

Medication Adherence and Improved Outcomes Among Patients With Type 2 Diabetes

Sarah E. Curtis, MPH; Kristina S. Boye, PhD; Maureen J. Lage, PhD; and Luis-Emilio Garcia-Perez, MD, PhD

Diabetes is a chronic and highly prevalent condition that may lead to severe complications, such as lower limb amputations, blindness, kidney failure, stroke, heart disease, and early death.¹ As of 2012, the estimated number of US adults (20 years or older) diagnosed with diabetes was 28.9 million, or 12.3% of the population.¹ For these individuals, the total cost of the disease in 2012 was \$245 billion, comprising \$176 billion in direct medical costs and \$69 billion in decreased productivity.² The majority of patients with diabetes (90% to 95%) have type 2 diabetes (T2D),¹ the prevalence of which is growing so rapidly that about 40% of all Americans are projected to be diagnosed with the disease at some point in their adult lives.³

Given the large and increasing number of patients with T2D and the associated burden, several recent studies have examined factors that may influence T2D treatment outcomes. One such factor is adherence to prescribed glucose-lowering agents (GLAs). Improved adherence to GLAs has been shown to be linked to a reduction in hospitalizations and/or emergency department (ED) visits,⁴⁻⁹ complications,^{6,10,11} and costs.^{5,9,12-15} However, limited research has focused on all classes of GLAs, and inclusion of the newer GLA classes is even rarer.^{5,7-9,11}

The goal of the present study was to further the literature examining connections between patient behavior and T2D treatment outcomes. To this end, our retrospective, naturalistic investigation used a US claims database to observe the medical records associated with a large population of Americans aged 18 to 64 years with T2D. This study examined the relationships between GLA adherence and patient outcomes, including acute care resource utilization, acute complications, and total costs.

METHODS

Truven's Health Analytics MarketScan Commercial Claims and Encounters database, including data from July 1, 2009, through June 30, 2014, was used for this study. This database consists of the healthcare records of millions of individuals who are covered

ABSTRACT

OBJECTIVES: Examine the association between adherence to glucose-lowering agents (GLAs) and patient outcomes in an adult type 2 diabetes (T2D) population.

STUDY DESIGN: Retrospective analysis.

METHODS: Truven's Commercial Claims and Encounters database supplied data from July 1, 2009, to June 30, 2014. Patients 18 to 64 years with T2D were included if they received a GLA from July 1, 2010, through June 30, 2011. Multivariable analyses examined the relationships among 3-year patient outcomes and adherence, defined as proportion of days covered 80% or more. Outcomes included all-cause medical costs, acute care resource utilization, and acute complications.

RESULTS: Although there was no statistically significant difference in total costs when comparing adherent and nonadherent patients (\$38,633 vs \$38,357; $P = .0720$), acute care costs (\$12,153 vs \$8233; $P < .0001$) and outpatient costs (\$16,964 vs \$15,457; $P < .0001$) were significantly lower for adherent patients. Adherence was also associated with a lower probability of hospitalization (22.71% vs 17.65%; $P < .0001$) and emergency department (ED) visits (45.61% vs 38.47%; $P < .0001$), fewer hospitalizations (0.40 vs 0.27; $P < .0001$) and ED visits (1.23 vs 0.83; $P < .0001$), and a shorter hospital length of stay (2.16 vs 1.25 days; $P < .0001$). Adherent patients were also less likely to be diagnosed with an acute complication in the 3-year post period (12.54% vs 9.64%; $P < .0001$).

CONCLUSIONS: Compared with nonadherence, adherence to GLAs among patients with T2D was associated with a significant reduction in acute care costs and resource utilization, outcomes that may positively impact the welfare of patients.

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by fully or partially capitated fee-for-service health plans. As such, the database provides detailed costs, use, and outcomes data for healthcare services performed in both inpatient and outpatient settings. Medical claims are linked to outpatient prescription drug claims and person-level enrollment information. The data are fully deidentified and compliant with the Health Insurance Portability and Accountability Act.

