Evaluation and Management of Diabetes Mellitus

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Diabetes mellitus is a major public health problem with tremendous medical and economic burdens. It is the seventh leading cause of death and the number one cause of end-stage renal disease, adult blindness, impotence, and nontraumatic lower-limb amputation in the United States. People with diabetes are 2 to 4 times more likely to suffer from stroke or from cardiovascular disease, and are twice as likely to die compared with age-matched individuals without diabetes. Diabetes cost the United States around $174 billion in 2007, $58 billion of which was related to disability, work loss, and early mortality. Although there is currently no known cure for diabetes, much progress has been made over the past 2 decades to improve the diagnosis and management of diabetes. Evidence has shown that applying aggressive interventions early can prevent or delay progression to microvascular complications that increase the mortality rate in diabetes. The authors review the guidelines for optimal evaluation of diabetes mellitus and discuss the current and emerging therapeutic options available in the United States. [*ADHB*. 2008;1(8):39-48.]

Diabetes mellitus is a chronic and devastating disease, affecting 8% of the US population.[1] Despite recent advances in diagnostic and therapeutic options, the incidence of diabetes continued to rise in 2007. According to the Centers for Disease Control and Prevention, approximately 24 million Americans are currently diagnosed with diabetes, an increase of 3 million over the past 2 years, and another 57 million are classified as having prediabetes.[1] About one third of the people with diabetes remain undiagnosed.

Worldwide, the prevalence of diabetes is projected to reach 366 million people by the year 2030.[2] Major increases in both macrovascular and microvascular complications can be projected on the basis of this growing prevalence. Indeed, recent studies have reported that life expectancy is reduced in patients with diabetes, with an estimated risk of death about twice that of the general population of similar age.[1,3] Men and women who are diagnosed with diabetes before the age of 40 have an average life expectancy reduction of 12 and 19 years, respectively.[4]

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The cost of diabetes to the US healthcare system is staggering; it was estimated to be around $174 billion in direct ($116 billion) and indirect ($58 billion) costs in 2007.[1]

Data from the United Kingdom Prospective Diabetes Study Group, the Diabetes Control and Complications Trial, and the Kumamoto study have clearly shown that early and aggressive glycemic interventions can reduce the risk of microvascular complications—retinopathy, nephropathy, and neuropathy—of diabetes.[5-7] Despite this knowledge, studies continue to show that most Americans with diabetes are not achieving the recommended treatment goals. Recent data from the National Health and Nutrition Examination Survey reported that only one third of diabetic patients are at goal with regard to glycemic and blood pressure control, and only half are meeting their cholesterol goals.[8] It is hopeful that the availability of published guidelines and algorithms will aid physicians to bring more patients to the desired glycemic, blood pressure, and lipid goals.

Diagnosis

The American Diabetes Association (ADA) currently recognizes 4 classifications of diabetes: type 1 diabetes, type 2 diabetes, other specific types of diabetes due to other causes, and gestational diabetes. Diagnostic criteria for diabetes mellitus are listed in **Table 1**. Fasting plasma glucose (FPG) continues to be

KEY POINTS

▲ Approximately 24 million Americans are currently diagnosed with diabetes, an increase of 3 million over the past 2 years; 57 million have prediabetes.

▲ The cost of diabetes to the US healthcare system in 2007 was estimated to be $174 billion, which included direct ($116 billion) and indirect ($58 billion) costs.

▲ Early, aggressive glycemic interventions can reduce progression to retinopathy, nephropathy, and neuropathy; nevertheless, most Americans with diabetes are not reaching treatment goals.

▲ Patients with diabetes should receive aggressive blood pressure lowering to reduce cardiovascular events.

▲ Evidence has shown that metformin, orlistat, acarbose, and troglitazone successfully reduce the progression of impaired glucose tolerance and impaired fasting glucose to diabetes, although to a lesser degree than diet and exercise.

▲ Lifestyle modifications remain the best treatment for type 2 diabetes, but most patients will not be able to follow a rigid diet and exercise regimen and will eventually require antihyperglycemic medications.

the diagnostic test of choice for diabetes.[9] Recent studies, however, have indicated that hemoglobin (Hb) A_{1C} may be a more stable,[10] convenient (ie, does not require fasting), and noninferior test compared with FPG.[11] An HbA_{1C} screening review panel has recently evaluated the current literature on this topic and concluded that HbA_{1C} should be "incorporated into criteria for screening and diagnosing diabetes."[12] As assays for HbA_{1C} testing become more reliable and less expensive, it is possible that HbA_{1C} will be accepted as an alternative screening and diagnostic test in the future.

