At a Glance

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US Cost-Effectiveness of Saxagliptin in Type 2 Diabetes Mellitus

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ABSTRACT

Objectives: To evaluate the cost-effectiveness of saxagliptin versus sulfonylurea (glipizide) added to metformin in patients with type 2 diabetes mellitus (T2DM) from a US payer perspective.

Study Design: Data from a 52-week randomized controlled trial comparing saxagliptin and glipizide in combination with metformin were used in a simulation model to estimate long-term health outcomes in a cohort of T2DM patients.

Methods: Evidence from a clinical trial and other published literature were used to assess disease progression rates and associated healthcare costs. Subjects were simulated in yearly time increments, and the model estimated the 5-year and lifetime (ie, 40-year) clinical and economic outcomes, taking into account the cost and disutility associated with weight gain and hypoglycemia events. The model estimated the incidence of microvascular and macrovascular complications, diabetes-specific mortality, all-cause mortality, and costs and quality-adjusted life-years (QALYs) associated with the treatment strategies.

Results: The analysis suggests that compared with glipizide plus metformin the 5-year QALY gain for saxagliptin plus metformin was 0.53 with a cost of $13,374 per QALY. At 40 years, lifetime QALY gain for saxagliptin plus metformin rose to 2.64 per patient and cost per QALY was reduced to $1052. Sensitivity analysis indicated disutility values were a key driver, whereas the impact of overall costs was more modest.

Conclusions: Over a T2DM patient's lifetime, addition of saxagliptin to metformin is associated with improvement in QALYs when considering cost and disutility due to treatment side effects. Cost effectiveness is within acceptable cost-effectiveness threshold in the United States.

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Recent data estimate that 10.7% of Americans 20 years and older have diabetes, with 90% to 95% of these having type 2 diabetes mellitus (T2DM).[1] The incidence of diabetes in adults (ages 18-79 years) nearly tripled from 493,000 in 1980 to more than 1.5 million in 2007 in the United States.[2] As a result, the 2007 direct and indirect costs attributed to diabetes amounted to $174 billion in the United States alone[3] and are likely to rise in the future with increasing disease prevalence.

Despite the availability of multiple antidiabetic agents, approximately 43% of treated T2DM patients do not achieve glycemic control as defined by the American Diabetes Association (ADA) treatment guidelines[4] (glycated hemoglobin [A1C] <7%).[5] One barrier to effective glycemic control may be poor adherence to oral antidiabetic agents. Poor adherence can result from the occurrence of medication side effects and/or tolerability issues,[6] including hypoglycemia and weight gain.[7]

The ADA recommends the use of a stepwise approach to target glycemic control, including the use of combination therapy when monotherapy plus lifestyle and therapeutic changes are insufficient. Furthermore, treatment goals should be individualized, balancing potential efficacy with such factors as safety, tolerability, ease of use, and adherence. For certain patients, healthcare providers may consider goals lower than the general A1C goal of less than 7% if these goals can be attained without significant hypoglycemia or other adverse effects.[4] The impact of hypoglycemia on patients varies widely, from events with mild but bothersome symptoms to an excessive decrease in blood glucose, which can result in more severe complications including coma, cardiac arrhythmias, or myocardial ischemia.[8] Hypoglycemia or fear of hypoglycemia may also affect patient behavior, leading to more frequent food consumption resulting in weight gain, which in turn can increase risk of cardiovascular events over time.[9] Other side effects associated with diabetes control agents, such as potential increases in body weight, can

have a negative impact on patient health by increasing the risk of cardiovascular disease, a major cause of morbidity and mortality in the diabetic population.[4,10,11]

Currently available oral antidiabetic agents may have comparable efficacy in terms of glycemic control; however, health outcomes associated with individual therapies may vary in side effect profiles and durability of glycemic control.[12] The ADA guidelines currently recommend metformin as first-line therapy for T2DM patients, with sulfonylureas or thiazolidinediones as second-line therapy for patients requiring further glycemic control. However, the sulfonylurea class is associated with weight gain and increased risk of hypoglycemia.[12,13] When used in combination with metformin, saxagliptin, an oral dipeptidyl peptidase-4 inhibitor, has demonstrated improvement in glycemic indices similar to that of other combinations with metformin.[14,15] Yet unlike other agents, saxagliptin has been shown to be weight neutral, with low risk of hypoglycemic events relative to sulfonylureas.[13,14]

