BACKGROUND: Effective glycemic control can reduce the risk of serious micro- and macrovascular complications in type 2 diabetes. However, many patients fail to reach glycemic targets due partly to low efficacy and adverse effects of treatment such as hypoglycemia or weight gain.

OBJECTIVE: To evaluate the short-term cost-effectiveness of liraglutide versus sitagliptin, in terms of cost per patient reaching a glycated hemoglobin (HbA1c) target with no hypoglycemia and no weight gain after 52 weeks, based on a recently published trial.

METHODS: Data were taken from a 52-week randomized, controlled trial (NCT00700817) in which adults with type 2 diabetes (mean age = 55 years, HbA1c = 8.4%, body mass index = 33 kg/m²) failing metformin monotherapy were randomly allocated to receive either liraglutide 1.2 mg, liraglutide 1.8 mg, or sitagliptin 100 mg daily, in addition to metformin. For the cost-effectiveness analysis, the proportion of patients achieving a clinically relevant composite endpoint, defined as HbA1c < 7.0%, with no reported hypoglycemia and no gain in body weight, was estimated using logistic regression. Trial data showed that 38.9% of patients on liraglutide 1.2 mg and 49.9% on liraglutide 1.8 mg achieved the composite endpoint, compared with 18.6% on sitagliptin at 52 weeks. Costs of antihyperglycemia medications were accounted for based on published wholesale acquisition costs in 2012 U.S. dollars.

RESULTS: Overall pharmacy costs (needle costs included) were higher for patients on liraglutide than sitagliptin. The cost per patient achieving an HbA1c less than 7% was lowest for patients receiving liraglutide 1.2 mg ($7,993) and highest for patients receiving sitagliptin ($11,570). When expressed as the mean cost per patient reaching target HbA1c with no hypoglycemia or weight gain (cost of control), costs were notably lower on liraglutide than on sitagliptin. Annual mean costs of control were $10,335 on liraglutide 1.2 mg and $11,755 on liraglutide 1.8 mg versus $16,858 on sitagliptin.

CONCLUSION: The mean cost per patient achieving control, defined as reaching HbA1c target with no hypoglycemia or weight gain, was lower with liraglutide than with sitagliptin based on data from a recently published 52-week clinical trial.


What this study adds

• In the United States alone, the American Diabetes Association estimated the total annual cost of diabetes at $174 billion in 2007, comprising $116 billion in medical expenditure and $58 billion in reduced workplace productivity.
• The LIRA-DPP-4 study reported by Pratley et al. (2010) and Pratley et al. (2011) compared the safety and efficacy of liraglutide 1.2 mg and liraglutide 1.8 mg with sitagliptin 100 mg in type 2 diabetes patients previously failing metformin therapy.
• The key challenges in the successful treatment of type 2 diabetes include maintaining tight glycemic control (particularly young type 2 diabetes patients, while it is not considered as important in older patients), minimizing the risk of hypoglycemia, controlling cardiovascular risk factors such as blood pressure and serum lipid levels, and reducing or controlling body weight. Most long-established diabetes interventions are designed to improve glycemic control but do little to address other risk factors and meet the multifaceted needs of the type 2 diabetes patient.
• Modulation of incretin activity (gastrointestinal hormones involved in the regulation of gut motility, secretion of gastric acid, control of glucose-dependent pancreatic enzyme secretion, gall bladder contraction, and nutrient absorption) is a novel therapeutic option that is associated with improved glycemic control and weight loss, thereby meeting some of the complex needs of patients with type 2 diabetes.

What is already known about this subject

• The World Health Organization has estimated that more than 346 million people worldwide have diabetes and describe the condition as an "emerging global epidemic."
The World Health Organization (WHO) has estimated that more than 346 million people worldwide have diabetes and describe the condition as an "emerging global epidemic." Type 2 diabetes mellitus accounts for approximately 90% of all diabetes cases, making it one of the largest health care challenges facing many developed and developing countries. Current estimates suggest that diabetes is responsible for 5%-13% of total health care expenditure in most developed countries. In the United States alone, the American Diabetes Association (ADA) estimated the total annual cost of diabetes at $174 billion in 2007, comprising $116 billion in medical expenditure and $58 billion in reduced workplace productivity. Medical costs attributed to diabetes included $58 billion to treat diabetes-related complications, $31 billion in general medical costs, and $27 billion in care to directly treat the condition. Of particular note are the increases in costs to health care payers in the United States. Between 1994 and 2007, spending on pharmaceuticals for treatment of type 2 diabetes has increased by 87%, from $6.7 billion to $12.5 billion. This represents a considerable burden, and it is essential that use of this investment is optimized to achieve the best possible clinical outcomes.

