REVIEW

Type 2 diabetes mellitus and the cardiometabolic syndrome: impact of incretin-based therapies

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Abstract: The rates of type 2 diabetes mellitus, obesity, and cardiovascular disease (CVD) continue to increase at epidemic proportions. It has become clear that these disease states are not independent but are frequently interrelated. By addressing conditions such as obesity, insulin resistance, stress hyperglycemia, impaired glucose tolerance, and diabetes mellitus, with its micro- and macrovascular complications, a specific treatment strategy can be developed. These conditions can be addressed by early identification of patients at high risk for type 2 diabetes, prompt and aggressive treatment of their hyperglycemia, recognition of the pleiotropic and synergistic benefits of certain antidiabetes agents on CVD, and thus, avoiding potential complications including hypoglycemia and weight gain. Incretin-based therapies, which include glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-IV (DPP-IV) inhibitors, have the potential to alter the course of type 2 diabetes and associated CVD complications. Advantages of these therapies include glucose-dependent enhancement of insulin secretion, infrequent instances of hypoglycemia, weight loss with GLP-1 receptor agonists, weight maintenance with DPP-IV inhibitors, decreased blood pressure, improvements in dyslipidemia, and potential beneficial effects on CV function.

Keywords: cardiovascular disease, glucose control, GLP-1 receptor agonists, DPP-IV inhibitors

Introduction

Type 2 diabetes mellitus produces acute and chronic toxicity to vascular endothelium in patients as a result of exposure to postprandial glucose (PPG) spikes and continuous hyperglycemia. This culminates in the development of microvascular (eg, retinopathy, nephropathy, neuropathy) and macrovascular (eg, peripheral vascular disease, myocardial infarction [MI], stroke) complications.[1]

Damage to blood vessels starts early in the disease process, and as a result, patients often present with cardiovascular disease (CVD) and its associated complications before actually meeting the diagnostic criteria for type 2 diabetes.[2–4] Hyperglycemia is a continuous risk factor, with no apparent glycated hemoglobin (HbA$_{1c}$) threshold above which complications begin.[5,6] Because type 2 diabetes and CVD are so closely interrelated, treatment should focus on the shared pathophysiologic mechanisms of the 2 diseases.

This article will review the association between altered glucose metabolism, obesity, and CV risk. Current concepts on the pathophysiology of type 2 diabetes and proof of concept studies supporting future investigation into the benefits of incretin-based therapies on diabetes and CV outcomes will be discussed.

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Altered glucose metabolism and CVD risk

Clinical studies, including the San Antonio Heart Study,[7] the West of Scotland Coronary Prevention Study,[4] and the Heart Outcomes Prevention Evaluation (HOPE) Study,[8] have shown the complex interplay between CVD, altered glucose metabolism, and obesity. The risk for CVD events (CVD-related mortality, MI, stroke) increases across quintiles of homeostasis model assessment of insulin resistance[7]; Sattar and colleagues[4] also demonstrated incrementally increased risk for CVD events (hazard ratio [HR] = 1.76; 95% confidence interval [CI], 1.44–2.15) and diabetes (HR = 3.50; 95% CI, 2.51–4.90) with each additional finding of components of the metabolic syndrome. Components of the metabolic syndrome included elevated triglycerides (TGs) $\geq$ 150 mg/dL, lowered high-density lipoprotein cholesterol (HDL-C) $<$ 40 mg/dL, fasting glucose $\geq$110 mg/dL, systolic blood pressure (SBP) $\geq$130 mm Hg or diastolic BP (DBP) $\geq$ 85 mm Hg, and body mass index (BMI) $>$ 28.8 kg/m^2. Increased waist-to-hip ratio and waist circumference all worsen the prognosis for men and women with CVD and highlight the importance of weight management in patients with CV risk.[9]

The Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe (DECODE)[3] and Whitehall[2] studies have corroborated that the risk of CVD-related morbidity and mortality may start significantly before the diagnosis of type 2 diabetes. This finding has been reported in several studies. In the Cardiovascular Health Study, fasting glucose $\geq$115 mg/dL was associated with elevated CVD risk (HR = 1.66; 95% CI, 1.39–1.98).[10] The Nurses' Health Study showed that risk for CVD began to increase $\geq$15 years before diagnosis of diabetes (Figure 1).[11] The Norfolk study (Figure 2) documented a steady increase in CV events corresponding to an HbA$_{1c}$ $\geq$ 5% in men and $\geq$6% in women ($P < 0.001$ for all).[12] Haffner and colleagues[13] reported that patients with diabetes, but with no prior MI, have the same risk for an MI as individuals without diabetes, who have had a prior MI. This suggests that CV risk factors in patients with diabetes need to be identified early and treated aggressively.[13]

In fact, multifactorial intervention aimed at controlling all CVD risk factors that may be present in a given patient is an important aspect of individualized treatment for patients with type 2 diabetes. The Steno-2 study[14] randomized 160 patients with type 2 diabetes, who also had persistent microalbuminuria to intensive multifactorial intervention (target HbA$_{1c}$ $<$ 6.5%) or conventional therapy. Intensive therapy in the Steno-2 study also had goals for fasting serum total cholesterol $<$175 mg/dL, fasting serum TG level $<$ 150 mg/dL, and BP $<$ 130/80 mm Hg. Patients were treated with renin – angiotensin system blockers regardless of BP and received low-dose aspirin as primary prevention for CVD events. Patients in the Steno-2 study were followed for a mean of 7.8 years with subsequent follow-up for a mean of 5.5 years. The primary clinical end point for the Steno-2 study was "any cause" time to death at 13.3 years. Twenty-four patients in the intensive-therapy group died compared with 40 in the conventional-treatment group (HR = 0.54;
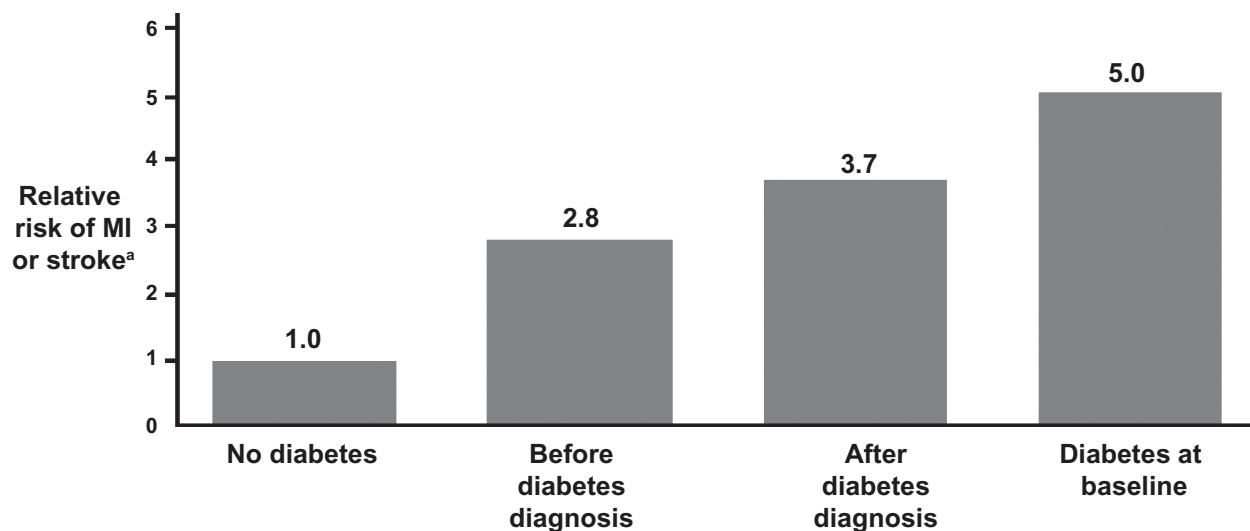