In a 52-week, multicenter, randomized, phase 3b trial, Goke et al[14] found that treatment with saxagliptin plus metformin compared with glipizide plus metformin was associated with a significantly smaller proportion of patients with at least 1 hypoglycemic event (13/428 or 3.0% vs 156/430 or 36.3%) and a divergent impact on body weight, with an adjusted mean change from baseline equal to –1.1 kg with saxagliptin versus +1.1 kg with glipizide. In addition, the study showed a significantly smaller rise in the A1C percentage from week 24 to week 52 with saxagliptin versus glipizide (0.001% vs 0.004%, respectively), indicating a sustained glycemic effect beyond week 24. Additional findings from Kahn et al, who evaluated the durability of glycemic control of recently diagnosed T2DM patients receiving glucose-lowering monotherapy, showed glyburide had the highest cumulative incidence of failure compared with rosiglitazone and metformin, defined as a confirmed level of fasting plasma glucose of more than 180 mg/dL at 5 years.[16] We hypothesized that saxagliptin may play a role in decreasing morbidity and reducing associated healthcare costs given its favorable glycemic durability and tolerability profile.

The objective of the current analysis was to estimate the long-term cost-effectiveness of saxagliptin compared with sulfonylurea (glipizide) added to metformin in T2DM patients from the US payer perspective.

PRACTICAL IMPLICATIONS

Saxagliptin, in combination with metformin, provides a durable, well-tolerated, and cost-effective treatment option for type 2 diabetes mellitus and may alleviate the undesirable side effects of hypoglycemia and weight gain.

- Cost and disutility associated with side effects such as hypoglycemia and weight gain are important components of cost-effectiveness research.
- Hypoglycemia can lead to additional negative outcomes such as frequent food consumption and subsequent cardiovascular disease, and therefore should be minimized during diabetes treatment.
- Saxagliptin may improve glycemic control through lower rates of discontinuation subsequent to the favorable safety profile.

METHODS

Patient Population and Treatment Strategies

Patient characteristics were based on US demographic data found in the literature and were also comparable to characteristics of the Goke et al trial population.[14,17] When information on a specific variable was not available, then the Goke et al trial was used as a reference. The model cohort included T2DM patients between the ages of 25 and 64 years whose diabetes was not controlled on metformin alone and who needed add-on treatment to achieve glycemic control. **Table 1** highlights the baseline characteristics of the modeled patients.

Treatment comparators were metformin plus saxagliptin versus metformin plus glipizide as intensive second-line therapy. Patients inadequately controlled on either treatment arm (ie, reaching an A1C threshold level of 7.5%) received rescue therapy with NPH insulin as add-on treatment.[18] The effect of A1C in the first year with insulin was assumed to be –1.1%.[19] Treatment effects for each regimen, derived from the literature and the Goke et al trial,[14] were applied to the simulated cohort of patients within the model. A 4% discontinuation rate of study medications due to adverse events was assumed for both treatment arms[14] and patients who discontinued were assumed to enter rescue therapy.

Model Structure

The current analysis is based on a US adaptation of a previously published model.[20-22] The Cardiff Long-Term Cost Utility Model, a stochastic simulation model, was designed to evaluate the impact of new diabetes therapies, based on the United Kingdom Prospective Diabetes Study (UKPDS) 68.[23] The model was subsequently adapted to a number of other payer systems (Granstrom O, Bergenheim K, McEwan P, Sennfalt K, Henriksson M. Cost-effectiveness of saxagliptin [Onglyza] in type 2 diabetes in Sweden, unpublished observations, 2009).[24-27] In

