Effect of Diabetes Treatment-Related Attributes on Costs to Type 2 Diabetes Patients in a Real-World Population

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ABSTRACT

BACKGROUND: Type 2 diabetes mellitus (T2DM) results in a substantial economic burden on patients, health care systems, and society. Most literature assessing the cost of T2DM focuses on the long-term complications of the disease, the association between glucose control and cost, and patient characteristics resulting in poor and costly outcomes. However, it is likely that attributes specific to diabetes therapy can affect the use of costly resources.

OBJECTIVE: To estimate the effect of diabetes treatment-related attributes, such as improved efficacy, adherence, and reduced risk for hypoglycemia, on costs to T2DM patients.

METHODS: An observational, retrospective study was conducted using the Optum Clinformatics Database, which links medical and pharmacy claims to laboratory results. Patients aged ≥ 18 years with T2DM who had ≥ 1 anti-diabetic medication claim; ≥ 1 hemoglobin A1c (A1c) test result; continuous enrollment in the health plan from April 1, 2010, to March 31, 2011; and at least 1 follow-up day were included. Nondiabetes specific total, inpatient, outpatient, emergency room, and other costs (along with antidiabetes medication costs) were defined for each patient. Generalized linear models with logarithm link were used to predict the 1-year and cumulative 3-year costs. Demographic factors and comorbidities were included as covariates in addition to the diabetes treatment-related attributes.

RESULTS: In the entire analysis cohort, the average 3-year cost per patient was \$74,862. The percentage effect on cost of diabetes treatment-related variables ranged from -18% to 429%. Drug adherence was associated with lower inpatient, outpatient, and emergency room costs and higher drug costs. Hypoglycemia was associated with higher inpatient, outpatient, emergency room, and other direct costs (except antidiabetic drug costs). Compared with A1c values $\leq 7\%$, patients with higher levels were associated with higher total and drug costs.

CONCLUSIONS: Study results demonstrate the association between diabetes treatment-related attributes and costs, including inpatient, outpatient, drug, and total costs. This association raises the question: what would the effect of a new diabetes therapy, with high efficacy, high adherence, and reduced risk of hypoglycemia have on economic outcomes?

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- Treatment of T2DM and its complications are a huge burden on health care payers and patients.
- Adherence to diabetes treatment improves patient outcomes.

What this study adds

- Improved adherence to diabetes medications was associated with higher drug cost but was also associated with lower inpatient, outpatient, and emergency room costs.
- The effect of hypoglycemia on cost depended on patient severity and the cost category being analyzed, but in general, hypoglycemia was associated with higher costs.
- Higher hemoglobin A1c levels were associated with higher overall total costs, since patients with poor glucose control tended to use more health care resources than those patients in control.

Type 2 diabetes mellitus (T2DM) is a chronic disease resulting in a significant economic burden to patients, payers, and society. The incidence and prevalence of the disease is anticipated to increase given the aging population, increases in obesity, and other factors. About 33% of the U.S. population is projected to have T2DM by 2050.¹ Because of the high prevalence and chronic nature of the disease, the national health care expenditure attributed to patients with T2DM is over 10%.² These expenditures are from medication costs and long-term complications of the disease. For example, the total direct costs of T2DM in the United States exceeds \$174 billion each year, with \$27 billion in medical costs (\$8.6 billion for oral agents and \$3.7 billion for insulin) and the remainder related to other medical expenditures (e.g., hospital inpatient care, cost of complications, and visits).³ These estimates do not include additional indirect costs such as time off from work and lost productivity, which further emphasizes the enormous burden that diabetes places on society.

The burden of diabetes is anticipated to increase given the aging population despite advances in diabetes therapies over recent years, which are slightly more effective or have less safety concerns (i.e., hypoglycemia). Therefore, there remains an unmet need for new treatments that allow patients to adhere to their medications, maintain glucose control, and reduce health care use for their disease.

What is already known about this subject

- The prevalence of type 2 diabetes mellitus (T2DM) is expected to increase given the aging population.

It is well established that glucose control (hemoglobin A1c < 7%) reduces the long-term complications (and hence cost) of T2DM⁴; however, recent literature has found that other factors also drive cost. For example, Meyers et al. (2014) reported that obesity, comorbid conditions, and the use of insulin are all associated with “high-cost” T2DM patients, compared with “lower-cost” patients.⁵ Another driver of cost is patient nonadherence, since for every 25% increase in medication adherence, a patient’s hemoglobin A1c (A1c) is reduced by 0.34%.⁶ Furthermore, there is an inverse relationship between adherence and total direct cost, especially hospitalization costs, suggesting that total costs over time are driven by expensive hospitalizations among patients with T2DM as compared with patients without T2DM.⁶

With the rising cost of treating T2DM, and the focus of the American Diabetes Association on individualized care and treatment, the role of specific treatments and their attributes (e.g. reduced side effects or incremental improvements in A1c) could play a central part in reducing health care costs by directly affecting patient adherence. In addition, providing patients with fixed-dose combination therapies to simplify their prescribed regimens are more likely to result in optimal glucose control and reduce health care costs. For example, one study of naive T2DM patients found fixed-dose combination patients to have the lowest diabetes-related costs, compared with loose-dose combination or step therapy (\$1,641 compared with \$2,099 and \$1,900, respectively).⁷ Studying the effect of diabetes treatment-related attributes on costs of T2DM may provide insight into the potential cost savings when introducing a new antidiabetic therapy.

