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Costs and consequences associated with newer medications for glycemic control in type 2 diabetes

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Running title: Costs and consequences of glycemic control

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Objective: Newer medications offer more options for glycemic control in type 2 diabetes. However, they come at considerable costs. We undertook a health economic analysis to better understand the value of adding two newer medications (exenatide and sitagliptin) as second-line therapy to glycemic control strategies for new-onset diabetic patients.

Design: We performed a cost-effectiveness analysis for the U.S. population age 25 to 64. A lifetime analytic horizon and healthcare system perspective were used. Costs and quality-adjusted life years (QALYs) were discounted at 3% annually, and costs are presented in 2008 US$. We compared three glycemic control strategies: (1) glyburide as a second-line agent (2) exenatide as a second-line agent (3) sitagliptin as a second-line agent. Outcome measures included QALYs gained, incremental costs, and the incremental cost-effectiveness ratio associated with each strategy.

Results: Exenatide and sitagliptin conferred 0.09 and 0.12 additional QALYs respectively, relative to glyburide as second-line therapy. In base case analysis, exenatide was dominated (cost more and provided fewer QALYs than the next most expensive option) and sitagliptin was associated with an incremental cost-effectiveness ratio of $169,572 per QALY saved. Results were sensitive to assumptions regarding medication costs, side-effect duration, and side effect-associated disutilities.

Conclusions: Exenatide and sitagliptin may confer substantial costs to healthcare systems. Demonstrated gains in quality and/or quantity of life are necessary for these agents to provide economic value to patients and healthcare systems.

Diabetes mellitus is increasingly endemic in the United States. In 2007, 23.5 million of all Americans aged >20 years had diabetes compared to 18.0 million in 2002. (1) Diabetes was the seventh leading cause of death in 2006. (1) It remains the leading cause of blindness, end stage renal disease and non-traumatic amputations. $116 billion in direct health care costs are attributable to diabetes annually. (2)

Large clinical trials from the United States and Europe have demonstrated that tighter glycemic control can prevent diabetic complications in individuals with recent onset disease; (3,4) in older individuals with longer disease duration, recent studies have found no cardiovascular benefit of tight control (5) and possible harm. (6). In the past several years, the FDA has approved nine new products for glycemic control. (7) Some are new forms or combinations of existing classes, while others belong to new therapeutic classes such as amylin analogs, glucagon-like peptide-1 receptor agonists, incretins, and dipeptidyl peptidase-IV inhibitors.

While these agents increase the management options available, they come at increased costs. (8) Previous analyses of the health economics of glycemic control were published prior to the FDA approval of many new agents. (9 - 11) Recent studies have examined the cost-effectiveness of exenatide or sitagliptin in European populations, reflecting costs and management appropriate for the modeled populations but not necessarily reflective of the United States. (12 - 14)

In this analysis, we estimate the costs associated with the two most prescribed examples of these new medications, exenatide and sitagliptin. We project the gains in health outcomes necessary to have these newer medications pose good economic value for patients with new-onset diabetes, using the incremental cost-effectiveness ratio as our metric.

METHODS

Overview. Our model is an extension of a previously published model, (11) using as its platform the published model's analytic algorithm but changing treatment regimens and inputs, in keeping with the newer medications being considered. Adults enter the analysis at diabetes diagnosis and progress through the model until death or age 95. Only patients newly diagnosed between the ages of 25 and 64 are included. It is assumed that there is a ten-year lag between diabetes onset and diagnosis.

Patients have an annual risk of diabetic complications, modified by age, race and sex, time since diabetes onset, time since diagnosis, treatment, glycated hemoglobin achieved, smoking, hypertension and/ or concomitant hypercholesterolemia. It is assumed that hypertensives progress to complications more rapidly than non-hypertensives and that glycemic control has no impact on the progression of coronary heart disease. Costs accrue due to diabetes treatment and treatment of diabetic complications. Costs are averted when complications are averted. (15)

The summary metric used to estimate the value of exenatide and sitagliptin is the incremental cost-effectiveness ratio (ICER). In this analysis, ICER = (Costs of treatment – Averted diabetes complication-related costs)/ (quality-adjusted life years gained). Costs were calculated from a healthcare system perspective, using a lifetime analytic

horizon. Key model assumptions are summarized in Tables 1 and 2.