Figure 1 The "ticking clock" hypothesis. Glucose abnormalities increase cardiovascular risk even before the diagnosis of diabetes is made. Multivariate relative risks and 95% confidence intervals of myocardial infarction (MI) or stroke according to diabetes status. The Nurses' Health Study, N = 117,629 women, aged 30–55 years; follow-up 20 years (1976–1996). Adapted with permission from Hu FB, Stampfer MJ, Haffner SM, Solomon CG, Willett WC, Manson JE. Elevated risk of cardiovascular disease prior to clinical diagnosis of type 2 diabetes. *Diabetes Care*. 2002;25(7):1129–1134.[11] Copyright © 2002 American Diabetes Association.
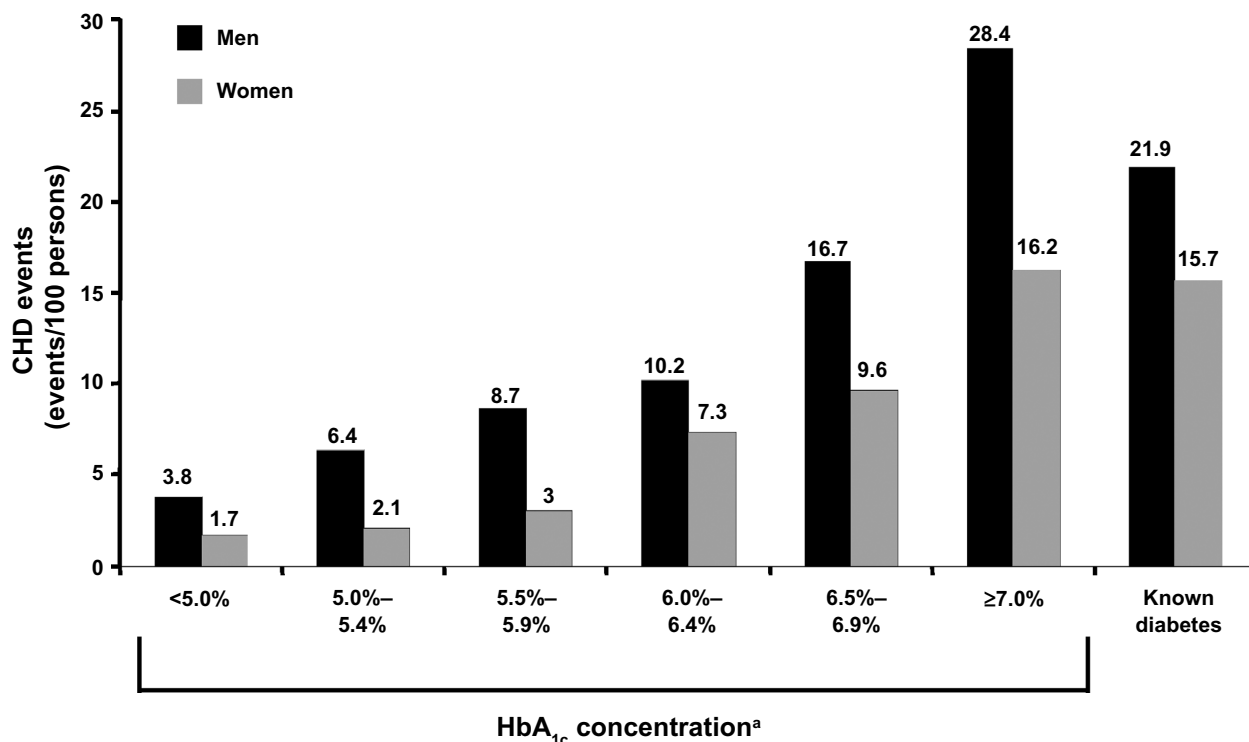**Note:** [a]Adjusted; n = 1,508, diabetes at baseline; n = 5,894, new-onset diabetes.

Figure 2 Glycated hemoglobin (HbA$_{1c}$) and heart disease in type 2 diabetes. HbA$_{1c}$ predicts CHD in type 2 diabetes. Rates for total CHD events by category of HbA$_{1c}$ concentration and known diabetes in 4,462 men and 5,570 women aged 45–79 years. Adapted with permission from Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. *Ann Intern Med.* 2004;141(6):413–420.[12] Copyright © 2004 American College of Physicians.
Note: [a]$P < 0.001$ for linear trend across HbA$_{1c}$ categories.
Abbreviation: CHD, coronary heart disease.

95% CI, 0.32–0.89; $P = 0.02$). Intensive integrated treatment was also associated with a lower risk of death from CVD (HR = 0.43; 95% CI, 0.19–0.94; $P = 0.04$) and CVD events (HR = 0.41; 95% CI, 0.25–0.67; $P < 0.001$) versus conventional treatment.[14] The results from the Steno-2 study support the view that intensive integrated therapy in high-risk patients with type 2 diabetes has the potential to decrease the risk for both microvascular and macrovascular complications and mortality.

Hospital inpatient considerations for glycemia and CVD

The strong correlation between altered glucose metabolism/hyperglycemia and CVD outcomes has also been reported in the critical care setting.[15–17] Muhlestein et al[16] showed that

glucose abnormalities are prevalent in patients with coronary artery disease and that even mild glucose elevations are associated with an increased mortality in patients undergoing percutaneous coronary intervention. Mortality was increased >3-fold in patients with fasting glucose concentrations >110 mg/dL, underscoring the importance of early detection and treatment of hyperglycemia.[16] A systematic overview found that blood glucose concentrations on hospital admission are an independent predictor of long-term morbidity and mortality in patients following an acute MI, regardless of diabetes mellitus status. Nondiabetic patients with glucose concentrations ≥6.1–8.0 mmol/L (Table 1; for converting mmol/L units to mg/dL units and vice versa in this article, see Table 1) had a 3.9-fold (95% CI, 2.9–5.4) higher risk of mortality than similar individuals with lower

Table 1 Conversion table

	Convert mmol/L to mg/dL	Convert mg/dL to mmol/L
Blood glucose	Multiply by 18	Divide by 18 or multiply by 0.055
TC, LDL-C, HDL-C	Multiply by 38.67	Divide by 38.67 or multiply by 0.025
Triglycerides	Multiply by 88.57	Divide by 88.57 or multiply by 0.011

Abbreviations: TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

glucose concentrations.[15] In a prospective study of nondiabetic patients, 35% of patients admitted to a coronary care unit with acute MI developed impaired glucose tolerance (IGT) at discharge (95% CI, 28–43) and 40% had IGT (95% CI, 32–48) 3 months later. The incidence of newly diagnosed diabetes in this population was 31% (95% CI, 24–38) and 25% (95% CI, 18–32), respectively. These data suggest that fasting and postchallenge hyperglycemia might be used as early markers of individuals at high risk during the initial phase of an acute MI.[17]

The impact of intensive glycemic control on survival in critically ill, hospitalized patients remains unknown due to varied study results.[18,19] In one study of hyperglycemic patients hospitalized for acute MI, glucose normalization postadmission was associated with lower mortality. This mortality benefit was noted whether or not the patients received insulin.[18] However, in the Normoglycemia in Intensive Care Evaluation (NICE) and Survival Using Glucose Algorithm Regulation (SUGAR) Study, intensive glucose control increased mortality in patients in the intensive care unit (ICU).[19] Patients (N = 6104) who were expected to require treatment in the ICU for 3 or more consecutive days were randomized within 24 hours of admission to either intensive glucose control (target range, 81–108 mg/dL) or conventional glucose control (target ≤180 mg/dL). Death occurred in 27.5% of patients in the intensive control group and 24.9% in the conventional group (for intensive control, odds ratio = 1.14; 95% CI, 1.02–1.28; P = 0.02). Patients in the intensive group (6.8%) reported more severe hypoglycemia (blood glucose <40 mg/dL) than patients in the conventional group (0.5%, P < 0.001). It remains unclear what effect hypoglycemia had on mortality in this study.

