

Advances in therapy for type 2 diabetes: GLP-1 receptor agonists and DPP-4 inhibitors

■ ABSTRACT

Type 2 diabetes mellitus (T2DM) is intrinsically connected to overweight and obesity. It is a complex metabolic disorder that predisposes patients to, and is associated with, cardiovascular disease. In addition to the triumvirate of core defects associated with T2DM (involvement of the pancreatic beta cell, the muscle, and the liver), other mechanisms including hyperglucagonemia, accelerated gastric emptying, and incretin deficiency/resistance are also involved. This has led to the development of incretin-based therapies, such as glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors. These newer therapies have beneficial effects on glycosylated hemoglobin A1c (HbA1c) levels, weight, and pancreatic beta-cell function.

■ KEY POINTS

Hormonal deficiencies in T2DM are related to abnormalities in the secretion of amylin, glucagon, and incretin hormones.

In clinical trials, GLP-1 receptor agonists reduced HbA1c levels, had beneficial effects on weight, and caused less hypoglycemia than insulin analogues.

Both GLP-1 receptor agonists and DPP-4 inhibitors improve pancreatic beta-cell function.

Incretin-based therapies have been incorporated into recently updated clinical guidelines for treatment of T2DM.

The prevalence of type 2 diabetes mellitus (T2DM) is increasing exponentially worldwide. According to the Centers for Disease Control and Prevention, more than 23 million Americans had diabetes in 2007.¹ Globally, the prevalence of diabetes, of which T2DM accounts for 90% to 95% of cases,¹ is expected to increase from 171 million in 2000 to 366 million in 2030.² The National Health and Nutrition Examination Survey (NHANES) showed that about 66% of Americans were overweight or obese between 2003–2004.³ Data from a Swedish National Diabetes Register study showed both overweight and obesity as independent risk factors for cardiovascular disease (CVD) in patients with T2DM.⁴

This article presents an overview of the evolving concepts of the pathophysiology of T2DM, with a focus on two new therapeutic classes: the glucagon-like peptide-1 (GLP-1) receptor agonists and the dipeptidyl peptidase-4 (DPP-4) inhibitors.

■ THE PATHOPHYSIOLOGY OF T2DM

The American Association of Clinical Endocrinologists (AACE) describes T2DM as “a progressive, complex metabolic disorder characterized by coexisting defects of multiple organ sites including insulin resistance in muscle and adipose tissue, a progressive decline in pancreatic insulin secretion, unrestrained hepatic glucose production, and other hormonal deficiencies.”⁵ Other defects include accelerated gastric emptying in patients with T2DM, especially those who are obese or who have the disease for a long duration.^{6,7}

Hormonal deficiencies in T2DM are related to abnormalities in the secretion of the beta-cell hormone amylin, the alpha-cell hormone glucagon, and the incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide (GIP).^{8,9} In addition to the triumvirate of core defects associated with T2DM (involvement of the pancreatic beta cell, muscle, and liver), other mechanisms of disease onset have been advanced, including accelerated lipolysis, hyperglucagonemia, and incretin deficiency/resistance.⁹ Also, the rate of basal hepatic glucose production is markedly increased in patients with T2DM, which is closely

correlated with elevations in fasting plasma glucagon concentration.⁹

The incretin effect—the intestinal augmentation of secretion of insulin—attributed to GLP-1 and GIP is reduced in patients with T2DM.¹⁰ The secretion of GIP may be normal or elevated in patients with T2DM while the secretion of GLP-1 is deficient; however, cellular responsiveness to GLP-1 is preserved while responsiveness to GIP is diminished.¹¹

Both endogenous and exogenous GLP-1 and GIP are degraded *in vivo* and *in vitro* by the enzyme DPP-4,¹² a ubiquitous, membrane-spanning, cell-surface aminopeptidase that preferentially cleaves peptides with a proline or alanine residue in the second amino-terminal position. DPP-4 is widely expressed (eg, in the liver, lungs, kidney, lymphocytes, epithelial cells, endothelial cells). The role of DPP-4 in the immune system stems from its exopeptidase activity and its interactions with various molecules, including cytokines and chemokines.¹³

■ INCRETIN-BASED THERAPIES: GLP-1 RECEPTOR AGONISTS AND DPP-4 INHIBITORS

Exenatide is a GLP-1 receptor agonist that is resistant to DPP-4 degradation. Based on preclinical studies, exenatide, which shares a 53% amino acid sequence identity with human GLP-1, is approximately 5,500 times more potent than endogenous GLP-1 in glucose lowering.^{14,15} Among the acute actions of exenatide is glucose-dependent insulinotropism, the end result of which may be a reduced risk of hypoglycemia.¹⁶ This contrasts with insulin secretagogues (eg, sulfonylureas), which increase insulin secretion regardless of glucose concentrations.

Exenatide received US Food and Drug Administration (FDA) approval in 2005 and is indicated for the treatment of patients with T2DM.^{13,17} Exenatide is administered BID as a subcutaneous (SC) injection in doses of 5 or 10 μ g within 1 hour before the two major meals of the day, which should be eaten about 6 hours apart.¹⁸

Approved in 2006, sitagliptin was the first DPP-4 inhibitor indicated for adjunctive therapy to lifestyle modifications for the treatment of patients with T2DM.¹⁷ The recommended dosage of oral sitagliptin is 100 mg QD. A single-tablet formulation of the combination of sitagliptin and metformin was approved by the FDA in 2007.¹⁹ Another DPP-4 inhibitor, saxagliptin, was approved in July 2009 for treatment of patients with T2DM either as monotherapy or in combination with metformin, sulfonylurea, or a thiazolidinedione (TZD).²⁰ The DPP-4 inhibitor vildagliptin is approved in the European Union and Latin America but not in the United States. Vildagliptin is available as a 50-

100-mg daily dosage; it has been recommended for use at 50 mg QD in combination with a sulfonylurea or at 50 mg BID with either metformin or a TZD.¹⁸

■ GLP-1 RECEPTOR AGONISTS AND DPP-4 INHIBITORS IN DEVELOPMENT

Exenatide is currently being evaluated as a once-weekly formulation.^{21,22} Compared with the BID formulation, exenatide once weekly has been shown to produce significantly greater improvements in glycemic control, with similar reductions in body weight and no increased risk of hypoglycemia.²¹

Also undergoing regulatory review is the partly DPP-4-resistant acylated GLP-1 receptor agonist liraglutide.¹³ Liraglutide, a human analogue GLP-1 receptor agonist, has 97% linear amino acid sequence homology to human GLP-1.^{23,24} Based on its prolonged degradation time and resulting 10- to 14-hour half-life, liraglutide is anticipated to be dosed once daily.^{13,25,26}

Other GLP-1 receptor agonists and DPP-4 inhibitors are in varying stages of development.²⁷ Albiglutide is a long-acting GLP-1 receptor agonist that is generated by the genetic fusion of a DPP-4-resistant GLP-1 to human albumin. Based on pharmacokinetic studies, albiglutide has a half-life of 6 to 8 days. AVE0010, an exendin-4-based GLP-1 receptor agonist, was shown in a 28-day T2DM clinical trial to have an affinity four times greater than native GLP-1 for the human GLP-1 receptor.²⁷ Taspoglutide (R1583), a human analogue GLP-1 receptor agonist, was evaluated in three randomized, placebo-controlled studies as a GLP-1 receptor agonist. Alogliptin, a DPP-4 inhibitor currently in development, has been shown to be safe and effective in studies as monotherapy and in combination with other antidiabetes agents.^{28–30}

■ CLINICAL TRIALS: GLP-1 RECEPTOR AGONISTS AND DPP-4 INHIBITORS

This section summarizes clinical trials of GLP-1 receptor agonists and DPP-4 inhibitors. The summary is based on literature published from 2005 to 2009 relevant to phase 3 or 4 T2DM clinical trials with currently available agents, or agents with pending new drug applications.

