Glucagon-Like Peptide-1 Receptor Agonists for Diabetes Mellitus: A Role in Cardiovascular Disease

Nathaniel R. Smilowitz, MD; Robert Donnino, MD; Arthur Schwartzbard, MD

Diabetes mellitus, defined as a fasting plasma glucose of $\geq 126$ mg/dL or a glycosylated hemoglobin A1c level (HbA1c) of $\geq 6.5\%$, afflicts $\approx 12.9\%$ of adults in the United States and nearly 285 million adults worldwide.\cite{12} Diabetes mellitus is a major risk factor for the development of cardiovascular disease, independently conferring a 2-fold excess risk of coronary heart disease and stroke.\cite{6} Macrovascular events in diabetes mellitus remain the leading cause of mortality, and the burden of cardiovascular disease attributable to diabetes mellitus has increased over the past decade.\cite{4} An increase in the prevalence of obesity has contributed to the rise in diabetes mellitus. Additionally, obesity independently increases the risk of cardiovascular disease in patients with diabetes mellitus.\cite{5}

Although strict glycemic control unequivocally reduces the microvascular complications of diabetes mellitus, the macrovascular benefits of intensive therapy have been difficult to establish, with conflicting results from large clinical trials.\cite{6-9} Multifactorial strategies are recommended to reduce cardiovascular risk in diabetes mellitus through enhanced glycemic control, blood pressure reduction, lipid management, weight loss, and physical activity.\cite{10} Unfortunately, despite aggressive interventions for hyperglycemia, $<50\%$ of patients achieve standard HbA1c targets with conventional therapy.\cite{11} Polyparmacy is required to achieve glycemic control in the majority of patients within 3 years of diagnosis.\cite{13–15} Although combinations of drug classes can synergistically target multiple pathophysiological defects, novel therapies are required to manage diabetes mellitus and mitigate cardiovascular risks. Dipeptidyl-peptidase IV (DPP-IV) inhibitor and glucagon-like peptide-1 (GLP-1) receptor agonist incretin therapies were developed to complement conventional treatment options for diabetes mellitus. Despite promising initial reports of cardioprotective effects, DPP-IV inhibitors have failed to demonstrate improved cardiovascular outcomes in large clinical trials.\cite{13–15} Randomized studies to evaluate cardiovascular outcomes associated with GLP-1 receptor agonists are currently underway.

This review presents an overview of GLP-1 receptor agonist therapy in the treatment of patients with type 2 diabetes mellitus, focusing on the clinical evidence for currently available therapies, adverse effects, and the implications of therapy for patients at high risk of cardiovascular disease.

Pathophysiology of Diabetes Mellitus and the Role of Incretins

Type 2 diabetes mellitus is associated with a complex array of metabolic derangements, principally characterized by a progressive hormonal failure of adequate insulin release from pancreatic $\beta$-cells. At first diagnosis of diabetes mellitus, $\beta$-cell function is typically $50\%$ lower than baseline and progressively declines despite treatment.\cite{14} Other pathophysiological defects include inappropriate glucagon release, aberrant hepatic glucose output, insulin resistance, increased lipolysis, and apoptosis of pancreatic $\beta$-cells leading to a relative deficit in $\beta$-cell mass. Glucose toxicity and lipotoxicity from elevated circulating free fatty acids and triglycerides are believed to accelerate declines in $\beta$-cell function.\cite{17}

The blunted efficacy of incretins also plays a pivotal role in the pathogenesis of diabetes mellitus. Incretins are peptides secreted by gastrointestinal cells in response to the ingestion of oral nutrients to potentiate pancreatic $\beta$-cell insulin production in normal homeostasis. An “incretin effect” was first established in the 1960s when the administration of enteral glucose provoked a more robust release of endogenous insulin than an equivalent parenteral glucose load.\cite{18} Two molecules, glucose-dependent insulinoptide polypeptide and GLP-1, account for nearly $90\%$ of the “incretin effect.” Glucose-dependent insulinoptide polypeptide is secreted by the K cells in the proximal small intestine and augments glucose-stimulated insulin release.\cite{19} It is rapidly degraded by DPP-IV, limiting the plasma half-life to 5 to 7 minutes. GLP-1 is a 30-amino-acid peptide secreted from the L cells of the distal small intestine in response to luminal stimulation. Circulating GLP-1 is also rapidly degraded by DPP-IV, yielding a plasma half-life of only 1 to 2 minutes. GLP-1 binds receptors expressed in the endocrine pancreas, stimulates glucose-dependent insulin secretion from the pancreatic $\beta$-cells, enhances insulin gene transcription and biosynthesis, and inhibits glucagon secretion.\cite{20} In animal models, GLP-1 can reduce cellular apoptosis in the pancreatic $\beta$-cells and promote $\beta$-cell proliferation and neogenesis.
from pancreatic progenitor cells. GLP-1 attenuates gastrointestinal secretions, mobility, and gastric emptying, and may have direct effects on the hypothalamus to decrease appetite, causing earlier satiety and promoting weight loss. Weight loss, in turn, reduces insulin resistance and can facilitate normoglycemia. Many of the normal metabolic effects of GLP-1 appear to be independent of the GLP-1 receptor, suggesting dual pathways of GLP-1 action or plasticity in the incretin axis.

