

Comparison of Costs and Utilization Between Users of Insulin Lispro Versus Users of Regular Insulin in a Managed Care Setting

KRISTINA CHEN, PharmD, MS; EUNICE Y. CHANG, PhD; KENT H. SUMMERS, PhD, RPh;
ROBERT L. OBENCHAIN, PhD; KRISTINA S. YU-ISENBERG, PhD, MPH, RPh; and PETER SUN, MD, PhD

ABSTRACT

OBJECTIVE: To compare medical and pharmacy costs and utilization between patients with diabetes who received insulin lispro versus regular human insulin.

METHODS: A retrospective analysis of medical and pharmacy claims was conducted among continuously enrolled users of insulin lispro or regular insulin during the identification period, March 1, 2000, through February 28, 2001, within a large managed care organization. This study improved upon the methodology used in previous studies by (a) stratifying (rather than 1:1 matching) individuals by their likelihood to use insulin lispro using the propensity score binning technique, and (b) refining the study inclusion criteria to include only patients with 3 or more fills of the insulin under study (lispro or regular) to exclude individuals who may have been on either product for a short time. Because the propensity score binning technique groups patients with similar baseline characteristics within strata (bins) and not among individual patients, almost the entire available sample is retained in the analysis, unlike propensity score matching, where large numbers of patients can be excluded depending on the matching scheme. Therefore, the propensity score binning technique, because it uses more complete information, is less likely to produce biased results. Patients were grouped into 5 bins (quintiles) based on their estimated likelihood to receive insulin lispro rather than regular insulin. The propensity score model used baseline characteristics of age, gender, comorbidities, use of oral antidiabetic medications, prescription copayment, and diabetes-related costs and utilization. Overall cost and utilization differences (lispro minus regular insulin) during the 12-month follow-up period were calculated using weights inversely proportional to variances of within-bin differences.

RESULTS: Of 6,436 patients, 1,972 (30.6%) received insulin lispro and 4,464 (69.4%) received regular insulin. The propensity score estimation produced 5 bins, each containing between 1,287 and 1,288 patients, utilizing all patients in the analysis. Patients in the lower-numbered propensity score quintiles were older, more likely to use oral antidiabetic medications, and had more comorbidities than those in the higher-numbered quintiles. As quintile number increased, the percentage of insulin lispro users also increased. The weighted mean annual cost difference (lispro minus regular insulin) per patient was +\$79 ($P < 0.001$) for diabetes-related pharmacy cost, +\$212 ($P < 0.001$) for total pharmacy cost, -\$75 ($P < 0.857$) for diabetes-related medical cost, -\$2,286 ($P < 0.011$) for nondiabetes medical cost, and -\$2,327 ($P = 0.072$) for total medical cost.

CONCLUSIONS: Compared with regular insulin users, insulin lispro users incurred higher diabetes-related and total pharmacy costs but lower nondiabetes medical costs and similar total medical costs. Fewer hospitalizations among insulin lispro as compared with regular insulin users contributed to lower nondiabetes medical costs and similar total medical costs.

KEYWORDS: Insulin, Lispro, Managed care, Costs, Propensity score

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Diabetes imposes a substantial economic burden to society with the total annual cost estimated to be \$132 billion in medical expenditures and lost productivity.¹ Diabetes-related hospitalizations totaled 16.9 million days and represented 44% of the \$92 billion in direct medical expenditures attributable to diabetes. Ramsey et al. reported that, in 1998, an employer's mean annual per capita costs (direct medical plus medically related absenteeism costs) were significantly higher for diabetes beneficiaries than for control subjects, with an incremental cost of \$4,410 per year.² With the prevalence of diabetes increasing with age and in certain racial and ethnic populations, timely access to preventive care, diagnosis, and treatment is critical to improving the quality of life for individuals with diabetes.

