

CE IN THE MORNINGS

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Establishing Glycemic Goals and Therapeutic Strategies in Type 2 Diabetes

A continuing education (CE) activity entitled *Diabetes: Exploring the Risks and Benefits of Emerging Type 2 Therapies* was presented as one of four CE in the Mornings topics at the 46th ASHP Midyear Clinical Meeting and Exhibition in New Orleans, Louisiana, in December 2011. The program was presented by Susan Cornell, Pharm.D., CDE, FAPhA, FADE. In a live webinar conducted on March 8, 2012, Dr. Cornell used several patient cases to illustrate factors to consider when establishing glycemic goals and selecting appropriate combination drug therapy for type 2 diabetes based on patient characteristics. The highlights of the webinar pertaining to these factors are described in this e-Newsletter, and highlights pertaining to new and emerging incretin-based therapies will be discussed in an e-Newsletter to be released in May 2012.

Initiative Faculty

Susan Cornell, Pharm.D., CDE, FAPhA, FADE
Assistant Director of Experiential Education
Associate Professor of Pharmacy Practice
Midwestern University Chicago College of Pharmacy
Downers Grove, Illinois

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On-demand CPE Activities

If you were unable to attend the live symposium, *Diabetes: Exploring the Risks and Benefits of Emerging Type 2 Therapies*, conducted at the 2011 ASHP Midyear Clinical Meeting, a **1-hour CPE activity is available on demand.**



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Question: What is the current thinking about the etiology of type 2 diabetes, and what are the implications for treating the disease?

In the past, type 2 diabetes was thought of as a disease involving the pancreas, but it is now recognized as a chronic disease associated with defects in multiple organs, including the pancreas, liver, peripheral tissues, gastrointestinal (GI) tract, adipose tissues, brain, and possibly the kidneys.¹ The disease

is characterized by a progressive loss of pancreatic β -cell function.² This loss typically begins 9-12 years before the disease is diagnosed and continues after diagnosis despite treatment, although some interventions can attenuate the loss of or even improve β -cell function.²

Diabetes is a major cause of morbidity and mortality from cardiovascular disease and other complications.³ Early diagnosis and intervention are needed to mitigate the impact of the disease.

Managing hyperglycemia, hypertension, and dyslipidemia plays an important role in reducing cardiovascular risk in patients with type 2 diabetes. Improvements in glycemic control but not in management of hypertension or dyslipidemia have been observed in patients with diabetes in recent years. In American adults with diabetes, the rates of glycemic control (A1c <7%), blood pressure control (systolic and diastolic blood pressure <130/80 mm Hg), and achievement of lipid goals (low density lipoprotein cholesterol <100 mg/dL) were 57.1%, 45.5%, and 46.5%, respectively, in 2006.^{4,5} Only 12.2% of patients achieved all three therapeutic goals simultaneously. Thus, there is considerable room for improvement in the treatment of patients with diabetes to reduce their cardiovascular risk.

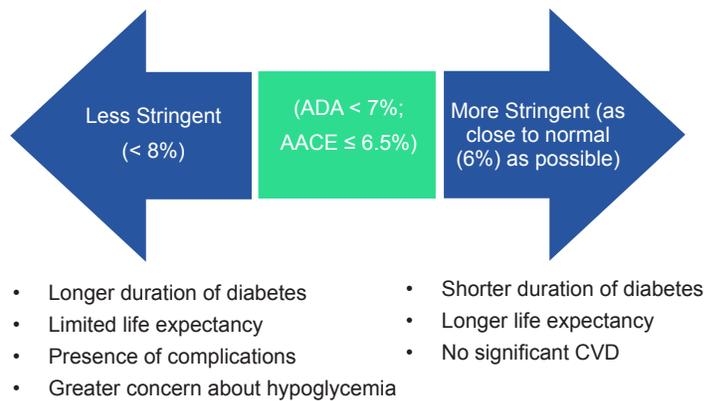
Table 1.
Key Factors to Consider In Selecting Therapeutic Goals and Interventions in Patients with Type 2 Diabetes Mellitus^{5,6}

- How long the patient has had diabetes (i.e., remaining β -cell function)
- Which plasma glucose level is not at target
 - fasting alone
 - postprandial alone
 - both fasting and postprandial
- The degree of A1c-lowering effect required to achieve goal
- Patient preference for route of administration
 - oral
 - inhaled
 - injectable
- The drug side effect profile and patient's ability to tolerate side effects
 - hypoglycemia
 - weight gain
- Comorbid conditions (e.g., cardiovascular disease, depression, osteoporosis)

Question: What factors should be taken into consideration in selecting therapeutic goals and strategies to achieve these goals in patients with type 2 diabetes?

