analog regimen and discontinuing oral agents

Initiating Insulin Therapy: Case 1 – Barbara

- Barbara agrees to initiate once-daily insulin therapy while continuing to take metformin and glyburide
 - She begins by taking 10 units of long-acting insulin analog at bedtime
 - After 1 week, her FBG averages 165 mg/dL
 - Her insulin analog dose is eventually titrated to 22 units once daily, until her FBG is at goal
- After 3 months, her FBG averages 110 mg/dL, her A1C is 6.9% (eAG, 151 mg/dL), and she reports having more energy
- A1C will be monitored every 2 to 3 months
- Prandial insulin may need to be added at a later time

Barbara and her physician agree to initiate once-daily basal insulin while she remains on her oral agents. Adding a third oral agent or a GLP-1 agonist was not selected because of the worsening glucose control. They decided to select a therapy that would give the greatest potential for A1C lowering.

She starts with 10 units of a long-acting insulin analog at bedtime. The dose is titrated up to 22 units after 2 weeks, based on FBG readings every 3 to 4 days.

After 3 months of this regimen, Barbara's FBG is within the target range and her A1C has declined by 2.1%. She feels more energetic and says that she is motivated to continue with her diabetes self-management program.

Barbara's A1C will be monitored every 2 to 3 months. Her diabetes educator discusses the progressive nature of type 2 diabetes with her. Both her physician and her diabetes educator inform Barbara that she may need to add mealtime doses of a rapid-acting insulin analog at a later date.

Initiating Insulin Therapy: Case 2 – George

Description	64-year-old white man Weight: 84 kg (184 lb); height: 173 cm (68 in); BMI: 28 kg/m ²
Current A1C	11.0% (eAG, 269 mg/dL)
Lifestyle	Married, 1 adult child and 2 grandchildren Retired high school teacher Usually eats at home with wife Reports having 3 meals of uniform size and carbohydrate content; also has midnight snack
Diabetes history, symptoms	Diagnosed with type 2 diabetes 12 years ago Symptomatic hyperglycemia and fatigue over 2-week period History of retinopathy and peripheral neuropathy Diabetic ulcers debrided on both feet 1 year earlier
Medications	Metformin, 1000 mg BID; glyburide, 5 mg BID; pioglitazone, 45 mg/d Willing to start on insulin due to severity of symptoms

George is a 64-year-old white man who has a BMI of 28 kg/m². His current A1C is 11.0%.

George is married and has 1 adult child and 2 grandchildren. He retired from high school teaching 6 months ago. He usually eats at home with his wife. He reports that his 3 daily meals are of uniform size and carbohydrate content. He also eats a small bedtime snack.

George was diagnosed with type 2 diabetes 12 years ago. He has a history of retinopathy and peripheral neuropathy and had diabetic ulcers debrided on both feet 1 year earlier. He reports that he has experienced symptomatic hyperglycemia and fatigue for the last 2 weeks.

Currently, George takes metformin 1000 mg twice daily, glyburide 5 mg twice daily, and pioglitazone 45 mg once daily. Although he dislikes injections, he is now willing to start insulin therapy because of the severity of his symptoms.

Initiating Insulin Therapy

Case 2 – George

BG Log From Previous Week

Day	BG Levels (mg/dL)		
	FBG	2 Hours Postbreakfast	2 Hours Postdinner
Monday	192	353	*
Tuesday	210	*	301
Wednesday	212	*	*
Thursday	195	344	*
Friday	*	*	330
Saturday	201	*	*
Sunday	220	260	366

*BG not checked. ADA goals: preprandial, 70–130 mg/dL; postprandial, <180 mg/dL.

This slide shows George's BG log from the previous week. FBG levels average 200 mg/dL and PPG levels average 350 mg/dL. Clearly, George's BG values are well out of the ADA target range.

Initiating Insulin Therapy: Case 2 – George

- George has uncontrolled and symptomatic hyperglycemia on 3 oral agents, suggesting that he is experiencing beta-cell failure
- Insulin therapy is clearly indicated, since he has already experienced microvascular complications
- Potential insulin regimens
 - Once-daily long-acting insulin analog
 - Once-daily premixed insulin analog
 - Twice-daily premixed insulin analog
 - Basal/bolus insulin analog therapy

George has uncontrolled and symptomatic hyperglycemia while taking 3 oral agents, suggesting that he is experiencing beta-cell failure.

Insulin therapy is clearly indicated, since he has already experienced microvascular complications.

Potential insulin regimens for George are:

- Once-daily long-acting insulin analog
- Once-daily premixed insulin analog
- Twice-daily premixed insulin analog
- Basal/bolus insulin analog therapy.