For inclusion in the study, patients were required to have received at least 2 diagnoses of T2D using *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes 250.x0 or 250.x2^{16,17} in the time period of July 1, 2010, through June 30, 2011 (ie, the identification window), and to have received at least 1 prescription for a GLA within the identification window; the date of the first such prescription was identified as the index date. Additionally, patients were required to be aged 18 to 64 years as of the index date and to have had continuous insurance coverage from 1 year leading up to the index date (the pre-period) through 3 years following the index date (the post period), as well as valid patient demographic data. Patients were excluded from the analyses if they received a diagnosis of type 1 diabetes (*ICD-9-CM* codes: 250.x1 or 250.x3) or pregnancy (*ICD-9-CM* codes: 630.xx-670.xx, V22.xx-V23.xx, V30.xx-V39.xx) at any time from the start of the pre-period through the end of the post period. **Figure 1** illustrates how each of these criteria affected sample size.

The analyses focused on the relationship between patient adherence and outcomes, where adherence was proxied by the proportion of days covered (PDC). The PDC is a measure of adherence used by both the Pharmacy Quality Alliance¹⁸ and CMS, and it was defined as the percentage of days an individual received at least 1 GLA in the first year of the post period. For all medications except insulin, the PDC was constructed using the “days supplied” field provided in the database. For insulin, this was calculated as the average number of days between fills for an insulin prescription.¹⁹ Consistent with Healthcare Effectiveness Data and Information Set guidelines for the use of oral GLAs²⁰ and with previous research, patients were categorized as adherent if they achieved a PDC threshold of at least 80%.^{6,8,21,22}

Outcomes of interest included costs, acute care resource utilization, and acute complications. Costs were subdivided into 4 categories—acute care (hospitalization and ED), outpatient, drug, and total—and all were converted to 2014 prices using the medical component of the Consumer Price Index. In all cases, costs were calculated using gross payments to a provider for a service. Acute care resource utilization was defined as the probability of a hospitalization or an ED visit, the number of hospitalizations or ED visits, and the hospital length of stay (LOS). Acute complications

TAKEAWAY POINTS

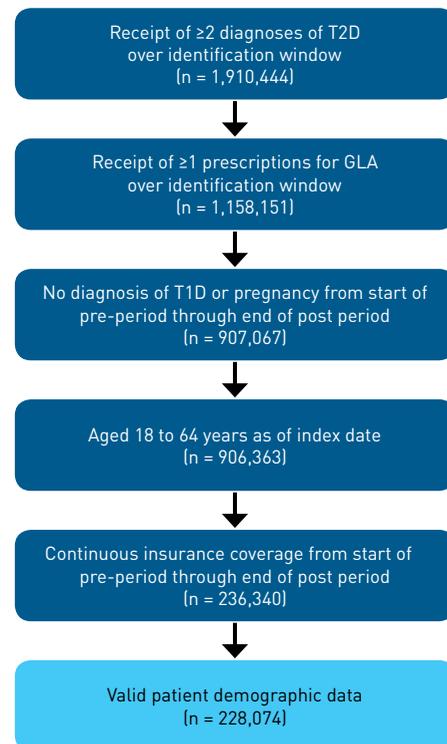
Compared with nonadherent patients, adherent patients had:

- ▶ Less likelihood of a hospitalization or an emergency department (ED) visit.
- ▶ Fewer hospitalizations and fewer ED visits.
- ▶ Reduced acute care costs and outpatient costs.
- ▶ Increased drug costs.
- ▶ Better patient outcomes.
- ▶ No significant difference in total medical costs.

were identified based on receipt of a diagnosis of hyperglycemia (*ICD-9-CM* code: 790.29), hypoglycemia (*ICD-9-CM* codes: 250.8, 251.0, 251.1, or 251.2), or diabetic or hypoglycemic coma (*ICD-9-CM* codes: 250.3, 251.0).

