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USING PHARMACY CLAIMS DATA TO EVALUATE ADHERENCE AND
PERSISTENCE WITH PRESCRIBED MEDICATIONS
IN PATIENTS WITH DIABETES MELLITUS

BY
PAMELA J JOHNSON

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN
PHARMACEUTICAL SCIENCES

UNIVERSITY OF RHODE ISLAND

2004

DOCTOR OF PHILOSOPHY DISSERTATION
OF
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UNIVERSITY OF RHODE ISLAND

2004

ABSTRACT

Background: Patients with diabetes mellitus often take prescription medications throughout their lives to maintain glycemic control and/or treat co-morbid conditions such as dyslipidemia. The effect of glycemic control and reductions in lipid levels in the prevention of diabetes-related complications has been demonstrated. However, one important factor affecting the pharmacological management of glycemic control and dyslipidemia is adherence and persistence (i.e., continuous use) with treatment.

Objective: The objective of this research was to 1) use measurements of medication availability, gaps in therapy, and surplus medication to assess adherence with sulfonylurea medications, evaluate the relationship between these measures, and examine patient- and medication-related characteristics that may influence adherence with sulfonylureas; 2) evaluate adherence with lipid-lowering medications in patients with diabetes mellitus and examine the effect of patient- and medication-related characteristics on adherence; 3) assess persistence with lipid-lowering medications and evaluate patient- and medication-related characteristics that may influence discontinuation of lipid-lowering treatment in patients with diabetes mellitus.

Data Source/Methods: Analyses were performed using pharmacy claims data. The data source provided all prescription claims (288,171 dispensations) between April 27, 1997 and May 16, 1999 for 4,503 patients with diabetes. The cohort for the first study was comprised of patients prescribed sulfonylurea medications while new users of lipid-lowering medications comprised the study population for the other two studies. Adherence was measured by continuous and dichotomous measurements of medication availability, gaps in therapy, and surplus medication while persistence was defined as

continuation of therapy with a sufficient quantity of medication to cover the observation period. Regression models were used to analyze the effect of patient-related and medication-related characteristics and adherence and persistence with medications.

Results: Sulfonylurea medication was available to patients for an average of 89% of days during a 12-month period. This continuous measure of medication availability correlated with measures of gaps in therapy and surplus medication which showed that on average, patients had 15% of days in which medication was not available and 5% of days with surplus medication during the 12-month study period. Interestingly, rates of adherence were similar whether nine or 12 months of prescription claims were examined, suggesting that an additional three months of data did not add any information to the assessment of medication adherence. None of the patient- or medication-related characteristics in the multivariate regression model significantly influenced adherence with sulfonylureas ($F_{5,387}=0.59$; $p=0.7065$).

Approximately 66% of patients filled enough lipid-lowering medication prescriptions to cover at least 80% or more days in a nine-month observation period. Adherence differed by the class of lipid-lowering medication prescribed at the index date: patients prescribed statin and non-statin medications had an average Continuous multiple-interval measure of Medication Availability (CMA) of $84.1\% \pm 22.3\%$ and $70.0\% \pm 31.7\%$, respectively ($p=0.2627$). Adherent patients ($\geq 80\%$) were less likely to be prescribed insulin therapy (OR=0.304, 95% CI=0.114, 0.815, $p=0.0180$) and more likely to be prescribed statin medications (OR=4.709, 95% CI=0.996, 22.268, $p=0.0506$) compared with non-adherent patients. No other study factors significantly influenced adherence with lipid-lowering therapy.

Of the 165 patients prescribed statin medications, 74% persisted with treatment over six months, 59% over 12 months, and 46% over 18 months of observation. At six months, 60% of patients persisted with non-statin treatment while only 26% of patients were persistent over 12 and 18 months of observation. Approximately 26% of patients who discontinued treatment did so after the initial dispensing. One in 10 patients switched to another lipid-lowering medication: the majority of switches were to another medication within the same class. Compared with patients prescribed statins, patients prescribed non-statin medications were more than twice as likely to discontinue treatment (HR=2.240; 95% CI= 1.260, 3.982; $p=0.0060$). Age, gender, type of health plan, number of concomitantly prescribed medications and antidiabetic medication regimen, were not found to be a significant influence on discontinuation of lipid-lowering therapy.

Conclusions: Patients with diabetes obtained less medication than prescribed over six-, nine-, 12- and 18-month periods of observation. Measures of medication availability, gaps in therapy, surplus medication and persistence provide an overall picture of medication adherence. The findings of this research provide insight into sub-optimal adherence and persistence with antidiabetic and lipid-lowering medications among patients with diabetes mellitus. These observations highlight the need for health care providers to establish a partnership with patients to improve adherence and persistence with medications.

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PREFACE

This dissertation is organized using the manuscript format. Part 1 consists of three research studies that form the main body of the dissertation. Part 2 contains appendices that provide details required by the University of Rhode Island but are not usually presented in publications.

PART 1

Study 1

Using Prescription Claim Records to Assess Measures of Medication Adherence (Medication Availability, Gaps, and Surplus) with Sulfonylureas in Patients with Diabetes Mellitus

Study 2

Using Prescription Claim Records to Evaluate Adherence with Lipid-lowering Medications in Patients with Diabetes Mellitus

Study 3

Using Prescription Claim Records to Evaluate Persistence with Lipid-lowering Medications in Patients with Diabetes Mellitus

PART 2

Appendix A. Background and Review of the Problem

Appendix B. Details of Methodology

Appendix C. Confidentiality of Data

Appendix D. Overview of Major Findings

Appendix E. Interventions to Improve Adherence with Prescribed Medication Regimens for Patients with Diabetes Mellitus

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Study 1

Using Prescription Claim Records to Assess Measures of Medication Adherence (Medication Availability, Gaps, and Surplus) with Sulfonylureas in Patients with Diabetes

ABSTRACT

Background: Medication adherence with antidiabetic medications is key in the multi-faceted management of diabetes to achieve glycemic control. Estimates of adherence with sulfonylureas in patients with diabetes mellitus vary from 31% to 83% depending on the study. Although there is no standard way to evaluate medication adherence, adherence is generally based on a continuous measure of medication availability that is often dichotomized using either an 80% or 90% level. Few studies analyze gaps in therapy and surplus medication.

Objective: The objective of this study was to measure adherence with sulfonylureas based on continuous and dichotomous measures of medication availability, gaps, and surplus and evaluate the relationship between these measures. In addition, patient-related and medication-related characteristics that may influence adherence with sulfonylureas in patients with diabetes mellitus were examined.

Methods: This was a retrospective analysis of six-, nine-, and 12-months of prescription claim records in patients with diabetes dispensed sulfonylureas. Medication adherence was assessed by three continuous multiple-interval proportions: the total number of days in which medication was available to the patient (CMA), gaps in therapy (CMG), and surplus medication (CMOS) which were dichotomized based on clinically relevant levels. Medication availability of sulfonylureas during the 12-month period of observation was modeled as a function of clusters of patient- and medication-related characteristics.

Results: A total of 988 patients with diabetes (58% males; mean age, 59.2 ± 10.9 years) had at least two prescription claims for sulfonylurea medications from December 1, 1997 through December 31, 1998. Overall, sulfonylurea medication was available for an average of 89% of days during a 12-month period. This continuous measure of medication availability correlated with measures of gaps in therapy and surplus medication which showed that on average, patients had 15% of days in which medication was not available and 5% of days with surplus medication during the 12-month observation period. Measures of medication availability were significantly correlated with gaps in therapy ($r = -0.95$) and surplus medication ($r = 0.41$) ($p < 0.0001$). Continuous and dichotomous measures of adherence with sulfonylureas were significantly correlated with the strongest relationships observed between CMA and an 80% level of adherence ($r = 0.82$) and CMG and a 20% level of gaps in therapy ($r = 0.84$) ($p < 0.0001$). Interestingly, rates of adherence were similar whether nine or 12 months of prescription claims were examined, suggesting that an additional three months of data did not add any information to the assessment of medication adherence. None of the patient-related (age, gender and type of health plan) or medication-related (number of concomitantly prescribed medications and number of sulfonylurea pills per day) characteristics in the multivariate regression model significantly influenced adherence with sulfonylureas in our patient population ($F_{5,987} = 0.59$; $p = 0.7065$).

Conclusions: Patients with diabetes obtained less sulfonylurea medication than prescribed over six-, nine-, and 12-month periods of observation as evidenced by low measures of medication availability and surplus and a high proportion of gaps in therapy. All these measures can be used alone but as illustrated by the findings of this study, the combination of all three measures of adherence concurrently provides an overall picture of medication adherence. Understanding the integral components,

such as age and medication-related characteristics, associated with adherence is a crucial component of designing effective diabetes management plans. Further research is needed to evaluate the appropriate level of adherence associated with glycemic control in patients with diabetes.

Key Words: sulfonylurea, diabetes, adherence, CMA, CMG, CMOS, medication gap, medication availability, medication surplus

INTRODUCTION

Since Hippocrates, physicians have been plagued by concerns over patients' adherence to medication regimens.¹⁻³ In general, the scope of nonadherence ranges across all age groups and medical disciplines and can be influenced by many factors including tolerability of the medication, complexity of the medication regimen, cost and convenience of the therapy, and characteristics of the patient, medical system and physician.¹⁻⁴ Adherence with prescribed medications is an important component of disease management especially for patients with chronic diseases who must often obtain prescription refills throughout their lives.⁵

Adherence^{*} has been defined as the extent to which a patient freely chooses to follow physicians' orders (i.e., by taking medications or modification of lifestyle changes such as diet and exercise) with medical advice.⁶ The term adherence captures the increasing complexity of medical care by characterizing patients taking a more active and voluntary role in defining and pursuing goals for their own medical treatment.³ Adherence consists of the initial fill of the prescribed medication, consumption of the medication, and acquisition of refills.

In spite of pharmacotherapeutic advances, a major barrier to management of diabetes is the extent to which individuals adhere to their prescribed treatment regimens.⁷ Patients with diabetes mellitus are at particular risk for non-adherence with antidiabetic treatment regimens,⁸ which may have a deleterious effect on glycemic control. Estimates of adherence with sulfonylureas vary widely from a low of 31% to 83%,^{7, 9-11} depending on the methodology employed.

There are several ways to evaluate adherence in a patient population. Indirect

^{*} Adherence and compliance are used interchangeably in the literature. Although the term compliance has negative connotations, it is still in use and will be referred to in this study if utilized in the cited published material.

methods include patient interviews or questionnaires, pill counts, review of prescription records and claims, and electronic monitoring devices, while direct methods of adherence include pharmacologic markers and direct observation of the patient taking the medication.¹²⁻¹⁴ The method chosen to measure medication adherence can significantly affect the results.¹⁵ For example, the rate of adherence with sulfonylureas was 83% when prescription records were examined¹¹ while rates of 79% and 97% were observed using Medication Event Monitoring System (MEMS) data and pill count, respectively.¹⁶ While no single method of adherence is appropriate for all settings or outcomes, database records of dispensed prescriptions may represent one of the most accurate methods of assessing medication utilization in a patient population.^{17, 18}

Several investigations have compared use of medications measured in pharmacy records with other sources of medication use. Pharmacy data and self-administered questionnaires showed good agreement for antihypertensives, lipid-lowering medications, oral antidiabetic medications, and oral contraceptives (kappa values between 0.6-0.8).¹⁹ Pharmacy records were a reliable source of medication exposure as estimated in a home-based inventory.²⁰ Refill compliance was significantly correlated (Pearson correlation coefficient of 0.31, $p < 0.05$) with MEMS data, specifically with tablet compliance (measured as the percentage of tablets used).²¹ Grymonpre and colleagues found no difference in mean adherence rates, by medication, as estimated by pharmacy claims data or self report.²²

Studies have found that measures of medication adherence (i.e., measures of medication availability and gaps in therapy) based on pharmacy claims were a reliable source of medication exposure. Correlations between medication adherence, using measures of medication availability or gaps, and measures of drug exposure (e.g., phenytoin and digoxin drug levels) and medication effects (e.g., blood pressure)

were statistically significant, with Pearson correlation coefficients between 0.30 and 0.42.¹²

Thus, pharmacy claims provide a reliable tool to measure adherence with long-term medications. Although prescription refill data does not verify administration of the therapy regimen, it does signify availability of medication. This method of assessing adherence is based on the assumption that if the medication is not available for use, patients clearly cannot adhere with the medication regimen.

Various measures have been developed to assess adherence with medications using pharmacy claims although a gold standard does not exist. The best measure likely depends on the intended use of the data. For example, in order to formulate patient diabetes education programs, a finding of low medication adherence measured by gaps in therapy may suggest that a refill reminder program is needed.

Measurements of medication adherence are usually classified three ways: 1) single-interval versus multiple-interval; 2) continuous versus categorical; and 3) measures that assess availability of medication, gaps in therapy or surplus/oversupply (i.e., stockpiling) of medication. Categorizations of the total number of days supply have been used as a surrogate measure of adherence.⁷ For all of these classifications, the time period of observation is a principal component.

Most often, adherence with medications is assessed on multiple-intervals, as the degree of adherence is not a single event but an accumulation of many pill-takings or neglects. Generally, a continuous measure of adherence is calculated by dividing the sum of the days supply between the first and last fill by the number of days from first to last fill of medication (i.e., the number of days in which medication is available for use). This measurement, termed Medication Possession Ratio (MPR) or Continuous multiple-interval measure of Medication Availability (CMA) (hereafter,

measures of medication availability will refer to CMA), provides an overall assessment of the amount of medication available for use during a specified time period under observation. The conclusions based on an analysis of CMA is dependent upon the choice of denominator as the time period used in the denominator can be either the length of therapy which is individualized or calendar time (e.g., 365 days for a 12-month assessment) which is the same for every person in the study population. When length of therapy is used as the denominator, the continuous measure of adherence is affected by gaps and oversupplies of medication. In contrast, using calendar time, adherence is affected both by medication gaps and oversupply as well as discontinuations of treatment.²³

This continuous measurement is frequently converted to a dichotomous variable (e.g., adherent or non-adherent^{9, 24, 25} or acceptable or fair/poor²⁶) based on a choice of various levels (e.g., 80%, 90%, or 95%). However, an explanation of the rationale for choosing a particular level is often not provided. While the convention has been to define good adherence as carrying out either 80% or 90% of the recommended behaviors, there is no standard on which to base this level of adherence with many medications.^{27, 28} In a few cases, medication-specific or condition-specific levels for taking medication have been defined. Consumption of at least 80% of prescribed antihypertensive medication was sufficient to maintain control of blood pressure.^{29, 30} Higher adherence rates ($\geq 90\%$) with antiretroviral therapy have been associated with virologic success rates.³¹⁻³⁴ Such levels are difficult to determine as they must take into account the likelihood, clinical consequences, and time course of treatment failure.³⁵

Supplementing analyses of medication availability with an analysis of gaps and surplus medication indicates whether the patient is actually taking the medication as prescribed.³⁶⁻⁴⁰ Gaps in therapy or stockpiling of medication may be due to

reasons of patient convenience (e.g., a patient-initiated medication holiday) or dosage adjustments. For example, patients may reduce their dosage thus extending the period of medication-taking beyond the estimated depletion date (i.e., the fill date of a prescription claim plus the days supply). In this situation, the patient is taking medication throughout the time period without any actual gaps in medication use. Thus, not all gaps represent non-adherence with medication.

Finally, researchers have measured medication adherence using different time periods of observation ranging from months to several years. When reporting adherence with sulfonylureas as a continuous measure, the mean proportion of time with available medication varies greatly: 77% over a 4-month period,⁴¹ 49% to 80% over a one-year period,^{10, 42, 43} and 42% to 83% over a two-year period.^{10, 11, 43} While variations in study design, patient population characteristics, and the definition and actual calculation of the continuous measure of medication availability may account for the wide range of rates, the length of observed time is an important component in any assessment of medication adherence.

While many published reports have studied the accordance between methods of medication adherence,^{16, 21, 22, 44} to the best of our knowledge, no study has examined the relationship between the various types of measures of medication adherence using pharmacy claims data. Recognizing the potential limitations of evaluating medication adherence by a single measure, this study was designed to measure adherence with sulfonylureas based on continuous and dichotomous measures of medication availability, gaps, and oversupply and evaluate the relationship between these measures using six, nine, and 12 months of pharmacy claims data. In addition, this study examined factors that may influence adherence with sulfonylureas in patients with diabetes mellitus.

METHODS

Study Design

This study was a retrospective analysis of adherence with sulfonylurea medications utilizing pharmacy claim prescription records in a cohort of patients with diabetes.

Dataset

Data examined in the analysis were obtained from 198 Consumer Value Stores (CVS) pharmacies located in Pennsylvania that provided prescription medications for 4503 patients with diabetes identified by specific therapeutic classes (insulins, oral antidiabetic medications-sulfonylureas and other oral antidiabetic medications) between April 27, 1997 and May 16, 1999. Patients were either enrolled in a nurse-based diabetes management plan or local/state/federal programs or paid for their prescriptions with cash payments.

This prescription claims data extract includes records of dispensed outpatient pharmacy prescription records for all prescriptions. The following information was obtained from the CVS dataset for this analysis: patient characteristic variables such as birth date, gender, and health plan agency as well as prescription-related variables including quantity of medication dispensed, days supply of medication dispensed, and date the prescription was dispensed. No personally identifying information was provided.

Sulfonylurea Medications Available in Dataset

Each sulfonylurea medication in the database was categorized into 1 of 3 categories: (1) first-generation sulfonylurea medications: acetohexamide (Dymelor®), chlorpropamide (Diabinese®), tolazamide (Tolinase®), tolbutamide (Orinase®); (2) second-generation sulfonylurea medications: glipizide (Glucotrol®), Glucotrol XL® and

glyburide (DiaBeta®, Glynase®, Micronase®); and (3) third-generation sulfonylurea medication: glimepiride (Amaryl®).

Study Population

The study population was drawn from 2770 persons who had prescription fills for sulfonylurea medications in the database. Patients whose records were eligible for inclusion were persons ≥ 18 years of age who (1) filled a prescription for a sulfonylurea medication during the index window of December 1, 1997 to December 31, 1997 (n=1411); (2) were dispensed at least two fills of a sulfonylurea medication (n=1372); and (3) had continuous dispensations of prescriptions at the pharmacy (n=1296). A continuous dispensation of prescriptions was confirmed by the dispensation of any medication six months prior to the index date and in the twelfth month after the index date (i.e., the date of the sulfonylurea prescription claim during the index window). Patients dispensed multiple dosages of the same sulfonylurea were excluded from the analyses (n=23).

Data Analysis

Prescription claims for all patients who satisfied the inclusion/exclusion criteria were examined for the 12-month period from December 1997 through December 1998. This period was selected to allow for a sufficient amount of data (i.e., a “washout” period prior to the index date and at the end of the observation period to eliminate time periods of potentially incomplete data). Subsequent analyses examined claims for a six- and nine-month time period; since the inclusion criterion of at least two refills was not met, 8 (0.8%) and 3 (0.3%) patients were excluded from the six- and nine-month analyses, respectively.

The most commonly prescribed sulfonylureas were the second-generation sulfonylureas. Due to the small proportion of patients prescribed first- or third-generation sulfonylurea medications (9%), comparisons of this group of patients

with patients prescribed second-generation sulfonylureas (91%) lacked statistical power. Thus, categorization of sulfonylurea medication was not evaluated in the analysis.

Dataset Preparation

Prior to analysis, the dataset was checked for outliers for the variable days supply as it was an integral component of all calculations of medication adherence. Days supply, presumed to be incorrectly recorded for two patients, was imputed based on the days supply recorded for other sulfonylurea dispensations in the database. Patients with incomplete records (i.e., missing transaction dates) for sulfonylurea medications were excluded from the analysis (n = 285).

Measures of Adherence

Measures of adherence selected for evaluation in this study included continuous and dichotomous measures of medication availability, deficits and oversupply based on research published by Fairman and Motheral²³ and Steiner and Prochazka.¹⁸ Table 1-1 describes the measures of adherence evaluated in this study along with the formulae used in the calculations. Continuous measures of medication availability, gaps in therapy, and surplus medication were expressed as a percentage. The days supply for the last prescription fill was not included in our calculation of CMA as there was no way to determine whether the patient continued to take the medication after the last prescription fill.

To assess CMA as a dichotomous measure, CMA was categorized into levels of 80% and 90% adherence as these levels are commonly reported in the literature and clinical judgment that adherence with sulfonylureas is essential to maintain glycemic control. That is, patients who were dispensed enough sulfonylurea medication to cover at least 80% (or 90%) of days of therapy were classified as adherent. Since this calculated ratio may exceed 100% if a patient obtains refills

before their supply has been exhausted, patients with a CMA >100% were classified as over-adherent.

Continuous multiple-interval measures of gaps in therapy or surplus sulfonylurea medication included CMG and CMOS, respectively. To evaluate these measures using dichotomous categorizations, levels of 10% and 20% (i.e., equivalent to three and six days per month) were selected based on a previous report of gaps and oversupply with sulfonylurea medications^{18, 36} and clinical judgment about the impact of missed doses or surplus sulfonylurea medication in this patient population.

Predictive Variables of Interest

The relationship of medication adherence and patient-related and medication complexity characteristics has been published extensively even though the findings are inconsistent.^{11, 13, 36, 45-47} Several of these factors, such as age, gender, health plan agency, number of prescription medications, and use of insulin, were examined in the present study. Dosing instructions were unavailable in this database to calculate daily dose, another potential predictive factor, therefore a surrogate measure, the number of sulfonylurea pills^{*} per day, was examined. These factors were constructed from the prescription profile of each patient and classified as patient-related characteristics (age, gender, health plan agency) or medication-related characteristics (number of sulfonylurea pills per day, use of insulin, and number of concomitantly prescribed medications).

Age, a continuous variable, was based on the transaction date for the sulfonylurea prescription filled during the index window. The patients' health plan, used to acquire sulfonylurea medication during the index window, was categorized as

^{*} Terminology used in this study to encompass all formulations of sulfonylurea medications (e.g., capsules, tablets)

either a nurse-based diabetes management plan or other (e.g., local/state/federal programs or cash payments).

Use of insulin was based on whether a patient was prescribed insulin during the observation period (yes or no). The number of sulfonylurea pills prescribed per day was calculated by dividing the quantity of medication dispensed by the days supply and dichotomized as 1, >1. The number of concomitantly prescribed medications included all medications (except antidiabetic medications and supplies) dispensed during the observation period and was analyzed as a continuous variable.

Univariate Analysis

Descriptive statistics were used to determine patient- and medication-related characteristics. The data was presented as mean $\pm$ SD (range) for continuous variables and frequencies (percentage) for categorical variables. Continuous and dichotomous measures of medication adherence were evaluated overall and by the time period of observation (i.e., six-, nine-, and 12-months). The frequency distribution of the medication adherence measurements CMA, CMG, and CMOS are presented in Figures 1A-1 to 1A-3. Correlation coefficients were computed to determine the relationship between the measures of medication availability, gaps in therapy, and surplus medication.