Treatment strategies. We assumed that intensive glycemic control is now standard of care in the United States. Three intensive glycemic control strategies were modeled: (1) glyburide as second-line treatment strategy, (2) exenatide as second-line treatment strategy, (3) sitagliptin as second-line treatment strategy. In each strategy, patients were treated with combinations of metformin, the second-line agent specific to the strategy, rosiglitazone, and NPH insulin.

In all three strategies, patients requiring medication were started on metformin. If glycemic control was not achieved with metformin alone, other medications were added, based on modeled rates of treatment failure (see supplemental Table in the online appendix which is available at http://care.diabetesjournals.org). All three strategies incorporated rosiglitazone as third-line therapy.

Risks of diabetic complications. The methods used to estimate the probabilities of diabetic complications have been described elsewhere. (15) In brief, probabilities depended on time since diagnosis, time between onset and diagnosis, age, sex, race, glycemic levels, smoking, cholesterol levels, and hypertension (Table 1). Time since diagnosis, glycemic level, and hypertension affected all transition probabilities. Time between onset and diagnosis affected glycemic level at the time of diagnosis. Age, sex, smoking, and cholesterol level affected transition probabilities associated with coronary heart disease (CHD) and stroke. Race affected glycemic levels and mortality. Alternative treatment strategies impacted transition probabilities by altering a patient's modeled trajectory of glycated hemoglobin levels over time.

Glycemic control. All three strategies were assumed to provide the same degree of glycemic control, and hence, the same effects on risks of diabetic complications. This assumption was based on results from clinical trials of sitagliptin and exenatide.(16 - 21)

Medication side effects. Health outcomes differed on the basis of side-effect profiles. Side-effect profiles were developed for each of the second-line medications (glyburide, exenatide and sitagliptin) based on literature review. Utilities (positive gains in quality of life) or disutilities (losses in quality of life) were applied to reflect these profiles. We grouped these effects into five categories: weight gain/ loss, hypoglycemia, nausea/ other gastrointestinal effects, upper respiratory infections, and the disutility associated with an injectable formulation. Each side effect could be experienced by the proportion of the population receiving a given drug at a given time. The effects of weight gain/ loss, nausea and upper respiratory infection were assumed to last for two years (13); all others were assumed to last for the duration that the medication was taken.

Glyburide was associated with a weight gain of 3% experienced by all, nausea experienced by 4.2% and hypoglycemia experienced by 36.1%. Exenatide was associated with a weight loss of 5% (experienced by all), hypoglycemia (experienced by 16%), nausea and other gastrointestinal effects (experienced by 57%), and a disutility due to being an injectable medication. Sitagliptin was associated with weight neutrality, hypoglycemia (experienced by 6.2%), and an increased risk of minor upper respiratory infections (experienced by 3.5%). All three side-effect profiles

resulted in a net disutility for each year the respective medication was taken (Table 2).

Management of hypertension and hypercholesterolemia. It was assumed that patients with hypertension would receive antihypertensive medications and that patients with hypercholesterolemia would be placed on statins. The methods used were analogous to those previously published. (11)

Costs. All costs are presented in 2008 US dollars (Table 1). Both costs and health benefits were discounted at 3% annually and estimated from the healthcare system perspective.

Costs of glycemic control included the costs of the drugs themselves, the costs of equipment needed for self-injection of insulin, the costs of glucose monitoring, and the costs of outpatient care associated with routine follow-up for diabetics.

Costs of diabetes complications were drawn from the same literature sources and used the same methods of calculation as in the previously published model. (11) These costs included costs of procedures, inpatient and outpatient care, specialist visits and medications required in the management of diabetic nephropathy, neuropathy, retinopathy, CHD, and stroke.