Screening

Routine screening for type 1 diabetes is currently not recommended by any organization. Due to the low incidence and the lack of known preventive measures for type 1 diabetes, screening for this disease in healthy people is not cost-effective. In contrast, many experts believe that screening for type 2 diabetes is indicated because of the long—7 years—presymptomatic phase often seen in this population.[12] Although microvascular complications may take years to develop, macrovascular morbidity and mortality are significantly elevated in individuals before the diagnosis of diabetes is made.[13] The ADA currently recommends that screening be considered in all individuals ≥45 years of age. If normal, the screening test should be repeated every 3 years. For individuals with 1 or more risk factors for type 2 diabetes (**Table 2**), screening should be done at any age.[9]

FPG is the screening test of choice for the ADA and the American Heart Association,[14] whereas the 2-hour oral glucose tolerance is the preferred test for the American Association of Clinical Endocrinologists (AACE).[15] In contrast, the US Preventive Services Task Force (USPSTF) has recently updated their diabetes screening recommendations and concluded that the evidence is still insufficient to recommend for or against routine screening of asymptomatic adults for prediabetes or type 2 diabetes. The only population where screening is indicated, according to the USPSTF, is people whose blood pressure is >135/80 mm Hg. Convincing evidence has demonstrated that aggressive lowering of blood pressure in patients with diabetes reduces the incidence of cardiovascular events and mortality.[16]

Prevention

Prevention of progression to diabetes is essential, considering the serious medical and economic consequences of the disease and the lack of cure. Several clinical trials have demonstrated that lifestyle modifications alone or in conjunction with pharmacologic therapies can prevent or delay the development of type 2 diabetes. Individuals who lose 7% of their body weight and maintain 150 minutes of exercise weekly can reduce the rate of progression from impaired glucose tolerance (IGT) to diabetes by 58%.[17] Studies have demonstrated that the use of several pharmacologic agents—metformin,[17] orlistat,[18]

Table 1	Diagnostic Criteria for Diabetes Mellitus		
Classification	Fasting plasma glucose, mg/dL	2-h oral glucose tolerance test, mg/dL*	Random plasma glucose, mg/dL
Normal	<100	<140	
Prediabetes			
Impaired fasting glucose	≥100-125		
Impaired glucose tolerance		≥140-199	
Diabetes	≥126†	≥200†	>200‡

*75-g glucose dose.
†Abnormal test must be repeated on subsequent day.
‡Must occur with hyperglycemic symptoms: polydipsia, polyphagia, polyuria, blurred vision.
Source: Executive summary: standards of medical care in diabetes—2008. *Diabetes Care.* 2008;31(suppl 1):S5-S54.

acarbose,[19] and troglitazone[20]—can successfully reduce the progression of IGT and impaired fasting glucose (IFG)[9] to diabetes, although to a lesser degree than diet and exercise.

The ADA endorses lifestyle modifications as the initial treatment for prediabetes. If pharmacologic intervention is required, metformin is the only drug that is recommended in conjunction with diet and exercise in high-risk patients (those with both IGT and IFG).[9]

Glycemic Control

Glycemic goals as recommended by the ADA and AACE are summarized in **Table 3**. At an HbA_{1C} level of <7%, long-term microvascular and macrovascular risks from hyperglycemia are minimized. Recognizing that there is no threshold to the benefits of lowering HbA_{1C}, experts now stress that HbA_{1C} be reduced to the lowest possible level at which frequent hypoglycemic episodes do not occur. Every 1% reduction in HbA_{1C} is associated with a 40% reduction in microvascular complications.[9]

Methods to achieve glycemic goals are lifestyle modifications and pharmacologic treatments. Although lifestyle modifications (ie, diet, exercise, and/or behavioral interventions) remain the best and first-line treatment, most patients will not be able to follow a rigid diet and exercise regimen and will eventually require the use of antihyperglycemic medications.