The purpose of this study was to estimate the effect of diabetes treatment-related attributes on costs to T2DM patients, with a focus on the drivers of cost, namely glycemic control, adherence, and hypoglycemic events.

Methods

Database

United Health Group insurance claims data from the Optum Clinformatics Database was the source of data for this study. The database includes approximately 13 million covered lives annually, with an estimated 57.2 million patients with claims activity from quarter 1, 2000, to quarter 2, 2014. Data elements include patient demographics, enrollment start and end dates, inpatient and outpatient medical claims, pharmacy claims, and selected laboratory results.

Study Design and Population

The inclusion period for this study was from April 1, 2010, through March 31, 2011, with the index date set on March 31, 2011. The follow-up period was from April 1, 2011, until the last day covered or March 31, 2014. All costs were tallied in the follow-up period. The study population included

those patients aged at least 18 years who had at least 1 claim with an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis code indicating T2DM; at least 1 claim for a diabetes therapy; at least 90 days of enrollment before the index date; at least 1 A1c result; and continuous enrollment during the entire inclusion period. Patients with unknown age and gender and zero days of follow-up were excluded.

Cost Analysis

Potential cost drivers measured during the study period were divided into 2 categories: patient characteristics and treatment characteristics. Patient characteristics included age, gender, geographic location, and comorbidities. Treatment characteristics included endocrinologist visits; adherence (defined by the proportion of days covered [PDC] by any antidiabetic medication, including multiple antidiabetic medications); A1c level (defined by the average of A1c values after interpolating the existing A1c data); and hypoglycemic events (identified by ICD-9-CM codes).

Diabetes health care costs were assessed over 1 year and 3 years following the index date (follow-up period) and stratified into the following categories: inpatient, outpatient emergency room (ER), diabetes medications, and all other.

Statistical Analysis

The study sample was divided into a test sample (80% random sample) and a validation sample (remaining 20%); the former was used to build the predictive cost equations, and the latter was used for the validation purpose. Generalized linear models were developed to estimate the cumulative 1- and 3-year costs for each cost category, as well as the total costs, adjusting for the demographic and clinical characteristics previously listed, as well as the length of follow-up after the index date. In the regression model, all the covariates were treated as categorical except adherence, which was an ordinal variable but was treated as a continuous variable.

All variables were included in the model, and a backwards selection approach was used in which each variable was tested at a significance level of 0.1. If a variable was not statistically significant, it was dropped from the model. Therefore, all variables presented in the results were considered significant in the model selection process at the significance level of 0.1. The models were fit using gamma, Poisson, negative binomial, and zero-inflated negative binomial (ZINB) distributions, keeping only variables with a *P* value of ≤ 0.1 . The model distribution assumption with the smallest Akaike information criterion (AIC) value, indicating the best goodness of fit, was retained.

The predictive equation was further validated by several different approaches, including analysis of the model’s goodness-of-fit statistics, replication of model fit in the validation sample, and estimation of the model’s discrimination

TABLE 1 Study Population

Inclusion/Exclusion Criteria	Sample Remaining
At least 1 claim with an ICD-9-CM code indicating type 2 diabetes during the inclusion period	865,970
At least 1 claim for a diabetes therapy during the inclusion period	688,054
At least 1 A1c test result during the inclusion period	179,617
Continuous health plan enrollment during the inclusion period	143,543
Aged at least 18 years during the inclusion period	143,263
Known age or sex	143,248
At least 1 day in follow-up period	141,409
Final study population	141,409

A1c = hemoglobin A1c; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

of high- and low-cost patients. The goodness of fit for generalized linear models was estimated using the scaled deviance and the scaled Pearson's chi-square. The scaled deviance and the scaled Pearson's chi-square follow a chi-square distribution with the regression's residual degrees of freedom; smaller values with nonsignificant *P* values indicate acceptable fit. When the scaled deviance and the scaled Pearson's chi-square statistics are divided by the regression's residual degrees of freedom, smaller values indicate better fit, with ratios close to 1.0 indicating the highest degree of fit.⁸ In addition to assessing the goodness-of-fit statistics generated in the test sample, the parameter estimates obtained from the test sample were fit to the validation sample.

After fitting the models to the validation sample, the ratio of the scaled deviance and scaled Pearson's chi-square statistics to their degrees of freedom was compared with those of the fit statistics generated from the test sample model. If the parameter estimates are internally consistent, then the ratio of the fit statistics to their degrees of freedom should be comparable between the test sample regressions and the validation sample regressions. Finally, the parameter estimates obtained from the test samples were used to score predicted costs for patients in the validation sample, and the actual 1- and 3-year costs of the validation sample were calculated based on each patient's actual claims.

Actual costs were dichotomized into a binary cost variable. Receiver operating characteristic (ROC) analyses were then performed; the area under curve (AUC) for the ROC curve was reported; and a statistical test was performed to determine if the model could correctly classify low-cost and high-cost patients.