Type 2 diabetes is a complex and progressive disease, which is associated with significant morbidity and mortality. As a result, patients with type 2 diabetes benefit from a multifactorial approach to disease management, as demonstrated in the Steno-2 study, which compared conventional treatment for multiple risk factors with intensive multifactorial treatment that consisted of the use of behavioral modifications and pharmaceutical interventions to achieve aggressive hemoglobin A1c (HbA1c), blood pressure, cholesterol, and lipid targets. The key challenges in the successful treatment of type 2 diabetes include maintaining tight glycemic control, minimizing the risk of hypoglycemia, controlling cardiovascular risk factors such as blood pressure and serum lipid levels, and reducing or controlling body weight. Most long-established diabetes interventions are designed to improve glycemic control but do little to address other risk factors and meet the multifaceted needs of the type 2 diabetes patient.

Modulation of incretin activity (gastrointestinal hormones involved in the regulation of gut motility, secretion of gastric acid, control of glucose-dependent pancreatic enzyme secretion, gall bladder contraction, and nutrient absorption) is a novel therapeutic option that is associated with improved glycemic control and weight loss, thereby meeting some of the complex needs of patients with type 2 diabetes, although it should be acknowledged that metformin remains the preferred first-line treatment. This has led to the development of 2 new classes of antidiabetic therapy: degradation-resistant glucagon-like peptide-1 (GLP-1) receptor agonists (which mimic the action of GLP-1 in stimulating insulin and suppressing glucagon secretion, inhibiting gastric emptying, and reducing appetite and food intake), such as liraglutide and exenatide, and inhibitors of dipeptidyl peptidase-4 (DPP-4; the protease that rapidly degrades GLP-1 and other incretins including gastric inhibitory peptide [GIP]), such as sitagliptin and vildagliptin. Clinical trials with GLP-1 receptor agonists (liraglutide and exenatide) have shown substantial reductions in fasting and post-prandial glucose concentrations, HbA1c (0.5-1.6%), and were associated with weight loss (2-5 kilograms [kg]). Data from published studies indicate that GLP-1 receptor agonists may be associated with a more substantial reduction in HbA1c in comparison with DPP-4 inhibitors (0.5%-1.6% reduction vs. 0.5%-1.0% reduction). Weight loss has been shown to be associated with liraglutide and exenatide treatment, whereas DPP-4 inhibitors are weight neutral and have been associated only with the prevention of weight gain. Metformin remains the first-line therapy for achieving glycemic control in type 2 diabetes patients, but for patients failing to achieve glycemic control on metformin, GLP-1 receptor agonists and DPP-4 inhibitors offer alternatives to sulphonylureas, glinidines, and thiazolidinediones.

Although there is a growing body of clinical data available on these new agents, and several health economic analyses have been published comparing them with long-established interventions, there is a paucity of data on the cost-effectiveness of GLP-1 receptor agonists in comparison with DPP-4 inhibitors. The aim of the present analysis was to evaluate, in a transparent way, the short-term cost-effectiveness of a GLP-1 analog (liraglutide, Victoza, Novo Nordisk) in comparison with a DPP-4 inhibitor (sitagliptin, Januvia, Merck, Sharp and Dohme) in the U.S. setting from the perspective of a health care payer. The analysis was based on recently reported data from a head-to-head clinical trial comparing liraglutide with sitagliptin when added on to metformin over 52 weeks of therapy.