The duration of the illness is one of many factors that influence the selection of therapeutic goals and strategies in patients with type 2 diabetes (Table 1). Pancreatic β -cell function and endogenous insulin production are greatly diminished in patients with a long duration of illness. The need to preserve β -cell function to the extent possible and minimize hypoglycemia and weight gain are considerations in selecting drug therapy. Aggressive glucose-lowering therapy can shock the system of patients with a long duration of diabetes, especially if it has been poorly controlled. Life expectancy also is a consideration because the goals for a patient with a limited life expectancy often are less aggressive than those for patients with a longer life expectancy (Figure 1).⁷

Figure 1.
Setting Glucose Targets

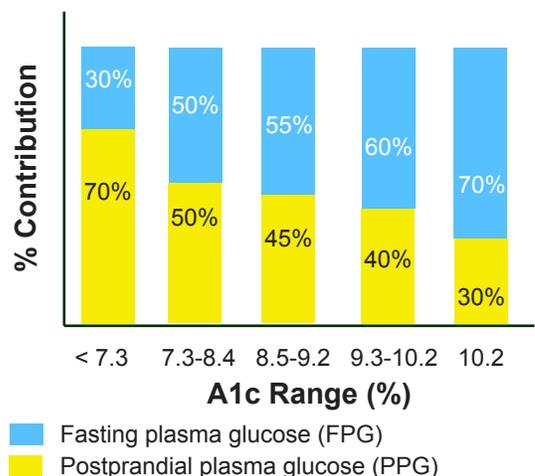


Source: Reference 7.

The extent to which the A1c needs to be lowered to achieve the recommended goal and whether fasting, postprandial, or both plasma glucose levels are not at goal values are considerations in selecting therapeutic strategies. Elevated fasting plasma glucose levels are associated with microvascular complications (e.g., retinopathy, nephropathy, neuropathic complications), and elevated postprandial

plasma glucose levels are associated with macrovascular complications (i.e., cardiovascular disease). The contributions of fasting and postprandial hyperglycemia to the overall diurnal variation in plasma glucose concentrations in patients with type 2 diabetes depends on the A1c (Figure 2).⁸ At a high A1c value (e.g., 10.2%), fasting hyperglycemia is responsible for a

Figure 2.
Fasting vs. Postprandial Glucose Relationship to A1c



Source: Reference 8.

much larger percentage (70%) of the variability in plasma glucose concentrations than postprandial hyperglycemia (30%). Conversely, at a low A1c value (e.g., <7.3%), postprandial hyperglycemia is responsible for a much larger percentage (70%) of the variability in plasma glucose concentrations than fasting hyperglycemia (30%).

Question: What evidence-based guidelines are available for the management of type 2 diabetes? How are they similar, and how do they differ?

Various organizations have released recommendations for glycemic goals and treatment algorithms for type 2 diabetes. The glycemic goals recommended by the American Association of Clinical Endocrinologists (AACE) are lower (i.e., more aggressive) than those recommended by the American Diabetes Association (Table 2).

In a statement and algorithm for glycemic control in patients with type 2 diabetes from AACE and the American College of Endocrinology, drug therapy is based on the patient's current A1c level (Table 3).⁹ The magnitude of the reduction in A1c needed to achieve this goal also influences therapeutic strategies.

Table 2.
Recommendations from Authoritative Groups for Glycemic Goals in Patients with Type 2 Diabetes^{5,7}

Measure of Glycemic Control	AACE	ADA
A1c (%)	<6.5	<7.0
Fasting glucose (mg/dL)	<110 (fasting plasma glucose)	70-130 (pre-prandial capillary plasma glucose)
Postprandial glucose (mg/dL)	<140 (2-hr post-prandial plasma glucose)	<180 (peak post-prandial capillary plasma glucose)

AACE = American Association of Clinical Endocrinologists
ADA = American Diabetes Association

Table 3.
AACE/ACE Algorithm for Glycemic Control in Patients with Type 2 Diabetes Based on Current A1c Value⁹

Current A1c (%)	Recommended Treatment Strategy
≤7.5	Start with monotherapy and if it fails, proceed to dual therapy and then triple therapy. If these interventions fail, initiate insulin therapy, with or without additional oral agents
7.6-9.0	Start with dual therapy because the A1c goal is not likely with monotherapy. If dual therapy fails, proceed to triple therapy and then insulin therapy, with or without additional oral agents.
>9.0	If the patient is asymptomatic, start with triple therapy (e.g., metformin plus a GLP-1 agonist or DPP-4 inhibitor plus a sulfonylurea or thiazolidinedione). If the patient is symptomatic or therapy with similar medications has failed, initiate insulin therapy, with or without additional oral agents.

