Clinical Outcomes and Adherence to Medications Measured by Claims Data in Patients With Diabetes

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OBJECTIVE — Although poor medication adherence may contribute to inadequate diabetes control, ways to feasibly measure adherence in routine clinical practice have yet to be established. The present study was conducted to determine whether pharmacy claims–based measures of medication adherence are associated with clinical outcomes in patients with diabetes.

RESEARCH DESIGN AND METHODS — The study setting was a large, integrated delivery and financial system serving the residents of southeastern Michigan. The study population consisted of 677 randomly selected patients aged $\geq$18 years with a diagnosis of diabetes, hypercholesterolemia, and hypertension and who filled at least one prescription for either an antidiabetic, lipid-lowering, or antihypertensive drug in each of the 3 study years (1999–2001). The main outcome measures were HbA_{1c}, LDL cholesterol levels, and blood pressure.

RESULTS — Nonadherent patients had both statistically and clinically worse outcomes than adherent patients. Even after adjusting for demographic and clinical characteristics, nonadherence was significantly associated with HbA_{1c} and LDL cholesterol levels. A 10% increase in nonadherence to metformin and statins was associated with an increase of 0.14% in HbA_{1c} and an increase of 4.9 mg/dl in LDL cholesterol levels. Nonadherence to ACE inhibitors was not significantly associated with blood pressure.

CONCLUSIONS — Claims-based measures of medication adherence are associated with clinical outcomes in patients with diabetes and may therefore prove to be useful in clinical practice. More research is needed on methods to introduce claims-based adherence measurements into routine clinical practice and how to use these measurements to effectively improve adherence and health outcomes in chronic care management.

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N onadherence to medications is a common problem in clinical practice, especially among patients with asymptomatic chronic conditions such as diabetes, hypertension, and hypercholesterolemia (1–4). A recent meta-analysis has showed that the average adherence in patients with diabetes is 67.5%, which is lower than that found among many conditions (5). Also, recently, a specific systematic review on adherence to medications for diabetes showed that average adherence to oral hypoglycemic agents ranged from 36 to 93% (6). In general, poor adherence to medications has been shown to be associated with the development of complications, disease progression, avoidable hospitalizations, premature disability, and death. In total, the costs associated with poor medication adherence are estimated to approach $100 billion per year (7). Despite these known consequences, adherence rates have remained unchanged since the 1970s (1,8).

Nonadherence is the result of a complex interaction among the social environment, the patient, and the health providers (9). Adherence to medications is not routinely measured in clinical practice, and a gold standard that can be easily implemented, even for research purposes, does not exist (1,5,10–12). Yet claims data have been shown to be a useful source of adherence information with some degree of both predictive and convergent validity, and its use in routine clinical practice appears both feasible and sustainable, especially in comparison with using other methods of monitoring adherence such as electronic monitoring (13,14). Although some self-report measurements of adherence have similar validity to claims-based measurements, their sensitivity is low, especially when used by clinicians (11–13).

There is now building evidence that pharmacologically treating patients with diabetes to improve their metabolic profile (glycemia and cholesterol) and blood pressure is cost-effective (15,16). Thus, there is reason to believe that improving medication adherence might be cost-effective as well (7), especially among patients with diabetes, where the prevalence of hypercholesterolemia and hypertension is higher than in the general population (17), and their cardiovascular risk factor control is far from optimal (18).

In the present study, we examined the association between claims-based measures of medication adherence and clinical outcomes such as HbA_{1c}, blood pressure, and LDL cholesterol in a sample of diabetic patients.

RESEARCH DESIGN AND METHODS — The study was conducted in a large, salaried, multispecialty physician group practicing in the mid-

western U.S. The study sample was limited to insured patients with prescription drug coverage continuously enrolled in an affiliated health maintenance organization between 1 January 1999 and 31 December 2001. Other inclusion criteria included age ≥18 years as of 31 December 1999; diagnosed (at least one ICD-9 code) with diabetes, hypertension, and dyslipidemia during the period of 1999–2001; and at least one prescription drug claim for either an antidiabetic, lipid-lowering, or antihypertensive drug in each of the study years (1999–2001). Patients using insulin were excluded because there is not a feasible method to measure adherence to injectables from claims data, and unmeasured adherence to insulin could confound the effects of adherence to the oral medications. Among patients meeting these criteria, a random sample of 677 patients was drawn.