Improving glycemic control is paramount to preventing or minimizing diabetes-related complications that negatively impact morbidity and mortality. Previous studies have demonstrated that tight glycemic control is associated with increased clinical benefit and decreased economic burden.³⁻⁵ In the United Kingdom Prospective Diabetes Study of newly diagnosed type 2 diabetes patients, it was found that every percentage point decrease in glycosylated hemoglobin (HbA1c) reduced the risk

Authors

KRISTINA CHEN, PharmD, MS, is a senior research associate, Cerner Health Insights, Beverly Hills, California (at the time of this study, she was an outcomes researcher, pharmacoeconomics and outcomes research, Prescription Solutions, Costa Mesa, California); EUNICE Y. CHANG, PhD, is chief statistician, health informatics and outcomes research, Prescription Solutions, Costa Mesa, California; KENT H. SUMMERS, PhD, RPh, is an associate professor, Purdue University School of Pharmacy, West Lafayette, Indiana (at the time of this study, he was a research scientist, U.S. medical outcomes research, Eli Lilly and Company, Indianapolis, Indiana); ROBERT L. OBENCHAIN, PhD, is a research advisor, U.S. medical outcomes research, Eli Lilly and Company, Indianapolis, Indiana; KRISTINA S. YU-ISENBERG, PhD, MPH, RPh, is manager, applied outcomes and analysis, Medical Affairs Commercial Operations, GlaxoSmithKline, Research Triangle Park, North Carolina (at the time of this study, she was manager, pharmacoeconomics and outcomes research, Prescription Solutions, Costa Mesa, California); PETER SUN, MD, PhD, is a research scientist, health economics and outcomes research, Eli Lilly and Company, Indianapolis, Indiana.

AUTHOR CORRESPONDENCE: Kristina Chen, PharmD, MS, c/o Eunice Y. Chang, PhD, Chief Statistician, Health Informatics and Outcomes Research, Prescription Solutions, 3515 Harbor Blvd., Mail Stop LC-07-264, Costa Mesa, CA 92626. Tel: (888) 398-5189; E-mail: information@rxsolutions.com

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of microvascular complications by 35%.⁴ In addition, a large health maintenance organization (HMO) in Washington state that examined the effect of glycemic control on health care costs and utilization showed that a 1% or greater improvement in glycemic control resulted in a cost saving of \$685 to \$950 per patient per year after adjusting for demographic factors, baseline HbA1c level, and complications.⁵

An insulin analog, lispro (Humalog), is one of the advancements in the treatment of diabetes mellitus. Insulin lispro is a rapid-acting human insulin analog with a faster onset of action and shorter duration of action than regular insulin, thus closely emulating the normal pattern of insulin secretion seen in non-diabetic individuals. This clinical property allows insulin lispro to be administered at mealtime, resulting in flexibility with regard to the timing of the administration that closely resembles the patient's lifestyle. Better glycemic control and lower incidence of postprandial hypoglycemia with insulin lispro compared with regular insulin have been demonstrated in multiple clinical trials in patients with type 1 diabetes⁶⁻¹³ and type 2 diabetes.^{14,15}

It is possible that the clinical benefits of insulin lispro may not justify its higher direct cost, compared with alternatives commonly used in practice. It may well be that physicians reserve the use of insulin lispro for select patients, which affects the outcomes of direct cost comparisons. A few economic studies of insulin lispro exist,^{16,17} but only one study has been conducted that adequately addresses treatment selection bias and compares cost and utilization between insulin lispro patients and regular insulin patients.¹⁸ The objective of our study was to examine diabetes-related and nondiabetes-related cost and resource utilization among insulin lispro and regular insulin patients using a propensity score approach that controls for treatment selection bias. Our study improves upon the methodology used in previous studies by (a) stratifying (rather than 1:1 matching) individuals by likelihood to use insulin lispro, and (b) refining the study inclusion criteria to include only patients with 3 or more fills of the insulin under study (lispro, regular) to exclude individuals who may have been on either product for a short time. Because the propensity score binning technique groups patients with like baseline characteristics within strata (bins) and not among individual patients, almost the entire available sample is retained in the analysis, unlike propensity score matching, where large numbers of patients can be excluded depending on the matching scheme. Therefore, the propensity score binning technique, because it uses more complete information, is less likely to produce biased results. The propensity score binning technique, or "full" matching, is, in principle, superior to any other alternative matching technique for observational studies.¹⁹ We also address whether the clinical advantages of insulin lispro translate into potential economic benefits for insulin lispro compared with regular insulin in a managed care setting.