Table 1 summarizes the data on the effects of the GLP-1 receptor agonists on glucose lowering based on glycosylated hemoglobin (HbA1c) mean changes from baseline, body weight, and hypoglycemia. Eleven studies were identified for exenatide, including three pivotal trials,^{31–33} three insulin-comparator studies,^{34–36} one long-term study,³⁷ one monotherapy study (a use for which it is not currently indicated),³⁸ one head-to-head study with a DPP-4 inhibitor,³⁹ and two studies with exenatide once weekly (which is currently investiga-

TABLE 1
Effects of the GLP-1 receptor agonists on HbA1c, weight, and hypoglycemia in patients with T2DM

Study	Study population/ duration of therapy	Study agents	HbA1c (mean ΔBL)	Weight (mean ΔBL)	Hypoglycemia
EXENATIDE					
DeFronzo 2005 ³¹	Pivotal study in patients receiving MET N = 272/30 wk	E: 5 or 10 µg BID SC PL	E: -0.40% to -0.78% PL: +0.8% (<i>P</i> < .002)	E: -1.6 kg to -2.8 kg PL: -0.3 kg (<i>P</i> < .001)	E vs PL: 5% vs 5%
Kendall 2005 ³²	Pivotal study in patients receiving MET and an SU N = 733/30 wk	E: 5 or 10 µg BID SC PL	E: -0.6% to -0.8% PL: +0.2% (<i>P</i> < .0001)	E: -1.6 kg PL: -0.9 kg (<i>P</i> ≤ .01)	E vs PL: 23% vs 13%
Zinman 2007 ³³	Pivotal study in patients receiving a TZD ± MET N = 233/16 wk	E: 10 µg BID SC PL	E: -0.89% PL: +0.09% (<i>P</i> < .001)	E: -1.75 kg PL: -0.24 kg (<i>P</i> < .001)	E vs PL: 11% vs 7%
Barnett 2007 ³⁴	IN-comparator noninferiority study N = 138/2 16-wk trial periods	E: 10 µg BID SC IN GL: QD titrated to FSG ≤ 5.6 mmol/L	E: -1.36% IN GL: -1.36% (<i>P</i> < .001)	E: -2.0 kg to -2.2 kg IN GL: +1.0 kg to +2.3 kg	E vs IN GL: 15% vs 25%
Heine 2005 ³⁵	IN-comparator study in patients with HbA1c 7.0%–10.0% despite MET and SU N = 551/26 wk	E: 10 µg BID SC IN GL: QD titrated to FBG < 5.6 mmol/L (100 mg/dL)	E: -1.11% IN GL: -1.11%	E: -2.3 kg IN GL: +1.8 kg	E vs IN GL: 7.3 vs 6.3 events/patient-yr
Nauck 2007 ³⁶	IN-comparator study N = 501/52 wk, while continuing with MET and SU	E: 5 µg BID SC for 4 wk, 10 µg thereafter Biphasic IN AS BID SC, titrated to optimal control	E: -1.04% IN AS: -0.89%	E: -2.5 kg IN AS: +2.9 kg (<i>P</i> < .001)	E vs IN AS: 17% vs 25%
Klonoff 2008 ³⁷	Long-term open-label study to assess glycemic control, CV risk, and hepatic injury markers N = 217 completed 3 yr of therapy, N = 151 completed 3.5 yr of therapy	E: 5 or 10 µg BID SC for 30 wk, then 5 µg BID SC for 4 wk, then 10 µg BID SC for ≥ 3 yr	At 3 yr: E: -1.0% (<i>P</i> < .0001) At 3.5 yr: E: -0.8% (<i>P</i> < .0001)	At 3 yr: E: -5.3 kg (<i>P</i> < .0001) At 3.5 yr: E: -5.3 kg (<i>P</i> < .0001)	Hypoglycemia with E, usually mild to moderate: 40%
Moretto 2008 ³⁸	Monotherapy study N = 232/24 wk	E: 5 or 10 µg BID SC PL	E: -0.7% to -0.9% PL: -0.2%	E: -2.8 kg to -3.1 kg PL: -1.4 kg	E vs PL: 4% vs 1%
DeFronzo 2008 ³⁹	First clinical head-to-head study between a GLP-1 receptor agonist and a DPP-4 inhibitor, in patients receiving MET N = 61/crossover study with two treatment periods of 2 wk preceded by 1-wk PL lead-in and no interval washout	E: 5 µg BID SC for 1 wk, then 10 µg BID SC for 1 wk ST: 100 mg QD PO for 2 wk	E: -15 mg/dL (FPG) ST: -19 mg/dL (FPG) (<i>P</i> = .3234)	E: -0.8 kg ST: -0.3 kg (<i>P</i> = .0056)	No major hypoglycemic events with E or ST

Table continues on next page

tional).^{21,22} Five primary efficacy studies with liraglutide were also identified.^{23,25,26,40,41}

Table 2 summarizes the corresponding data for the DPP-4 inhibitors. Ten studies with sitagliptin were identified, including four monotherapy studies,^{42–45} one head-to-head study with a GLP-1 receptor agonist,³⁹ and five studies in which sitagliptin was used in combination or as add-on therapy.^{46–50} Five saxagliptin studies are reviewed, including two in which saxagliptin was used in combination with metformin and one in combination with glyburide.^{51–55} Six studies with vildagliptin were reviewed,^{56–61} but no trials specific to the single-tablet formulation of sitagliptin plus metformin were identified.