Multivariable analyses were used to examine the relationship between outcomes of interest and patient adherence. All analyses controlled for the individual patient’s characteristics (age, sex, region of residence, and insurance coverage), preperiod

FIGURE 1. Inclusion–Exclusion Criteria and Sample Size*



GLA indicates glucose-lowering agent; T1D, type 1 diabetes; T2D, type 2 diabetes. *Identification window is defined as July 1, 2010, through June 30, 2011. Index date is defined as first receipt of GLA in identification window. Pre-period is defined as 1 year prior to index date; post period is defined as index date through 3 years post index date.

general health status, comorbidities, medication use, and providers. General health was proxied by the Charlson Comorbidity Index (CCI), which is scored on a scale of 0 to 33 based on the presence of comorbidities such as cardiovascular diseases, dementia, chronic pulmonary disease, hypertension, liver disease, and malignancies.^{23,24} The severity of any diabetes complication was proxied using the Diabetes Complications Severity Index (DCSI), which is scored on a scale of 0 to 13 based on the presence of conditions such as retinopathy, neuropathy, nephropathy, and metabolic disorders.²⁵ In addition, the models also included comorbidities that have been shown to be common in patients with diabetes and were not captured in either the CCI or DCSI score. Specifically, anxiety has been shown to be prevalent in patients with diabetes,²⁶ comorbid depression has been shown to be linked to nonadherence,²⁷ and hyperlipidemia has been used in previous studies that examined the relationship between adherence and outcomes.²⁸ Therefore, this study included indicator variables for pre-period diagnoses of anxiety (*ICD-9-CM* codes: 300.xx except 300.3x and 300.4x), depression (*ICD-9-CM* codes: 296.2, 296.3, 300.4, or 311.xx), and hyperlipidemia (*ICD-9-CM* codes: 272.1-272.4).

The analyses also controlled for provider visits/services during the pre-period, with indicator variables for renal dialysis therapy and for visits to a cardiologist, endocrinologist, family medicine practitioner, or internal medicine practitioner. Also included as covariates in the model were the number and type of GLAs prescribed and overall medication use in the first 3 months of the post period. These factors were captured by an indicator variable for insulin use, the number of noninsulin classes of GLAs prescribed, and the number of non-GLA medications prescribed. The classes of noninsulin GLAs included alpha-glucosidase inhibitors, amylin analogs, biguanides, dipeptidyl peptidase-4 inhibitors, dopamine agonists, glucagon-like peptide-1 receptor agonists, meglitinides, sodium-glucose co-transporter-2 inhibitors, sulfonylureas, thiazolidinediones, and oral fixed combinations.

General linear models with a gamma distribution and log link were used to examine all-cause outpatient, drug, and total costs. Two-part models were used to examine acute care costs, in which the first part captured the probability of an all-cause or diabetes-related acute care visit and the second part estimated costs among users of the service. Resource utilization was examined by estimating negative binomial regressions for the number of hospitalizations, the number of ED visits, and hospital LOS. Logistic regressions were used to examine the probability of hospitalization, ED use, or acute complication. Differences in the estimated outcomes were then examined by adherence status. To calculate whether differences in outcomes between adherent and nonadherent patients were statistically significant, *t* tests were used. All analyses were conducted using SAS version 9.3 (SAS Institute, Inc; Cary, North Carolina). A *P* value of <.05 was considered to be statistically significant.

RESULTS

Table 1 presents descriptive statistics for the 228,074 individuals included in the study. The majority of patients were male (53.75%), and the mean age was 52 years (standard deviation [SD] = 7.1). Patients most commonly resided in the South (42.08%) or North Central (24.42%) regions of the country, and most were covered by preferred provider organizations (53.95%) or a health maintenance organization (21.33%). More than half the patients visited a family medicine practitioner (54.24%), and over one-third (40.37%) had at least 1 internal medicine visit in the pre-period; less frequently, they visited a cardiologist (17.11%) or endocrinologist (8.23%). Approximately 1 in 8 patients (13.12%) received a prescription for insulin in the first 3 months of the post period, and patients were prescribed an average 1.42 noninsulin classes of GLA, including oral fixed combination drugs as a distinct class, and 4.87 non-GLA medications over this same time period.

