Incorporating Incretin-Based Therapies Into Clinical Practice: Differences Between Glucagon-Like Peptide 1 Receptor Agonists and Dipeptidyl Peptidase 4 Inhibitors

JAIME A. DAVIDSON, MD

Type 2 diabetes mellitus (DM) is a prevalent disorder that affects children, adolescents, and adults worldwide. In addition to risks of microvascular disease, patients with type 2 DM often have multiple risk factors of macrovascular disease; for example, approximately 90% of patients with type 2 DM are overweight/obese. Type 2 DM is a complex disease that involves a variety of pathophysiologic abnormalities, including insulin resistance, increased hepatic glucose production, and abnormalities in the secretion of hormones, such as insulin, glucagon, amylin, and incretins. Incretins are gut-derived peptides with a variety of glucoregulatory functions. Incretin dysfunction can be treated with glucagon-like peptide 1 (GLP-1) receptor agonists (eg, exenatide and liraglutide) or inhibitors of dipeptidyl peptidase 4 (DPP-4) (eg, sitagliptin and saxagliptin), the enzyme that degrades GLP-1. The GLP-1 receptor agonists and DPP-4 inhibitors both elevate GLP-1 activity and substantially improve glycemic control. The GLP-1 receptor agonists are more effective in lowering blood glucose and result in substantial weight loss, whereas therapy with DPP-4 inhibitors lowers blood glucose levels to a lesser degree, and they are weight neutral. Treatment with GLP-1 receptor agonists has demonstrated durable glycemic control and improvement in multiple cardiovascular disease risk factors. In addition, unlike insulin or sulfonylureas, treatment with a GLP-1 receptor agonist or a DPP-4 inhibitor has not been associated with substantial hypoglycemia. These factors should be considered when selecting monotherapy or elements of combination therapy for patients with type 2 DM who are overweight/obese, for patients who have experienced hypoglycemia with other agents, and when achieving glycemic targets is difficult.

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BP = blood pressure; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; DM = diabetes mellitus; DPP-4 = dipeptidyl peptidase 4; DURATION = Diabetes therapy Utilization: Researching changes in A1c, weight and other factors Through Intervention with exenatide ONce weekly; FDA = US Food and Drug Administration; FPG = fasting plasma glucose; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide 1; HbA_{1c} = hemoglobin A_{1c}; HDL-C = high-density lipoprotein cholesterol; HOMA-β = homeostasis model assessment of β-cell function; IDF = International Diabetes Federation; LDL-C = low-density lipoprotein cholesterol; LEAD = Liraglutide Effect and Action in Diabetes; PPG = postprandial glucose

From the Division of Endocrinology, University of Texas, Southwestern Medical Center, Dallas.

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Address correspondence to Jaime A. Davidson, MD, 7777 Forest Ln, Ste C204, Dallas, TX 75230 (davidsonmdsbcbglobal.net).

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The International Diabetes Federation (IDF) estimates that the prevalence of diabetes mellitus (DM) is 285 million globally and that this number will increase to 439 million by 2030; nearly 95% of these cases will be type 2 DM.¹⁻³ In the United States, the percentage of adults diagnosed as having DM was 6.5% between 1999 and 2002 and 7.8% between 2003 and 2006⁴; the number of patients with diagnosed and undiagnosed DM will increase to approximately 44 million in 2034.⁵ The US Centers for Disease Control and Prevention estimates that the lifetime risk of developing DM for individuals born in 2000 is 1 in 3 for males and almost 2 in 5 for females. Nearly half of all Latino/Hispanics born in 2000 risk developing diabetes.⁶

Because the risk of coronary heart disease (CHD) within 10 years of the diagnosis of type 2 DM is nearly 20%, DM has been characterized as a CHD risk factor with the same effect as dyslipidemia, smoking, and hypertension.⁷ In addition, DM is associated with a significantly increased risk of stroke, hypertension, blindness, kidney disease, neuropathies, and amputations.² Patients with a diagnosis of diabetes at the age of 40 years will die approximately 14 years earlier than those without the disease.⁶ Unfortunately, despite the recent emphasis on achieving hemoglobin A_{1c} (HbA_{1c}) targets of less than 7.0% recommended by the American Diabetes Association⁸ or 6.5% recommended by the American Association of Clinical Endocrinologists/American College of Endocrinology⁹ and the IDF,¹⁰ as well as control of hyperlipidemia, data from the Framingham Heart Study indicate that individuals with type 2 DM have not experienced decreases in CHD and cardiovascular disease (CVD) risk factors necessary to overcome their increased risks of CVD events.¹¹

Because of a number of factors, type 2 DM is being diagnosed at a younger age at epidemic proportions and may account for 33% or more of cases of DM in children and young adults.¹²⁻¹⁴ The increase in type 2 DM has been paralleled by a similar increase in the prevalence of overweight/obesity.¹³ Approximately one-fifth of US children and two-thirds of adults are either overweight or obese, which is a major factor in the recent increase in newly diagnosed cases of type 2 DM.¹⁵⁻¹⁷ In addition to the relationship between abdominal obesity and the metabolic syndrome in patients with type 2 DM, overweight/obesity is also independently associated with increased risks of CHD and CVD.^{18,19}

The morbidity and mortality of DM are associated with increased health care costs and utilization. In 2007, total medical care costs for DM in the United States exceeded \$170 billion.²⁰ By 2034, annual diabetes-related spending is expected to increase to \$336 billion.⁵ In office practice, the burden of type 2 DM is also seen in the waiting room. Between 1996 and 2006, the percentage of ambulatory visits of adults with DM increased 40%, a number greater than that reported for hypertension (28%) and depression (27%).²¹