Table 1. Baseline Patient Demographic and Clinical Characteristics

Patient Characteristics	Mean Value	Reference
Age, y	60	17
Proportion female	52%	14
Height, m	1.68	14
Proportion Afro-Caribbean	0.1%	14
Proportion smokers	15%	14
Total cholesterol, mg/dL	181	17
High-density lipoprotein cholesterol, mg/dL	45	17
Systolic blood pressure, mm Hg	130	17
Weight, kg	96	17

this model, baseline diabetes-related parameters, disutility values associated with side effects and injection, and cost values were based on US-specific data. UKPDS-based life tables and risk equations for predicting risks of diabetes-related complications were used.[28]

The lifetime horizon was chosen in order to capture all relevant events and related complications associated with diabetes progression, and subjects were simulated in yearly time increments. A 5-year analysis was also conducted to capture the payer perspective and to examine the shorter-term outcomes of interest. Evidence from the Goke et al clinical trial as well as the UKPDS study and published literature were used to model disease progression over time in patients.[14,23,29] Direct costs and disutility values attributed to hypoglycemia and weight gain were adapted to US Medicare reimbursement values.[29-35]

Model Input

Hypoglycemia. Rates of hypoglycemia events were taken from the Goke clinical trial[14] and included all hypoglycemia episodes from mild events characterized as "having an awareness of the event but easily tolerated," moderate events classified as "discomfort enough to cause some interference with usual activity," and severe events, defined as an "inability to carry on usual activity."[14]

Because hypoglycemia has a significant impact on a patient's health-related quality of life during an episode, the disutility[36] associated with the event itself was captured in the model. A patient experiencing frequent symptomatic or severe hypoglycemic events may also develop a fear for future events, which is considered in the disutility value (**Table 2**).[29]

Weight Gain. In this model, cost of long-term cardiovascular disease as it relates to weight gain is driven by the association between body weight and congestive heart failure. Weight may have additional indirect impact due to changes in low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, fasting insulin, and blood pressure that occurs with weight gain.[38]

Probability of weight gain was obtained from a health maintenance organization (HMO) population,[31] and annual weight change values were derived from the saxagliptin clinical trial reported by Goke et al.[14] In addition to its direct association with increased cardiovascular risk, weight gain associated with diabetes treatment may also affect patient health-related quality of life, resulting in utility losses. The impact of weight gain on utilities was therefore also considered in the model[29,39] (Table 2). The health-related quality of life weight changes were modeled linearly for transparency, where each unit change in body mass index or body weight was associated with identical utility weight.

Durability. A treatment's durability measure is the length of time at which the A1C effect is sustained. In this analysis, durability was considered as a nonlinear A1C drift based on the divergent A1C durability in the long-term extension study of saxaglipin.[14] The constant drift values of 0.208% for the sulfonylurea arm and 0.052% for the saxagliptin arm were applied to the model as an assumption, to project long-term differences between the 2 treatments in the absence of long-term data. Existing evidence also supports the better durability of agents within the dipeptidyl peptidase-4 class over 2 years relative to other drug classes, including glipizide.[13] Furthermore, because patients on second-line therapy who reach a predefined A1C threshold of 7.5% are switched to add-on insulin rescue therapy, the analysis also considered the disutility associated with the injection of insulin[40] (Table 2).

Cost Inputs. **Table 3** provides the direct costs used in the model for diabetes-related events. Direct diabetes-specific costs included medication acquisition cost, administration devices, and costs associated with the treatment of diabetes-related events such as ischemic heart disease, myocardial infarction, congestive heart failure, stroke, amputation, blindness, and end-stage renal disease. Fatal, nonfatal, and maintenance costs were considered in these cost values.