Any innovation that would afford intensive, inpatient control of glucose without undue hypoglycemia, including continuous intravascular glucose monitors, improved staff training in use of intensive protocols, and/or the use of experimentally validated treatment regimens, may improve outcomes in critically ill patients with hyperglycemia.[20] Moreover, any pharmacologic therapy that could potentially reduce the need for antihyperglycemic agents that increase risk of hypoglycemia (ie, sulfonylureas [SFUs], glinides, insulin), when treating inpatients with stress/steroid-induced diabetes or pre-existing diabetes, should be investigated for its ability to reduce morbidity and mortality in this population.

Aggressive glucose lowering

Microvascular and CV risks increase in patients with a longer duration of diabetes and a higher HbA_{1c}, with hyperglycemia being a continuous risk factor independent of HbA_{1c} level.[5,21,22] Initiation of intensive therapy soon after diabetes is diagnosed reduced the risk of microvascular and macrovascular diseases, with additional benefits seen in patients with HbA_{1c} < 7%.[6,21,23] Patients with a longer duration of diabetes and pre-existing complications failed to show benefit with an HbA_{1c} of ~7% in the Veterans Administration Diabetes Trial (VADT),[24] an HbA_{1c} < 6.5% in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study,[25] and in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study,[26] with an actual increased rate of fatal MIs in ACCORD. However, a subgroup analysis showed a likely protective effect in patients with a shorter duration of diabetes or earlier atherosclerotic disease in VADT[22] and reductions in CV outcomes in patients in ADVANCE without pre-existing microvascular or macrovascular disease and in patients in ACCORD without prior CV events (primary prevention) or baseline HbA_{1c} < 8%. Moreover, in the ACCORD trial, it seems possible that unrecognized hypoglycemia and weight gain may have been major issues regarding its adverse outcomes.[22] In addition, data from 2 meta-analyses that include the above studies, as well as the United Kingdom Prospective Diabetes Study (UKPDS)[23] and the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROACTIVE) study, showed that lower glucose levels reduced MIs and CV events albeit with no effect on all-cause mortality.[27,28]

Currie et al[29] published the results of a recent retrospective cohort study analyzing survival of patients with type 2 diabetes as a function of HbA_{1c}. Two cohorts of patients with type 2 diabetes (age, 50 years and older) were analyzed from the United Kingdom General Practice Research Database from November 1986 to 2008. The first cohort included 27,965 patients who had treatment intensified from oral monotherapy to combination oral therapy. The second cohort included 20,005 patients who had intensification with an insulin-containing regimen. The primary outcome was all-cause mortality. HbA_{1c} was broken out by deciles, and survival was analyzed as a function of HbA_{1c} decile. For the combined cohorts, compared with the HbA_{1c} decile with the lowest HR (median HbA_{1c}, 7.5%; interquartile range [IQR], 7.5%–7.6%), the adjusted HR of all-cause mortality in the lowest HbA_{1c} decile (median, 6.4%; IQR, 6.1%–6.6%) was 1.52 (95% CI, 1.32–1.76) and in the highest HbA_{1c} decile (median, 10.5%; IQR, 10.1%–11.2%) was 1.79 (95% CI, 1.5–2.06). Results showed a U-shaped curve association, with the lowest HR at approximately 7.5%.

In summary, low and high mean HbA_{1c} values were associated with increased all-cause mortality and cardiac events,

and an HbA_{1c} value of approximately 7.5% was associated with the lowest all-cause mortality.[29] Although these results lend support to the findings of ACCORD, the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) glycemic goals are still valid and clinicians should strive to reduce HbA_{1c} as low as possible for as long as possible, without causing undue hypoglycemia and weight gain. Figure 3 is a hypothetical representation of the natural history of diabetic subjects enrolled in CV outcome studies.[30]

These data highlight the importance of being able to balance the benefits and risks of medications when making treatment decisions using antidiabetes agents that minimize the risk of hypoglycemia and weight gain, and possibly even lead to weight loss.

The new AACE/American College of Endocrinology (ACE) guidelines[31] emphasized this by recommending oral hypoglycemic agents (SFUs/glinides) last, if at all. Early use of incretins along with metformin (MET) and thiazolidinediones (TZDs) and early use of combination therapy are also recommended.

Thus, based on the pathophysiology of type 2 diabetes and its association with increased CVD risk,[32] the current goals advocated by the ADA, the European Association for the Study of Diabetes, and the AACE are to achieve the lowest possible HbA_{1c} without undue risk of hypoglycemia and weight gain with appropriate individualization. In fact, the ADA has recognized this approach and is supporting a study comparing[33] the biguanide, MET, the TZD, pioglitazone, and the glucagon-like peptide-1 (GLP-1) receptor agonist, exenatide, with treatment according to its own guidelines that advocate the use of SFUs or early insulin therapy after the failure of MET.[34]

The role of incretins in the pathophysiology of type 2 diabetes

Treatment of patients with type 2 diabetes has traditionally focused on improving reduced β-cell function, preventing increased peripheral insulin resistance/hepatic gluconeogenesis, as well as reducing the rate of absorption of nutrients from the gut.[35] These issues have been addressed with various hypoglycemic and antidiabetic regimens including SFUs, MET, TZDs, and α-glucosidase inhibitors. Unfortunately, treatment with some of these agents is associated with hypoglycemia, weight gain, increased CV risks, and other adverse events.[36]

It is now known that the pathophysiology of type 2 diabetes is much more complex than previously believed and that there are other important mechanisms involved in glucose metabolism. Nauck et al[37] found differences in β-cell secretory
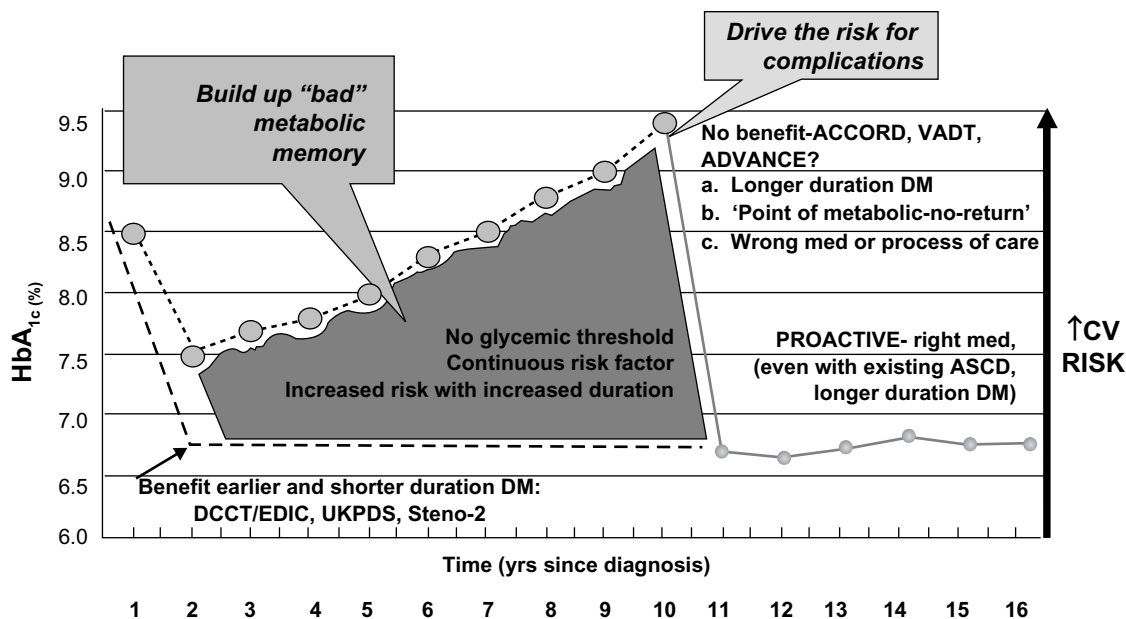

