

The Intersection of Safety and Adherence: New Incretin-Based Therapies in Patients with Type 2 Diabetes Mellitus

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One of the challenges facing health care providers in the treatment of patients with type 2 diabetes mellitus is maintaining the balance between achieving hemoglobin A_{1c} targets while simultaneously minimizing adverse events—most notably hypoglycemia and weight gain—that may negatively affect adherence to therapy and thus treatment outcomes. Incretin-based treatments, such as glucagon-like peptide-1 (GLP-1)–receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, are the newest class of therapies for the management of patients with type 2 diabetes. Data from clinical trials in which liraglutide, exenatide, saxagliptin, or sitagliptin were employed as monotherapy or added to ongoing antidiabetic treatment indicate that the incretin-based therapies have very low risk for the development of hypoglycemia and either decrease body weight (GLP-1–receptor agonists) or are weight neutral (DPP-4 inhibitors). Decreased risk for hypoglycemia and weight gain may improve adherence. Avoiding weight gain, which is commonly associated with older oral antidiabetic agents and some insulins, also has the potential to decrease the risk for cardiovascular disease. Future pharmacoeconomic studies may demonstrate translation of these benefits into good cost-effectiveness for these therapies.

Key Words: cost, liraglutide, hypoglycemia, exenatide, sitagliptin, vildagliptin, saxagliptin, weight.

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An estimated 23.6 million people in the United States (7.8% of the population) have diabetes mellitus.¹ Diabetes was the seventh leading cause of death in the United States in 2006 and was listed as the underlying cause of death on 72,507 death certificates.¹ The American Diabetes Association (ADA) has estimated that the cost of diabetes in the United States is \$174 billion, with \$116 billion attributed to direct medical expenditure and \$58 billion attributed to lost productivity.² The patient and societal burden

resulting from diabetes is, in large measure, due to the long-term microvascular (e.g., retinal, renal) and macrovascular (e.g., cardiac) complications of this disease.^{2,3}

Results from landmark studies have demonstrated that treatment designed to meet conventional glycemic goals (i.e., hemoglobin A_{1c} [A1C] < 7%) can significantly decrease the risk of long-term complications of diabetes in patients with type 1 or type 2 disease.^{4,5} However, one of the challenges facing health care providers is maintaining the balance between achieving A1C targets while simultaneously minimizing adverse events, most notably hypoglycemia and weight gain, that may negatively affect adherence to therapy and thus treatment outcomes. The importance of striking such a balance is further

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underscored by the joint position statement of the ADA, the American College of Cardiology, and the American Heart Association that recommends that health care providers strive to minimize the occurrence of hypoglycemia and other adverse events while targeting A1C levels less than 7.0%.⁶

Factors other than the ability of the drug to achieve the desired goal (A1C lowering in the case of diabetes) contribute to the effectiveness versus the efficacy of therapy. The efficacy of an agent is the result produced under ideal conditions, such as those in a controlled clinical trial in which patients are carefully selected on the basis of well-defined entry criteria and closely managed to maximize adherence to treatment and minimize the consequences of treatment-associated adverse events. In contrast, effectiveness reflects the treatment benefit achieved with a given agent under real-world conditions in which adverse events and other factors may influence adherence to and persistence with treatment.⁷ Adverse events have two potentially important effects in determining the effectiveness of therapy. They may negatively affect patient adherence, and they may cause health care professionals to not titrate drug dosages to those shown to achieve the greatest efficacy in controlled clinical trials.⁸⁻¹⁰

Adherence to therapy is poor for many patients with diabetes, and failure to adhere to treatment has been linked to poor treatment outcomes for patients with this disease. A review of the literature from 1966–2003 indicated that adherence to oral hypoglycemic agents ranged from 36–93% among patients who continued their treatment for 6–24 months.¹¹ Results from multiple studies have demonstrated significant correlations between adherence to antidiabetic therapy and glycemic control in patients with type 2 diabetes. A cross-sectional study that included 800 patients who were managed in a diabetes clinic indicated that the mean A1C for patients with high adherence to treatment was 6.87% whereas the A1C for those with low adherence was 7.91% ($p \leq 0.01$).¹² Another retrospective observational study of 2741 patients with type 2 diabetes (medical records from only 249 patients had information about glycemic control) who were starting oral therapy indicated an overall adherence rate of 81%, with 65% of patients having 80% or greater adherence to prescribed dosing.¹³ Results from this study showed that each 10% increment in adherence was associated with a 0.1% reduction in A1C

level ($p=0.0004$). An observational records-based study of 1099 patients with type 2 diabetes who were receiving insulin indicated that mean adherence to insulin therapy was 71% and that treatment adherence was a significant predictor of A1C level.¹⁴

Patient adherence to therapy may also influence provider willingness to advance treatment when necessary in patients with type 2 diabetes. Results from a cohort of 2065 patients with type 2 diabetes who started treatment and were followed for 3 or more years indicated that those in the lowest quartile for adherence to their treatment regimens were significantly less likely to have their treatment intensified within 12 months of their first elevated A1C value than those in the highest quartile for adherence.¹⁵ These results support the view that poor adherence not only interferes with the potential effectiveness of prescribed antidiabetic therapy, but also contributes to the clinical inertia that often characterizes management of patients with type 2 diabetes.^{15, 16}

An economic analysis suggested that there may be a considerable cost benefit to optimizing adherence and thus A1C lowering with antidiabetic drugs.¹⁷ If patients who had not achieved the ADA's recommended A1C level of below 7.0% would meet and maintain these levels, it was estimated that \$35 billion in direct medical cost savings over 10 years would result. When the indirect costs of inadequately controlled diabetes were considered, this estimate increased to \$50 billion (4% of total annual U.S. health care costs).