Methods

Source of Clinical Trial Data

In 2010, Pratley et al. reported results from the LIRA-DPP-4 study, a parallel-group, open-label trial in participants (aged
Patients were randomly allocated to receive 26 weeks of treatment with 1.2 mg (n = 225) or 1.8 mg (n = 221) subcutaneous liraglutide once daily or 100 mg oral sitagliptin once daily (n = 219) at sites in Europe and North America, in addition to metformin. Detailed results with exclusion criteria described have been published previously and show that greater mean reductions in HbA1c and body weight were achieved with liraglutide 1.8 mg and liraglutide 1.2 mg than with sitagliptin. All 3 treatments were well tolerated, with only 1 major hypoglycemic event reported in the liraglutide 1.2 mg arm and minor hypoglycemia rates of approximately 5% in all 3 treatment groups. Nausea was more common with liraglutide (59 [27%] patients on 1.8 mg; 46 [21%] on 1.2 mg) than with sitagliptin (10 [5%]), with most events being transient.

On completion of the trial, patients were given the option of enrolling in a 26-week extension study and continuing on the trial regimens. Of participants completing the initial 26-week study, 497 of 554 (90%) entered into the extension, with 436 of 497 (88%) completing 52 weeks of treatment. At the end of the study, liraglutide (1.8 and 1.2 mg) remained superior to sitagliptin in terms of reducing HbA1c from baseline to 52 weeks (mean decreases of -1.51%, -1.29%, and -0.88% reported for liraglutide 1.8 mg, liraglutide 1.2 mg, and sitagliptin, respectively; P < 0.0001 for differences between both liraglutide groups vs. sitagliptin). Mean weight loss was also greater with liraglutide 1.8 mg (-3.68 kg) and 1.2 mg (-2.78 kg) than sitagliptin (-1.16 kg; both P < 0.0001). No major hypoglycemic episodes were reported in the extension study. The proportions of patients experiencing minor hypoglycemia were 8.3%, 8.1%, and 6.4% in the liraglutide 1.8 mg, liraglutide 1.2 mg, and sitagliptin arms, respectively. Treatments were also well tolerated in the extension study, with adverse event rates lower than those in the first 26 weeks. Clinical effect (including change in HbA1c, body mass index [BMI], systolic blood pressure, hypoglycemic events, and nausea) and resource use data (e.g., diabetes medications) were extracted from the study reports by Pratley et al., detailing the initial 26-week trial and the subsequent extension period of the LIRA-DPP-4 study, to inform the evaluation of cost-effectiveness.

Clinical Data Used in the Economic Evaluation
The proportion of patients achieving a clinically relevant composite endpoint, defined as HbA1c < 7.0% with no reported hypoglycemia and no gain in body weight, was estimated using logistic regression, with treatment received and country as fixed effects and baseline HbA1c and body weight as covariates. The model used the full analysis set with a last observation carried forward approach to missing data. Data from both 26 weeks and 52 weeks of follow-up showed that significantly more patients on liraglutide reached the composite endpoint (HbA1c < 7%, no weight gain, and no hypoglycemia) on liraglutide than on sitagliptin (Figure 1). The odds ratios for achieving the composite endpoint for liraglutide versus sitagliptin were 2.80 (95% confidence interval [CI] 1.74 to 4.48) and 4.37 (2.74 to 6.98) for liraglutide 1.2 mg and 1.8 mg, respectively (both doses P < 0.0001). Among patients on liraglutide 1.2 mg, 34.9% reached the composite endpoint at 26 weeks, and 38.9% reached it after 52 weeks of follow-up. A greater percentage of patients achieved control in the liraglutide 1.8 mg treatment group, where values of 45.9% (26 weeks) and 49.9% (52 weeks) were reported. In the sitagliptin group, only 13.5% (26 weeks) and 18.6% (52 weeks) of patients reached the composite endpoint of HbA1c < 7%, no weight gain, and no hypoglycemia. In all 3 treatment groups, a higher proportion
of patients achieved the composite endpoint after 52 weeks than after 26 weeks. When expressed as a number of patients needed to treat, 4.5 more patients would need to be treated with sitagliptin than with liraglutide 1.2 mg to get 1 patient to the composite control endpoint at 26 weeks (Figure 2). In comparison with liraglutide 1.8 mg, 5.2 more patients would need to be treated with sitagliptin to have a single patient reach the composite control endpoint at 26 weeks. Similar observations were made at the 52-week time point, with 2.8 and 3.4 more patients needing to be treated with sitagliptin to reach the composite control endpoint than with liraglutide 1.2 and 1.8 mg, respectively.