Effects on HbA1c and weight

GLP-1 receptor agonists reduced HbA1c. Based on the studies reviewed in **Table 1**, exenatide BID reduced baseline HbA1c by a maximum of -1.5% at 30 weeks.^{21,31,32} Exenatide has demonstrated sustained reductions in HbA1c of -0.8% for up to 3.5 years in an open-label extension trial.³⁷ Even greater reductions in HbA1c (-1.4% at 15 weeks and -1.9% at 30 weeks) have been reported with the once-weekly formulation under clinical development.^{21,22} Liraglutide, another GLP-1 receptor agonist under development, has reported HbA1c reductions from baseline up to -1.67% at 14 weeks,^{40,41} up to -1.1% at 26 weeks,^{23,26} and up to -1.14% at 52 weeks.²⁵ The reductions quoted generally

TABLE 1 (continued)**Effects of the GLP-1 receptor agonists on HbA1c, weight, and hypoglycemia in patients with T2DM**

Study	Study population/ duration of therapy	Study agents	HbA1c (mean Δ BL)	Weight (mean Δ BL)	Hypoglycemia
Kim 2007 ²²	Pilot study of E once weekly ^a N = 45/15 wk	E: 0.8 or 2.0 mg QW SC PL	E QW: -1.4% to -1.7% PL: $+0.4\%$ ($P < .0001$)	E QW: -3.8 kg PL: 0 kg ($P < .05$)	E QW vs PL: 25% vs 0%
Drucker 2008 ²¹	DURATION-1 study: E QW ^a vs E BID N = 295/30 wk	E: 2 mg QW SC E: 10 μ g BID SC	E QW: -1.9% E BID: -1.5% ($P = .023$)	E QW: -3.7 kg E BID: -3.6 kg ($P = .89$)	No major hypoglycemic events with E QW or E BID
LIRAGLUTIDE^a					
Vilsbøll 2007 ⁴¹	Placebo-controlled study N = 165/14 wk	L: 0.65, 1.25, or 1.90 mg QD SC PL	L: -0.98% to -1.45% PL: $+0.29\%$ ($P < .0001$)	L: -2.99 kg PL: -1.78 kg ($P = .390$ for L 1.90 mg)	No major or minor hypoglycemic events with L or PL
Seino 2008 ⁴⁰	Dose-response study in Japanese patients treated with diet \pm oral agents N = 226/14 wk	L: 0.1, 0.3, 0.6, or 0.9 mg QD SC PL	L: -0.72% to -1.67% PL: $+0.09\%$	L: -0.48 kg to $+0.13$ kg PL: -0.95 kg	No major or minor hypoglycemic events with L or PL
Nauck 2009 ²⁶	LEAD-2 study N = 1,091/26 wk, in combination with MET and in patients previously treated with oral agents	L: 0.6, 1.2, or 1.8 mg/d QD SC G: 4 mg QD PO PL	L: -0.7% to -1.0% G: -1.0% PL: $+0.1\%$	L: -1.8 kg to -2.8 kg G: $+1.0$ kg PL: -1.5 kg ($P < .0001$ vs G; $P \leq .01$ vs PL)	No major hypoglycemic events with L, G, or PL
Garber 2009 ²⁵	LEAD-3-Mono N = 746/52 wk, as monotherapy	L: 1.2 or 1.8 mg QD SC G: 8 mg QD PO	L: -0.84% to -1.14% G: -0.51% ($P < .001$)	L: -2.0 kg to -2.5 kg G: $+1.0$ kg	No major hypoglycemic events with L or G
Marre 2009 ²³	LEAD-1 SU N = 1,041/26 wk, added to SU (G) 2–4 mg/d	L: 0.6, 1.2, or 1.8 mg QD SC + R PL R = L PL + R 4 mg/d PL = L PL + R PL	L: 1.2 mg or 1.8 mg: -1.1% ($P < .0001$) R: -0.4% ($P < .0001$) PL: $+0.2\%$	L: 1.2 mg or 1.8 mg: -0.2 kg to $+0.7$ kg R: $+2.1$ kg PL: $+0.1$ kg	Minor hypoglycemia: $< 10\%$ for all

^a Both the parenterally administered once-weekly formulation of exenatide and QD liraglutide are under regulatory review with pending new drug applications; exenatide was granted US Food and Drug Administration approval in 2005 and is currently available only as a BID formulation.^{13,17,19}

AS = aspartate; BID = twice daily; CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; DURATION-1 = Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention with Exenatide Once Weekly-1; E = exenatide; FBG = fasting blood glucose; FPG = fasting plasma glucose; FSG = fasting serum glucose; G = glimepiride; GL = glargine; GLP-1 = glucagon-like peptide-1; HbA1c = glycosylated hemoglobin; IN = insulin; L = liraglutide; LEAD = Liraglutide Effects and Actions in Diabetes; MET = metformin; PL = placebo; PO = by mouth; QD = once daily; QW = once weekly; R = rosiglitazone; ST = sitagliptin; SC = subcutaneous; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione; Δ BL = change from baseline.

refer to means, and individual patients may have greater or lesser responses. Also, baseline HbA1c is a significant determinant of the potential HbA1c reduction. Higher baseline values drop more significantly than do baseline values that are closer to normal.

Weight reduction with GLP-1 receptor agonists. In addition to effective glucose lowering, the GLP-1 receptor agonists, particularly exendin-4 agonists, produced beneficial effects on weight (Table 1). Exenatide BID elicited mean weight reductions up to -3.6 kg at 30 weeks^{21,31,32} and -5.3 kg at 3.5 years.³⁷ Exenatide once weekly resulted in mean weight reductions of up to -3.8 kg at 15 weeks²² and -3.7 kg at 30 weeks.²¹ Effects on weight with liraglutide varied from a mean

reduction of up to -2.99 kg to a slight gain of up to $+0.13$ kg at 14 weeks^{40,41} and with weight loss of up to -2.8 kg at 26 weeks^{23,26} and up to -2.5 kg at 52 weeks.²⁵ In this review, only exenatide has been assessed in insulin-comparator studies, where it was shown to reduce weight compared with the insulin analogues, which led to weight gain.^{34–36}

Hypoglycemia. Patients receiving exenatide experienced lower rates of hypoglycemia (up to 17%) than patients treated with either insulin glargine or insulin aspart ($\sim 25\%$).^{34,36} The rate of hypoglycemia with exenatide is comparable to that seen with metformin (up to 21%) in a systematic review of oral antidiabetes agents conducted by the Agency for Healthcare Research and

TABLE 2
Effects of DPP-4 inhibitors on HbA1c, weight, and hypoglycemia in patients with T2DM