Multivariate Analysis

To analyze the effect of various factors that may influence adherence with sulfonylurea medications over 12 months, multiple regression models were built using CMA as the continuous dependent variable. This measure of medication availability was chosen as the dependent variable as it provides an overall view of adherence and is affected by gaps and surplus medication from fill to refill. Regression diagnostics included assessing the frequency distribution of the dependent variable, collinearity of study variables, the influence of outliers, and analyzing residuals.⁴⁸

As recommended by Hatcher and Stepanski,⁴⁹ the possible correlations between the study variables were assessed using the PROC CORR procedure.⁵⁰ These correlations provided an assessment of the bivariate relationship between the dependent variable and the predictor variables. Correlation coefficients are shown in Table 1A-1 and will be described in the Results section.

The presence of collinearity between the independent variables was examined using the methodology of Kleinbaum and colleagues⁴⁸ by the PROC REG procedure.⁵⁰ Independent variables with a condition index greater than 30 (moderate to severe collinearity) and proportion of variations greater than 0.5 were further examined for collinearity with other independent variables. When there was collinearity between two variables, the variable showing the strongest association with adherence with sulfonylureas was kept in the model. None of the six predictive factors had a proportion pattern that exhibited collinearity with another variable (Table 1A-2).

Simple descriptive statistics were computed for the dependent variable, CMA, and continuous independent variables to assess the influence of potential outliers. The five lowest and five highest values for these variables and frequency histograms were examined to detect potential data entry errors and outliers. Several outlying observations were detected for CMA and the number of concomitantly prescribed medications that upon further examination did not appear to be data errors but correct values for these variables. Thus, all observations remained in the dataset for analysis.

Two clusters, patient-related and medication-related characteristics, were entered into the multiple linear regression model of adherence with sulfonylureas in a hierarchical approach.^{11, 49, 51} This approach provided an estimate of the relative contribution of each cluster in the explanation of the variance in the dependent

variable, CMA. The beta weights (standardized regression estimates) and standard error are presented for each variable along with the F-value and adjusted R^2 for the entire model. Multiple regression analysis was performed with the PROC REG procedure.⁵⁰

To assess the appropriateness of the fitted multiple linear regression model, a set of standardized and studentized residual plots were analyzed to check the validity of the regression assumptions (Figures 1A-4 and 1A-5). Figures 1A-6 and 1A-7 show plots of studentized residuals against the continuous independent variables, age and number of concomitantly prescribed medications, respectively. These tables show a random scatter of the data points above and below the line $e = 0$ with almost all the data points being within the band defined as $e = \pm 2s$ as expected when the assumptions are satisfied.

The *a priori* alpha level of significance was set at $p < 0.05$. All data analyses were conducted using SAS release 8.2.⁵⁰

RESULTS

Description of the Study Population

A total of 2770 patients received prescriptions for sulfonylurea medications. Of these patients, 1644 were excluded because there were no prescription claims for a sulfonylurea medication between December 1, 1997 and December 31, 1997 or had incomplete transaction dates for all sulfonylurea prescription claims during the observation period; 39 did not have at least two prescription claims for sulfonylureas during the observation period; 76 patients did not have continuous dispensations of prescriptions at the pharmacy (i.e., a prescription claim for any medication in the six months prior to and 12 months after the index date); and 23 patients were prescribed

more than one sulfonylurea dosage (Figure 1-1). A total of 988 patients were included in the study analyses: 571 (58%) males and 417 (42%) females with an average age of 59.2 ± 10.9 years (range, 22 - 88 years) (Table 1-2). Over half (54%) were enrolled in a nurse-based diabetes management plan.

The most commonly prescribed sulfonylureas were the second-generation sulfonylureas: glyburide (57%) and glipizide (35%), 7% of patients were prescribed glimepiride and 2% prescribed a first-generation sulfonylurea. More than half (59%) of the patients were prescribed a dose of more than one sulfonylurea pill per day. The majority of patients (97%) did not receive a concomitant prescription for insulin during the observation period. During the observation period, patients were prescribed an average of 8 ± 7 medications (range, 0 - 44) other than antidiabetic medications and supplies.

Evaluation of Single-Interval and Multiple-Interval Measures of Adherence with Sulfonylureas

The data illustrated in Table 1-3 is representative of the array of single-interval and multiple-interval measures of medication adherence calculated in this study. Single-interval measures of medication availability (CSA), gaps (CSG), and oversupply (CSOS) provide an accurate representation of adherence with sulfonylureas from fill to refill. These measures allow an individual assessment of medication adherence and highlights particular times of non-adherence with medication, for example, patient-initiated medication holidays or dose reductions or overdoses. In contrast, multiple-interval measures of medication availability (CMA), gaps (CMG), and oversupply (CMOS) provide a broad assessment of medication adherence over an extended period of time.

The data demonstrates single- and multiple-interval measures of adherence with sulfonylureas presented for an individual patient. Over a period of 354 days, this

patient received 45 days of medication from fill to fill (i.e., interval) that resulted in a total of 225 days supply of sulfonylurea medication. There were three intervals in which medication was not available for a total of 169 days whereas in the other two intervals, there were 40 days of surplus medication. Based on examination of single-interval measures of adherence, this patient had a range of 23% to 214% of days in which medication was available, 6% to 77% of days with gaps in therapy, and 55% to 114% of days with surplus medication. These single-interval measures show a wide range of adherence during the 354 days of therapy compared to the multiple-interval measures that demonstrate a single assessment of adherence during this time period.

Upon closer examination, there was one interval in which a 150 day gap in therapy was observed. The length of this gap should prompt a discussion between the patient and health care provider to 1) determine the cause and 2) mutually agree on a plan to improve adherence. In comparison, a multiple-interval analysis of gaps would show that gaps in therapy were occurring but would not demonstrate the length or the number of gaps.

In describing the results of this study, the focus will be on the multiple-interval measures of adherence as they are more descriptive when evaluating overall adherence in patient populations.

Evaluation of Continuous and Dichotomous Measures of Adherence with Sulfonylureas

Overall, patients had an average period of observation (i.e., date from first sulfonylurea dispensation to last fill in the observation period) of 315 ± 52 days (range, 32 to 364 days). Based on CMA, medication was available for an average of $89\% \pm 18\%$ (range, 10% to 150%) of days during the 12-month observation period (Table 1-4). When CMA was dichotomized, 78% and 66% of patients had sufficient

medication to cover at least 80% and 90% of days in the observation period, respectively.

An analysis of gaps in therapy supports the findings of medication availability. Medication was not available for an average of $15\% \pm 16\%$ of days (range, 0 to 90%) during 12 months. Thus, patients had an average of 47 (i.e., $15\% \times 315$ days) days with gaps in therapy with nine (1%) patients prescribed sulfonylureas during the 12-month observation period having no gaps in therapy, 23 (2%) had one gap and the majority (956 (97%)) of patients had more than one gap. Some of the gaps were brief: 71% of the gaps lasted for seven days or less while 17% of the gaps lasted more than two weeks. An analysis of dichotomous measures of gaps in therapy showed that 46% of patients had $\geq 10\%$ of days during the 12-month observation period not covered by medication. That is, these patients had gaps in sulfonylurea therapy for three or more days per month. Almost 1 in 4 patients had gaps in therapy for six or more days per month.

During the observation period, the mean proportion of days of surplus medication (CMOS) was $5\% \pm 7\%$ days (range, 0 to 80%) among patients prescribed sulfonylurea medications. Overall, 146 (15%) of patients in the study population had no surplus supply of sulfonylurea medication during the 12-month observation period while the majority of patients (85%) had surplus of sulfonylurea medication. Overall, 22% of medication oversupplies covered more than seven days. Dichotomous measures demonstrated that 15% of patients had $\geq 10\%$ of days with surplus medication while 5% had $\geq 20\%$ of days during the observation period with excess sulfonylurea medication. Another way to assess surplus medication was by examining the proportion of patients with CMA $>100\%$. During the 12-month observation period, 20% of patients had a CMA $>100\%$ indicating acquisition of more sulfonylurea medication than prescribed (i.e., stockpiling).

Evaluation of the Relationship between Measures of Adherence with Sulfonylureas

As shown in Tables 1-5a to 1-5d, correlations for all continuous and dichotomous measures were statistically significant ($p < 0.0001$). Measures of medication availability were significantly correlated with measures of gaps in therapy ($r = -0.95$) and surplus medication ($r = 0.41$) (Table 1-5a). Similarly, measures of gaps in therapy were significantly correlated with measures of surplus medication ($r = -0.20$).

While the continuous measure of medication availability, CMA, was correlated with both dichotomous categorizations, the strongest relationship was observed between CMA and adherence dichotomized with the 80% level ($r = 0.82$) (Table 1-5b). The continuous measure of gaps in therapy was strongly associated with the 20% level of dichotomization ($r = 0.84$) while the correlation between dichotomous categorizations and the continuous measure of surplus medication (CMOS) were similar ($r \leq 0.79$) (Tables 1-5c and 1-5d).

Evaluation of Measures of Adherence with Sulfonylureas Grouped by Time of Observation

To evaluate the effect of observed time on the measures of adherence, subsequent analyses examined prescription claims for six and nine months. Table 1-6 shows a comparison of the adherence measures obtained from these two time periods alongside the measures from the 12-month observation period. Since calculation of measures of adherence require at least two prescription claims during the period of observation, eight and three subjects had only one prescription claim for sulfonylurea medication and were excluded from the six and nine month analyses, respectively.

As might be expected, as the length of follow-up time increased, measures of available medication decreased while measures of gaps in therapy and oversupplies of medication increased. Interestingly, findings from nine and 12 months of

observation were similar suggesting that an additional three months of claims data was not adding any information to the overall picture of adherence in our patient population.

Based on CMA, the average proportion of days with available sulfonylurea medication was statistically lower over six-, nine-, and 12-months of observation: 92%, 90%, and 89%, respectively ($p = 0.0137$). Similar, small decreases were observed when medication availability was assessed using the dichotomous measures of 80% and 90% levels of adherence. A statistically significant difference was observed in the three periods of observation when patients were classified as over-adherent (CMA >100%) ($p=0.0057$).

Continuous measures of medication gaps were lowest with six months of observation as compared to examinations of nine and 12 months of prescription claims. An average of 13% of days with gaps in therapy was observed during six months of observation while 15% of days had gaps when the observation time increased to nine and 12 months ($p=0.0195$). Similar findings were observed for dichotomous measures of medication gaps. In contrast, continuous and dichotomous measures of surplus medication did not seem to be affected by the amount of time under observation.

Predictive Factors of Adherence with Sulfonylureas using a Continuous Measure of Medication Availability (CMA)

Predictive factors were analyzed by both bivariate correlation and multiple linear regression. Due to the disproportionate number of patients in the categorizations of concomitantly prescribed insulin, the variable insulin use was not included in the regression modeling. As shown in Table 1A-1, correlations for all variables were non-significant ($p \geq 0.2441$). The strongest relationship was observed between CMA and age ($r = 0.03709$).

Table 1-7 presents the results of the hierarchical multiple regression model. The overall model containing the patient-related characteristics (e.g., age, gender, and health plan agency) cluster did not predict adherence with sulfonylurea medications ($F_{3, 987} = 0.86$; $p=0.4632$). The variance explained by this cluster was 0.04%. The addition of medication-related characteristics in the model increased the adjusted R^2 to 0.21%. However, none of the patient- or medication-related characteristics in the full model significantly influenced adherence with sulfonylureas in our patient population ($F_{5, 987} = 0.59$; $p=0.7065$).

Beta weights (standardized multiple regression coefficients) of the full model were reviewed to assess the relative importance of the variables in the prediction of CMA. In the final model, none of the study factors significantly influenced adherence (i.e., availability of sulfonylurea medication) in this patient population. Although not a significant predictor of medication availability in this patient population, increasing age by one-year increments led to an increase in the rate of adherence of approximately 4.1% ($p=0.2072$). An increase in the number of concomitantly prescribed medications had an inverse relationship with CMA ($p=0.5985$). Higher rates of adherence were also observed for males, patients enrolled in a nurse-based diabetes management plan, and patients prescribed one sulfonylurea pill per day ($p\geq 0.3152$).

DISCUSSION

It is well known that adherence with prescription medication is complex. Despite its complexity, adherence is a challenging area of investigation from the variety of measures of medication adherence to the numerous methods used for evaluation. No standard way of measuring or reporting medication adherence has been established.

In the present study, we were able to evaluate adherence with sulfonylureas and establish the relationship between measures of adherence based on their ability to quantify medication availability, gaps, and surplus medication. Since the period of observation is an integral component of adherence measures, adherence with sulfonylurea medications using six and nine months of prescription claims was compared with the primary 12-month period of observation.

Adherence with Sulfonylureas

During the 12-month observation period, patients had an average 89% of days covered with available medication. Thus, most patients obtained less medication than prescribed. Analyses of gaps and surplus medication were in accord with this finding. Patients had an average of 15% of study days in which medication was not available while there was surplus medication for 5% of days. That is, patients had an average of 47 days without medication and 16 days with surplus sulfonylurea medication over a 12-month period. Although information on why gaps and surplus medication occurred was not available, these findings have clinical relevance as non-adherence with sulfonylureas or over dosages may have a deleterious effect on glycemic control and cause adverse effects.

Our findings were similar to those reported by Morningstar and colleagues.³⁶ To the best of our knowledge, this is the only published report that examined gaps and oversupply of sulfonylureas along with medication availability. Prescription claims in 3,358 patients in a senior prescription medication insurance program under Medicare in Nova Scotia were evaluated for a three-year period of observation. Although these rates were not stratified by prescription medication, this study found that patients prescribed first- or second-generation sulfonylureas or biguanides had an average of 86% of days with available medication, 16% of days not covered by medication, and an average of 3% of days with surplus medication.

Relationship between Measures of Adherence with Sulfonylureas

As illustrated in Table 1-3, examination of multiple-interval measures provide an assessment of adherence over an extended period of time while single-interval measures allow a detailed assessment of adherence from medication fill to fill (i.e., interval). By examining single-interval measures of adherence, we observed a gap of 150 days without medication during one interval. While only a small proportion of medication refills are dispensed exactly on the date of depletion,⁵² gaps in therapy may be caused by dosage adjustments, patient-initiated medication holidays, related to a cost barrier or simply forgetfulness whereas over-adherence with sulfonylureas may lead to serious adverse effects such as hypoglycemia. Identification of lengthy periods of gaps in therapy or stockpiling medication should encourage dialogue between the patient and health care provider to ascertain the cause and reach agreement on a strategy to improve medication adherence. Thus, single-interval measures are meaningful to assess medication adherence on an individual basis while multiple-interval measures are advantageous for assessing medication adherence in a patient population over a specified period of time.

Often, researchers choose to describe medication adherence with dichotomous measures even though there is no standard of an “acceptable” level of medication adherence. One study reported that HbA_{1c} was 0.19% lower for each 10% increase in adherence with oral antidiabetic medications ($p < 0.0001$) in a population of 829 patients enrolled in a university-based internal medicine clinic.⁵³ Dichotomous levels of 80% and 90% adherence were selected for this study based on existing literature and on clinical judgment about the impact of missed doses or surplus sulfonylurea medication to the patient with diabetes. While these measures give a broad view of medication adherence, further research is needed to establish the level

of adherence with antidiabetic medications associated with maintenance of optimal glycemic levels in patients with diabetes.

Relying solely on a single measure of medication adherence, such as CMA, provides the health care provider one-dimension of information regarding appropriate and adequate use of a medication within a population.¹⁵ As illustrated in this study, by combining assessments of medication availability with analyses of gaps in therapy and surplus medication, the scope of the problems of non-adherence with sulfonylurea medications is more defined. All of these dimensions are equally important in evaluations of medication adherence.

While we observed a statistically significant difference in CMA using six-, nine-, and 12-months of observation, we were unable to evaluate whether this difference (3%) is clinically meaningful. Further study is needed in the area of adherence and its effect on clinical outcomes such as glycemic control in patients with diabetes.

As we have shown, consideration of the time period of observation is an important component in evaluating medication adherence. Early in therapy, dosages may be adjusted and it may be difficult to measure gaps or surpluses accurately. Christensen observed that over compliance (i.e., compliance rates >100%) diminished with longer observation periods.⁵⁴ While we were unable to identify patients as new users of sulfonylurea therapy, our results similarly showed the proportion of patients with CMA >100% significantly decreased from 25% with six-months of observation to 20% with 12-months of observation.

When using prescription refill patterns as a measure of adherence, the measured adherence approaches actual adherence as the follow-up period is lengthened.⁵⁵ When using sufficiently long follow-up periods (e.g., one year), the amount of medication dispensed can be assumed to equal the amount of medication

consumed. Results of a pharmacy claims study of adherence with antipsychotic medications at six and 12 months demonstrated the importance of longer adherence assessments.⁵⁶ A study evaluating prescription refill patterns of 570 hypertensive patients over a two-year period showed that examination of four dispensing dates (with three months' days supply) was enough to obtain an accurate picture of adherence; additional information gathered during a second year of observation was of minor importance. These observations were confirmed by findings from another study of adherence with 20 commonly prescribed medications.⁵⁷

Our findings confirmed that as the length of follow-up time increased from six months to 12 months, the proportion of available medication to cover the number of observation days slightly decreased whereas the proportion of gaps in therapy increased. While this is not an unexpected finding, it is probably due to an attenuation effect since the calculation of continuous adherence measures is affected by observation time from first dispensation of prescription to the last fill (i.e., the denominator in the formulae). Interestingly, we observed similar adherence rates from examination of nine months and 12 months of pharmacy claims. Thus, nine months of data was adequate to assess adherence with sulfonylureas in this patient population.

Factors that may influence Adherence with Sulfonylureas

The present study did not find any patient- or medication-related characteristics that significantly influenced medication availability with sulfonylureas. Pharmacy claims data lack clinical information that may influence patients' use of medication, such as physical and cognitive ability, health beliefs, and adverse effects experienced by the patient. Thus, our multiple linear regression model may be biased due to incompleteness of the model.

We were unable to evaluate the categorization of sulfonylurea medication as a study factor due to the low proportion of patients prescribed first- or third-generation

sulfonylureas in this patient population. Several factors may explain the low proportions. First, although all sulfonylureas have similar efficacy, second-generation sulfonylureas are more potent and have few adverse events when taken as prescribed when compared to first-generation sulfonylureas.^{58, 59} Second, data on glimepiride, a third-generation sulfonylurea, may be limited in this dataset as it was first marketed in the U.S. in 1997- the first year of data collected for this dataset.

This study utilized pharmacy-based measures of adherence. This pharmacy-based methodology has a distinct-advantage of permitting population-based research²¹ and has been applied in studies of large populations.⁶⁰⁻⁶³ One important advantage of a retrospective review of prescription refill records is avoidance of the Hawthorne effect (i.e., improvement in adherence when the patient is under observation).¹³ Additional strengths of this approach are that it is not susceptible to reporting bias or tampering.⁶⁴ Obtaining pharmacy claims is an unobtrusive method of data collection, allowing a naturalistic estimate of adherence.⁶⁵

The strengths of the present study include the length of the assessment period (12 months) and the use of a variety of measures of adherence based on pharmacy refill records. In addition, the fact that over half of the patients were enrolled in a diabetes management plan may have minimized any effect of financial burden on refill rates and increased the likelihood that the pharmacy records were complete.

We should point out several limitations of this study. The accuracy of medication adherence calculations from pharmacy claims relies on an accurate days supply variable. Although, for most medications, days supply is relatively accurate, there are circumstances in which an erroneous error may exist.⁶⁶ During our preliminary data clean up, there were two occurrences in which the days supply variable did not match the days supply recorded for other sulfonylurea prescription

claims for that patient. Thus, these values were imputed to coincide with data from the other claims during the observation period. While we may have inappropriately corrected data or missed other data entry errors, we are fairly confident that our data are accurate.

Without access to the dosage instructions printed on the prescription label, it was not possible to determine the actual daily dose (e.g., QD, BID) of sulfonylureas in the present study. Our choice of a surrogate for daily dose, number of pills per day, may have overestimated the effect of this variable on adherence with sulfonylureas. Nonetheless, our findings are consistent with those of previous studies that observed lower rates of adherence with an increase in dosing frequency.^{9, 11, 36}

Since the database included patients with diabetes who were dispensed sulfonylureas through CVS pharmacies in Pennsylvania, the results from this study may not be generalizable to the wider population of patients with diabetes.

CONCLUSION

By assessing adherence with a variety of measurement tools, this study demonstrated that patients with diabetes obtained less sulfonylurea medication than prescribed over six-, nine-, and 12-month periods of observation. One measure of adherence, such as CMA, presents a misleading picture of medication adherence. Inclusion of an analysis of gaps and surplus medication provides an overall picture of medication adherence in a patient population. The observations of this study illustrate that a nine-month examination of prescription claims was adequate to assess the rates of adherence. Continuous and dichotomous measures of medication availability, gaps in therapy and surplus medication were significantly correlated. However, since there is no standard of measuring medication adherence, further research is needed

to evaluate the appropriate level of adherence associated with glycemic control in patients with diabetes.

It is important for health care providers to be able to appreciate the complexity of a diabetic's treatment regimen and understand the psychological, physiological, environmental, and regimen-specific factors that affect patient's adherence to treatment regimens. For example, a finding of gaps in therapy may suggest that a refill reminder program needs to be incorporated into a patients' diabetes management plan. Evaluation of medication adherence based on a combination of measures will increase knowledge of the extent of adherence with sulfonylureas in this patient population and guide future diabetes management plans.

TABLES

Table 1-1. Measures of adherence

Measure	Definition	Formula
<u>Medication Availability</u>		
CSA	Continuous, Single-interval measure of medication Availability	Days supply obtained during an interval divided by the total number of days in that interval
CMA	Continuous, Multiple-interval measure of medication Availability	Sum of the days supply between the first and last fill divided by total number of days from first to last fill
<u>Medication Unavailable for Use</u>		
CSG	Continuous, Single-interval measure of medication Gaps	Number of days that medication was unavailable for use (i.e., gap)* in an interval divided by the total number of days in that interval
CMG	Continuous, Multiple-interval measure of medication Gaps	Total number of days with a gap in medication* divided by total number of days from first to last fill
<u>Oversupply of Medication Available for Use</u>		
CSOS	Continuous, Single-interval measure of medication Oversupply	Number of days that oversupply/surplus [†] medication was available for use in an interval divided by the total number of days in that interval
CMOS	Continuous Multiple-interval measure of Over-Supply	Total number of days that oversupply/surplus [†] medication was available for use divided by total number of days from first to last fill

* A gap is the number of days between the assumed depletion date of one fill (claim's fill date plus days supply) and the fill date of the next refill. When no gap occurs, gap = 0.

† A surplus is the (+) number of days between the assumed depletion date of one fill (claim's fill date plus days supply) and the fill date of the next refill.