Initiating Insulin Therapy

Case 2 – George

- Twice-daily premixed insulin analog selected
 - Initial dose: 10 units prebreakfast, 10 units predinner
 - Titrated up to 30 units prebreakfast, 20 units predinner

BG Results After 3 Weeks

Day	BG Levels (mg/dL)				
	Before Breakfast	2 H Post-breakfast	Before Dinner	2 H Post-dinner	Bedtime
Friday	141	*	140	*	151
Saturday	127	*	*	196	*
Sunday	132	190	142	210	*
Monday	130	211	120	*	145

*BG not checked. ADA goals: preprandial, 70–130 mg/dL; postprandial, <180 mg/dL.

George and his physician discuss the advantages and disadvantages of the various approaches to initiating insulin therapy. He eventually chooses a twice-daily premixed regimen because it will provide both meal and basal insulin coverage. A basal/bolus regime was also a good option, but George wanted to limit the number of injections to 2 per day. Since George reports that his meals are of uniform size and carbohydrate content and he eats a bedtime snack, this regimen is compatible with his meal plan. George makes his decision with the knowledge that he might eventually need to transition to a basal/bolus regimen.

The diabetes educator discusses the various insulin delivery options with George, and he decides to use a disposable pen. He is pleased by how easy it is to dial a dose and appreciates the discreet appearance of the pen.

George begins his twice-daily premixed regimen by taking 10 units before breakfast and 10 units before dinner. These doses are gradually titrated up to 30 units prebreakfast and 20 units predinner, based on FBG and PPG readings phoned in to his diabetes team.

The table on this slide shows George's fasting, postprandial, and bedtime BG readings after 3 weeks of insulin therapy. At that point his average FBG level is 130 mg/dL and his average PPG level is 200 mg/dL.

Changing the Insulin Regimen

Case 2 – George

Status After 3 Months of Insulin Therapy

- Weight gain of 10 pounds; current BMI, 29.5 kg/m²
- Signs of suboptimal glycemic control
 - A1C has improved from 11.0% to 9.0% (eAG, 212 mg/dL), but is still above goal
 - Awakening with symptoms of hypoglycemia twice in the previous week

Three months after beginning insulin therapy, George has gained 10 pounds, and his BMI has risen to 29.5 kg/m². His physician observes that a weight gain of this magnitude is not unusual after transitioning to insulin. However, he refers George to a diabetes educator so that he and his wife can fine-tune their meal and exercise plan.

At this point there are several signs that George's glycemic control is still less than optimal. Although his A1C has improved from 11% to 9%, it is still above goal. His glucose log confirms that the elevations are occurring postprandially. Additionally, George reports having awakened with symptoms of hypoglycemia twice in the previous week. Review of George's BG log also reveals some issues.

Changing the Insulin Regimen Case 2 – George

BG Log, 3 Months After Beginning Insulin Therapy

Day	BG Levels (mg/dL)				Comment
	Before Breakfast	Before Dinner	2 H Post-dinner	3 AM	
Friday	190	155	*	*	—
Saturday	175	110	239	*	—
Sunday	200	139	210	57	Woke up, ate snack
Monday	195	172	*	*	—
Tuesday	177	140	220	55	Woke up, ate snack
Wednesday	180	60	320	*	Small lunch; skipped 2nd injection
Thursday	200	153	215	*	—

*BG not checked. ADA goals: preprandial, 70–130 mg/dL; postprandial, <180 mg/dL.

The log shows that, after 3 months of insulin therapy, the average FBG level is 180 mg/dL and the average PPG level is 220 mg/dL.

After going over the log, George's physician first points out the high 2-hour postdinner BG values on Saturday, Sunday, and Tuesday. When questioned about whether his eating patterns have changed, George remarks that he has recently begun eating dinners that are larger, with a higher carbohydrate content, than his other meals.

As requested by his physician, George made a note in his log if he experienced hypoglycemic symptoms, skipped a meal or an insulin dose, or engaged in more than usual physical activity. This type of information is extremely valuable for interpreting BG readings that are markedly out of range, and helps the patient to see the connection between his or her BG level and everyday events.

Review of George's BG log reveals 3 notable BG excursions, which are highlighted in orange and discussed on the next slide.

Changing the Insulin Regimen: Case 2 – George

Three-Month Follow-up Visit With Physician

- Discussion of glycemic excursions based on BG log
 - On Sunday night (BG, 55 mg/dL) and Tuesday night (BG, 57 mg/dL), George awoke with symptoms of hypoglycemia, which he treated with a snack
 - On Wednesday (2 H postdinner BG, 320 mg/dL), George ate a smaller lunch than usual, played outdoors for several hours with his grandchildren, and skipped his dinnertime insulin dose because his predinner BG was low (60 mg/dL)
- George agreed to transition to a basal/bolus insulin regimen to achieve tighter glycemic control and allow for more flexibility in his meal and activity patterns

George and his physician use his BG log to discuss the reasons for George's glycemic excursions during the previous week.