Study	Study population/ duration of therapy	Study agents	HbA1c (mean ΔBL)	Weight (mean ΔBL)	Hypoglycemia
SITAGLIPTIN^a					
Aschner 2006 ⁴²	Monotherapy N = 741/24 wk	ST: 100 or 200 mg QD PO PL	ST: -0.61% to -0.76% PL: +0.18% (<i>P</i> ≤ .001 vs PL)	ST: -0.1 kg to -0.2 kg (neutral effect) PL: -1.1 kg (<i>P</i> < .001)	ST vs PL: 1% vs 1%
Raz 2006 ⁴⁴	Monotherapy N = 521/18 wk, with inadequate glycemic control on diet and exercise	ST: 100 or 200 mg QD PO PL	ST: -0.36% to -0.48% PL: +0.12%	ST: -0.2 kg to -0.6 kg PL: -0.7 kg	ST vs PL: 1% vs 0%
Scott 2007 ⁴⁵	Monotherapy N = 743/12 wk	ST: 5, 12.5, 25, or 50 mg BID PO GLP: 5 mg/d PO (electively titrated up to 20 mg/d) PL	ST: -0.15% to -0.54% GLP: -0.76% PL: +0.23%	ST: +0.1 kg to +0.4 kg (relative to PL) GLP: +1.3 kg (relative to PL)	ST vs GLP vs PL: 2% vs 17% vs 2%
Nonaka 2008 ⁴³	Monotherapy, in Japanese patients N = 151/12 wk	ST: 100 mg QD PO PL	ST: -0.65% PL: +0.41% (<i>P</i> < .001)	ST: -0.1 kg PL: -0.7 kg	No hypoglycemic episodes with ST or PL
DeFronzo 2008 ³⁹	First clinical head-to-head study between a DPP-4 inhibitor and a GLP-1 receptor agonist, in MET-treated patients N = 61/crossover study with two treatment periods of 2 wk preceded by 1-wk PL lead-in and no interval washout	ST: 100 mg QD PO for 2 wk E: 5 μg BID SC for 1 wk, then 10 μg BID SC for 1 wk	ST: -19 mg/dL (FPG) E: -15 mg/dL (FPG) (<i>P</i> = .3234)	ST: -0.3 kg E: -0.8 kg (<i>P</i> = .0056)	No major hypoglycemic events with ST or E
Charbonnel 2006 ⁴⁶	N = 701/24 wk, added to ongoing MET therapy	ST: 100 mg QD PO PL	ST: -0.67% PL: -0.02% (<i>P</i> < .001)	ST: -0.6 kg to -0.7 kg PL: -0.6 kg to -0.7 kg (both <i>P</i> < .05 vs BL, but <i>P</i> = .835 between groups)	ST vs PL: 1% vs 2%
Rosenstock 2006 ⁵⁰	N = 353/24 wk; added to ongoing TZD (pioglitazone) therapy	ST: 100 mg QD PO PL	ST: -0.85% PL: -0.15%	ST: +1.8 kg PL: +1.5 kg (<i>P</i> = NS)	ST vs PL: 1% vs 0%
Hermansen 2007 ⁴⁷	In patients inadequately controlled with G or G + MET N = 441/24 wk	ST: 100 mg QD PO PL	ST: -0.45% PL: +0.28% (<i>P</i> < .001)	ST: +0.8 kg PL: -0.4 kg (<i>P</i> < .001)	ST vs PL: 12% vs 2%
Nauck 2007 ⁴⁸	In patients inadequately controlled with MET N = 1,172/52 wk	ST: 100 mg QD PO + MET ≥ 1,500 mg/d GLP: 5 mg/d (titrated to 20 mg/d) + MET ≥ 1,500 mg/d	ST: -0.67% GLP: -0.67%	ST: -1.5 kg GLP: +1.1 kg	ST vs GLP: 5% vs 32%
Raz 2008 ⁴⁹	Added to ongoing MET N = 190/30 wk	ST: 100 mg QD PO + MET ≥ 1,500 mg/d PL + MET ≥ 1,500 mg/d	ST: -1.0% PL: 0.0%	ST: -0.5 kg PL: -0.5 kg	ST vs PL: 1% vs 0%
SAXAGLIPTIN^a					
Chacra ⁵¹	Patients inadequately controlled with sulfonylurea N = 768/24 wk	SX: 2.5 or 5 mg/d + GLY 7.5 mg/d PL + GLY: 10 mg/d	SX: -0.54% to -0.64% GLY: +0.08% (<i>P</i> = .0001)	SX: +0.7 kg to +0.8 kg GLY: +0.3 kg	SX: 13.3% to 14.6% GLY: 10.1%
DeFronzo ⁵²	Patients inadequately controlled with MET N = 743/24 wk	SX: 2.5, 5, or 10 mg/d + MET PL + MET	SX: -0.59% to -0.69% MET: +0.13% (<i>P</i> < .0001)	SX: -0.53 kg to -1.43 kg MET: -0.92 kg	< 1% in all groups

Table continues on next page

TABLE 2 (continued)

Effects of DPP-4 inhibitors on HbA1c, weight, and hypoglycemia in patients with T2DM

Study	Study population/ duration of therapy	Study agents	HbA1c (mean Δ BL)	Weight (mean Δ BL)	Hypoglycemia
Jadzinsky ⁵³	Treatment-naïve patients N = 1306/24 wk	SX: 5 or 10 mg/d + MET 500 mg/d SX: 10 mg + PL MET: 500 mg/d (MET titrated up to 2,000 mg/d)	SX + MET: -2.5% SX: -1.7% MET: -2.0% (<i>P</i> < .0001 vs monotherapy)	SX: -1.4 kg to -1.8 kg SX: -1.1 kg MET: -1.6 kg	≤ 2% in all groups
Rosenstock ⁵⁴	Treatment-naïve patients N = 401/24 wk	SX: 2.5, 5, or 10 mg/d PL	SX: -0.43% to -0.54% PL: +0.19% (<i>P</i> < .0001)	SX: -0.1 kg to -1.2 kg PL: -1.4 kg	None confirmed
Rosenstock ⁵⁵	Dose-ranging trial N = 338/12 wk (low-dose) N = 85/6 wk (high-dose)	Low dose: SX: 2.5, 5, 10, 20, 40 mg/d or PL High dose: SX: 100 mg/d or PL	Adjusted mean Δ Low dose: SX: -0.45% to -0.63% (<i>P</i> = .9888) PL: -0.27% High dose: SX: -1.09% PL: -0.36%	Not significant	Two mild cases in high-dose cohort
VILDAGLIPTIN^a					
Dejager 2007 ⁵⁶	Drug-naïve patients N = 632/24 wk	V: 50 mg QD PO V: 50 mg BID PO V: 100 mg QD PO PL	V: -0.8% to -0.9% PL: -0.3% (<i>P</i> < .01)	V: -0.3 kg to -1.8 kg PL: -1.4 kg	No hypoglycemic events with V 50 mg BID or PL; one hypoglycemic event for two patients on V 50 mg QD and one patient on V 100 mg QD
Pan 2008 ⁵⁹	Drug-naïve patients N = 661/24 wk	V: 100 mg/d, given as 50 mg BID PO A: Up to 300 mg/d, given TID PO	V: -1.4% A: -1.3%	V: -0.4 kg A: -1.7 kg (<i>P</i> < .001)	No hypoglycemic events with V or A
Pi-Sunyer 2007 ⁶⁰	Drug-naïve patients N = 354/24 wk	V: 50 mg QD PO V: 50 mg BID PO V: 100 mg QD PO PL	V: -0.5% to -0.8% PL: 0.0	V: 0.0 kg to -0.4 kg PL: -1.4 kg	No confirmed hypoglycemia reported
Schweizer 2007 ⁶¹	Drug-naïve patients with baseline HbA1c 7.5% to 11.0% N = 780/52 wk	V: 100 mg QD PO MET titrated to 2,000 mg QD PO	V: -1.0% MET: -1.4% (<i>P</i> < .001)	V: +0.3 kg MET: -1.9 kg (<i>P</i> < .001)	V vs MET: < 1% for each group
Garber 2007 ⁵⁷	Add-on to TZD (pioglitazone) therapy N = 463/24 wk	V: 50 mg QD PO V: 100 mg QD PO PL	V: -0.8% to -1.0% PL: -0.3%	V: +0.1 kg to +1.3 kg relative to PL PL: +1.4 kg	No severe hypoglycemic events reported with V or PL
Göke 2008 ⁵⁸	N = 463/52-wk extension of a previously published, multicenter, randomized, parallel-group study (Schweizer 2007 ⁶¹)	V: 100 mg QD PO MET: 2,000 mg QD PO	V: -1.0% MET: -1.5% (<i>P</i> < .001)	V: +0.5 kg MET: -2.5 kg	Only one confirmed hypoglycemic event reported with V