Results

Study Population

Within the Optum Clinformatics Database, 865,970 patients were identified with the T2DM diagnosis codes during the inclusion period, and 141,409 patients met the inclusion/

exclusion criteria previously described (Table 1). Patients tended to be older with a mean age of 61 years (standard deviation [SD]=13 years); have at least 1 comorbidity (hypertension, *n*=118,016, 83.46%); have hyperlipidemia (*n*=119,405, 84.44%); and be in poor glycemic control (73% patients had an A1c>7%; Table 2).

Cumulative 1-Year and 3-Year Costs

The average costs per patient adjusting for the follow-up period are presented in the first row of Table 3A and Table 3B. The allocation of cost in each cost category was similar in 1-year and 3-year costs (\$23,322 and \$74,862, respectively.) Over 40% of the total costs were from inpatient costs, with average cost per patient being \$9,733 (42% of total costs) for 1-year costs and \$32,790 (44% of total costs) for 3-year costs, respectively.

Regression Analysis of Cost Drivers

Eighty percent (*n*=113,128) of patients were randomly selected for cost regression, and the baseline characteristics were comparable to the overall population (data not shown). Determined by AIC, ZINB models were selected for inpatient and ER costs. For outpatient, drug, other and total costs, gamma models were used.

The percentage of effect on 1-year and 3-year costs of diabetes treatment-related variables is presented in Table 3A and Table 3B, respectively. All variables presented in the tables were significant unless otherwise specified. The full model results are presented in Appendix A (available in online article).

For 1-year costs, higher adherence was associated with lower inpatient, outpatient, and ER costs but higher drug and other costs (e.g., other medications or costs incurred in other facilities than the hospital). The total costs were slightly higher in patients with higher adherence. The effect of hypoglycemia on cost depended on the severity level of the hypoglycemia event (whether an ER visit or hospitalization was warranted) and the cost category analyzed, but in general, hypoglycemia was associated with higher costs. Also, a higher A1c level was associated with lower outpatient and other costs but higher drug and overall total costs.

For 3-year costs, the effect of cost drivers on each cost category was similar to the 1-year costs except the extent of adherence, which had no significant impact on the 3-year cumulative total costs. At 3 years, levels of A1c were not significantly associated with 3-year cumulative outpatient cost.

Validation

In terms of model fit statistics, the scaled deviance/degree of freedom ranged from 1.24 to 1.37 and from 1.23 to 1.34 in the test sample for 1-year and 3-year costs, respectively (Appendix B, available in online article). The scaled Pearson chi-square/degree of freedom ranged from 0.64 to 3.94 and from 0.67 to 3.55 in the test sample for 1-year and 3-year costs, respectively.

TABLE 2 Patient Baseline Characteristics

Characteristics		Characteristics	
Final study population	N = 141,409	Endocrinologist visits, n (%)	
Sex, n (%)		Yes	21,893 (15.5)
Male	72,024 (50.9)	No	119,516 (84.5)
Female	69,385 (49.1)	PDC, continuous, mean (SD) median	0.78 (0.2) 0.9
Age, years, mean (SD) median	61.12 (12.8) 61.0	PDC categories, n (%)	
Age category, years, n (%)		0%-19%	3,827 (2.7)
18-39	7,275 (5.1)	20%-39%	9,292 (6.6)
40-49	18,405 (13.0)	40%-59%	16,268 (11.5)
50-64	58,701 (41.5)	60%-79%	26,093 (18.5)
≥ 65	57,028 (40.3)	≥ 80%	85,929 (60.8)
Geographic location, n (%)		Hospitalized/ER hypoglycemia, n (%)	
Midwest	11,514 (8.1)	Hospitalized/ER hypoglycemia ^b	1,254 (0.9)
Northeast	8,984 (6.4)	Nonhospitalized/ER hypoglycemia ^c	7,268 (5.1)
South	89,767 (63.5)	No hypoglycemia	132,887 (94.0)
West	28,032 (19.8)	A1c level, continuous, mean (SD) median	7.30 (1.0) 7.2
Other ^a	1 (0.0)	A1c category, n (%)	
Unknown	3,111 (2.2)	≤ 7%	37,829 (26.8)
Comorbidities, n (%)		> 7% to ≤ 8%	84,762 (59.9)
Renal disease	29,909 (21.2)	> 8% to ≤ 9%	9,698 (6.9)
Vascular disease	34,585 (24.5)	> 9%	9,120 (6.5)
Chronic pulmonary disease	22,771 (16.1)	Antidiabetic medication category, n (%)	
Connective tissue disease-rheumatic disease	3,487 (2.5)	Bolus	2,359 (1.7)
Peptic ulcer	1,434 (1.0)	Premixed insulin	6,048 (4.3)
Mild liver disease	7,764 (5.5)	Basal bolus	12,625 (8.9)
Moderate or severe liver disease	623 (0.4)	Basal + GLP-1	2,026 (1.4)
Hypertension	118,016 (83.5)	Basal + OADs	8,253 (5.8)
Hyperlipidemia	119,405 (84.4)	Basal only	2,828 (2.0)
Obesity	19,126 (13.5)	OAD + GLP-1	5,254 (3.7)
Gastrointestinal disease	31,257 (22.1)	2+ OAD	51,777 (36.6)
Pancreatitis	1,182 (0.8)	1 OAD	50,239 (35.5)
Foot disease	6,798 (4.8)		
Neuropathy	22,154 (15.7)		
Retinopathy	19,295 (13.6)		

^aThere was only 1 patient identified in this subgroup, and the number was too small that the subgroup was dropped in the regression.