Treatment Options

The ADA and the European Association for the Study of Diabetes have copublished an algorithm to guide practitioners in the use of oral and/or parenteral antihyperglycemic agents available for the treatment of type 2 diabetes (**Figure**). A "road map to achieve glycemic goals" has also been developed by the AACE and the American College of Endocrinology and was revised in April 2008.[21]

Oral Antihyperglycemic Agents

Six major classes of oral drugs are currently available for management of type 2 diabetes in the United States (**Table 4**). These medications can be divided into 4 broad categories based on their mechanisms of action—secretagogues, sensitizers, carbohydrate absorption inhibitors, and dipeptidyl peptidase-4 (DPP-4) inhibitors. These drugs are indicated in patients who do not respond to 3 months of lifestyle modifications.

Biguanides (sensitizers). Metformin is the only biguanide available in the United States. Its main

Table 2	Risk Factors for Type 2 Diabetes

First-degree relative with diabetes

High-density lipoprotein cholesterol ≤35 mg/dL and/or triglyceride ≥250 mg/dL

History of gestational diabetes or delivery of a baby weighing >9 lb

History of vascular disease

Hypertension (≥140/90 mm Hg in adults)

IGT or IFG on previous testing

Member of a high-risk ethnic group (ie, African American, Native American, Hispanic, Asian American, Pacific Islander)

Obesity (body mass index >25 kg/m^2)

Physical inactivity

Women with polycystic ovarian syndrome

IGT indicates impaired glucose tolerance; IFG, impaired fasting glucose.
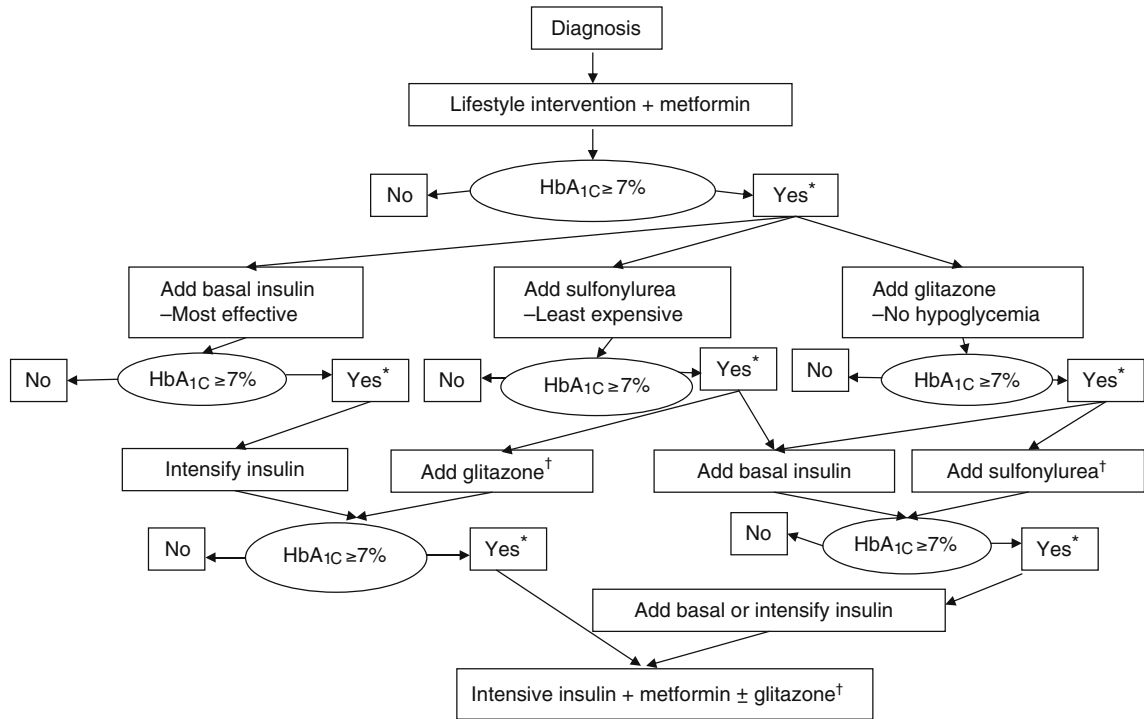*Source*: Executive summary: standards of medical care in diabetes—2008. *Diabetes Care*. 2008;31(suppl 1):S5-S54.