Treatment costs in the model assumed a $6.11 daily cost[32] of branded saxagliptin for the first 10 years, and then assumed a $1.00 cost per day as the best estimate for a generic oral antidiabetic medication based on current

Table 2. Clinical Input Variables and Disutility Values

Variable	Value	Reference
Diabetes-related parameter		
Average A1C at diagnosis, %	7	17
A1C threshold for adding on insulin, %	7.5	18
Mean time from diagnosis to start of the simulation, y	5.4	14
Treatment impact on A1C, %	−0.57	14
Side effect–related parameter		
Probability of hypoglycemic event		
Saxagliptin, %[a]	3	14
Sulfonylurea (glipizide), %[a]	36	14
Insulin, number of events per patient per year	1.5	Unpublished observations[b]
Annual weight change, kg		
Saxagliptin	−1.1	14
Sulfonylurea (glipizide)	+1.1	14
Insulin	+2.5	37
Probability of weight gain in first year, %		
Sulfonylurea (glipizide)	51	31
Probability of discontinuing treatment, %[c]	4	14
Disutility related to weight gain	−0.06	29
Disutility related to symptomatic hypoglycemic events	−0.08	29
Disutility of injection	−0.065	39
A1C durability		
Saxagliptin	0.052	14
Sulfonylurea (glipizide)	0.208	14

A1C indicates glycated hemoglobin.
[a]The probability of hypoglycemic events is equal to the proportion of patients reporting at least 1 hypoglycemic event at week 52 in the Goke et al clinical trial.[14]
[b]Granstrom O, Bergenheim K, McEwan P, Sennfalt K, Henriksson M. Cost-effectiveness of saxagliptin [Onglyza] in type 2 diabetes in Sweden, unpublished observations, 2009.
[c]The difference in discontinuation rates was found to be insignificant in the Goke et al clinical trial[14]; therefore, a discontinuation of 4% was attributed to both arms of the analysis.

market price standards. Daily costs of sulfonylurea and metformin were assumed to be $1.47 and $0.36, respectively.[32] The daily cost of insulin, assuming a 50/50 mix and a 1 mL injection once per day, was set at $9.97[33] and included the cost of syringe ($0.12 per syringe).[33]

The clinical study reported mild, moderate, and severe hypoglycemic events.[14] Of patients in the glipizide plus metformin group, 1.6% had severe hypoglycemic events compared with none of the patients in the saxagliptin plus metformin group. Other studies have also found low levels of hypoglycemic events in patients on the saxagliptin plus metformin regimen.[13,41] The Medicare National Average Allowance for outpatient cost of $125 was applied only to the 1.6% of patients who experienced severe hypoglycemic events. Because the other events did not require medical assistance, these events were assumed to accrue no additional costs.[30] The $246.93 cost of weight gain was based on an HMO population and estimated the total healthcare cost for every 1% increase in weight.[31] For each year in which weight gain occurred, this cost was applied.

Indirect costs, which are typically considered to be associated with loss of productivity or activity impairment, were not considered in this model. All costs were inflated to 2009 values using the medical care component of the consumer price index reported by the US Bureau of Labor Statistics.[42] Economic and clinical outcomes were discounted at a rate of 3%.[32,33]

RESULTS

Base Case Analysis

The main differences observed in the Goke clinical trial[14] between the metformin plus saxagliptin and metformin plus glipizide arms were in their side effect profiles, with patients in the saxagliptin arm experiencing fewer hypoglycemic events, lower risk of severe hypoglycemic events, and a small weight decrease, whereas the glipizide arm had a higher occurrence of hypoglycemia

Table 3. Direct Costs for Diabetes-Related Events (Discounted at a Rate of 3%)

Diabetes-Related Event	Cost, $	Reference
Annual treatment		
Metformin[a]	131.40	32
Saxagliptin[a]	2230.15	32
Sulfonylurea (glipizide)[a]	536.55	32
Insulin[b]	3682.85	33
Macrovascular/microvascular event		
Ischemic heart disease	4421.24	34
Myocardial infarction	15,892.71	34
Congestive heart failure	12,044.99	34
Stroke	6774.17	34
Amputation	15,782.50	34
Blindness	1066.79	34
End-stage renal disease	24,748.00	35
Annual maintenance after an event		
Ischemic heart disease	522.16	34
Myocardial infarction	1458.41	34
Congestive heart failure	4178.35	34
Stroke	554.26	34
Amputation	4943.40	34
Blindness	75.97	34
End-stage renal disease	67,848.70	35
Side effect–related event		
Weight gain	246.93	31
Severe hypoglycemia event[c]	125	30
Hypoglycemia events requiring medical assistance[d]	170	30