Measures adapted from Steiner and Prochazka *Journal of Clinical Epidemiology* (1997) and Fairman and Motheral *Journal of Managed Care Pharmacy* (2000)

Table 1-2. Characteristics of the study population (N = 988)

Characteristic	Frequency (%) or mean $\pm$ SD (range)
Age (years)	59.2 $\pm$ 10.9 (22-88)
Gender	
Male	571 (57.8)
Female	417 (42.2)
Health Plan*	
Nurse-based diabetes management plan	536 (54.2)
Other	452 (45.8)
Sulfonylurea Medication Regimen [†]	
1 st generation sulfonylureas	18 (1.8)
acetohehexamide	1 (0.1)
chlorpropamide	11 (1.1)
tolazamide	3 (0.3)
tolbutamide	3 (0.3)
2 nd generation sulfonylureas	904 (91.3)
glipizide	341 (34.5)
glyburide	561 (56.8)
3 rd generation sulfonylureas	68 (6.9)
glimepiride	68 (6.9)
Number of Pills per Day	
1	410 (41.5)
>1	578 (58.5)
Use of Insulin [‡]	
Yes	30 (3.0)
No	958 (97.0)
Number of Medications [§]	8 $\pm$ 7 (0-44)

* Health plan used to dispense sulfonylurea medication during the index window.

Other includes local/state/federal health care programs, cash payments, etc.

[†] Sulfonylurea medication classified during the index window.

[‡] Use of insulin during observation period.

[§] Number of medications (other than antidiabetic medications or supplies) prescribed during observation period.

Abbreviations: SD = 1 standard deviation

Table 1-3. Illustration of single- and multiple-interval measures of adherence with sulfonylurea medication

Prescription Interval	Day of fill	Days of Supply Obtained	Days in Interval	Days with treatment gap in interval	Days with treatment surplus in interval	CSA	CSG	CSOS
1	12/26/97	45						
2	01/24/98	45	29	0	16	1.56	0	0.55
3	03/26/98	45	61	16	0	0.74	0.26	0
4	05/13/98	45	48	3	0	0.94	0.06	0
5	06/03/98	45	21	0	24	2.14	0	1.14
6	12/15/98	45*	195	150	0	0.23	0.77	0
Total		225	354	169	40			
<i>Medication Availability</i>								
CMA (%)	63.6							
<i>Medication Deficits</i>								
CMG (%)	47.7							
<i>Medication Oversupply</i>								
CMOS (%)	11.3							

* Days supply was not used in the calculation of CMA as the next fill date is unknown.

Abbreviations: CMA = continuous measure of medication availability; CMG = continuous measure of medication gap; CMOS = cumulative multiple-interval measure of over-supply; CSA = single interval measure of medication availability; CSG = continuous single interval measure of medication gap; CSOS = continuous single-interval measure of medication oversupply.

Table 1-4. Measures of adherence with sulfonylureas in patients with diabetes
(N = 988)

Adherence Measure (%)	Frequency (%) or mean $\pm$ SD (range)
<i>Medication Availability</i>	
CMA*	89.3 $\pm$ 18.4 (10.0 – 150.4)
$\geq 80\%^{\dagger}$	775 (78.4)
$\geq 90\%^{\dagger}$	647 (65.5)
$> 100\%$	194 (19.6)
<i>Medication Gap</i>	
CMG*	15.0 $\pm$ 16.2 (0 – 90.0)
$\geq 10\%$	454 (46.0)
$\geq 20\%$	240 (24.3)
<i>Medication Surplus</i>	
CMOS*	5.1 $\pm$ 7.4 (0 – 79.9)
$\geq 10\%$	146 (14.8)
$\geq 20\%$	45 (4.6)

* Calculated using period of observation (i.e., the number of days between first and last

fill during the observation period) as the denominator

$\dagger$ Adherent with at least 80% (90%) days of therapy

Abbreviations: CMA= continuous multiple-interval measure of medication availability;
CMG = continuous multiple-interval measure of gap; CMOS= cumulative multiple-
interval measure of oversupply; SD = standard deviation

Table 1-5a. Bivariate correlation of continuous measures of medication availability, gaps, and surplus

Correlation coefficient	CMA	CMG	CMOS
CMA	1.000		
CMG	-0.95198*	1.000	
CMOS	0.41317*	-0.20144*	1.000

* P <0.0001

Abbreviations: CMA= continuous multiple-interval measure of medication availability;
 CMG = continuous multiple-interval measure of gap; CMOS= cumulative multiple-interval measure of oversupply.

Table 1-5b. Bivariate correlation of continuous and dichotomous measures of medication availability

Correlation coefficient	CMA	CMA ≥80%	CMA ≥90%
CMA	1.000		
CMA ≥80%	0.82110*	1.000	
CMA ≥90%	0.76040*	0.72213*	1.000

* P <0.0001

Abbreviations: CMA= continuous multiple-interval measure of medication availability.

Table 1-5c. Bivariate correlation of continuous and dichotomous measures of gaps in therapy

Correlation coefficient	CMG	CMG ≥10%	CMG ≥20%
CMG	1.000		
CMG ≥10%	0.69026*	1.000	
CMG ≥20%	0.83781*	0.61432*	1.000

* P <0.0001

Abbreviations: CMG = continuous multiple-interval measure of gap.

Table 1-5d. Bivariate correlation of continuous and dichotomous measures of surplus medication

Correlation coefficient	CMOS	CMOS ≥10%	CMOS ≥20%
CMOS	1.000		
CMOS ≥10%	0.78836*	1.000	
CMOS ≥20%	0.75255*	0.52460*	1.000

* P <0.0001

Abbreviations: CMOS= cumulative multiple-interval measure of oversupply.

Table 1-6. Measures of adherence with sulfonylureas in patients with diabetes grouped by time period of observation*

Measure (%)	6 months n = 980*	9 months n = 985*	12 months n = 988
<i>Medication Availability</i>			
CMA [†]	91.7 [§] ± 18.7 (21.6 – 159.1)	90.0 [§] ± 18.5 (12.2-155.8)	89.3 [§] ± 18.4 (10.0 – 150.4)
≥80% [‡]	792 (80.8)	785 (79.7)	775 (78.4)
≥90% [‡]	681 (69.5)	638 (64.8)	647 (65.5)
≥100%	243** (24.8)	209** (21.2)	194** (19.6)
<i>Medication Gap</i>			
CMG [†]	13.1 [§] ± 15.4 (0 – 78.4)	14.5 [§] ± 15.8 (0 – 87.8)	15.0 [§] ± 16.2 (0 – 90.0)
≥10%	380** (38.8)	435** (44.2)	454** (46.0)
≥20%	209 (21.3)	231 (23.5)	240 (24.3)
<i>Medication Surplus</i>			
CMOS [†]	4.8 ± 9.0 (0 – 81.5)	5.1 ± 8.4 (0 – 83.9)	5.1 ± 7.4 (0 – 79.9)
≥10%	135 (13.8)	153 (15.5)	146 (14.8)
≥20%	61 (6.2)	52 (5.3)	45 (4.6)

Data are presented as frequency (%) or mean ± SD (range)

* Time period of observation examined 6, 9, or 12 months of pharmacy claims data. 8 patients excluded with only 1 sulfonylurea fill during 6-month period and 3 patients excluded with only 1 sulfonylurea fill during 9-month period.

[†] Calculated using period of observation (i.e., the number of days between first and last fill) as the denominator

[‡] Adherent with at least 80% (90%) days of therapy

[§] P < 0.05

** P < 0.01

Abbreviations: CMA= continuous multiple-interval measure of medication availability; CMG = continuous multiple-interval measure of gap; CMOS= cumulative multiple-interval measure of oversupply; SD = standard deviation.

Table 1-7. Beta estimates of predictive factors of adherence* with sulfonylurea medications in patients with diabetes

Variable	Beta estimate (SE)	Beta estimate (SE)
Intercept	0 (3.29078)	0 (3.43503)
<i>Patient-related characteristics</i>		
Age (years)	0.03924 (0.05377)	0.04092 (0.05465)
Gender (1 =female)	-0.00931 (1.18887)	-0.00713 (1.20259)
Health plan (1 = other)	-0.03424 (1.18093)	-0.03227 (1.18775)
<i>Medication-related characteristics</i>		
No. of pills per day (1 = >1)		-0.01011 (1.19830)
Number of concomitantly prescribed medications		-0.01724 (0.09212)
Model F-value (p-value)	0.86 (0.4632)	0.59 (0.7065)
Adjusted R ²	0.0004	0.0021

* Continuous measure of medication availability (CMA)

Abbreviations: SE = standard error

Table 1A-1. Bivariate correlation of CMA* and all 6 predictive variables

	CMA*	Age	Gender	Health plan	Concomitant medication	No. of SU pills/day
Correlation coefficient	1.000	0.03709	-0.00792	-0.03141	-0.01528	-0.01499
p value		0.2441	0.8036	0.3240	0.6314	0.6379

* Continuous measure of medication availability (CMA)

Abbreviations: CMA= continuous multiple-interval measure of medication availability; SU = sulfonylurea.

Table 1A-2. Collinearity diagnostics*

Variable	Condition Index	Intercept	Proportion of variation				
			Age	Gender	Health Plan	No. of ConMed	No. of pills/day
Intercept	1.00000	0.00143	0.00154	0.01587	0.01611	0.01396	0.01443
Age	2.71477	0.00002771	0.00004427	0.60022	0.30821	0.00199	0.01919
Gender	3.07310	0.00074987	0.00052353	0.13499	0.48962	0.00000232	0.39949
Health plan	3.49445	0.00044223	0.00142	0.19083	0.11254	0.57139	0.24819
No. of ConMed	4.37622	0.03170	0.04052	0.04945	0.07293	0.40926	0.27847
No. of pills/day	16.58110	0.96564	0.95594	0.00864	0.00057832	0.00340	0.04022

* Dependent variable was a continuous measure of medication availability (CMA)

FIGURES

Figure 1-1. Eligibility criteria of study population

Figure 1A-1. Frequency distribution of the measurement: CMA

Figure 1A-2. Frequency distribution of the measurement: CMG

Figure 1A-3. Frequency distribution of the measurement: CMOS

Figure 1A-4. Two-dimensional plot of residuals against the dependent variable, CMA

Figure 1A-5. Two-dimensional plot of studentized residuals against the dependent variable, CMA

Figure 1A-6. Two-dimensional plot of studentized residuals against age

Figure 1A-7. Two-dimensional plot of studentized residuals against number of concomitantly prescribed medications

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Study 2

Using Prescription Claim Records to Evaluate Adherence with Lipid-lowering Medications in Patients with Diabetes Mellitus

ABSTRACT

Background: Current American Diabetes Association guidelines recommend aggressive treatment of diabetic dyslipidemia that may include pharmacologic therapy with lipid-lowering therapy. Adherence with lipid-lowering therapy is essential to achieve targeted lipid levels within treatment guidelines. Low adherence with lipid-lowering medications has been documented in several patient populations such as the elderly and Health Maintenance Organization members.

Objective: The objective of this study was to evaluate adherence with lipid-lowering medications in patients with diabetes mellitus. In addition, the effect of patient- and medication-related characteristics on adherence was examined.

Methods: Using pharmacy claim records, a retrospective cohort study of patients with diabetes mellitus identified new users of lipid-lowering therapy. Patients had an initial prescription for a lipid-lowering medication between November 1, 1997 and April 30, 1998 with at least two refills in a nine-month observation period. Adherence was measured by the Continuous multiple-interval measure of Medication Availability (CMA) using length of therapy as the denominator. Logistic regression models were used to assess the effects of patient- and medication-related characteristics on a dichotomous measure of adherence using 80% and 90% levels of adherence.

Results: The study cohort comprised of 90 patients with diabetes (52% males; mean age of 60.3 years (range 30-79 years)). The majority (91%) of patients were prescribed a statin medication. Patients were observed for an average 225 days

(range of 59 to 270 days). Overall, mean ($\pm$ SD) CMA was $82.8\% \pm 23.4\%$ (range of 14.3% to 124.8%). Adherence differed by class of lipid-lowering medication prescribed at the index date, although not a statistically significant difference. Patients prescribed statin and non-statin medications had an average CMA of $84.1\% \pm 22.3\%$ and $70.0\% \pm 31.7\%$, respectively ($p=0.2627$). Approximately 66% of patients filled enough lipid-lowering medication prescriptions to cover at least 80% or more days while only 46% of patients had sufficient medication to cover 90% or more days of therapy during a nine-month observation period. In the final logistic regression model, adherence was influenced by antidiabetic medication regimen and class of lipid-lowering medication prescribed at the index date. Adherent ($\geq 80\%$) patients were less likely to be prescribed insulin therapy (OR=0.304, 95% CI=0.114, 0.815, $p=0.0180$) and more likely to be prescribed statin medications (OR=4.709, 95% CI=0.996, 22.268, $p=0.0506$) compared with non-adherent patients. No study factor (age, gender, health plan, antidiabetic medication, class of index lipid-lowering medication, number of concurrent prescription medications) significantly influenced adherence using a 90% level of adherence.

Conclusions: Adherence with lipid-lowering therapy in patients with diabetes mellitus was less than optimal. Non-adherence was associated with insulin therapy and non-statin medications. This data supports previous investigations that observed an effect of class of lipid-lowering medications and insulin therapy on medication adherence. Further research is needed to examine the relationship between adherence and lipid levels and explore the effect of study factors such as antidiabetic medication regimen patient beliefs, prescriber characteristics on medication adherence among patients with diabetes mellitus.

Key Words: lipid-lowering therapy, dyslipidemia, diabetes, adherence

INTRODUCTION

Diabetes mellitus is associated with co-morbid conditions such as dyslipidemia¹ which contributes to higher rates of cardiovascular disease.^{2,3} According to the Centers for Disease Control and Prevention (CDC), 97% of adults with diabetes have one or more lipid abnormalities although only 32% receive treatment with diet, exercise or pharmacotherapy.⁴

The American Diabetes Association (ADA) guidelines and the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III) recommend aggressive treatment of diabetic dyslipidemia.^{5, 6} Current ADA recommendations emphasize treatment to lower low-density lipoprotein cholesterol (LDL-C) levels to <100 mg/dl, even in patients with no history of cardiovascular disease (Table 2-1).^{7, 8} Based on the Third National Health and Nutrition Examination Survey (NHANES III), it is estimated that 9.2 million adults with diabetes require treatment for LDL-C levels >100 mg/dl.⁹

The ATP III report for the management of high blood cholesterol in the United States recognizes two major approaches to therapy for dyslipidemia: lifestyle management and pharmacological therapy.⁶ Therapeutic lifestyle changes, such as weight management and increased physical activity are a major factor in the treatment of diabetic dyslipidemia. Current ADA guidelines recommend initiation with pharmacological therapy after lifestyle intervention has been implemented.⁸ Generally, in patients with diabetes, pharmacological therapy should follow when a three- to six-month trial of lifestyle modifications alone fails to adequately lower LDL-C levels.^{10, 11}

Medications available to treat dyslipidemia include HMG-CoA reductase inhibitors (statins), bile acid sequestrants, nicotinic acid, and fibrates. Typically the lipid-lowering medication selected is largely dependent on the nature of the patient's

dyslipidemia.^{11, 12} Statins are recommended first-line therapy for reducing LDL-C levels in patients with diabetes⁵ yet statins also increase high-density lipoprotein cholesterol (HDL-C) concentrations and recently have been shown to reduce triglyceride levels as well.¹³ Fibrates have been used as monotherapy to treat diabetic dyslipidemia as they effectively reduce triglycerides and increase HDL-C levels although they may be used in combination with statin therapy if the patients' LDL-C does not reach the target level.¹² Bile acid sequestrants may be used as second-line therapy although they may aggravate hypertriglyceridemia and are associated with unpleasant gastrointestinal side effects.^{11, 14, 15} Nicotinic acid can be given to patients with diabetes, although it is generally avoided because it may cause worsening hyperglycemia.^{15, 16}

The relationship between reductions in lipid levels and target treatment goals has been demonstrated.¹⁷⁻²¹ For example, in a comparison with 1998 target values defined by the ADA, >75% of patients with type 2 diabetes mellitus treated with 30 weeks of atorvastatin reached triglyceride treatment goals and 71% and 85% of patients treated with 10mg and 80mg atorvastatin respectively, reached LDL-C treatment goals.¹⁸ Statin medications were more likely to achieve a LDL-C target goal of ≤ 100 mg/dL than non-statin therapy in a cohort of patients with diabetes mellitus.²¹ Patients with diabetes treated with at least three months of lipid-lowering therapy were 36% more likely to achieve NCEP target LDL-C levels than those without diabetes ($p=0.04$).¹⁷

However, one important factor affecting the pharmacological management of dyslipidemia is adherence.^{*} Physicians have been plagued by concerns over patients' adherence to medication regimens since Hippocrates.²²⁻²⁴ Adherence has been defined as the extent to which a patient freely chooses to follow physicians' orders (i.e., by taking medications or modification of lifestyle changes such as diet and exercise) with medical advice.²⁵ Adherence consists of the initial acquisition of medication, the consumption of the medication in the prescribed method, and acquisition of refills.

Few studies have demonstrated a connection between medication adherence and lipid levels in patients with dyslipidemia. The Helsinki Heart Study, a coronary primary prevention trial using gemfibrozil, found that serum lipid levels varied linearly with the level of medication adherence.²⁶ The mean change in LDL-C was -10.1% among patients who consumed $\geq 90\%$ of the scheduled dosage of gemfibrozil in contrast with a mean change of +2.6% when adherence with mean daily capsule count was $< 50\%$.²⁶ In addition, data from the five-year Heart Protection Study examined adherence and reduction of lipid levels in patients with diabetes. After making allowances for compliance (82% of patients were compliant defined as $> 80\%$ of the scheduled medication taken) actual use of 40mg simvastatin daily would lower LDL-C by about 58 mg/dL.²⁷ These results highlight an important factor: adherence affects the pharmacological management of dyslipidemia and consequently a patient's ability to achieve target lipid levels.

Adherence with lipid-lowering therapy has been documented in patient populations such as the elderly, patients with a history of myocardial infarction (MI)

^{*} Adherence and compliance are used interchangeably in the literature. Although the term compliance has negative connotations, it is still in use and will be referred to in this study if utilized in the cited published material.

and members of Health Maintenance Organizations (HMOs). Regardless of the patient population, these studies provide evidence that adherence with lipid-lowering medications is varied and often sub-optimal. While these studies document rates of adherence with lipid-lowering medications in clinical practice, several studies examined diabetes as a covariate in their analyses with inconsistent results. Among elderly patients, diabetes was associated with better adherence with lipid-lowering therapy.²⁸⁻³⁰ In contrast, diabetes was associated with non-compliance with fluvastatin³¹ while Mansur and colleagues did not find a relationship between adherence with statin therapy and diabetes.³²

While many studies have documented the frequent utilization of lipid-lowering medications among patients with diabetes.^{33, 34} and reviewed the topic of diabetic dyslipidemia,^{11, 16, 35, 36} few studies have specifically examined adherence with lipid-lowering therapy in patients with diabetes. Thus, the aim of this study was to evaluate adherence with lipid-lowering medications in patients with diabetes mellitus using prescription claims data. The present study was designed to 1) estimate adherence in patients identified as new users of lipid-lowering medications and 2) identify factors that might influence adherence with lipid-lowering medications among patients with diabetes mellitus.

METHODS

Study Design

This was a retrospective cohort study of patients with diabetes using pharmacy claim prescription records.

Dataset

Data examined in the analysis were obtained from 198 Consumer Value Stores (CVS) pharmacies located in Pennsylvania that provided prescription

medications for 4503 patients with diabetes identified by specific therapeutic classes (insulins, oral antidiabetic agents-sulfonylureas and other oral antidiabetic agents) between April 27, 1997 and May 16, 1999. Patients were either enrolled in a nurse-based diabetes management plan or acquired their prescription through a local/state/federal program or paid with cash payments. The data represents patients' utilization of lipid-lowering medications, though some patients may have filled prescriptions elsewhere.

This prescription claims data extract includes records of dispensed outpatient pharmacy prescription records for all prescriptions. The following information was obtained from the CVS dataset for this analysis: patient characteristic variables such as birth date, gender, and health plan agency as well as prescription related variables including quantity of medication dispensed, days supply of medication dispensed, and date the prescription was dispensed. No personally identifying information was provided.

Study Population

Patients were eligible for inclusion in the study population if they (1) had an initial prescription claim for a lipid-lowering medication between November 1, 1997 and April 30, 1998 with at least two refills during a nine-month observation period (n=831); (2) were a new user of lipid-lowering therapy (n=136); (3) had no dispensations for combination lipid-lowering medication (defined as a claim for a second lipid-lowering medication within 30 days of the index medication) (n=0); and (4) continuously used the pharmacy to fill prescriptions (i.e., the patient had a least one prescription filled for any medication in the three months prior to the index date and in the last three months of the observation period) (n=91). Patients who switched class of lipid-lowering medication to another class during the observation period were

excluded from the analysis as class of lipid-lowering medication was evaluated as the primary independent variable (n=1).

The date of the initial lipid-lowering prescription between November 1, 1997 and April 30, 1998 was classified as the index date. Each patient was observed for nine months from the index date: all prescription claims for lipid-lowering medications from this time period were retrieved from the dataset.

Presumed new users were defined as patients having no prescription claim for a lipid-lowering medication in the 90 days before the index date. Thus, patients with less than 90 days of data prior to the index date were excluded. This classification to identify new users of therapy has been previously described.^{37, 38}

Lipid-Lowering Medications Available in Dataset

Data from all patients receiving lipid-lowering prescription fills were extracted from the dataset. As shown in Table 2-2, this dataset contains prescription claims on the following lipid-lowering medications: (1) Statins (3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors): atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin; (2) Fibrates: fenofibrate and gemfibrozil; (3) Bile acid sequestrants: cholestyramine resin and colestipol; and (4) Nicotinic acid: niacin. One of the objectives of this study was to document adherence with lipid-lowering medications. However, due to the small number of patients prescribed non-statin medications, class of index lipid-lowering medication was identified as the primary independent variable. This variable was categorized as statin or non-statin (fibrates, bile acid sequestrants, and nicotinic acid) based on 1) previous reports of adherence with lipid-lowering medications^{28, 39} and 2) statin medications are considered first-line therapy for patients with diabetes.^{7, 36, 40}

Potential Confounding Variables

The following potential confounding variables were evaluated in this analysis: age, gender, health plan, antidiabetic medication regimen, and the number of concomitantly prescribed medications. These factors were classified as patient-related characteristics (age, gender, health plan) or medication-related characteristics (antidiabetic medication regimen, number of concurrent medications) constructed from the prescription profile of each patient. The primary independent variable, class of lipid-lowering medication, was based on the prescription filled on the index date.