In healthy individuals, incretin release is responsible for nearly 50% to 70% of insulin secreted in response to ingested carbohydrates. However, in patients with type 2 diabetes mellitus, the incretin axis appears to be markedly compromised. Early studies reported reduced postprandial GLP-1 secretion in diabetic patients that was associated with muted incretin-mediated glucose-dependent insulin secretion. More recent data have called this finding into question, demonstrating a variable response of GLP-1 secretion and suggesting that GLP-1 levels depend on other factors such as age and plasma glucagon level. GLP-1 resistance, not necessarily deficiency, may contribute to the deterioration of the incretin effect in diabetes mellitus.

The Incretin Axis as a Drug Target

Two classes of incretin-based therapy have been developed to treat diabetes mellitus. Synthetic GLP-1 receptor agonists resistant to DPP-IV are attractive incretin mimetics because of their hypoglycemic effects, delayed gastric emptying and a propensity for weight loss, and potential cardiovascular benefits. Oral DPP-IV inhibitors delay enzymatic degradation of endogenous incretin peptides and offer more modest improvements in insulin secretion and decreased glucagon production. Exogenous glucose-dependent insulinotropic polypeptide has not been regarded as an attractive drug therapy based on the peptide’s blunted downstream insulinotropic effects in the setting of diabetes mellitus.

The first incretin mimetic, exenatide, is a 39-amino-acid synthetic GLP-1 receptor analogue resistant to DPP-IV degradation. It is based on the exendin-4 peptide identified in the salivary secretions of the Heloderma suspectum (ie, Gila monster) in 1992. The US Food and Drug Administration (FDA) approved exenatide in April 2005 as a twice-daily injectable adjunctive treatment for the management of diabetes mellitus. A once-weekly injectable formulation of exenatide with an extended half-life of 2 weeks was also developed. Both formulations undergo renal clearance and are associated with nausea, vomiting, and headaches in patients with severe renal impairment.

Liraglutide, a human GLP-1 analogue with a 1-aminooacid substitution (Arg34Lys) and palmitic acid side chain with a glutaryl spacer also achieved resistance to DPP-IV degradation, and has a long half-life of 13 hours. In contrast to exenatide, liraglutide is not renally cleared and appears safe in patients with renal insufficiency. The FDA approved liraglutide in 2010 as a once-daily injectable therapy for glycemic control in type 2 diabetes mellitus. Several new GLP-1 agonists remain in development, including albiglutide and lixisenatide.

Clinical Outcomes of GLP-1 Receptor Agonist Therapy

Glycemic end points have long been sufficient to demonstrate efficacy and ensure regulatory approval of new therapies in diabetes mellitus. In 2008, the FDA released guidance for industry requesting that novel antidiabetic therapies demonstrate acceptable cardiovascular safety in clinical outcomes trials. Reductions in macrovascular outcomes and cardiovascular mortality are now viewed as an important goal of new diabetic therapies in patients with cardiovascular disease.

GLP-1 agonists hold great promise to improve the management of diabetes mellitus and its complications (Table 1). GLP-1 therapies offer potent glycemic control with a glucose-dependent incretin effect that mitigates the risk of hypoglycemia. The highest maintenance doses of GLP-1 agonists yield mean HbA1c reductions of -1.1 to -1.6%. The GLP-1 agonist class achieves a mean weight loss of 2.0 to 2.4 kg relative to placebo and 4.8 kg of weight loss versus insulin in trials lasting 20 to 52 weeks. The subcutaneous route of administration and tolerability of the class remain concerns. GLP-1 analogues are associated with gastrointestinal side effects, in particular, an increase in nausea, vomiting, and diarrhea. Gastrointestinal symptoms are dose related and typically abate with time and gradual dose titration.