[a]Costs of metformin, saxagliptin, and sulfonylurea (glipizide) were calculated by using First Databank, WAC DACON weighted cost per day.
[b]Cost of insulin included the cost of syringe and assumed a 50/50 mix, 1 mL injection once daily.
[c]Severe hypoglycemic events were classified as such by the site physician and were given the Medicare National Average Allowance cost for established patient outpatient service level 5 (Current Procedural Terminology [CPT] 99215).
[d]Hypoglycemia events requiring medical assistance were given the Medicare National Average Allowance cost for emergency department visits level 5 (CPT 99285).

events and weight gain. **Table 4** presents the results for the base case cost-effectiveness analysis evaluating the impact of metformin plus saxagliptin versus metformin plus sulfonylurea, while considering the disutility associated with weight gain and all hypoglycemia episodes, as well as the cost attributed to weight gain and specifically severe hypoglycemic events.

The number of all hypoglycemia episodes was significantly lower for saxagliptin patients. For the hypothetical cohort of 1000 T2DM patients, compared with patients treated with sulfonylurea, patients treated with saxagliptin avoided 1243 hypoglycemic events in the first 5 years, at an incremental cost of $5703 per hypoglycemic event avoided and 1201 hypoglycemic events at an incremental cost of $2308 per event avoided in the 40-year follow-up. In addition, there were 10.53 cardiovascular events avoided at 40 years, with an incremental cost of $263,355 per event avoided for the saxagliptin-treated patients. The side effect benefits attributed to saxagliptin translated into a 5-year quality-adjusted life-year (QALY) gain equal to 0.53 and an incremental cost per QALY gained of $13,366 compared with sulfonylurea plus metformin. The lifetime (40-year) QALY gain was 2.65 per patient at a reduced cost per QALY of $1047, indicating a higher decrement in quality of life over time for the sulfonylurea-treated patients.

Sensitivity Analysis

In order to test the impact of each input parameter on the results, 1-way sensitivity analyses (in the form of distinct scenarios) and probabilistic sensitivity analyses were performed. **Table 5** outlines the various scenario

Table 4. Base Case Results[a]

Cost or QALY	5-Year Results	40-Year Results
Incremental cost for saxagliptin patients		
Per QALY	$13,366	$1047
Per hypoglycemia event avoided	$5703	$2308
Per CV event avoided	$9,352,534	$263,355
Results per patient	Sulfonylurea + Metformin	Saxagliptin + Metformin (Difference)
5-Year results		
Discounted cost	$8276	$15,370 ($7094)
Discounted QALYs	3.48	4.01 (0.53)
40-Year results		
Discounted cost	$62,367	$65,139 ($2772)
Discounted QALYs	8.37	11.02 (2.65)

CV indicates cardiovascular; QALY, quality-adjusted life-year.
[a]Includes the disutility due to weight gain and hypoglycemia, and the cost due to weight gain and severe hypoglycemia.

analyses and the subsequent findings. The scenarios focused on the drivers of the model including the cost/disutility of hypoglycemia and weight gain.

When evaluating sensitivity around the subgroup of hypoglycemic events accruing cost, attributing a cost value only to events requiring medical assistance did not significantly change the outcome. A Medicare National Average Allowance[34] for an emergency department visit of $170 was applied to the 0.9% of metformin plus glipizide patients[14] requiring medical assistance, resulting in a 5-year cost per QALY of $13,597 and a 40-year cost per QALY of $1513. These results indicate that the differences from the base case analysis may primarily be driven by the disutility associated with weight gain and hypoglycemic events, with the impact of overall costs being more modest.

Including only the cost and disutility associated with hypoglycemia resulted in 5-year and 40-year cost differences of $7664 and $4431, respectively, compared with the base case analysis values of $7094 and $2772. In addition, 1.33 QALYs were added in the long term compared with 0.28 QALYs at 5 years.