Figure 3 Understanding cardiovascular outcome studies in type 2 diabetes mellitus. These data highlight the importance of balancing the benefits and risks of antidiabetes medications when making treatment decisions using agents that minimize the risk of hypoglycemia and weight gain, and possibly lead to weight loss.
Note: So given epidemiology, pathophysiology, aim for <6.0%, start early, use right meds, without hypoglycemia and visceral weight gain. Adapted with permission from del Prato S. Megatrials in type 2 diabetes. From excitement to frustration? *Diabetologia.* 2009;52(7):1219–1226.[30] Copyright © 2009 Springer.
Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; ASCD, atherosclerotic cardiovascular disease; CV, cardiovascular; DCCT/EDIC, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications; DM, diabetes mellitus; HbA_{1c}, glycated hemoglobin; PROACTIVE, Prospective Pioglitazone Clinical Trial in Macrovascular Events; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

responses between oral and intravenous glucose challenges that were attributable to factors other than glycemia (the incretin effect). The incretin-based pathway was found to account for ~70% of the insulin response to orally ingested glucose.[37,38] The key activities of this pathway occur primarily through the actions of 2 intestinal insulin-stimulating hormones: GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 and GIP have various actions in the body, including slowing gastric motility, increasing satiety, improving glycemic control, and reducing postprandial fatty acids (Figure 4).[39] For a variety of reasons, GLP-1 has been found to be more amenable to therapeutic manipulation than GIP (patients with type 2 diabetes are resistant to GIP administration) and, therefore, has been the focus of more intensive research.[39,40]

It has been suggested that a decreased GLP-1 response to food may contribute to the progression of type 2 diabetes. This was confirmed in a study which reported that meal-stimulated

GLP-1 response was decreased in patients with type 2 diabetes. The authors concluded that this response may contribute to the decreased incretin effect seen in patients with type 2 diabetes.[41] Administration of GLP-1 was shown to increase both first- and second-phase insulin response,[42] improve insulin secretion and inhibit glucagon secretion,[43] and normalize glucose levels in patients with type 2 diabetes.[44] In addition, GLP-1-mediated effects on insulin and glucagon levels in patients with type 2 diabetes are glucose-dependent, and exogenous administration of GLP-1 does not induce hypoglycemia.[45]

This characteristic may be a result of GLP-1's effect on the insulin secretion amplification pathway rather than on the direct triggering pathway.[46–49] Figure 5 depicts the pathways for glucose-stimulated secretion of insulin.[50]

Preclinical studies suggest that there are several potential pathways of GLP-1-mediated protection of the β-cell, including direct effects on signaling cascades that induce
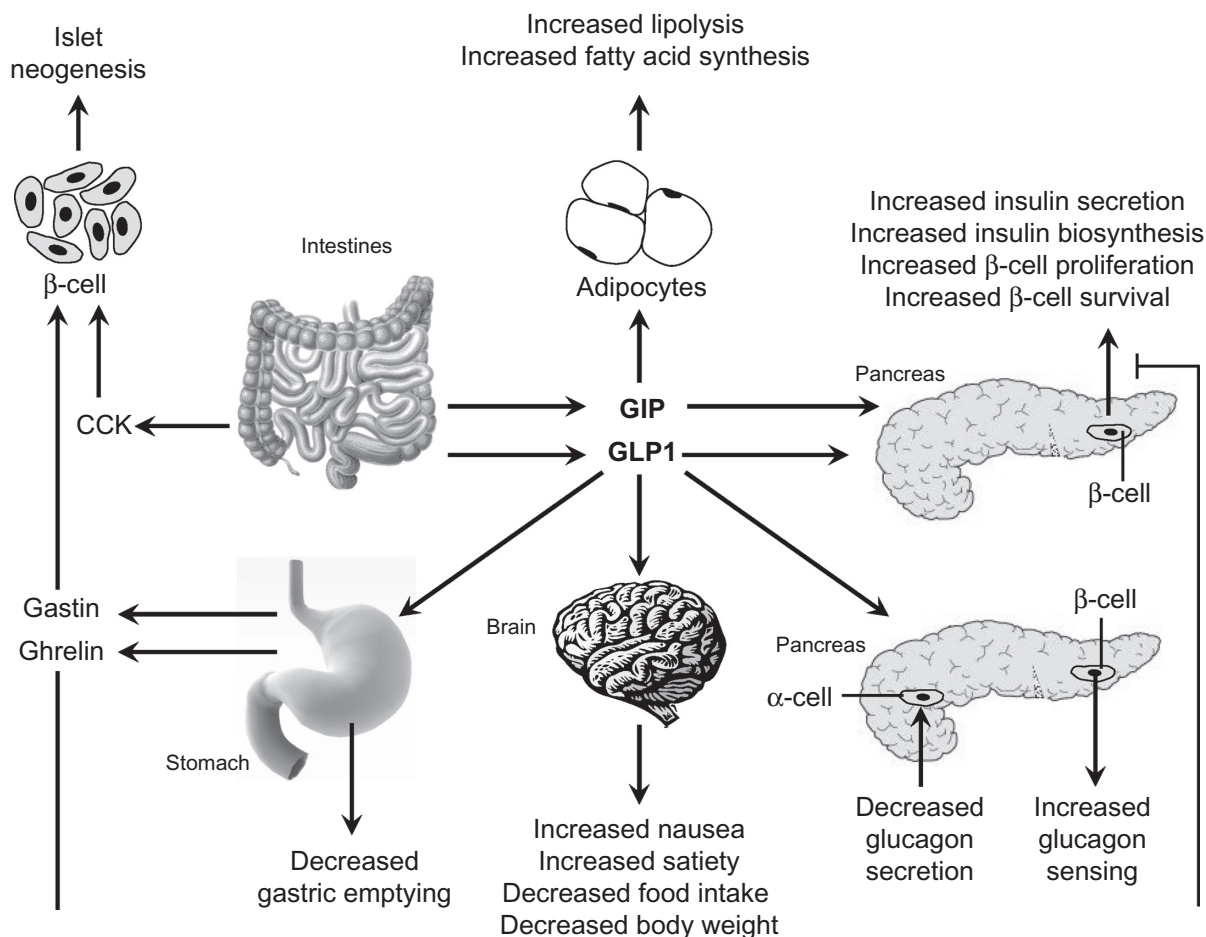