**Evaluation of Cost-Effectiveness**

Cost-effectiveness was evaluated in terms of cost per patient treated to control (cost of control) defined as a composite endpoint appropriate to the effective management of a type 2 diabetes patient based on published guidance. In the consensus statement published by the ADA and the European Association for the Study of Diabetes (EASD) in 2009, the recommended glycemic goal of HbA1c < 7% is supported based on a previous ADA recommendation, taking into account practicality and the projected reduction in complications over time. Metformin is recommended as the initial pharmacological therapy in type 2 diabetes because of its effect on glycemia and desirable profile of “absence of weight gain or hypoglycemia, and generally low level of side effects.” When lifestyle intervention and metformin fail to achieve or sustain glycemic goals, addition of long-established therapies such as sulfonylurea or basal insulin, although effective in terms of improving glycemic control, often increase the risk of hypoglycemia and are generally associated with weight gain. Based on this, a composite endpoint was defined for the present analysis to represent effective control reflecting the ADA/EASD guidance as follows: HbA1c < 7% with no reported hypoglycemia and no weight gain. This composite endpoint matched a predefined secondary endpoint in the 26-week clinical trial and the extension study reported by Pratley et al.²³²⁴

A model was developed in Microsoft Excel 2003 (Redmond, WA) to evaluate the pharmacy costs associated with antihyperglycemia treatment and the number of patients reaching the composite endpoint (HbA1c < 7% with no reported hypoglycemia and no weight gain) in the LIRA-DPP-4 26-week trial and in the extension study up to 52 weeks.²³²⁴ Mean daily per patient costs of treatment were calculated based on published wholesale acquisition costs in 2012 in the United States for metformin, liraglutide, sitagliptin, and for needles (used for subcutaneous injection of liraglutide).²³ Doses of metformin were assumed to be 1,500 mg per day in all treatment groups, since mean doses were not published by Pratley et al., with sensitivity analyses performed assuming higher and lower mean doses. Doses of liraglutide (1.8 mg or 1.2 mg once daily) and sitagliptin (100 mg once daily) were based on the trial protocol. Annual costs were estimated by multiplying daily costs by 365 (Table 1). All costs were reported in 2012 U.S. dollars, and no discounting was applied, since costs were not projected beyond a 1-year time horizon.

Data from the LIRA-DPP-4 study were also used to provide estimates of the proportion of patients reaching the composite endpoint (HbA1c < 7% with no reported hypoglycemia and no weight gain), as well as the number needed to treat to reach the composite endpoint in each treatment arm. The costs of treatment for each treatment group (liraglutide 1.2 mg, liraglutide 1.8 mg, and sitagliptin) were then estimated based on the number of patients in each group, and this was used, with the proportion of patients reaching the composite endpoint, to estimate the total pharmacy cost associated with treatment for 1 patient to reach the composite endpoint goal (cost of
control). This analysis was performed on the 26-week data (where annual costs were divided by 2) from the original trial and the 52-week data from the extension study (where annual costs were used). These estimates provide a combined measure of both costs (antihyperglycemia medication costs) and effectiveness (patients reaching the composite endpoint) and was therefore used to estimate the cost-effectiveness of liraglutide 1.2 mg and 1.8 mg in relation to sitagliptin.

Sensitivity Analyses

Sensitivity analyses were performed to investigate the effects of variation in input data on cost-effectiveness outcomes (specifically, cost per patient reaching the composite endpoint). Input cost parameters, specifically needle costs, liraglutide costs, and sitagliptin costs, were increased and decreased by 20% in separate sensitivity analyses. Mean doses of concomitant metformin were varied from the base case assumption of 1,500 mg to 1,000 mg and 2,000 mg. The percentage of patients reaching the composite endpoint was varied within the range of the upper and lower 95% CIs for each of the 3 treatment groups to explore the sensitivity of results to changes in this parameter. Probabilistic sensitivity analysis was conducted, with sampling around both costs and proportion of patients achieving the composite endpoint.

