

# Cost Sharing, Adherence, and Health Outcomes in Patients With Diabetes

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Approximately 23.6 million individuals in the United States have diabetes, a serious metabolic disorder that affects all systems of the body, particularly the neurologic and cardiovascular systems.<sup>1</sup> Proper medication management among patients with diabetes is a key component of preventing diabetes-related complications.<sup>2</sup>

Inadequate medication adherence among patients with chronic illness has been associated with increased healthcare utilization, costs, and risk for adverse health outcomes.<sup>3,4</sup> Encinosa and colleagues studied adherence among privately insured patients with diabetes on oral antidiabetic medication (OAD), finding that improved adherence was associated with decreased hospitalization and emergency department (ED) costs.<sup>5</sup> Similarly, Sokol and colleagues found that a high level of medication adherence among privately insured patients with diabetes was associated with decreased condition-specific medical spending.<sup>6</sup> Regarding health outcomes, Ho and colleagues found that nonadherence to OAD among privately insured patients with diabetes was associated with an increase in glycosylated hemoglobin (A1C) levels, all-cause hospitalizations, and all-cause mortality.<sup>7</sup> Such evidence underscores the value of medication adherence to patient health.

These findings also suggest that important differences may exist between patients who are adherent and those who are nonadherent, and these potential selection effects may affect the relationship between adherence and outcomes. Thus, rigorous methods must be adopted to account for possible endogeneity in the relationship between adherence and outcomes.

Barriers to medication adherence such as high patient cost sharing for prescription drugs inhibit patient adherence.<sup>3,4,8</sup> Few studies have linked the effects of cost sharing to adherence, and subsequently, to outcomes. Hunt and colleagues measured the relationships between cost sharing and adherence and between adherence and glycemic control among patients with diabetes, finding a positive relationship between cost sharing and A1C level.<sup>9</sup> However, the ultimate effects of cost sharing on diabetes-related complications, through adherence, are not yet well known.

This study contributes to the literature in several ways. First, we investigated the relationships between cost sharing and adherence to antidiabetic medication. Second, we

addressed the relationship among adherence, diabetes-related complications, and utilization measures using rigorous methods. We assumed

**Objectives:** To assess the relationship between cost sharing and adherence to antidiabetic medications in patients with type 2 diabetes and to examine the relationship between medication adherence and outcomes, including complication rates, medical service utilization, and workplace productivity measures.

**Study Design:** A retrospective, cross-sectional study analyzing the healthcare experience of patients with type 2 diabetes on oral antidiabetic medication (OAD) with or without insulin (n = 96,734) and patients on OAD only (n = 55,356) with employer-sponsored insurance in the 2003-2006 MarketScan Database.

**Methods:** Using a 2-stage residual inclusion model, the first stage estimated the effects of cost sharing on adherence to antidiabetic medications in an 18-month time frame (January 2003 through June 2004). Adherence was determined from the percentage of days covered. The second stage estimated the effects of adherence on complication rates (eg, retinopathy, neuropathy, peripheral vascular disease), medical service utilization rates, and measures of productivity (absence days and short-term disability days) in the subsequent 2 years (July 2004 through June 2006).

**Results:** A \$10 increase in the patient cost-sharing index resulted in a 5.4% reduction in adherence to antidiabetic medications for patients on OAD only and a 6.2% reduction in adherence for patients on OAD with or without insulin. Adherence was associated with lower rates of complications (eg, amputation/ulcers, retinopathy) and also was associated with fewer emergency department visits and short-term disability days.

**Conclusions:** Medical plans, employers, and policy makers should consider implementing interventions targeted to improve antidiabetic medication adherence, which may translate to better outcomes.

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### Take-Away Points

This retrospective, cross-sectional study investigated the relationships between cost sharing and adherence to antidiabetic medication, and among adherence, diabetes-related complications, and utilization measures.

- Higher levels of patient cost sharing for antidiabetes medications were associated with lower levels of adherence (percentage of days covered) to antidiabetic medications. For example, among patients on oral antidiabetic medications only, those whose cost-sharing amount was \$10 higher had adherence rates that were 5.4% lower.
- Antidiabetic medication adherence was associated with lower rates of many diabetes-related complications (eg, amputation/ulcer and retinopathy), and with fewer inpatient visits, emergency department visits, and short-term disability days.
- Medical plans, employers, and policy makers should consider ways to promote adherence to medications, including reduced patient cost sharing.

### Measures

Adherence was measured as the percentage of days covered (PDC), expressed as the percentage of days with an antidiabetic medication on hand during the 18-month time period (January 2003 through June 2004).<sup>10</sup> The PDC was first calculated for each therapeutic class (ie, sulfonylureas, meglitinides, biguanides, thiazolidinediones, alpha-glucosidase inhibitors, insulin) based on prescription drug claims, using the fill date and the

a more comprehensive view of the impact of medication adherence, also incorporating measures of productivity for employees with diabetes. We used 2-stage residual inclusion models to estimate these relationships and produce consistent estimates.

## METHODS

This study is based upon the Thomson Reuters MarketScan Database, 2002-2006, which represents the healthcare experience of more than 21 million enrollees with employer-sponsored benefits annually. Inpatient medical, outpatient medical, and outpatient pharmacy claims, absenteeism data (dates of absence from work due to illness), and claims for short-term disability benefits were linked to enrollment information to create the analytic data set.