We subsequently examined the impact of treatment durability on results. When accounting for a potential delay in switching to insulin rescue therapy, while assuming a –1.1% effect[22] on A1C in the first year on insulin, patients on saxagliptin avoided 1409 hypoglycemic events in the long term compared with patients on glipizide, resulting in 1.27 QALYs added and a 40-year incremental cost of $1770 per patient compared with $4497 at 5 years.

When the durability analysis included cost and disutility due to weight gain in addition to hypoglycemia events, patients in the saxagliptin arm avoided 1409 hypoglycemic events and 47.74 cardiovascular events compared with patients on glipizide. In addition, 2.29 QALYs were added, while incremental costs were $144 per patient. Therefore, taking into account saxagliptin's improved durability and the impact of cost and disutility of hypoglycemic events and weight gain, saxagliptin was found to be a cost-effective option compared with glipizide as an add-on to metformin, at a low cost.

In order to take into account the uncertainty around estimated parameters in the base-case model, a probabilistic sensitivity analysis was conducted on the 40-year model (Table 5). The sensitivity analysis was based on 1000 simulations of the cohort. Inputs that were updated with US-specific values (eg, baseline demographics and event probability, cost, and disutility associated with weight gain and hypoglycemia) were varied across their respective bounds (or distributions). However, other variables found in the model were not varied (eg, disutility associated with diabetes-related events). Results showed a mean incremental cost-effectiveness ratio (ICER) of –$1980.08, with saxagliptin plus metformin appearing to be dominant. This may be due to the fact that only select US-specific parameters were varied.

DISCUSSION

The current model provided long-term cost-effectiveness data for saxagliptin as add-on to metformin versus glipizide in a population of US T2DM patients. The model results indicate that saxagliptin, used in combination with metformin as second-line treatment for T2DM, is a cost-effective treatment option. The benefit of saxagliptin treatment is largely found in its favorable side effect profile compared with that of glipizide with respect to weight gain and hypoglycemic events. Such side effects can lead to additional treatment complications such as low adherence, an important factor in

Table 5. Sensitivity Analysis Results

Scenario Analysis	5-Year Results	40-Year Results
Impact of including the disutility due to weight gain and hypoglycemia, and the cost due to weight gain and hypoglycemic events requiring medical assistance		
Incremental cost per QALY	$13,597	$1513
Incremental cost per hypoglycemia event avoided	$5802	$3338
Incremental cost per CV event avoided	$9,513,725	$380,897
Impact of including hypoglycemic event cost and disutility[a]		
Incremental cost per QALY	$27,846	$3335
Incremental cost per hypoglycemia event avoided	$6162	$3689
Incremental cost per CV event avoided	$10,104,036	$420,943
Impact of different durability, including hypoglycemic event cost and disutility[a]		
Incremental cost per QALY	$17,502	$1391
Incremental cost per hypoglycemia event avoided	$2452	$1257
Incremental cost per CV event avoided	$472,042	$37,078
Impact of different durability, including cost and disutility for both hypoglycemic events and weight gain[a]		
Incremental cost per QALY	$8030	$63
Incremental cost per hypoglycemia event avoided	$2141	$102
Incremental cost per CV event avoided	$412,237	$3020
Probabilistic sensitivity analysis per patient (40-year results)	**Sulfonylurea + Metformin**	**Saxagliptin + Metformin**
Discounted cost	$698,095 (± $524,112)	$694,952 (± $514,660)
Discounted QALYs	8.23 (± 3.35)	9.81 (± 4.05)
Incremental cost per QALY	–	−$1980.08

CV indicates cardiovascular; QALY, quality-adjusted life-year.
[a]All reported hypoglycemic adverse events during the short-term treatment period included events easily managed by subjects, events requiring nonmedical assistance, and events requiring medical assistance.

successful treatment. For example, a retrospective cohort study conducted by Rozenfeld et al demonstrated that a 10% increase in oral medication adherence was associated with a 0.1% reduction in A1C level.[43] Over time, however, as more patients on both treatments go onto insulin rescue therapy, the attenuated benefit results in a diminishing number of hypoglycemic events avoided. The long-term gains in QALY measures and improved cost per QALY are more sensitive to disutility associated with undesirable side effects and modestly sensitive to cost allocation.