Age was based on the transaction date for the index lipid-lowering prescription fill and was treated as a continuous variable in the univariate data analyses and a categorical variable in the multivariate analyses. The patients' health plan, used to acquire the index lipid-lowering medication, was dichotomized as either a nurse-based diabetes management plan or other (e.g., local/state/federal programs or cash payments).

Based on the prescribed antidiabetic regimen during the observation period, antidiabetic medication regimen was classified as oral medication for patients dispensed only oral antidiabetic medications or insulin therapy for patients dispensed either insulin monotherapy or insulin in combination with oral antidiabetic medications. The number of concurrent medications consisted of a count of all medications, excluding lipid-lowering medications and diabetic supplies such as blood glucose test strips or tuberculin syringes, dispensed during the observation period. This variable was treated as a continuous variable in the univariate data analyses and a categorical variable in the multivariate analyses.

Data Analysis

Prescription claims for all patients who satisfied the inclusion/exclusion criteria were examined for a nine-month observation period.

Dataset Preparation

Prior to analysis, the dataset was checked for outliers for the following variables: days supply and posted transaction date of the prescription claim. One patient had a days supply recorded as three; this patient's days supply was imputed to 30 to coincide with the days supply recorded for other fills and the quantity dispensed. Patients with incomplete records (i.e., missing transaction dates) for lipid-lowering medications were excluded from the analysis (n=173).

Calculation of Adherence Measures

Adherence was measured by the Continuous multiple-interval measure of Medication Availability (CMA) using length of therapy as the denominator as described by Steiner and colleagues.^{41, 42} This measure provided a continuous assessment of medication availability during the observation period and is based on the assumption that patients cannot be adherent with medication therapy if they have not obtained sufficient quantities of medication.

CMA was calculated for each patient using the following formula: sum of the days supply between the first and last prescription fill of lipid-lowering medication divided by the number of days of therapy between the first and last prescription during the observation period. Adherence was expressed as a percentage and indicated the percentage of time between the first and last dispensation that a patient had medication available during the observation period.

The following example illustrates the calculation of CMA for this study:

<u>Transaction Date of Lipid-lowering Medication</u>	<u>Days Supply</u>
July 26, 1998	30
August 26, 1998	30
September 28, 1998	30
October 27, 1998	30
November 30, 1998	30
<i>Total days supply between July 26, 1998 and November 30, 1998:</i>	
30 + 30 + 30 + 30 = 120 days	
<i>Total number of days between July 26, 1998 and November 30, 1998:</i>	
127 days	
<i>Thus, this patient's CMA was:</i>	
$120 / 127 \times 100\% = 94.5\%$	

The convention has been to define adequate adherence as carrying out 80% of the recommended behaviors.^{43, 44} In this study, adherence was categorized using a level of 80% medication coverage (i.e., patients who were dispensed enough lipid-lowering medication to cover 80% of days in the observation period). Patients were classified as adherent ($\geq 80\%$) or non-adherent ($< 80\%$) based on this level. This level of adherence is commonly used in adherence studies.⁴⁵⁻⁴⁸

Although 80% has been justified as a standard since it is used conventionally in clinical trials for safety and efficacy assessments that support new drug registrations⁴⁹⁻⁵¹ and there is evidence that this level of adherence is sufficient to reduce LDL-C levels in patients with diabetes mellitus,²⁷ we also chose to evaluate a higher level of adherence with lipid-lowering therapy that might be needed to lower the risk of cardiovascular mortality in patients with diabetes. A sensitivity analysis will assess a 90% level of adherence that was utilized in the Helsinki Heart Study.²⁶

Univariate Analysis

Descriptive statistics, mean $\pm$ SD for continuous variables and frequencies (percentage) for categorical variables, were used to present patient- and medication-related characteristics. Chi-square (X^2) tests and t-tests were performed to determine significant differences for the categorical and continuous variables, respectively. X^2 and t-tests were used to analyze the proportions of study factors between patients who were adherent ($\geq 80\%$ or $\geq 90\%$) or non-adherent (<80 or $<90\%$) with lipid-lowering therapy.

The Shapiro-Wilk test of normality was used to assess the frequency distribution of the continuous variables: age, CMA and number of concurrent prescription medications. Age was normally distributed (W statistic= 0.9785; $p=0.1495$). CMA and number of concurrent prescription medications were not normally distributed as demonstrated by statistically significant Shapiro-Wilk tests ($p<0.0001$); non-parametric rank tests were used to determine significant differences for these two variables. The frequency distribution of the 80% and 90% levels of adherence measurements are presented in Figures 2A-1 and 2A-2, respectively.

Multivariate Analysis

Logistic regression was used to model the effects of study factors on adherence with lipid-lowering therapy, using two different levels of adherence as a categorical dependent variable ($<80\%$, $\geq 80\%$ and $<90\%$, $\geq 90\%$) and the primary variable of interest, class of lipid-lowering medication prescribed at the index date. The logistic regression model was built with significant predictive variables and interaction terms as described by Hosmer and Lemeshow.⁵² Assessments of the factors that might influence adherence with lipid-lowering therapy included parametric assessment of continuous variables, an assessment of potential confounding variables, collinearity among the independent variables, and an assessment of

multiplicative interaction between the independent variables. All assessments were conducted using both the 80% and 90% levels of adherence.

Parametric Analysis of Continuous Variables

Parametric assessment of two continuous variables, age and number of concomitantly prescribed medications, was based on the methodology described by Hosmer and Lemeshow.⁵² These variables were categorized based on the quartiles of the frequency distribution, using the first quartile as the reference group. After modeling the dependent variable, adherence, with the quartile-based variable, a plot of the odds ratio for the quartiles was visually examined for linearity. If linearity was observed, the variable remained continuous. Conversely, if linearity was not supported, the variables required categorizations based on cut-points observed in the plot.

The quartile-based parametric analysis suggested that categorization was needed for inclusion of the continuous variables, age and number of concomitant medications, in the logistic regression model. Based on visual examination of the plots of odds ratio, age was categorized in three levels (30-55, 56-65, >65) and number of concomitant medications was dichotomized (1-5, >5) (Tables 2A-1a and 2A-1b).

Assessment of Collinearity

Since logistic regression model fitting is sensitive to collinearity among the independent variables, the presence of collinearity between the independent variables was examined.^{52, 53} Independent variables with a condition index greater than 30 (moderate to severe collinearity) and proportion of variations greater than 0.5 were further examined for collinearity with other independent variables. If there was collinearity between the two variables, the variable showing the strongest association

with adherence with lipid-lowering therapy was kept in the model. None of the six study variables exhibited signs of collinearity (Table 2A-2).

Assessment of Multiplicative Interactions

Multiplicative interaction between the independent variables was assessed using the -2 Log Likelihood (LL) difference between the models (i.e., the Chunk test) as described by Kleinbaum.⁵⁴ A logistic regression model of factors that might influence medication adherence was conducted for the full model (all independent variables, two- and three-way interaction terms) and reduced models: all independent variables plus two-way interaction terms and a model containing only the independent variables. The -2 LL difference in the model versus the model with reduced terms was tested for significance using X^2 test values. Interaction was not present if the -2 LL difference was less than the X^2 statistic.

Several interaction terms, including all of the three-way interaction terms, had an odds ratio (OR) >999.999 and the validity of the model was questionable suggesting that these terms needed to be removed from the model. Upon further examination, the proportion of patients in the categorizations of 50% of the three-way interaction terms was $\leq 20\%$. Separate logistic regression models of adherence tested these interaction terms; none of the terms significantly influenced adherence with lipid-lowering therapy. Examining the -2 LL difference between the models, the reduced model of independent variables was not statistically significant from the model that included two-way interaction terms (Tables 2A-3a and 2A-3b).

Assessment of Confounding Variables

Based on the technique of Hosmer and Lemeshow,⁵² an assessment of potential confounding variables (age, gender, health plan, antidiabetic medication regimen and number of concomitant medications) was conducted on the no-interaction model. X^2 tests were conducted to test the effect of the potential confounding variables on the

dependent variable (dichotomous level of adherence) and primary independent variable (class of index lipid-lowering medication). A confounding variable would be identified if an association (i.e., the X^2 test statistic showed statistical significance, $p < 0.05$) were present with both the dependent and primary independent variables. No study factors were identified as a confounding variable (Tables 2A-4a and 2A-4b).

Final Logistic Regression Model

Significant study factors from the bivariate and multivariate logistic regression models along with the primary independent variable were incorporated into the final model of adherence with lipid-lowering therapy; a stepwise procedure of model selection (entry criteria=0.10) confirmed this choice.

Analyses were conducted utilizing adherence categorizations with adherence defined as $\geq 80\%$. A sensitivity analysis was conducted using $\geq 90\%$ adherence. All statistical tests were two-tailed and the *a priori* alpha test of significance was set at $p < 0.05$. All data analyses were conducted using SAS release 8.02.⁵⁵

RESULTS

Description of the Study Population

Of the 1276 patients prescribed lipid-lowering medication, 857 had a prescription claim from November 1, 1997 and April 30, 1998. Of these patients, 695 were current users of lipid-lowering therapy; 26 patients were excluded because they did not have at least two prescription refills for a lipid-lowering medication during a nine-month observation period; 45 did not have continuous prescription dispensations from the pharmacy (i.e., a prescription claim for any medication in the 90 days prior to the index date and in the last three months of the observation period); and one patient switched to another class of lipid-lowering medication (Figure 2-1).

A total of 90 patients were included in the study analyses: 47 (52%) males and 43 (48%) females with an average age of 60.3 ± 9.9 years (range, 30-79 years). Patient- and medication-related characteristics of the study population are shown in Table 2-3. Approximately half of the patients were enrolled in a nurse-based diabetes management plan at the time of the index lipid-lowering medication prescription. Almost three-quarters of the patients (72%) were prescribed only oral antidiabetic medications during the observation period; either insulin monotherapy or insulin in combination with oral hypoglycemic agents was prescribed for 28% of patients. The mean ($\pm$ SD) number of concomitantly prescribed medications was 8 ± 5 (range of 1 to 27); 80% of patients were prescribed 1-10 concomitant medications.

While the majority of patients (91%) were prescribed a statin medication as their index lipid-lowering medication, eight patients were prescribed a non-statin medication: seven patients prescribed fibrates and one patient was a prescribed bile acid sequestrant.

The average number of days of observation was 225 days (range of 59 to 270 days). Half of the patients received more than seven dispensations of lipid-lowering medication during the nine-month observation period (Table 2-4).

Adherence with Lipid-lowering Therapy

Overall, mean ($\pm$ SD) CMA was $82.8\% \pm 23.4\%$ (range, 14.3%-124.8%). Adherence significantly differed by class of lipid-lowering medication prescribed at the index date: patients prescribed statin and non-statin medications had a mean ($\pm$ SD) CMA of $84.1\% \pm 22.3\%$ and $70.0\% \pm 31.7\%$, respectively ($p=0.2627$) (Table 2-5). Of those patients in the statin group, patients prescribed atorvastatin had the highest mean CMA of 87.8%, followed by patients prescribed pravastatin (85.9%), simvastatin (82.8%) and fluvastatin (79.3%). One patient prescribed lovastatin had a

CMA of 68.4%. Mean CMA for patients prescribed gemfibrozil and cholestyramine are 71.5% and 59.0%, respectively.

Two-thirds of the patients (66%) had sufficient lipid-lowering medication to cover 80% or more days in a nine-month observation period; these patients were classified as adherent. Patient- and medication-related characteristics were similar between patients classified as adherent and non-adherent except for antidiabetic medication regimen and class of lipid-lowering medication prescribed at the index date (Table 2-6). Adherent patients were less frequently prescribed insulin therapy than non-adherent patients ($p=0.0297$). Additionally, adherent patients were more frequently prescribed a statin medication than a non-statin although this proportion was not statistically significant ($p=0.0802$).

Logistic Regression Model of Adherence ($\geq 80\%$)

In the bivariate logistic regression model of adherence ($\geq 80\%$), only antidiabetic medication regimen had a statistically significant effect on adherence: patients prescribed insulin therapy (i.e., either insulin monotherapy or insulin in combination with oral antidiabetic medications) were less likely to adhere with lipid-lowering therapy than patients prescribed only oral antidiabetic medications (Table 2-7).

Table 2-8 presents results from the multivariate logistic regression model of adherence ($\geq 80\%$). Controlling for all study factors, antidiabetic medication regimen significantly influenced adherence with lipid-lowering medications. Patients prescribed insulin therapy were less likely to have sufficient lipid-lowering medication to cover at least 80% or more days in a nine-month observation period than patients prescribed only oral antidiabetic medications (OR=0.172; 95% CI=0.053,0.554; $p=0.0032$). All other study factors did not significantly affect adherence with lipid-lowering medication ($p\geq 0.1048$). In a stepwise logistic regression model, which added one

study factor at a time, antidiabetic medication regression and class of lipid-lowering medication met the entry criteria of $p \leq 0.10$.

Thus, the resulting final model of adherence ($\geq 80\%$) incorporated the significant covariates from the multivariate regression model (Table 2-9). The likelihood of patients achieving adherence with lipid-lowering medication was lower for patients prescribed insulin therapy (OR= 0.304, 95% CI=0.114, 0.815, $p=0.0180$) compared with patients prescribed only oral antidiabetic medications. Compared with patients prescribed non-statin medications, patients prescribed a statin medication were four-fold more likely to be adherent with treatment (OR=4.709, 95% CI=0.996, 22.268, $p=0.0506$); this parameter was close to statistical significance in the final model.

Sensitivity Analysis

A sensitivity analyses was conducted using adherence defined as having adequate lipid-lowering medication to cover at least 90% or more days in a nine-month observation period. Results of the univariate analyses were similar to those observed with the 80% level of adherence. In summary, only 46% of patients were adherent with lipid-lowering therapy. Patient- and medication-related characteristics were similar for adherent ($\geq 90\%$) and non-adherent patients ($p \geq 0.1956$) (Table 2-10). In bivariate logistic regression models, no study factor significantly influenced adherence (Table 2-11). Similarly, no study factors significantly affected adherence in the multivariate regression model controlling for all study factors (Table 2-12). Since no study variable significantly influenced adherence, there were no significant predictors to include in a final regression model using a 90% level of adherence.

DISCUSSION

The value of treating dyslipidemia is well established: lipid-lowering pharmacotherapy reduces lipid levels and consequently the risk of cardiovascular complications. Yet, dyslipidemia is a chronic, asymptomatic condition that may require daily pharmacotherapy. Thus, adherence with lipid-lowering therapy is an important component in the treatment of dyslipidemia. This study provided an opportunity to evaluate adherence with lipid-lowering therapy in patients with diabetes.

We observed a mean CMA with lipid-lowering therapy of $82.8 \pm 23.4\%$. Our results are higher than rates reported for Medicaid and managed care populations^{28,56-58} which may reflect a selection bias due to the patient population selected for the dataset: patients prescribed oral antidiabetic medications or insulin therapy for treatment of hyperglycemia. These patients with diabetes may be more adherent with medication regimens than patients whose hyperglycemia is treated with diet modification and/or exercise. Thus, our sample of patients may not reflect the general population of patients with diabetes. Further study is needed to assess adherence with lipid-lowering therapy in patients with diabetes.

The results of this study support the findings of previous investigations that demonstrate better adherence with statin than non-statin medications.^{28, 39} In general, rates of adherence with statins are consistency higher than with non-statin medications, especially bile acid sequestrants and niacin. For example, in patients aged 65 years or older, the highest rate of adherence was observed with statin medications ($64\% \pm 30\%$ of days covered in one-year) while the lowest was with cholestyramine ($37\% \pm 29\%$ of days covered).²⁸

Since the reason for discontinuation of therapy is not captured in pharmacy claims data, we could not determine why more patients adhered with statin therapy

than non-statin treatment. These findings may reflect greater convenience of dosing regimens for statins.^{28, 59} Poor palatability and multiple dosing frequency of some of the non-statin medications (e.g., bile acid sequestrants) are related to poor adherence.⁶⁰ Therapeutic ineffectiveness, patient's perception of need for therapy and adverse events have been reported as a contributing factors for discontinuation of lipid-lowering therapy.^{37, 59, 61}

Statins are recommended as first-line pharmacotherapy in the majority of hyperlipidemic patients, including patients with diabetes mellitus in part because of their potency, convenient dosing and tolerability.^{7, 36, 40} Bile acid sequestrants are not appropriate therapy in patients with diabetes as they tend to worsen hypertriglyceridemia, and nicotinic acid worsens glycemic control.^{14, 15, 62} Both statins and fibrates are better lipid-lowering therapy choices for patients with diabetes. Thus, it was not unexpected that the majority of patients in our cohort were prescribed a statin or fibrate medication.

An interesting finding was the overall percentage of patients prescribed lipid-lowering medications in this population. Of the 4503 patients with diabetes in the dataset, 28% were prescribed lipid-lowering medications. According to the CDC, 32% of adults with diabetes and lipid abnormalities receive treatment with diet, exercise or pharmacotherapy.⁴ Harris reported that 53% of patients with type 2 diabetes diagnosed with dyslipidemia were treated with diet or medication.⁶³ While we did not have data on diet and exercise therapy in our cohort, we observed that over a quarter of the patients in this study population were being treated for lipid abnormalities. This proportion of patients prescribed pharmacotherapy may be related to the health plan the patient was enrolled in; approximately half were enrolled in a nurse-based diabetes management plan at the index date. Several investigations demonstrate that implementation of follow-up, patient-mediated interventions, and patient education by

nurses resulted in better care of patients with diabetes and better control of metabolic parameters.⁶⁴⁻⁶⁶

Studies have shown that several factors such as prescriber characteristics, physician-patient relationship, patient beliefs, and characteristics of medication complexity play a role in adherence with prescribed lipid-lowering medications.^{22, 67-69} Although the use of pharmacy claims data did not allow an assessment of patient beliefs or prescriber characteristics, we evaluated the relationship between adherence with lipid-lowering therapy and several patient- and medication-related characteristics.

In this study, patients prescribed insulin therapy (i.e., either insulin monotherapy or insulin in combination with oral antidiabetic medications) were more likely to be non-adherent (<80% of days covered with sufficient quantity of medication) with lipid-lowering treatment than patients prescribed only oral medications. Larsen and colleagues observed that patients who received insulin therapy were at a 38% higher risk for discontinuation with statin therapy than patients treated with oral antidiabetic agents.⁷⁰ Similarly, oral antidiabetic medication use was associated with a 28% increase in adherence with antidiabetic therapy compared with patients not using oral antidiabetic medications.⁷¹ It is known that insulin therapy is complex: the need to mix and inject insulin preparations and taking multiple injections combined with the fear of injections may result in poor adherence with this treatment regimen.⁷²⁻⁷⁵ Further study is needed to examine antidiabetic medication regimen as a covariate on medication adherence among patients with diabetes mellitus

As previously described, patients prescribed statin medications were more adherent with lipid-lowering therapy than patients prescribed non-statin medications. Using an 80% level of adherence, we observed an effect of class of lipid-lowering medication prescribed at the index date on adherence. This effect was absent in the

regression model of $\geq 90\%$ adherence. Sung and colleagues⁵⁶ also observed no class effect on compliance with lipid-lowering therapy in a logistic regression model of $\geq 90\%$ adherence; no explanation was given by the authors. This finding may be due to the fact that 16% of our patients had a CMA between 80-90%; this change in the proportion of patients classified as adherent may be sufficient to weaken the class effect of lipid-lowering medications. As this level of medication adherence has resulted in reductions of lipid parameters,⁷⁶ this finding needs to be further explored.

There are inconsistent reports of factors that predict adherence with medications such as medication complexity (i.e., number of daily doses, number of medications) and occurrence and severity of adverse effects; while factors generally not significantly associated with adherence include age and gender.^{49, 51, 68, 77} Problems with medication adherence occur more frequently when patients are older;^{30, 47, 67} receive more medications,^{58, 67, 78} have to take their medications regularly^{58, 79, 80} and over a long period of time.⁸¹ For example, younger patients were less adherent with lipid-lowering therapy than older patients.^{30, 47, 67} Sung and colleagues report factors with an inverse relationship with compliance include female gender and chronic illnesses.⁵⁸ In addition, the strongest correlate of poor medication compliance was complexity of medication regimens, namely an increased frequency of dosing, resulted in decreased compliance with lipid-lowering therapy.⁵⁸ The number of prescribed medications was inversely correlated to compliance.^{67, 78} Our data did not exhibit a significant effect of age, gender or number of concomitantly prescribed medications on adherence with lipid-lowering therapy.

Limitations

Our cohort was comprised of patients identified as new users of lipid-lowering therapy. Studies have shown that newly treated patients were less adherent with lipid-lowering medications than patients taking the same medications for longer

periods of time.^{28, 30, 47} Our definition of a new user (patients without prescriptions for a lipid-lowering medication for a three-month pre-index time period) has been previously described in other investigations^{37, 38} while other investigations use a six-month or one-year pre-index assessment period to classify new users of therapy.^{28,47,57, 58, 82-84} Since we used a time period of three months and additionally could not determine whether patients received medication samples in a doctor's office, we may have misclassified some patients as new users of lipid-lowering therapy.

There are inherent limitations of using pharmacy claims data to assess adherence. One limitation is the inability to assess whether the patient is actually taking the medication and/or taking the medication as prescribed. Documentation of a prescription fill does not always correlate with patient adherence with therapy. This could potentially overestimate medication adherence. However, it is reasonable to assume that regularly purchased medications are being consumed.⁸⁵

Another limitation is the assumption that patients fill all their medications at the same pharmacy. Some patients may fill prescribed medications at another pharmacy leading to an underestimation of the patient's medication supply. Since we excluded patients without continuous use of the pharmacy for prescription dispensations were excluded from our study population, this would not likely have affected our results.

The accuracy of the data in the reported pharmacy claims was not verifiable. It was not possible to confirm the prescription fill information with other data sources such as medical records, pill counts, or medication diaries. In addition, pharmacy claims lack clinical information that may have an influence on patients' medication adherence, such co-morbid conditions and medication adverse effects experienced by the patient. Without this information, we could not correlate our estimates to reasons for non-adherence in this study. Thus, modeling the factors that might affect

adherence with lipid-lowering therapy may be biased due to incompleteness of the model.

Notwithstanding these limitations, pharmacy claims data can be a useful source of data in population-based studies when direct measurements are not feasible. Several studies have shown significant associations between refill adherence and other measures of adherence.^{42, 86-89} Numerous investigations have used prescription claims databases to determine the rate or degree of adherence with prescribed therapy.^{23, 42, 45, 49, 61, 78, 84, 90-97} Thus, utilizing a pharmacy claims database may represent the best means to capture utilization data of medication in a patient population.

Since the database included patients with diabetes who were dispensed lipid-lowering medications through CVS pharmacies in Pennsylvania and patients prescribed pharmacotherapy, the findings from this study may not be generalizable to the wider population of patients with diabetes.