Health benefits. Prevention of diabetes complications results in a reduced risk of mortality and improved quality of life. In the model, strategies associated with improved glycemic control reduced the transition probabilities leading to diabetic complications at all stages, thereby reducing the risks of death due to CHD, stroke, nephropathy or neuropathy. Retinopathy was assumed to lead to blindness but not to alter the risk of death. Quality-of-life was captured by incorporating health utilities (Table 1) into the model, where a utility of one describes a period of time lived in perfect health and a utility of zero is assigned to death. Utility values between 0 and 1 describe life lived in less than perfect health and are used in the calculation of quality-adjusted life years. (22)

All analyses were performed in custom software built by the original study team. (15)

RESULTS

All three strategies were assumed to confer the same benefits in terms of reductions in major health outcomes as a result of diabetes-related complications. They were assumed to differ in their side-effect profiles only, and these side effects were not assumed to alter risks of complications. The impacts of these side-effects were incorporated into the model as quality of life gains or losses.

Using sitagliptin as a second-line treatment for type 2 diabetes in adults under 65 years of age is associated with additional intervention costs of $20,213 per person over their lifetime than a baseline strategy using glyburide as second-line therapy. Using exenatide as a second-line treatment is associated with an additional cost of $23,849 over their lifetime compared to glyburide as second-line therapy. The differences in intervention costs among the three strategies were due to differences in medication costs, summarized in Figure 1.

Incremental cost-effectiveness results are summarized in Table 3. Changes in costs and QALYs were calculated using comparisons to the next most expensive strategy, as well as to the common baseline of the strategy incorporating glyburide as second-line therapy. The strategy incorporating sitagliptin as second-line therapy was associated with

an incremental cost-effectiveness ratio of $169,572 per QALY saved, relative to glyburide as second-line therapy. Because exenatide was (1) associated with an injectable formulation with an accompanying disutility and (2) had higher medication associated costs, the strategy incorporating exenatide as second-line therapy was dominated by that incorporating sitagliptin, meaning that it was both more expensive and less effective in terms of QALYs saved.

In one-way sensitivity analysis, where the disutility associated with an injectable medication was set to zero, exenatide ceased to be dominated and was associated with an incremental cost-effectiveness ratio of $932,308 per QALY saved. In two-way sensitivity analysis, when the disutility associated with an injectable medication was set to zero and exenatide's medication cost was decreased by 25%, exenatide exerted weak, also termed extended, dominance over sitagliptin and was associated with a cost-effectiveness ratio of $167,002 per QALY saved.

When utility gains and losses associated with weight changes were assumed to last a lifetime, the incremental cost-effectiveness ratios associated with sitagliptin was $141,833 per QALY saved. In this analysis, exenatide ceased to be dominated and was associated with an incremental cost-effectiveness ratio of $932,308 per QALY saved. In both the analysis where the disutility associated with injectable medication was negated and in this lifetime weight change analysis, the net disutility associated with exenatide was zero, leading to similar results. When incremental cost-effectiveness analysis was performed using metformin and glyburide with insulin as third-line therapy (as opposed to rosiglitazone), exenatide remained dominated and the cost-effectiveness ratio associated with sitagliptin minimally changed to $173,300 per QALY saved.

Finally, when discount rates for costs and QALYs were assumed to be 5%, the exenatide strategy remained dominated: the incremental cost effectiveness ratio associated with sitagliptin was $154,389 per QALY saved.

DISCUSSION

Our results suggest that widespread use of exenatide and sitagliptin as second-line agents in the glycemic control of patients with diabetes could be associated with $731 to $862 million additional direct healthcare costs in the United States. Additional quality-adjusted life would be gained, due to improved side-effect profiles associated with these drugs. These gains would cost roughly $170 thousand per QALY for sitagliptin. In the base case analysis, exenatide is dominated, being both more costly and less effective than sitagliptin.