AACE = American Association of Clinical Endocrinologists;
ACE = American College of Endocrinology;
DPP-4 = dipeptidyl peptidase;
GLP-1 = glucagon-like peptide

Question: What are the advantages and disadvantages of currently available medications for the treatment of type 2 diabetes?

A wide variety of agents and drug classes are available that vary in the organ defect addressed, route of administration, effects on plasma glucose, adverse effects, and cautions (Table 4). Some of these agents are thought to protect β -cell function whereas others do not. No one agent or class of drugs addresses all of the organ defects associated with type 2 diabetes. The differences among the agents and patient characteristics should be taken into consideration in selecting drug therapy for an individual. All drug therapies should be used to augment, not replace lifestyle modification (i.e., dietary modification, physical activity, losing weight if overweight).

Question: What target A1c and therapeutic approach should be chosen for a man who works as an interstate trucker and was recently diagnosed with type 2 diabetes if he has an A1c of 8.6% and a body mass index (BMI) of 32 kg/m²?

The A1c goal for this man should be <7.0% (preferably <6.5% based on AACE recommendations), which means he needs a reduction in A1c of at least 1.6% (preferably more). His current A1c suggests that fasting hyperglycemia is responsible for 55% of the variability in plasma glucose concentrations and postprandial hyperglycemia accounts for the other 45% (Figure 2). Therefore, both fasting and postprandial glucose need to be addressed when choosing drug therapy. Most patients with an A1c greater than 7.5% require combination therapy using agents with complementary mechanisms of action.⁷ This patient is obese (a BMI of 30 kg/m² or higher is obese, with 25-29.9 kg/m² considered overweight), so the need to avoid weight gain influences the choice of drug therapy.

The biguanide metformin, which primarily affects fasting plasma glucose, and a short- or long-acting glucagon-like peptide-1 (GLP-1) agonist might be used initially because both drugs promote weight loss. Short-acting GLP-1 agonists (e.g., conventional twice-daily exenatide) primarily affect postpran-

dial plasma glucose, and long-acting GLP-1 agonists (e.g., once-daily liraglutide and a once-weekly form of exenatide approved by the Food and Drug Administration in January 2012) affect both fasting and postprandial glucose. The need to inject GLP-1 agonists subcutaneously may pose a problem for the patient. This patient's occupation may prohibit him from using insulin or other injectable agents. An oral dipeptidyl peptidase (DPP)-4 inhibitor may be a suit-

“**Therapeutic goals and interventions for type 2 diabetes must be tailored to the patient's characteristics and needs. One size does not fit all.**”

—Susan Cornell, Pharm.D., CDE, FAPhA, FADE

able alternative to the GLP-1 agonist because it is weight neutral and primarily affects postprandial plasma glucose (Table 4). Sulfonylureas probably should be avoided in this patient because they promote weight gain and do not preserve β -cell function. The thiazolidinedione pioglitazone also can cause weight gain, but the onset of this effect is late (after 4-8 weeks of therapy), and any weight gain from pioglitazone might be negated by the weight loss associated with metformin. Therefore, pioglitazone might be used with metformin initially or added if the target A1c is not achieved with metformin plus a GLP-1 agonist or DPP-4 inhibitor.

Table 4.
Advantages and Disadvantages of Drug Therapies for Type 2 Diabetes^{9,10}