A retrospective, cross-sectional study was conducted among patients aged 18 years or older with diabetes who used OAD (sulfonylureas, meglitinides, biguanides, thiazolidinediones, or alpha-glucosidase inhibitors) and were continuously enrolled from January 1, 2002, through June 30, 2006. Patients were included if they filled at least 2 prescriptions for an antidiabetic agent from January 1 through June 30, 2003, and had a diagnosis of diabetes (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 250.xx) as indicated by 1 ED visit, 1 inpatient admission, or 2 outpatient visits at least 30 days apart. Patients also were required to have the first observed fill for an OAD occurring in 2002 or the first quarter of 2003. Patients with a diagnosis of type 1 diabetes or gestational diabetes (ICD-9-CM code 648.8x) were excluded. The final samples consisted of 96,734 patients with type 2 diabetes on OAD with or without insulin in the full sample and 55,356 patients who filled an OAD prescription only (no insulin). We created 2 additional subsets of patients who were employees with available absenteeism data (n = 1829; n = 1040 OAD only) and short-term disability data (n = 3027; n = 1753 OAD only).

intended days supply of medication from each claim. Information from prescriptions filled in the fourth quarter of 2002 provided prescription utilization information for early 2003. If a patient refilled the same medication before the end of the days supply from the previous prescription fill, then the days supply for the new prescription was appended to the end of the previous fill. If a patient switched medication within a therapeutic class, the remainder of the previous prescription was discarded and coverage commenced with the supply of the new medication. Days of hospitalization were counted as adherent days (to at least 1 antidiabetes medication), as some of the factors that influence patient medication adherence may change during days of hospitalization. For insulin prescriptions, where the days supply may not indicate the full extent of coverage, we multiplied the days supply of each fill by 1.5.<sup>11</sup> We produced results using various algorithms for insulin adherence and adherence to OAD alone for those patients who used insulin with no material change in findings.

After calculating the number of days that medication was on hand in each medication class, we compiled the information from all therapeutic classes into a single measure and measured adherence based on whether a patient had any antidiabetes medication on hand on each day. Consistent with previous studies, patients were classified as adherent to antidiabetic medications if the PDC equaled or exceeded 80%,<sup>7,12</sup> a threshold at which clinical benefits are most likely to occur.

Complications were recorded using dummy variables that indicated the complication occurred on a claim from July 2004 through June 2006. Codes for each complication are noted in **Table 1**. Utilization events for July 2004 through June 2006 included physician office visits, ED visits, and inpatient admissions, coded as the number of events in the 24-month period. Patients with productivity data available (with days of absence and short-term disability reported) were included in the productivity analysis, even if zero days were reported.

**Explanatory Variables**

Patient cost sharing for antidiabetic medications was measured, using a cost-sharing index created for each employer/plan combination. The index was based on the average cost-sharing amount (ie, copayment, coinsurance) per prescription (standardized to a 30-day supply) for brand and generic drugs in each antidiabetic medication class. The index aggregated the brand and generic copayments using weights, developed from the overall proportion of utilization of brand and generic drugs within each medication class.<sup>13,14</sup> If we were to examine cost sharing for the medications filled by each patient, this method might introduce selection bias, as more adherent consumers might be selecting medications (eg, generics) on the basis of cost-sharing amounts. Thus, aggregating cost sharing into levels for each employer/plan combination reduced the effects of selection bias related to actual, individual-level cost sharing and related choices. The coinsurance flag indicated which plans used coinsurance (a percentage of the total payment) for prescription drug cost sharing versus a flat fee copayment. Any mail-order use in the past year, which can be associated with higher levels of adherence,<sup>15</sup> also was indicated. As outpatient physician visit cost sharing has been associated with reductions in the use of prescription drugs,<sup>16</sup> the per-visit amount was included in the models.

Other explanatory variables associated with medication adherence were included in the models. Patient-level sociodemographic characteristics included sex, age, census region, urban residence, and median income in the patient's area of residence (by ZIP code) from the US Census files. An indicator for employee status (vs spouse/dependent) was included, along with plan type (eg, health maintenance organization, preferred provider organization). An indicator for a visit to a related specialist (ie, cardiologist, endocrinologist) in the past year accounted for disease severity and possible differences in practice patterns.

To account for differences in health status, the following explanatory variables were incorporated into the models as well. Because newly diagnosed patients may have different utilization patterns than patients with existing disease,<sup>17</sup> a flag indicated whether a patient was newly diagnosed with type 2 diabetes in 2003. Scores on the Charlson Comorbidity Index, a numeric scale reflecting the risk of death or serious disability in the next year based on the presence of a diagnosis for 1 of 19 conditions (eg, diabetes, heart disease, cancer) in

**Table 1.** Definitions of Diabetes-Related Complications

Diabetes-Related Complication	ICD-9-CM Diagnosis or Procedure Codes
Acute myocardial infarction	410.xx
Amputation/ulcer	701.2x, 707.xx, 84.10-84.19
Cerebrovascular disease	430.xx-438.xx
Neuropathy	250.6x, 337.1x, 357.2x, 713.5x
Peripheral vascular disease	38.4x, V43.4, 440.xx, 443.9x, 785.4x
Renal events	581.xx-586.xx
Retinopathy	362.0x, 362.1x

*ICD-9-CM indicates International Classification of Diseases, Ninth Revision, Clinical Modification.*

the 12-month preindex period, were included.<sup>18</sup> The Charlson Comorbidity Index is associated with cost and other utilization measures such as length of stay and readmissions.<sup>18</sup> The total patient out-of-pocket burden for chronic conditions (medical and drug) in the preindex year also may reflect lower health status. For prescription drug claims, chronic out-of-pocket spending was classified per claim by using the National Drug Code and Redbook for drug claims (claims with a drug type of “maintenance”) and for medical claims by using the chronic conditions listed in the Charlson Comorbidity Index (as identified by a nosologist).