Early placebo-controlled trials of twice-daily exenatide as an adjunct to sulfonylureas, thiazolidinediones, metformin, or combination therapy reported nearly a 0.9% decrease in HbA1c with minimal hypoglycemia, dose-dependent weight loss, and only mild gastrointestinal side effects. Durable benefits of long-term exenatide therapy were observed in a ≥3-year open-label follow-up to the initial clinical trials, with sustained improvements in glycemic control, enhanced lipid profiles, and persistent weight loss. Despite these encouraging findings, analyses from extensions of the initial trials must be interpreted with caution, because patients able to

### Table 1. Prescribing GLP-1 Agonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Exenatide (Twice Daily)</th>
<th>Exenatide (Once Weekly)</th>
<th>Liraglutide</th>
<th>Lixisenatide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Availability</td>
<td>Byetta</td>
<td>Bydureon</td>
<td>Victoza</td>
<td>Lyxumia</td>
</tr>
<tr>
<td>Initial dose</td>
<td>5 μg subQ (60 min before meal)</td>
<td>2 mg subQ (without regard to meals)</td>
<td>0.6 mg subQ daily once weekly, then increase to 1.2 mg daily</td>
<td>10 μg daily for 14 days, then increase to 30 μg daily</td>
</tr>
<tr>
<td>Maximal dose</td>
<td>10 μg subQ twice daily (twice daily)</td>
<td>2 mg subQ (without regard to meals)</td>
<td>1.8 mg subQ once weekly</td>
<td>20 μg daily</td>
</tr>
<tr>
<td>Renal adjustment</td>
<td>Caution with eGFR 30–50</td>
<td>Caution with eGFR 30–50</td>
<td>Caution with renal impairment</td>
<td>Caution with eGFR 30–50</td>
</tr>
<tr>
<td>Half-life</td>
<td>2.4 h</td>
<td>2 wk</td>
<td>13 h</td>
<td>3 h</td>
</tr>
</tbody>
</table>

ADR indicates adverse drug reaction; eGFR, estimated glomerular filtration rate; EU, European Union; GLP-1, glucagon-like peptide-1; and subQ, subcutaneous.
complete the trial reflect a selection bias that may deliver inappropriately optimistic results. Exenatide also demonstrated enhanced glycemic control in patients already receiving basal insulin with or without metformin and/or pioglitazone without an increased rate of hypoglycemia and with significant weight loss. These early studies established exenatide as an effective adjunctive therapy to reduce HbA1c in patients already on a broad range of conventional diabetic regimens.

The development of once-weekly exenatide delivered incremental improvements in glucose control in comparison with twice-daily therapy and provided 1.6% to 1.9% reductions in HbA1c that were sustained at 2 years. Weight loss, modest improvements in systolic blood pressure, serum lipid profiles, decreased triglycerides, total cholesterol, and low-density lipoprotein cholesterol were also observed. The GLP-1 agonist liraglutide also amassed provocative clinical outcomes data. Liraglutide provides superior HbA1c reductions (1.12%) with similar weight loss and less common side effects of nausea and minor hypoglycemia. In an open-label comparison of daily liraglutide and once-weekly exenatide in patients with poorly controlled diabetes mellitus on oral hypoglycemic agents, liraglutide demonstrated a larger reduction in HbA1c and a greater reduction in body weight. The study failed to meet the primary end point of exenatide noninferiority.

GLP-1 agonists also compare favorably in comparison with conventional classes of diabetes mellitus therapy. Exenatide demonstrated HbA1c lowering (1.5%) that was superior to sitagliptin or pioglitazone (0.9% and 1.2%, respectively) and was also associated with significantly lower body weight and a comparable safety profile. Randomized comparisons of exenatide and liraglutide with sitagliptin confirmed superior HbA1c lowering with the GLP-1 agonist therapy with more frequent gastrointestinal side effects but similar rates of hypoglycemia. Liraglutide also demonstrated durable superiority to glimepiride monotherapy in early type 2 diabetes mellitus with greater reductions in A1C, blood pressure, and body weight, with fewer hypoglycemic episodes.