Hypoglycemia

Hypoglycemia is a key adherence-limiting factor in many patients with diabetes. Intensive glycemic control is associated with an increased frequency of hypoglycemia,⁴ and studies suggest that hypoglycemia may be a major barrier to the achievement of goal A1C values.¹⁸ Hypoglycemia may occur in patients being treated with certain oral agents or insulin. Sulfonylureas stimulate the release of insulin from β cells by binding to sulfonylurea receptors, which results in closure of potassium channels, β -cell depolarization, and exocytosis of insulin. All of these actions are independent of plasma glucose levels; and longer-acting sulfonylureas (e.g., glyburide) are associated with higher risk for hypoglycemia.^{19, 20} The risk for this adverse effect is lower with shorter-acting sulfonylureas (e.g., repaglinide).²⁰

²¹ Compared with sulfonylureas, oral antidiabetic agents that have other mechanisms of action, including metformin and thiazolidinediones, have been associated with a lower frequency of hypoglycemia.^{21, 22}

Insulin therapy is often associated with hypoglycemia, which may be due, at least in part, to mismatching of the pharmacokinetic and pharmacodynamic profiles of older insulins (regular human insulin and neutral protamine Hagedorn [NPH] insulin) and physiologic insulin secretion. The advent of long- and rapid-acting insulin analogs has significantly decreased, but not eliminated, hypoglycemia in patients receiving insulin therapy.^{23, 24} Other factors not directly related to antidiabetic agents that may contribute to development of hypoglycemia are defective and deficient counterregulatory responses and relative hyperinsulinization.^{18, 25}

The majority of hypoglycemic episodes manifest as mild symptoms that usually respond to self-management; however, with severe hypoglycemia, symptoms can become quite serious and result in loss of consciousness, seizures, coma, or even death. As a result, patients with diabetes may experience significant fear associated with the possibility of experiencing hypoglycemic events. This can have an important impact on their health-related quality of life.²⁶ In addition, there can be significant maladaptive behavioral modifications that arise as a result of hypoglycemia, which can include an avoidance of intensification of therapy or a failure to take drug therapy to achieve blood glucose targets.^{27, 28} Perhaps more troubling is the possibility that patient nonadherence, which may originate due to fear of hypoglycemia, may lead to a worsening of hypoglycemia frequency and severity through inappropriate intensification of therapy by the health care provider.²⁹ In this case, health care providers, concerned that patients are not achieving A1C goals, respond with more aggressive medical management, possibly resulting in severe cases of hypoglycemia.

The risk for hypoglycemia is increased in the elderly, and this adverse event may have very serious consequences in this population. Elderly patients with diabetes may have more impaired regulation of blood glucose than younger individuals with the disease. In addition, elderly patients are more likely to be taking drugs that may decrease hypoglycemia awareness (e.g., β -blockers). Decreased kidney function may reduce clearance of some oral antidiabetic drugs,

and older patients may become confused and take extra doses of drugs.³⁰ Hypoglycemia may lead to serious falls in the elderly, and it is also associated with increased mortality risk in older hospitalized patients.^{30, 31} Blood glucose excursions may also be larger and more frequent in elderly individuals with diabetes and may increase the risk for hypoglycemic and hyperglycemic episodes.³²

A complete understanding of the impact of hypoglycemia on morbidity and mortality of patients with diabetes is still a focus of much interest, and our knowledge in this area continues to develop. A recent review of results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial suggested that this adverse event may have contributed to mortality in some patients who died during the study.³³ It was suggested further that future studies of cardiovascular risk reduction in patients with diabetes should focus on treatments with lower risk for hypoglycemia. It has also been shown that a history of severe hypoglycemic episodes in elderly patients with type 2 diabetes is associated with increased risk for dementia.³⁴

Incretin-Based Therapy and Hypoglycemia in Patients with Type 2 Diabetes

Incretin-based drugs, such as the glucagon-like peptide-1 (GLP-1)-receptor agonists and the dipeptidyl peptidase-4 (DPP-4) inhibitors, are the newest class of therapies for the management of patients with type 2 diabetes. These drugs increase the levels of GLP-1, either by activating the GLP-1 receptor or by slowing the degradation of native GLP-1. An important advantage of these agents is that GLP-1 does not cause glucose-independent increases in insulin secretion and does not result in substantial increases in insulin concentrations or action independent of elevations in glucose level.^{35, 36} Therefore, it might be expected that these agents would have a low risk for hypoglycemia when used to treat patients with diabetes. However, administration of a GLP-1-receptor agonist does increase insulin secretion in the absence of glucose level elevations if used in combination with sulfonylurea drugs. Some 30–40% of patients treated with both a sulfonylurea and a GLP-1-receptor agonist experience mild hypoglycemia. This is because sulfonylureas increase β -cell adenosine triphosphate potassium channel activity and increase insulin secretion independent of glucose level elevations; this