^bHospitalized/ER hypoglycemia refers to the number of patients that had hospitalization or ER admission because of hypoglycemia.

^cNonhospitalized/ER hypoglycemia refers to the number of patients that ever experienced hypoglycemia but did not need hospitalization or ER admission.

A1c = hemoglobin A1c; ER = emergency room; GLP-1 = glucagon-like peptide-1; OAD = oral antidiabetic drugs; PDC = proportion of days covered; SD = standard deviation.

Smaller values of scaled deviance/degree of freedom and scaled Pearson's chi-square/degrees of freedom indicate better fit, with ratios close to 1.0 indicating the highest degree of fit. The results of scaled deviance/degree of freedom indicate the reasonable fit of our model.

Model fit was evaluated in the validation sample using the same parameter estimates from the regression of the test sample. Consistent results were found for the scaled deviance/degree of freedom and the scaled Pearson's chi-square/degree of freedom between the test and validation samples.

The results of the ROC analyses showed that the models could correctly classify low-cost and high-cost patients for the test sample (Table 4). The threshold to classify low cost and high cost was the median of the actual costs. Two additional sensitivity analyses using the first quartile and the third

quartile were also tested. The statistical tests were performed for each ROC analysis, and the results showed that the model can significantly correctly classify low-cost and high-cost patients.

Discussion

The incidence and prevalence of diabetes continues to grow worldwide. The effect of obesity and an aging population has contributed to a projected increase in health care expenditure attributed to patients with T2DM to 15% by 2031.² This study investigated the total direct costs incurred for T2DM patients and the effect of diabetes treatment-related attributes and found that high adherence to antidiabetic agents was associated with reduced inpatient, outpatient, and ER costs. Results suggest that despite the availability of safe and effective diabetes

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TABLE 3 Effect of Diabetes Treatment-Related Attributes on 1-Year and 3-Year Cumulative Costs^a

A. 1-Year Cumulative Costs							
		Inpatient	Outpatient	Emergency	Drug	Other ^b	Total
Average cost per patient, ^c \$		9,733	7,013	395	1,743	4,438	23,322
Cost Driver	Subgroup	Percentage of Change from Reference Group, ^d %					
Adherence (%) ^e	(80, 100)	-12.0	-19.7	-12.5	542.9	63.5	5.8
	(60, 80)	-9.2	-15.2	-9.6	303.7	44.6	4.3
	(40, 60)	-6.2	-10.4	-6.5	153.6	27.9	2.9
	(20, 40)	-3.1	-5.4	-3.3	59.2	13.1	1.4
	(0, 20)	reference group					
Hypoglycemia event	Hospitalized/ER event	32.9	30.6	67.1	10.4	24.5	59.4
	Nonhospitalized/ER event	22.6	30.8	12.5	19.0	19.2	33.3
	No hypoglycemia event	reference group					
A1c level	>9%	5.5	-11.4	26.2	131.2	-18.7	12.6
	8%-9%	-5.9	-4.1	-3.0	108.2	-13.5	5.8
	7%-8%	8.7	-0.9	6.2	45.2	-11.4	6.1
	0%-7%	reference group					
B. 3-Year Cumulative Costs							
		Inpatient	Outpatient	Emergency	Drug	Other ^b	Total
Average cost per patient, ^c \$		32,790	22,299	1,290	5,124	13,359	74,862
Cost Driver	Subgroup	Percentage of Change from Reference Group, ^d %					
Adherence (%) ^e	(80, 100)	-16.8	-22.1	-17.9	429.1	54.5	NE ^f
	(60, 80)	-12.9	-17.0	-13.7	248.9	38.6	NE ^f
	(40, 60)	-8.8	-11.7	-9.4	130.0	24.3	NE ^f
	(20, 40)	-4.5	-6.0	-4.8	51.7	11.5	NE ^f
	(0, 20)	reference group					
Hypoglycemia event	Hospitalized/ER event	49.3	36.8	108.0	10.5	26.3	57.8
	Nonhospitalized/ER event	23.8	29.7	12.3	16.4	17.4	31.1
	No hypoglycemia event	reference group					
A1c level	>9%	19.8	NE ^f	24.7	138.9	-16.7	20.1
	8%-9%	2.6	NE ^f	1.9	116.7	-10.0	9.5
	7%-8%	15.0	NE ^f	13.0	49.5	-9.7	9.0
	0%-7%	reference group					

^aAdjusted covariates include age; sex; region; comorbidity (vascular disease, chronic pulmonary disease, connective tissue disease-rheumatic disease, peptic ulcer, mild liver disease, renal disease, moderate or severe liver disease, hypertension, hyperlipidemia, obesity, gastrointestinal disease, pancreatitis, foot disease, and neuropathy); and endocrinologist visits (yes or no).

^bOther includes the costs for which the point of service was not identified and non-antidiabetes medication costs.