Methods

We used a retrospective cohort design to compare costs and health care utilization between insulin lispro and regular human insulin users after correcting for observed treatment selection bias using the propensity score method (details are described in the statistical analyses section). We used the database from Prescription Solutions, a large managed care organization with approximately 3.3 million members in the Western United States. The estimated prevalence of diabetes (percentage of members with a submitted claim listing a diabetes diagnosis, *International Classification of Diseases, 9th Revision*, [ICD-9] 250.xx) in this population was 6.8% in 2002, which is similar to the national prevalence of 6.3% in 2002.¹ This database contains member demographic and plan enrollment characteristics as well as information regarding pharmacy and medical care utilization. For each pharmacy claim, data such as the drug dispensed, the dispensing date, the quantity and days supply, ingredient cost (the allowed charge for the medication minus dispensing fee) of medications, and member copayment are available. Data for both inpatient and outpatient medical claims include the date and place of service, diagnosis codes (*International Classification of Diseases, 9th Revision, Clinical Modification* [ICD-9-CM]), current procedural terminology codes, and costs associated with utilization of each health resource. All claims undergo quality assurance edits before being stored in a standard format in a central data warehouse. This database has been used in previous health care services and economic studies.²⁰⁻²³

Study Sample

We identified all patients who filled at least one prescription for any short-acting (regular) insulin (Generic Product Identifier [GPI-8] codes 27103010, 27104010, or 27104015) or insulin lispro (GPI-8 code 27104005) during the 12-month identification period, March 1, 2000, to February 28, 2001. Insulin aspart (Novolog) (GPI-8 code 27104002) was not included in our analysis since there was no utilization at the time of the study. The selected patients were then stratified as insulin lispro users or regular human insulin users based on type of prescription fill of insulin during the identification period. The date of the first fill of insulin during the identification period was designated as the index date for those on insulin lispro, otherwise the first fill of regular insulin was used as the index date. The final insulin lispro study group included patients who had at least 2 additional insulin lispro fills during the 12-month follow-up period, defined as the period immediately following the index date. Similarly, the final regular insulin group constituted those with at least 2 additional regular insulin fills with no fill of insulin lispro during the follow-up period. Patients in the insulin lispro group could receive regular insulin during the follow-up period to allow for regimens combining insulin lispro and regular insulin. Patients switching from insulin lispro (after

having filled at least 3 prescriptions, thereby qualifying for inclusion in the analysis) to regular insulin were included in the insulin lispro group; however, those switching from regular insulin to insulin lispro were excluded. For both study groups, we excluded patients with a diagnosis of gestational diabetes (ICD-9-CM 648.8) as well as patients who were not continuously enrolled in the health plan during the 6-month preindex period and 12-month follow-up period after the index date.

Outcome Measures

Health resource utilization and costs for medical and pharmacy services during the follow-up period, stratified as diabetes or nondiabetes-related, were the primary outcomes of interest. Health resource utilization included hospitalizations and outpatient physician visits. Utilization and costs were classified as diabetes-related if the primary diagnosis in the medical claim was indicative of diabetes, diabetes-related complications, diabetes-related comorbidities (hypertension, nephropathy, neuropathy, or retinopathy), or if prescription claims were for insulin or oral antihyperglycemic medications.

Hospitalizations and outpatient physician costs were calculated from provider-submitted charges on medical and hospital claims. Charges were used for this analysis rather than the amount paid to the provider since the amount paid for most outpatient services in the capitated managed care environment was \$0. Pharmacy costs were determined using "ingredient cost," which is the allowed charge for the drug excluding pharmacy dispensing fees. Drug manufacturer discounts and patient copayments have not been subtracted from the ingredient cost.

Statistical Analyses

Selection bias is a potential limitation in observational studies that do not randomly assign patients to treatment groups.^{24,25} To minimize selection bias, we used propensity score techniques to balance the treatment groups at baseline. We used the propensity score binning technique, which is a flexible estimator that uses the propensity score to match individuals within a discrete number of strata (bins).²⁶ Propensity score binning allows the treatment effect that varies across discrete partitions of the sample to be estimated with almost no functional form assumptions, grouping patients with similar baseline characteristics within the same bins.