Table 1. Rates of Minor Hypoglycemia and Changes in Body Weight Reported in Liraglutide Studies

Study	Duration (wks)	Treatment Groups	Rate of Minor Hypoglycemia	Weight Change (kg) ^a
LEAD-1 (n=1041) ³⁷	26	Liraglutide 0.6, 1.2, or 1.8 mg/day Rosiglitazone 4 mg/day Placebo (+ ongoing glimepiride 2–4 mg/day in all groups)	Liraglutide groups ^{a, b} : 0.6 mg: 0 1.2 mg: 0.34 (p=0.0024 vs rosiglitazone and p=0.048 vs placebo) 1.8 mg: 0.30 (p=0.0065 vs rosiglitazone) Rosiglitazone: –0.05 Placebo: 0.17	Liraglutide groups: 0.6 mg: 0.8 (p<0.05 vs placebo, p<0.0001 vs rosiglitazone) 1.2 mg: 0.4 (p<0.05 vs placebo, p<0.0001 vs rosiglitazone) 1.8 mg: –0.2 (p<0.05 vs placebo, p<0.0001 vs rosiglitazone) Rosiglitazone: 0.22 (p<0.05 vs placebo) Placebo: –0.1
LEAD-2 (n=1091) ³⁸	26	Liraglutide 0.6, 1.2, or 1.8 mg/day Glimepiride 4 mg/day Placebo (+ ongoing metformin 1 g twice/day in all groups)	Liraglutide groups ^c : 0.6 mg: 1.2% 1.2 mg: –1.7% 1.8 mg: 0% Glimepiride: 14.4% (p<0.001 vs combined liraglutide) Placebo: 2.5%	Liraglutide groups: 0.6 mg: –4.3 1.2 mg: –5.1 1.8 mg: –5.3 Glimepiride: –1.6 (p<0.0001 vs combined liraglutide) Placebo: 2.5
LEAD-3 (n=746) ³⁹	52	Liraglutide 1.2 or 1.8 mg/day Glimepiride 8 mg/day	Liraglutide groups ^{a, b} : 1.2 mg: 0.30 1.8 mg: 0.25 Glimepiride: 1.96 (p<0.0001 vs each liraglutide dose)	Liraglutide groups: 1.2 mg: –2.05 1.8 mg: –2.45 Glimepiride: 1.12 (p=0.0001 vs each liraglutide dose)
LEAD-4 (n=533) ⁴⁰	26	Liraglutide 1.2 or 1.8 mg/day Placebo (+ ongoing metformin 1 g twice/day + rosiglitazone 4 mg twice/day in both groups)	Liraglutide groups ^{a, b} : 1.2 mg: 0.2 1.8 mg: 0.4 Placebo: 0.2	Liraglutide groups: 1.2 mg: –1.6 (p<0.0001 vs placebo) 1.8 mg: –2.6 (p<0.0001 vs placebo) Placebo: 0.6
LEAD-5 (n=581) ⁴¹	26	Liraglutide 1.8 mg/day Insulin glargine Placebo (+ ongoing metformin 1 g twice/day + glimepiride 2–4 mg/day in all groups)	Liraglutide: 10.7% ^c Insulin glargine: 12.2% Placebo: 16.7%	Liraglutide: –3.43 (insulin glargine [p<0.0001] and placebo [p=0.0001]) Insulin glargine: –2.04 Placebo: 1.62
LEAD-6 (n=434) ⁴²	26	Liraglutide 1.8 mg/day Exenatide 10 µg twice/day (+ ongoing metformin and/or sulfonylurea in both groups)	Liraglutide: 1.93 ^{a, b} Exenatide: 2.60 (p=0.0131 vs liraglutide)	Liraglutide: –3.24 Exenatide: –2.87

Between-group differences are not significant if no p value is presented.

^aData are placebo-corrected values for active agents; negative values indicate hypoglycemia rates were lower than placebo and body weight reductions were greater than placebo. Actual absolute values are presented for placebo.

^bData are mean no. of events/patient-year.

^cData are percentages of patients with event, not normalized by study duration.

hypoglycemic effect is enhanced by a GLP-1-receptor agonist in the presence of increased glucose levels.³⁵

Glucagon-Like Peptide-1–Receptor Agonists

Liraglutide

Liraglutide is a new once-daily human GLP-1-receptor agonist that has been approved in

Europe for the treatment of type 2 diabetes and is in late-stage review by the U.S. Food and Drug Administration (FDA). The Liraglutide Effect and Action in Diabetes (LEAD) studies have provided most of the data on this drug (Table 1^{37–42}). These six studies evaluated the effects of liraglutide on glycemic control, body weight, and β-cell function, and established the safety and tolerability profiles of this new GLP-1-receptor

Table 2. Rates of Hypoglycemia and Changes in Body Weight Reported in Exenatide Studies