Table 3	Targets for Glycemic Control	
Targets	**ADA**	**AACE**
Hemoglobin A_{1C}	<7%	<6.5%
Preprandial glucose	70-130 mg/dL	<110 mg/dL
Postprandial glucose	<180 mg/dL (peak)	<140 mg/dL at 2 h from start of meal

ADA indicates American Diabetes Association; AACE, American Association of Clinical Endocrinologists.

Sources: Executive summary: standards of medical care in diabetes—2008. *Diabetes Care*. 2008;31(suppl 1):S5-S54; American Association of Clinical Endocrinologists. Medical guidelines for clinical practice for the management of diabetes mellitus. *Endocr Pract*. 2007;13(suppl 1):1-68.

action is to decrease hepatic glucose production and enhance insulin sensitivity. As monotherapy, metformin is very effective in decreasing plasma glucose level, reducing HbA_{1C} by approximately 1% to 2% compared with diet or placebo.[22] Aside from its glycemic effect, metformin also lowers triglycerides and low-density lipoprotein cholesterol.[23] By itself, it does not cause weight gain nor hypoglycemia.[24] Gastrointestinal (GI) discomfort, which usually resolves over time with continuation of the medication or dose reduction, is the most common side effect of metformin. To minimize the risk of lactic acidosis, metformin should not be given to patients with renal dysfunction (serum creatinine ≥1.5 mg/dL in men, ≥1.4 mg/dL in women). Because of its cost and benign side-effect profile, metformin is considered a first-line drug in the treatment of diabetes. It can be used concurrently with lifestyle modifications at the

Figure **Algorithm for the Metabolic Management of Type 2 Diabetes**

Diagnosis

Lifestyle intervention + metformin

HbA$_{1C}$ ≥ 7% — No / Yes*

Add basal insulin –Most effective

Add sulfonylurea –Least expensive

Add glitazone –No hypoglycemia

No ← HbA$_{1C}$ ≥7% → Yes*

No ← HbA$_{1C}$ ≥7% → Yes*

No ← HbA$_{1C}$ ≥7% → Yes*

Intensify insulin

Add glitazone†

Add basal insulin

Add sulfonylurea†

No ← HbA$_{1C}$ ≥7% → Yes*

No ← HbA$_{1C}$ ≥7% → Yes*

Add basal or intensify insulin

Intensive insulin + metformin ± glitazone†

Reinforce lifestyle intervention at every visit.

*Check HbA$_{1C}$ every 3 months until <7% and then at least every 6 months.

†Although 3 oral agents can be used, initiation and intensification of insulin therapy is preferred based on effectiveness and expense.

Hb indicates hemoglobin.

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time of diagnosis or even for diabetes prophylaxis.[9,22] To date, it remains 1 of only 2 oral antihyperglycemic medications that have been shown to reduce macrovascular complications.[23]

Sulfonylureas (secretagogues). Sulfonylureas are the oldest class of antihyperglycemic agents, first introduced to the US market in 1946. Their primary action is to promote insulin secretion from the pancreas. Similar to metformin, sulfonylureas are effective at decreasing plasma glucose level, reducing HbA$_{1C}$ by approximately 1% to 2%.[22] Hypoglycemia and weight gain are the 2 major side effects of this class. Because they are the least expensive of all antihyperglycemic medications, sulfonylureas—which are second-line agents after lifestyle modifications and metformin—are the drugs of choice for patients with financial considerations.

Nonsulfonylurea secretagogues (secretagogues). Repaglinide (a meglitinide) and nateglinide (a phenylalanine) function in the same manner as sulfonylureas,

by increasing insulin secretion from the pancreas, and they reduce HbA$_{1C}$ at the same level (–1.5%).[22] They are structurally different from the sulfonylureas and have a faster onset of action; thus, they should be taken at mealtime to reduce the risk of hypoglycemia.[23] Because these agents are metabolized exclusively by the liver, they can be used in patients with renal insufficiency.[25]

In head-to-head trials against sulfonylureas, meglitinides and phenylalanines have not been found to be superior in terms of improving postprandial control.[26,27] At a cost of 3 to 4 times more than sulfonylureas,[23] it is unlikely that these drugs will be widely used.