CONCLUSION

The observations of this study indicate that adherence with lipid-lowering therapy in patients with diabetes mellitus was less than optimal. Patients prescribed a statin medication as their initial lipid-lowering medication exhibited greater adherence compared with patients prescribed non-statin medications. Non-adherence was associated with insulin therapy and non-statin medications. This data supports previous investigations that observed an effect of class of lipid-lowering medications and insulin therapy on medication adherence.

The ATP III report stresses that adherence issues need to be addressed to attain the highest possible levels of coronary heart disease risk reduction.⁶ Interventions to improve adherence include factors that focus on the patient such as

simplifying medication regimens, reinforcing and rewarding adherence, and encouraging the support of family and friends as well as factors that focus on the physician and medical office and health delivery system.

Ideally, future studies should assess the relationship between adherence and lipid levels and explore the effect of study factors such as antidiabetic medication regimen, patient beliefs, and prescriber characteristics on medication adherence. Identifying these factors would help design optimal lipid-lowering therapy regimens for patients with diabetes and develop appropriate and effective interventions to modify factors that improve patient adherence with lipid-lowering therapy.

TABLES

Table 2-1. Pharmacological management of lipid abnormalities in adult patients with diabetes

Lipid Abnormality	Target Patients	Pharmacological Options	Comments
Elevated LDL-C	<100 mg/dL	<i>First choice:</i> statin therapy <i>Second choice:</i> bile acid sequestrant resins or fenofibrate	Reducing LDL-C is the first priority
Low HDL-C	>45 mg/dL (men) >55 mg/dL (women)	Glycemic control Nicotinic acid or fibrates	Nicotinic acid is relatively contraindicated*
Elevated triglycerides	<200 mg/dL	Improved glycemic control Fibric acid derivative High-dose statin, if LDL-C is also elevated	
Combined hyperlipidemia	As above	<i>First choice:</i> improved glycemic control plus high-dose statin <i>Second choice:</i> hypoglycemic therapy plus high-dose statin plus fibric acid derivative <i>Third choice:</i> hypoglycemic control plus statin plus nicotinic acid	Combination therapy with a statin and nicotinic acid* or with gemfibrozil or fenofibrate may increase risk of myositis

* Nicotinic acid should be restricted to ≤ 2 g/day- short-acting nicotinic acid is preferred in patients with diabetes.

Abbreviations: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol

Source: Henry, RR. *Clinical Diabetes*. 2001;19(3): 113-120 adapted from American Diabetes Association. *Diabetes Care*. 2003;26(suppl 1):S82-S85.

Table 2-2. Lipid-lowering medications

Class	
Generic (brand) name	
<i>HMG CoA reductase inhibitors (Statin)</i>	<i>Bile acid sequestrants</i>
atorvastatin (Lipitor [®])	cholestyramine resin (Questran [®])
fluvastatin (Lescol [®])	colestipol (Colestid [®])
lovastatin (Mevacor [®])	
pravastatin (Pravachol [®])	<i>Nicotinic acid</i>
simvastatin (Zocor [®])	niacin (Niaspan [®])
	<i>Fibrates</i>
	fenofibrate (Tricor [®])
	gemfibrozil (Lopid [®])

Abbreviations: HMG CoA= 3-hydroxy-3-methylglutaryl coenzyme A

Table 2-3. Characteristics of the study population

Characteristic	N = 90
<i>Patient-related</i>	
Age (years)	60.3 ± 9.9 (30-79)
Gender	
Male	47 (52.2)
Female	43 (47.8)
Health Plan*	
Nurse-based diabetes management plan	49 (54.4)
Other health plan	41 (45.6)
<i>Medication-related</i>	
Antidiabetic Medication Regimen†	
Oral medication	65 (72.2)
Insulin therapy	25 (27.8)
Number of Concomitant Medications‡	8 ± 5 (1-27)
Class of Lipid-lowering Medication, by Index Prescription	
HMG-CoA reductase inhibitor	82 (91.1)
Fibrates	7 (7.8)
Bile acid sequestrants	1 (1.1)

Values expressed as number (%) or mean ± standard deviation (SD) (range).

* Health plan used to acquire the index lipid-lowering medication. Other health plans include local/state/federal programs or cash payments.

† Antidiabetic medication regimen prescribed during the observation period.

Insulin therapy includes insulin monotherapy or in combination with oral medication.

‡ Number of concomitant medications prescribed during the observation period.

Abbreviations: HMG CoA= 3-hydroxy-3-methylglutaryl coenzyme A

Table 2-4. Frequency of lipid-lowering prescription claims during a nine-month observation period

Number of Lipid-lowering Medication Prescription Claims	Number (%) of Patients
3	10 (11.1%)
4	12 (13.3%)
5	8 (8.9%)
6	8 (8.9%)
7	7 (7.8%)
8	17 (18.9%)
9	18 (20.0%)
10	7 (7.8%)
11	2 (2.2%)
12	1 (1.1%)
Total	90

Table 2-5. Mean CMA (%) by lipid-lowering medication prescribed at the index date

Index Lipid-lowering Medication	Number of Patients	CMA Mean (SD)
Statin		84.1 (22.3)
<i>HMG CoA reductase inhibitors</i>		
atorvastatin	27	87.8 (21.9)
fluvastatin	4	79.3 (23.0)
lovastatin	1	68.4
pravastatin	2	85.9 (4.2)
simvastatin	48	82.8 (23.3)
Non-Statin		70.0 (31.7)
<i>Fibrates</i>		
gemfibrozil	7	71.5 (33.9)
<i>Bile acid sequestrants</i>		
cholestyramine resin	1	59.0
Total	90	82.8 (23.4)

Abbreviations: CMA = Continuous multiple-interval measure of Medication Availability; HMG CoA= 3-hydroxy-3-methylglutaryl coenzyme A; SD = 1 standard deviation

Table 2-6. General characteristics of adherent and non-adherent patients*

Characteristic	Non-Adherent (<80%) N = 31	Adherent (≥80%) N = 59	p-value
<u>Patient-related</u>			
Age (years)	59.1 ± 11.1 (36-78)	60.9 ± 9.2 (30-79)	0.4332
Gender			0.4212
Male	18 (58.1)	29 (49.1)	
Female	13 (41.9)	30 (50.9)	
Health Plan [†]			0.3445
Nurse-based diabetes management plan	19 (61.3)	30 (50.9)	
Other health plan	12 (38.7)	29 (49.1)	
<u>Medication-related</u>			
Antidiabetic Medication Regimen [‡]			0.0297
Oral medication	18 (58.1)	47 (80.0)	
Insulin therapy	13 (41.9)	12 (20.0)	
Number of Concomitant Medications [§]	7 ± 4 (2-20)	8 ± 5 (1-27)	0.3660
Class of Index Lipid-lowering Medication			0.0802
Statin	26 (83.9)	56 (94.9)	
Non-Statin	5 (16.1)	3 (5.1)	

Values expressed as number (%) or mean ± standard deviation (SD) (range).
Percentages may not equal 100% due to rounding.

* Adherence is defined as 80% or more of the prescription dispensed.

[†] Health plan used to acquire the index lipid-lowering medication. Other health plans include local/state/federal programs or cash payments.

[‡] Antidiabetic medication regimen prescribed during the observation period.

Insulin therapy includes insulin monotherapy or in combination with oral medication.

[§] Number of concomitant medications prescribed during the observation period.

Table 2-7. Bivariate logistic regression models for adherence*

Independent Variable (IV)	Odds Ratio	95% CI _{OR}	Pr>X ²
Age (years)			
30-55	1.000		
56-65	1.320	0.441, 3.953	0.6198
>65	1.907	0.656, 5.538	0.2356
Gender			
Males	1.000		
Females	1.432	0.596, 3.443	0.4221
Health Plan [†]			
Nurse-based diabetes management plan	1.000		
Other health plan	1.531	0.632, 3.708	0.3458
Antidiabetic Medication Regimen [‡]			
Oral medications	1.000		
Insulin therapy	0.354	0.136, 0.918	0.0327
Number of Concomitant Medications [§]			
1-5	1.000		
> 5	0.589	0.244, 1.426	0.2409
Class of Index Lipid-lowering Medication			
Non-Statin	1.000		
Statin	3.590	0.797, 16.169	0.0960

* Adherence is defined as 80% or more of the prescription dispensed. For descending logistic regression model, coded as 0 = $\geq 80\%$; 1 = $< 80\%$.

[†] Health plan used to acquire the index lipid-lowering medication. Other health plans includes local/state/federal programs or cash payments.

[‡] Antidiabetic medication regimen prescribed during the observation period.

Insulin therapy includes insulin monotherapy or in combination with oral medication.

[§] Number of concomitant medications prescribed during the observation period.

Abbreviations: CI= confidence interval; OR = Odds Ratio

Table 2-8. Multivariate logistic regression models for adherence*

Independent Variable (IV)	Odds Ratio	95% CI _{OR}	Pr>X ²
Age (years)			
30-55	1.000		
56-65	0.983	0.288, 3.360	0.9785
>65	1.690	0.518, 5.520	0.3848
Gender			
Males	1.000		
Females	2.241	0.778, 6.455	0.1351
Health Plan [†]			
Nurse-based diabetes management plan	1.000		
Other health plan	2.111	0.724, 6.160	0.1714
Antidiabetic Medication Regimen [‡]			
Oral medications	1.000		
Insulin therapy	0.172	0.053, 0.554	0.0032
Number of Concomitant Medications [§]			
1-5	1.000		
> 5	2.263	0.817, 6.264	0.1161
Class of Index Lipid-lowering Medication			
Non-Statin	1.000		
Statin	3.925	0.752, 20.484	0.1048

* Adherence is defined as 80% or more of the prescription dispensed. For descending logistic regression model, coded as 0 = $\geq 80\%$; 1 = $< 80\%$.

[†] Health plan used to acquire the index lipid-lowering medication. Other health plans include local/state/federal programs or cash payments.

[‡] Antidiabetic medication regimen prescribed during the observation period.

Insulin therapy includes insulin monotherapy or in combination with oral medication.

[§] Number of concomitant medications prescribed during the observation period.

Abbreviations: CI= confidence interval; OR = Odds Ratio

Table 2-9. Final logistic regression model of adherence*

Independent Variable (IV)	Odds Ratio	95% CI _{OR}	Pr>X ²
Antidiabetic Medication Regimen [†]			
Oral medications	1.000		
Insulin therapy	0.304	0.114, 0.815	0.0180
Class of Index Lipid-lowering Medication			
Non-Statin	1.000		
Statin	4.709	0.996, 22.268	0.0506

* Adherence is defined as 80% or more of the prescription dispensed. For descending logistic regression model, coded as 0 = $\geq 80\%$; 1 = $< 80\%$.

[†] Antidiabetic medication regimen prescribed during the observation period.

Insulin therapy includes insulin monotherapy or in combination with oral medication.

Abbreviations: CI = confidence interval; OR = Odds Ratio

Table 2-10. General characteristics of adherent and non-adherent patients*

Characteristic	Non-Adherent (<90%) N = 49	Adherent (≥90%) N = 41	p-value
<u>Patient-related</u>			
Age (years)	60.3 ± 10.7 (36-79)	60.3 ± 8.9 (30-76)	0.9989
Gender			0.8030
Male	25 (51.0)	22 (53.7)	
Female	24 (49.0)	19 (46.3)	
Health Plan [†]			0.8911
Nurse-based diabetes management plan	27 (55.1)	22 (53.7)	
Other health plan	22 (44.9)	19 (46.3)	
<u>Medication-related</u>			
Antidiabetic Medication Regimen [‡]			0.5116
Oral medication	34 (69.4)	31 (75.6)	
Insulin therapy	15 (30.6)	10 (24.4)	
Number of Concomitant Medications [§]	7 ± 4 (1-20)	8 ± 6 (2-27)	0.1956
Class of Index Lipid-lowering Medication			0.6317
Statin	44 (89.8)	38 (92.7)	
Non-Statin	5 (10.2)	3 (7.3)	

Values expressed as number (%) or mean ± standard deviation (SD) (range).

* Adherence is defined as 90% or more of the prescription dispensed.

[†] Health plan used to acquire the index lipid-lowering medication. Other health plans include local/state/federal programs or cash payments.

[‡] Antidiabetic medication regimen prescribed during the observation period.

Insulin therapy includes insulin monotherapy or in combination with oral medication.

[§] Number of concomitant medications prescribed during the observation period.

Table 2-11. Bivariate logistic regression models for adherence*

Independent Variable (IV)	Odds Ratio	95% CI _{OR}	Pr>X ²
Age (years)			
30-55	1.000		
56-65	0.889	0.294, 2.685	0.8346
>65	2.240	0.799, 6.282	0.1253
Gender			
Males	1.000		
Females	0.900	0.392, 2.065	0.8031
Health Plan [†]			
Nurse-based diabetes management plan	1.000		
Other health plan	1.060	0.461, 2.438	0.8911
Antidiabetic Medication Regimen [‡]			
Oral medications	1.000		
Insulin therapy	0.731	0.287, 1.865	0.5123
Number of Concomitant Medications [§]			
1-5	1.000		
> 5	0.928	0.398, 2.166	0.8629
Class of Index Lipid-lowering Medication			
Non-Statins	1.000		
Statins	1.439	0.323, 6.423	0.6332

* Adherence is defined as 90% or more of the prescription dispensed. For descending logistic regression model, coded as 0 = $\geq 90\%$; 1 = $< 90\%$.

[†] Health plan used to acquire the index lipid-lowering medication. Other health plans include local/state/federal programs or cash payments.

[‡] Antidiabetic medication regimen prescribed during the observation period.

Insulin therapy includes insulin monotherapy or in combination with oral medication.

[§] Number of concomitant medications prescribed during the observation period.

Abbreviations: CI = confidence interval; OR = Odds Ratio

Table 2-12. Multivariate logistic regression models for adherence*

Independent (IV)	Variable	Odds Ratio	95% CI _{OR}	P<X ²
Age (years)				
	30-55	1.000		
	56-65	0.870	0.277, 2.729	0.8109
	>65	2.264	0.774, 6.621	0.1357
Gender				
	Males	1.000		
	Females	0.973	0.395, 2.397	0.9529
Health Plan [†]				
	Nurse-based diabetes management plan	1.000		
	Other health plan	1.032	0.413, 2.577	0.9468
Antidiabetic Medication Regimen [‡]				
	Oral medications	1.000		
	Insulin therapy	0.673	0.245, 1.847	0.4424
Number of Concomitant Medications [§]				
	1-5	1.000		
	> 5	1.302	0.522, 3.249	0.5714
Class of Index Lipid-lowering Medication				
	Non-Statin	1.000		
	Statin	1.152	0.240, 5.531	0.8595

* Adherence is defined as 90% or more of the prescription dispensed. For descending logistic regression model, coded as 0 = $\geq 90\%$; 1 = $< 90\%$.

[†] Health plan used to acquire the index lipid-lowering medication. Other health plans includes local/state/federal programs or cash payments.

[‡] Antidiabetic medication regimen prescribed during the observation period.

Insulin therapy includes insulin monotherapy or in combination with oral medication.

[§] Number of concomitant medications prescribed during the observation period.

Abbreviations: CI = confidence interval; OR = Odds Ratio

Table 2A-1a.

Parametric form analysis for continuous independent variables

Independent Variable	N	Coding	Dependent Variable: Adherence* Odds Ratio
Age (years)			
30-54	22	age (referent)	1.0
55-61	23	age1	1.961
62-67	25	age2	1.038
> 67	20	age3	1.615
Number of Concomitant Medications [†]			
0-3	17	conmed (referent)	1.0
4-5	23	conmed1	2.032
6-8	26	conmed2	2.000
> 8	24	conmed3	1.778

* Adherence is defined as 80% or more of the prescription dispensed. For descending logistic regression model, coded as 0 = $\geq 80\%$; 1 = $< 80\%$.

[†] Number of concomitant medications prescribed during the observation period.

Table 2A-1b.

Parametric form analysis for continuous independent variables

Independent Variable	N	Coding	Dependent Variable: Adherence* Odds Ratio
Age (years)			
0-54	22	age (referent)	1.0
55-61	23	age1	2.722
62-67	25	age2	1.375
> 67	20	age3	1.167
Number of Concomitant Medications [†]			
0-3	17	conmed (referent)	1.0
4-5	23	conmed1	1.310
6-8	26	conmed2	0.893
> 8	24	conmed3	0.688

* Adherence is defined as 90% or more of the prescription dispensed. For descending logistic regression model, coded as 0 = $\geq 90\%$; 1 = $< 90\%$.

[†] Number of concomitant medications prescribed during the observation period.

Table 2A-2. Collinearity diagnostics

Variable	Condition Index	Proportion of variation							
		Intercept	Age_re1	Age_re2	Gender	ADreg	Lipid-class	Health plan	Conmed_re
Intercept	1.00000	0.00269	0.00699	0.00676	0.01143	0.01197	0.00315	0.01163	0.01108
Age_re1	2.18303	0.000106	0.22205	0.18218	0.00573	0.00002	0.00052	0.00059	0.00270
Age_re2	2.74354	0.00376	0.02964	0.02332	0.00232	0.86124	0.00378	0.00023	0.00006
Gender	2.80216	0.000048	0.01311	0.00024	0.36219	0.00104	0.00002	0.38553	0.00249
ADreg	3.70544	0.000105	0.09404	0.05045	0.13163	0.02761	0.00007	0.04744	0.76032
Lipidclass	4.05600	0.01067	0.19784	0.08278	0.46242	0.09254	0.02028	0.55419	0.02195
Health plan	5.21337	0.06460	0.41841	0.65017	0.00327	0.00216	0.13191	0.00007	0.18745
Conmed_re	10.6426	0.91803	0.01793	0.00410	0.02101	0.00342	0.84027	0.00047	0.01395

Table 2A-3a.

Log Likelihood (LL) ratio test: logistic regression model of adherence*

Model	-2 LL	Df	LL Difference	χ^2_{df}	Significance
Full Model	94.846	12			
Reduced Model	100.110	5 [†]	5.264	11.07	NS

*Adherence is defined as 80% or more of the prescription dispensed. For descending logistic regression model, coded as 0 = $\geq 80\%$; 1 = $< 80\%$.

[†] Df of full model minus reduced model

Full Model includes all univariate variables and two-way interaction terms

Reduced Model includes all univariate variables

Abbreviations: -2LL = -2 Log Likelihood; Df = degrees of freedom;

NS = not significant

Table 2A-3b.

Log Likelihood (LL) ratio test: logistic regression model of adherence*

Model	-2 LL	Df	LL Difference	χ^2_{df}	Significance
Full Model	111.691	12			
Reduced Model	119.208	5 [†]	7.517	11.07	NS

* Adherence is defined as 90% or more of the prescription dispensed. For descending logistic regression model, coded as 0 = $\geq 90\%$; 1 = $< 90\%$.

[†] Df of full model minus reduced model

Full Model includes all univariate variables and two-way interaction terms

Reduced Model includes all univariate variables

Abbreviations: -2LL = -2 Log Likelihood; Df = degrees of freedom;

NS = not significant

Table 2A-4a. Test for confounding variables in the logistic regression modeling of adherence*

Potential Confounding Independent Variables	Class of Index Lipid-lowering Medication	Adherence χ^2 (p-value)
Age		
30-55 years (referent)	1.0	1.0
56-65 years	0.1672 (0.6826)	0.0290 (0.8647)
>65 years	2.7668 (0.0962)	1.1810 (0.2772)
Gender		
Male (referent)	1.0	1.0
Female	0.0174 (0.8951)	0.6469 (0.4212)
Health Insurance Plan [†]		
Nurse-based diabetes management plan (referent)	1.0	1.0
Other Health Plans	1.4958 (0.2213)	0.8935 (0.3445)
Antidiabetic Medication Regimen [‡]		
Oral Medications (referent)	1.0	1.0
Insulin Therapy	1.0216 (0.3121)	4.7246 (0.0297)
Number of Concomitant Medications [§]		
1-5 (referent)	1.0	1.0
>5	0.3659 (0.5453)	1.3860 (0.2391)

* Adherence is defined as 80% or more of the prescription dispensed. For descending logistic regression model, coded as 0 = $\geq 80\%$; 1 = $< 80\%$.

[†] Health plan used to acquire the index lipid-lowering medication. Other health plans includes local/state/federal programs or cash payments.

[‡] Antidiabetic medication regimen prescribed during the observation period.

Insulin therapy includes insulin monotherapy or in combination with oral medication.

[§] Number of concomitant medications prescribed during the observation period.

Table 2A-4b. Test for confounding variables in the logistic regression modeling of adherence*

Potential Confounding Independent Variables	Class of Index Lipid-lowering Medication	Adherence
	χ^2 (p-value)	
Age		
30-55 years (referent)	1.0	1.0
56-65 years	0.1672 (0.6826)	1.5871 (0.2077)
>65 years	2.7668 (0.0962)	3.9497 (0.0469)
Gender		
Male (referent)	1.0	1.0
Female	0.0174 (0.8951)	0.0623 (0.8030)
Health Insurance Plan [†]		
Nurse-based diabetes management plan (referent)	1.0	1.0
Other Health Plans	1.4958 (0.2213)	0.0188 (0.8911)
Antidiabetic Medication Regimen [‡]		
Oral Medications (referent)	1.0	1.0
Insulin Therapy	1.0216 (0.3121)	0.4308 (0.5116)
Number of Concomitant Medications [§]		
1-5 (referent)	1.0	1.0
>5	0.3659 (0.5453)	0.0299 (0.8629)

* Adherence is defined as 90% or more of the prescription dispensed. For descending logistic regression model, coded as 0 = $\geq 90\%$; 1 = $< 90\%$.

[†] Health plan used to acquire the index lipid-lowering medication. Other health plans includes local/state/federal programs or cash payments.

[‡] Antidiabetic medication regimen prescribed during the observation period.

Insulin therapy includes insulin monotherapy or in combination with oral medication.

[§] Number of concomitant medications prescribed during the observation period.

FIGURES

Figure 2-1. Eligibility criteria of study population

Figure 2A-1. Frequency distribution of the measurement: adherence (80%)

Figure 2A-2. Frequency distribution of the measurement: adherence (90%)

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Study 3

Using Prescription Claim Records to Evaluate Persistence with Lipid-lowering Medications in Patients with Diabetes Mellitus

ABSTRACT

Background: Dyslipidemia, a risk factor for cardiovascular disease, is modifiable in patients with diabetes mellitus. However, treatment of diabetic dyslipidemia may require long-term lipid-lowering pharmacotherapy. Studies have shown low rates of persistence with lipid-lowering medications especially in the first year of treatment; however, few studies have specifically examined persistence with lipid-lowering therapy in patients with diabetes.

Objective: The objective of this study was to assess persistence with lipid-lowering medications and evaluate patient- and medication-related characteristics that may influence discontinuation of lipid-lowering treatment in patients with diabetes mellitus.