No. of Patients	Study Duration (wks)	Treatment Groups	Rate of Hypoglycemia ^a	Weight Change (kg) ^a
232 ⁴⁴	24	Exenatide 5 or 10 µg twice/day Placebo	Exenatide groups ^b : 5 µg: 0.18 10 µg: 0.50 Placebo: 0.03 (p=0.01 vs combined exenatide)	Exenatide groups: 5 µg: -1.4 (p=0.004 vs placebo) 10 µg: -2.0 (p<0.001 vs placebo) Placebo: -1.4
501 ⁴⁵	52	Exenatide 5 µg twice/day x 4 wks, then 10 µg twice/day thereafter Biphasic insulin aspart (+ ongoing metformin + sulfonylurea in both groups)	Exenatide: 4.7 ^b Insulin: 5.6	Exenatide: -2.9 (p<0.001 vs insulin) Insulin: 2.6
138 ⁴⁶	32	Exenatide 10 µg twice/day Insulin glargine	Exenatide: 14.7% ^c Insulin: 25.2%	Exenatide: -1.6 Insulin: 0.6 (p<0.001 vs exenatide)
551 ⁴⁷	26	Exenatide 10 µg twice/day Insulin glargine	Exenatide: 7.3 ^b Insulin: 6.3	Exenatide: -2.3 Insulin: 1.8 (p<0.001 vs exenatide)

Between-group differences are not significant if no p value is presented.

^aData are placebo-corrected values for active agents; negative values indicate hypoglycemia rates were lower than placebo and body weight reductions were greater than placebo. Actual absolute values are presented for placebo.

^bData are mean no. of events/patient-year.

^cData are percentages of patients.

agonist in patients with type 2 diabetes who were unable to maintain glycemic control with dietary modification and exercise alone or with other single or combination oral antidiabetic drugs. In the LEAD trials, liraglutide was examined as monotherapy and in combination with one or two oral agents. Minor hypoglycemia was defined as a plasma glucose concentration below 56 mg/dl or whole-blood glucose concentration below 50 mg/dl, with or without symptoms of hypoglycemia, that was managed by the patient.³⁷ Major hypoglycemia was defined as hypoglycemia requiring third-party assistance or medical intervention.³⁷ Major hypoglycemic episodes were rare with liraglutide and occurred only when it was used in combination with a sulfonylurea.⁴³ In the LEAD-1 study, there was a slightly, but significantly, higher incidence of minor hypoglycemia with liraglutide than with placebo and rosiglitazone, when each was added to glimepiride (p=0.0024 and p=0.048 for liraglutide 1.2 mg/day vs rosiglitazone and placebo, respectively; and p=0.0065 for liraglutide 1.8 mg/day vs rosiglitazone).³⁷ In the LEAD-2 study, there was a significantly lower frequency of minor hypoglycemia with liraglutide 0.6–1.8 mg/day than with glimepiride when each was added to metformin (p<0.001 for combined liraglutide versus glimepiride).³⁸ Results from the LEAD-3 study also indicated a significantly lower incidence of minor hypoglycemia with

liraglutide 1.2 and 1.8 mg/day versus glimepiride when each was used as monotherapy (p<0.0001 for each comparison).³⁹ Results from the LEAD-4 study indicated no significant differences in the incidence of minor hypoglycemia between liraglutide 1.2 or 1.8 mg/day and placebo when added to metformin.⁴⁰ There were also no significant differences in the frequency of minor hypoglycemia when liraglutide 1.8 mg/day, placebo, or insulin glargine was added to metformin and glimepiride in the LEAD-5 study.⁴¹ The incidence of minor hypoglycemia was significantly lower for liraglutide 1.8 mg/day versus exenatide (p=0.0131) in the LEAD-6 study when each was added to metformin, a sulfonylurea, or a combination of both agents.⁴²

Exenatide

Exenatide has been used as monotherapy or add-on treatment in a large number of studies in patients with type 2 diabetes. The agent has been directly compared with insulin in several trials. The monotherapy trial and comparative studies are summarized in Table 2.^{44–47} Results from a comparison of exenatide 5 or 10 µg twice/day and placebo as monotherapy indicated a significantly higher incidence of hypoglycemia (defined as signs or symptoms of hypoglycemia, or a self-monitored blood glucose level below 64 mg/dl, regardless of whether it was associated

Table 3. Rates of Hypoglycemia and Changes in Body Weight Reported in Sitagliptin Studies

No. of Patients	Study Duration (wks)	Treatment Groups	Rate of Hypoglycemia ^a	Weight Change (kg) ^b
521 ⁴⁸	18	Sitagliptin 100 or 200 mg/day Placebo	Sitagliptin groups: 100 mg: 1.5% 200 mg: 1.0% Placebo: 0%	Sitagliptin groups: 100 mg/day: 0.1 200 mg/day: 0.5 Placebo: -0.7
741 ⁴⁹	24	Sitagliptin 100 or 200 mg/day Placebo	Sitagliptin groups: 100 mg: 1.3% 200 mg: 0.8% Placebo: 0%	Sitagliptin groups: 100 mg: 0.9 200 mg: 1.0 Placebo: -1.1 (p<0.01 vs combined sitagliptin)
1172 ⁵⁰	52	Sitagliptin 100 mg/day Glipizide 20 mg/day (+ ongoing metformin ≥ 1500 mg/day in both groups)	Sitagliptin: 5% Glipizide: 32% (p<0.001 vs sitagliptin)	Sitagliptin: -1.5 Glipizide: 1.1 (p<0.001 vs sitagliptin)

Between-group differences are not significant if no p value is presented.