^a The orally administered sitagliptin was granted US Food and Drug Administration (FDA) approval in 2006; a single-tablet formulation of the combination of sitagliptin and metformin gained US FDA approval in 2007.^{17,19} Saxagliptin was approved by the FDA in 2009.²⁰ Although used in Latin America and the European Union, vildagliptin has yet to receive regulatory approval in the United States.¹⁸

A = acarbose; BID = twice daily; BL = baseline; DPP-4 = dipeptidyl peptidase-4; E = exenatide; FPG = fasting plasma glucose; G = glimepiride; GLP = glipizide; GLP-1 = glucagon-like peptide-1; GLY = glyburide; HbA1c = glycosylated hemoglobin; MET = metformin; PL = placebo; PO = by mouth; QD = once daily; SC = subcutaneous; ST = sitagliptin; SX = saxagliptin; TID = three times daily; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione; V = vildagliptin; Δ BL = change from baseline.

Quality.⁶² No major hypoglycemic events were reported in the liraglutide studies reviewed. The incidence of hypoglycemia reported with DPP-4 inhibitors (Table 2) is also low (2% or less in most studies). The glucose-dependent mechanisms of the incretin-based therapies minimizes the risk of hypoglycemia.

DPP-4 inhibitors and sustained HbA1c reduction. The effects of the DPP-4 inhibitors on HbA1c and weight, either as monotherapy or in combination with other agents, were evaluated in studies ranging in duration from 12 to 52 weeks (Table 2). No studies were identified that compared the glycemic control effects of DPP-4 inhibitors and insulin analogues. Sitagliptin led to a mean reduction in HbA1c from baseline of up to -0.65% at 12 weeks,^{43,45} up to -0.48% at 18 weeks,⁴⁴ up to -0.85% at 24 weeks,^{42,46,47,50} up to -1.0% at 30 weeks,⁴⁹ and up to -0.67% at 52 weeks.⁴⁸ Saxagliptin mean reductions in HbA1c ranged from -0.43% to -1.17% .⁵¹⁻⁵⁴ Data from four 24-week T2DM studies⁵⁶⁻⁶⁰ showed vildagliptin reducing HbA1c up to -1.4% at 24 weeks, with the greatest reduction in a study that involved drug-naïve patients with a relatively short duration of disease (mean, 1.2 years).⁵⁹ Reductions in HbA1c of -1.0% were sustained in a 52-week study⁶¹ and its 52-week extension.⁵⁸

DPP-4 inhibitors: weight neutral. The DPP-4 inhibitors appear to have a weight-neutral effect (Table 2). The effects of sitagliptin on weight ranged from a loss of -1.5 kg⁴⁸ at 52 weeks to a gain of $+1.8$ kg at 24 weeks.⁵⁰ Weight changes with saxagliptin ranged from a mean reduction of -1.8 kg⁵³ to a gain of $+0.7$ kg.⁵¹ Two vildagliptin studies showed varying effects on weight ranging from a loss of up to -1.8 kg from baseline⁵⁶ to a gain of up to $+1.3$ kg⁵⁷ relative to placebo, both at 24 weeks.

Potential for CV risk reduction

Potentially beneficial effects on CV risk factors, including blood pressure (ie, reduction) and lipid concentrations (ie, differential effects on low-density lipoprotein and high-density lipoprotein cholesterol), were identified in seven GLP-1 receptor studies—three with exenatide (two with exenatide BID,^{37,38} and one with the investigational exenatide once weekly²¹) and four with liraglutide.^{23,25,26,41} For the DPP-4 inhibitors, three studies were identified—two with sitagliptin^{45,50} and one with vildagliptin⁶¹—in which potentially beneficial effects on CV risk factors were demonstrated. The data have been encouraging, although the clinical implications have yet to be fully understood.

Head-to-head comparison

A recent study compared the effects of the GLP-1 receptor agonist exenatide and the DPP-4 inhibitor sitagliptin on postprandial glucose (PPG) concentrations, insulin and glucagon secretion, gastric intake,

and caloric intake.³⁹ Although limited by a short treatment duration (2 weeks), the study showed that the GLP-1 receptor agonist had a greater effect than the DPP-4 inhibitor in reducing PPG concentrations, a more potent effect in increasing insulin secretion and decreasing postprandial glucagon secretion, and a relatively greater effect in reducing caloric intake; and that it decreased the rate of gastric emptying (sitagliptin had no effect). These differences suggest that exenatide may provide a greater degree of GLP-1 receptor activation than the more physiologic concentrations of GLP-1 reached with DPP-4 inhibition.³⁹ Results of a scintigraphic study showed that exenatide substantially slows the gastric emptying that is accelerated in patients with T2DM. This could be another beneficial mechanism in treating postprandial glycemia.⁶³

Adverse effects

Exenatide has shown effects on hepatic injury markers (ie, improvement in alanine and aspartate aminotransferases) for up to 3.5 years of treatment.³⁷ For the GLP-1 receptor agonist and DPP-4 inhibitor studies reviewed, the adverse events were generally mild and included nausea and vomiting, nasopharyngitis, and mild hypoglycemia.

Meta-analysis conclusions

The published clinical trial data presented in this review expand the body of evidence on the safety and efficacy of incretin-based therapy in patients with T2DM. These data include the results of a meta-analysis by Amori et al,¹⁷ which examined randomized controlled trials of 12 weeks' or longer duration that compared incretin-based therapy with placebo or other diabetes medications and reported HbA1c changes in adults with T2DM. The meta-analysis showed that incretin-based therapies reduced HbA1c more than placebo (weighted mean difference, -0.97% [95% confidence interval (CI), -1.13% to -0.81%] for GLP-1 receptor agonists and -0.74% [95% CI, -0.85% to -0.62%] for DPP-4 inhibitors) and were noninferior to other antidiabetes agents. Treatment with a GLP-1 receptor agonist (ie, exenatide) caused weight loss (-1.4 kg and -4.8 kg vs placebo and insulin, respectively) while DPP-4 inhibitors (ie, sitagliptin, vildagliptin) were weight neutral.¹⁷

Beta-cell function

Evidence regarding the effects of incretin-based therapies, particularly the exendin-4 GLP-1 receptor agonists, on beta-cell function in patients with T2DM continues to accumulate. When assessing long-term (1 year) exenatide treatment in patients with T2DM, a trial (n = 69) comparing exenatide with the basal insu-

lin analogue insulin glargine showed that exenatide and insulin glargine resulted in similar reductions in HbA1c (-0.8% vs -0.7% ; $P = .55$).⁶⁴ However, exenatide significantly reduced body weight while insulin glargine resulted in weight gain (-3.6 kg vs $+1.0$ kg; $P < .0001$). In terms of beta-cell function, arginine-stimulated C-peptide secretion during hyperglycemia increased 2.46-fold from baseline after 52 weeks of exenatide treatment compared with 1.31-fold with insulin glargine treatment ($P < .0001$).⁶⁴