As a consequence of the interrelated factors involved in the pathophysiology of type 2 DM, it is important that treatment considerations include the overall effect on the patients' risks of adverse or unwanted effects. For example, although insulin and sulfonylureas decrease HbA_{1c} levels, they are associated with weight gain and hypoglycemia.²² Introduced in 2005 as a new treatment option for patients with type 2 DM, incretin therapy can be divided into 2 classes: (1) glucagon-like peptide 1 (GLP-1) receptor agonists and (2) dipeptidyl peptidase 4 (DPP-4) inhibitors. Incretin therapy offers benefits over many of the other currently available treatments.^{22,23} It significantly lowers HbA_{1c}, fasting plasma glucose (FPG), and postprandial glucose (PPG) levels; does not increase the risk of hypoglycemia; and promotes weight loss or is weight neutral.

This article provides an overview of incretin-based therapies in the treatment of patients with type 2 DM, specifically focusing on the similarities and differences between GLP-1 receptor agonists and DPP-4 inhibitors while discussing recent evidence of the specific benefits offered by both classes of incretins.

DIABETES CARE: THERE IS ROOM FOR IMPROVEMENT

Intensive treatment targeted to achieving an HbA_{1c} level less than 7.0% substantially decreases the incidence of microvascular disease in patients with DM.²⁴⁻²⁷ However, the effect of intensive therapy on macrovascular disease is still unclear; epidemiological evidence and data from recent trials suggest there are benefits, particularly if treatment is initiated early in the course of the disease and in patients with a shorter duration of DM (less burden of CHD).²⁸⁻³² Two recent meta-analyses of clinical studies that evaluated intensive vs standard therapy and the risk of cardiovascular outcomes concluded that intensive therapy significantly reduced the risk of cardiovascular events but not cardiovascular death or all-cause mortality.^{33,34}

Continued research on the pathophysiology and potential new treatments for patients with type 2 DM is warranted despite improved efforts to reach glycemic targets. Although the mean levels of HbA_{1c} in patients with DM

significantly decreased between 1999 and 2002 and 2003 and 2006 (7.6% vs 7.1%; $P < .05$), only 12% of patients achieve HbA_{1c} (<7.0%), blood pressure (BP) (<130/80 mm Hg), and low-density lipoprotein cholesterol (LDL-C) (<100 mg/dL) goals.⁴

As a means of improving outcomes in patients with type 2 DM, the American Diabetes Association has launched an initiative to reduce cardiovascular risk factors (Figure 1).³⁵ The goal of this initiative is to focus attention on prevention, recognition, and treatment of the modifiable risk factors that comprise the metabolic syndrome (Table 1).¹⁸ Clinicians are further encouraged to promote lifestyle changes that can prevent or delay onset of type 2 DM and optimize glycemic control as well as take measures to prevent complications of diabetes.⁸

TREATING TYPE 2 DM WITH INCRETIN THERAPY

Type 2 DM is the result of interactions among elements of a complex array of metabolic abnormalities. Although the spectrum of metabolic alterations includes insulin resistance in muscles and in the liver plus progressive β -cell failure (the classic triad), 5 additional elements make substantial contributions to the development and evolution of the disease: (1) alterations in enteroendocrine physiology, (2) increased lipolysis in fat cells, (3) increased glucagon secretion, (4) increased renal reabsorption of glucose, and (5) central nervous system insulin resistance with appetite dysregulation.²³ Because of the relationship of these 8 factors to the pathophysiology of type 2 DM and its associated morbidity and mortality, they have been referred to as the "ominous octet."²³

These 8 interrelated factors have important implications for optimizing outcomes in patients with type 2 DM. First, multiple abnormalities suggest that several drugs may be required to correct the abnormal pathophysiology. Second, treatment must not only address surrogate markers of disease, such as elevated HbA_{1c} levels, but also known pathogenic mechanisms. Finally, to prevent or slow progressive deterioration in β -cell function, the interval between onset of type 2 DM (time zero) and its diagnosis must be shortened so that treatment can be instituted earlier. In recognition of these imperatives, treatment should include a combination of interventions.²³

In the 1960s, data suggested that enteral glucose elicited a much greater secretion of insulin than an isoglycemic amount of glucose administered intravenously.³⁶⁻³⁸ This potentiation of insulin secretion by the gut was referred to as the *intestinal secretion* of insulin or incretin effect. The incretin effect is due to 2 enteroendocrine hormones: glucose-dependent insulinotropic polypeptide (GIP) and GLP-1.³⁸ GIP is a 42-amino acid polypeptide synthesized

FIGURE 1. Factors that contribute to cardiometabolic risk: insulin resistance syndrome, overweight/obesity, abnormal lipid metabolism, age, gender, race, family history, smoking, hypertension, and inflammation or hypercoagulation. ApoB = apolipoprotein B; BP = blood pressure; CVD = cardiovascular disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

From *DOC News*,³⁵ with permission from the American Diabetes Association.

by K cells in the proximal small intestine,³⁷ and GLP-1 circulates as 2 equipotent 29- and 30-amino acid polypeptides released by enteroendocrine L cells in the small intestine and colon. Once secreted, incretins bind to distinct G-protein-coupled receptors on target tissues. Although GIP receptors have limited expression, GLP-1 receptors are widely distributed in α and β cells of the islets, central and peripheral nervous system, heart, endothelium, kidneys, lung, and gastrointestinal tract.³⁷ Experimentally,

acute disruption of GLP-1, but not GIP, leads to an increased level of fasting hyperglycemia.^{37,39} Furthermore, although GIP makes an important contribution to PPG homeostasis, its insulin modulatory properties are attenuated in patients with type 2 DM. Physiologic actions of GLP-1 include enhanced glucose-dependent insulin secretion, suppression of inappropriate glucagon secretion, regulation of gastric emptying, appetite suppression, weight reduction, β -cell proliferation, and neogenesis.³⁸ After release, the circulat-