In addition to providing characteristics for the entire population, **Table 1** also presents descriptive statistics comparing adherent with nonadherent patients. Adherent patients were significantly older (53.47 vs 51.18 years; *P* <.0001), more likely to be male (56.51% vs 50.80%; *P* <.0001), and less likely to reside in the South (38.93% vs 45.45%; *P* <.0001) compared with nonadherent patients. Adherent patients were also in better general health compared with nonadherent patients, as evidenced by lower rates of anxiety (2.79% vs 3.90%; *P* <.0001) and depression (5.44% vs 7.15%; *P* <.0001), as well as significantly lower rates of visits to a cardiologist (16.76% vs 17.48%; *P* <.0001). Adherent patients may have less severe diabetes compared with nonadherent patients, as evidenced by the significantly lower DCSI score (0.50 vs 0.52; *P* <.0001) and by less use of insulin in the first 3 months of the post period (9.84% vs 16.63%; *P* <.0001). However, adherent patients received significantly more noninsulin classes of medications in the first 3 months of the post period (1.63 vs 1.20; *P* <.0001), as well as a higher number of non-GLA medications (5.05 vs 4.68; *P* <.0001).

Figure 2 focuses on the association between adherence to GLAs and 3-year all-cause medical costs. As shown in this figure, adherence was associated with significant reductions in both acute care costs (\$8223 vs \$12,153; *P* <.0001) and outpatient costs (\$15,457 vs \$16,964; *P* <.0001) and significant increases in drug costs (\$14,816 vs \$9390; *P* <.0001). Consistent with significantly higher drug costs and significantly lower acute care costs and outpatient costs for adherent patients compared with nonadherent patients, there was no statistically significant difference in total costs between these 2 groups (\$38,357 vs \$38,633; *P* = .0720).

Table 2 examines the associations between adherence and resource utilization and complications, showing that adherence was associated with significant improvements in patient outcomes in all cases. Both the probability of a hospitalization (17.65% vs

TABLE 1. Descriptive Statistics, Overall and By Adherence Status^a

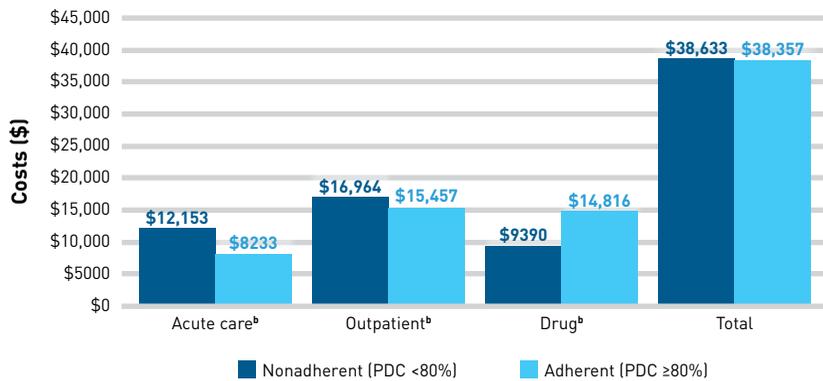
Variable (patient characteristics)	All (N = 228,074)		Nonadherent (PDC <80%) (n = 110,210)		Adherent (PDC ≥80%) (n = 117,864)	
	N or Mean	% or SD	N or Mean	% or SD	N or Mean	% or SD
Age, years (mean and SD)	52.36	7.09	51.18	7.61	53.47	6.37
Sex						
Male	122,593	53.75	55,985	50.80	66,608	56.51
Female	105,481	46.25	54,225	49.20	51,256	43.49
Region						
Northeast	29,274	12.84	12,406	11.26	16,868	14.31
North Central	55,692	24.42	25,670	23.29	30,022	25.47
South	95,973	42.08	50,094	45.45	45,879	38.93
West	47,135	20.67	22,040	20.00	25,095	21.29
Insurance plan type						
Comprehensive insurance	11,465	5.03	4,903	4.45	6,562	5.57
Exclusive provider organization	3,498	1.53	1,891	1.72	1,607	1.36
HMO	48,644	21.33	24,269	22.02	24,375	20.68
Point-of-service	26,254	11.51	12,215	11.08	14,039	11.91
PPO	123,046	53.95	59,134	53.66	63,912	54.23
CDHP/HDHP	15,167	6.65	7,798	7.08	7,369	6.25
General health and comorbidities in pre-period						
Charlson Comorbidity Index score (mean and SD) ^b	1.52	1.25	1.52	1.30	1.52	1.20
Diabetes Complications Severity Index (mean and SD)	0.51	0.98	0.52	1.02	0.50	0.94
Anxiety	7,585	3.33	4,296	3.90	3,289	2.79
Depression	14,289	6.27	7,881	7.15	6,408	5.44
Hyperlipidemia	101,469	44.49	47,411	43.02	54,058	45.86
Provider and prescriber visited in pre-period						
Cardiologist	39,016	17.11	19,266	17.48	19,750	16.76
Endocrinologist	18,772	8.23	8,920	8.09	9,852	8.36
Family medicine	123,709	54.24	60,998	55.35	62,711	53.21
Internal medicine ^b	92,082	40.37	44,356	40.25	47,726	40.49
Renal dialysis therapy	184	0.08	103	0.09	81	0.07
Medication use in first 3 months of post period						
Insulin	29,925	13.12	18,326	16.63	11,599	9.84
Number of noninsulin classes (mean and SD)	1.42	0.74	1.20	0.64	1.63	0.76
Number of non-GLA medications (mean and SD)	4.87	3.35	4.68	3.44	5.05	3.25
Adherence in first year of post period						
Proportion of days covered (mean and SD)	70.10	28.71	46.33	24.05	92.34	5.61