**Analytic Framework**

We analyzed the relationships among patient cost sharing for antidiabetic medication, adherence, and diabetes-related events or outcomes by first estimating the relationship between patient cost sharing for antidiabetic medication and adherence to antidiabetic medications (controlling for covariates) during an 18-month time frame (January 2003 through June 2004). We then estimated the relationship between adherence in the initial time frame and outcomes, controlling for covariates in the subsequent 2 years, July 2004 through June 2006.

Several hypotheses based on existing evidence that higher patient cost sharing reduces medication adherence<sup>3,4</sup> informed our approach. We anticipated that adherence would be associated with lower rates of ED visits and hospital admissions,<sup>6</sup> and would reduce the risk of diabetes-related events or outcomes, particularly for sequelae likely to develop in the near term.<sup>2,7,19</sup> For employees with productivity data, we hypothesized that adherence might have translated into higher levels of productivity.

**Multivariate Approach**

A 2-stage model was used to estimate the relationship between antidiabetic medication (OAD with or without insulin) adherence and health outcomes.

■ **Table 2.** Demographic Variables and Measures<sup>a</sup>

Demographic	Mean (SD)	
	Patients With Type 2 Diabetes on OAD Only (n = 55,356)	Patients With Type 2 Diabetes on OAD With or Without Insulin (n = 96,734)
<b>Variables (January 2003–June 2004)</b>		
<b>Mean age, y</b>	53.17 (6.47)	52.2 (7.82)
<b>Female (vs male)</b>	43.90%	46.10%
<b>Employee (vs dependent)</b>	69.40%	67.50%
<b>Urban (vs rural)</b>	75.00%	75.10%
<b>US Census region</b>		
Northeast	6.80%	6.50%
North Central	36.60%	36.80%
South	41.70%	41.90%
West	14.90%	14.80%
<b>Health plan type</b>		
Comprehensive	23.50%	23.80%
HMO/exclusive provider organization	15.70%	15.60%
Point-of-service plan	18.10%	18.00%
Preferred provider organization	42.80%	42.60%
<b>Income</b>	\$43,620.00 (\$14,540.00)	\$43,590.00 (\$14,590.00)
<b>Charlson Comorbidity Index score</b>	1.26 (0.99)	1.42 (1.16)
<b>Chronic out-of-pocket payments</b>	\$822.00 (\$3659.00)	\$1105.00 (\$6111.00)
<b>New patient</b>	1.10%	1.10%
<b>Patient saw a cardiologist, lagged</b>	14.30%	16.20%
<b>Patient saw an endocrinologist, lagged</b>	3.20%	7.10%
<b>Prescription drug copayment index</b>	\$11.42 (\$5.12)	\$11.45 (\$5.13)
<b>Prescription drug coinsurance</b>	17.40%	17.00%
<b>Mail order, lagged</b>	28.50%	28.50%
<b>Office visit copayment</b>	\$21.20 (\$16.70)	\$20.99 (\$16.58)
<b>Measures (July 2004–June 2006)</b>		
<b>Adherence</b>		
Adherent to antidiabetic medications (PDC ≥80%)	72.70%	74.50%
<b>Complications</b>		
Acute myocardial infarction	1.40%	2.00%
Amputation/ulcer	2.50%	4.50%
Cerebrovascular disease	6.60%	8.20%
Neuropathy	7.11%	12.42%
Peripheral vascular disease	4.80%	6.60%
Renal events	3.50%	6.60%
Retinopathy	7.30%	13.50%
<b>Utilization</b>		
ED visits	0.64 (1.71)	0.86 (2.27)
Inpatient admissions	0.26 (0.72)	0.41 (1.04)
Outpatient office visits	12.04 (9.25)	13.9 (10.8)
<b>Productivity</b>		
Absence days <sup>b</sup>	32.53 (31.1)	31.92 (32.02)
Short-term disability days <sup>c</sup>	13.28 (47.03)	17.43 (56.57)

ED indicates emergency department; HMO, health maintenance organization; OAD, oral antidiabetic medication; PDC, percent of days covered.

<sup>a</sup>Source of data: 2002-2006 Thomson Reuters MarketScan Database. Lagged measures were calculated in 2002.

<sup>b</sup>Data on absence days were available for 1040 patients with type 2 diabetes on OAD only and for 1829 patients with type 2 diabetes on OAD with or without insulin.

<sup>c</sup>Data on short-term disability days were available for 1753 patients with type 2 diabetes on OAD only and for 3027 patients with type 2 diabetes on OAD with or without insulin.

**First Stage: Cost Sharing and Adherence.** A logistic regression model was estimated for adherence (PDC  $\geq 80\%$ ) in the 18-month time period (January 2003 through June 2004). Explanatory variables included sociodemographic variables, employee status, health plan type, physician specialist visit, health status, and cost sharing.

**Second Stage: Adherence and Health Outcomes.** In the second stage, generalized linear models estimated events between July 2004 through June 2006. All models included the first-stage explanatory variables, except for the cost-sharing variables. The cost-sharing variables (cost-sharing index, coinsurance flag, office visit cost sharing, and previous mail-order use) served as instruments in the first-stage equation and thus were not included in the second stage. Using a 2-stage residual inclusion model, actual patient adherence and the residual from the first-stage model also were included in the second-stage model. The residual was included to produce consistent estimates in the nonlinear second stage and to adjust for any unobservable confounding in the second stage.<sup>20</sup> The coefficient of the residual term in the second stage also allowed an indication of endogeneity. If the coefficient of the residual is statistically significant, the inclusion of the residual term aids in reducing selection effects, making the estimates consistent. If the coefficient of the residual term is not statistically significant, consistent estimates are produced, possibly with a loss of efficiency.