TABLE 1. Criteria for the Metabolic Syndrome^a

Measure	Categorical cut points
Elevated waist circumference ^b	Population- and country-specific definitions
Elevated levels of triglycerides (drug treatment for elevated levels of triglycerides is an alternate indication ^c)	≥ 150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C levels is an alternate indication ^c)	< 40 mg/dL (1.0 mmol/L) in males and < 50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥ 130 mm Hg and/or diastolic ≥ 85 mm Hg
Elevated fasting glucose level ^d (drug treatment of elevated glucose levels is an alternate indicator)	≥ 100 mg/dL

^a HDL-C = high-density lipoprotein cholesterol.

^b It is recommended that the International Diabetes Federation (IDF) cut points be used for non-Europeans and either the IDF or American Heart Association/National Heart, Lung, and Blood Institute cut points used for people of European origin until more data are available.

^c The most commonly used drugs for elevated triglycerides and reduced HDL-C levels are fibrates and nicotinic acid. A patient taking one of these drugs can be presumed to have high triglycerides and low HDL-C levels. High-dose ω -3 fatty acids presume high levels of triglycerides.

^d Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the proposed criteria.

From *Circulation*,¹⁸ with permission from Lippincott Williams & Wilkins.

FIGURE 2. Modulating the incretin system: glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors available and in development. DM = diabetes mellitus.

^a Approved in the United States.

^b Approved in Europe.

Data from *Curr Pharm Des*⁵⁰ and *Mol Endocrinol*.⁵¹

ing levels of both GIP and GLP-1 rapidly decrease.³⁷ This is due to degradation by the ubiquitous cell surface serine peptidase DPP-4 and by glomerular filtration and renal tubular catabolism.⁴⁰⁻⁴²

There is significant attenuation of the insulinotropic effects of GLP-1 in patients with impaired glucose tolerance and patients with type 2 DM.^{43,44} Although the activity of GIP is also diminished, it is secreted in nearly normal amounts.⁴⁴ In addition, patients with type 2 DM show a small but significant decrease in their GLP-1 response to a meal.⁴⁴ Furthermore, patients with the disease have hyperglucagonemia that is refractory to glucose administration but that responds to GLP-1.⁴⁵ It has been postulated that GLP-1 deficiency contributes to the consistent decline in β -cell function that occurs during the course of type 2 DM.³⁸ Exogenous GLP-1, but not GIP, exerts potent glucose-lowering activity in patients with the disease. The potential benefits of restoring GLP-1 physiologic function has made the peptide a focus of efforts to correct the multiple metabolic abnormalities in patients with type 2 DM.

GLP-1 RECEPTOR AGONISTS AND DPP-4 INHIBITORS

The US Food and Drug Administration (FDA) approved exenatide, the first GLP-1 receptor agonist, in April 2005;

sitagliptin, the first commercial DPP-4 inhibitor, was approved 18 months later.⁴³ Both drugs are indicated as adjuncts to diet and exercise to improve glycemic control in adults with type 2 DM and are approved for use as monotherapy and in combination with metformin, sulfonylureas, and thiazolidinediones.^{46,47} Of note, as indicated in FDA bulletins, exenatide may be associated with pancreatitis. Saxagliptin was approved in July 2009 and is indicated for use as monotherapy and in combination with metformin, sulfonylureas, and thiazolidinediones.⁴⁸ Liraglutide was approved in January 2010 for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 DM. It can be used as monotherapy or in combination with metformin, a sulfonylurea, or a thiazolidinedione. The concurrent use of liraglutide and insulin has not been studied.⁴⁹ Of importance, as indicated in FDA bulletins, liraglutide may be associated with pancreatitis. Additionally, data from animal studies have associated liraglutide with medullary thyroid cancer; however, the relevance to humans is unknown.

Additional incretin-based therapies have been approved or are being developed (Figure 2).^{50,51} Members of the 2 therapy classes possess similarities and differences as discussed subsequently and in Table 2.^{22,52-59}

GLP-1 RECEPTOR AGONISTS

Exenatide is a synthetic formulation of exendin 4, a peptide identified in the venom of the Gila monster (*Heloderma suspectum*), and has 53% sequence identity with human GLP-1⁶⁰ but is considerably more resistant to DPP-4 degradation. Although the half-life of GLP-1 is less than 2 minutes, exenatide has a terminal half-life of 2.4 hours (with measurable concentrations for approximately 10 hours after dosing)^{46,61} and can be administered twice daily. Exenatide administered once weekly is under FDA regulatory review.