Automated health plan data and medical group administrative and clinical data were used to identify patients for sample inclusion and to compile data on dates of enrollment, demographics (age, sex, and race), laboratory testing results (plasma HbA$_{1c}$ and LDL cholesterol), and prescription drug use. Information on race/ethnicity available within this system is recorded in eight categories by the medical group front desk staff or hospital admitting staff. Data from a sample of 2,443 group model health plan patients aged 18–45 years with a visit to primary care in 2000 indicate that this race categorization is consistent with self-reported race 95% of the time ($\kappa = 0.87$) (19). BMI and blood pressure measurements were obtained by medical record abstraction by accredited record technicians who were unaware of the patients' medication adherence.

Prescription drug claims data were used to compute a continuous measure of medication gaps (CMG), a measure of nonadherence (14). This index indicates the proportion of days with gaps in medication refills over the days in the observation period. A patient was classified as nonadherent when the percentage of CMG was 20%. Nonadherence was measured for three classes of drugs: metformin, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), and ACE inhibitors. Within each drug class, CMG indexes were computed for those patients who filled at least one prescription per year ($n = 308$ for metformin, $n = 287$ for statins, and $n = 384$ for ACE inhibitors) and for the period comprised between the first prescription claim after 1 January 1999 and the last prescription available or 31 December 2001, whichever occurred first. Clinical outcomes were evaluated as the average of all measurements of HbA$_{1c}$, LDL cholesterol, and blood pressure available during the study period (1 January 1999 to 31 December 2001). Institutional review board approval was obtained for all aspects of this study.

Correlation between laboratory values (HbA$_{1c}$ and LDL cholesterol) or blood pressure measurements and CMG indexes was estimated using Pearson and Spearman correlation coefficients. Multivariable linear regression models were used to adjust for sociodemographic and clinic characteristics (BMI, number of total drugs for each outcome, and number of outcome measurements available). Based on a referee suggestion, a separate model with the difference between the last and the first measurement during the study period was included for each outcome (HbA$_{1c}$, LDL cholesterol, and blood pressure). Those models adjusted for the first outcome measurement available during the study period as well. SPSS version 11.0 was used for all statistical analysis, and significance was set at $P < 0.05$.

RESULTS — Mean age was 64 years (11). A total of 53% of the patients were women, 53% were Caucasian, 41% African American, and 5% were of another race/ethnicity. Mean (±SD) outcome levels were 8.0 ± 1.4 for HbA$_{1c}$, 116.9 ± 30.7 for LDL cholesterol, 33.1 ± 6.8 for BMI, and 138.5 ± 12.8 and 80.0 ± 7.2 for systolic (SBP) and diastolic blood pressure, respectively. Median (mean ± SD) measures of nonadherence to metformin, statins, and ACE inhibitors were 16.8 (21.6 ± 18.9), 13.2 (18.4 ± 17.7), and 7.3 (13.7 ± 16.1), respectively. Prevalences of nonadherence were 43, 36, and 23% for metformin, statins, and ACE inhibitors, respectively (Table 1).

The correlation coefficients between CMG scores and outcomes (HbA$_{1c}$, LDL cholesterol, and blood pressure) ranged from 0.15 to 0.32 and were highest for LDL cholesterol and lowest for SBP. Average levels of outcomes were significantly higher in the nonadherent than adherent group (Table 2).

After adjusting for age, sex, race, BMI, total number of active drugs for each outcome (antihypertensive drugs for blood pressure, antidiabetic oral agents for HbA$_{1c}$, and lipid-lowering drugs for LDL cholesterol), and number of outcome measurements, nonadherence was significantly and positively associated with both HbA$_{1c}$ and LDL cholesterol but not SBP (Table 3). The CMG score for ACE inhibitors was not significantly associated with diastolic blood pressure either (data not shown). A 10% increase in CMG percentage score (worse adherence) for metformin and statins was associated with an increase of 0.14% in HbA$_{1c}$ and an increase of 4.9 mg/dl in LDL cholesterol, respectively. Interactions between adherence and the other significant predictors included in the linear regression models were tested, but none were statistically significant ($P > 0.10$). The proportion of outcome variability explained by the three different outcome models ranged from 17 (SBP model) to 24% (HbA$_{1c}$ model). The LDL cholesterol model explained 22% of the variability. The separate models with the difference between last and first outcome measurement, as the dependent variable did not change the results and nonadherence indexes for metformin and statins, were still significantly associated with clinical outcomes (Table 4).