In addition, analyses were performed to investigate the effect of varying the composite endpoint to assess the cost per patient reaching single endpoints (HbA1c < 7%), dual endpoints (HbA1c < 7% and no weight gain; > 1%-point HbA1c decrease and > 3% weight loss; > 1%-point HbA1c decrease and > 5% weight loss), an alternate triple endpoint (HbA1c < 7%, no weight gain, and no nausea), and a quadruple endpoint (HbA1c < 7%, no weight gain, no hypoglycemia, and no nausea). The individual components of these exploratory composite endpoints reflect treatment targets for type 2 diabetes patients in published guidance (except nausea, which was included, since it is a common side effect of treatment with liraglutide and sitagliptin), although no claims are made in the product information for either liraglutide or sitagliptin to support SBP reductions with treatment.9 For reasons of conciseness, sensitivity analysis results are only shown for the 52-week dataset.

Results

Base Case Analysis

Evaluation of annual antihyperglycemia medication costs in the overall population, based on the trial protocol, indicated that liraglutide was more costly per patient than sitagliptin (Table 1). Liraglutide 1.2 mg was associated with annual costs of approximately $4,020, while liraglutide 1.8 mg was associated with a cost of approximately $5,866, around $885 and $2,730, respectively, more than sitagliptin ($3,136).

These values were used to estimate the cost per patient successfully reaching the composite endpoint of HbA1c < 7%, no weight gain, and no hypoglycemia. After 26 weeks of

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**TABLE 1** Summary of Annual Pharmacy Costs Based on Pratley et al. (2010) Clinical Trial

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide 1.2 mg ($)</th>
<th>Liraglutide 1.8 mg ($)</th>
<th>Sitagliptin 100 mg ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin (1,500 mg daily)</td>
<td>142.90</td>
<td>142.90</td>
<td>142.90</td>
</tr>
<tr>
<td>Liraglutide/sitagliptin</td>
<td>3,690.64</td>
<td>5,535.96</td>
<td>2,992.64</td>
</tr>
<tr>
<td>Needles (Novofine autocover 30 gauge)</td>
<td>186.95</td>
<td>186.95</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>4,020.49</td>
<td>5,865.81</td>
<td>3,135.53</td>
</tr>
</tbody>
</table>

All costs were estimated based on published wholesale acquisition costs in the United States and expressed in 2012 U.S. dollars. Metformin doses were assumed to be 1,500 mg per day and were assumed to be equivalent in all 3 treatment groups. Needle use was assumed to be 1 per day for liraglutide treatment groups. Costs were annualized by multiplying daily costs by 365. mg = milligrams.
Sensitivity analyses showed that variation in input parameters by ± 20% and variation in clinical input parameters within the range of the 95% CIs did not change the finding that the cost of achieving the composite endpoint (cost of control) with liraglutide 1.2 mg and 1.8 mg was lower than the cost with sitagliptin after 52 weeks of treatment (Table 2). Variation in the acquisition cost of needles for liraglutide administration had only a modest effect on results. Increasing the cost of liraglutide 1.2 mg by 20% led to a cost of control of $12,233, approximately $4,625 less than the cost of control with sitagliptin ($16,858). Decreasing the cost of sitagliptin by 20% brought the cost of control down to $13,640, which was still higher than the cost of control with liraglutide 1.2 mg ($10,335) and liraglutide 1.8 mg ($11,755). Decreasing the cost of liraglutide 1.8 mg by 20% led to a cost of control of $9,536, approximately $799 lower than that for liraglutide 1.2 mg in the base case. Changing the metformin doses that patients received had only a very small impact on the cost of achieving control.