The potency of GLP-1 agonists affords an opportunity to delay the initiation of insulin. In the Liraglutide Effect and Action in Diabetes 5 (LEAD-5) trial, patients with diabetes mellitus who were on metformin and sulfonylurea therapy were randomly assigned to liraglutide or insulin glargine. Liraglutide demonstrated improved reductions in HbA1c in comparison with insulin (1.33% versus 1.09%), meeting the study noninferiority end point. In addition, liraglutide was associated with weight loss in comparison with the weight gain observed in the cohort receiving insulin (treatment difference 3.43 kg). Blood pressure reductions were observed in the GLP-1 arm, but not in the cohort receiving insulin. There were no differences between liraglutide and insulin in the occurrence of hypoglycemic episodes, but liraglutide was associated with significantly more nausea and diarrhea. Once-weekly exenatide also demonstrated similar success in head-to-head trials with insulin. Although these trials suggest that GLP-1 agonists provide glycemic control superior to insulin, inadequate titration of insulin could limit the external validity of the study findings.

Beyond Glucose Control: The Promise for Cardiovascular Disease

GLP-1 agonist therapy holds promise in the management of diabetic patients with poorly controlled hyperglycemia and cardiovascular disease (Table 2). Multiple mechanisms of hyperglycemia’s detrimental effects on the cardiovascular system have been postulated, including the effects of advanced glycation end-products, impaired endothelial function, aberrant thrombosis and fibrinolysis, increased inflammation, atherogenic dyslipidemia, and increased plasma levels of free fatty acids. Beyond excellent glycemic control, GLP-1 agonists promote weight loss, lower plasma lipids, and reduce blood pressure. Cardioprotective effects, ischemic conditioning, and enhanced endothelial function have also been associated with GLP-1 agonists in small clinical trials.

Table 2. Clinical Effects of GLP-1 Agonists

<table>
<thead>
<tr>
<th>GLP-1 Agonists</th>
<th>Clinical Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycemic control</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin A1C</td>
<td>Mean A1C reduction of 1.1%–1.6%</td>
</tr>
<tr>
<td>Postprandial effects</td>
<td>Reduced postprandial hyperglycemia</td>
</tr>
<tr>
<td>Gastric emptying and appetite</td>
<td>Reduced appetite and delayed gastric emptying</td>
</tr>
<tr>
<td>Established cardiovascular risk factor effects</td>
<td></td>
</tr>
<tr>
<td>Body weight</td>
<td>Weight loss of 2.0–2.4 kg relative to placebo and 4.8 kg of weight loss vs insulin</td>
</tr>
<tr>
<td>Lipid profile</td>
<td>Reductions in total cholesterol, low-density lipoprotein cholesterol, triglycerides, and apolipoprotein B levels</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Reductions in systolic blood pressure of 2–4 mmHg</td>
</tr>
<tr>
<td>Cardiovascular benefits under investigation</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>Hemodynamic improvements in heart failure</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>Improved vascular endothelial function</td>
</tr>
<tr>
<td></td>
<td>Improved ischemic conditioning</td>
</tr>
<tr>
<td>Risks and concerns*</td>
<td></td>
</tr>
<tr>
<td>Common ADRs</td>
<td>Nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Uncommon ADRs</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Safety concerns</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Medullary thyroid cancer</td>
</tr>
<tr>
<td></td>
<td>Pancreatic cancer</td>
</tr>
<tr>
<td></td>
<td>Increased heart rate (2 bpm)</td>
</tr>
</tbody>
</table>

ADR indicates adverse drug reaction. *See text for details.
GLP-1 Agonists in Heart Failure

Animal Models

Preliminary data from animal models raise the possibility of a benefit in heart failure. In preclinical studies, the disruption of GLP-1 receptors in the murine heart led to diastolic heart failure, increased left ventricular (LV) end-diastolic pressures, and increased LV wall thickness. A 3-month course of continuous GLP-1 agonist infusion in spontaneously hypertensive heart failure–prone obese rats was associated with prolonged survival, preserved LV function, enhanced myocardial glucose uptake, and reduced apoptosis. GLP-1 infusion in dogs with pacing-induced cardiomyopathy resulted in significant increases in stroke volume and cardiac output.