Figure 4 Actions of gastrointestinal hormones on key tissues in glucose homeostasis. Both GIP and GLP-1 promote insulin biosynthesis, insulin secretion, and islet β-cell survival. GLP-1 exerts additional actions, including inhibition of glucagon secretion and gastric emptying, and induction of food intake. GIP has a direct effect on adipocytes coupled to energy storage. In contrast, CCK and gastrin do not regulate plasma glucose levels but could be important for stimulation of islet neogenesis. Reprinted with permission from Girard J. The incretins: from the concept to their use in the treatment of type 2 diabetes. Part A: incretins: concept and physiological functions. *Diabetes Metab.* 2008;34(6 Pt 1):550–559.[39] Copyright © 2008 Elsevier.
Abbreviations: CCK, cholecystokinin; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1.
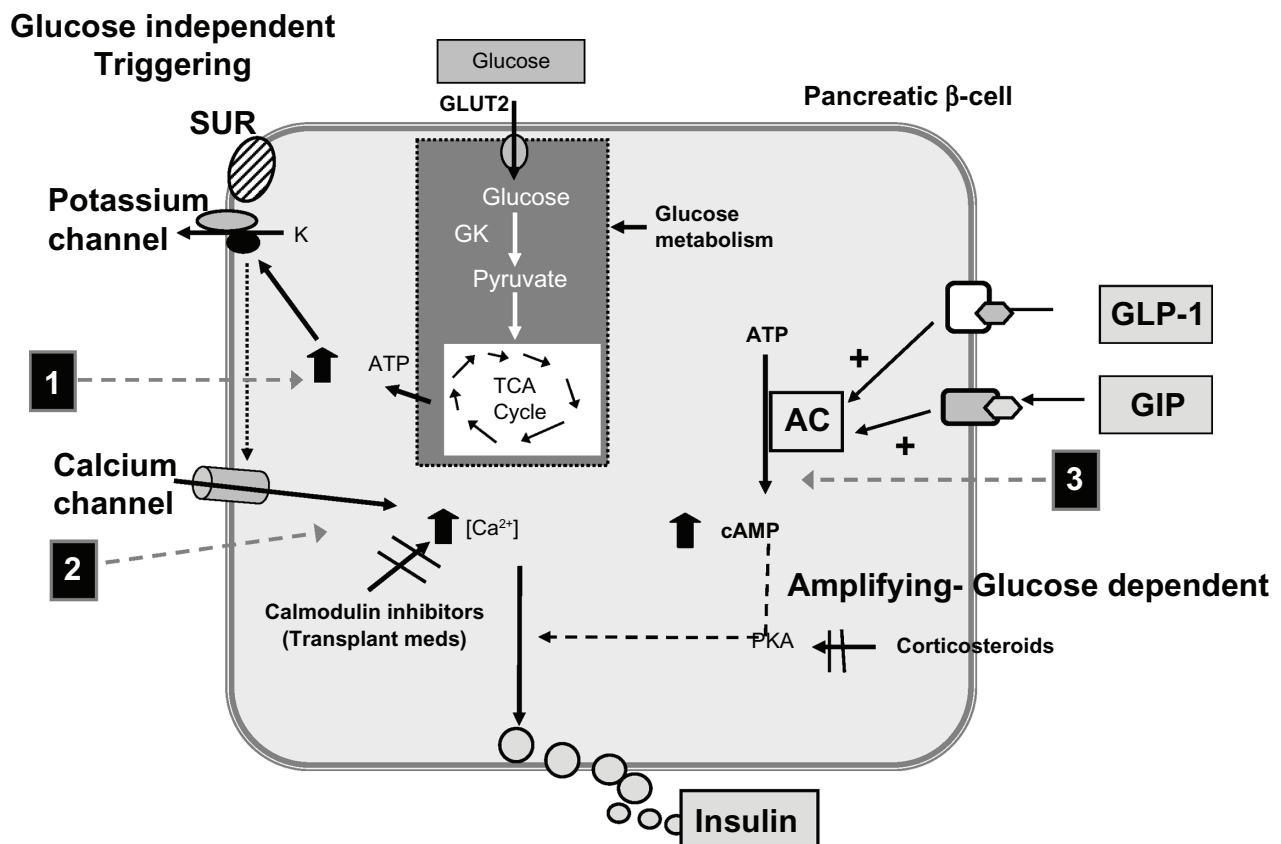
Figure 5 Glucose-stimulated secretion of insulin and potential mechanisms of interference by selected medications. Also, the potential mechanism by which GLP-1 may overcome these hyperglycemic effects. Adapted with permission from Van Raalte DH, Ouwens DM, Diamant M. Novel insights into glucocorticoid-meidated diabetogenic effects: towards expansion of therapeutic options? *Eur J Clin Invest.* 2009;39(2):81–93.[50] Copyright © 2009 John Wiley and Sons.
Abbreviations: AC, adenyl cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; GIP, glucose-dependent insulinotropic polypeptide; GK, glucokinase; GLP-1, glucagon-like peptide-1; GLUT2, glucose transporter 2; PKA, protein kinase A; SUR, sulfonylurea receptor; TCA, tricaroboxylic acid (Kreb's cycle).

β-cell proliferation, increase pancreatic islet regeneration, and reduce β-cell apoptosis. These effects may be mediated by GLP-1's influence on the transcription factor pancreas duodenum homeobox-1 (PDX-1).[51,52] PDX-1 expression has been found essential for integrating GLP-1 receptor-dependent signals, regulating α-cell glucagon secretion, and for the growth, differentiated function, and survival of islet cells in mice.[53] In addition, GLP-1 has been shown to counteract the negative effect of steroids on the β-cell secretion of insulin. This may be, in part, related to its effects on PDX-1.[54] Glucocorticoids, such as dexamethasone, suppress pancreatic β-cell gene expression by interfering with islet-specific gene enhancers. Dexamethasone has also been shown to induce β-cell apoptosis in mouse models, an effect reversible with administration of synthetic GLP-1.[54]

Moreover, GLP-1 seems to overcome steroids' acute negative effects, as well as transplant medication effects (eg, calmodulin inhibitors)[55] on the insulin amplifying pathway.[56]

In clinical trials, the effects of GLP-1 receptor agonists on β-cell function can be measured with surrogate markers of insulin secretion and/or homeostasis model assessment indices of β-cell function (HOMA-B). Beneficial effects of GLP-1 on pancreatic function have been documented in clinical studies. In 1 study, plasma glucose concentrations were significantly lowered during intravenous infusion of GLP-1 in 8 patients with type 2 diabetes and stress hyperglycemia following major surgery. Fasting glucose was in normal range within 150 minutes but remained elevated during placebo infusion ($P < 0.001$). GLP-1 infusion led to a significant increase in insulin secretion ($P < 0.001$) and suppression of glucagon secretion ($P = 0.041$), with no reports of hypoglycemic events.[57] In addition, 1-year treatment with exenatide demonstrated improvement in glucose- and arginine-stimulated insulin secretion[58] while 3-year treatment showed sustained HOMA-B improvement.[59]

Limited data have demonstrated a potential benefit for the short-term use of intravenous GLP-1 to be effective in patients with stress-induced diabetes (eg, postoperative hyperglycemia), especially in patients with prediabetes, or in patients with type 2 diabetes that have been treated with prior

oral hypoglycemic and antidiabetes therapies. By impacting the hyperglycemic effects of glucagon and steroids (2 stress hormones), GLP-1 (and agents with incretin effects such as the GLP-1 receptor agonists) may be leveraged to decrease the need for SFU, glinide, or insulin use in hospitalized patients, and therefore, the potential development of treatment-related hypoglycemia.[60,61]

Additional actions and benefits of incretins

The pharmacologic actions of GLP-1 extend well beyond the pancreas, as GLP-1 receptors have been found in smooth muscle cells, cardiac myocytes, endocardium, vascular endothelium, and hypothalamus.[38,40,62] Improved CV status, including enhanced cardiomyocyte viability after ischemia-reperfusion injury and increased systolic function in preclinical models,[63] relaxation of rat conduit arteries,[64] and peripheral vasodilation in healthy volunteers and patients with type 2 diabetes,[63] and reduction of inflammatory markers[63] have been demonstrated with GLP-1 administration.