With respect to the direct beta-cell effects of liraglutide, a preclinical study reported that liraglutide improved glucose homeostasis in marginal mass islet transplantation in diabetic mice.⁶⁵ In this study, liraglutide was shown, in a mouse model, to reduce the time to normoglycemia after islet cell transplantation (median time, 1 vs 72.5 days; $P < .0001$). The effects of liraglutide on beta-cell function also were assessed in 13 patients with T2DM. After 7 days of treatment, liraglutide improved beta-cell function, which was associated with improvement in glucose concentration.⁶⁶ Liraglutide improved potentiation of insulin secretion during the first meal, owing in part to restoration of the potentiation peak (which is markedly blunted in T2DM), in a phenomenon similar to that observed with exenatide.⁶⁷

Beneficial effects on beta-cell function have also been reported with DPP-4 inhibitors. In a model-based analysis of patients with T2DM, it was shown that sitagliptin improved basal, static, and dynamic responsiveness of pancreatic beta cells to glucose. The results were observed when sitagliptin was administered both as an add-on to metformin therapy and as monotherapy.⁶⁸ A 52-week, double-blind, randomized, parallel-group study compared vildagliptin 50 mg/day and placebo in 306 patients with T2DM and mild hyperglycemia (HbA1c, 6.2% to 7.5%). Vildagliptin was shown to significantly increase fasting insulin secretory tone, glucose sensitivity, and rate sensitivity, all of which are aspects of beta-cell function.⁶⁹

Summary

Based on the ability of incretin-based therapies to address various disease mechanisms, including beta-cell defects (ie, hyperglycemia), hormone-related abnormalities (ie, hyperglucagonemia, incretin deficiency/resistance), and accelerated gastric emptying (especially with GLP-1 receptor agonists); their favorable effects on weight (reduction with GLP-1 receptor agonists and neutral with DPP-4 inhibitors); their beneficial effects on CV risk factors; and their good safety profile (ie, hypoglycemia risk comparable with metformin), these agents could be considered therapeutic advances for the treatment of patients with T2DM.

INCRETIN-BASED THERAPIES IN GUIDELINES AND ALGORITHMS

The 2007 AACE medical guidelines for clinical practice for the management of diabetes recognized the place of the incretin-based therapies and included them among the pharmacologic options.⁵ Exenatide was specifically recommended for combination therapy with metformin, a sulfonylurea (secretagogue), a sulfonylurea plus metformin, or a TZD. Sitagliptin was recommended for use as monotherapy or in combination with metformin or a TZD.⁵

In 2009, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes convened a consensus panel to produce an algorithm for the initiation and adjustment of therapy for patients with T2DM. In this algorithm, GLP-1 receptor agonists were considered appropriate in certain clinical scenarios (eg, when hypoglycemia was an issue or weight loss was a major consideration during treatment). However, the groups also noted a need for more data on long-term safety and the cost of treatment with incretin-based therapies.⁷⁰

The AACE and the American College of Endocrinology recently developed “road maps” for managing patients with T2DM. In patients with T2DM who are naïve to therapy, DPP-4 inhibitors are among the recommended first options when the initial HbA1c is 6.0% to 7.0% and as a combination therapy component when HbA1c reaches 7.0% to 9.0%. In patients who have already received monotherapy for 2 to 3 months and whose HbA1c is 6.5% to 8.5%, treatment options include combination therapy with a DPP-4 inhibitor and metformin or a TZD. Another option includes the initiation of treatment with a GLP-1 receptor agonist in combination with a TZD, with metformin or a sulfonylurea, or with metformin and a sulfonylurea.⁷¹

The role of GLP-1 receptor agonist therapies and their incorporation into T2DM treatment algorithms was noted at the 2008 annual meeting of the ADA. In the Banting lecture, Ralph A. DeFronzo, MD, advocated the early use of triple-drug therapy with metformin, exenatide, and a TZD in the management of patients with T2DM.⁹

CONCLUSION

T2DM, which is linked to weight gain and obesity, is a complex disease that predisposes patients to and is associated with CVD. A better understanding and appreciation of the role of the incretin system in the pathogenesis of T2DM has led to the development of incretin-based therapies, such as the GLP-1 receptor agonists and DPP-4 inhibitors. As more experimental and clinical evidence becomes available, subtle nuances are emerging that distinguish the roles of these two therapeutic classes.

DISCLOSURES

Dr. Davidson reported that he has received grant support from Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, MannKind Corporation, Novo Nordisk, Pfizer Inc., and Sanofi-Aventis; consulting/advisory fees from AstraZeneca, Boehringer Ingelheim GmbH, Bristol-Myers Squibb, Eli Lilly and Company, F. Hoffmann-La Roche Ltd., Genexx Biotechnology Corporation, Johnson & Johnson, Novo Nordisk, and Takeda Pharmaceutical Company Limited; and speakers' bureau fees from Eli Lilly and Company, Novo Nordisk, and Takeda Pharmaceutical Company Limited. He reported that he has stock ownership interest in Eli Lilly and Company, Genexx Biotechnology Corporation, GlaxoSmithKline, and Pfizer, Inc., managed by Royal Alliance Associates, Inc. Dr. Davidson reported that he received no honorarium for writing this article.

Dr. Davidson reported that he wrote this article and received no assistance with content development from unnamed contributors. He reported that BlueSpark Healthcare Communications, a medical communications company, assisted with preliminary literature searches, reference verification, proofing for grammar and style, table and figure rendering based on author instructions, copyright permission requests, and identification of topical overlap with other manuscripts in this supplement.