CONCLUSIONS — The introduction of nonadherence information into clinical practice has the potential to improve both adherence and clinical outcomes. However, before introducing nonadherence information in routine clinical practice, it is critical to ensure that such information can be obtained economically and is associated with meaningful clinical outcomes. The present study provides evidence that claims-based measurements of nonadherence are associated with relevant intermediate outcomes in patients with diabetes. These associations are clinically and statistically significant for HbA$_{1c}$ and LDL cholesterol. The association between ACE inhibitor nonadherence and blood pressure measurements was no longer significant in the multivariable models. However, nonadherence levels for ACE inhibitors were low. Only 23% of the patients on

Table 1—*Sociodemographic, nonadherence, and clinic characteristics*

Characteristics	
n	677
Age (years) (means ± SD)	63.9 ± 10.6
Women (%)	53.2
Race (%)	
Caucasian	53.3
African American	41.4
Other	5.3
Clinical outcomes [means ± SD (n)]	
HbA_{1c} (%)	8.0 ± 1.4 (675)
LDL cholesterol (mg/dl)	116.9 ± 30.7 (659)
Blood pressure (mmHg)	138.5 ± 12.8/80.0 ± 7.2 (674)
BMI (kg/m^2)	33.1 ± 6.8 (560)
Treatments during each study year [% (n)]	
Metformin	45.5 (308)
Statins	42.4 (287)
ACE inhibitors	56.7 (384)
Number of drugs used [means (median)]	
Oral antidiabetic drugs (among metformin users)	2.1 (2)
Lipid-lowering drugs (among statin users)	1.1 (1)
Antihypertensive drugs (among ACE inhibitor users)	2.6 (2)
Nonadherence indices (CMG percentages)* [median (means ± SD)]	
Metformin	16.8 (21.6 ± 18.9)
Statins	13.2 (18.4 ± 17.7)
ACE inhibitors	7.3 (13.7 ± 16.1)
Prevalence of nonadherence (%)†	
Metformin	43
Statins	36
ACE inhibitors	23

*CMG indicates the proportion of days with gaps in medication refills over the days in the observation period. †Nonadherence is defined as CMG >20%.

ACE inhibitors were nonadherent. Also, the average number of drugs for blood pressure among patients treated with ACE inhibitors was higher than the average number of drugs among patients treated with either metformin or statins. When the number of drugs for blood pressure was introduced in the model, the variable was strongly associated with blood pressure and the nonadherence coefficient for ACE inhibitors was not statistically significant when compared with the one in the model that did not include the total number of drugs for blood pressure ($\beta = 0.09$, $P = 0.046$). Therefore, in this population of patients treated with ACE inhibitors and low nonadherence levels, treatment complexity was a much stronger predictor of blood pressure than nonadherence. The amount of HbA_{1c} variability explained by the multivariable linear models including CMG scores is moderate ($R^2 = 24\%$). However, it is slightly greater than the one ($R^2 \sim 10\%$) explained by other studies looking at overall HbA_{1c} predictors (20,21). Those studies included clinical and sociodemographic variables as predictors. Apart from adherence, other factors (duration and severity of disease, lifestyle, and self-management skills), which are not available from automated data sources, are important predictors of HbA_{1c}. However, even when such studies (21) have had some of these measurements available, they have only been able to explain ~10% of the variability. Our findings are consistent with those of Schectman, Nadkarni, and Voss (22), who evaluated the association between adherence to diabetes medications (measured using pharmacy prescription refill data) and HbA_{1c}. After adjusting for clinical and sociodemographic variables, they found that for each 10% increase in adherence, HbA_{1c} decreased by 0.16% ($P < 0.0001$). We are not aware of any other studies among patients with diabetes that look at the associations of claims-based measurements of adherence to lipid-lowering drugs and hypotensive agents with lipid levels and blood pressure, respectively. From the clinical point of view, our results highlight the potential use of claims-based measurements of nonadherence in designing and implementing interventions to improve both adherence and relevant clinical outcomes.