^cAverage costs are the mean costs derived from the study population adjusting for the follow-up period.

^dFor outpatient, drug, other, and total costs, the results of the gamma model are reported. For inpatient and ER costs, the results of the ZINB model are reported.

^eAdherence was defined by the PDC of any antidiabetes medication.

^fNE indicates those variables that are not significant in the model selection process at the significance level of $P < 0.1$. All other variables presented in the table were considered significant in the model selection process at the significance level of $P < 0.1$.

A1c = hemoglobin A1c; ER = emergency room; PDC = proportion of days covered; ZINB = zero-inflated negative binomial.

treatments, patients are nonadherent to treatment and remain in poor control of glucose levels. Treatment-related cost drivers, including adherence, hypoglycemia events, and A1c levels have varying effects on costs. In general, this study found that having documented hypoglycemia events and higher A1c are associated with higher 1-year and 3-year cumulative total costs. Improved adherence led to higher total 1-year total costs (given that greater adherence results in greater medication costs) but did not have an effect on 3-year total costs, implying that over time adherence to medications results in increase of

medication cost and a lowering of other costs such as inpatient, outpatient, and ER costs.

Hypoglycemia is a clear driver of total costs for patients with T2DM. This study found a 59.4% increase in total 1-year costs for patients who had a hospitalization/ER visit for a hypoglycemic event. This finding is not surprising given the results of a recent review article that identified the direct and indirect costs of hypoglycemia in the United States.¹⁰ Hypoglycemic episodes requiring medical attention incur an average of \$1,161 direct cost per episode. Therefore, avoidance of hypoglycemic events

TABLE 4 Validation Results of ROC Analysis (Area Under the Curve)

	Inpatient Costs	Outpatient Costs	ER Costs	DM Drug Costs	Other Costs	Total Costs
1-year cost equations						
AUC (median as cutoff)	0.559 ^a	0.678 ^a	0.672 ^a	0.713 ^a	0.733 ^a	0.713 ^a
AUC (Q1 as cutoff)	0.559 ^a	0.692 ^a	0.672 ^a	0.755 ^a	0.761 ^a	0.741 ^a
AUC (Q3 as cutoff)	0.559 ^a	0.674 ^a	0.672 ^a	0.772 ^a	0.737 ^a	0.715 ^a
3-year cost equations						
AUC (median as cutoff)	0.618 ^a	0.749 ^a	0.711 ^a	0.736 ^a	0.801 ^a	0.780 ^a
AUC (Q1 as cutoff)	0.618 ^a	0.791 ^a	0.711 ^a	0.774 ^a	0.850 ^a	0.8435 ^a
AUC (Q3 as cutoff)	0.627 ^a	0.728 ^a	0.721 ^a	0.812 ^a	0.782 ^a	0.744 ^a

Note: Median/Q1/Q3 of the actual cost were used as the cutoff to categorize high/low costs.

^aP<0.0001 from ROC contrast test to compare the AUC of the model to chance (AUC of 0.5).

AUC = area under the curve; DM = diabetes mellitus; ER = emergency room; Q = quartile; ROC = receiver operating characteristic.

with safe and effective medications has the potential to greatly decrease the burden of T2DM management overall.¹⁰

Numerous studies have shown that poor glycemic control is associated with poor patient outcomes, resulting in higher resource utilization and cost. This study found that total 1-year costs increased by 12.6%, 5.8%, and 6.1% for patients with A1c levels of >9%, 8%-9%, and 7%-8%, respectively, compared with patients who had adequately controlled A1c (<7%). This finding is in line with the Menzin et al. study (2010), which reported an increase in diabetes-related hospitalization costs incurred from poor glycemic control.⁹ Another administrative claims database study also confirmed that total diabetes-related costs are significantly higher at 1 year for those in poor control compared with those with A1c<7% (\$1,540 vs. \$1,171).¹¹

As previously discussed, most of the literature reports annual diabetes-related costs, whereas this study reports the total direct cumulative costs. This approach explains why the findings herein are larger than most estimates. The cumulative 1-year and 3-year costs per patient were \$23,322 and \$74,862 for adult patients with T2DM who were currently on antidiabetic drug therapy within our analysis, whereas other studies report these costs to be in the \$2,000-\$10,000 range (depending on the cost categories, severity of the patient population, focus of the study, and time frame considered).^{3,4}

Partitioning and allocating claims to be related or unrelated to diabetes were deemed unnecessary for our study given the interaction between diabetes and comorbidities such as cardiovascular or renal disease. The presence of T2DM as a condition increases the likelihood for other disorders that consume resources, so separating visits to physicians that are related or unrelated to diabetes would be arbitrary. Furthermore, our analysis represents a realistic view of a naturalistic cohort of diabetes patients and their costs over time (cumulative costs), reflecting a longer-term burden of this chronic and costly disease (as compared with an annual or point in time cost estimate, which only estimates the short-term economic impact of diabetes).

The findings of this study not only deepen the understanding between treatment-related attributes and the various types of costs, but also provide a practical tool to quantify the economic burden for certain patients with specific adherence, glycemic control (A1c), and safety profiles, which will become more important over time with the aging population and the growing prevalence of diabetes.