A prior analysis of the cost-effectiveness of glycemic control, based upon the United Kingdom Prospective Diabetes Study, was published prior to the FDA approval of many new medications used in diabetes management. (11) Our model represents an extension of this previously published model, which has now been used to address multiple diabetes-related policy questions. (11, 23, 24)

Previous analyses compared sitagliptin and exenatide individually to generic drugs. Because the treatment strategies used were different, countries under analysis were different, and comparator strategies were different, direct comparison of these analyses with the current analysis are difficult. (12 - 14) Importantly, this is the first cost-effectiveness analysis to compare exenatide and sitagliptin to one another

and to glyburide for second-line therapy in a single model. Because intensive glycemic control has become the accepted standard of care for healthier individuals less than 65 years of age, our analysis focuses on alternative strategies for achieving this goal. (25) Direct comparison of this analysis to the previous analyses is complicated by the fact that the current analysis is a comparison of intensive control strategies alone. In addition, unlike previous analyses, all three strategies made use of a metformin-first approach, with rosiglitazone as a third-line option and second-line therapy varying by strategy. Finally, our analysis incorporated hypertensive control and statin therapy, as would be current standard practice.

Nonetheless, review of previous studies makes clear that the extent to which non-glycemic control effects are attributed to newer glycemic control agents influences cost-effectiveness. (12 - 14) For example, exenatide use in the United Kingdom, relative to insulin glargine, was found to be dominated by insulin glargine in one study, while its use was found to be cost-effective (with a cost-effectiveness ratio of £22,420) in another. These different results are explained by the former model not attributing to exenatide improvements in blood pressure and in lipid profile (leading to improved cardiovascular outcomes), while the latter study did make these attributions. Because clinical trials of exenatide and sitagliptin have not found significant differences in diabetes complication rates, including cardiovascular events, we chose not to ascribe such benefits to either medication.

Our findings suggest that the potential scale of health benefits gained by use of exenatide and/ or sitagliptin, as a result of improved side-effect profiles, may be substantial. Relative to glyburide as second-line therapy, we found the use of sitagliptin and exenatide to be associated with an additional 0.09 and 0.12 QALYs per patient. This is comparable to the scale of health benefits provided by a number of highly effective preventive and treatment strategies. For example, the use of aspirin for secondary prevention of myocardial infarction in 45 year-old men has been estimated to provide a QALY gain of 0.04 per patient. (26) The use of statins in the secondary prevention of coronary artery disease has been associated with a QALY gain of 0.25 per patient. (27) The use of 23-valent pneumococcal vaccine to prevent disease in the elderly has been associated with a QALY gain of 0.003 per patient. (28)

We found results to be sensitive to assumptions regarding medication cost, incidence of medication effects and disutilities due to medication effects. Given the impact that such effects have on patients' daily lives and the importance of these quality-of-life effects on cost-effectiveness, further empiric study is necessary in understanding the preference-weighted quality of life impact of these effects, their costs and their consequences.

The American Diabetes Association and European Diabetes have recently published consensus guidelines for sequencing existing and new classes of medications as initial therapies in diabetes. (29) These recommendations are consistent with meta-analyses that indicate anti-glycemic oral agents and insulins used to treat diabetes have comparable efficacy, (30, 31) although they differ in other effects and significantly in costs. Spending on anti-diabetic agents nearly doubled from 6.3% of all prescription drug spending in 2004

to 12.3% in 2006, and costs of treatment increased sharply (9.5%) due to higher prices for non-generic drugs and a shift in treatment mix toward newer, more expensive products. (32)

Although side effects to older medications may justify the use of newer ones in individual cases, our study suggests that the additional costs of newer classes of drugs, when widely used in the large U.S. diabetic patient population, require that the value of these drugs be supported by substantial gains in health outcomes to be recommended on a population basis. Better understanding of the quality-of-life impacts of these drugs is necessary to make such a case strongly. For example, understanding the duration of weight loss effects of some of these medications and the potential downstream effects on macrovascular events (coronary heart disease, stroke) could contribute substantially to the value of some of these medications.

Our study has several limitations. Recently published long-term follow-up studies of intensive glucose control have demonstrated extended and improved treatment benefits, despite post-trial loss of between-group glycemic differences. (4) Our model did not integrate such legacy effects, relying instead on a direct relationship between glycemic control and diabetic complications. If such legacy effects differ by medication class then significant adjustment of the economic model would be necessary. The model incorporates disutilities due to medication effects, but does not yet account for costs due to management of side effects or medication switches that may occur due to side effects.