The construction of the propensity score model relies on the use of confounding variables that are potentially related to the outcome of interest and contribute to the selection of treatment with insulin lispro. The propensity score defines the probability of each individual patient to be treated with insulin lispro based on a given set of covariates. The use of propensity score analyses balances the distribution of covariates between the insulin lispro and regular insulin groups and thereby minimizes the influence of potential biases. Using baseline characteristics as independent predictors, the multivariable logistic regression model was constructed to predict the likelihood (propensity

score) of each individual patient receiving insulin lispro or regular insulin. This propensity score, ranging from 0 to 1, represents a summary value of the variables that correspond to the propensity of a given patient to receive insulin lispro.

In this study, we used the following baseline characteristics, from the preindex period, in the propensity score model: age at index date (continuous); gender (F/M); use of oral antihyperglycemic medications (Y/N); and prescription copayment (continuous) for the index medication, insulin lispro or regular insulin. In addition, a measure of comorbidity was included using the Deyo-adapted Charlson Index (continuous), which contains 17 categories of comorbid conditions, defined using ICD-9 diagnosis codes.²⁷ Finally, baseline diabetes and nondiabetes-related utilization and costs were also included in the model. The ability of the model to discriminate between patients who received insulin lispro and those who received regular insulin was estimated by the area under the receiver-operating characteristic (ROC) curve.

After a propensity score was assigned to each patient, the binning analysis was used to classify patients into 5 different strata (quintiles) based on the distribution of propensity scores, thereby grouping patients with the same range of propensity scores into the same quintile.²⁵ Quintiles were chosen because Cochran showed that stratification into quintiles usually removes 90% of the bias due to differing covariate distributions between treatment and controls.²⁸ We used *t* tests and chi-square tests to compare baseline characteristics between insulin lispro and regular insulin groups before and after the assignment to a propensity score based quintile.

Quintile-specific utilization and costs were compared between the insulin lispro and regular insulin groups. In addition, we combined the quintile-specific results into a summary score to calculate weighted mean utilization and cost differences (lispro minus regular) between the insulin lispro and regular insulin groups. The weighted average analysis combined results across quintiles by weighting estimated within-bin cost differences inversely proportional to their estimated variances.

Statistical analyses were performed using SAS version 8.2 (Cary, NC). All *P* values are for 2-tailed tests with statistical significance defined as $P \leq 0.05$.

Results

A total of 18,886 patients had at least one prescription claim for a short-acting insulin during the study identification period, March 1, 2000, through February 28, 2001. Of these patients, 6,436 patients (34.1%) met the study inclusion criteria: 1,972 (30.6%) insulin lispro patients and 4,464 (69.4%) regular insulin patients. Of those excluded from study eligibility, 10 (0.05%) were excluded due to gestational diabetes, 228 (12.1%) filled a prescription for insulin lispro during the follow-up period for the regular insulin treatment group,

Comparison of Costs and Utilization Between Users of Insulin Lispro Versus Users of Regular Insulin in a Managed Care Setting

7,456 (39.5%) did not have 2 or more prescription fills of insulin lispro or regular insulin, and 4,756 (25.2%) did not meet the continuous enrollment criteria.

Before applying the propensity score binning, patients treated with insulin lispro were younger, had fewer comorbidities, were less likely to use oral hyperglycemic medications, had more diabetes-related physician office visits, and had higher diabetes-related and total pharmacy costs but lower medical costs, than regular insulin patients ("All" row in Table 1). After performing the propensity score binning, all patients were retained and partitioned into quintiles containing between 1,287 and 1,288 patients overall in each quintile. Quintile 1 consisted of patients least likely to receive insulin lispro, whereas quintile 5 included those most likely to receive insulin lispro. Patients in the lower-numbered quintiles tended to be older, more likely to use oral antihyperglycemic medications, and had more comorbidities than those in the higher-numbered quintiles. In general, the insulin lispro and regular insulin groups were well balanced for the baseline characteristics that we assessed after stratification to a propensity score quintile (Table 1), with the exception of age, gender, and diabetes-related office visits for quintile 5, which was not perfectly well balanced after stratification. However, as evidenced by the ROC curve of 0.80, the logistic regression model used to estimate each patient's propensity to receive insulin lispro had good discriminative ability.