^aData are percentages of patients.

^bData are placebo-corrected values for active agents; negative values indicate body weight reductions were greater than placebo. Actual absolute values are presented for placebo.

with signs, symptoms, or treatment) with exenatide (p=0.01).⁴⁴ A comparison of exenatide, titrated to 10 µg twice/day, versus biphasic insulin aspart, each added to metformin plus a sulfonylurea, indicated similar risk of hypoglycemia (defined as a blood glucose level below 60 mg/dl or symptoms of hypoglycemia).⁴⁵ A comparison of exenatide with insulin glargine in patients with diabetes not controlled by metformin or sulfonylurea treatment also indicated similar risks of hypoglycemia (defined as any sign or symptom of hypoglycemia associated with a serum glucose level below 60 mg/dl).⁴⁶ However, three patients who received insulin glargine and none treated with exenatide experienced severe hypoglycemia (defined as a symptomatic episode associated with a glucose level below 50 mg/dl that required another person's assistance or recovery occurred after the administration of oral carbohydrate, glucagon, or intravenous glucose). Another comparison of exenatide and insulin glargine also indicated similar overall rates of hypoglycemia (defined as a blood glucose level below 60 mg/dl with symptoms of hypoglycemia).⁴⁷ Four patients in each treatment group experienced an episode of severe hypoglycemia (defined as a blood glucose below 50 mg/dl and requiring assistance from another person or prompt recovery occurred after administration of oral carbohydrate, glucagon, or intravenous glucose).

Dipeptidyl Peptidase-4 Inhibitors

Sitagliptin has been available in the United States for several years, and a second DDP-4 inhibitor, saxagliptin, has recently been approved by the FDA (Tables 3 and 4).⁴⁸⁻⁵⁵

Sitagliptin

Results from two studies in which sitagliptin was administered as monotherapy indicated no significant difference in the frequency of hypoglycemia (not defined in the study methods of either trial) versus placebo.^{48, 49} A comparison of the effects of adding sitagliptin or glipizide treatment in patients not adequately controlled with metformin indicated a significantly lower frequency of hypoglycemia with sitagliptin versus the sulfonylurea (p<0.001).⁵⁰

Saxagliptin

The efficacy and safety of saxagliptin have been evaluated in five clinical trials in which the drug was administered as monotherapy or combined with either metformin or glyburide.⁵¹⁻⁵⁵ Results from two comparisons of monotherapy with saxagliptin 2.5, 5, or 10 mg/day⁵¹ and 2.5, 5, 10, 20, or 40 mg/day⁵² versus placebo indicated no significant differences among treatments in the frequency of hypoglycemia (reported as adverse events based on symptoms only). There were also no significant differences in the frequency of hypoglycemia when saxagliptin 2.5 or 5 mg/day

Table 4. Rates of Hypoglycemia and Changes in Body Weight Reported in Saxagliptin Studies

No. of Patients	Study Duration (wks)	Treatment Groups	Rate of Hypoglycemia ^a	Weight Change (kg) ^a
401 ⁵¹	24	Saxagliptin 2.5, 5, or 10 mg/day Placebo	Saxagliptin groups: 2.5 mg: -3.4% 5 mg: -1.6% 10 mg: 1.9% Placebo: 6.3%	Saxagliptin groups: 2.5 mg: 0.2 5 mg: 1.3 10 mg: 1.3 Placebo: -1.4
338 ⁵²	12	Saxagliptin 2.5, 5, 10, 20, or 40 mg/day Placebo	Saxagliptin groups: 2.5 mg: NR 5 mg: NR 10 mg: 3.3% 20 mg: NR 40 mg: 6.2% Placebo: 1.5%	Saxagliptin groups: 2.5 mg: -1.54 5 mg: -1.43 10 mg: -0.74 20 mg: -1.79 40 mg: -0.62 Placebo: 0.51
768 ⁵³	24	Saxagliptin 2.5 or 5 mg/day + glyburide 7.5 mg/day Placebo + glyburide 10 mg/day	Saxagliptin groups: 2.5 mg: 3.2% 5 mg: 4.5% Placebo: 10.1%	Saxagliptin groups: 2.5 mg: 0.4 5 mg: 0.5 Placebo: 0.3
1306 ⁵⁴	24	Saxagliptin 10 mg/day, 5 mg/day + metformin 500 mg/day, or 10 mg/day + metformin 500 mg/day Metformin 500 mg/day	Saxagliptin groups: 10 mg: 1.5% 5 mg + metformin: 3.4% 10 mg + metformin: 5.0% Metformin: 4.0%	Saxagliptin groups: 10 mg: -1.1 5 mg + metformin: -1.8 10 mg + metformin: -1.4 Metformin: -1.6
743 ⁵⁵	24	Saxagliptin 2.5, 5, or 10 mg/day Placebo (+ ongoing metformin 1500–2500 mg/day in all groups)	Saxagliptin groups: 2.5 mg: 2.8% 5 mg: 0.2% 10 mg: -1.1% Placebo: 5.0%	Saxagliptin groups: 2.5 mg: -0.51 5 mg: 0.05 10 mg: 0.39 Placebo: -0.92

NR = not reported.