The present study has several limitations. First, patients taking insulin were excluded. Because of the limitations of claims data to measure adherence to insulin, we decided to measure adherence to antidiabetic oral drugs only. However, had data on insulin use been included in the HbA_{1c} model, the estimate of the association between nonadherence and HbA_{1c} could have been different, and the study's external validity would have increased. Nevertheless, the study by Schectman, Nadkarni, and Voss (22) adjusted for insulin use, and the association reported between adherence to oral agents and HbA_{1c} was almost identical to

Table 2—*Association between nonadherence levels and outcomes*

Characteristics/outcome of interest	HbA_{1c}	LDL cholesterol	SBP
n	308	287	384
Pearson's correlation (CMG)*	0.25†	0.32†	0.16†
Spearman's correlation (CMG)*	0.21†	0.30†	0.15†
Outcome levels (means ± SD)			
Nonadherent patients‡	8.5 ± 1.6§	124 ± 34.1§	143 ± 12.9§
Adherent patients	8.0 ± 1.2	103 ± 28.1	138 ± 12.4

*HbA_{1c} levels were correlated with nonadherence to metformin, LDL levels with nonadherence to statins, and SBP levels with nonadherence to ACE inhibitors. CMG indicates the proportion of days with gaps in medication refills over the days in the observation period. †$P < 0.01$. ‡Nonadherence is defined as CMG >20%. §$P < 0.01$ for differences between nonadherent and adherent patients.

Table 3—Multivariable linear regression: adjusted relationship of nonadherence (CMG indices) and clinical outcomes

HbA$_{1c}$ model (adjusted R^2 = 24%) (n = 257)				LDL model (adjusted R^2 = 22%) (n = 215)				SBP model (adjusted R^2 = 17%) (n = 310)			
Predictor	β	SE (β)	P	Predictor	β	SE (β)	P	Predictor	β	SE (β)	P
Intercept	9.263	0.849	0.000	Intercept	101.425	24.919	0.000	Intercept	112.625	8.806	0.000
CMG for metformin* (%)	0.014	0.004	0.000	CMG for statins (%)	0.486	0.115	0.000	CMG for ACE inhibitors (%)	0.058	0.043	0.174
Age	−0.041	0.008	0.000	Age	−0.536	0.216	0.014	Age	0.220	0.072	0.002
African American vs. Caucasian	0.234	0.158	0.141	African American vs. Caucasian	21.588	4.480	0.000	African American vs. Caucasian	0.163	1.419	0.909
Men vs. women	0.243	0.155	0.120	Men vs. women	−7.319	4.232	0.085	Men vs. women	−1.702	1.390	0.222
BMI	−0.007	0.012	0.563	BMI	0.019	0.363	0.958	BMI	0.211	0.103	0.040
Total number of anti-diabetic drugs	0.535	0.113	0.000	Total number of lipid-lowering drugs	−0.944	5.465	0.863	Total number of anti-hypertensive drugs	3.461	0.583	0.000
Number of HbA$_{1c}$ tests	−0.021	0.031	0.508	Number of LDL tests	2.551	0.932	0.007	Number of SBP measurements	−0.739	0.964	0.444

*CMG indicates the proportion of days with gaps in medication refills over the days in the observation period.

the one we are reporting. It is also noticeable that this consistency between study results holds even after considering that, while we only measured nonadherence to metformin, Schectman, Nadkarni, and Voss (22) measured and averaged adherence for all oral antidiabetic agents. Second, we were not able to control for other variables that are associated with the outcomes analyzed, such as lifestyle behaviors (diet and exercise), self-management skills (23), and other medical treatments. Some of these variables are also correlated with adherence and could have confounded the associations observed in our study. Third, we measured both nonadherence and outcomes during the same period (1999–2001). Therefore, we cannot clearly establish the temporal sequence of the estimated associations. However, nonadherence was positively associated with changes in both HbA$_{1c}$ and LDL cholesterol. Also, baseline adherence is the best predictor of future adherence (24), and when we used the last outcome measurement available instead of the average of all measurements available, the results were similar (data not shown).

Claims-based measurements of adherence to medications are not a perfectly valid method. Patients may obtain medications from alternative sources (via dual insurance coverage, samples, etc.) or may temporarily stop a medication because of a physician recommendation or side effects. Also, filling a prescription does not necessarily imply that the medication has been taken. On the other hand, there is no perfect method to measure adherence to medications (5) and claims-based measurements of adherence are not expensive to generate, are available in most managed care systems, and could be integrated within existing information technology (IT) clinical systems. When compared with electronic monitoring, Choo et al. (13) showed that adherence levels determined from pharmacy dispensing records correlate more closely with quantity than with timing of doses. Although not as robust as electronic monitoring, pharmacy refill rates for all antiretroviral medications were also as-

Table 4—Multivariable linear regression: adjusted relationship of nonadherence (CMG indices) and changes in clinical outcomes between the last and first outcome available