Each complication model was estimated using a logit link and a binomial family for the binary outcomes. Using 2 versions of the complication models to focus on the development of complications in the measurement period, complication models were estimated (1) controlling for previous complications by including indicator variables for the presence of each complication in 2002 and (2) for the subset of patients with no complications in 2002. The utilization and productivity models were estimated using a log link and a negative binomial model to reflect outcomes expressed as counts.

We also estimated the reduced form of each of the outcome equations to determine the strength and direction of the association between copayments and each outcome.

## RESULTS

The characteristics of the full and OAD-only samples are presented in **Table 2**. The full sample was 46% female and had an average age of 52.2 years. The majority of the full sample lived in the South, and three-fourths lived in urban areas. The median income in the patients' area of residence averaged about \$44,000. More than two-thirds of patients were employees (67.5%), and the majority of patients were enrollees in a preferred provider organization. The mean

cost-sharing index amount was \$11.45. Seventeen percent of individuals were subject to coinsurance, more than one-quarter (28.5%) had used a mail-order pharmacy in the past year, and the average physician office visit copayment was about \$20. Similar demographics were observed among OAD-only users.

Almost three-quarters of patients were adherent (PDC  $\geq 80\%$ ) from January 2003 through June 2004. Complication rates for OAD-only users ranged from 1.4% for an acute myocardial infarction (AMI) to 7.3% for retinopathy. Complication rates were higher (2.0% for an AMI and 13.5% for retinopathy) for all OAD users. Patients visited the ED on average less than once and had inpatient admissions less frequently than ED visits in the 2-year time frame. Employees reported slightly more than 30 days absent. OAD-only users had 13.3 short-term disability days, and the full sample had 17.4 short-term disability days.

**Table 3** presents results from the first-stage logistic regression estimates for adherence. Notably, as the level of prescription drug cost sharing (measured as the cost-sharing index) increased, adherence decreased. For all OAD users, the odds ratio (OR) was 0.974 (95% confidence interval [CI] = 0.970, 0.978). For OAD-only users, the OR was 0.978 (95% CI = 0.973, 0.984). Higher cost sharing for physician visits also was associated with lower levels of adherence, although the effects were not as large. For all OAD users, the OR was 0.996 (95% CI = 0.994, 0.997). For OAD-only users, the OR was 0.995 (95% CI = 0.993, 0.996). Patients with coinsurance had higher levels of adherence, as did patients who had previous mail-order use. All instruments were individually and jointly statistically significant in the first-stage (adherence) models ( $P < .01$ ).

**Figure 1** shows the adjusted relationship between cost-sharing index amounts ranging from \$10 to \$30 and the predicted probability of adherence. An increase from \$10 to \$20 in the cost-sharing index resulted in an average 4.2 percentage point reduction in the probability of being 80% adherent for OAD-only users and a 4.8 percentage point reduction for all OAD users.

Consistent with previous studies, the effects of selected explanatory variables on adherence were in the expected direction.<sup>8,21</sup> For example, females had lower levels of adherence, and as age increased, adherence also increased. Patients in higher-income areas exhibited higher levels of adherence.<sup>8</sup> Patients with a greater number of comorbidities (as indicated by the Charlson Comorbidity Index) were more adherent, which is consistent with descriptive findings in the article by Encinosa et al,<sup>5</sup> who reported that patients with more chronic conditions were more adherent. Chronic out-of-pocket payments were not associated with adherence, although the

■ **Table 3.** Adherence Model Estimates<sup>a</sup>

	Patients With Type 2 Diabetes on OAD Only (n = 55,356)			Patients With Type 2 Diabetes on OAD With or Without Insulin (n = 96,734)		
	Adjusted Odds Ratio	P > z	95% CI	Adjusted Odds Ratio	P > z	95% CI
<b>Prescription drug copayment index</b>	0.978	<.001	0.973, 0.984	0.974	<.001	0.970, 0.978
<b>Prescription drug coinsurance</b>	1.189	<.001	1.088, 1.299	1.182	<.001	1.103, 1.266
<b>Office visit copayment</b>	0.995	<.001	0.993, 0.996	0.996	<.001	0.994, 0.997
<b>Mail order, lagged</b>	2.208	<.001	2.098, 2.323	2.324	<.001	2.234, 2.419
<b>Age</b>	1.048	<.001	1.045, 1.052	1.032	<.001	1.030, 1.034
<b>Female (vs male)</b>	0.869	<.001	0.834, 0.905	0.834	<.001	0.809, 0.861
<b>Employee (vs dependent)</b>	0.988	.580	0.945, 1.032	0.947	.002	0.916, 0.979
<b>Urban (vs rural)</b>	0.875	<.001	0.833, 0.920	0.881	<.001	0.848, 0.915
<b>US Census region (reference = South)</b>						
Northeast	1.126	.006	1.034, 1.225	1.089	.012	1.019, 1.164
North Central	1.268	<.001	1.203, 1.335	1.195	<.001	1.148, 1.244
West	1.264	<.001	1.181, 1.353	1.202	<.001	1.141, 1.267
<b>Plan type (reference = PPO)</b>						
Comprehensive	1.085	.007	1.022, 1.153	1.069	.004	1.021, 1.119
HMO/exclusive provider organization	1.100	.004	1.031, 1.173	1.085	<.001	1.032, 1.139
Point-of-service plan	1.036	.254	0.975, 1.100	1.024	.324	0.977, 1.072
<b>Income in thousands</b>	1.010	<.001	1.008, 1.011	1.009	<.001	1.008, 1.010
<b>Charlson Comorbidity Index score</b>	1.043	<.001	1.021, 1.065	1.033	<.001	1.018, 1.047
<b>New patient</b>	0.147	<.001	0.122, 0.177	0.157	<.001	0.137, 0.181
<b>Chronic out-of-pocket payments in hundreds, lagged</b>	1.001	.162	1.000, 1.001	1.000	.794	1.000, 1.000
<b>Cardiologist</b>	0.921	.005	0.869, 0.976	0.970	.166	0.929, 1.013
<b>Endocrinologist</b>	0.979	.707	0.877, 1.093	1.133	<.001	0.743, 0.828