Alpha-glucosidase inhibitors (carbohydrate absorption inhibitors). Alpha-glucosidase inhibitors delay carbohydrate absorption in the small intestine, thereby lowering postprandial blood glucose without causing hypoglycemia.[28] They do not cause weight gain but are associated with significant GI side effects (ie, diarrhea,

Table 4 Oral Antihyperglycemic Agents

Drug		Mechanism of action	Hemoglobin A_{1C} reduction, %	Dose range	Adverse events	Comments	Cost for 30-day supply (range)*
Alpha-glucosidase inhibitors							
Acarbose (Precose)		Delay complex carbohydrate absorption	0.5-0.8	25-100 mg tid w/meals	Flatulence, diarrhea, abdominal pain	Titrate slowly to minimize GI effects	$73.79-$80.99
Miglitol (Glyset)				25-100 mg tid w/meals			$79.99-$99.99
Biguanides							
Metformin (Glucophage)		Decrease hepatic glucose output; increase peripheral glucose uptake	1-2	*IR:* 1000-2550 mg/d divided bid or tid *ER:* 500-2000 mg/d	Nausea, vomiting, diarrhea, flatulence	Take w/meals; avoid use in patients w/renal or hepatic impairment or CHF due to increased risk of lactic acidosis	*IR:* $24.99-$77.99 *ER:* $6.33-$25.32
Dipeptidyl peptidase-4 inhibitors							
Sitagliptin (Januvia)		Slow inactivation of incretin hormones	0.5-0.8	25-100 mg/d	Not clinically significant	Renal dose: 50 mg/d for CrCl ≥30 to <50 mL/min; 25 mg/d for CrCl <30 mL/min	$45.27-$181.09
Nonsulfonylurea secretagogues							
Nateglinide (Starlix)		Stimulate insulin secretion from the pancreas	1-1.5	60-120 mg tid	Hypoglycemia, weight gain	Take w/meals due to rapid onset	$154.11-$164.85
Repaglinide (Prandin)				0.5-4 mg tid to qid			$164.82-$396.08
Sulfonylureas							
First-generation	Chlorpropamide (Diabenese)	Stimulate insulin secretion from the pancreas	1-2	100-750 mg/d	Hypoglycemia, weight gain	Use of these agents has declined due to side effects and unpredictable results	$8.62-$31.49
	Tolazamide (Tolinase)			100-1000 mg/d given as a single dose or divided bid if dose is >500 mg/d			$12-$69.98
	Tolbutamide (Orinase)			250-3000 mg/d in divided doses			$5-$59.97
Second-generation	Glimepiride (Amaryl)			1-8 mg/d	Hypoglycemia, weight gain		$12.99-$29.98
	Glipizide (Glucotrol)			*IR:* 2.5-40 mg/d as a single dose or divided bid *ER:* 2.5-20 mg/d			*IR:* $3-$25.99 *ER:* $18.99-$39.98
	Glyburide (Micronase, Diabeta, Glynase)			1.25-20 mg/d as a single dose or divided bid (Glynase: 0.75-12 mg/d as a single dose or divided bid if dose >6 mg/d)			$12.99-$47.96 (Glynase: $4.33-$109.42)
Thiazolidinediones							
Pioglitazone (Actos)		Increase peripheral tissue insulin sensitivity	0.5-1.4	15-45 mg/d	Edema, weight gain	Black box warning: these agents can cause or exacerbate CHF; contraindicated in patients with NYHA class III or IV heart failure	$134.07-$195.99
Rosiglitazone (Avandia)				4-8 mg/d as a single dose or divided bid			$120.10-$223.49

*Cost calculated from generic, if available, and lowest bottle size available. GI indicates gastrointestinal; IR, immediate release; ER, extended release; CHF, congestive heart failure; CrCl, creatinine clearance; NYHA, New York Heart Association.

Sources: Lacy CF, Armstrong LL, Goldman MP, Lance LL, eds. *Drug Information Handbook.* 17th ed. Hudson, OH: Lexi-Comp; 2008. McEvoy GK, ed. *AHFS Drug Information.* Bethesda, MD: American Society of Health-System Pharmacists; 2008. Cost: www.drugstore.com.