Liraglutide is a GLP-1 receptor agonist with chemical modifications that promote albumin binding and DPP-4 resistance; liraglutide has a half-life of 11 to 13 hours and can be administered once daily.⁵⁶ Ongoing interests in the benefits of GLP-1 receptor agonist have led to the development of albiglutide, lixisenatide, and taspoglutide. The major differences between these agents and native GLP-1 are molecular modifications that improve their pharmacokinetic profiles and allow for less frequent dosing.⁶²

DPP-4 INHIBITORS

Sitagliptin and saxagliptin are selective, once-daily, oral DPP-4 inhibitors.^{47,48} A combination of sitagliptin and metformin is marketed in the United States; a combination of saxagliptin and metformin is under FDA review. Vildagliptin, another DPP-4 inhibitor, is approved in the

TABLE 2. Comparison of GLP-1 Receptor Agonists and DPP-4 Inhibitors^a

Effects/parameters	GLP-1 receptor agonists	DPP-4 inhibitors
Route of administration	Subcutaneous injection	Oral
Dosing/timing of administration	Once or twice daily ^b	Once daily
Insulin secretion	Enhanced ^c	Enhanced
HbA _{1c} reduction	−0.6% to −1.9% ^c	−0.5% to −0.8%
Postprandial hyperglycemia	Reduced ^c	Reduced
Glucagon secretion	Suppressed ^c	Suppressed
Body weight	Reduced	Neutral
Appetite	Suppressed ^c	No effect
Gastric emptying	Slowed significantly ^c	No effect
Hypoglycemia	Low rates	Low rates
GI AEs	Nausea, diarrhea	No significant GI AEs
CVD risk factors	Improved (with weight loss)	No consistent change

^a AEs = adverse events; CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase 4; GI = gastrointestinal; GLP-1 = glucagon-like peptide 1; HbA_{1c} = hemoglobin A_{1c}.

^b Exenatide once weekly has been submitted to the US Food and Drug Administration for regulatory review.

^c In head-to-head clinical studies, exenatide or liraglutide had a greater effect on these parameters than did the DPP-4 inhibitor sitagliptin.^{53,58,59}

Information derived from Nathan et al,²² Buse et al,⁵² DeFronzo et al,⁵³ Drucker et al,⁵⁴ Kendall et al,⁵⁵ Madsbad,⁵⁶ and Triplitt et al.⁵⁷

European Union and other countries, including Australia, for twice-daily administration and is currently under FDA regulatory review.⁵⁵ The DPP-4 inhibitors in clinical development include alogliptin, linagliptin, and ARI-2243. Interestingly, although ARI-2243 inhibits DPP-4, it also improves glucose tolerance in DPP-4 null mice, indicating that ARI-2243 may affect enzymes other than DPP-4.⁶²

KEY DIFFERENCES BETWEEN GLP-1 RECEPTOR AGONISTS AND DPP-4 INHIBITORS

Table 2 lists the key differences between the 2 classes of incretin-based therapies. Because the insulinotropic activity of incretins is glucose dependent, treatment as monotherapy or in combination with nonsulfonylurea oral agents is not associated with substantial hypoglycemia.^{46,63}

COMPARATIVE CLINICAL TRIALS

The key differences between the 2 classes have been observed in clinical trials. In a double-blind, randomized, multicenter, crossover trial (N=61), the effects of 2 weeks of twice-daily exenatide and sitagliptin were compared in metformin-treated adults with type 2 DM.⁵³ Both drugs similarly decreased FPG; however, exenatide lowered the 2-hour PPG level by a significant −75 mg/dL (to convert to g/L, multiply by 10) more than sitagliptin (133 vs 208 mg/dL; *P*<.0001).⁵³ After crossover, the 2-hour PPG level increased by +73 mg/dL in patients switched to sitagliptin and decreased by −76 mg/dL in those who had initially been treated with the DPP-4 inhibitor (*P*<.0001).⁵³ Furthermore, exenatide twice daily significantly slowed gastric emptying, whereas sitagliptin had no effect (*P*<.0001).⁵³ After 2 weeks of treatment with the GLP-1 receptor agonist, the

total caloric dinner time intake was decreased by −134 kcal vs baseline. However, patients who received the DPP-4 inhibitor increased their caloric intake during the test meal by almost an identical amount.⁵³

In the Diabetes therapy Utilization: Researching changes in A1c, weight and other factors Through Intervention with exenatide ONce weekly (DURATION) 2 trial, a 26-week study of exenatide once weekly (n=160) vs sitagliptin (n=166) vs pioglitazone (n=165), exenatide therapy resulted in a significantly greater reduction of HbA_{1c} compared with sitagliptin (−1.55% vs −0.92%; between-group difference, −0.63%; *P*<.05) and produced a 2-fold greater lowering of FPG (−32 vs −16 mg/dL [to convert to g/L, multiply by 10]; *P*<.05).⁵⁸ Other data suggest that these glycemic benefits reflect the difference between exenatide's pharmacological elevation of circulating GLP-1 (or equivalent) levels by 6- to 10-fold and the more physiologic 2- to 3-fold increase in GLP-1 activity with sitagliptin.^{47,63} In addition, after 26 weeks, patients treated with exenatide once weekly lost 1.8 kg more than those who received daily sitagliptin (*P*<.05).⁵⁸

Liraglutide was also compared with sitagliptin in a randomized, parallel-group, open-label trial in patients with type 2 DM inadequately controlled with metformin, who had a mean baseline HbA_{1c} level of 8.5%. Patients were randomized to receive 1.2 mg (n=221) or 1.8 mg (n=218) of liraglutide once daily or 100 mg of sitagliptin (n=219) daily for 26 weeks. A greater decrease in HbA_{1c} level from baseline was seen with liraglutide, 1.2 mg (−1.24%; 95% confidence interval [CI], −1.37 to −1.11) and 1.8 mg (−1.5%; 95% CI, −1.63 to −1.37), than with sitagliptin (−0.9%; 95% CI, −1.03 to −0.77). Estimated mean treatment differences for liraglutide vs sitagliptin were −0.34%

for 1.2 mg ($P<.0001$) and -0.6% for 1.8 mg ($P<.0001$). Nausea was more common with liraglutide (21% with the 1.2-mg dose and 27% with the 1.8-mg dose) than with sitagliptin (5%), and minor hypoglycemia was observed in approximately 5% of patients in each treatment group.⁵⁹