CDHP indicates consumer-driven health plan; GLA, glucose-lowering agent; HDHP, high-deductible health plan; HMO, health maintenance organization; PDC, proportion of days covered; PPO, preferred provider organization; SD, standard deviation.

^aDifferences in continuous variables were examined using *t* statistics, and differences in categorical variables were examined using χ^2 statistics.

^bIndicates that the difference between adherence thresholds was not statistically significant ($P \geq .05$).

FIGURE 2. All-Cause Costs, by Adherence Threshold^a



PDC indicates proportion of days covered.

^aResults of *t* tests that examined estimated outcomes from a multivariable regression model that controls for patient characteristics, preperiod general health status, comorbidities, medication use, providers, and patient adherence.

^bThe *t* tests, which compared differences in costs between nonadherent and adherent patients, were statistically significant (*P* < .05).

TABLE 2. Resource Utilization and Complications by Adherence Status^a

	Nonadherent (PDC <80%) (n = 110,210)		Adherent (PDC ≥80%) (n = 117,864)	
	Mean	SD	Mean	SD
Resource utilization				
Probability of hospitalization	22.71%	12.59%	17.65%	9.52%
Probability of ED visit	45.61%	12.09%	38.47%	10.49%
Number of hospitalizations	0.40	0.58	0.27	0.25
Number of ED visits	1.23	1.04	0.83	0.53
Hospital length of stay, days	2.16	4.18	1.25	1.43
Complications				
Probability of acute complication	12.54%	7.32%	9.64%	5.52%

ED indicates emergency department; PDC, proportion of days covered; SD, standard deviation.

^aResults of *t* tests, which examined estimated outcomes from a multivariable regression model that controlled for patient characteristics, pre-period general health status, comorbidities, medication use, and providers.

^bAll differences between adherent and nonadherent patients were statistically significant (*P* < .001).