Increasing the percentage of patients reaching target based on the 95% CI decreased the cost of control in all treatment arms and vice versa (Table 2). When the proportion of patients reaching target was increased to 46.5% on liraglutide 1.2 mg, the cost of control fell to $8,646. When the proportion of patients was decreased to 31.9% reaching control on liraglutide 1.2 mg, the cost of control increased to $12,603 ($4,255 lower than the sitagliptin value in the base case analysis). Increasing the percentage of patients reaching control on sitagliptin to 25.0% produced a cost of control value of $12,542, remaining higher than the base case values for liraglutide 1.8 mg and 1.2 mg. It was estimated that the proportion of patients

<table>
<thead>
<tr>
<th>Table 2: Summary of Sensitivity Analyses Results at 52 Weeks</th>
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</thead>
<tbody>
<tr>
<td><strong>Analysis</strong></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Base case</td>
</tr>
<tr>
<td>Probabilistic sensitivity analysis</td>
</tr>
<tr>
<td><strong>Variation in costs</strong></td>
</tr>
<tr>
<td>Cost of liraglutide 1.2 mg + 20%</td>
</tr>
<tr>
<td>Cost of liraglutide 1.2 mg - 20%</td>
</tr>
<tr>
<td>Cost of liraglutide 1.8 mg + 20%</td>
</tr>
<tr>
<td>Cost of liraglutide 1.8 mg - 20%</td>
</tr>
<tr>
<td>Cost of sitagliptin + 20%</td>
</tr>
<tr>
<td>Cost of sitagliptin - 20%</td>
</tr>
<tr>
<td>Cost of needles + 20%</td>
</tr>
<tr>
<td>Cost of needles - 20%</td>
</tr>
<tr>
<td><strong>Variation in percentage of patients reaching control</strong></td>
</tr>
<tr>
<td>Liraglutide 1.2 mg upper limit of 95% CI</td>
</tr>
<tr>
<td>Liraglutide 1.2 mg lower limit of 95% CI</td>
</tr>
<tr>
<td>Liraglutide 1.8 mg upper limit of 95% CI</td>
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<tr>
<td>Liraglutide 1.8 mg lower limit of 95% CI</td>
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<tr>
<td>Sitagliptin upper limit of 95% CI</td>
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<tr>
<td>Sitagliptin lower limit of 95% CI</td>
</tr>
<tr>
<td><strong>Variation in metformin dosing</strong></td>
</tr>
<tr>
<td>Daily dose of 2,000 mg</td>
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<tr>
<td>Daily dose of 1,000 mg</td>
</tr>
</tbody>
</table>

Values in bold are those which are different from the base case estimates (due to variation in input parameters). Costs are expressed in 2012 U.S. dollars and are rounded to the nearest dollar. The model used the full analysis set with a last observation carried forward approach to missing data. A total of 221 patients received at least 1 dose of liraglutide 1.2 mg, 218 patients received at least 1 dose of liraglutide 1.8 mg, and 219 received at least 1 dose of sitagliptin. CI = confidence interval; HbA1c = hemoglobin A1c; mg = milligrams.
achieving control on sitagliptin to match the cost of control with liraglutide 1.2 mg was 26.7% (a net increase of 8.1% on the value reported in the trial, equivalent to a relative increase of 43.4%). There is small overlap when the lower 95% CI of the sitagliptin arm with the upper 95% CIs of the liraglutide arms. This suggests that while there is a significant difference in the proportion of patients achieving control of the various regimens, when medication costs are considered, the difference in cost per patient is not significant at the 95% CI.

Changing the make up of the composite control endpoint produced results consistent with the base case analysis of HbA1c <7%, no weight gain, and no hypoglycemia, with the cost of control being consistently higher with sitagliptin than with liraglutide (Table 3). In addition to the base case composite endpoint, 2 other composite endpoints were defined in the trial protocol. The first of these was HbA1c <7% with no weight gain. Using this endpoint produced costs per patient reaching control of $9,158, $10,201, and $13,998 for liraglutide 1.2 mg, liraglutide 1.8 mg, and sitagliptin, respectively. The other predefined composite endpoint was HbA1c <7%, no weight gain, and SBP <130 mmHg. Fewer patients reached this endpoint in the liraglutide 1.2 mg (21.9%), liraglutide 1.8 mg (29.5%), and sitagliptin (10.5%) treatment groups relative to the base case, leading to cost of control values of $18,358, $19,884, and $29,862, respectively.