Drug or Drug Class	Organ Defect Addressed	Effects on Plasma Glucose	Advantages	Disadvantages
Oral Therapies				
α-glucosidase inhibitors (acarbose and miglitol)	GI tract	Postprandial	Weight neutral. Drug-induced diarrhea may be beneficial in patients with constipation.	Use with caution in patients with GI problems. Limited usefulness in patients with a long duration of diabetes due to gastroparesis. Expensive.
Biguanide (metformin)	Liver	Fasting	Promotes weight loss with low risk of hypoglycemia. Beneficial for patients who are overweight/obese or unable to tolerate other interventions to reduce CV risk. Inexpensive.	Risk of GI side effects. Use with caution in patients with renal or hepatic impairment.
Bromocriptine (dopamine agonist)	Brain	Postprandial	Beneficial for patients unable to meet blood pressure goals despite ACE inhibitor or ARB therapy. Provides modest A1c reduction.	Risk of hypotension and GI side effects (nausea).
Colesevelam (bile acid sequestrant)	GI tract and liver	Fasting and postprandial	Beneficial for patients unable to meet LDL cholesterol goal despite optimal statin therapy.	Risk of GI side effects. Limited usefulness in patients with a long duration of diabetes due to gastroparesis.
DPP-4 inhibitors (linagliptin, saxagliptin, and sitagliptin)	Liver, pancreas, brain	Postprandial	Weight neutral. Beneficial for patients unable to tolerate other interventions to reduce CV risk (low risk of hypoglycemia).	Expensive. Risk of upper respiratory tract infections.
Glinides (nateglinide and repaglinide)	Pancreas	Postprandial	Beneficial for patients with erratic meal patterns or renal insufficiency.	Risk of hypoglycemia and weight gain. Limited usefulness in patients with a long duration of disease and inadequate endogenous insulin production. Expensive.
Sulfonylureas	Pancreas	Fasting and postprandial	Inexpensive.	Risk of hypoglycemia and weight gain. Limited usefulness in patients with long duration of disease and inadequate endogenous insulin production. Provides no β-cell protection.
Thiazolidinedione (pioglitazone)	Peripheral tissues and fat	Fasting and postprandial	Beneficial for patients with comorbid dyslipidemia. Reduces insulin resistance, adipose tissue, and triglycerides.	Risk of edema and weight gain. Expensive.
Injectable Therapies				
GLP-1 agonists (exenatide and liraglutide)	GI tract, liver, pancreas, and brain	Postprandial (short-acting agents ^a) or fasting and postprandial (long-acting agents ^b)	Promote weight loss. Beneficial for overweight/obese patients.	Risk of GI side effects (nausea). Need for injection. Expensive.
Insulins	Pancreas and peripheral tissues	Fasting (intermediate- and long-acting), postprandial (regular, rapid-acting)	Beneficial for patients who are symptomatic or have high A1c or long duration of disease.	Risk of hypoglycemia and weight gain. Need for injection. Expensive (analogs).
Pramlintide (amylinomimetic)	GI tract, liver, pancreas, brain	Postprandial	Promotes weight loss. Beneficial for patients with poor PPG control despite insulin therapy or prone to weight gain on insulin therapy.	Risk of GI side effects. Need for injection. Expensive.

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; CV = cardiovascular; DPP = dipeptidyl peptidase; GI = gastrointestinal; GLP = glucagon-like peptide; LDL = low density lipoprotein; PPG = postprandial plasma glucose

^aShort-acting GLP-1 agonists include conventional twice-daily exenatide.

^bLong-acting GLP-1 agonists include once-daily liraglutide and a once-weekly form of exenatide approved by FDA in January 2012.

Question: How would the target A1c and therapeutic approach differ for a 79-year-old woman with a 22-year history of type 2 diabetes and a stable A1c of 8.1% for the past 4 years while receiving metformin 1 g twice daily and glimepiride 4 mg once daily? Her BMI is 25 kg/m² (borderline overweight) and she has a serum creatinine of 1.1 mg/dL (within the normal range for women). She resides in an assisted living apartment and has limited financial resources and mobility.

A less aggressive A1c (e.g., 7.5%) is suitable for this patient because of her advanced age, long duration of the disease, and limited life expectancy.⁷ Her A1c is close to this goal. Aggressive therapy and tight glycemic control are not warranted and may do more harm than good. Weight loss is not necessary in this borderline overweight patient. The risk of hypoglycemia and GI adverse effects are considerations in determining whether to modify her therapy. The A1c of 8.1% suggests that fasting and postprandial hyperglycemia each are responsible for 50% of the variability in plasma glucose concentrations (Figure 2). Metformin primarily affects fasting plasma glucose, and glimepiride affects both fasting and postprandial plasma glucose. These drugs are inexpensive for this senior citizen with limited financial resources. Increasing the dosage of metformin is not advisable because the dosage has already been optimized, and increasing the dosage of glimepiride could increase the risk of hypoglycemia and falls.

Basal insulin might be added to the metformin and glimepiride therapy for this patient, although insulin can cause weight gain and requires injection. Adding an oral DPP-4 inhibitor is an alternative to adding insulin that is weight neutral. Using an injectable GLP-1 agonist or oral bromocriptine (a dopamine agonist) instead of the DPP-4 inhibitor could cause nausea. A risk of hypotension is associated with bromocriptine, so the patient's blood pressure would need to be checked to ensure that it is not low before initiating bromocriptine.

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