Data for hypoglycemia are frequencies reported as adverse events based on symptoms only.

Between-group differences are not significant if no p value is presented.

^aData are placebo-corrected values for active agents; negative values indicate hypoglycemia rates were lower than placebo and body weight reductions were greater than placebo. Actual absolute values are presented for placebo.

or placebo was added to glyburide.⁵³ Combined results from these studies also indicated that 15 (0.4%) of 3556 patients receiving saxagliptin had symptomatic hypoglycemia confirmed by a fingerstick blood glucose level of 50 mg/dl or below. This proportion was approximately the same as that for placebo.^{51–55}

Summary

Results from clinical trials that have compared incretin-based therapies with placebo or other antidiabetic agents suggest that these new treatments have a low risk for hypoglycemia. However, it should be kept in mind that the hypoglycemic events were generally patient-reported events in most of the trials discussed. As might be expected from their mechanism of action, the frequency of hypoglycemia with these agents should be substantially lower than that for sulfonylureas and generally equivalent to that for

oral agents that do not directly and independently stimulate insulin secretion. When combined with oral insulin secretagogues, the frequencies of hypoglycemia with liraglutide and exenatide also appear similar to that for insulin glargine, a long-acting insulin analog that has been demonstrated to have a low frequency of hypoglycemia in many clinical trials.⁵⁶

Weight Gain

Prevention and treatment of obesity are major clinical problems encountered in the management of type 2 diabetes, and as many as 90% of patients with this disease are overweight.⁵⁷ Results from the most recent National Health and Nutrition Education Survey (1998–2004) indicated that more than 50% of undiagnosed diabetes in the United States is in obese adults and that being overweight confers a 50% increase in the risk for diabetes.⁵⁸ Obesity is associated

with very high medical costs. In 1998 the medical costs of obesity were estimated to be \$78.5 billion, with approximately 50% of this total funded by Medicare and Medicaid. Additional analyses indicated that the increased prevalence of obesity in the United States resulted in nearly \$40 billion of increased medical spending through 2006. It was estimated that the annual medical costs of obesity would be \$147 billion in 2008.⁵⁹

Treatment of type 2 diabetes with either oral agents or insulin can increase body weight, and the risk for this adverse event varies substantially from one agent to another. Among oral drugs, both thiazolidinediones (i.e., pioglitazone) and sulfonylureas have been associated with weight gain,^{60, 61} whereas metformin has been shown to result in weight reduction.⁶² Insulin treatment has also been shown to be associated with increases in body weight in patients with diabetes. However, the increases are smaller with long- and rapid-acting insulin analogs versus regular human and NPH insulin.^{63–66} Weight gain in patients receiving insulin may occur due to decreased glycosuria, resulting in more glucose absorption and higher retention of calories consumed. It may also result from patients eating more food to treat or prevent hypoglycemia or perceived hypoglycemia associated with intensive insulin treatment.⁶⁷

Available evidence suggests strongly that weight gain negatively affects adherence to treatment in patients with diabetes; this finding was substantiated in a survey of patients with type 2 diabetes.⁶⁸ A study of 99 patients with type 2 diabetes also indicated a negative relationship between body mass index and adherence to antidiabetic treatment.⁶⁹ Results from a survey of 5088 patients with type 1 or 2 diabetes indicated that 25% were concerned about body weight,⁷⁰ and results from a smaller survey of 121 patients with type 2 diabetes indicated that concern about weight gain was significantly correlated with lower adherence to treatment.⁷¹

It should also be emphasized that treatment-associated weight gain may negatively affect clinical outcomes of patients with diabetes in ways unrelated to adherence to treatment. Results from the Diabetes Control and Complications Trial (DCCT) showed that greater treatment-associated weight gain in patients intensively undergoing insulin therapy was associated with elevations in systolic blood pressure (7 mm Hg higher among patients in the

highest quartile for weight gain vs the lowest) and triglyceride (7.8% vs –14.4%), total cholesterol (3.8% vs –5.9%), and low-density lipoprotein cholesterol (6.8% vs –8.7%) levels, and reductions in high-density lipoprotein cholesterol (–3.8% vs 2.2%) levels. These results suggest that adverse effects of intensive insulin treatment on these factors may be more important than the reduction in A1C in determining the overall cardiovascular risk for patients with diabetes.⁷² Conversely, weight loss in patients with diabetes has been associated with decreased risk for all-cause mortality, as well as diabetes-specific and cardiovascular disease-specific mortality.⁷³ Weight loss in newly diagnosed patients with type 2 diabetes is associated with improved glycemic and blood pressure control. In contrast, patients with stable weight or weight gain are more likely to have above-goal A1C and blood pressure values.⁷⁴

Weight Changes Associated with Incretin-Based Therapies

Results from several recent meta-analyses have demonstrated that GLP-1-receptor agonists are generally associated with reductions in body weight in patients with diabetes.^{75–77} A meta-analysis has also indicated that DPP-4 inhibitors are weight neutral.⁷⁵ All of these findings are consistent with those in the clinical trials discussed earlier (Tables 1–4).^{37–42, 44–55}