Weighted Utilization and Costs in Follow-up Period

Quintile-specific data were combined to derive a summary score to calculate utilization and cost differences (lispro minus regular) between the insulin lispro and regular insulin groups using weights inversely proportional to variances of within-bin differences. There was no significant difference in the number and percentage of nondiabetes-related office visits and diabetes-related hospitalizations, respectively, for patients who received insulin lispro as compared with those who received regular insulin (Table 2). Insulin lispro patients, however, had a slightly greater number of diabetes-related office visits (+0.32, $P=0.083$) while having somewhat fewer nondiabetes-related hospitalizations (-3.3% , $P=0.073$) than regular insulin patients. In addition, insulin lispro patients incurred significantly higher average diabetes-related (+\$79, $P<0.001$) and total pharmacy costs (+\$212, $P<0.001$) than regular insulin patients (Figure 1). Both diabetes-related and total medical costs were not significantly lower for insulin lispro users ($-\$75$, $P=0.857$ and $-\$2,327$, $P=0.072$, respectively) but were significantly lower in nondiabetic medical costs ($-\$2,386$, $P=0.011$) during the 12-month follow-up period. Similar results were observed using weights equal to the sample size of quintiles (results not shown).

Discussion

Insulin lispro, with its faster onset and shorter duration of action, has been associated with effective lowering of postprandial

TABLE 1 Selected Baseline Characteristics (Measured During the 6-Month Preindex Period) Before ("All" Quintiles) and After Stratification by Propensity Score Quintile

	Quintile	Lispro	Regular	P Value
Number of patients	1	72	1,215	
	2	199	1,088	
	3	310	978	
	4	491	796	
	5	900	387	
	All	1,972	4,464	
Mean age at index date (years)	1	72.3	74.4	NS
	2	67.9	67.8	NS
	3	59.0	58.5	NS
	4	52.7	51.5	NS
	5	28.7	35.8	<0.001
	All	43.9	61.2	<0.001
Percentage female	1	45.8	58.4	0.035
	2	49.2	53.7	NS
	3	49.0	48.5	NS
	4	24.2	29.3	0.049
	5	52.1	43.9	0.007
	All	51.3	52.6	NS
Mean Charlson Comorbidity Index	1	4.4	5.1	NS
	2	3.7	3.6	NS
	3	3.3	3.1	NS
	4	2.6	2.6	NS
	5	2.0	2.3	0.017
	All	2.6	3.6	<0.001
Percent with oral hyperglycemic use	1	55.6	48.0	NS
	2	42.7	38.2	NS
	3	31.6	33.7	NS
	4	24.2	29.3	0.049
	5	21.8	20.9	NS
	All	27.3	36.8	<0.001
Mean diabetes-related office visits	1	9.3	8.2	NS
	2	10.7	9.9	NS
	3	11.8	11.1	NS
	4	17.3	18.3	NS
	5	10.9	13.5	0.009
	All	11.2	10.1	<0.001
Percent with a diabetes-related hospitalization	1	4.2	6.0	NS
	2	1.0	3.0	NS
	3	3.2	1.7	NS
	4	2.4	2.4	NS
	5	5.1	4.1	NS
	All	3.7	3.5	NS
Mean diabetes-related pharmacy costs (\$US)	1	381	296	0.011
	2	375	329	NS
	3	355	338	NS
	4	351	383	NS
	5	375	388	NS
	All	366	337	<0.001
Mean total pharmacy costs (\$US)	1	1,171	1,106	NS
	2	854	1,048	NS
	3	1,167	1,036	0.015
	4	1,143	1,063	NS
	5	1,222	1,360	NS
	All	1,183	1,091	0.001
Mean diabetes-related medical costs (\$US)	1	3,259	3,649	NS
	2	1,193	2,136	0.015
	3	1,632	1,545	NS
	4	1,484	1,709	NS
	5	2,717	1,798	NS
	All	2,106	2,313	NS
Mean total medical costs (\$US)	1	17,536	24,551	NS
	2	5,413	8,191	0.007
	3	8,206	5,570	NS
	4	3,619	4,737	NS
	5	4,599	4,723	NS
	All	5,477	11,153	<0.001