Methods: A retrospective study of pharmacy claim records of patients with diabetes mellitus identified new users of lipid-lowering therapy. Patients with an initial prescription dispensing for a lipid-lowering medication between November 1, 1997 and October 31, 1998 were observed for up to 18 months. Patients were classified as persistent with lipid-lowering therapy if the last prescription filled during the observation period provided a quantity of medication to cover the period until the end of follow-up (i.e., April 30, 1999). Discontinuation was flagged by identifying patients who (1) had more than three times the days supplied elapsed between the last prescription fill for lipid-lowering medication and the next fill or the end of the follow-up period; (2) switched to a medication in a class different than the index medication; or (3) had no refills for the lipid-lowering medication during the follow-up period. Switching of index lipid-lowering medication and re-initiation of lipid-lowering therapy

during the observation period were evaluated as separate endpoints. Kaplan-Meier methods and Cox regression models estimated the rate of discontinuation and identified factors associated with discontinuation of lipid-lowering therapy, respectively.

Results: A total of 190 patients with diabetes (53% males; mean age, 59.3 ± 10.4 years) had at least one prescription claim for a lipid-lowering medication during the observation period; the majority (87%) of patients were prescribed a statin medication. Overall, 58% of patients persisted with lipid-lowering therapy during the observation period. Persistency differed according to the class of lipid-lowering medication dispensed at the index date: patients prescribed statins were more persistent compared to patients prescribed non-statin medications (Log-rank $\chi^2=7.9101$; $p=0.0049$). Of the 165 patients prescribed statin medications, 74% persisted with treatment over six months, 59% over 12 months, and 46% over 18 months of observation. At 6 months, 60% of patients persisted with non-statin treatment; only 26% of patients were persistent over 12 and 18 months of observation. Approximately 26% of patients who discontinued treatment did so after the initial dispensing. One in 10 patients switched to another lipid-lowering medication: the majority of switches were to another medication within the same class. Compared with patients prescribed statins, patients prescribed non-statin medications were more than twice as likely to discontinue treatment (HR=2.240; 95% CI= 1.260, 3.982; $p=0.0060$). Age, gender, type of health plan, number of concomitantly prescribed medications and antidiabetic medication regimen, were not found to be a significant influence on discontinuation of lipid-lowering therapy.

Conclusions: Persistence with lipid-lowering therapy in patients with diabetes mellitus was sub-optimal. Patients prescribed statins were significantly more likely to persist with lipid-lowering therapy than patients prescribed non-statin medications.

More research is needed to elucidate factors that may influence persistence with lipid-lowering therapy in this patient population. These findings highlight the need for health care providers to work together with patients to improve persistence with lipid-lowering medications to reduce the risk of major cardiovascular events in patients with diabetes mellitus.

Key Words: lipid-lowering therapy, dyslipidemia, diabetes, persistence, discontinuation, switching

INTRODUCTION

Serum triglycerides, total cholesterol and low density lipoprotein-cholesterol (LDL-C) levels tend to be elevated in patients with type 2 diabetes even in patients with good glycemic control^{1, 2} whereas a similar pattern of dyslipidemia is observed in type 1 diabetes usually when glycemic control is poor.^{3, 4} This characteristic pattern is termed diabetic dyslipidemia.⁵

Along with hypertension and smoking, diabetes and dyslipidemia are well known risk factors for cardiovascular disease. The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III considers diabetes a coronary heart disease (CHD) risk equivalent because it confers a high risk of new CHD within 10 years in part because of its association with multiple risk factors.⁶

The United Kingdom Prospective Diabetes Study (UKPDS) observed an association of coronary disease risk with LDL-C among approximately 3000 patients with type 2 diabetes.⁷ Coronary artery disease was significantly associated with increased concentrations of LDL-C and triglycerides and decreased concentrations of high density lipoprotein cholesterol (HDL-C).⁷ Results from the Strong Heart Study demonstrated that every 10 mg/dL increase in LDL-C (starting with a low of 70 mg/dL) was associated with a 12% increase in risk of cardiovascular disease among patients with type 2 diabetes.⁸

Primary and secondary intervention trials have demonstrated that single medication lipid-lowering therapy can reduce cardiovascular morbidity and mortality.⁹⁻¹³ Although these trials included few patients with diabetes, post-hoc subgroup analyses of the Helsinki Heart Study, the Scandinavian Simvastatin Survival Study (4S) and the Cholesterol and Recurrent Events Study (CARE) trial indicate that lipid-lowering intervention in diabetes is likely to reduce the cardiovascular event rate.^{9, 14-17} The Heart Protection Study provided evidence that a

reduction in LDL-C would significantly reduce the risk of major vascular events such as first non-fatal myocardial infarction, coronary death, or stroke in patients with diabetes.¹ In addition, several trials are underway to determine the efficacy of lipid-lowering therapy for the primary and secondary prevention of CHD in patients with diabetes.¹⁸⁻²¹ Nonetheless, these studies suggest that dyslipidemia, a major risk factor for cardiovascular disease, is modifiable in patients with diabetes mellitus.

In the Diabetes Atorvastatin Lipid Intervention (DALI) trial of 217 patients with type 2 diabetes mellitus, 30-weeks of 10mg and 80mg (i.e., the lowest and highest doses) atorvastatin produced significant reductions in plasma triglyceride and LDL-C levels compared with placebo-treated patients.²² In a comparison with 1998 target values defined by the American Diabetes Association (ADA), >75% of patients in both treatment groups reached triglyceride treatment goals and 71% and 85% of patients treated with 10mg and 80mg atorvastatin respectively, reached LDL-C treatment goals.²²

While the efficacy of lipid-lowering medications has been proven during clinical trials, the effectiveness of lipid-lowering pharmacotherapy is partly dependent upon patient persistence with prescribed medications. Discontinuation of these medications may lead to failure to achieve lipid level goals potentially placing the patient with diabetes at risk for serious cardiovascular events such as coronary heart disease, myocardial infarction or stroke.

Several studies have shown that persistence with lipid-lowering therapy at one-year is often sub-optimal.²³⁻³³ For example, 32% of patients receiving lipid-lowering medication discontinued therapy within one year of initiation, with rates of discontinuation for lovastatin, gemfibrozil, bile acid sequestrants, and niacin reported as 13%, 28%, 34%, and 45%, respectively.²³ Using the United Kingdom General Practice Research Database (UK GPRD) for 22,408 patients who initiated lipid-

lowering therapy, only 69.8% of patients with a statin, 56.4% of patients with a fibrate, and 38.4% of patients prescribed a non-statin, non-fibrate medication still used the initial medication at the end of one-year.²⁴ Similarly, at 12 months, 60% of patients discontinued lipid-lowering therapy in a prospective study of 610 adults prescribed simvastatin, pravastatin or gemfibrozil; half of the discontinuations occurred within the first 3 months.²⁵ In this study, the predominant reasons for discontinuation included poor efficacy (32%) and the patient's uncertainty about the need for treatment (32%) while 7% discontinued due to adverse events.²⁵

Studies of longer-term usage of lipid-lowering medications report similar findings. In 970 patients enrolled in a lipid clinic, four-year cumulative discontinuation rates for niacin and bile acid sequestrants were 71% and 83%, respectively, in comparison with 28% for statin medications.³³ Similarly, five-year post study continuation rates were higher for statin users (64.3%) than for patients taking other lipid-lowering medications (36.6%).²⁶ A cohort study of 983 new users of statin medications demonstrated that statin use declined sharply as 80% of patients remained on therapy 45 days after initiation and only 33% and 13% of patients persisted with therapy at one and five years, respectively.²⁷ Of 3623 new users of statin therapy, 50% persisted with lipid-lowering therapy continuously for more than three years.²⁸

These studies demonstrate similar findings despite utilizing different methodologies to assess persistence with lipid-lowering therapy in various patient populations: patients' chronic use of lipid-lowering medication is poor with many patients discontinuing treatment as early as three months.

Few studies examined an association with diabetes and persistency with lipid-lowering medications. In a study of patients ≥ 65 years of age, diabetes was

associated with high persistence.²⁶ Treatment continuation with lipid-lowering medications was more frequent in patients with diabetes in the UK GPRD.²⁴

Non-persistence (i.e., discontinuation) of the recommended medication regimen poses a major barrier to achieving NCEP ATP III^{*} ⁶ recommended target goals for cholesterol management. Long-term pharmacotherapy is needed to treat dyslipidemia in patients who do not benefit from lifestyle modifications.⁶ Providing there has not been a lifestyle modification to compensate, patients with established dyslipidemia can no longer benefit from a reduction in lipid levels if they discontinue lipid-lowering therapy.

For most patients who persist with pharmacotherapy the benefits outweigh the risks. It has been shown that patients with dyslipidemia taking statin medication regularly had significant improvement in serum lipid levels in contrast with non-adherent patients. Results from the Helsinki Heart Study, a five-year study of 2046 middle-aged men with hypercholesterolemia, demonstrated that mean changes in lipid parameters varied with compliance with prescribed medication (Table 3-1).³⁴ In summary, over a five-year period, patients with $\geq 90\%$ compliance showed a greater mean change in lipid parameters than patients compliant with $< 50\%$ of prescribed gemfibrozil medication. After making allowances for non-compliance (18% of patients were non-compliant defined as $< 80\%$ of the scheduled medication taken) in the Heart Protection Study, actual use of 40mg simvastatin daily would lower LDL-C by about 58 mg/dL and reduce the rates of heart attacks, strokes and revascularization by

^{*} ATP I, published in 1988, identified LDL-C as the primary target of therapy and emphasized clinical management of patients with higher levels of LDL-C. ATP II, published in 1993, set a lower LDL-C goal, specifically a level equal to or less than 100 mg/dL in patients who already have CHD. ATP III adds a focus on prevention of CHD in persons with multiple risk factors. In the 2001 ATP III report, LDL-C remains the primary target of therapy. A key feature of ATP III is the definition of cut points for LDL-C goals and for initiation of LDL-lowering therapy.

about one-third.¹ Thus, in patients with a chronic disease such as diabetes mellitus, reductions in LDL-C levels and major vascular events are beneficial and continuous use of lipid-lowering therapy has an essential role.¹

These studies have documented a major role of lipid-lowering therapy in reducing the risks of major cardiovascular events and the importance of persistence with lipid-lowering medications. Many studies demonstrate low persistence rates with lipid-lowering therapy in specific patient populations. Thus, the aim of this study was to evaluate persistence with lipid-lowering medications in patients with diabetes mellitus using prescription claims data. The present study was designed to 1) estimate persistence in patients identified as new users of lipid-lowering medications; 2) evaluate switching of index lipid-lowering therapy; and 3) identify patient- and medication-related characteristics that may influence non-persistence with lipid-lowering therapy in patients with diabetes mellitus.

METHODS

Study Design

This was a retrospective cohort study of patients with diabetes using pharmacy claim prescription records.

Dataset

Data examined in the analysis were obtained from 198 Consumer Value Stores (CVS) pharmacies located in Pennsylvania that provided prescription medications for 4503 patients with diabetes identified by specific therapeutic classes (insulins, oral antidiabetic agents-sulfonylureas and other oral antidiabetic agents) between April 27, 1997 and May 16, 1999. Patients were either enrolled in a nurse-based diabetes management plan or acquired their prescription through a local/state/federal program or cash payments.

This prescription claims data extract includes records of dispensed outpatient pharmacy prescription records for all prescriptions. The following information was obtained from the CVS dataset for this analysis: patient characteristic variables such as birth date, gender, and health plan agency as well as prescription related variables including quantity of medication dispensed, days supply of medication dispensed, and date the prescription was dispensed. No personally identifying information was provided.

Study Population

Patients were eligible for inclusion in the study population if they (1) had a prescription claim for at least one lipid-lowering medication (see Table 3-2) between November 1, 1997 and October 31, 1998 (n=865); (2) were a new user of lipid-lowering therapy (n=728); (3) had no dispensations for combination lipid-lowering medication (defined as a claim for a second lipid-lowering medication filled within 30 days of the index medication) (n=727); and (4) filled a prescription for any medication from the CVS pharmacy in the six months prior to the index date and in the last three months of the observation period (i.e., a patient had at least one prescription dispensed for any medication during these time points) (n=190).

Presumed new users were defined as patients having no prescription claim for a lipid-lowering medication in the six months before the index date. Thus, patients with less than six months of data prior to the index date were excluded. This time period to identify new users of therapy has been previously described.^{35, 36}

The date of the first lipid-lowering prescription claim between November 1, 1997 and October 31, 1998 was classified as the index date. Each patient was observed for up to 18 months, through April 30, 1999. Person-time of observation was calculated as the amount of time from the index date (i.e., date of entry into the cohort) until the date of discontinuation or the end of the follow-up period.

Potential Factors of Association with Persistence

Baseline study factors, such as age, gender, health plan, antidiabetic medication regimen and number of concurrent medications, that may influence persistence were examined. These factors were classified as patient-related characteristics (age, gender, health plan) or medication-related characteristics (antidiabetic medication regimen, number of concurrent medications) constructed from the prescription profile of each patient. The primary independent variable, class of lipid-lowering medication, was based on the prescription filled on the index date.

Age was based on the transaction date for the index lipid-lowering medication prescription fill and was treated as a continuous variable in the analyses. The patients' health plan, used to acquire the index lipid-lowering medication, was dichotomized as either a nurse-based diabetes management plan or other (e.g., local/state/federal programs or cash payments).

Based on the antidiabetic regimen prescribed within 90 days of the index date, antidiabetic medication regimen was classified as oral medication for patients dispensed only oral antidiabetic medications or Insulin Therapy for patients dispensed either insulin monotherapy or insulin in combination with oral antidiabetic medications. The number of concurrent medications dispensed in the three months prior to the index date consisted of a count of all medications, excluding lipid-lowering medications and diabetic supplies such as blood glucose test strips or tuberculin syringes; this variable was treated as a continuous variable for analysis. This categorization of baseline (i.e., three months of pre-index data) has been previously described.²⁴

Data Analysis

Prescription claims for all patients who satisfied the inclusion/exclusion criteria were examined for an 18-month follow-up period.

Dataset Preparation

Prior to analysis, the dataset was checked for outliers for the following variables: days supply and posted transaction date of the prescription claim. Potential outliers were further examined; no data corrections were necessary in this data set. Patients with incomplete records (i.e., missing transaction dates) for lipid-lowering medications were excluded from the analysis (n=173).

Measures of Persistence, Discontinuation, and Switching

Patients were classified as persistent with lipid-lowering therapy if the last prescription filled during the observation period provided sufficient medication (i.e., three times the days supply) to cover the period until the end of follow-up (i.e., April 30, 1999). Patients were observed until the first occurrence of one of the following events: discontinuation of lipid-lowering therapy or end of the follow-up period (right censored).

Discontinuation of lipid-lowering therapy was identified if a patient (1) had more than three times the days supplied elapsed between the last prescription fill for lipid-lowering medication and the next fill or the end of the follow-up period; (2) switched to a medication in a class different than the index medication; or (3) had no refills for the lipid-lowering medication. Since the majority (90%) of patients were dispensed a 30 day supply, we utilized three times the elapsed days supply (which corresponds to approximately three months) beyond last fill as part of the definition for discontinuation. These time frames have been previously described in analyses of persistence with antihypertensive medications³⁷⁻³⁹ and lipid-lowering medications^{24, 29}

A medication switch was identified if the patient filled a prescription for a lipid-lowering medication other than the index medication during the observation period. As the exact date of discontinuation was unknown, the date of the last prescription fill prior to the switch was assigned as the date of discontinuation. Patients were allowed to switch from one medication to another as long as it remained in the same class as the index medication since class of lipid-lowering medication was evaluated as the primary independent variable.

Univariate Analysis

Descriptive statistics, mean $\pm$ SD (range) for continuous variables and frequencies (percentage) for categorical variables, were used to present patient- and medication-related characteristics. Chi-square (X^2) tests and t-tests were performed to determine significant differences for the categorical and continuous variables, respectively. X^2 and t-tests were used to analyze the proportions of study factors between patients who were persisted or discontinued with lipid-lowering treatment and by class of index lipid-lowering medication.

The Shapiro-Wilk test of normality was used to assess the frequency distribution of the continuous variables: age and number of concurrent prescription medications. Age was normally distributed (W statistic= 0.9867; $p=0.0697$) while the number of concurrent prescription medications was not normally distributed as demonstrated by a statistically significant Shapiro-Wilk test (W statistic= 0.9017; $p<0.0001$); non-parametric rank tests were used to determine significant differences for the later variable. The frequency distribution of the measurement for time to discontinuation is shown in Figure 3A-1.

Multivariate Analysis

Time-to-event (survival) analysis methodology was used to evaluate discontinuation with lipid-lowering therapy. Data was censored for patients persisting

with lipid-lowering medication on the last day of the follow-up period or if three times the days supply plus the transaction date of the last refill met or exceeded the last day of the follow-up period. Because the inclusion criteria required all patients in the cohort to continuously use the pharmacy for dispensations of prescription medications during the observation period, no patient was censored due to loss to follow-up.

Kaplan-Meier curves illustrated the time course of discontinuation with lipid-lowering therapy by class of index lipid-lowering medication (statin or non-statin). Statistical differences between time-to-event curves were determined by the log-rank test.

The Cox proportional hazards regression model generates hazard ratios (HR) and 95% confidence intervals (CI), which estimate the relative rates of persistency (i.e., discontinuation) with lipid-lowering therapy for baseline patient- and medication-related characteristics compared to a reference group.

Testing the Proportional Hazards Assumption

Before creating the Cox regression model, the proportional hazards assumption for each categorical variable was tested (i.e., ensuring that the HR remained constant over the follow-up period) by visual inspection of log(-log) curves of the time-to-discontinuation for the respective subgroups.⁴⁰⁻⁴² For non-proportional variables that significantly influences non-persistency with lipid-lowering therapy in the multivariate and bivariate Cox models, a modified Cox model would include stratification by the predictive variable. No study factor had an obvious violation of the proportional hazards assumption (Figures 3A-2 to 3A-5).

Assessment of Collinearity

The presence of collinearity between the independent variables was examined.^{41, 43} Independent variables with a condition index greater than 30

(moderate to severe collinearity) and proportion of variations greater than 0.5 were further examined for collinearity with other independent variables. If collinearity were detected between two variables, the variable showing the strongest association with discontinuation of lipid-lowering therapy would remain in the model. None of the six study variables exhibited signs of collinearity (Table 3A-1).

Assessment of Potential Confounding Variables

Based on the technique of Kleinbaum,⁴¹ the effect of potential confounding variables (age, gender, health plan, antidiabetic medication regimen and number of concomitant medications) was examined. The model containing only the primary independent variable, class of index lipid-lowering medication (model A) was compared with models containing each potential confounding variable along with the primary independent variable (adjusted model). The estimated HR from model A was compared with the estimated HR from the adjusted models. If the two estimates were meaningfully different, then confounding due to the variable in the adjusted model was identified. In addition, the -2 Log-Likelihood (LL) difference in model A versus the adjusted models was tested for significance using X^2 test values. Confounding was not present if the -2LL difference was less than the X^2 statistic. No study factor was identified as a potential confounding variable (Table 3A-2).

Assessment of Multiplicative Interactions

Fitting models that included two- and three-way interaction terms with the independent variables tested the presence of an interaction between the independent variables was assessed using the -2 LL difference between the models (i.e., the Chunk test) as described by Kleinbaum.⁴¹ The -2 LL difference in the model versus the model with reduced terms was tested for significance using X^2 test values (Table 3A-3). Interaction was not present if the -2 LL difference was less than the X^2 statistic. Significant interaction terms were tested in the models of independent

predictors using backward elimination as described by Kleinbaum.⁴¹ No significant two- or three-way interaction terms were identified using this methodology ($p>0.1402$).

Cox Regression Model: Time to Discontinuation with Lipid-lowering Therapy

The Cox regression model used non-persistence or time to discontinuation, in days, as the dependent variable. The procedure applied to select the most parsimonious (i.e., best) model from all possible model (bivariate and multivariate) combinations was based on the methodology described by Parmar and Machin.⁴⁰ The values of the LR statistic for each model were compared with a χ^2 distribution ($p<0.05$), using the appropriate degrees of freedom (Table 3A-4). The model with the smallest associated p-value was selected as the final model that predicted time to discontinuation of lipid-lowering therapy; a stepwise procedure of model selection (entry criteria=0.10) confirmed this choice.

Residuals were examined to investigate the lack of fit of the final model to a given patient such as a patient who discontinues very early or very late with respect to other patients with similar characteristics. Residuals from the final Cox regression model were plotted against the value of the linear predictor as described in Marubini and Valsecchi.⁴² For the model to have an overall good fit, it was expected that the dots would scatter around zero without showing any particular structure. Upon visual examination of the plots, there was no indication of a lack of fit of the model to the individual observations (Figures 3A-6 and 3A-7).

The *a priori* alpha level of significance was set at $p<0.05$. All data analyses were conducted using SAS release 8.2.⁴⁴

RESULTS

Description of the Study Population

Lipid-lowering medication prescription claims were available for 1276 patients. Of these patients, 411 were excluded because they did not have at least one prescription claim for a lipid-lowering medication between November 1, 1997 and October 31, 1998 and incomplete transaction dates for all lipid-lowering prescription claims during the observation period; 137 were current users of lipid-lowering therapy; 537 did not continuously use the pharmacy during the observation period (i.e., a prescription claim for any medication in the six months prior to the index date and in the last three months of the observation period); and one patient was prescribed combination lipid-lowering therapy (Figure 3-1). A total of 190 patients were included in the study analyses: 100 (53%) males and 90 (47%) females with an average age of 59.3 ± 10.4 years (range, 32-80 years). These patients were followed for a total of 47,372 person-days, a mean of 248 person-days.

Characteristics of the study population are shown in Table 3-3. Half (50%) of the patients were enrolled in the health plan that provided a nurse-based diabetes management plan. A majority (75%) of patients did not receive a prescription for insulin therapy within 90 days of the index date. At baseline (i.e., three months prior to the index date), patients were prescribed an average of 5 ± 3 concurrent medications other than lipid-lowering medications and diabetic supplies.

Statins were the most frequently (87%) prescribed lipid-lowering medication at the index date; 15 patients were prescribed fibrates, nine patients were prescribed a bile acid sequestrant and one patient was prescribed nicotinic acid. Patient- and medication-related characteristics were similar between patients prescribed a statin and non-statin medication; no statistically significant differences were observed ($p \geq 0.1340$) (Table 3-4).

Patterns of Persistence and Discontinuation with Lipid-lowering Medication

In general, persistence with lipid-lowering therapy was low. Overall, 58% of patients persisted with lipid-lowering medication. Patient- and medication-related characteristics stratified according to persistence or discontinuation are shown in Table 3-5. Class of index lipid-lowering medication was statistically significant ($p=0.0176$): patients prescribed statins were more likely to be persistent than patients prescribed non-statin medications. Proportions for all other study factors were similar among patients who persisted with lipid-lowering therapy and those patients who discontinued treatment.