Limitations

This study has some limitations to consider. Because of the observational nature of this study, the data may be biased by differences in clinical practice and limited by the nature of the information captured within the database. There were confounders that cannot be directly measured in the database. Laboratory values and other clinical variables (weight) and disenrollment/changes in health plans could not be assessed nor controlled for in this analysis and could affect the annual and cumulative costs if they were available. Also, the surrogate markers such as PDC were used to estimate adherence, which can overestimate true patient adherence, since time-varying exposure to the therapeutic agents may affect estimation of PDC. Although this is a limitation of the precise adherence to medications, the overall relationships between adherence and total cost was not deemed to be systematically affected.

Because this study was based on medical claims, some patients might not have had a full year of follow-up. Although this issue was taken into consideration and some adjustment based on the follow-up period was imposed on costs, the real costs can be underestimated or overestimated. Given the nature of medical claims, the lost to follow-up is unavoidable. Although the current adjustment method can mediate the bias as a result of this issue, it would be enlightening to restrict the patients with full length follow-up periods and make a comparison between the results.

Hypoglycemia episodes that did not lead to a health care visit can affect a patient's health status; however, given that these episodes do not lead to medical claims, they are not

captured in the database. Therefore, the actual burden of hypoglycemic events was likely underestimated. However, since the purpose of this study was to identify the major drivers of cost, the slight underestimation of hypoglycemic events that do not require medical attention are negligible.

An important cost driver of T2DM is weight, or body mass index (BMI). Unfortunately, the database does not capture BMI, so we could not control for this important confounder in the analysis. Finally, A1c levels were often unavailable in the database and required an interpolation of values, which potentially over- or underestimated the actual A1c for each patient. This interpolation might have over- or underestimated the real A1c values, further affecting the predictive relationship between A1c values and costs. More precise data for A1c values could explain more about the relationship between A1c and costs and would refine the predictive effect on costs.

Conclusions

This study provides a practical tool for calculating the effect of diabetes treatment attributes on various components, which is important to health care professionals and the wider health economic community with respect to understanding how new diabetes therapy options with improved efficacy, adherence, and reduced risk for hypoglycemic events may ease the burden of the disease.

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DISCLOSURES

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Effect of Diabetes Treatment-Related Attributes on Costs to Type 2 Diabetes Patients in a Real-World Population

APPENDIX A Full Model Results

A. Results for 1-Year Cost Analysis

Cost Category	Inpatient Costs	Outpatient Costs	ER Costs	DM Drug Costs	Other Costs	Total Costs
Distribution Assumption	ZINB Model	Gamma Model	ZINB Model	Gamma Model	Gamma Model	Gamma Model
Variable	Estimates					
Intercept	11.0676	7.9768	6.6008	4.8953	7.1932	9.0216
Sex (reference: male)						
Female	-0.1337	0.0375	0.0594	-0.1102	0.0339	NS
Male	0	0	0	0	0	NS
Age (reference: 18-39 years)						
40-49 years	0.2808	0.1776	0.1098	-0.0518	0.1073	0.0966
49-64 years	0.4309	0.3484	0.0911	-0.0334	0.3081	0.3338
≥65 years	0.1297	0.2699	0.7548	-0.4867	0.2213	0.3385
18-39 years	0	0	0	0	0	0
Geographic location (reference: Northeast)						
Midwest	-0.0665	0.0778	0.1661	-0.0181	-0.1829	-0.0667
South	-0.1823	0.1015	0.1202	-0.0372	-0.0561	-0.1112
West	-0.8922	-0.0612	-0.1325	-0.074	-0.0258	-0.3796
Unknown	-2.2988	-0.1308	-0.526	-0.0972	0.1237	-0.6855
Northeast	0	0	0	0	0	0
Comorbidity (reference: no comorbidity)						
Vascular disease: Yes	0.217	0.3751	0.3647	NS	0.3192	0.4954
Vascular disease: No	0	0	0	NS	0	0
Chronic pulmonary disease: Yes	0.1173	0.2404	0.3227	NS	0.4137	0.3814
Chronic pulmonary disease: No	0	0	0	NS	0	0
Connective tissue disease, rheumatic disease: Yes	NS	0.4016	0.1282	-0.0774	0.5208	0.3508
Connective tissue disease, rheumatic disease: No	NS	0	0	0	0	0
Peptic ulcer: Yes	0.2155	NS	NS	NS	NS	NS
Peptic ulcer: No	0	NS	NS	NS	NS	NS
Mild liver disease: Yes	0.1164	0.3916	0.1252	NS	0.2252	0.2639
Mild liver disease: No	0	0	0	NS	0	0
Renal disease: Yes	NS	0.5179	0.0923	0.1834	0.2457	0.3834
Renal disease: No	NS	0	0	0	0	0
Moderate or severe liver disease: Yes	NS	NS	NS	NS	0.5492	0.4724
Moderate or severe liver disease: No	NS	NS	NS	NS	0	0
Hypertension: Yes	NS	0.1362	0.2203	0.0512	0.0997	0.1319
Hypertension: No	NS	0	0	0	0	0
Hyperlipidemia: Yes	NS	NS	NS	0.1057	NS	NS
Hyperlipidemia: No	NS	NS	NS	0	NS	NS
Obesity: Yes	NS	0.148	0.1039	0.1142	0.066	0.1219
Obesity: No	NS	0	0	0	0	0
Gastrointestinal disease: Yes	0.0868	0.3789	0.2805	-0.0257	0.2075	0.3584
Gastrointestinal disease: No	0	0	0	0	0	0
Pancreatitis: Yes	0.3637	0.1981	0.1776	NS	0.1846	0.4717
Pancreatitis: No	0	0	0	NS	0	0
Foot disease: Yes	0.1924	0.3608	0.1699	0.0783	0.2163	0.3887
Foot disease: No	0	0	0	0	0	0
Neuropathy: Yes	NS	0.1346	0.1317	0.1665	0.1888	0.1854
Neuropathy: No	NS	0	0	0	0	0
Retinopathy: Yes	0.0601	0.2053	NS	0.2784	0.109	0.1177
Retinopathy: No	0	0	NS	0	0	0
Endocrinologist visit (reference: no endocrinologist visit)						
Yes	NS	0.2316	NS	0.6146	0.2982	0.2239
No	NS	0	NS	0	0	0
Adherence ^a	-0.032	-0.055	-0.0335	0.4652	0.1229	0.0141