Table 5	Insulin Preparations				
Drug	Onset	Peak	Duration	Comments	Cost (10-mL vial)
Rapid-acting					
Insulin Aspart (NovoLog)	10-20 min	1-3 h	3-5 h	Administer within 15 min before or immediately after meals	$94.25
Insulin Glulisine (Apidra)	25 min	45-48 min	4-5 h		$90.68
Insulin Lispro (Humalog)	15-30 min	0.5-2.5 h	3-6.5 h		$89.99
Short-acting					
Insulin Regular (Novolin R, Humulin R)	30-60 min	1-5 h	6-10 h	Administer 30 min before meals	$45.99-$49.99
Intermediate-acting					
Insulin NPH (Novolin N, Humulin N)	1-2 h	6-14 h	16-24+ h	Cloudy appearance	$46.99-$49.99
Long-acting					
Insulin Detemir (Levemir)	1.1-2 h	3.2-9.3 h	5.7-24 h (dose-dependent)	Don't mix with other insulins	$95.30
Insulin Glargine (Lantus)	1.1 h	None	24 h		$97.73
Premixed					
70% Insulin Aspart Protamine/30% Insulin Aspart (NovoLog Mix 70/30)	10-20 min	1-4 h	24 h	Cloudy appearance; administer within 15 min before meals	$95.03
75% Insulin Lispro Protamine/25% Insulin Lispro Protamine (Humalog Mix 75/25)	15-30 min	2 h	22 h		$96.89
50% Insulin Lispro Protamine/50% Insulin Lispro Protamine (Humalog Mix 50/50)					Not available
70% Insulin NPH/30% Insulin Regular (Humulin 70/30, Novolin 70/30)	30 min	1.5-12 h	24 h	Cloudy appearance; administer within 30 min before meals	$46.26-$49.99
50% Insulin NPH/50% Insulin Regular (Humulin 50/50)	30-60 min	1.5-4.5 h	7.5-24 h		$49.99

Sources: Lacy CF, Armstrong LL, Goldman MP, Lance LL, eds. *Drug Information Handbook*. 17th ed. Hudson, OH: Lexi-Comp; 2008. McEvoy GK, ed. AHFS Drug Information. Bethesda, MD: American Society of Health-System Pharmacists; 2008. Cost: www.drugstore.com.

abdominal pain, flatulence)[24]; thus, long-term compliance is a significant issue with these drugs. Unlike the biguanides, alpha-glucosidase inhibitors are not considered first-line therapy because of their minimal glycemic control (HbA$_{1C}$ −0.5%)[22] and higher costs.[23]

Thiazolidinediones (sensitizers). Thiazolidinediones (TZDs; rosiglitazone and pioglitazone) reduce insulin resistance by binding to peroxisome proliferator–activated receptors-γ (PPAR-γ) in the peripheral muscles, liver, and adipose tissues. This, in turn, alters the transcription of genes that positively regulate glucose uptake. As monotherapy, they lower HbA$_{1C}$ by 0.5% to 1.4%.[22] Their onset of action is slower than that of the sulfonylureas, but they do not cause hypoglycemia.[28] In addition to lowering blood glucose, these agents exert beneficial effects on lipid metabolism, as

Table 6 Noninsulin Injectable Antihyperglycemic Agents

Drug	Mechanism of action	Hemoglobin A$_{1C}$ reduction, %	Dose range	Adverse events	Comments	Cost for 30-day supply (range)
Amylin analog						
Pramlintide (Symlin)	Acts in conjunction with insulin to prolong gastric emptying, reduce postprandial glucose secretion, and promote appetite suppression	0.5-1	*Type 1 DM:* 15-60 µg SC immediately before each meal *Type 2 DM:* 60-120 µg SC immediately before each meal	Nausea, vomiting	Black box warning: coadministration w/ insulin may induce severe hypoglycemia	$127.58/ 5-mL vial
Incretin mimetic						
Exenatide (Byetta)	Stimulates insulin secretion; slows gastric emptying, suppresses glucagon release, induces satiety	0.5-1	5-10 µg SC bid within 60 min before morning and evening meals	Nausea, vomiting, diarrhea	Acute pancreatitis has been reported during postmarketing experience	$213.03 (5-µg cartridge)- $229.27 (10-µg cartridge)

*Cost calculated from generic, if available, and lowest bottle size available.
DM indicates diabetes mellitus; SC, subcutaneous.
Sources: Lacy CF, Armstrong LL, Goldman MP, Lance LL, eds. *Drug Information Handbook.* 17th ed. Hudson, OH: Lexi-Comp; 2008. McEvoy GK, ed. *AHFS Drug Information.* Bethesda, MD: American Society of Health-System Pharmacists; 2008. Cost: www.drugstore.com.

well as improve surrogate markers for pancreatic beta-cell regeneration and vascular inflammation.[15,28]