CI indicates confidence interval; HMO, health maintenance organization; OAD, oral antidiabetic medication; PPO, preferred provider organization.  
<sup>a</sup>Adherence models were estimated based on experience in January 2003 through June 2004.

chronic out-of-pocket-payment variable was a lagged variable (measured during the year before the adherence time frame), so it was intended to represent the amount of copayment burden. Because of its construction, it is likely to be a proxy for health status. Perhaps the time separation in measurement affected the strength of the association.

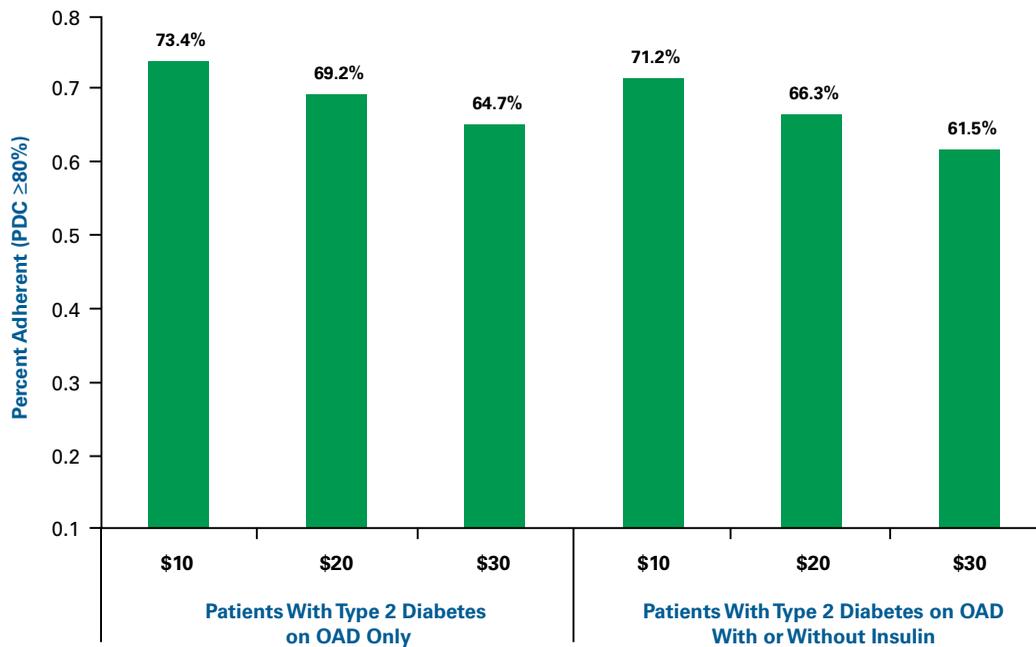
The relationship between adherence and events is detailed in **Table 4A** and **Table 4B**. The full sample of OAD users who were adherent had a lower likelihood of all complications. OAD-only users who were adherent had a lower likelihood of amputation/ulcers, AMI, neuropathy, renal events, and retinopathy. Among OAD-only users, cerebrovascular disease and peripheral vascular disease rates were not significantly different for adherent patients when using the 2-stage residual inclusion approach. However, in both cases, the coefficient of the residual indicated that there was little likelihood of endogeneity, so we reestimated the models with a 1-stage approach

and found significantly lower rates of cerebrovascular disease for adherent patients (OR = 0.900; 95% CI = 0.829, 0.977) and continued to find no significant difference in peripheral vascular disease rates.

**Figure 2** shows the predicted mean effect size of each of these complications for adherent and nonadherent patients in terms of the likelihood of each complication. For example, 1.8% of patients adherent to antidiabetic medications in January 2003 through June 2004 were likely to have an AMI in the next 2 years, and more than twice as many (4%) nonadherent patients were likely to have an AMI.

The number of ED visits was significantly lower among adherent patients, while the number of physician visits was higher among adherent patients. Inpatient admission rates were no different for adherent and nonadherent OAD-only users, but were lower for all OAD users. As with cerebrovascular disease, because there was no indication of endogeneity

■ **Figure 1.** Predicted Effects of Prescription Drug Cost Sharing on Adherence to Antidiabetes Medications<sup>a</sup>



PDC indicates percentage of days covered.  
<sup>a</sup>Adherence was measured from January 2003 through June 2004.  
 Source: 2002-2004 Thomson Reuters MarketScan Database.

in the 2-stage residual inclusion inpatient admission models for OAD-only users, we reestimated the inpatient admission outcome model with a 1-stage model and found that adherence was associated with lower admission rates (incidence rate ratio = 0.808; 95% CI = 0.769, 0.850).