Change in HbA$_{1c}$ model* (adjusted R^2 = 49%) (n = 257)				Change in LDL model* (adjusted R^2 = 43%) (n = 215)				Change in SBP model* (adjusted R^2 = 43%) (n = 310)			
Predictor	β	SE (β)	P	Predictor	β	SE (β)	P	Predictor	β	SE (β)	P
Intercept	7.837	1.251	0.000	Intercept	−2.158	24.529	0.930	Intercept	84.979	12.440	0.000
CMG for metformin† (%)	0.015	0.005	0.006	CMG for statins (%)	0.317	0.110	0.004	CMG for ACE inhibitors (%)	−0.005	0.053	0.926
Age	−0.041	0.011	0.000	Age	0.245	0.210	0.244	Age	0.135	0.090	0.135
African American vs. Caucasian	−0.003	0.207	0.987	African American vs. Caucasian	8.273	4.425	0.063	African American vs. Caucasian	−4.946	1.770	0.006
Men vs. women	0.146	0.203	0.474	Men vs. women	−1.162	4.032	0.773	Men vs. women	−3.130	1.728	0.071
BMI	−0.011	0.016	0.485	BMI	0.353	0.343	0.304	BMI	0.071	0.126	0.573
First HbA$_{1c}$	−0.795	0.050	0.000	First LDL	−0.578	0.050	0.000	First SBP	−0.652	0.048	0.000
Total number of anti-diabetic drugs	0.299	0.150	0.047	Total number of lipid-lowering drugs	10.935	5.172	0.036	Total number of anti-hypertensive drugs	0.089	0.753	0.906
Number of HbA$_{1c}$ tests	0.029	0.040	0.471	Number of LDL tests	0.180	0.902	0.842	Number of SBP measurements	−2.140	1.308	0.103

*A positive parameter estimate indicates the outcome worsened (increased) with increments in independent variable. †CMG indicates the proportion of days with gaps in medication refills over the days in the observation period.

sociated with virologic response, and the highest specificity was attained when both the Medical Event Monitoring System and pharmacy refills were used in combination (25).

The consequences of making adherence information available to patients and physicians are unknown. Thus, although some have argued that it would be desirable to introduce adherence measurements into routine clinical practice and that its introduction is feasible at a sustainable cost using administrative data sources (26,27), adherence information could potentially lead to confrontation between clinicians and their patients (28,29). In this sense, especially in chronic diseases like diabetes, even the concept of adherence has been questioned and other terms like self-management have been proposed to better describe the patient-provider relationship (29). Also, recent evidence suggests that giving adherence information alone to clinicians does not improve adherence rates. Instead, adherence rates improved only when physicians received both nonadherence information and training on how to use such information (30,31).

The Chronic Care Model proposed by Bodenheimer, Wagner, and Grumbach (32,33) and the concept of productive physician-patient interactions offer a model of how adherence-to-medications data could be used by both patients and clinicians to improve health outcomes. In a patient-centered model, clinicians do not judge or overreact to patients' final decisions regarding medication adherence. Rather, clinicians try to facilitate an atmosphere where patients feel comfortable enough to report their worries, side effects, and reservations regarding prescribed medications and use empathy, positive reinforcement, and support to motivate the patients toward adherence self-management. The model also provides a framework in which other non-physician health professionals could be involved in monitoring and improving adherence and in which patients could also access the data to self-monitor adherence (self-efficacy). Also consistent with this model would be the use of informatics tools that are accessible to both patients and providers and allow patients to provide feedback data (updated information on drugs being used, remaining pills, over-the-counter drug use, side effects, etc.) to the system to further refine adherence measurements. In light of this potential, the absence of initiatives to implement outpatient computerized prescription systems in the U.S. is surprising (34). A computerized prescription system would connect clinicians IT systems to pharmacy data and would represent a clear improvement over the use of claims data. Data linkage via automated reminders would allow clinicians to monitor and improve adherence in real time and could also contribute to medication safety monitoring in the outpatient setting (35).

Claims-based measures of adherence to medications are associated with health outcomes in patients with diabetes, thus making them relevant measures for intervention. More research is needed on methods to introduce adherence measurements into routine clinical practice and how to use these measurements to effectively improve adherence and health outcomes in chronic care management. Unless feasible adherence measurements are introduced in routine clinical practice, the status quo of low adherence levels and the unavailability of effective tools to improve medication adherence is likely to remain unchallenged.

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