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Effect of Diabetes Treatment-Related Attributes on Costs to Type 2 Diabetes Patients in a Real-World Population

APPENDIX A Full Model Results (continued)

A. Results for 1-Year Cost Analysis

Cost Category	Inpatient Costs	Outpatient Costs	ER Costs	DM Drug Costs	Other Costs	Total Costs
Distribution Assumption	ZINB Model	Gamma Model	ZINB Model	Gamma Model	Gamma Model	Gamma Model
Hypoglycemia (Reference: no hypoglycemia)						
Nonhospitalized/ER hypoglycemia	0.2038	0.2682	0.1179	0.1737	0.176	0.2878
Hospitalized/ER hypoglycemia	0.2845	0.267	0.5136	0.0989	0.2189	0.4665
No hypoglycemia	0	0	0	0	0	0
A1c level (reference: ≤7%)						
7%-8%	0.0832	-0.0095	0.0603	0.3732	-0.1213	0.0588
8%-9%	-0.0607	-0.0423	-0.0303	0.7333	-0.145	0.0565
>9%	0.0536	-0.1207	0.2325	0.8383	-0.2075	0.1187
≤7%	0	0	0	0	0	0

B. Results for 3-Year Cost Analysis

Cost Category	Inpatient Costs	Outpatient Costs	ER Costs	DM Drug Costs	Other Costs	Total Costs
Distribution Assumption	ZINB Model	Gamma Model	ZINB Model	Gamma Model	Gamma Model	Gamma Model
Variable	Estimates					
Intercept	10.4881	8.0584	6.0139	5.0883	7.217	9.1081
Sex (reference: male)						
Female	-0.1304	NS	0.0904	-0.1096	0.0212	NS
Male	0	NS	0	0	0	NS
Age (reference: 18-39 years)						
40-49 years	0.1707	0.2156	0.1334	-0.0458	0.1298	0.1102
49-64 years	0.3747	0.3921	0.2073	-0.0448	0.3197	0.3706
≥65 years	0.0755	0.3029	0.814	-0.5418	0.2705	0.4148
18-39 years	0	0	0	0	0	0
Geographic location (reference: Northeast)						
Midwest	-0.0433	0.0985	0.1373	-0.0001	-0.1544	-0.0435
South	-0.1911	0.1154	0.0723	-0.0387	-0.0253	-0.1088
West	-0.9283	-0.0959	-0.2351	-0.1017	0.0597	-0.4
Unknown	-2.3012	-0.1897	-0.5066	-0.1115	0.1646	-0.7714
Northeast	0	0	0	0	0	0
Comorbidity (reference: no comorbidity)						
Vascular disease: Yes	0.2976	0.343	0.4431	NS	0.2869	0.473
Vascular disease: No	0	0	0	NS	0	0
Chronic pulmonary disease: Yes	0.1807	0.2318	0.3642	NS	0.3933	0.3574
Chronic pulmonary disease: No	0	0	0	NS	0	0
Connective tissue disease, rheumatic disease: Yes	0.1282	0.374	0.1514	-0.0785	0.5274	0.3495
Connective tissue disease, rheumatic disease: No	0	0	0	0	0	0
Peptic ulcer: Yes	0.1915	NS	NS	NS	0.1081	0.126
Peptic ulcer: No	0	NS	NS	NS	0	0
Mild liver disease: Yes	0.1208	0.3141	0.1671	NS	0.2201	0.2386
Mild liver disease: No	0	0	0	NS	0	0
Renal disease: Yes	0.1139	0.5776	0.1156	0.1646	0.2522	0.4002
Renal disease: No	0	0	0	0	0	0
Moderate or severe liver disease: Yes	0.3707	0.2196	NS	NS	0.5293	0.5622
Moderate or severe liver disease: No	0	0	NS	NS	0	0
Hypertension: Yes	NS	0.1284	0.2553	0.0491	0.0833	0.1551
Hypertension: No	NS	0	0	0	0	0
Hyperlipidemia: Yes	NS	NS	NS	0.1227	NS	-0.0246
Hyperlipidemia: No	NS	NS	NS	0	NS	0
Obesity: Yes	0.0608	0.1287	0.0927	0.122	0.0583	0.108
Obesity: No	0	0	0	0	0	0
Gastrointestinal disease: Yes	0.157	0.3228	0.3267	NS	0.1872	0.303