The number of days of short-term disability was significantly lower for adherent patients ( $P < .01$  for both the full sample and the OAD-only users). When calculating the predicted mean effect size for short-term disability, non-adherent patients in the full sample received an average of 18 more days of short-term disability (40 days nonadherent, 22 days adherent) (not shown). Nonadherent OAD-only users received an average of 8 more days of short-term disability (24 days) than adherent patients (16 days) (not shown).

Absence effects were mixed, with slightly higher rates of absence among patients who were adherent. However, OAD-only users who were adherent had the same rates of absence as those who were nonadherent.

**Table 5** summarizes the direction and strength of the reduced-form coefficients of the prescription drug and physician visit copayment variables on each set of outcomes. In about three-quarters of the reduced-form models, higher copayments were associated with higher levels of each adverse outcome, although not all estimates were statistically significant.

## DISCUSSION

In this large cohort of patients with type 2 diabetes who were users of OAD and enrolled in employer-sponsored plans, we found a wealth of positive effects of adherence to antidiabetic medications. Importantly, this study found that adherent patients had lower rates of the diabetes-related complications examined, a finding that extends previous work on adherence and diabetes-related outcomes to include complications. Ho and colleagues found that nonadherence to OAD, antihypertensives, or statins was related to increased A1C levels, higher systolic and diastolic blood pressure, and higher low-density lipoprotein cholesterol levels.<sup>7</sup> Further, Hunt and colleagues linked higher levels of patient cost sharing with inadequate adherence and ultimately increased A1C levels.<sup>9</sup>

This study also found that adherence to OAD among the full patient sample was associated with lower rates of ED visits and inpatient admissions. Existing literature shows an inverse relationship between medication adherence and hospitalizations or ED visits.<sup>4-7,17,22,23</sup> Our results corroborate these findings among the commercially insured in employer-sponsored plans.

We also found that adherence was associated with productivity benefits in terms of fewer short-term disability days, revealing that the benefits of adherence affect productivity.

■ **Table 4A.** Effects of Adherence on Complications, Utilization, and Indirect Costs for Patients With Type 2 Diabetes on OAD Only (n = 55,356)<sup>a</sup>

Measure and Type of Ratio	Ratio	P > z	95% CI	P Test of Exogeneity <sup>b</sup>
<b>Complications, OR</b>				
Amputation/ulcer	0.430	.014	0.219, 0.843	.030
Acute myocardial infarction	0.285	.005	0.118, 0.687	.014
Cerebrovascular disease	0.826	.358	0.549, 1.241	.679
Neuropathy	0.598	.014	0.397, 0.901	.020
Peripheral vascular disease	0.962	.432	0.875, 1.059	.939
Renal events	0.534	.040	0.293, 7.000	.024
Retinopathy	0.644	.048	9.000, 0.996	.003
<b>Utilization, IRR</b>				
ED visits	0.800	.018	0.665, 0.962	.835
Inpatient admissions	0.946	.672	0.733, 1.221	.213
Physician office visits	1.670	<.001	1.481, 1.883	<.001
<b>Productivity, IRR</b>				
Absence days <sup>c</sup>	0.639	.150	0.348, 1.180	.142
Short-term disability days <sup>d</sup>	0.672	.009	0.477, 0.946	.117

CI indicates confidence interval; ED, emergency department; IRR, incidence rate ratio; OAD, oral antidiabetic medication; OR = odds ratio; PPO, preferred provider organization.  
<sup>a</sup>Coefficients represent the effects of adherence on each outcome in each second-stage equation.  
Coefficients in the complication models are expressed as ORs and are partial elasticities in the utilization and productivity models.  
<sup>b</sup>The test of exogeneity reflects the significance of the coefficient of the residual in the second-stage equation.  
<sup>c</sup>Data on absence days were available for 1040 patients.  
<sup>d</sup>Data on short-term disability days were available for 1753 patients.

However, in the overall cohort of OAD users (OAD with or without insulin), absence rates were higher among adherent compared with nonadherent employees, which may correspond to the length of illness. For instance, nonadherent patients may require longer spells of absence, constituting short-term disability, whereas adherent patients may incur short-term absences covered by vacation or sick days.

We also found that prescription drug and physician copayments were inversely associated with adherence. In the first-stage models, we found that an increase from \$10 to \$20 in the cost-sharing index was associated with an average 4.2 percentage point reduction in the probability of being 80% adherent for OAD-only users and a 4.8 percentage point reduction for the full sample. This association translates to a price elasticity in the OAD-only group of -0.054 and of -0.062 among all OAD users.

This key finding is consistent with previous literature regarding the effects of higher cost sharing on antidiabetic medication adherence. Specifically, Chernew and colleagues found that the price elasticity for OAD medications for patients with type 2 diabetes was around -0.05.<sup>8</sup> Additionally, Colombi and colleagues measured the effect of the per-user average copayment of all prescription medications on anti-

diabetic medication adherence and found that patients in the high-copayment group were more likely to have lower levels of adherence, with a reduction of 14 percentage points in overall adherence between the medium (\$10-\$19) and high (\$20+) copayment groups.<sup>17</sup> Hunt and colleagues found that an increase in cost sharing by \$5 resulted in a decrease of 6% in the odds of being adherent to OAD.<sup>9</sup> Differences in the magnitude of previous findings and the findings here point to differences in measuring cost sharing; we used several measures of cost sharing to mitigate selection bias.