Comparative studies have also demonstrated the benefits of GLP-1 receptor agonist therapy vs DPP-4 inhibition on β -cell function. In a 2-week crossover study, exenatide significantly improved insulinogenic index compared with sitagliptin ($P=.02$) and the rate of insulin secretion over 30 minutes vs sitagliptin ($P=.0017$).⁵³ Although both drugs decreased the mean plasma glucagon concentration from baseline, the GLP-1 receptor agonist produced a significantly greater reduction ($P=.0011$).⁵³ Both exenatide and sitagliptin reduced postprandial triglyceride concentrations; however, the decrease was significantly greater with exenatide vs sitagliptin ($P=.0118$). Nausea was the most common adverse event reported with each drug, and no major episodes of hypoglycemia were reported.^{53,58}

NONCOMPARATIVE CLINICAL TRIALS

Effects on Glycemic Control. GLP-1 Receptor Agonists. A meta-analysis of the effects of GLP-1 receptor agonists showed that these pharmacotherapies decrease HbA_{1c} levels by -0.97% (95% CI, -1.13 to -0.81).⁴³ Compared with placebo-treated patients, exenatide-treated patients were more likely to achieve HbA_{1c} levels less than 7.0%.

Three 30-week, double-blind, placebo-controlled trials were conducted to assess the efficacy and safety of exenatide twice daily in the treatment of patients with type 2 DM ($N=1446$) suboptimally controlled with sulfonylureas and/or metformin.⁶⁴⁻⁶⁶ Patients continued with their oral hypoglycemic drug and were randomized to receive exenatide in dosages of either 5 or 10 μg twice daily or placebo. At the conclusion of the trials, levels of HbA_{1c} were significantly reduced by -0.8% to -0.9% in both exenatide treatment arms vs placebo ($P\leq.001$). Exenatide at 10 μg twice daily lowered HbA_{1c} levels by -1.3% vs little change with placebo ($P<.05$) in patients with baseline HbA_{1c} levels 9.0% or higher; in patients with baseline HbA_{1c} levels less than 9.0%, reductions were nearly -0.6% vs up to $+0.3\%$ with placebo ($P<.01$).⁶⁴⁻⁶⁶

With regard to exenatide once weekly, a 30-week trial ($n=148$) provided significantly greater improvements in glycemic control than exenatide twice daily ($n=147$) with HbA_{1c} reductions of -1.9% vs -1.5% ($P=.0023$). Reductions in body weight (-3.7 vs -3.6 kg) were similar between the 2 treatment groups. There was no increased risk of hypoglycemia with the once-weekly formulation (1 case among 186 patients not receiving background sulfonylurea therapy and approximately 15% in each exenatide group receiving background sulfonylurea).⁵⁴ The improvements

in glycemic control, body weight, and cardiometabolic risk factors associated with exenatide once weekly were sustained during 2 years of treatment.⁶⁷

Liraglutide has been shown to be effective and well tolerated in several clinical trials as monotherapy or in combination with sulfonylureas, metformin, or thiazolidinediones.⁶⁸⁻⁷⁰ Reductions in HbA_{1c} of -1.14% were seen with liraglutide monotherapy after 52 weeks of therapy with 1.8 mg/d compared with -0.51% with 8 mg/d of glimepiride ($P<.0001$), with weight losses up to -3.5 kg. Nausea, which was reported in approximately 30% of patients treated with liraglutide, tended to occur early in therapy and abated as treatment continued.⁶⁸

The phase 3 Liraglutide Effect and Action in Diabetes (LEAD) program involved 6 clinical trials with more than 4400 patients with type 2 DM. The results from the trials showed liraglutide was associated with HbA_{1c} reductions in the range of -0.5% to -1.5% with combination therapy; weight losses ranged from -0.2 to -3.2 kg. Nausea was the most commonly observed adverse effect and decreased in incidence and severity after several weeks of treatment.⁵⁶ Significant improvements in β -cell function as measured by homeostasis model assessment of β -cell function (HOMA- β) and the proinsulin-insulin ratio have been reported in the LEAD program.⁵⁶

In the 26-week, open-label LEAD-6 trial, a once-daily dosage of 1.8 mg of liraglutide ($n=233$) was compared with a twice-daily dosage of 10 μg of exenatide ($n=231$) in patients with type 2 DM not adequately controlled with metformin, a sulfonylurea, or both. Liraglutide was associated with significantly lower HbA_{1c} levels (-1.12% vs -0.79% with exenatide; $P<.0001$),⁵² and both drugs promoted similar weight losses. Nausea was reported in 26% of liraglutide-treated patients and in 28% of exenatide-treated patients. More patients given liraglutide experienced serious (5.1% vs 2.6%) and severe (7.2% vs 4.7%) adverse events.⁵²

DPP-4 Inhibitors. The DPP-4 inhibitors are effective in improving glycemic control when used as monotherapy or in combination.⁶³ DeFronzo et al⁷¹ evaluated the efficacy and safety of saxagliptin vs placebo in 743 patients with type 2 DM inadequately controlled with metformin. Saxagliptin in dosages of 2.5, 5, and 10 mg/d showed statistically significant adjusted mean decreases from baseline to week 24 vs placebo in HbA_{1c} (-0.59% , -0.69% , and -0.58% , respectively, vs $+0.13\%$; all $P<.0001$). Weight reductions and the incidence of hypoglycemic episodes were similar to those with placebo.⁷¹