In the LEAD studies, change in body weight was examined as a secondary end point, and it was powered to detect a 3% difference in all studies except LEAD-6, which did not provide this information. Results for liraglutide versus rosiglitazone or placebo as add-on therapy to glimepiride indicated all liraglutide doses resulted in significantly less weight gain than rosiglitazone (all $p < 0.0001$), and the liraglutide 1.8-mg group also had significantly less weight gain relative to placebo ($p < 0.05$).³⁷ Liraglutide was also associated with less weight gain than glimepiride when both drugs were added to metformin ($p < 0.0001$);³⁸ or when each was used as monotherapy ($p = 0.0001$).³⁹ Liraglutide also resulted in significantly less weight gain compared with placebo when both were added to metformin ($p < 0.0001$),⁴⁰ and compared with insulin glargine ($p < 0.0001$) or placebo ($p = 0.0001$) when all were added to metformin plus glimepiride.⁴¹ Addition of either liraglutide or exenatide to metformin and/or a sulfonylurea resulted in similar weight reductions.⁴²

Results for exenatide indicated that it was associated with significantly greater reductions in body weight versus placebo ($p=0.004$ for the 5- μg group and $p<0.001$ for the 10- μg group), biphasic insulin aspart ($p<0.001$), and insulin glargine ($p<0.001$ in each of two trials).^{44–47}

Clinical trials with sitagliptin indicated that the agent resulted in a significantly greater weight gain from baseline versus placebo ($p<0.01$) in one of two studies and significantly less weight gain than glipizide when each was added to metformin ($p<0.001$).^{48–50} Results from clinical trials with saxagliptin also indicated that treatment with this DPP-4 inhibitor was associated with reductions in body weight. However, none of these decreases were significantly different from those observed with placebo, metformin, or for the combination of saxagliptin plus glyburide versus up-titrated glyburide.^{51–55}

Economic Consequences of Hypoglycemia, Weight Gain, and Poor Adherence to Antidiabetic Therapy

Hypoglycemia, weight gain, and poor adherence have all been shown to significantly increase the cost of managing patients with diabetes. Analysis of claims data from a large Midwestern health plan from 1992–1998 identified 7659 members (2118 treated with insulin) with type 1 or type 2 diabetes.⁷⁸ Over the 6-year period, 16% of insulin-treated patients experienced hypoglycemia that required medical attention with a mean cost/episode of \$1186 (\$7.04/patient-mo). Whereas the cost of managing insulin-associated hypoglycemia was lower than that related to the long-term complications of diabetes, this financial burden to the health plan was still viewed as significant.

Results from a more recent study of 2443 employees with diabetes requiring insulin therapy and for whom information about short-term disabilities and medical encounters was available indicated that 16.6% had a diagnosis of hypoglycemia (19.9% of those using insulin and 4.0% of those taking oral drugs) during an average follow-up of 2.5 years.⁷⁹ Hypoglycemia resulted in 40%, 53%, and 15% more hospitalizations, emergency department visits, and outpatient care visits, respectively, and the annualized medical cost for patients with hypoglycemia was \$3241. Patients with hypoglycemia also had 77% more short-term disability days than those not experiencing this

event. It was noted that mild episodes of hypoglycemia that did not lead to a medical intervention may still have caused adverse effects that are not included in these estimates.

Results from a recent study indicated that even a small increase in body weight may be associated with a significant increase in treatment costs in patients with type 2 diabetes.⁸⁰ In this study, administrative claims, electronic laboratory data, and medical record information were abstracted for 458 patients with type 2 diabetes enrolled in a health maintenance organization from July 1, 1997–October 31, 2005. Patients included in the study had a baseline weight measurement and a second weight measurement approximately 6 months later. They were also required to be receiving at least one antidiabetic drug therapy within 1 month of the baseline weight measurement date. Overall, 48.9% of patients experienced weight gain of at least 1 pound between the two weight measurements and were considered weight gainers. The average 1-year total health care cost was \$7260 for those who gained weight (3.9% increase in weight) and \$5541 for those who did not ($p=0.046$), and the mean diabetes-related costs were \$2141 and \$1869, respectively ($p=0.006$). Economic analysis of results from the DCCT showed that intensive insulin therapy, even with associated weight gain, decreased the costs associated with diabetes complications, but that intensive treatment without weight gain achieved these benefits plus a further \$523/patient decrease in treatment costs.⁸¹

Adherence also has a significant influence on health care costs for patients with diabetes. A systematic literature review from 1990–2005 indicated that high adherence to antidiabetic therapy was associated with a reduction in health care costs that were mostly related to a reduction in hospitalizations.⁸² A retrospective analysis using insurance claims data for 57,687 patients with diabetes indicated that increased adherence to therapy was associated with fewer emergency department visits and inpatient admissions, as well as decreased medical costs.⁸³ Similarly, analysis of results for 775 patients in a Medicare health maintenance organization showed that adherence to treatment, as measured by medication possession ratio, was the strongest predictor of annual health care costs and that there was an 8.6–28.9% reduction in total health care costs with each 10% increase in medication possession ratio ($p<0.001$).⁸⁴