To understand the effects of copayments on outcomes, we estimated reduced-form models on the outcomes and found a positive relationship between copayments and most of the adverse events. Because our system was nonlinear, the association between copayments and outcomes was likely suggestive, but not entirely representative, of the relationship that we are proposing exists between cost sharing and outcomes. Thus, we interpreted the findings directionally and found that lowering copayments holds promise as a means to improve health.

There also may be some concern about employers with more generous copayments (lower copayments) having more generous disability policies, so there would be an existing in-

**Table 4B.** Effects of Adherence on Complications, Utilization, and Indirect Costs for Patients With Type 2 Diabetes on OAD With or Without Insulin (n = 96,734)<sup>a</sup>

Measure and Type of Ratio	Ratio	P > z	95% CI	P Test of Exogeneity <sup>b</sup>
<b>Complications, OR</b>				
Amputation/ulcer	0.429	<.001	0.290, 0.635	<.001
Acute myocardial infarction	0.418	.001	0.247, 0.709	.011
Cerebrovascular disease	0.728	.025	0.552, 0.960	.153
Neuropathy	0.657	.001	0.514, 0.839	<.001
Peripheral vascular disease	0.739	.056	0.542, 1.008	.107
Renal events	0.454	<.001	0.323, 0.636	<.001
Retinopathy	0.763	.033	0.596, 0.978	<.001
<b>Utilization, IRR</b>				
ED visits	0.679	<.001	0.609, 0.756	.003
Inpatient admissions	0.705	<.001	0.615, 0.808	.036
Physician office visits	1.425	<.001	1.319, 1.539	<.001
<b>Productivity, IRR</b>				
Absence days <sup>c</sup>	1.185	.040	1.008, 1.393	.041
Short-term disability days <sup>d</sup>	0.548	<.001	0.396, 0.759	.002

CI indicates confidence interval; ED, emergency department; IRR, incidence rate ratio; OAD, oral antidiabetic medication; OR = odds ratio; PPO, preferred provider organization.  
<sup>a</sup>Coefficients represent the effects of adherence on each outcome in each second-stage equation.  
Coefficients in the complication models are expressed as ORs and are partial elasticities in the utilization and productivity models.  
<sup>b</sup>The test of exogeneity reflects the significance of the coefficient of the residual in the second-stage equation.  
<sup>c</sup>Data on absence days were available for 1829 patients.  
<sup>d</sup>Data on short-term disability days were available for 3027 patients.

verse relationship between copayments and disability days. However, our 2-part results, adjusted for selection bias, show an inverse relationship between copayments and adherence, and another inverse relationship between adherence and disability days. As such, our reported results are in the opposite direction of this concern and may be biased downward. Although there was insufficient overlap to study net productivity effects, additional research measuring the net productivity gains (absence plus short-term disability) may provide insight into the consequences of inadequate adherence on indirect costs.

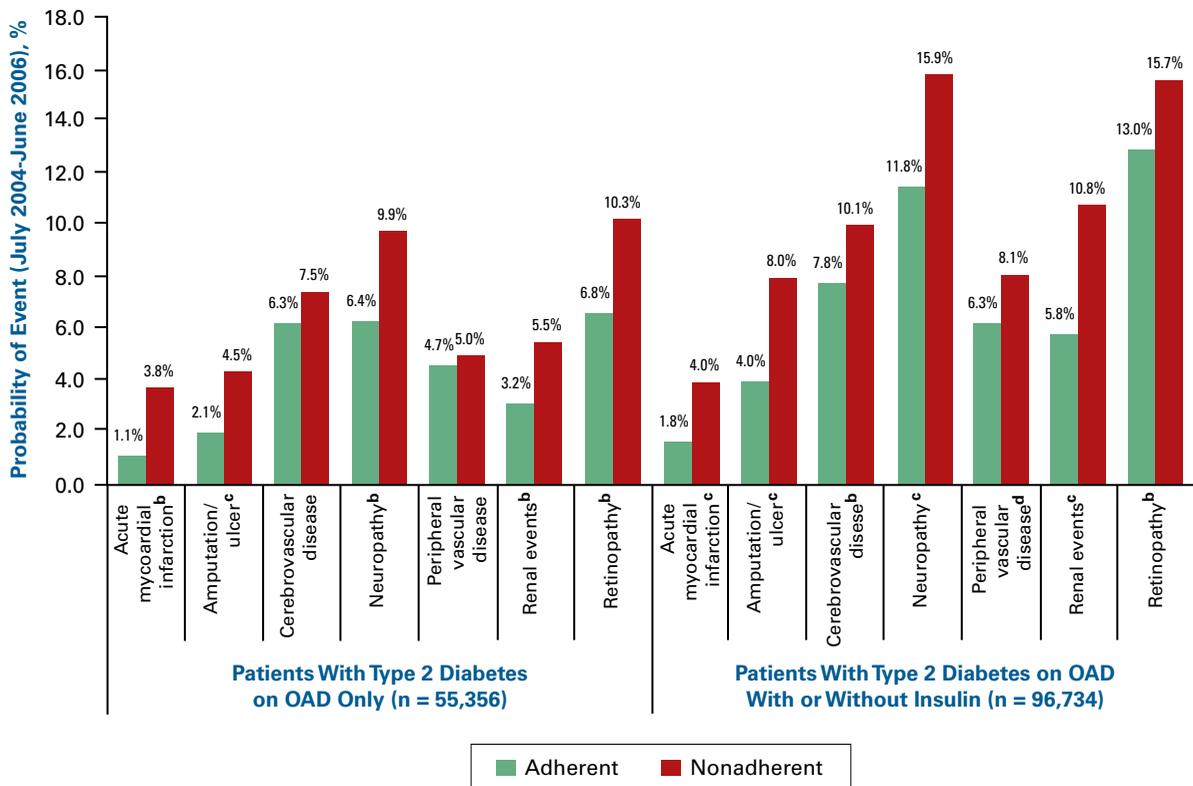
The study was based on administrative data; thus, actual antidiabetic medication consumption patterns cannot be ascertained. The adherence measure assumed that filling behavior was correlated with medication consumption patterns. We do not know the entirety of the prescribed antidiabetic medication regimen, so we could only determine whether there was at least 1 medication on hand, which is a conservative standard of adherence.