22.71%; *P* < .0001) and of an ED visit (38.47% vs 45.61%; *P* < .0001) were significantly lower for adherent patients compared with nonadherent patients. Similarly, the number of hospitalizations (0.27 vs 0.40; *P* < .0001), the number of ED visits (0.83 vs 1.23; *P* < .0001), and hospital LOS (1.25 vs 2.16; *P* < .0001) all significantly diminished as adherence improved. The probability of an acute complication also significantly decreased as adherence improved. Specifically, adherence was associated with a significant reduction in the probability of an acute complication being diagnosed over the 3-year post period (9.64% vs 12.54%; *P* < .0001).

Two sensitivity analyses were conducted to test the robustness of the results. First, all analyses were reestimated using the

medication possession ratio (MPR) rather than the PDC as the measure of adherence. Second, to control for the possibility of selection bias, an instrumental variables model²⁹ was estimated using, as instruments, the co-payments and coinsurance associated with GLAs prescribed in the first 3 months of the post period. The findings were generally not sensitive to these alternative specifications, except that there was a statistically significant difference between the all-cause total costs of the adherent relative to the nonadherent patients in both alternative models. Specifically, when MPR was the measure of adherence, total costs were significantly lower for adherent relative to nonadherent patients (\$37,852 vs \$39,282; *P* < .0001). Meanwhile, in the instrumental variables model, total costs were significantly higher for adherent compared with nonadherent patients (\$38,755 vs \$38,221; *P* = .0005).

DISCUSSION

The present study was constructed to quantify the outcomes associated with adherence to GLA therapy among patients with T2D. Findings support a large body of previous research that has revealed a link between GLA adherence and improved patient outcomes.⁴⁻⁹ Moreover, the current investigation has extended the literature by including all classes of GLAs and treatment records of a large (228,074) cross-national population of adults with T2D over a 3-year post period. The study controlled for a wide range of factors that may affect patient outcomes and examined the robustness of results to alternative

measures of adherence and methodologies. The following sections discuss the major findings of this study in the context of previous research.

Acute Care Resource Utilization

Consistent with earlier literature,^{4,6,15,30,31} the adherent patients in the present study had a significantly lower use of hospital and ED resources relative to the nonadherent patients. This finding is important in both economic and humanistic terms. From a monetary standpoint, the decreased use of acute care was associated with the substantially reduced acute care costs of the adherent cohort. In addition to benefiting payers, reduced acute care costs

may lessen the economic burden of diabetes for society as a whole. For instance, hospitalization, just 1 component of acute care, accounted for 43% of all direct diabetes spending in the United States in 2012.²

Regarding humanistic benefits, acute care costs may indicate patient disengagement and poor healthcare management in contrast to drug and some outpatient spending, which have been shown to be associated with improved disease control.³² In addition, acute care is associated with unexpected loss of time, productivity, and workdays for patients and caregivers, as well as other indirect costs.² Hospitalization also carries intrinsic health risks, such as the chance of contracting a healthcare-associated infection.³³ Thus, medication spending that leads to a decreased use of acute care may be considered worthwhile, particularly when such expenditures are offset by other cost reductions, as in our study.

Complications

The results of previous research that examined chronic microvascular and macrovascular complications have indicated that the odds of developing such conditions diminished as adherence improved.^{6,10,11} Given that chronic complications may best be examined over a significantly longer time horizon than the 3-year post period of this study, the present investigation focused on the relationships among adherence and acute complications, including hyperglycemia, hypoglycemia, and diabetic or hypoglycemic coma. Like the chronic complications examined in earlier research, the acute complications were taken as indicators of the quality of diabetes management. For instance, a diagnosis of hyperglycemia indicates that the body has too little insulin or is not using insulin properly,³⁴ hypoglycemia has been reported to be associated with GLA therapy,^{35,36} and severe hypoglycemia results in coma, reduced consciousness, or prolonged or recurrence or hypoglycemia for up to 60 hours.³⁷

Furthermore, clinical trial data have shown, and the results of several previous observational studies have indicated, that the risk of hypoglycemic events increased as sulfonylurea or insulin therapy was intensified.³⁶ Although intensified treatment is different from adherence to prescribed medication, fears of hypoglycemia and its consequences have been shown to be a barrier to patient adherence to GLA therapy.³⁵ Contrary to such fears, the adherent patients in the current investigation, relative to the nonadherent patients, had substantially lower rates of hyperglycemia, hypoglycemia, and diabetic or hypoglycemic coma. These results are consistent with the diminished need for acute care observed among the adherent patients. Taken together, the reductions in both acute complications and acute care indicate that the adherent patients in this study had better-managed T2D relative to the nonadherent individuals. By extension, it might also be argued that their adherence contributed to a better quality of life.