A recent meta-analysis has raised the possibility that rosiglitazone may increase the risk of myocardial infarction (not seen with pioglitazone).[29] Because of the methodological limitations of this analysis, numerous studies, including one from the US Food and Drug Administration (FDA),[30] were subsequently initiated to reevaluate these findings. Results from these studies were mixed and inconclusive,[30-32] prompting the FDA to recommend caution in the use of TZDs and to mandate the inclusion of a black box warning in the package inserts of TZDs relaying the 2-fold increased risk of fluid retention and heart failure with this class.[33] The future of TZDs remains strong. But at a cost of 2 to 3 times more than the cost of metformin, TZDs should only be considered after failure of lifestyle modifications and metformin.[9]

DPP-4 inhibitors. These medications represent the newest class of oral antihyperglycemic medications, introduced to the US market in 2006. This class inhibits the breakdown of endogenous glucagon-like peptide 1 (GLP-1),[15] a compound that can control or even reverse some of the metabolic derangements seen in type 2 diabetes. Sitagliptin, the only FDA-approved drug in this class to date, has been shown to lower

HbA$_{1C}$ by 0.5% to 0.8%.[22] One advantage of this DPP-4 is that it only works when blood glucose is elevated; thus, the risk for hypoglycemia is minimal. Other advantages include once-daily administration, oral availability, and, more important, weight neutrality.[34] Sitagliptin is effective and safe in patients with renal insufficiency, including those on hemodialysis; however, dose adjustments will be necessary based on the severity of renal impairment.[35] Although the appropriate role of DPP-4 inhibitors is still unclear, sitagliptin's efficacy and safety profile suggests that this class is a reasonable treatment option for type 2 diabetes.

Parenteral Antihyperglycemic Agents

The 3 parenteral antihyperglycemic classes currently available in the United States are insulins (**Table 5**), and amylin analogs and incretin mimetics (**Table 6**).

Insulins. Insulin is the best agent for reducing blood glucose concentrations. It is mandatory in patients with type 1 diabetes but is a second-line therapy for patients with type 2 diabetes who have failed lifestyle modifications with or without oral antihyperglycemic therapy.[22] Patients receiving insulin therapy are more likely to develop hypoglycemia and weight gain than patients taking oral medications.[36] However, the recent advent of rapid-acting as well as long-acting insulins

Table 7	In the Pipeline: Selected Emerging Antihyperglycemic Compounds	
Drug category	**Mechanism of action**	**Comments**
Glucokinase activators	Activate key enzymes to increase hepatic glucose metabolism	Several drugs are currently in phase 2 clinical trials
Sodium-glucose cotransporter 2 inhibitors	Inhibit reabsorption of glucose at the proximal tubule of the kidney, thereby decreasing systemic hyperglycemia	Low potential for hypoglycemia
11β -hydroxysteroid dehydrogenase 1 (11β -HSD 1) inhibitors	Inhibit an enzyme responsible for activating cortisone to cortisol, thus minimizing antiglycemic effects of cortisol	Low potential for hypoglycemia, may have beneficial effects on metabolic syndrome
Glucagon receptor antagonists	Block glucagon from binding to hepatic receptors, thereby decreasing gluconeogenesis	Low potential for hypoglycemia
Cannabinoid-1 (CB-1) receptor antagonists	Block CB-1 receptors systemically	Marketed as an obesity drug, may cause psychiatric symptoms

Source: Inzucchi SE, McGuire DK. New drugs for the treatment of diabetes mellitus: part II: incretin-based therapy and beyond. *Circulation.* 2008;117:574-584.

has significantly reduced these risks.[24] Insulin detemir, the newest long-acting insulin analog in the United States, has consistently shown in clinical trials to be very effective in reducing blood glucose levels with less weight gain than other basal insulins.[37]

Incretin mimetics. Incretins are hormones that are secreted by cells in the small intestine during an oral nutrient load. GLP-1 is one incretin that has antihyperglycemic effects. In the presence of hyperglycemia, GLP-1 causes the release of insulin from the pancreas, shuts down glucagon secretion, slows down gastric emptying, and acts on the hypothalamus to increase satiety.[38]