REFERENCES

- 2007 National Diabetes Fact Sheet. Centers for Disease Control and Prevention Web site. <http://www.cdc.gov/diabetes/pubs/estimates07.htm>. Updated: July 23, 2008. Accessed September 25, 2009.
- Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; 27:1047–1053.
- Prevalence of overweight and obesity among adults: United States 2003–2004. Centers for Disease Control and Prevention Web site. http://www.cdc.gov/nchs/products/pubs/pubd/hestats/overweight/overwght_adult_03.htm. Published: April 2006. Accessed September 23, 2009.
- Eeg-Olofsson K, Cederholm J, Nilsson PM, et al. Risk of cardiovascular disease and mortality in overweight and obese patients with type 2 diabetes: an observational study in 13,087 patients. *Diabetologia* 2009; 52:65–73.
- AACE Diabetes Mellitus Clinical Practice Guidelines Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. *Endocr Pract* 2007; 13(suppl 1):S4–S68.
- Bertin E, Schneider N, Abdelli N, et al. Gastric emptying is accelerated in obese type 2 diabetic patients without autonomic neuropathy. *Diabetes Metab* 2001; 27:357–364.
- Weytjens C, Keymeulen B, Van Haleweyn C, Somers G, Bossuyt A. Rapid gastric emptying of a liquid meal in long-term type 2 diabetes mellitus. *Diabet Med* 1998; 15:1022–1027.
- Stonehouse AH, Holcombe JH, Kendall DM. GLP-1 analogues, DPP-IV inhibitors and the metabolic syndrome. In: Fonseca V, ed. *Therapeutic Strategies in Metabolic Syndrome*. Oxford, UK: Atlas Medical Publishing Ltd; 2008: 137–157.
- DeFronzo RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes* 2009; 58:773–795.
- Nauck M, Stöckmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. *Diabetologia* 1986; 29:46–52.
- Nauck MA, Heimesaat MM, Orskov C, Holst JJ, Ebert R, Creutzfeldt W. Preserved incretin activity of glucagon-like peptide 1 [7-36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. *J Clin Invest* 1993; 91:301–307.
- Deacon CF, Johnsen AH, Holst JJ. Degradation of glucagon-like peptide-1 by human plasma in vitro yields an N-terminally truncated peptide that is a major endogenous metabolite in vivo. *J Clin Endocrinol Metab* 1995; 80:952–957.
- Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 2006; 368:1696–1705.
- Eng J, Kleinman WA, Singh L, Singh G, Raufman J-P. Isolation and characterization of exendin-4, an exendin-3 analogue, from *Heloderma suspectum* venom: further evidence for an exendin receptor on dispersed acini from guinea pig pancreas. *J Biol Chem* 1992; 267:7402–7405.
- Young AA, Gedulin BR, Bhavsar S, et al. Glucose-lowering and insulin-sensitizing actions of exendin-4: studies in obese diabetic (*ob/ob*, *db/db*) mice, diabetic fatty Zucker rats, and diabetic rhesus monkeys (*Macaca mulatta*). *Diabetes* 1999; 48:1026–1034.
- Kolterman OG, Buse JB, Fineman MS, et al. Synthetic exendin-4 (exenatide) significantly reduces postprandial and fasting plasma glucose in subjects with type 2 diabetes. *J Clin Endocrinol Metab* 2003; 88:3082–3089.
- Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. *JAMA* 2007; 298:194–206.
- Davidson JA, Parente EB, Gross JL. Incretin mimetics and dipeptidyl peptidase-4 inhibitors: innovative treatment therapies for type 2 diabetes. *Arq Bras Endocrinol Metabol* 2008; 52:1039–1049.
- Alexander GC, Sehgal NL, Moloney RM, Stafford RS. National trends in treatment of type 2 diabetes mellitus, 1994–2007. *Arch Intern Med* 2008; 168:2088–2094.
- US Department of Health and Human Services. FDA approves new drug treatment for type 2 diabetes. US Food and Drug Administration Web site. <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm174780.htm>. Published July 31, 2009. Accessed September 18, 2009.
- Drucker DJ, Buse JB, Taylor K, et al; for the DURATION-1 Study Group. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet* 2008; 372:1240–1250.
- Kim D, MacConnell L, Zhuang D, et al. Effects of once-weekly dosing of a long-acting release formulation of exenatide on glucose control and body weight in subjects with type 2 diabetes. *Diabetes Care* 2007; 30:1487–1493.
- Marre M, Shaw J, Brändle M, et al; for the LEAD-1 SU Study Group. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with type 2 diabetes (LEAD-1 SU). *Diabetes Med* 2009; 26:268–278.
- Knudsen LB, Nielsen PF, Huusfeldt PO, et al. Potent derivatives of glucagon-like peptide 1 with pharmacokinetic properties suitable for once-daily administration. *J Med Chem* 2000; 43:1664–1669.
- Garber M, Henry R, Ratner R, et al; for the LEAD-3 (Mono) Study Group. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet* 2009; 373:473–481.
- Nauck M, Frid A, Hermansen K, et al; for the LEAD-2 Study Group. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (Liraglutide Effect and Action in Diabetes)-2 study. *Diabetes Care* 2009; 32:84–90.
- Baggio LL, Drucker DJ, Maida A, Lamont BJ. ADA 2008: incretin-based therapeutics. *MedscapeCME Web site*. <http://www.medscape.com/viewprogram/15786>. Accessed September 18, 2009.
- Fleck P, Christopher R, Covington P, Wilson C, Mekki Q. Efficacy and safety of alogliptin monotherapy over 12 weeks in patients with type 2 diabetes. Paper presented at: 68th Annual Meeting of the American Diabetes Association; June 6–10, 2008; San Francisco, CA. Abstract 479-P.
- DeFronzo RA, Burant CF, Fleck P, Wilson C, Mekki Q, Pratley RE. Effect of alogliptin combined with pioglitazone on glycemic control in metformin-treated patients with type 2 diabetes. Paper presented at: 69th Annual Meeting of the American Diabetes Association; June 5–9, 2009; New Orleans, LA. Abstract 2024-PO.
- Nauck M, Ellis G, Fleck P, Wilson C, Mekki Q. Efficacy and safety of alogliptin added to metformin therapy in patients with type 2 diabetes. Paper presented at: 68th Annual Meeting of the American Diabetes Association; June 6–10, 2008; San Francisco, CA.