On Sunday night and Tuesday night, George had episodes of symptomatic hypoglycemia, with 3 AM BG levels of 55 mg/dL and 57 mg/dL, respectively. He treated these episodes by eating a 15 gram snack.

On Wednesday, George's 2-hour postdinner BG level was 320 mg/dL. He explains that he had eaten a smaller lunch than usual on that day and then played outdoors for several hours with his grandchildren. He skipped his dinnertime dose of premixed insulin analog because his predinner BG level was only 60 mg/dL.

The physician observes that it is time for George to transition to a basal/bolus insulin regimen for several reasons. His meals are no longer uniform in their size and content, his A1C is 9%, and he has experienced several notable glycemic excursions during the previous week. The physician reassures George that making this change is likely to provide better glycemic control and allow for more flexible meal and activity patterns.

George agrees to begin basal/bolus insulin therapy and is relieved to learn that both his long-acting and his rapid-acting insulin analog can be delivered by insulin pen.

Changing the Insulin Regimen

Case 2 – George

- Initial basal/bolus regimen
 - Long-acting insulin analog: 20 units at bedtime
 - Rapid-acting insulin analog: 20 units total (8 units at breakfast, 3 units at lunch, 9 units at dinner)

BG Results After 4 Days

Day	BG Levels (mg/dL)				
	Before Breakfast	Before Lunch	Before Dinner	2 H Post-dinner	Bedtime
Friday	180	150	190	*	160
Saturday	175	177	140	235	162
Sunday	190	139	181	215	166
Monday	195	130	172	*	170

*BG not checked.

ADA goals: preprandial, 70–130 mg/dL; postprandial, <180 mg/dL.

George begins his basal/bolus insulin regimen by taking 20 units of long-acting insulin analog at bedtime. He also takes a total of 20 units of rapid-acting insulin analog at mealtimes. The initial distribution of his rapid-acting insulin analog dose is 8 units at breakfast, 3 units at lunch, and 9 units at dinner. This distribution reflects his usual patterns of carbohydrate consumption at the different meals.

The slide shows George's BG results after 4 days of basal/bolus insulin therapy. Review of the log shows that overall glycemic control is improving, with no notable glycemic excursions. His average FBG level is 185 mg/dL and his average PPG is 225. These values indicate that further adjustment to George's insulin regimen is needed to optimize glycemic control.

Changing the Insulin Regimen Case 2 – George

- To improve FBG levels, long-acting insulin analog dose is increased by 20%, to 24 units
 - Dose is further titrated to achieve FBG levels in target range (70–130 mg/dL)
- To improve PPG levels, George employs carbohydrate counting to adjust each mealtime dose of rapid-acting insulin analog, using his ICR of 1:8
- After 6 weeks, average FBG is 115 mg/dL and average PPG is 140 mg/dL
- After 3 months, A1C is 6.6%

To improve his FBG levels, George's long-acting insulin analog dose is increased to 24 units. This dose is further titrated to achieve FBG levels in the target range of 70–130 mg/dL.

To improve his PPG levels, George was taught how to adjust his insulin to his expected carbohydrate intake. He was instructed to utilize carbohydrate counting at each meal to modify his rapid-acting insulin analog dose using his ICR of 1:8.

After 6 weeks, both George's FBG and PPG levels are at levels recommended by the ADA. His average FBG level is 115 mg/dL and his average PPG level is 140 mg/dL.

After 3 months, his A1C is 6.6% and therefore is also at goal.

George reports that he is pleased by the flexibility and improved glycemic control he has gained since beginning his basal/bolus insulin analog regimen.

Summary

- The prevalence of type 2 diabetes in the United States has increased greatly in recent years, and many patients are not meeting glycemic targets
- Insulin treatment for type 2 diabetes enables patients to achieve and maintain their glycemic targets
- The goal of initiating insulin is to achieve glycemic control with minimal risk of hypoglycemia
- The insulin regimen chosen should be matched to the patient's needs and capabilities
- Patients can achieve maximum lifestyle flexibility and tight glycemic control with a basal/bolus regimen, using a rapid-acting insulin analog for mealtime coverage and a long-acting insulin analog for basal coverage

- The prevalence of type 2 diabetes in the United States has increased markedly in recent years, and many patients are not meeting glycemic targets.
- Insulin treatment for type 2 diabetes enables patients to achieve and maintain their glycemic targets.
- The goal of initiating insulin is to achieve glycemic control with minimal risk of hypoglycemia.
- The insulin regimen chosen should be matched to the patient's needs and capabilities.
- Patients can achieve maximum lifestyle flexibility and tight glycemic control with a basal/bolus regimen, using a rapid-acting insulin analog for mealtime coverage and a long-acting insulin analog for basal coverage.