A 72-hour infusion of GLP-1 added to standard therapy in acute MI patients with and without diabetes (n = 10) significantly improved left ventricular ejection fraction (LVEF) (29 ± 2% to 39 ± 2%, $P < 0.01$) compared with controls (n = 11) as measured by echocardiograms after reperfusion and after completion of GLP-1 administration.[65] CV benefits were also seen in patients with congestive heart failure after MI, who received 5 weeks of GLP-1 infusion (n = 12). These patients showed a significant improvement in LVEF regardless of diabetic status (21%–27%, $P < 0.001$) compared with no change in patients on standard therapy alone (21%–22%).[66] Infusion of GLP-1 peri-MI also improved regional functional recovery in the peri-infarct zone in humans (n = 10).[65] Sokos et al[67] investigated the effect of a continuous 48-hour infusion of GLP-1 beginning 12 hours before coronary artery bypass graft (CABG) surgery in 10 patients with coronary heart disease and preserved LV function. This resulted in a reduced need for vasopressors, reduced arrhythmias, and significantly better glycemic control in the pre- and perioperative periods (95 mg/dL vs 140 mg/dL, $P \leq 0.02$), with 45% less insulin requirements to achieve the same level of glycemia as in controls (n = 10) in the postoperative period (139 mg/dL vs 140 mg/dL).[67] Concurrent use of GLP-1 receptor agonists with insulin has not been studied and cannot be recommended; however, studies are needed to evaluate their efficacy and safety together.

Additional extrapancreatic effects of incretins have been reported.[38,40] The impact of GLP-1 on gastric emptying has been described earlier. The mechanisms responsible for the slowing of gastric emptying appear complex and may involve activation of signaling mechanisms in both central and peripheral nervous system.[38,40] Similar mechanisms may be responsible for early satiety. Intracerebroventricular and peripheral administration of GLP-1 has been shown to inhibit food intake in rodents. The GLP-1 receptors affected have been localized to the hypothalamic nuclei.[38,40] The ability of GLP-1 receptor agonists to produce weight loss has been well demonstrated in clinical trials.[59] Additional effects of GLP-1 have been reported on the nervous system (antiapoptotic effect on neuronal cells), the renal system (natriuresis), and the hypothalamic-pituitary axis, but the clinical significance of these effects remain undetermined.[38]

The impact of incretin-based therapies on CVD-related risk factors

Attempts to limit the use of GLP-1 as a therapeutic agent in the treatment of type 2 diabetes have advanced in recent years. One of the major barriers to the potential use of GLP-1 therapy is its short half-life in the circulation,[41] which is due largely to its inactivation by the enzyme dipeptidyl peptidase-IV (DPP-IV).[40] Although GLP-1 is rapidly released in response to oral glucose from L cells in the gut, it has a half-life of only ~2 minutes in the circulation and thus contributes to the first-phase insulin response.[68] These findings led to the development of incretin mimetics, such as GLP-1 receptor agonists that are resistant to DPP-IV degradation, and DPP-IV inhibitors, which inhibit the proteolytic cleavage and inactivation of GLP-1.[40,41] DPP-IV inhibitors increase the concentration of endogenous GLP-1 by ~2-fold.

GLP-1 receptor agonists

Exenatide was the first incretin mimetic approved by the US Food and Drug Administration (FDA). It is a synthetic version of the naturally occurring salivary protein of the Gila monster, exendin-4, which has a 53% sequence identity to human GLP-1, is resistant to DPP-IV degradation, and demonstrates *in vivo* binding to human β-cell GLP-1 receptors.[40,69] Exenatide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. Exenatide can be used as monotherapy or in combination with MET, SFU, and/or TZD and is administered twice-a-day by subcutaneous injection. Concurrent use of exenatide with insulin has not been studied and therefore cannot be recommended.[70]

Data from 30-week studies conducted in 963 patients with type 2 diabetes and inadequate glycemic control with SFU,

MET, and combinations of these agents demonstrated that the addition of 5 and 10 µg of exenatide was associated with significant decreases of −0.60% and −0.86%, respectively, from baseline HbA$_{1c}$ ($P < 0.002$ for all).[71–73] Patients treated with exenatide also showed progressive, dose-dependent weight loss of −1.6 kg (5 µg) and −2.8 kg (10 µg) ($P < 0.01$ vs placebo).[71–73] Exenatide-treated patients were more likely to achieve a HbA$_{1c}$ ≤ 7% (5 µg [27%] and 10 µg [34%]) than placebo-treated patients (9%, $P < 0.0001$).[73] The most frequently reported adverse events in these studies were generally mild or moderate and gastrointestinal in nature; no severe hypoglycemia was observed.[71–73]

The glucose- and weight-reducing effects of exenatide in 217 patients previously treated with SFU and/or MET have been sustained for up to 3 years. Initial reductions in HbA$_{1c}$ from baseline to week 30 (−0.9%) were sustained to week 82 (−1.1%)[74] and to 3 years (−1.0%, $P < 0.0001$)[59]; 48% of patients treated with exenatide achieved HbA$_{1c}$ ≤ 7% at week 82 and 46% at 3 years.[59,74] Exenatide reduced body weight from baseline (−2.1 kg) after 30 weeks of treatment, with continued reductions observed at week 82 (−4.4 kg)[74] and at 3 years (−5.3 kg, $P < 0.0001$).[59]

Data from a number of studies have shown that the addition of exenatide or insulin glargine or aspart to patients with type 2 diabetes and poor glycemic control on SFUs and MET is associated with similar reductions in HbA$_{1c}$ (up to −1.36%). However, patients gained up to +1.8 kg of weight after the addition of insulin but lost up to −2.3 kg of weight with exenatide.[75–77] Exenatide was also associated with fewer instances of hypoglycemia than insulin glargine or aspart.[75–77] Thus, for the same degree of glycemic control, exenatide was associated with less hypoglycemia.

Treatment with exenatide was also associated with beneficial effects on other components of CVD risk, including dyslipidemia and elevated BP. After 3.5 years of exenatide treatment, 217 patients with type 2 diabetes demonstrated a 12% reduction in TG (−44.4 mg/dL), 5% in total cholesterol (−10.8 mg/dL), 6% in low-density lipoprotein cholesterol (−11.8 mg/dL), and a 24% increase in HDL-C (8.5 mg/dL) from baseline. In addition, both SBP (−3.5 mm Hg) and DBP (−3.3 mm Hg) were reduced from baseline values.[59]

Exenatide has also produced significant improvements in CV risk factors, inflammatory cytokines, postprandial oxidative stress, and anthropomorphic parameters in patients with metabolic syndrome without type 2 diabetes.[78–81] A meta-analysis of patients in the exenatide database showed an unadjusted incidence of experiencing ≥1 CV event was 2.0% for exenatide and 2.6% for controls (relative risk = 0.69;

95% CI, 0.46–1.04).[82] Assuming that the apparent reduction in CV outcomes is significant and reproducible, it has been estimated that use of exenatide over a 10-year period of time should result in a 50% decrease in the cumulative incidence of MI compared with MET and/or SFUs.[83]

Transient nausea has been reported in patients treated with exenatide in clinical trials. Practicing clinicians have learned many techniques to prevent or minimize the risk of nausea. One study[84] showed that gradual dose escalation successfully reduced the proportion of patients experiencing dose-limiting nausea and vomiting without compromising glycemic control. In the authors' experience, patients should inject exenatide with their first bite of food and stop eating when they feel full. If patients continue to eat despite fullness, they may develop bloating and gastrointestinal upset, with eventual nausea and vomiting. These effects are presumably due to the slowing of gastric emptying seen with exenatide.[85] Titration of exenatide to a dose of 10 µg can occur after 1 month of therapy based on clinical response. Patients can delay eating up to 1 hour after administration but should take the drug with the first bite of a meal to reduce the risk of gastrointestinal upset. Patients are likely to lose their appetite between meals because of exenatide's hypothalamic effects to suppress appetite.[40] This sensation very infrequently develops into nausea, which is usually mild in nature, and resolves within 2 weeks. Occasionally, the nausea can become intolerable, which accounts for the withdrawal of 3% of patients from clinical studies because of nausea and 1% because of vomiting.[70]