In a 52-week trial, 50 mg of vildagliptin once daily ($n=56$) or placebo ($n=51$) was added to ongoing metformin therapy with glycemic control evaluated at 12 weeks and 52 weeks.⁷² Vildagliptin lowered HbA_{1c} levels by -0.7% more

than placebo ($P<.0001$) during the first 12 weeks. After 1 year, there was no change in HbA_{1c} reduction with vildagliptin, but HbA_{1c} levels increased in patients receiving placebo such that the between-group difference in change in HbA_{1c} level was -1.1% ($P<.0001$). There were no differences in changes in body weight between the 2 treatment groups after 1 year of therapy (-0.4 kg with vildagliptin and -0.5 kg in the placebo group). Also, there was no significant change in any serum lipid parameter in either of the groups. Cough, nasopharyngitis, and worsening hypertension were reported more often in the vildagliptin group. Reports of hypoglycemia were similar between the 2 treatment groups.⁷²

Sitagliptin ($n=175$) or placebo ($n=178$) was added to ongoing pioglitazone-treated patients with HbA_{1c} levels 7.0% or greater and 10.0% or less and evaluated for 24 weeks.⁷³ Sitagliptin significantly reduced HbA_{1c} levels from baseline compared with placebo (between-group difference mean change from baseline, -0.7% ; $P<.001$).⁷³ There was no increased risk of hypoglycemia with sitagliptin (2 episodes vs 0 with placebo). The number of patients discontinuing the study because of clinical adverse events was higher in the sitagliptin-treated group (5.7% vs 1.1% ; $P<.05$), but the incidence of discontinuations due to drug-related adverse events was the same (0.6%) in each group. The incidence of abdominal pain was higher in patients receiving sitagliptin vs placebo (3.4% vs 0% ; $P<.05$).⁷³

The efficacy and safety of sitagliptin or glipizide were compared in patients with type 2 DM not adequately controlled with metformin.⁷⁴ Patients were randomized to receive sitagliptin ($n=588$) or glipizide ($n=584$) and followed up for 52 weeks. Both treatments resulted in a reduction of HbA_{1c} level of -0.67% . Patients receiving sitagliptin lost weight, with a mean change from baseline of -1.5 kg, whereas patients treated with glipizide gained $+1.1$ kg on average ($P<.001$). The proportion of patients experiencing hypoglycemia was significantly greater with glipizide (32% vs 5% with sitagliptin; $P<.001$).⁷⁴ When combined with pioglitazone, both sitagliptin and vildagliptin produced greater decreases in HbA_{1c} than placebo and allowed more patients to reach glycemic targets of less than 7.0% .⁶¹

Effects of Body Weight and Appetite. GLP-1 Receptor Agonists. A meta-analysis of clinical trials of exenatide showed that treatment was associated with a progressive, dose-dependent weight loss that did not plateau after 30 weeks.⁴³ In a 3-year, open-label extension study involving 217 patients, weight change at week 12 averaged -1.6 kg and continued to progressively decrease during the observation period. At 3 years, the average weight loss was -5.3 kg from baseline ($P<.0001$), with 84% of patients losing weight and 50% of patients losing at least 5% of baseline weight.⁷⁵ Patients treated with liraglutide in the LEAD

program also lost up to -3 kg during weeks 26 to 52.⁵⁶ Significant weight loss has also been reported with liraglutide once daily (1.8 mg) during 2 years compared with glimepiride (-2.7 kg vs $+1.1$ kg; $P<.05$).⁶⁸

Because patients treated with GLP-1 receptor agonists experience nausea, it is reasonable to postulate that weight loss is a consequence of adverse gastrointestinal events. However, it was reported that weight loss also occurs with GLP-1 receptor agonist therapy in patients without severe nausea.^{66,76} In addition, when nausea occurs, it is during the initial weeks of therapy and decreases thereafter, whereas weight loss is progressive, as noted previously.^{43,55,66} Positron emission tomographic scans in humans demonstrate a correlation between peak postmeal GLP-1 levels and neuronal activity associated with satiety and regulation of food intake in the prefrontal cortex and hypothalamus.⁷⁷ Thus, the effects of GLP-1 receptor agonist therapy on appetite appear to be, at least in part, central in origin.⁶³

DPP-4 Inhibitors. In a meta-analysis of 13 trials reporting data on body weight changes with DPP-4 inhibitors, body weight increased slightly compared with placebo.⁴³ In noninferiority trials, sitagliptin and vildagliptin had favorable weight profiles compared with glipizide and the thiazolidinediones, respectively, but not compared with metformin.⁴³ A 54-week study randomized 1901 patients to receive placebo, sitagliptin or metformin monotherapy, or combination metformin and sitagliptin therapy. The combination regimen, as well as metformin monotherapy, was associated with weight loss; however, there was no change in weight with sitagliptin monotherapy.⁷⁸

Effects of BP and Lipids. GLP-1 Receptor Agonists. Exenatide has been reported to decrease systolic BP (up to -3.7 mm Hg) and diastolic BP (up to -2.3 mm Hg).⁷⁹ Okerson et al⁸⁰ analyzed the effects of exenatide vs placebo or insulin on BP measurements from pooled data from 6 clinical trials, including 2171 patients studied for 6 months or longer. They found that overall exenatide was associated with a significantly greater reduction of systolic BP compared with placebo (difference of -2.8 mm Hg; $P=.0002$) or insulin (difference of -3.7 mm Hg; $P<.0001$). No significant group differences in diastolic BP were observed. Most intergroup differences were observed in patients with systolic BP of 130 mm Hg or higher, and the largest differences were observed in patients with systolic BP of 150 mm Hg or higher.