- Abstract 477-P.
31. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 2005; 28:1092–1100.
 32. Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care* 2005; 28:1083–1091.
 33. Zinman B, Hoogwerf BJ, Durán García S, et al. The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med* 2007; 146:477–485.
 34. Barnett AH, Burger J, Johns D, et al. Tolerability and efficacy of exenatide and titrated insulin glargine in adult patients with type 2 diabetes previously uncontrolled with metformin or a sulfonylurea: a multinational, randomized, open-label, two-period, crossover non-inferiority trial. *Clin Ther* 2007; 29:2333–2348.
 35. Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widell MH, Brodows RG; for the GWAA Study Group. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med* 2005; 143:559–569.
 36. Nauck MA, Duran S, Kim D, et al. A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. *Diabetologia* 2007; 50:259–267.
 37. Klonoff DC, Buse JB, Nielsen LL, et al. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. *Curr Med Res Opin* 2008; 24:275–286.
 38. Moretto TJ, Milton DR, Ridge TD, et al. Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naïve patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther* 2008; 30:1448–1460.
 39. DeFronzo RA, Okerson T, Viswanathan P, Guan X, Holcombe JH, MacConell L. Effects of exenatide versus sitagliptin on postprandial glucose, insulin and glucagon secretion, gastric emptying, and caloric intake: a randomized, cross-over study. *Curr Med Res Opin* 2008; 24:2943–2952.
 40. Seino Y, Rasmussen MF, Zdravkovic M, Kaku K. Dose-dependent improvement in glycemia with once-daily liraglutide without hypoglycemia or weight gain: a double-blind, randomized, controlled trial in Japanese patients with type 2 diabetes. *Diabetes Res Clin Pract* 2008; 81:161–168.
 41. Vilsbøll T, Zdravkovic M, Le-Thi T, et al. Liraglutide, a long-acting human glucagon-like peptide-1 analog, given as monotherapy significantly improves glycemic control and lowers body weight without risk of hypoglycemia in patients with type 2 diabetes. *Diabetes Care* 2007; 30:1608–1610.
 42. Aschner P, Kipnes MS, Luncford JK, Sanchez M, Mickel C, Williams-Herman DE; for the Sitagliptin Study 021 Group. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care* 2006; 29:2632–2637.
 43. Nonaka K, Kakikawa T, Sato A, et al. Efficacy and safety of sitagliptin monotherapy in Japanese patients with type 2 diabetes. *Diabetes Res Clin Pract* 2008; 79:291–298.
 44. Raz I, Hanefeld M, Xu L, Caria C, Williams-Herman D, Khatami H; for the Sitagliptin Study 023 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. *Diabetologia* 2006; 49:2564–2571.
 45. Scott R, Wu M, Sanchez M, Stein P. Efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy over 12 weeks in patients with type 2 diabetes. *Int J Clin Pract* 2007; 61:171–180.
 46. Charbonnel B, Karasik A, Liu J, Wu M, Meininger G; for the Sitagliptin Study 020 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. *Diabetes Care* 2006; 29:2638–2643.
 47. Hermansen K, Kipnes M, Luo E, Fanurik D, Khatami H, Stein P; for the Sitagliptin Study 035 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. *Diabetes Obes Metab* 2007; 9:733–745.
 48. Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP; for the Sitagliptin Study 024 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. *Diabetes Obes Metab* 2007; 9:194–205.
 49. Raz I, Chen Y, Wu M, et al. Efficacy and safety of sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes. *Curr Med Res Opin* 2008; 24:537–550.
 50. Rosenstock J, Brazg R, Andryuk PJ, Lu K, Stein P; for the Sitagliptin Study 019 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther* 2006; 28:1556–1568.
 51. Chacra AR, Tan GH, Apanovitch A, Ravichandran S, List J, Chen R; for the CV181-040 Investigators. Saxagliptin added to a submaximal dose of sulphonylurea improves glycaemic control compared with uptitration of sulphonylurea in patients with type 2 diabetes: a randomised controlled trial. *Int J Clin Pract* 2009; 63:1395–1406.
 52. DeFronzo RA, Hissa MN, Garber AJ, et al. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. *Diabetes Care* 2009; 32:1649–1655.
 53. Jadzinsky M, Pfützner A, Paz-Pacheco E, Xu Z, Allen E, Chen R; for the CV181-039 Investigators. Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial. *Diabetes Obes Metab* 2009; 11:611–622.
 54. Rosenstock J, Aguilar-Salinas C, Klein E, Nepal S, List J, Chen R; for the CV181-011 Study Investigators. Effect of saxagliptin monotherapy in treatment-naïve patients with type 2 diabetes. *Curr Med Res Opin* 2009; 25:2401–2411.
 55. Rosenstock J, Sankoh S, List JF. Glucose-lowering activity of the dipeptidyl peptidase-4 inhibitor saxagliptin in drug-naïve patients with type 2 diabetes. *Diabetes Obes Metab* 2008; 10:376–386.
 56. Dejager S, Razac S, Foley JE, Schweizer A. Vildagliptin in drug-naïve patients with type 2 diabetes: a 24-week, double-blind, randomized, placebo-controlled, multiple-dose study. *Horm Metab Res* 2007; 39:218–223.
 57. Garber AJ, Schweizer A, Baron MA, Rochotte E, Dejager S. Vildagliptin in combination with pioglitazone improves glycaemic control in patients with type 2 diabetes failing thiazolidinedione monotherapy: a randomized, placebo-controlled study. *Diabetes Obes Metab* 2007; 9:166–174.
 58. Göke B, Hershon K, Kerr D, et al. Efficacy and safety of vildagliptin monotherapy during 2-year treatment of drug-naïve patients with type 2 diabetes: comparison with metformin. *Horm Metab Res* 2008; 40:892–895.
 59. Pan C, Yang W, Barona JP, et al. Comparison of vildagliptin and acarbose monotherapy in patients with type 2 diabetes: a 24-week, double-blind, randomized trial. *Diabetologia* 2008; 25:435–441.
 60. Pi-Sunyer FX, Schweizer A, Mills D, Dejager S. Efficacy and tolerability of vildagliptin monotherapy in drug-naïve patients with type 2 diabetes. *Diabetes Res Clin Pract* 2007; 76:132–138.
 61. Schweizer A, Couturier A, Foley JE, Dejager S. Comparison between vildagliptin and metformin to sustain reductions in HbA(1c) over 1 year in drug-naïve patients with type 2 diabetes. *Diabetes Med* 2007; 24:955–961.
 62. Bolen S, Feldman L, Vassy J, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mel-

- litus. *Ann Intern Med* 2007; 147:386–399.
63. **Linnebjerg H, Park S, Kothare PA, et al.** Effect of exenatide on gastric emptying and relationship to postprandial glycemia in type 2 diabetes. *Regul Pept* 2008; 151:123–129.
 64. **Bunck MC, Diamant M, Cornér A, et al.** One-year treatment with exenatide improves beta-cell function, compared with insulin glargine, in metformin-treated type 2 diabetic patients: a randomized, controlled trial. *Diabetes Care* 2009; 32:762–768.
 65. **Merani S, Truong W, Emamaullee JA, Toso C, Knudsen LB, Shapiro AM.** Liraglutide, a long-acting human glucagon-like peptide 1 analog, improves glucose homeostasis in marginal mass islet transplantation in mice. *Endocrinology* 2008; 149:4322–4328.
 66. **Mari A, Degn K, Brock B, Rungby J, Ferrannini E, Schmitz O.** Effects of the long-acting human glucagon-like peptide-1 analog liraglutide on beta-cell function in normal living conditions. *Diabetes Care* 2007; 30:2032–2033.
 67. **Mari A, Nielsen LL, Nanayakkara N, DeFronzo RA, Ferrannini E, Halseth A.** Mathematical modeling shows exenatide improved beta-cell function in patients with type 2 diabetes treated with metformin or metformin and a sulfonylurea. *Horm Metab Res* 2006; 38:838–844.
 68. **Xu L, Man CD, Charbonnel B, et al.** Effect of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on beta-cell function in patients with type 2 diabetes: a model-based approach. *Diabetes Obes Metab* 2008; 10:1212–1220.
 69. **Mari A, Scherbaum WA, Nilsson PM, et al.** Characterization of the influence of vildagliptin on model-assessed β -cell function in patients with type 2 diabetes and mild hyperglycemia. *J Clin Endocrinol Metab* 2008; 93:103–109.
 70. **Nathan DM, Buse JB, Davidson MB, et al.** Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009; 32:193–203.
 71. **Jellinger PS, Davidson JA, Blonde L, et al; for the ACE/AACE Diabetes Road Map Task Force.** Road maps to achieve glycemic control in type 2 diabetes mellitus: ACE/AACE Diabetes Road Map Task Force. *Endocr Pract* 2007; 13:260–268.

Correspondence: Jaime A. Davidson, MD, 7777 Forest Lane, Suite C204, Dallas, TX 75230; davidsonmd@sbcglobal.net