Of the 165 patients prescribed statin medications, 74% persisted with treatment over six months, 59% over 12 months, and 46% over 18 months of observation. At six months, 60% of patients in the non-statin group persisted with treatment; only 26% of patients were persistent over 12 and 18 months of observation. Kaplan-Meier curves of non-persistence statistically differed for patients prescribed statin and non-statin therapy (Log-rank $X^2 = 7.9101$; $p = 0.0049$) (Figure 3-2). It should be noted that for both classes of lipid-lowering medications there was a steep drop in patients persisting with therapy around 90 days; a sensitivity analysis was conducted and is discussed below.

Among patients who discontinued treatment, 23 (26%) patients interrupted treatment after a single prescription. When the data for patients who discontinued after a single prescription fill were excluded from analysis, substantial non-persistence remained: only 47% and 68% of patients prescribed non-statin and statin therapy, respectively, persisted with lipid-lowering therapy at 18 months although the statistical difference between the classes was no longer observed (Log-rank $X^2=3.5037$; $p=0.0612$) (Figure 3-3). In contrast to Figure 3-2, the steep drop in the two curves disappears. This may be due to classification of the time to discontinuation

variable (i.e., three times the days supply). In this patient population, the majority of patients were dispensed a 30 day supply of medication. Thus, using this classification, time of discontinuation would equal (3X30) or 90 days for patients who discontinued after first fill. Since in actuality patients may fill a prescription only once, these patients were included in subsequent analyses.

Of the 87 patients who discontinued lipid-lowering therapy, 28 (32%) restarted lipid-lowering medication during the observation period; the median time to re-initiation was 63 days (range 2-316 days). The majority of patients (22, 79%) remained with the same medication as prescribed at the index date with four patients prescribed a higher dosage while six patients restarted with another medication in the same class as the index lipid-lowering medication (Table 3-6). Almost half (43%) restarted therapy after the initial lipid-lowering medication prescription was not refilled.

Switching of Lipid-lowering Medications

Patients were classified as switching medication if they filled a prescription for a lipid-lowering medication other than the index medication during the observation period. Overall, 19 (10%) of patients switched to another lipid-lowering medication. The majority (84%) of the patients who switched medication changed to another medication in the same class as the index lipid-lowering medication (Table 3-7). Fifteen patients prescribed a statin medication switched to a different statin medication while two patients switched to a non-statin medication. Of these patients, one patient switched back to the index statin medication. Of the 25 patients initially prescribed a non-statin medication, one patient each switched to another non-statin and statin medication during the observation period.

Predictors of Time to Discontinuation

Hazard ratios (HR) and 95% CI for all study factors that potentially influence discontinuation with lipid-lowering therapy are shown in Table 3-8. Controlling for all

study factors, class of index lipid-lowering medication was a significant predictor of discontinuation of treatment ($p=0.0051$). Patients prescribed insulin therapy were 50% more likely to discontinue lipid-lowering therapy than patients prescribed oral antidiabetic medications only, although this study factor did not significantly influence discontinuation ($p=0.1706$). All other variables, age, gender, health plan and number of concomitantly prescribed medications had little to no effect on discontinuation with lipid-lowering therapy in this patient population ($p\geq 0.4720$).

The final Cox regression model showed that discontinuation with lipid-lowering therapy was related to class of index lipid-lowering medication (Table 3-9). Compared with patients prescribed statin medications, patients prescribed non-statin medications were more than twice as likely to discontinue lipid-lowering therapy ($HR=2.240$; 95% CI= 1.260, 3.982; $p=0.0060$). Inclusion of other study factors or interaction terms into the Cox regression model did not significantly influence non-persistence with lipid-lowering therapy.

DISCUSSION

Our findings provide evidence of low persistence with lipid-lowering medications in patients with diabetes. While few studies have demonstrated that diabetes was related to higher persistence with lipid-lowering therapy^{24, 26-30} this study provided an opportunity to evaluate persistence with lipid-lowering therapy among patients with diabetes. Our findings extend the information previously published in other patient populations.^{23-25, 28-32}

Our data supports the findings of other investigations²³⁻²⁵ in that patients prescribed statin medications are more likely to persist with lipid-lowering therapy than patients prescribed non-statin medications. Since the reason for discontinuation or change in therapy (i.e., switches or dosage changes) is not captured in pharmacy

claims data, we could not determine why more patients continued with statin therapy than non-statin treatment at the end of six, 12, and 18 months of observation. These findings may reflect greater convenience of dosing regimens for statins or differing adverse event profiles of these medications.^{26, 45} Therapeutic ineffectiveness, patient's perception of need for therapy and adverse events have been reported as a contributing factors for discontinuation of lipid-lowering therapy.^{23, 25}

Although bile acid sequestrants, fibrates and nicotinic acid are prescribed to treat dyslipidemia, statins are recommended as first-line pharmacotherapy in the majority of hyperlipidemic patients, including patients with diabetes mellitus in part because of their potency, convenient dosing and tolerability.⁴⁶⁻⁴⁸ Statins, first introduced in the United States in 1987, reduce LDL-C levels, raise HDL-C levels and recently have been shown to reduce triglyceride levels as well.⁴⁹ Major statin trials have established the value of lowering LDL-C and triglyceride levels in reducing the rate of major cardiovascular events.⁹⁻¹³ Subgroup analyses of some of these landmark trials suggest that statins have beneficial effects across the lipid profile and reduce major cardiovascular events in patients with type 2 diabetes. It was not unexpected that the majority of patients in our cohort were prescribed statin medications.

An interesting finding was that the majority of patients who switched medication replaced their initial medication with another medication from the same class. Similar to our results, Yang and colleagues reported that 13% of patients switched to another lipid-lowering medication; almost half of these patients remained within the same class of medication as the initial medication.²⁴ Compared with patients who continued lipid-lowering treatment, patients who switched therapy frequently received non-statin medications as the initial therapy.²⁴ These findings may reflect greater convenience of dosing regimens for statins.^{26, 45} Poor palatability and

multiple dosing frequency of some of the non-statin medications (e.g., bile acid sequestrants) are related to poor adherence.⁵⁰ Therapeutic ineffectiveness, patient's perception of need for therapy and adverse events have been reported as a contributing factors for discontinuation of lipid-lowering therapy.^{23, 25, 45}

In an analysis of the influence of patient- and medication-related characteristics on discontinuation of lipid-lowering therapy, we found that patients prescribed insulin therapy (i.e., either insulin monotherapy or insulin in combination with oral antidiabetic medications) were more likely to discontinue lipid-lowering treatment than patients prescribed oral medications only. These findings are consistent with those of Larsen and colleagues who observed that patients who received insulin therapy were at a 38% higher risk for discontinuation with statin therapy than patients treated with oral antidiabetic agents.²⁸ It is known that insulin therapy is complex: the need to mix and inject insulin preparations and taking multiple injections combined with the fear of injections may result in poor adherence with this treatment regimen⁵¹⁻⁵⁴ which may lead to poor persistency with other medications. Further study is needed to examine antidiabetic medication regimen as a covariate on persistence with lipid-lowering medications among patients with diabetes mellitus.

The relationship between other predictive study factors and persistence with lipid-lowering medications has been studied although with inconsistent results. For example, older age was associated with higher persistence.^{24, 25, 26} The use of concurrent cardiovascular medications was associated with a higher rate of treatment continuation^{24, 25} while the number of non-cardiovascular medications was inversely associated with higher continuation rates.^{24, 26} Yang and colleagues found that females were more likely to discontinue lipid-lowering therapy²⁴ while Larsen and colleagues did not observe an association with gender and treatment continuation.²⁸ Our findings did not indicate an effect of age, gender or number of concomitantly

prescribed medications on discontinuation with lipid-lowering therapy in our patient population.

Limitations

Even though it is an imperfect measure of the patients' lifetime prescription history, the first date of a prescription fill is commonly used as the time the patient enters the cohort. Many researchers use a one-year pre-index time frame to assess classification of new and long-term users^{24, 28, 37, 38, 55-57} while others use shorter periods of six to ten months.^{35, 58} Our objective was to estimate persistence over 18 months of follow-up and two years of prescription claims were available in this database thus only six months of data was available for pre-index assessments of new users of therapy. Although reports on methodology of measuring persistence with medications state that at least six months is sufficient to identify patient as incident users of therapy^{59, 60} this shorter time period may have led to misclassification of new users of lipid-lowering therapy that could affect our study results, especially since we were not able to determine whether patients received medication samples in a doctor's office.

Since the database included patients with diabetes who were dispensed lipid-lowering medications through CVS pharmacies in Pennsylvania, the results from this study may not be generalizable to the wider population of patients with diabetes.

While claims data provide some advantage related to the availability to perform pharmacoepidemiological analyses, they also have a number of limitations that could affect the validity of study results. One limitation is the assumption that patients fill all their medications at the same pharmacy. Some patients may fill prescribed medications at another pharmacy leading to an underestimation of the patient's medication supply. Since a total of 529 patients without continuous use in

the CVS pharmacy system were excluded from our study population, this would not likely have affected our results.

Pharmacy claims data does not allow direct observation of discontinuation of therapy. Thus, discontinuation and time-to-discontinuation is assumed to have occurred when no refill claim is entered into the database. A component of our definition of discontinuation (i.e., elapsed fill intervals greater than three times the days supply) was based on previous investigations^{24, 25, 37-39} that utilized similar criteria for defining discontinuation of treatment to allow for sufficient time to refill prescriptions. Other investigators used varying lengths of time to define discontinuation ranging from 30 to 60 days^{28, 31, 32, 55, 57} to four to six months of elapsed time since last fill.^{23, 35, 36, 61, 62} Our findings were consistent with previous studies of discontinuation rates with lipid-lowering therapy. Nonetheless, our definition of discontinuation may have affected our estimates of discontinuation in this patient population as evidenced by the range of time to re-initiation of treatment after discontinuation (i.e., 2-316 days)

We included patients with only one lipid-lowering prescription claim in this study in order to replicate real life situations. Our sensitivity analysis, which excluded these patients, still demonstrated an increased risk of discontinuation for patients prescribed non-statin medications compared with patients prescribed statins, although the statistical significance disappeared. Thus, although we may have overestimated the risk of non-persistence with lipid-lowering therapy in this patient population, we don't feel that including these patients in subsequent analyses compromised our results.

Pharmacy claims lack clinical information that may influence patients' use of medication, such as co-morbid conditions, serum lipid levels, and adverse effects experienced by the patient. Statin medications are generally well tolerated; Andrade

and colleagues reported that 7% of patients prescribed lovastatin and 26% of patients prescribed niacin discontinued treatment due to adverse events.²³ Hiatt and colleagues report that cumulative discontinuation rates for niacin and bile acid sequestrants at one year were 48% and 59%, respectively, in comparison with 10% for statin medications.³³ In this study, the primary reason for discontinuation of niacin and bile acid sequestrants was adverse events.³³ Without information such as rates of adverse events, we could not correlate our estimates to reasons for discontinuation or switching of medications in this study. Thus, modeling the factors that might affect persistence with lipid-lowering therapy may be biased due to incompleteness of the model.

The accuracy of the data in the reported pharmacy claims was not verifiable. It was not possible to confirm prescription claim information with other data sources such as medical records, pill counts, or medication diaries.

Notwithstanding these limitations, pharmacy claims data can be a useful source of data in population-based studies when direct measurements are not feasible. Utilizing a pharmacy claims database may represent the best means to capture utilization data of medication in a patient population as clinical trials are limited predictors of treatment discontinuation in actual medical practice. The one-year probability of discontinuation for lipid-lowering therapy was substantially higher in Health Maintenance Organizations than in randomized clinical trials.²³

CONCLUSION

The observations of this study indicate that persistence with lipid-lowering therapy in patients with diabetes mellitus was sub-optimal. Patients prescribed a statin medication as their initial lipid-lowering medication exhibited greater persistency compared with those patients prescribed non-statin medications. Further research is

needed to uncover reasons for low persistence with lipid-lowering therapy in patients with diabetes. These findings highlight the need for health care providers to manage persistence with lipid-lowering medications that may reduce the risk of major cardiovascular events in patients with diabetes mellitus.

Our results have important implications for persistency with pharmacotherapy for dyslipidemia in patients with diabetes. First, since statins are the recommended first line of therapy for this patient population, it is essential to document persistence with lipid-lowering therapy in a "real-world" setting. Secondly, it is known that statins are generally well tolerated and have been reported to reduce LDL-C levels, significantly decreasing the risk of cardiovascular events and total mortality. In an effort to optimize the choice of therapeutic regimens and improve patients' continuous use of lipid-lowering therapy, clinical practice guidelines, patient education, and quality of care assessments should emphasize factors that predispose patients to non-persistency with lipid-lowering therapy.

TABLES

Table 3-1. Relationship between lipid parameter changes and compliance in the Helsinki Heart Study (n = 1963 males treated with 600mg gemfibrozil BID)

Lipid Parameter	Compliance*	
	< 50%	≥90%
Total cholesterol	-0.02%	-11.4%
LDL cholesterol	+2.6%	-10.1%
HDL cholesterol	+2.7%	+13.3%
Triglycerides	-6.2%	-40.0%

* Compliance was defined as mean daily capsule count and reported as a percentage of scheduled daily dose

Table 3-2. Lipid-lowering medications

Class	Generic (brand) name
<i>HMG CoA reductase inhibitors (Statin)</i>	<i>Bile acid sequestrants</i>
atorvastatin (Lipitor [®])	cholestyramine resin (Questran [®])
fluvastatin (Lescol [®])	colestipol (Colestid [®])
lovastatin (Mevacor [®])	
pravastatin (Pravachol [®])	<i>Nicotinic acid</i>
simvastatin (Zocor [®])	niacin (Niaspan [®])
	<i>Fibrates</i>
	fenofibrate (Tricor [®])
	gemfibrozil (Lopid [®])

Abbreviations: HMG CoA= 3-hydroxy-3-methylglutaryl coenzyme A

Table 3-3. Characteristics of the study population

Characteristic	N = 190
<i>Patient-related</i>	
Age (years)	59.3 ± 10.4 (32-80)
Gender	
Male	100 (52.6)
Female	90 (47.4)
Health Plan*	
Nurse-based diabetes management plan	95 (50.0)
Other health plans	95 (50.0)
<i>Medication-related</i>	
Antidiabetic Medication Regimen†	
Oral medication	143 (75.3)
Insulin therapy	47 (24.7)
Number of Prescription Medications‡	5 ± 3 (0-17)
Class of Lipid-lowering Medication, by Index Prescription	
HMG-CoA reductase inhibitor (statins)	165 (86.8)
Fibrates	15 (7.9)
Bile acid sequestrants	9 (4.7)
Nicotinic acid	1 (0.5)

Values expressed as number (%) or mean ± standard deviation (SD) (range).

Percentages may not equal 100% due to rounding

* Health plan used to acquire the index lipid-lowering medication. Other health plans includes local/state/federal programs or cash payments.

† Antidiabetic medication regimen dispensed within 90 days of the index date.

Insulin therapy includes insulin monotherapy or in combination with oral medication.

‡ Number of prescription medications in the three months prior to index lipid-lowering medication.

Abbreviations: HMG CoA= 3-hydroxy-3-methylglutaryl coenzyme A

Table 3-4. Characteristics of the study population by class of index lipid-lowering medication

Characteristic	Statin N = 165	Non-Statins N = 25	p-value
<i>Patient-related</i>			
Age (years)	59.3 ± 10.2 (32-80)	58.9 ± 12.0 (39-80)	0.8554
Gender			0.3549
Male	89 (53.9)	11 (44.0)	
Female	76 (46.1)	14 (56.0)	
Health Plan*			0.1340
Nurse-based diabetes management plan	79 (47.9)	16 (65.2)	
Other health plans	86 (52.1)	9 (64.0)	
<i>Medication-related</i>			
Antidiabetic Medication Regimen†			0.2786
Oral medication	122 (73.9)	21 (84.0)	
Insulin therapy	43 (26.1)	4 (16.0)	
Number of Prescription Medications‡	5 ± 3 (0-17)	5 ± 4 (1-17)	0.4134

Values expressed as number (%) or mean ± standard deviation (SD) (range).

* Health plan used to acquire the index lipid-lowering medication. Other health plans includes local/state/federal programs or cash payments.

† Antidiabetic medication regimen dispensed within 90 days of the index date.

Insulin therapy includes insulin monotherapy or in combination with oral medication.

‡ Number of prescription medications in the three months prior to index lipid-lowering medication.

Table 3-5. Characteristics of the study population by the pattern of persistence with lipid-lowering therapy

Characteristic	Persisters* N = 110	Discontinuers* N = 80	p-value
<i>Patient-related</i>			
Age (years)	59.4 ± 9.9 (35-79)	59.1 ± 11.2 (32-80)	0.8689
Gender			0.2282
Male	62 (56.4)	38 (47.5)	
Female	48 (43.6)	42 (52.5)	
Health Plan [†]			0.7694
Nurse-based diabetes management plan	54 (49.1)	41 (51.3)	
Other health plans	56 (50.9)	39 (48.7)	
<i>Medication-related</i>			
Antidiabetic Medication Regimen [‡]			0.1527
Oral medication	87 (79.1)	56 (70.0)	
Insulin therapy	23 (20.9)	24 (30.0)	
Number of Prescription Medications [§]	5 ± 3 (0-17)	5 ± 4 (1-17)	0.9059
Class of Lipid-lowering Medication, by Index Prescription			0.0176
Statins	101 (91.8)	64 (80.0)	
Non-Statins	9 (8.2)	16 (20.0)	

Values are number (%) or mean ± standard deviation (SD) (range)

*Persisters are defined as patients who persisted with lipid-lowering medication using the class dispensed at the index date; Patients who did not persist with lipid-lowering therapy were defined as Discontinuers.

[†] Health plan used to acquire the index lipid-lowering medication. Other health plans includes local/state/federal programs or cash payments.

[‡] Antidiabetic medication regimen dispensed within 90 days of the index date.

Insulin therapy includes insulin monotherapy or in combination with oral medication.

[§] Number of prescription medications in the three months prior to index lipid-lowering medication.

Table 3-6. Frequency of re-initiation* of lipid-lowering therapy during the 18-month follow-up period (N = 28)

Index lipid-lowering medication ↓	Lipid-lowering medication prescription at re-initiation							
	Statins					Non-Statins		
	atorvastatin	fluvastatin	lovastatin	pravastatin	simvastatin	cholestyramine	gemfibrozil	
Statins								
atorvastatin	2 [†]				1			
fluvastatin		1						
lovastatin					1			
pravastatin				1				
simvastatin	2			1	14 [‡]			
Non-Statins								
cholestyramine						2	1	
gemfibrozil							2	

* A patient re-initiated lipid-lowering therapy after meeting the criteria for discontinuation (i.e., patient (a) had more than three times the days supplied elapsed between the last prescription fill for lipid-lowering medication and the next fill or the end of the follow-up period; (b) switched to a medication in a class different than the index medication; or (c) had no refills for the lipid-lowering medication during the observation period)

[†] One patient had a dosage increase

[‡] Three patients had a dosage increase

Table 3-7. Frequency of switching* of lipid-lowering therapy during the 18-month follow-up period (N = 19)

Index lipid-lowering medication ↓	Lipid-lowering medication prescription at switch						
	Statins					Non-Statins	
	atorvastatin	fluvastatin	lovastatin	pravastatin	simvastatin	gemfibrozil	fenofibrate
Statins							
atorvastatin				3 [†]	4		1
fluvastatin					1		
pravastatin					2		
simvastatin	2		2	1		1	
Non-Statins							
cholestyramine						1	
gemfibrozil	1						

* A medication switch was identified if the patient filled a prescription for a lipid-lowering medication other than the index medication during the observation period

[†] One patient switched back to atorvastatin

Table 3-8. Cox regression model: time to discontinuation with lipid-lowering therapy in patients with diabetes

Study Factor	Unadjusted		Adjusted*	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
<i>Patient-related</i>				
Age	0.993 (0.971, 1.017)	0.5800	0.994 (0.972, 1.017)	0.6196
Gender				
Male	1.0		1.0	
Female	1.325 (0.844, 2.081)	0.2209	1.188 (0.742, 1.903)	0.4720
Health Plan†				
Nurse-based diabetes management plan	1.0		1.0	
Other health plans	0.917 (0.584, 1.439)	0.7061	0.919 (0.567, 1.490)	0.7317
<i>Medication-related</i>				
Antidiabetic Medication Regimen‡				
Oral medication	1.0		1.0	
Insulin therapy	1.378 (0.841, 2.257)	0.2035	1.457 (0.850, 2.498)	0.1706
Number of Prescription Medications§	1.005 (0.937, 1.076)	0.8987	1.000 (0.929, 1.076)	0.9953
Class of Lipid-lowering Medication, by Index Prescription				
Statin	1.0		1.0	
Non-Statin	2.240 (1.260, 3.982)	0.0060	2.308 (1.285, 4.147)	0.0051

* adjusted for all study factors in the table

† Health plan used to acquire the index lipid-lowering medication. Other health plans includes local/state/federal programs or cash payments.

‡ Antidiabetic medication regimen dispensed within 90 days of the index date.

§ Number of prescription medications in the three months prior to index date.