Since drug acquisition costs are higher with saxagliptin plus metformin compared with sulfonylurea plus metformin, total costs for the saxagliptin patients tend to be slightly higher; however, improvement in QALYs and mitigation of the increased costs from reduced diabetes-related events compared with sulfonylurea plus metformin cause the cost-effectiveness ratio to decline as the model time horizon is lengthened.

Previous published literature[44] has shown that the benefits of incremental glycemic control may be associated with significant increases in cost of T2DM treatment. Sinha et al,[44] who conducted an economic analysis in which they compared both exenatide and sitagliptin with glyburide as second-line therapies to metformin, concluded that exenatide and sitagliptin are not cost-effective. Comparison of the 2 studies showed that differences in the ICER values were primarily driven by the assumptions around the cost of treatment and the disutility values attributed to hypoglycemia. The present model considered a $6.11 cost per day for saxagliptin. After 10 years of therapy, the generic price was then considered at a value of $1 per day versus the average $6.51 per day used in the Sinha et al study. Sinha and colleagues also used a value of 0.0064 disutility due to hypoglycemia compared with 0.08 in this analysis. The Sinha et al study is limited in consideration of the potential cost/utility benefits of therapeutic side effects. In addition, disutility values used in this study[29] differ from those used in other utility studies such as that of Currie et al,[45] because of factors such as the inclusion criteria for the patient population, varying definitions for hypoglycemia severity, and the period for which hypoglycemia was evaluated. When assessing ICER values of various therapies, the cost and disutility

attributed to weight gain, hypoglycemia, and the relative durability of a given therapy's treatment effect can have a substantial impact on the cost-effectiveness results and should be considered.[39]

As with all economic analyses, there are limitations to the current modeling analysis. Given the younger age range of the population, using Medicare costs may be a less accurate representation of the potential costs. However, the Medicare fee schedule is a well-recognized benchmark for cost data in the United States[46,47] and likely provides a conservative estimate of costs associated with both treatments. Furthermore, using private payer costs may change the overall costs, but would not impact the cost difference.

The present study excluded the cost for patients with mild or moderate hypoglycemia events and included the cost of severe hypoglycemia events as an outpatient cost, in order to make a moderate cost assumption. Considering that inpatient hospitalization is more costly than outpatient treatment, limiting the analysis to outpatient cost is likely a conservative estimation of the cost savings attributed to avoiding hypoglycemic events (Granstrom O, Bergenheim K, McEwan P, Sennfalt K, Henriksson M. Cost-effectiveness of saxagliptin [Onglyza] in type 2 diabetes in Sweden, unpublished observations, 2009).

In addition, patients often do not seek treatment for all hypoglycemia events, which could lead to an underestimation of costs in the study due to lack of event reporting. Further underestimation of cost savings may result from the exclusion of indirect costs such as those attributable to patient education, support, and monitoring.

Finally, all events can affect patient lives through both physical discomfort and psychological distress such as fear of hypoglycemia. A potential limitation may be overestimating the impact of hypoglycemia events on disutility, since fear of hypoglycemia is considered in the disutility values used for this analysis.

CONCLUSIONS

Saxagliptin in combination with metformin provides a durable, well-tolerated, and cost-effective treatment option[13,48] for T2DM and may address some of the unmet medical need in diabetes treatment attributable to undesirable side effects of hypoglycemia and weight gain. Additionally, enhanced glycemic control decreases the risk and prevents the potential high costs of future hypoglycemic events compared with glipizide.[49] While most diabetes treatments demonstrate comparable glycemic control, the variable side effect profiles of diabetes treatments may have an impact on patients' health-related quality of life. These side effects can also lead to differential long-term costs to the US healthcare system, thereby emphasizing the importance of the lifetime analysis. Therefore, it is important to take into consideration all aspects of new therapeutic agents to determine the most appropriate treatment for each individual patient.

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