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APPENDIX A Full Model Results (continued)

B. Results for 3-Year Cost Analysis

Cost Category	Inpatient Costs	Outpatient Costs	ER Costs	DM Drug Costs	Other Costs	Total Costs
Distribution Assumption	ZINB Model	Gamma Model	ZINB Model	Gamma Model	Gamma Model	Gamma Model
Comorbidity (reference: no comorbidity)						
Gastrointestinal disease: No	0	0	0	NS	0	0
Pancreatitis: Yes	0.3482	0.1773	0.2406	NS	0.1612	0.4011
Pancreatitis: No	0	0	0	NS	0	0
Foot disease: Yes	0.238	0.3229	0.2327	0.084	0.2031	0.3664
Foot disease: No	0	0	0	0	0	0
Neuropathy: Yes	NS	0.1412	0.1722	0.1676	0.1954	0.1954
Neuropathy: No	NS	0	0	0	0	0
Retinopathy: Yes	0.0831	0.2358	NS	0.2668	0.1114	0.1506
Retinopathy: No	0	0	NS	0	0	0
Endocrinologist visit (reference: no endocrinologist visit)						
Yes	NS	0.1918	-0.0787	0.6071	0.291	0.1929
No	NS	0	0	0	0	0
Adherence	-0.0459	-0.0623	-0.0492	0.4165	0.1087	NS
Hypoglycemia (reference: no hypoglycemia)						
Nonhospitalized/ER hypoglycemia	0.2139	0.2598	0.1157	0.1517	0.1608	0.2706
Hospitalized/ER hypoglycemia	0.4011	0.3136	0.7325	0.1	0.2336	0.4563
No hypoglycemia	0	0	0	0	0	0
A1c level (reference: ≤ 7%)						
7%-8%	0.1401	NS	0.1219	0.4022	-0.1015	0.086
8%-9%	0.026	NS	0.019	0.7735	-0.1054	0.0908
> 9%	0.1808	NS	0.2207	0.871	-0.1833	0.1831
≤ 7%	0	NS	0	0	0	0

Note: NS is not significant. These variables are not significant predictors of costs in the variable selection process (using a threshold of $P < 0.1$) and therefore are not included in the cost equation.

^aAdherence was defined as an ordinal variable but was considered as a continuous variable, since a linear relationship with cost variables was observed.

A1c = hemoglobin; DM = diabetes mellitus; ER = emergency room; ZINB = zero-inflated negative binomial.

APPENDIX B Validation Results of Model Statistical Fits for 1-Year and 3-Year Cost Equations

Statistic	Inpatient Costs		Outpatient Costs		ER Costs		DM Drug Costs		Other Costs		Total Costs	
	Value	Value/df	Value	Value/df	Value	Value/df	Value	Value/df	Value	Value/df	Value	Value/df
Validation results of 1-year cost equations												
Test sample												
Scaled deviance	462,259	NA ^a	153,642	1.36 ^b	390,021	NA ^a	154,859	1.37 ^b	153,183	1.35 ^b	140,721	1.24 ^b
Scaled PearsonX2	232,038	2.05 ^b	263,408	2.33 ^b	212,332	1.88 ^b	72,025	0.64 ^c	139,602	1.23 ^b	445,765	3.94 ^b
Validation sample												
Scaled deviance	–	–	39,575	1.40 ^b	–	–	38,208	1.35 ^b	39,123	1.39 ^b	35,407	1.25 ^b
Scaled PearsonX2	–	–	76,077	2.69 ^b	–	–	17,879	0.63 ^c	30,570	1.08 ^b	96,529	3.42 ^b
Validation results of 3-year cost equations												
Test sample												
Scaled deviance	854,126	NA ^a	150,113	1.33 ^b	665,540	NA ^a	151,634	1.34 ^b	146,837	1.30 ^b	138,738	1.23 ^b
Scaled PearsonX2	313,883	2.78 ^b	262,704	2.32 ^b	265,768	2.35 ^b	75,659	0.67 ^c	151,036	1.34 ^b	401,251	3.55 ^b
Validation sample												
Scaled deviance	–	–	38,592	1.37 ^b	–	–	37,620	1.33 ^b	37,855	1.34 ^b	34,742	1.23 ^b
Scaled PearsonX2	–	–	71,496	2.53 ^b	–	–	19,140	0.68 ^c	34,669	1.23 ^b	87,593	3.10 ^b

^aInpatient and emergency costs were results gained with the ZINB model, for which the scaled deviance was not available and the same validation method was not applicable because of technical limitation in the SAS program.

^bIndicates that $P < 0.0001$.

^cIndicates that $P > 0.1$.

DM = diabetes mellitus; df = degree of freedom; ER = emergency room; NA = not available; ZINB = zero-inflated negative binomial.