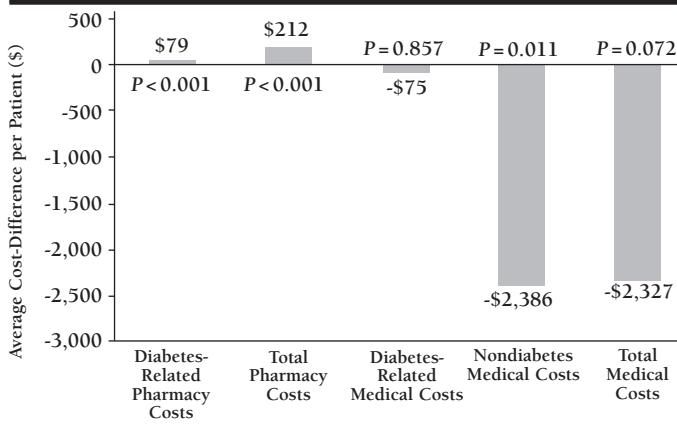
NS=not significant.

TABLE 2 Weighted* Resource Utilization Differences in 12-Month Follow-up Period From Binning Method

Utilization Difference (Insulin Lispro Minus Regular Insulin)	Mean (SE)	P Value
Diabetes-related office visits	0.3 (0.2)	0.083
Nondiabetes-related office visits	-0.1 (0.3)	0.876
Diabetes-related hospitalizations (%)	1.6 (1.1)	0.122
Nondiabetes-related hospitalizations (%)	-3.3 (1.9)	0.073

* Weights = inversely proportional to observed variances of within-bin differences.

FIGURE 1 Weighted* Cost Difference (Lispro Minus Regular Insulin) in 12-Month Follow-up Period



* Weights = inversely proportional to observed variances of within-bin differences.

hyperglycemia and less incidence of postprandial hypoglycemia compared with regular insulin.^{6,7} This clinical property of insulin lispro enables patients with diabetes to inject at meal-time rather than 30 to 45 minutes before, an advantage over regular insulin, which has been demonstrated to improve some patients' satisfaction with treatment and quality of life.²⁹⁻³¹ Our objective was to compare cost and health resource utilization between insulin lispro and regular insulin in a naturalistic setting from a health plan perspective.

Overall, we found that patients treated with insulin lispro tended to be younger, had fewer comorbidities, were less likely to use oral antihyperglycemic medications, and had a higher average number of physician office visits than patients treated with regular insulin during the 6-month baseline period. Given the differences in baseline characteristics of these 2 treatment groups, we used the propensity score binning method to balance individual covariates between the insulin lispro and regular insulin groups and, as a result, minimize the selection bias seen in observational studies. After patients were stratified into similarly composed quintiles based on the distribution of propensity scores, we found that insulin lispro patients had

significantly higher diabetes-related and total pharmacy costs in the 12-month follow-up period compared with regular insulin patients. The significantly higher pharmacy cost associated with insulin lispro was not surprising since the direct ingredient cost of insulin lispro is greater than that for regular insulin. Our finding is consistent with another insulin lispro study that showed significantly higher pharmacy expenditures for insulin lispro users as compared with their propensity score-matched regular insulin users.¹⁸

In contrast, insulin lispro patients tended to have similar or marginally lower diabetes-related and total medical costs than regular insulin patients, as evidenced by the weighted medical cost differences averaged across quintiles. The use of regular insulin was associated with an additional \$2,386 in nondiabetes-related medical costs, but the +\$75 diabetes-related and +\$2,327 total medical cost per patient per year were not statistically significant. Our findings are consistent with another study that showed that insulin lispro patients had significantly more office visits but fewer inpatient hospitalizations, which corresponded to significantly higher office visit costs but lower inpatient hospital costs compared with regular insulin patients.¹⁸ Fewer inpatient hospitalizations for insulin lispro patients may be related to the dosing flexibility of insulin lispro. This added flexibility, as well as improvements in glycemic control and decreases in the risk of severe hypoglycemia, may also contribute to better overall management of the patient's health, thus resulting in fewer nondiabetes-related hospitalizations and lower overall medical costs. However, it should be pointed out that the standard error for the medical cost measures was relatively large (in excess of \$400) compared with < \$70 for the prescription cost variables.