Decreases in systolic BP with liraglutide were in the 0.6 -to 7.9 -mm Hg range.⁷⁹ In the meta-analysis of the LEAD-1, -2, and -5 trials, liraglutide was associated with a reduction of systolic BP of 1.9 to 4.5 mm Hg. No change in diastolic BP was observed.⁵⁶ Changes in BP have not been reported with DPP-4 inhibitor treatment.⁷⁹

In a meta-analysis of 3 trials that evaluated the effects of GLP-1 receptor agonists on lipids during 12 to 52 weeks,

small or inconsistent effects of the drugs on diabetic dyslipidemia were reported.⁴³ After 3 years of exenatide therapy in 151 patients for whom data were available, exenatide resulted in the following mean changes from baseline: total cholesterol, -5.0% ($P=.0007$); LDL-C, -6.0% ($P<.0001$); triglycerides, -12% ($P<.0003$); and high-density lipoprotein cholesterol (HDL-C), $+24\%$ ($P<.0001$). Two years of treatment with exenatide once weekly also produced significant improvements in systolic BP (-3.2 mm Hg; 95% CI, -5.5 to -0.8 mm Hg), total cholesterol (-9.7 mg/dL; 95% CI, -16.4 to -2.9 mg/dL), and triglycerides (-18% ; 95% CI, -24% to -12%).⁶⁷

In LEAD-4, liraglutide, 1.8 mg, was associated with reductions in lipid parameters compared with placebo. The mean change from baseline in 533 patients evaluated after 24 weeks was as follows: total cholesterol, -77.2 mg/dL; LDL-C, -8.9 mg/dL; HDL-C, -1.5 mg/dL; and triglycerides, -28.3 mg/dL.⁷⁰

DPP-4 Inhibitors. A systematic review and meta-analysis of incretin therapy in patients with type 2 DM⁴³ summarized 14 trials that evaluated the effects of DPP-4 on lipid levels. Although the data showed no consistent effect, there was an overall favorable trend on levels of triglycerides, HDL-C, and LDL-C. In a study of sitagliptin added to metformin therapy, sitagliptin was associated with reductions in triglycerides (-4.8% ; $P\leq.05$ vs placebo) and increases in HDL-C ($+4.3\%$), LDL-C ($+11.4\%$), and total cholesterol ($+4.9\%$; $P\leq.05$ vs placebo) during 26 weeks of therapy in patients with type 2 DM.⁸¹ Raz et al⁸² showed no significant between-group differences in fasting blood lipid levels between sitagliptin vs placebo in 521 patients with type 2 DM treated for 30 weeks. In a study of 19 patients with mild-to-moderate hypertension but without DM who were taking stable antihypertensive medication, 5 days of sitagliptin produced significant but small reductions in 24-hour systolic BP (-2.0 to -2.2 mm Hg) and diastolic BP (-1.6 to -1.8 mm Hg) compared with placebo ($P<.05$).⁸³

Saxagliptin or placebo was added to metformin therapy for 24 weeks in 743 patients with type 2 DM. Mean changes in fasting lipid levels were reported to be the same in the saxagliptin and metformin group compared with the placebo and metformin group.⁷¹ Patients with type 2 DM ($N=401$) naive to drug therapy were treated with saxagliptin or placebo for 24 weeks.⁸⁴ Saxagliptin resulted in only modest numerical improvements from baseline in total cholesterol and had no clear effects on other fasting lipids.

Durability of Glycemic Control. GLP-1 Receptor Agonists. Because DM is a chronic disorder, durability of a drug's effect on glycemic control, weight, and β -cell function is important when long-term treatment is considered. In an open-label extension trial, the effect of exenatide on glycemic control was shown to be durable for 3 years

or longer.⁷⁵ In a patient population with a mean baseline HbA_{1c} level of 8.2%, 3 years of treatment with exenatide twice daily decreased HbA_{1c} levels -1.0% . In patients with baseline HbA_{1c} levels of 9.0% or higher, the mean reduction of HbA_{1c} after 3 years more than doubled (-2.1%).⁷⁵ A preliminary report also supports the long-term benefits of exenatide once weekly. A total of 75% of patients completing the 30-week controlled trial also finished the 2-year open-label trial. Exenatide once weekly decreased and maintained HbA_{1c} levels by -1.8% .⁶⁷

Liraglutide once daily also improves long-term glycemic control. In the 52-week LEAD-3 trial, liraglutide monotherapy decreased mean HbA_{1c} level -1.14% vs -0.51% with glimepiride.⁵⁶ In an open-label extension of the LEAD-3 trial in which 73% of patients completed an additional 1 year of therapy, for a total of 2 years, liraglutide continued to show glycemic benefits, with significantly more patients achieving an HbA_{1c} level less than 7.0% (58% with liraglutide, 1.8 mg/d, vs 37% with glimepiride, 8 mg/d; $P<.05$).⁶⁸

DPP-4 Inhibitors. Studies also support the long-term benefits of DPP-4 inhibition on glycemic control. For 54 weeks, sitagliptin (100 mg) plus metformin (2000 mg) reduced levels of HbA_{1c} -1.9% from baseline, which was maintained during the entire study period.⁷⁸ When used as monotherapy, sitagliptin maintained a reduction of HbA_{1c} of -1.6% from baseline for the 2-year study period.⁸⁵ Combination therapy with vildagliptin plus metformin has also been shown to significantly decrease HbA_{1c} compared with placebo plus metformin for 52 weeks (between-group difference in HbA_{1c}, -1.1% ; $P<.0001$).⁷² Combined, these studies offer evidence that supports the durability of glycemic control provided by DPP-4 inhibitor monotherapy and combination therapy with metformin.