In addition, 3 composite endpoints were analyzed post hoc. Using an endpoint of > 1%-point decrease in HbA1c and > 3% weight loss from baseline, results were analogous to the base case with cost of control values of $12,220 (liraglutide 1.2 mg), $12,119 (liraglutide 1.8 mg), and $21,044 (sitagliptin). Similarly, when an endpoint of > 1% decrease in HbA1c and > 5% weight loss was analyzed, costs of control were $20,409, $21,024, and $34,456 for liraglutide 1.2 mg, liraglutide 1.8 mg, and sitagliptin, respectively. Incorporating no nausea into the base case composite endpoint (based on the observation that nausea was the most frequently reported adverse event for liraglutide in the trial) reduced the proportion of patients achieving the endpoint in all 3 treatment groups. As a result, the costs of control values were higher than those in the base case, but the cost of control with both liraglutide 1.2 mg ($14,009) and liraglutide 1.8 mg ($16,523) remained lower than the cost of control value with sitagliptin ($26,349).

### Discussion

The present analysis provides evidence that the mean cost per patient achieving control, defined as reaching HbA1c target with no hypoglycemia or weight gain, was lower with liraglutide than with sitagliptin from the perspective of a U.S. health care payer. These findings, based on a previously published clinical trial, were true of both the 1.2 mg and 1.8 mg doses of liraglutide, although the cost of control was lowest with the 1.2 mg dose. The original studies reported by Pratley et al. showed that significantly more patients on liraglutide than on sitagliptin achieved the predefined secondary endpoint of HbA1c <7% with no hypoglycemia or weight gain. Although the acquisition costs associated with the liraglutide regimens were higher than for the sitagliptin regimen from a health care payer perspective, the cost per patient achieving control was lower. One-way sensitivity analyses showed that that the cost of control with liraglutide 1.2 mg remained lower than that for sitagliptin throughout plausible variation in cost and clinical input parameters in the study. In addition, changing the definition of the composite endpoint based on predefined and post hoc definitions similarly provided supporting evidence that cost of control, defined as a composite endpoint, is likely to be lower with liraglutide than with sitagliptin.

The present analysis can be regarded as novel in terms of the measure of cost-effectiveness reported. It does not rely on a
standard incremental cost-effectiveness ratio (such as cost per quality-adjusted life year [QALY] gained), instead relying on a cost per patient reaching a composite endpoint. The composite endpoint was predefined in the clinical trial protocols (as a secondary endpoint) and is consistent with published guidance on the treatment of type 2 diabetes.\(^\text{9}\) In the 2012 ADA standards report, there is a recommendation to move beyond the traditional glucocentric approach that focuses solely on controlling hyperglycemia with minimal risk of hypoglycemia.\(^\text{26}\) It states that optimized therapies should also address the comorbidities associated with diabetes, specifically obesity, hypertension, and dyslipidemia. With this multifactorial approach in mind, the LIRA-DPP-4 study data demonstrated significant improvements in the proportion of patients achieving glycemic control with no hypoglycemia or weight gain with liraglutide over sitagliptin. To further consider the multifactorial approach to treatment, SBP should be considered. While liraglutide 1.2 mg did not significantly reduce SBP compared with sitagliptin in the LIRA-DPP-4 study, a decrease was observed in the liraglutide 1.8 mg group that was consistent with results of the LEAD-1 and LEAD-2 trials.\(^\text{14,27}\)

The approach of estimating the cost of control (in terms of patients reaching the composite endpoint) has the benefit of balancing the costs and effects of the agents under investigation in a simple and transparent way and is suitable for a short time horizon. For health care payers in the United States, this type of short-term cost-effectiveness analysis may provide more salient information on the relative merits of new agents on the formulary than the conventional long-term, complex evaluations of cost-effectiveness in diabetes. It should be noted, however, that the cost of control concept is not without its limitations. It does not offer any willingness-to-pay context (the question of how much is a health care payer willing to pay per patient achieving control is an open one) and fails to offer any generalizability across analyses or therapeutic areas (as the cost per quality-adjusted life-year gained does). Moreover, it does not capture other clinical outcomes, for example, the impact of the increased incidence of transient nausea associated with liraglutide reported by Pratley et al.\(^\text{23,24}\)