Given the dosage form of insulin, measures of days supply can have a lower correlation to actual consumption patterns. However, in this study, all patients had type 2 diabetes and were on OAD, so when insulin was used, it was mostly

supplemental to OAD. We present a conservative measure of insulin adherence based on 1.5 times days supply, a multiplier determined empirically by Kleinman and colleagues to correspond with actual use.<sup>11</sup> As a comparison, with this measure of insulin days, 74.5% of patients were adherent; when using OAD-only (without insulin) criteria to calculate PDC for the same patients, 68.4% of patients were adherent. We ran sensitivity analyses on the models that excluded insulin days (OAD alone); a second set of sensitivity analyses used the days supply for the insulin claims to calculate PDC and saw no material difference in findings.

Further, we measured adherence in an 18-month time frame and complications and service utilization in the subsequent 2 years. If these time periods were extended, the benefits of adherence might become more pronounced. Patients discontinuing medication use after achieving diabetes management would be classified here as nonadherent. We expect this number to be low, although adherence is generally associated with lower rates of utilization and complications; if these patients were misclassified as nonadherent, these results would be biased toward zero. We varied the adherence threshold to meet or exceed 90% or 100% and consistently found better outcomes associated with adherence. Thus,

**Figure 2.** Predicted Effects of Adherence on Complication Rates for Patients With Type 2 Diabetes<sup>a</sup>



<sup>a</sup>Source of data: 2002-2006 Thomson Reuters MarketScan Database. Adherence was measured from January 2003 through June 2004 and complications were measured from July 2004 through June 2006.

<sup>b</sup>.01 < P ≤ .05.

<sup>c</sup>P ≤ .01.

<sup>d</sup>.05 < P ≤ .10.

further research should incorporate clinical data, including information on side effects, disease severity, and A1C levels, if available, and measure effects over a longer study period.

In addition, some explanatory variables such as race were not available. Our study focused on a sample of patients with employer-sponsored insurance. In patient populations where the percentage of income spent on healthcare is higher, the effects of cost sharing on adherence may be larger than these results.

Benefit plan documents reveal that fewer than 10% of plans applied out-of-pocket maximums to prescription drug copayments. In the event that these maximums applied to prescription drug copayments and patients with high spending in these plans were assessed a zero copayment after some point in the year, patients who were assigned to a higher copayment level in our study would actually have lower copayments and would be more likely to become adherent. We believe that this phenomenon biases our reported first-stage results downward.

In the adherence models, if more adherent patients se-

lected plans with lower prescription drug cost-sharing levels, then the cost-sharing effects on adherence presented here would be biased upward. In the complication and utilization models, patients with more advanced disease may be less adherent to medications, which would bias the adherence effects upward. However, use of the 2-stage residual inclusion model mitigates selection concerns. There was no evidence of unobservable confounding (via a nonsignificant coefficient on the residual term) in approximately half of the models; in the other half, the inclusion of the residual term aided in reducing these effects, producing consistent estimates. As stated above, all instruments were statistically significant in the first-part models; however, as of this writing, we know of no existing overidentification test for a 2-stage residual inclusion model. We posit the relationship of the instruments to the endogenous variables, but were unable to test this relationship directly.

## CONCLUSION

**Table 5.** Direction and Significance of the Reduced-Form Effects of Copayments on Outcomes

Type of Copayment	Outcome	Higher		Lower	
		Significant	Nonsignificant	Nonsignificant	Significant
<b>Patients With Type 2 Diabetes on OAD Only (n = 55,356)</b>					
<b>Prescription drug</b>	Complications	3	3	1	—
	ED visits/inpatient visits	1	—	1	—
	Short-term disability	—	—	—	1
	Absence	1	—	—	—
<b>Physician</b>	Complications	1	6	—	—
	ED visits/inpatient visits	1	—	—	1
	Short-term disability	—	—	1	—
	Absence	—	—	—	1
<b>Patients With Type 2 Diabetes on OAD With or Without Insulin (n = 96,734)</b>					
<b>Prescription drug</b>	Complications	3	2	1	1
	ED visits/inpatient visits	1	—	—	1
	Short-term disability	—	—	1	—
	Absence	1	—	—	—
<b>Physician</b>	Complications	1	6	—	—
	ED visits/inpatient visits	1	—	—	1
	Short-term disability	—	1	—	—
	Absence	—	—	—	1

ED indicates emergency department; OAD, oral antidiabetic medication.

The results indicate that higher antidiabetic medication cost sharing is associated with lower adherence; and adherence to antidiabetic medications generally results in lower rates of complications, short-term disability, ED visits, and hospitalizations among patients with type 2 diabetes. Financial incentives to improve adherence, such as lower levels of cost sharing, may translate to better patient outcomes and lower employer costs resulting from increased productivity and decreased healthcare utilization. Medical plans, employers, and policy makers should consider implementation of interventions targeted to improve and maintain high levels of adherence to improve indirect and direct measures of health and well-being.

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