Rare cases of pancreatitis have been reported in patients treated with exenatide including fatal and nonfatal hemorrhagic or necrotizing pancreatitis. Exenatide postmarketing surveillance data are not sufficient to establish a drug-related causality. Recent reviews have not documented an increased risk of pancreatitis with exenatide compared with other antidiabetes agents.[86,87] However, until more data become available, treatment with exenatide should not be started in patients with a history of pancreatitis and should be discontinued in patients who exhibit symptoms of acute pancreatitis. If pancreatitis is confirmed, exenatide should not be restarted.[70]

There have been postmarketing reports of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure, and acute renal failure, sometimes requiring hemodialysis or kidney transplantation. Reversibility of altered renal function has been observed in many cases with supportive treatment and

discontinuation of the potentially causative agents, including exenatide. Exenatide has not been shown to be nephrotoxic in preclinical or clinical studies. Exenatide should not be used in patients with severe renal impairment (creatinine clearance <30 mL/min).[70]

Many patients are nervous about getting a subcutaneous injection. This fear is often inadvertently instilled by physicians and can often be alleviated through proper education in the office.

An extended-release formulation of exenatide, dosed once weekly, has been submitted to the US FDA for regulatory review. Treatment with exenatide once weekly has been associated with improved HbA$_{1c}$, BP, and lipid levels in patients with type 2 diabetes.[88,89] After 30 weeks of treatment, exenatide once weekly produced significantly greater changes in HbA$_{1c}$ than exenatide BID (−1.9% vs −1.5%, $P = 0.0023$), with a significantly greater proportion of patients achieving target HbA$_{1c} \leq$ 7% (77% with exenatide once weekly vs 61% with exenatide BID, $P = 0.0039$).[89] One year of treatment with exenatide once weekly resulted in improvements in HbA$_{1c}$ (−2.0%), weight (−4.1 kg), and SBP and DBP (6.2 mm Hg and 2.8 mm Hg, respectively from baseline; $P < 0.05$).[88] Exenatide once weekly is associated with a reduced risk for nausea.

Reductions in fasting blood glucose and PPG with the first treatment injection could make exenatide once weekly an ideal therapy to administer to patients prior to hospital admission (ie, for surgery), to treat stress hyperglycemia with likely improved glycemic control and a decrease in in-hospital hypoglycemia. Because of its extended effects on blood glucose levels, exenatide once weekly should be investigated for its ability to treat patients prior to hospital admission.

Liraglutide, another GLP-1 receptor agonist, is 97% homologous to GLP-1 with an acyl moiety that promotes noncovalent binding to albumin. This reduces its degradation by DPP-IV, prolongs its half-life to ~13 hours, and allows for once-daily administration.[69,90,91] Liraglutide has been approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. It is not recommended as first-line therapy for patients inadequately controlled with diet and exercise. It can be used as monotherapy or in combination with MET, a SFU, or a TZD. The concurrent use of liraglutide and insulin has not been studied.[92] Liraglutide has also been approved in the European Union for adjunctive use in patients with type 2 diabetes and inadequate glycemic control with MET, SFU, MET and SFU, or MET and TZD combination therapy. Liraglutide is

administered once daily via subcutaneous injection.[92] In the Liraglutide Effect and Action in Diabetes (LEAD) studies, treatment with liraglutide (doses up to 1.8 mg) was associated with equivalent or greater improvements in HbA$_{1c}$ and weight than comparator treatments including MET, combination of MET and SFU or TZD, and combination of MET, SFU, and insulin glargine.[90,93–97] The LEAD studies also showed that liraglutide was associated with improvements in SBP and DBP.[96,98–101]

In clinical trials, liraglutide therapy has been associated with pancreatitis. Eight cases were reported during intermediate- and long-term trials in the liraglutide clinical development program. Seven of the cases were in patients treated with liraglutide and 1 case in a patient receiving a comparator. Of the 7 cases in liraglutide-treated patients, 5 were reported as acute pancreatitis and 2 were reported as chronic pancreatitis. There is no conclusive data establishing a risk of pancreatitis with liraglutide. After initiation of liraglutide, and after dose increases, clinicians should observe patients carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, liraglutide and other potentially suspect agents should be discontinued. If pancreatitis is confirmed, liraglutide should not be restarted.[92]

Liraglutide has a "box" warning in its full prescribing information for the risk of thyroid C-cell tumors in humans. The warning is as follows: liraglutide causes thyroid C-cell tumors at clinically relevant exposures in rodents. It is unknown whether liraglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance could not be determined by clinical or nonclinical studies.[92] The basis for this warning arises from carcinogenicity studies that showed proliferative changes in the C-cells of the thyroid gland in rodents receiving liraglutide. These proliferative changes included benign and malignant C-cell neoplasia (eg, MTC) and were dose-dependent and treatment-duration-dependent.[92] Serum calcitonin is a biomarker of MTC. As a result of the findings in rodents, serum calcitonin levels were measured during clinical trials with liraglutide. At weeks 26 and 52 in clinical trials, adjusted mean serum calcitonin levels were higher in liraglutide-treated patients than placebo patients, but were not higher than patients receiving active comparator. There have been no clear-cut cases of MTC in patients treated with liraglutide. Liraglutide-treated patients who develop elevated serum calcitonin levels or thyroid nodules on physical examination or neck imaging should be referred to an endocrinologist for further evaluation.[92]

Other GLP-1 receptor agonists in clinical development that have demonstrated glucose and weight-lowering effects

include taspoglutide and albiglutide. Taspoglutide has been shown to reduce HbA_{1c} (up to -1.2%) and weight (up to -2.8 kg) when added to MET,[102] and albiglutide reduced fasting plasma glucose (FPG) and postprandial concentrations in patients with type 2 diabetes.[103]

DPP-IV inhibitors

Sitagliptin is the first US FDA-approved DPP-IV inhibitor. It has been shown to stimulate glucose-dependent insulin secretion and inhibit glucagon secretion, as well as mitigate fasting and PPG concentrations and reduce elevated HbA_{1c}. Treatment with orally administered sitagliptin has demonstrated efficacy with a once-daily dosage regimen.[104] After 18 weeks of treatment in 521 patients with type 2 diabetes, HbA_{1c} was significantly reduced with sitagliptin (100 and 200 mg) compared with placebo (placebo-subtracted HbA_{1c} reduction, -0.60% and -0.48%, respectively). Sitagliptin also improved FPG, HOMA-B, and fasting proinsulin:insulin ratio but had a neutral effect on body weight.

The incidence of hypoglycemia did not differ significantly between sitagliptin and placebo.[105] In a 24-week study, the addition of sitagliptin to MET in 1,091 patients with type 2 diabetes was associated with placebo-subtracted HbA_{1c} changes from baseline up to -2.07% ($P < 0.001$ for comparisons vs placebo and coadministration vs respective monotherapies). The incidence of hypoglycemia was low (0.5%–2.2%) across active treatment groups and did not differ significantly from placebo (0.6%).[106]

In another study of 441 patients, the addition of sitagliptin to glimepiride $\pm$ MET reduced HbA_{1c} by -0.74% ($P < 0.001$) versus placebo after 24 weeks. The addition of sitagliptin reduced FPG by -20.1 mg/dL ($P < 0.001$) and increased HOMA-B by 12% ($P < 0.05$) relative to placebo. Weight and incidences of hypoglycemia increased in the sitagliptin treatment group compared with placebo ($+0.8$ vs -0.4 kg; $P < 0.001$ and 12% vs 2%, respectively).[107]

Saxagliptin is another DPP-IV inhibitor that has received US FDA approval. In addition to its glucose-lowering potential, saxagliptin may also have some cardioprotective effects.[108] An analysis of 8 randomized, double-blind, phase IIb/III trials, involving 3,356 subjects randomized to saxagliptin and 1,251 subjects randomized to comparator, showed no increased CV risk with saxagliptin as monotherapy or in combination. The data raise the possibility of a cardioprotective effect that requires further study.[108] Other DPP-IV inhibitors in clinical development include alogliptin[109] and vildagliptin (which is currently available in the European Union and Latin America but has not been approved in the United States).