There are a number of challenges involved in estimating the short-term cost-effectiveness of diabetes interventions as acknowledged in the ADA’s guidelines for the computer modeling of diabetes and its complications.\(^\text{28}\) The chronic nature of the disease and the myriad micro- and macrovascular complications, allied to risk factor changes over time, mean that evaluating the cost-effectiveness of interventions that modify risk factors, for example, HbA1c, and can therefore influence the risk of complications over time, is a complex challenge. As a result, diabetes models are often complex, and most cost-effectiveness analyses are run over a long-term time horizon to adequately capture end-stage complications. In the present analysis, we sought to offer a different approach by using a composite endpoint (in line with published guidance) as a surrogate for long-term outcomes and a simple modeling approach with no complex statistical analysis to keep the assessment of cost-effectiveness transparent for nonhealth economists. It is not intended to replace conventional long-term modeling analyses, and indeed, a long-term cost-effectiveness evaluation of liraglutide versus sitagliptin based on the same trials offers interesting and complementary information to the present study.\(^\text{29}\)

Recommendations from a professional organization such as the ADA or a standardized approach (using this or other endpoints) for short-term cost-effectiveness analyses in diabetes would be a welcome addition for researchers in this area.

**Limitations**

A potential limitation of the analysis is that adherence to the study medications was assumed to be 100% in all 3 treatment groups. Although this has the potential to lead to an overestimation of pharmacy costs, in the absence of real-life data on adherence for liraglutide and sitagliptin as well as the impact of nonadherence on clinical outcomes, it would have been very difficult to incorporate adherence into this analysis.

A further limitation of the present analysis may be in the estimation of costs. The analysis used wholesale acquisition costs, which do not take into account rebates or discounts that may reduce acquisition costs from a health care payer perspective. For the purpose of transparency, only the costs of antihyperglycemia medications were captured. The analysis did not take into account additional costs such as those associated with the self-monitoring of blood glucose (although there is no evidence to suggest that patients receiving liraglutide and sitagliptin would have different self-monitoring of blood glucose uses, and therefore, the incremental impact on the results of the study would be minimal) or costs associated with diabetes-related complications or the side effects of treatment. As such, the overall costs from a health care payer perspective may be underestimated. However, the addition of such costs would not have notably changed the outcome in terms of the relative cost of control with liraglutide and sitagliptin (the incidence of costly complications in the trials was very low) but may have added unnecessary complexity to the estimation of costs. In contrast, the acquisition costs for metformin may be high relative to certain generic preparations that may have resulted in a slight overestimation of pharmacy costs. However, as metformin costs were applied equally in all 3 treatment groups, reducing the metformin costs would have no impact on the incremental findings (i.e., differences between treatment groups).

Another potential limitation may be the robustness of the input data from the clinical trials. Both the original 26-week study and the extension study were open-label trials (owing to the nature of comparison of an oral agent with an injection). This may have led to patients having different expectations...
of the effects of liraglutide or sitagliptin, which potentially may have influenced adherence to lifestyle recommendations. Although the extent of any such effect is difficult to assess, it is reassuring that the efficacy findings are in line with the results of other head-to-head trials comparing GLP-1 receptor agonists with DPP-4 inhibitors. For example, when exenatide once-weekly (DURATION-2) or tasuglitate (T-emerge 4) were compared with sitagliptin over 26 weeks, HbA1c was reduced by 1.5% and 1.3% with exenatide once-weekly and tasuglitate, respectively, compared with 0.9% with sitagliptin.\textsuperscript{30,31} Weight loss with sitagliptin was a little better in the LIRA-DPP-4 study than in previous trials where it has been generally shown to be weight neutral.\textsuperscript{23,24}

**Conclusion**

A short-term evaluation of the cost-effectiveness of liraglutide versus sitagliptin shows that the mean cost per patient achieving control, defined as reaching HbA1c target with no hypoglycemia or weight gain, was lower with liraglutide than with sitagliptin in a U.S. setting.


Evaluating the Short-Term Cost-Effectiveness of Liraglutide Versus Sitagliptin in Patients with Type 2 Diabetes Failing Metformin Monotherapy in the United States