Selection bias is a potential limitation in observational studies, such as case-control or cohort studies, that do not randomly assign patients to treatment groups. Misleading outcomes may result from differences in patient characteristics at the time of treatment that affect the decision to treat with insulin lispro or regular insulin. We attempted to minimize selection bias by using the propensity score method to balance baseline covariates between patients who were prescribed insulin lispro and those who were prescribed regular insulin. We further stratified patients into 5 quintiles based on the distribution of propensity scores, improving the ability to compare patient outcomes among those with similar baseline characteristics. By comparing only within each quintile, we minimized selection bias that could potentially affect economic outcomes. Additionally, because we used all available patient data that represented diverse geographic regions, the results are more amenable to generalization to other diabetic populations.

Limitations

Despite the advantages associated with propensity score techniques, the study involved several limitations. First, propensity

score methods only control for known or measurable factors.²⁴ Thus, if we failed to include other covariates that may affect the propensity of a patient to receive insulin lispro versus regular insulin, then it is possible that patients within each quintile were not entirely homogenous. Covariates that were not available included socioeconomic status, HbA1c values, duration of diabetes, and disease severity. However, because our propensity score model had good discriminative ability (ROC of 0.80), we believe that this limitation did not compromise our results. Second, since the propensity score was derived from a combination of risk factors, the individual effect of each factor and its impact on the overall effect could not be adequately determined.^{26,32,33}

The decision not to exclude patients in the insulin lispro group who may have switched to regular insulin during the course of follow-up may have confounded the results. However, because this proportion is likely to be small, their inclusion is not believed to have affected the study results. Additionally, adherence patterns between insulin lispro users and regular insulin users were not included as a covariate in the analysis. Differing adherence patterns between the products may have influenced the results and may be worthy of future research.

To represent pharmacy costs, we used drug ingredient cost, before the addition of pharmacy dispensing fees or the subtraction of drug manufacturer discounts and before subtraction of member cost-share amounts. Therefore, drug ingredient cost may overstate the actual net health plan cost and represents more closely the combined health plan and member drug costs. Since this study was conducted among members of capitated health plans, it was necessary for us to use provider-submitted hospital and medical charges. These charges overstate actual health plan costs, but there is no reason to suggest that these submitted charges would differ systematically between the study groups.

Conclusions

After controlling for selection bias, we found that insulin lispro patients, compared with regular insulin patients, had significantly higher diabetes-related and nondiabetes-related pharmacy costs while having similar or lower diabetes-related and total medical costs as a result of fewer inpatient hospitalizations. Despite the higher product cost of insulin lispro, this study found that savings in medical costs and fewer hospitalizations might offset these costs. These findings, combined with other evidence supporting improved glycemic control and decreased risk for severe hypoglycemia, suggest that use of insulin lispro may improve cost outcomes as well as clinical outcomes. Further research is necessary to determine whether there are differences in cost and utilization patterns, particularly related to hospitalization, between insulin lispro and regular insulin in a longer follow-up period. Moreover, the addition of other covariates, such as HbA1c levels, medication adherence, and

disease duration and severity may provide better explanation for the fewer hospitalizations observed in insulin lispro patients compared with regular insulin patients.

DISCLOSURES

Prescription Solutions received funding for this study from Eli Lilly and Company, which makes lispro, and, in conducting this study, worked collaboratively with authors Robert L. Obenchain and Peter Sun, current employees of Eli Lilly, and author Kent H. Summers, an employee of Eli Lilly at the time of this study; funding was obtained by Summers and Sun. Author Eunice Y. Chang is employed by Prescription Solutions and has received funding from other pharmaceutical companies for outcomes research studies; authors Kristina Chen and Kristina S. Yu-Isenberg were employees of Prescription Solutions at the time of this study.

Chen served as principal author of the study. Study concept and design and analysis and interpretation of data were contributed by Chen, Chang, Summers, Obenchain, and Yu-Isenberg; statistical expertise was contributed by Chang and Obenchain. Drafting of the manuscript was primarily the work of Chen and Yu-Isenberg, and its critical revision was the work of all authors. Administrative, technical, and/or material support was provided by Chen and Sun.

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