In clinical studies, DPP-IV inhibitors have been associated with improvements in BP, dyslipidemia, and inflammatory cytokine levels but have not been shown to accelerate weight loss in patients with type 2 diabetes.[110–112] DPP-IV therapy has been associated with an increased incidence of upper respiratory infections, nasopharyngitis, and headache. Other rare, but more serious, adverse events include hypersensitivity reactions and anaphylaxis.[110,113] Postmarketing surveillance shows that between October 16, 2006 and February 9, 2009, 88 cases of acute pancreatitis were reported to the US FDA in association with sitagliptin therapy, including 2 cases of hemorrhagic or necrotizing pancreatitis. The manufacturer has been asked to update their product labeling as a result of these spontaneous case reports.[114]

GLP-1 receptor agonists versus DPP-IV inhibitors

The effects of exenatide and sitagliptin were compared in a 2-week study in which 61 patients with type 2 diabetes received 5 µg BID of exenatide subcutaneously for 1 week, then 10 µg for 1 week, or 100 mg of oral sitagliptin every morning for 2 weeks. Patients crossed over to the alternate therapy after 2 weeks of treatment. Exenatide had a significantly greater effect in reducing 2-hour PPG concentration (133 mg/dL) than sitagliptin (208 mg/dL, $P < 0.0001$), although the effects of both agents in reducing FPG was similar. Exenatide also significantly improved the insulinogenic index of insulin secretion (1.50, $P = 0.0239$), reduced postprandial glucagon secretion (0.88, $P = 0.0011$), slowed gastric emptying (0.56, $P < 0.0001$), and reduced total caloric intake (-134 kcal vs $+130$ kcal, $P = 0.0227$) compared with sitagliptin.[85] An additional comparative study is ongoing, which will provide more information to clinicians, who must select the right drug for the appropriate patient, matching drug and patient characteristics.

Investigational incretin use perioperatively: CABG

To reap the potential acute benefits of incretin use perioperatively as suggested by studies with GLP-1 used in surgery,[61] including the possibility of avoiding the use of hypoglycemic agents postoperatively (especially in patients not previously known to have diabetes or only requiring prior oral therapy for diabetes preadmission), incretins have been used in surgery including CABG and open-heart surgery (Table 2). Our experience at the University of Pennsylvania in ~100 patients has shown that sitagliptin is well tolerated and is equal to ~20 U of insulin, whereas

Table 2 Perioperative glycemic guidelines used at the University of Pennsylvania

	Medications		Identify patient	Preoperative day	Operative day	Postoperative day 1–x	Until discharge
	Preadmin	In-hospital					
CABG/ operations requiring insulin drips			**At risk, HbA$_{1c}$ ~5.8 and >**				
Non-diabetes mellitus							
		IV insulin drip			√	√ (until AM day 3)	
		Incretin[a]				Start	√
		SFU/Pio/MET as below					√
		CF fast-analog				√ (when off drip)	√
IFG/IGT/DM							
		Incretin[a]		√ or start	√	√	√
		SFU/glinide		√	X	X	Consider
		Pio[b]		√		√	√
		MET[c]		X	X	X	Only if stable
		IV insulin drip			√	√ (stop AM day 3)	
	Basal insulin						
	Bolus insulin					If normal PO- may not need if on incretin	If normal PO
		CF fast-analog				√ (when off drip)	√
Non-CABG Non-diabetes mellitus					**Postoperative bloodglucose >180**	**Postoperative blood glucose >180**	
		Incretin SFU/Pio/MET as below				Start	√
		CF aspart				√	√
IFG/IGT/DM							
		Incretin[a]	√ or start	√	√	√	√
		SFU/glinide		√	X	X	Consider
		Pio[b]		√	X	√	√
		MET[c]		X	X	X	Only if stable
		Basal insulin		√	√	√	√
		Bolus insulin		If normal meals		If normal PO-may not need if on incretin	If normal meals
		CF fast-analog				√	√

Notes: [a]Incretin administration: exenatide may be administered when patient is either NPO or PO (when operative-associated nausea is gone). DPP-IV inhibitors administered only when patient is PO. [b]Pioglitazone can only be administered if the patient does not have a history of congestive heart failure. [c]Metformin Cr < 1.5 male, <1.4 female, age <70 years.
Abbreviations: CABG, coronary artery bypass graft; HbA$_{1c}$, glycated hemoglobin; IV, intravenous; SFU, sulfonylurea/glinide; Pio, pioglitazone; MET, metformin; CF, correction factor; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; DM, diabetes mellitus; PO, per oral; DPP-IV, dipeptidyl peptidase-IV inhibitor; NPO, nothing by mouth; X, not given; √, given.

exenatide is equal to ~40 U of insulin. According to a written communication from G. Umpierrez (January 13, 2010), when one stops insulin drips on day 3 using post-CABG insulin drip protocols, most patients with drip rates <2.5 U/h for the last 6 hours do quite well with sitagliptin alone. Though there has been some concern about perioperative nausea with exenatide, this has occurred infrequently since only ~1% of patients have a hypothalamic super sensitivity to the agent. Clinically reported nausea is predominantly related to eating after feeling "full." As most patients have less food intake following surgery, nausea after surgery has not been a significant issue.

Conclusion

Current guidelines from the ADA advocate SFU use early in the diabetes disease process. The ADA only recommends GLP-1 receptor agonists (eg, exenatide) if there are concerns about the development of hypoglycemia or weight gain. Given the detrimental effects of these variables on CVD and further glycemic control, it seems very prudent to take these factors into account when considering antidiabetes agents. Thus, guidelines that avoid the use of oral antidiabetes agents associated with hypoglycemia and weight gain (eg, AACE/ACE algorithm) are more logical and becoming increasingly popular in treating patients with diabetes, even perioperatively.

Type 2 diabetes and CVD share many pathophysiologic nuances as they continue to grow at epidemic rates. Since these conditions are interrelated, optimized treatment strategies for patients with type 2 diabetes should not only focus solely on hyperglycemia but also address other CVD risk factors, including overweight/obesity, elevated BP, and dyslipidemia. The results of studies such as Steno-2 highlight the importance of controlling all CV risk factors in patients with type 2 diabetes. The confusing results from outcome studies that examined these variables in patients with type 2 diabetes, such as ACCORD, ADVANCE, and NICE-SUGAR, may be secondary to the use of nonideal hypoglycemic agents (eg, SFUs in ADVANCE). Moreover, therapies that increase hypoglycemia and weight (ACCORD) and thus suggest increased fatal MIs should not lead to glycemic therapeutic nihilism. As vascular damage accrues early in the type 2 diabetes disease process and is directly related to the abnormal metabolic environment/hyperglycemia, the addition of incretin-based therapies to the antidiabetes agent armamentarium offers strong potential for treatments that work on the underlying defects of type 2 diabetes by decreasing glycemic levels without hypoglycemia, and while reducing weight and CV risk factors. Clinical data continues to accumulate supporting the use of incretin-based therapies as optimal therapy for glucose lowering, as well as for reducing the risk of CVD-related morbidity and mortality, although more data, particularly on CV outcomes, is required.

Acknowledgment

Disclosure

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