Diabetes is an epidemic disease that imposes substantial morbidity, premature mortality, and costs on the U.S. population. Appropriate treatment choices are necessary to minimize the economic burden associated with this prevalent disease. Our study suggests that to provide good economic value, newer medications, such as sitagliptin and exenatide, need to confer health benefits in scale with the additional costs they bring to the healthcare system.

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26 – 35 are available in the on-line appendix at http://care.diabetesjournals.org.

Table 1. Assumptions Regarding Model Parameters. WSP = wholesale price. HgbA1c = glycated hemoglobin.

Parameter	Value	Reference
Diabetes-related parameters		
Interval between onset of diabetes and diagnosis, years	10	(15)
Average hemoglobin A1c at time of diagnosis	6.80%	(15)
Treatment impact on HgbA1c	-2.90%	(15)
Rate of change in HgbA1c, on treatment	0.20%	(15)
Hazard Rates:		
Normal to microalbuminuria	0.02371	
Microalbuminuria to nephropathy	0.06561	
Normal to peripheral neuropathy	0.0294	
Normal to photocoagulation	0.0079	
Side effect-related parameters		
Probability of weight gain while on glyburide (first two years)	100%	(33)
Probability of weight loss while on exenatide (first two years)	100%	(33)
Probability of hypoglycemia:		
Glyburide	36.10%	(12)
Sitagliptin	6.20%	(12)
Exenatide	16.00%	(34)
Probability of nausea/ other gastrointestinal side effects while on glyburide	4.20%	(19)
Probability of nausea/ other gastrointestinal side effects while on exenatide	57.00%	(13)
Probability of upper respiratory infection while on sitagliptin	3.50%	(19)
Costs per day		
Metformin, 2000 mg	$1.42	WSP, (35)
Glyburide, 7.5 mg	$0.42	WSP, (35)
Sitagliptin, 100 mg	$6.06	WSP, (35)
Exenatide, 20 mcg	$8.37	WSP, (35)
Rosiglitazone, 8 mg	$5.59	WSP, (35)
NPH insulin, 10 units	$0.90	WSP, (35)
Injection-related supplies	$0.52	WSP, (35)
Annual Utilities following		
-- Blindness	0.69	(15)
-- stroke	0.5	(15)
-- ESRD	0.61	(15)
-- LEA	0.8	(15)

Table 2. Side-effect related quality-of life assumptions. A positive number (utility) indicates a gain in quality of life, and a negative number (disutility) indicates a loss in quality of life. GI = gastrointestinal.

Side effect	Glyburide	Exenatide	Sitagliptin	References
Weight gain/loss	-0.0031	0.0013	0	(33)
Hypoglycemia	-0.0064	-0.0005	-0.0002	(12,34,36)
Nausea /GI side-effects	0	-0.0005	0	Authors' assumption; (13,33)
Upper respiratory infections	0	0	-0.0001	(13)
Injectable	0	-0.0032	0	Authors' assumption
Overall disutility associated with side effects, after weighting*	-0.0095	-0.0029	-0.0003	

* The overall disutility was calculated as the weighted sum of the side effect utilities/ disutilities, where the weights were (1) the probability a patient was on a given medication at a point in time, and (2) the probability the side effect occurred.

Table 3. Results of Cost-effectiveness Analysis. Changes in costs and QALYs are calculated relative to the next most expensive treatment strategy. QALY = quality-adjusted life years.

Intensive Control - Treatment Strategies	Cost of medications	Total costs	Incremental costs	QALYs	Incremental QALYs	Incremental cost-effectiveness ratio	Cost-effectiveness ratio, relative to glyburide strategy
Glyburide as second-line therapy	$65,205	$146,950	--	15.2143	--	--	--
Sitagliptin as second-line therapy	$85,418	$4167,163	$20,213	15.3335	0.1192	$169,572	$169,572
Exenatide as second-line therapy	$89,054	$170,799	$3,636	15.2998	-0.0337	dominated	$278,935

Figure Legends

Figure 1: Daily treatment costs. Over 15 years the average daily treatment costs for the glyburide, sitagliptin and exenatide strategies were $2.98, $6.51 and $7.26 respectively.

Figure 1