Although not focused exclusively on

Table 5. Comparison of Treatment Outcomes in the LEAD-1 Study

Outcome	Liraglutide 1.8-mg Group	Liraglutide 1.2-mg Group	Rosiglitazone 4-mg Group
Hemoglobin A _{1c} (%)	-1.13 ± 1.05 ^a	-1.08 ± 1.04 ^a	-0.44 ± 1.05
Systolic blood pressure (mm Hg)	-2.81 ± 13.07	-2.56 ± 1.04	-0.93 ± 12.71
Lipid levels (mg/dl)			
Total cholesterol	-11.99 ± 13.07 ^a	5.06 ± 37.31	7.42 ± 37.14
LDL	-8.09 ± 29.85 ^a	-2.36 ± 29.28	4.43 ± 29.15
HDL	-1.57 ± 7.50 ^a	-0.84 ± 7.28	0.75 ± 7.23
Triglycerides	-14.72 ± 132.28 ^a	-17.64 ± 130.23 ^a	1.73 ± 129.63
Body mass index (kg/m ²)	-0.08 ± 1.11 ^a	0.12 ± 1.13	0.78 ± 1.13
Major hypoglycemia (events/patient/year)	0.01	0	0
Minor hypoglycemia (events/patient/year)	0.47	0.50	0.12

Data are mean ± SD changes from baseline or mean values.

^aDifference was significant (p<0.05) compared with rosiglitazone 4-mg group.

HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol.

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hypoglycemia, weight gain, or adherence, pharmacoeconomic analysis supports the use of incretin-based therapies. The economic benefit of liraglutide has been compared with that of rosiglitazone using data from LEAD-1. This analysis employed the Center for Outcomes Research (CORE) diabetes model, a validated cohort model that uses epidemiologic data from long-term clinical trials to simulate morbidity, mortality, and costs of diabetes.⁸⁵ This model projects outcomes for patient populations with diabetes. It includes information about baseline cohort characteristics and history of complications, diabetes management, concomitant drugs, screening strategies, and changes in physiologic parameters over time. The modeling study included hypothetical cohorts of 5000 patients with type 2 diabetes treated with liraglutide 1.2 or 1.8 mg/day or rosiglitazone 4 mg/day who were followed for 30 years. As the price for liraglutide in the United States is still yet to be determined, this analysis considered only the cost of complications and concomitant drugs (e.g., statins, aspirin) but not the antidiabetic regimens studied (liraglutide or rosiglitazone). Results based on changes from baseline for A1C, lipid profiles, blood pressure, body mass index, and risks for major and minor hypoglycemic events observed with these treatments in LEAD-1 (Table 5) indicated 30-year survival rates of 15.0% and 16.0% for liraglutide 1.2 and 1.8 mg/day versus 12.6% for rosiglitazone.⁸⁶ The respective cardiovascular death rates after 30 years were 69.7%, 68.4%, and

72.5%. Overall cumulative costs/patient were \$38,963 and \$39,239, respectively, for liraglutide 1.2 and 1.8 mg/day versus \$40,401 for rosiglitazone.

Results from a second modeling study used the CORE diabetes model to assess the economic benefits of treatment with metformin alone or metformin plus a sulfonylurea (glimepiride) versus liraglutide plus metformin in patients with type 2 diabetes.⁸⁷ Modeling results indicated that the superior glycemic and weight control achieved with liraglutide plus metformin (0.82% and 3 kg lower compared with metformin alone and glimepiride plus metformin, respectively) would result in increases in life expectancy of 0.33 and 0.18 years, respectively, and in quality-adjusted life expectancy of 0.29 and 0.14 quality-adjusted life-years, respectively, versus metformin alone and metformin plus sulfonylurea. These results suggest that the short-term metabolic benefits of adding liraglutide to metformin may result in long-term improvements in clinical outcomes, but further prospective studies are needed to address this issue.

As with all new classes of drugs, more information regarding the cost-effectiveness of GLP-1-receptor agonists and DPP-4 inhibitors is required. Most pharmacoeconomic analyses are conducted in conjunction with phase IV clinical trials as part of the postmarketing surveillance process. This is in part due to the fact that the FDA does not mandate inclusion of pharmacoeconomic data to gain approval. Nevertheless, insurance groups, managed care institutions, and

hospital formulary committees will need these data to make a more informed, rational decision about the pharmacoeconomic value provided by incretin-based therapies.

Conclusion

The effectiveness of antidiabetic therapy in routine clinical practice is influenced by multiple variables, including efficacy demonstrated in controlled clinical trials as well as additional factors—most notably adherence—that determine how drug therapy is actually used. The occurrence of adverse events can negatively affect adherence, and this has been shown to be the case for both hypoglycemia and treatment-associated weight gain in patients with diabetes. Results obtained to date for incretin-based antidiabetic therapies support the view that these agents have low risk for hypoglycemia and are either weight neutral or decrease body weight. These effects have not been directly linked to enhancement of adherence with incretin-based treatment, but it is reasonable to suggest that relationships that apply to both oral antidiabetic drugs and insulin will also be the case for GLP-1-receptor agonists and DPP-4 inhibitors. Hypoglycemia, weight gain, and poor adherence have all been associated with increased overall cost of care for patients with diabetes, and therapies, such as incretins, that positively affect all of these variables may ultimately be shown to decrease the cost of care.

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