Costs

As noted in the introductory section, a number of previous investigations have demonstrated a link between GLA adherence and lower total costs.^{5,9,12-15} However, an extensive review of the literature, encompassing 37 studies, found that this link is inconsistent given that there are increased drug costs associated with better adherence.³⁰ In concert with the findings of the literature review, adherence in the present study was associated with greater drug costs. However, these higher costs were entirely offset by decreases in acute care and outpatient services, and there was no significant difference in total medical costs among this patient population when comparing adherent and nonadherent patients. However, it should be noted that this finding was not robust to alternative model specifications.

This study found that there was no statistically significant difference in total costs when comparing adherent (PDC \geq 80%) with nonadherent (PDC $<$ 80%) patients, most likely due to the increased medication costs associated with adherence. However, there were significant reductions in outpatient costs and acute care costs associated with adherent versus nonadherent patients. In addition, there are also potentially large offsets in acute care and outpatient costs associated with even small changes in adherence. For example, a 1% increase in adherence was associated, on average, with acute care cost savings of \$25,160 per 1000 persons, or \$5,738,276 among all 228,074 individuals over the 3-year post period. Such increases in acute care costs suggest more hospitalizations among nonadherent patients compared with adherent patients, which has been shown to be associated with poorer long-term outcomes and decreased health-related quality of life.³⁸

Limitations

The findings of this study must be interpreted within the context of the limitations. First, the analyses were based on observational health insurance claims data that described a population of commercially insured patients with T2D who may or may not be representative of the majority of Americans with T2D. Secondly, the use of diagnostic codes was not as rigorous as formal assessments and may underrepresent certain conditions, such as hypoglycemia. Third, the use of claims data precluded the analyses from directly controlling for undocumented factors, such as glycated hemoglobin levels, race, duration of diabetes, or socioeconomic class, whereas any of these factors may be associated with patient outcomes. Fourth, although the claims data facilitated the observation of prescriptions filled, they were unable to provide insight into whether, or in what manner, the medication was taken. Fifth, the association between adherence to specific GLA classes or medications and patient outcomes, as well as the association between patient glycemic control and outcomes, are beyond the scope of this research. Finally, the study focused on statistical significance and was unable to determine whether differences in outcomes represented minimal clinically important differences.

CONCLUSIONS

Generally robust to a wide range of sensitivity analyses, the results of this study indicate that GLA adherence is associated with significant improvements in acute care outcomes, as measured by the probability of a hospitalization, the probability of an ED visit, the number of hospitalizations, the number of ED visits, and hospital LOS. The odds of an acute complication also declined as adherence improved. Consistent with these findings, improved adherence was also associated with decreased acute care and outpatient costs, with no significant change in total costs. Furthermore, even small changes in patient adherence were found to have potentially large cost implications, with a 1% increase in adherence associated with acute care cost reductions of \$25,160 for 1000 individuals, or \$5,738,276 for the entire population, over the 3-year post period. The findings of this study suggest that adherence to GLAs among adults with T2D may lead to significant benefits for patients without increasing payer costs. ■

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Author Affiliations: Global Patient Outcomes and Real World Evidence (SC, KSB), and Global Medical Affairs (LEG-P), Eli Lilly and Company, Indianapolis, IN; HealthMetrics Outcomes Research, LLC (MJL), Bonita Springs, FL.

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Address Correspondence to: Maureen J. Lage, PhD, HealthMetrics Outcomes Research, 27576 River Reach Dr, Bonita Springs, FL 34134. E-mail: lagemj@hlthmetrics.com.

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