Exenatide is the first synthetic GLP-1 to be introduced in the United States. Possessing many of the properties of endogenous GLP-1, exenatide can lower HbA_{1C} by 0.5% to 1%.[22] Aside from its antiglycemic effect, exenatide can also induce weight loss. Patients who were treated with exenatide for 30 weeks had an average weight loss of 4.4 kg,[39] which was maintained when the study was extended for another 22 weeks using a longer-acting version of exenatide.[40] Nausea is the most common side effect of exenatide, which usually subsides with continuation of this medication.[38]

The FDA has recently alerted physicians to 6 cases of necrotizing pancreatitis thought to be related to exenatide use[41]; this is in addition to the 30 cases of nonnecrotizing pancreatitis reported by the FDA in October 2007. Although the exact relationship between pancreatitis and the drug is still unknown, it is recommended that patients receiving exenatide and presenting with abdominal pain be evaluated promptly.

Amylin analogs. Amylin is a neuropeptide that is cosecreted with insulin by pancreatic beta-cells in response to food intake. Amylin complements insulin's action by suppressing glucagon release, slowing gastric emptying, and inducing satiety.[15,42]

Pramlintide is the only amylin analog currently available in the United States. Approved as an adjunctive treatment for patients with type 1 or type 2 diabetes who are not optimally controlled with short-acting insulin (mealtime insulin), pramlintide can lower HbA_{1C} by 0.5% to 1%.[22] To lower the risk of hypoglycemia, the dose of premeal insulin should be reduced by 50% when pramlintide is initiated. In clinical trials, the use of pramlintide has been associated with modest weight loss.[42] The most common side effect is nausea, which usually subsides with continuation of treatment. The availability of a pen formulation has made pramlintide more user-friendly; however, the future of this drug class is still uncertain because of its cost, need for multiple injections, and relatively modest therapeutic profile.

In the Pipeline

A multitude of new compounds with very distinct mechanisms of action are being developed in the United States to be added to the clinician's armamen-

tarium for the treatment of diabetes. A selected number of these emerging compounds are outlined in **Table 7**.

Conclusions

Lifestyle modification is recognized as the mainstay of therapy for diabetes. Metformin is considered the first-line oral antihyperglycemic drug. If immediate lowering of blood glucose level is required, insulin should be used. Exenatide and DPP-4 inhibitors are 2 new classes with favorable weight profiles. Optimal management should focus not only on glycemic control but also on comorbid conditions that often accompany this potentially life-threatening condition, including hypertension, dyslipidemia, and obesity. ■

Disclosure Statement

Dr Felicetta is on the Speaker's Bureau of Merck and sanofi-aventis. Drs Nguyen and Nguyen have no potential or apparent conflict of interest to report.

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Stakeholder Perspective

Evidence-Based Diabetes Management

PAYERS: At a time when the future of the US healthcare system is the subject of a great deal of debate, this excellent review of the current evidence guiding the screening, diagnosis, and treatment of diabetes is indeed timely.

Diabetes is one of the key disease states associated with controllable health impact in terms of future patient disability and system cost. Diabetes illustrates how over time we have been able to identify an etiology and understand the disease process and how it can be slowed, thereby mitigating its long-term effects, albeit without a "cure."

By achieving "adequate control" of glucose, long-term microvascular complications may be delayed or prevented, resulting in a reduction in retinal and renal pathology, cardiac disease, and stroke. These negative end points are devastating in terms of patient disability and catastrophic in term of total downstream costs. Yet despite a robust treatment armamentarium, we fail to achieve adequate control in too many patients.

Through education and promotion of healthy lifestyle (ie, appropriate diet and exercise) we must slow the epidemic of obesity that will swell the future ranks of diabetic patients. We must be vigilant in screening and monitoring at-risk populations to ensure that secondary prevention and early treatment are initiated in a timely manner. Patients must understand their disease and the steps they can take to participate in their care to reduce the likelihood of complications. We must strive to achieve adequate glucose control and blood pressure while monitoring for early signs of renal, retinal, and neuropathic impact.

Because the disease onset and the eventual development of complications may be separated by years if not by decades, physicians and payers involved in early treatment may not benefit from the reductions in complications and may not be responsible for the consequences of poor control. Therefore, through monitoring "process indicators," all payers and providers must be held responsible (using quality control and health plan monitoring measures) for achieving the best possible results to reduce long-term complications. We must allow neither the fractured system nor the misaligned incentives to serve as barriers to achieving the best short- and long-term outcomes for every diabetic patient.

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