Effects on β -Cell Function. A characteristic of type 2 DM is the progressive worsening of glycemic control.⁸⁶ After only 3 years of treatment, approximately 50% of patients will require more than 1 drug to control their disease, and after 9 years, only 25% of patients can control their disease with 1 drug.⁸⁷ Loss of glycemic control is due to the progressive loss of β -cell function. This deterioration occurs regardless of whether treatment is with lifestyle intervention, a sulfonylurea, metformin, or insulin.⁸⁷ Thus, the potential to alter the progressive loss of β -cell function is an attractive goal.

GLP-1 Receptor Agonists. Preclinical studies using islet cell lines, normal islets, and rodents have shown that exenatide can improve β -cell function and increase β -cell mass.⁸⁸ Controlled clinical trials have demonstrated that exenatide improves first- and second-phase insulin secretion.^{89,90} In a 1-year trial of metformin-treated patients, administration of exenatide twice daily or insulin glargine produced similar improvements in HbA_{1c} levels ($P=.55$).⁹¹

However, exenatide improved β -cell function as assessed by stimulated C-peptide secretion significantly more than the long-acting insulin ($P < .0001$).⁹¹ This benefit required ongoing therapy; after discontinuation of treatment, β -cell function returned to pretreatment values within 4 weeks in both groups. β -Cell function, as measured by HOMA- β , was significantly improved after 3 years of exenatide therapy in 92 patients for whom data were available (change from baseline, 52.4% to 70.1% at 3 years; $P < .0001$).⁷⁵ In a meta-analysis of the LEAD-1, -2, and -5 studies, liraglutide was found to significantly improve β -cell function as measured by HOMA- β and the proinsulin-insulin ratio.⁵⁶

DPP-4 Inhibitors. The effect of DPP-4 inhibition on β -cell function is less clear. In a systemic review of the literature, sitagliptin significantly improved β -cell physiology vs placebo when measured by HOMA- β , as well as the proinsulin-insulin ratio of secretion.⁹² However, the results could not confirm that the DPP-4 inhibitor provided benefits on the markers beyond those produced by metformin with or without glimepiride or pioglitazone.⁹² Because there are some inherent limitations to assessing the effects of DPP-4 inhibition on β -cell function, additional study seems appropriate.

Incidence of Hypoglycemia. Because GLP-1 stimulates insulin secretion and suppresses glucagon production in a glucose-dependent fashion, its glucose-lowering activity is attenuated as blood glucose approaches the hypoglycemic threshold.⁹³ Therefore, it is reasonable to anticipate that incretin therapy would be associated with a low rate of hypoglycemia. Studies of both GLP-1 receptor agonists and DPP-4 inhibitors confirm that the risk of hypoglycemia with monotherapy is similar to that with placebo.^{22,93} The incidence of hypoglycemia increases when an incretin is administered in combination with a sulfonylurea.^{61,93}

CONCLUSION

Diabetes is a cardiovascular risk factor equivalent and an increasing public health burden. Despite increasing emphasis on achieving targeted HbA_{1c} goals, optimum control of type 2 DM is often inadequate. Consequently, there is an ongoing search for new and improved therapies. Incretin dysfunction is a key element in the pathophysiology of the disease and contributes to multiple components of the ominous octet. Agents are now available that were designed to address the abnormal incretin physiology in patients with type 2 DM. They are divided into 2 classes: (1) GLP-1 receptor agonists that correct the dysfunction by supplying the hormone in pharmacological amounts or (2) DPP-4 inhibitors that restore physiologic levels of GLP-1 by inhibiting its degradation. Because these 2 approaches have important similarities and differences, phy-

sicians treating patients with DM must be aware of factors that might suggest one treatment approach over the other. Agents in both classes have positive effects on glycemic control while minimizing the risk of hypoglycemia. Nausea is associated more with GLP-1 receptor agonist therapy than with DPP-4 inhibitors. Although DPP-4 inhibitors can be administered orally, GLP-1 receptor agonists require subcutaneous administration. Thus, they may be the initial choice when a second oral agent is considered. However, DPP-4 inhibitors have a less significant effect on glycemic control, are weight neutral, and produce minimal changes in other cardiovascular risk factors. Because type 2 DM is a progressive disease and overweight/obesity is a major problem, many patients will be candidates for GLP-1 receptor agonist therapy. These agents have a significantly greater effect on glycemic control, appetite, weight, and other cardiovascular risk factors than do DPP-4 inhibitors. Clinical data suggest that GLP-1 receptor agonists improve β -cell function, whereas the effects of DPP-4 inhibitors are less clear. Clinical outcome trials are needed to assess the effects of these agents on type 2 DM disease progression and risk of cardiovascular events.

CLINICAL PEARLS

- Incretin-based therapies include 2 distinct therapeutic classes: the GLP-1 receptor agonists and the DPP-4 inhibitors.
- There are distinct differences between the GLP-1 receptor agonists and DPP-4 inhibitors that affect their use in patients with type 2 DM.
- Therapy with GLP-1 receptor agonists is accompanied by weight loss; DPP-4 inhibitors are weight neutral.
- Durability of glycemic control for 3 years or longer has been demonstrated with the GLP-1 receptor agonist exenatide in patients continuing to undergo therapy.
- The low risk of hypoglycemia seen with GLP-1 receptor agonists and DPP-4 inhibitors may be important to consider in patients who have experienced hypoglycemia with other antidiabetes agents.

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