Clinical Data

Early clinical studies in humans have shown promise, but with conflicting findings. In a nonrandomized study of 12 patients with New York Heart Association class III/IV chronic heart failure, a continuous 12-week infusion of GLP-1 improved LV ejection fraction and 6-minute walk in comparison with 9 heart failure patients on standard therapy. In contrast, a randomized double-blind study of a 48-hour GLP-1 infusion in 15 patients without diabetes mellitus with less severe New York Heart Association class II to III compensated heart failure demonstrated no significant beneficial hemodynamic effects and episodes of hypoglycemia early in the infusion protocol. It is important to recognize the limitations of trials that use GLP-1 agonists as a continuous infusion. This formulation and route of administration may differ substantially from the commercially available injectable GLP-1 agonists approved for intermittent use in diabetes mellitus. Therefore, effects observed following GLP-1 infusions must be interpreted carefully and may not pertain to currently available incretin therapy. Furthermore, long-term outcomes of GLP-1 agonists in patients with heart failure remain unproven. Despite promising preclinical studies of DPP-IV inhibitors in animals with reduced ventricular function, a large clinical trial of saxagliptin in humans was associated with an increased rate of heart failure hospitalizations. Although an increased signal for heart failure was not apparent in other trials, a class effect among incretins cannot be fully excluded and caution is required. Still, because many traditional hypoglycemic agents are associated with fluid retention that is undesirable in the setting of heart failure, GLP-1 agonists may fill an important niche. The favorable side-effect profile of GLP-1 agonists and possible pleiotropic effects warrant additional studies in patients with diabetes mellitus and heart failure.

GLP-1 Agonists in Ischemia

Animal Models

GLP-1 agonists may also play a role in ischemic conditioning. Cardioprotective effects of GLP-1 therapies have been observed in animal models of myocardial ischemia, with reductions in infarct size and preserved cardiac function perhaps as a result of enhanced myocardial glucose uptake.

Clinical Data

Evidence supporting GLP-1–based therapies in the setting of myocardial ischemia in humans is limited. A small nonrandomized study identified that a 72-hour infusion of GLP-1 after percutaneous coronary intervention for acute myocardial infarction was associated with significant improvements in post–myocardial infarction LV ejection fraction and wall motion in comparison with placebo. In another small study, GLP-1 infusion 12 hours before coronary artery bypass graft surgery was associated with less need for postoperative inotropic support and improved glycemic control in comparison with insulin. Most recently, several randomized trials of exenatide before reperfusion in patients with ST-segment elevation myocardial infarction undergoing urgent primary percutaneous coronary revascularization with drug-eluting
some controversy relating to GLP-1 agonist safety is likely to continue until long-term safety data are available. Prospective studies are warranted to determine the extent, if any, of the potential adverse effects of long-term GLP-1 agonist therapy.

Conclusions
Diabetes mellitus–related cardiovascular complications remain a significant cause of morbidity and mortality, despite the use of conventional hypoglycemic agents. New pharmacological agents are urgently needed. Incretin therapies represent a novel approach to glycemic control by restoring multiple pathophysiological defects of diabetes mellitus. Incretin therapies augment glucose-stimulated insulin secretion, reduce glucagon production, and limit β-cell apoptosis in animal models. Among incretins in clinical practice, GLP-1 agonists provide considerable reductions in HbA1C with minimal risk of hypoglycemia. Consequently, GLP-1 agonists are positioned second-line after metformin in consensus algorithms for diabetes mellitus management, despite cost, injectable formulation, frequent gastrointestinal side effects, and the previously addressed safety concerns. In addition to enhanced glycemic control, GLP-1 agonists demonstrate...
antihypertensive properties, can improve lipid profiles, and cause weight loss, which may decrease insulin resistance and further improve glycemic control. Small clinical trials demonstrate improved endothelial function and some promising cardioprotective benefits. Studies of GLP-1 agonists in patients with acute myocardial ischemia warrant further investigation in larger patient cohorts undergoing percutaneous coronary interventions. There is a dearth of data regarding the outcomes of GLP-1 agonists in patients with diabetes mellitus and heart failure, and clinical trials are necessary to establish safety. Although some evidence suggests that GLP-1 agonist therapy is associated with reductions in cardiovascular events, the related DPP-IV inhibitor drug class appears to offer no such benefit. Large trials of GLP-1 agonists currently underway will provide valuable long-term data on cardiovascular safety and clinical outcomes. Theoretical risks of pancreatitis have caused controversy, but available evidence supports the safety of GLP-1 agonist use. At present, identifying the optimal candidates for GLP-1 therapy necessitates an individualized assessment of glycemic control, medical comorbidities, and the presence of cardiovascular risk factors. GLP-1 agonist therapy can delay insulin initiation or reduce insulin doses. There may be a role for GLP-1 agonists in patients with prediabetes and cardiovascular risk factors, but this requires further study. In conclusion, cardiovascular risk factor reduction offers a compelling rationale to incorporate GLP-1 agonist therapy early in the management of diabetes mellitus in patients at risk for cardiovascular disease.

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