Abbreviations: CI = confidence intervals

Table 3-9. Final Cox regression model: time to discontinuation with lipid-lowering therapy in patients with diabetes

Factor	Regression Coefficient	Hazard Ratio* (95% CI)	p-value
Class of Lipid-lowering Medication, by Index Prescription			
Statin		1.0	
Non-Statin	0.80650	2.240 (1.260, 3.982)	0.0060

Global $X^2 = 6.5434$ ($p = .0105$)

Abbreviations: CI = confidence intervals

Table 3A-1. Collinearity diagnostics

Variable	Condition Index	Proportion of variation						
		Intercept	Lipidclass	Age	Gender	ADregimen	Health plan	Conmed
Intercept	1.00000	0.00133	0.00753	0.00138	0.01521	0.01416	0.01457	0.01107
Lipidclass	2.17328	0.0000105	0.73534	0.0000100	0.00348	0.10630	0.02370	0.00133
Age	2.60887	0.00127	0.06756	0.00173	0.04200	0.72132	0.10170	0.00929
Gender	2.82434	0.0002495	0.15894	0.0002969	0.50295	0.12588	0.20088	4.311104E-7
ADregimen	3.74263	0.00462	0.01299	0.00600	0.37869	0.00567	0.63565	0.17806
Health plan	4.81068	0.02738	0.01443	0.03072	0.05262	0.01841	0.02138	0.80012
Conmed	17.2459	0.96514	0.00320	0.95987	0.00504	0.00825	0.00213	0.00012424

Table 3A-2. Test for confounding variables

Variable Name	$\beta_{\text{lipidclass}}$	HR _{lipidclass}	Pr > χ^2 *	-2LL	LR statistic	p-value [†]	Significance
Model A: lipidclass	0.67362	1.961	0.0161	785.470	-	-	-
Lipidclass + age	0.67104	1.956	0.0166	785.345	0.125	3.84	NS
Lipidclass + gender	0.65003	1.916	0.0205	783.977	1.493	3.84	NS
Lipidclass + healthplan	0.67129	1.957	0.0167	785.448	0.022	3.84	NS
Lipidclass + ADregimen	0.71144	2.037	0.0114	782.659	2.811	3.84	NS
Lipidclass + conmed	0.68068	1.975	0.0157	785.178	0.292	3.84	NS

* p-value associated with χ^2 test of overall model[†] p-value associated with χ^2 distribution with appropriate degrees of freedom

Abbreviations: HR = Hazard Ratio; -2LL = -2 Log Likelihood; LR = Likelihood Ratio; NS = non significant at p=0.05 level

Table 3A-3. Likelihood Ratio (LR) statistic: modeling of time to discontinuation

Model	-2 LL	Df*	LR		
			Statistic	p-value†	Significance
Full Model	575.268	20			
Reduced Model 1	604.818	9	29.550	16.92	SIG
Reduced Model 2	607.661	5	2.843	11.07	NS

* Df of fuller model minus reduced model with less variable terms

† p-value associated with χ^2 distribution for appropriate degrees of freedom

Full Model includes all univariate variables, two-way and three-way interaction terms

Reduced Model 1 includes all univariate variables and two-way interaction terms

Reduced Model 2 includes all univariate variables

Abbreviations: -2LL = -2 Log Likelihood; Df = degrees of freedom; NS = not significant; SIG = statistically significant at $p=0.05$ level

Table 3A-4. Likelihood Ratio (LR) statistics for choosing the best model of time to discontinuation with lipid-lowering therapy

Model	-2LL	Model df	p-value*	LR Statistic	p-value†	Significance
Null (no covariates)	617.530	-				
Full model: all IVs	607.661	6	0.0870	11.044	12.59	NS
Age	617.225	1	0.5807	0.305	3.84	NS
Gender	616.030	1	0.2206	1.500	3.84	NS
Lipidclass	610.987	1	0.0105	6.543	3.84	SIG
Healthplan	617.388	1	0.7061	0.142	3.84	NS
ADregimen	615.978	1	0.2128	1.552	3.84	NS
Conmed	617.514	1	0.8997	0.016	3.84	NS
Age + Gender	615.740	2	0.4084	1.790	5.99	NS
Age + lipidclass	610.738	2	0.0335	6.792	5.99	NS
Age + Healthplan	617.099	2	0.8059	0.431	5.99	NS
Age + ADregimen	615.678	2	0.3960	1.852	5.99	NS
Age + Conmed	617.196	2	0.8460	0.334	5.99	NS
Gender + lipidclass	609.827	2	0.0212	7.703	5.99	NS
Gender + Healthplan	615.982	2	0.4611	1.548	5.99	NS
Gender + ADregimen	614.953	2	0.2756	2.577	5.99	NS
Gender + Conmed	616.025	2	0.4712	1.505	5.99	NS
Lipidclass + Healthplan	610.945	2	0.0371	6.585	5.99	NS
Lipidclass + ADregimen	608.668	2	0.0119	8.862	5.99	SIG
Lipidclass + Conmed	610.916	2	0.0366	6.614	5.99	NS
Healthplan + ADregimen	615.611	2	0.3830	1.919	5.99	NS
Healthplan + Conmed	617.339	2	0.9087	0.191	5.99	NS
ADregimen + Conmed	615.927	2	0.4486	1.603	5.99	NS
Lipidclass + gender + ADregimen	608.042	3	0.0235	9.488	7.81	SIG
Lipidclass + age + lipage	610.370	3	0.0670	7.160	7.81	NS
Lipidclass + age + gender + lipagegen	609.490	4	0.0901	8.040	9.49	NS
Lipidclass + age + gender + lipage + lipagegen	609.040	5	0.1312	8.490	11.07	NS
Lipidclass + gender + conmed + lipgencon	608.904	4	0.0712	8.626	9.49	NS
Lipidclass + age + gender + conmed + lipage + lipagegen + lipgencon	607.584	6	0.1269	9.946	12.59	NS
All IVs + lipage + lipagegen + lipgencon	604.659	9	0.1685	12.871	16.92	NS

* p-value associated with χ^2 test of overall model

† p-value associated with χ^2 distribution with appropriate degrees of freedom

Abbreviations: -2LL = -2 Log Likelihood; IV = independent variables; LR = likelihood ratio statistic; NS = non significant at p=0.05 level; SIG = statistically significant at p=0.05 level

FIGURES

Figure 3-1. Eligibility criteria of study population

Figure 3-2. Kaplan-Meier time-to-event curves of persistence with lipid-lowering medications in patients with diabetes, stratified by class of index lipid-lowering medication

Figure 3-3. Kaplan-Meier time-to-event curves of persistence with lipid-lowering medications in patients with diabetes (excluding patients with one lipid-lowering medication prescription), stratified by class of index lipid-lowering medication

Figure 3A-1. Frequency distribution of the measurement: time to discontinuation

Figure 3A-2. Test of Proportional Hazard Assumption: Gender

Figure 3A-3.
Test of Proportional Hazard Assumption: Class of Index Lipid-Lowering Medication

Figure 3A-4. Test of Proportional Hazard Assumption: Healthplan

Figure 3A-5. Test of Proportional Hazard Assumption: Antidiabetic Medication Regimen

Figure 3A-6. Martingale residual plot of final Cox regression model

Figure 3A-7. Deviance residual plot of final Cox regression model

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APPENDIX A

Background and Review of the Problem

Since Hippocrates, physicians have been plagued by concerns over patients' adherence to medication regimens.^{1,2} The terms compliance, adherence, and concordance have been used in the literature to describe the manner in which a patient manages a prescribed medication regimen. Compliance has been defined as the extent to which the patients' history of medication administration corresponds to the actual prescribed regimen³ whereas the term adherence captures the increasing complexity of medical care by characterizing patients taking a more active and voluntary role in defining and pursuing goals for their own medical treatment⁴ while concordance focuses on the patients' agreement with treatment and harmony in the physician-patient relationship. Adherence will be the preferred term used in this research.

Three phases are used to describe a patient's dosing history:

- Acceptance of the medication treatment and regimen during the initial patient/physician consultation leading to actual dispensation of the prescription;
- Adherence with the dosing regimen;
- Persistence with therapy once it's initiated.⁵

There are several methods for measuring medication adherence although none is considered a gold standard. Indirect measures include patient interviews or questionnaires, pill counts, review of prescription records and claims, and electronic monitoring devices, while direct measures of adherence include pharmacologic

markers and direct observation of the patient taking the medication.⁶⁻⁸ The selection of the measurement depends on the type of intervention being evaluated, resources of the organization, and patient confidentiality (e.g., contacting patients whether by mail or in person).

While no single measure of adherence is appropriate for all settings or outcomes, database records of dispensed prescriptions may represent one of the most accurate methods of assessing medication utilization in a patient population.^{9, 10} Prescription records allow the assessment of patients with multiple medication regimens based on refill patterns. Because this method of assessment is unobtrusive and does not influence adherence behavior (e.g., the Hawthorne effect), pharmacy databases are suitable for long-term monitoring of medication use in population studies.¹¹ Although prescription refill data does not verify administration of the therapy regimen, it does signify availability of medication. This method of assessing adherence is based on the assumption that if the medication is not available for use, patients clearly cannot adhere with the medication regimen.

Although pharmacy claims databases contain all the data necessary to determine medication adherence, various measures of adherence have been utilized. For instance, continuous measures of medication availability such as Medication Possession Ratios (MPR) or Continuous, multiple-interval measures of Medication Availability (CMA) are commonly used while some researchers evaluate gaps in therapy and medication oversupply. A review by Fairman and Motheral¹² illustrates the process of selecting the right tool to measure medication adherence. For example, an analysis of gaps in refills can be used to determine whether a medication adherence program successfully reduced the number of medication holidays whereas if a program were aimed at encouraging patients to use their chronic medication on a regular basis, a continuous measure of medication availability (i.e., CMA or MPR)

would be an appropriate measurement tool. However, a study determining the nature and extent of adherence should use all the measures described allowing for an evaluation of the problem prior to developing a targeted solution.

Research suggests that predictors of medication adherence vary according to the population or disease state under evaluation. In general, the scope of adherence ranges across all age groups and medical disciplines and can be influenced by many factors including tolerability of the medication, complexity of the medication regimen, cost and convenience of the therapy, and characteristics of the patient, medical system and physician. Although some associations have been reported between adherence and demographic characteristics (e.g., age, sex, marital status, social class) and disease factors, the direction of these associations was inconsistent between studies.^{1, 13-16} In addition, there are inconsistent reports of factors that predict adherence with medications such as medication complexity (e.g., class of medication, number of daily doses, number of medications) and occurrence of adverse effects.^{13,14,17} The most significant influences on compliance are patient's beliefs about medications and about medicine in general¹⁸ however, few investigations evaluate patients' own beliefs and their perspective on health and illness in research on compliance with medications.¹⁹

Failure to follow prescribed medication regimens jeopardizes a patients' health and well-being, interferes with a physician's therapeutic efforts and poses a considerable financial burden upon health care systems.^{5, 13, 20} Estimates of rates of noncompliance with prescribed therapeutic regimens typically range from 30% to 60%.²¹ Because of its potentially negative consequences, medication adherence may be one of the greatest therapeutic challenges facing healthcare professionals.²²⁻²⁴

Medication adherence is especially important for patients with chronic diseases who must often obtain prescription refills throughout their lives.²⁵

Patients with diabetes mellitus are at particular risk for non-adherence to antidiabetic treatment regimens.²⁶ Once diagnosed, patients with diabetes are confronted with the need for lifestyle modifications including nutrition and exercise therapy and treatment with an antidiabetic medication is often unavoidable. The importance of glycemic control in preventing and minimizing diabetes-related complications is well recognized.²⁷⁻²⁹ However, diabetes is no longer a disease of sugar alone.³⁰ Attention to other cardiovascular risk factors is also an important aspect of diabetes management. Cardiovascular disease is up to four times more common in patients with diabetes than those without and 50% of patients with diabetes have evidence of cardiovascular disease at the time of diagnosis.³¹ Reductions in blood pressure and blood lipid levels may be needed to reduce diabetes-related complications. All of this requires a substantial degree of treatment adherence from patients. A major barrier to management of diabetes mellitus and co-morbidity is the extent to which individuals adhere to their prescribed treatment regimens.³²

This research focused on adherence and persistence with prescribed medications in patients with diabetes mellitus. The aim of the first study was to evaluate adherence with sulfonylurea medications using continuous and dichotomous measurements such as medication availability, gaps in therapy and surplus medication. The effect of the length of observation and the relationship between these adherence measurements were investigated along with the influence of patient- and medication-related characteristics on adherence with sulfonylureas. This study should provide insight into the variety of measures currently used for investigations of

adherence, as there is no standard method to evaluate and report rates of adherence with medication. The findings of this study may also increase knowledge on the extent of medication adherence with sulfonylureas.

The aim of the second study was to evaluate adherence with lipid-lowering therapy among patients with diabetes. Since persistence with medication regimens is an integral part of diabetes management, the aim of the third study was to examine persistence with lipid-lowering therapy. Patient- and medication-related characteristics that may influence adherence and persistence were also evaluated. The findings from these two studies should expand current knowledge on adherence and persistence with lipid-lowering therapy among patients with diabetes mellitus.

The observations from these three studies may guide the health care provider to integrate patient-education and other intervention programs into diabetes management as a means to improve medication adherence. Enhancing adherence and persistence with prescribed medications should have a profound impact on health outcomes of patients with diabetes.

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APPENDIX B

Details of Methodology

The data for this research project was provided by Consumer Value Stores (CVS) pharmacies to the University of Rhode Island Applied Pharmaceutical Sciences department. The data was derived from 198 CVS pharmacies located in Pennsylvania and includes records of dispensed outpatient pharmacy prescription records of patients with diabetes mellitus. Patients were enrolled either in a nurse-based diabetes management plan or acquired their prescription through a federal, state, or local program or paid with cash. The data represents patients' utilization of lipid-lowering medications, although some patients may have filled prescriptions elsewhere.

This prescription claims data extract contains dispensation data from complete prescription records (all medications) for patients with diabetes who were identified by specific therapeutic classes (insulins, oral antidiabetic agents-sulfonylureas and other oral antidiabetic agents). The data includes all pharmacy records between April 27, 1997 and May 16, 1999 (288,171 observations) for 4503 patients with diabetes. The dataset contains information on patient characteristic variables such as birth date, gender, and health insurance plan as well as prescription-related variables including quantity of medication dispensed, days supply of medication dispensed, and date the prescription was dispensed (Table B-1).

Re-labeling of Medication Names

Using a Physician's Desk Reference, sulfonylurea and lipid-lowering medications were identified using the medication name (LABELNM). The medications were then categorized by class- first, second, or third generation for sulfonylurea

medications or statin and non-statin for lipid-lowering medications. In order to code the study variable, antidiabetic regimen, all hypoglycemic agents were coded as oral (i.e., oral antidiabetic agents) or insulin (e.g., Humalog®, Novopen®, etc.). Diabetic supplies such as blood glucose monitoring test strips and syringes were coded as supply; this categorization was used to exclude prescription claims for these items from counting the number of concomitantly prescribed medications.

The variables, LABELNM, DAYSSUPP, QTY, and POSTXNDT, were transposed to create one record per patient. With the dataset in this format, calculations of measurements of adherence and persistence and categorization of study variables were performed as described in Tables B-2- to B-4.

All variable coding and statistical analyses were conducted using PC SAS release 8.02. SAS procedures used for descriptive statistics and univariate and multivariate analyses are listed in Table B-5.

Table B-1. Variables available in the CVS pharmacy dataset

Variable	Label	Description
ID	Identification Number	Unique patient identifier
BDATE	Date of Birth	Patient date of birth
GENDER	Gender	M=male; F=female
LABELNM	Label Name	Name of medication dispensed- includes strength and formulation
NDC	National Drug Code	Unique identifier of medication dispensed
POSTXNDT	Posted transaction date	Date the medication was dispensed
DAYSSUPP	Days Supply	Days supply of medication dispensed
QTY	Quantity	Quantity of medication dispensed
FILL_NBR	Fill Number	The number of the fill
AVAILFIL	Available Refills	Number of refills remaining on the prescription
RX_NBR	RX Number	Number assigned by the pharmacy for each prescription fill
AWPPRICE	AWP Price	The average wholesale price of the prescription medication
AGENCYNM	Agency Name	Name of the health insurance plan used to acquire prescriptions
AGENCYID	Agency Identification Number	Unique identification number of the health insurance plan used to purchase prescriptions
DEA	Drug Enforcement Number	Unique identification number assigned to the prescribing physician
STORENO	Store Number	Unique number of the pharmacy dispensing the medication

Table B-2. Variable specifications for Study 1

Variable	Description	Coding in Dataset	Coding for Analyses
CMA	continuous multiple-interval measure of medication availability	Sum of the days supply between first and last fill for sulfonylurea divided by the number of days from first to last fill	Continuous variable
CSA	continuous, single-interval measure of medication availability	Days supply obtained during an interval divided by the total number of days in that interval	Continuous variable
CSG	continuous, single-interval measure of medication gaps	Number of days that medication was unavailable for use in an interval divided by the total number of days in that interval	Continuous variable
CMG	continuous, multiple-interval measure of medication gaps	Total number of days in treatment gaps divided by the total number of days from first to last fill	Continuous variable
CSOS	continuous, single-interval measure of medication oversupply	Number of days that surplus medication was available for use in an interval divided by the total number of days in that interval	Continuous variable
CMOS	continuous multiple-interval measure of over-supply	Total number of days in treatment surplus divided by the total number of days from first to last fill	Continuous variable
Medication Availability	categorization of CMA	CMA dichotomized on $\geq 80\%$ ($\geq 90\%$)	ADHERENCE_80 <80%; $\geq 80\%$

		adherence with treatment regimen	ADHERENCE_90 <90%; ≥90%
Gaps in therapy	categorization of CMG	CMG dichotomized on ≥10% (≥20%) gaps in therapy	CMG_10 <10%; ≥10% CMG_20 <20%; ≥20%
Surplus Medication	categorization of CMOS	CMOS dichotomized on ≥10% (≥20%) surplus medication	CMOS_10 <10%; ≥10% CMOS_20 <20%; ≥20%
Sulfonylurea medication	Brand and generic (where applicable) used to code sulfonylurea medication and class of sulfonylurea medication	<p>Coded based on label name (LABELNM) Acetohexamide: acetohexamide 250mg tablet, Dymelor 250mg tablet, Dymelor 500mg tablet</p> <p>Chlorpropamide: chlorpropamide 100mg tablet, chlorpropamide 250mg tablet, Diabinese 100mg tablet, Diabinese 250mg tablet</p> <p>Glimepiride: Amaryl 1mg tablet, Amaryl 2mg tablet, Amaryl 4mg tablet</p> <p>Glipizide: glipizide 5mg tablet, glipizide 10mg tablet, Glucotrol 5mg tablet, Glucotrol 10mg tablet, Glucotrol XL 5mg tablet SA, Glucotrol XL 10mg tablet SA</p> <p>Glyburide: glyburide 1.25mg tablet, glyburide</p>	INDEXCLASS_RE 0 = 2 nd generation SU- glipizide, glyburide 1 = 1 st generation SU - acetohexamide, chlorpropamide, tolazamide, tolbutamide 2 = 3 rd generation SU- glimepiride

		2.5mg tablet, glyburide 5mg tablet, glyburide MICRO 1.5mg TAB, glyburide MICRO 3mg tablet, glyburide MICRO 6mg tablet, DiaBeta 1.25mg tablet, DiaBeta 2.5mg tablet, DiaBeta 5mg tablet, Glynase 1.5mg PRESTAB Glynase 3mg PRESTAB, Glynase 6mg PRESTAB, Micronase 1.25mg tablet, Micronase 2.5mg tablet, Micronase 5mg tablet	
		Tolazamide: tolazamide 100mg tablet, tolazamide 250mg tablet, tolazamide 500mg tablet, Tolinase 100mg tablet, Tolinase 250mg tablet	
		Tolbutamide: tolbutamide 500mg tablet, Orinase 500mg tablet	
Age	Age	Transaction date of sulfonylurea medication during index window minus date of birth (BDATE)	Continuous variable
Gender	Gender	M=male F=female	GENDER_RE 0 = Male 1 = Female
Health plan	Health plan used for sulfonylurea	Health plan used to fill sulfonylurea	HEALTHPLAN 0 = nurse-based

	medication	medication during index window	diabetes management plan 1 = other (including local and state programs, cash payments)
Number of Medications	Number of prescribed medications during study period	Medications other than antidiabetic medications and supplies were counted.	Continuous variable
Use of Insulin	Use of insulin during study period	Was patient prescribed insulin during study period?	INSUSE 0 = no 1 = yes
Number of pills per day	Number of sulfonylurea pills prescribed per day	Days supply of sulfonylurea prescription fill divided by quantity of medication dispensed	DOSE 0 = 1 per day 1 = >1 per day

Table B-3. Variable specifications for Study 2

Variable	Description	Coding in Dataset	Coding for Logistic Regression Analysis
CMA	continuous multiple-interval measure of medication availability	Calculated from days supply (sum of the days supply between first and last claim for lipid-lowering medication and days of therapy (number of days of therapy between the first and last prescription fill of lipid-lowering medication); continuous variable	n/a
Adherence	access to at least 80% (90%) of lipid-lowering medication based on calculated CMA	Coded based on CMA; categorized using 80% and 90% levels	ADHERENCE_80 0 = ≥ 80 1 = < 80 ADHERENCE_90 0 = ≥ 90 1 = < 90
Lipid-lowering medication	Brand and generic (where applicable) used to code lipid-lowering medication and class of lipid-lowering medication	Coded based on label name (LABELNM) <u>Cholestyramine</u> : Cholestyramine light packet; Cholestyramine light powder; Cholestyramine powder; Questran light packet; Questran light powder; Questran packet; Questran powder <u>Colestid</u> : Colestid 1gm tablet; Colestid flavored granules; Colestid granules; Colestid granules	LIPIDCLASS 0 = Non-Statin (cholestyramine resin, colestipol, fenofibrate, gemfibrozil, niacin) 1 = Statin (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin)

packet

Lopid: Gemfibrozil
600mg tablet; Lopid
600mg tablet

Lesol: Lescol 20mg
capsule; Lescol
40mg
capsule

Lipitor: Lipitor 10mg
tablet; Lipitor 20mg
tablet; Lipitor 40mg
tablet

Mevacor: Mevacor
10mg tablet;
Mevacor 20mg
tablet; Mevacor
40mg tablet

Niacin: Niacin
100mg tablet; Niacin
250mg capsule SA;
Niacin 500mg tablet;
Niaspan 500mg
tablet SA; Niaspan
750mg tablet SA

Pravachol:
Pravachol 10mg
tablet; Pravachol
20mg tablet;
Pravachol 40mg
tablet

Tricor: Tricor 67mg
capsule

Zocor: Zocor 10mg
tablet; Zocor 20mg
tablet; Zocor 40mg
tablet; Zocor 5mg
tablet; Zocor 80mg
tablet

Age

Age

Calculated as first
transaction date
minus year of birth
(YRBORN)

AGE_RE
0, 0 = <55 years
0, 1 = 56-65 years
1, 0 = >65 years

Gender	Gender	Coded as M=males F=females	GENDER_RE 0 = Males 1 = Females
Health Plan	Health plan used to acquire lipid-lowering medication prescribed at index date	Categorized as nurse-based diabetes management plan or other including local/state programs and cash payments	HEALTHPLAN 0 = nurse-based diabetes management plan 1 = other
Number of Concomitant Medications	Number of concomitant medications prescribed during study period	Medications other than lipid-lowering medication were counted as concomitant medication	CONMED_CNT 0, 0 = 1-5 0, 1 = 6-10 1, 0 = >10
Antidiabetic Medication Regimen	Antidiabetic medication dispensed during study period	Categorized as Insulin therapy (patients dispensed either insulin monotherapy or insulin in combination with oral agents) or Oral (patients dispensed oral antidiabetic medications)	ADREG 0 = oral medications only 1 = insulin therapy

Table B-4. Variable specifications for Study 3

Variable	Description	Coding in Dataset	Coding for Analyses
Discontinuation	N/A	A discontinuation of lipid-lowering medication was identified if a patient (1) had more than three times the days supplied elapsed between the last prescription fill for the index lipid-lowering medication and the next fill or the end of the follow-up period; or (2) switched lipid-lowering medication to another class; or (3) had no refills for the index medication during the observation period.	TIMETODC Continuous variable
Censor	N/A	Patients with continuous coverage of lipid-lowering medication were censored throughout observation period	CENSOR 0 = failure (discontinuation) 1 = censored
Lipid-lowering medication	Brand and generic (where applicable) used to code lipid-lowering medication and class of lipid-lowering medication	Coded based on label name (LABELNM) <u>Baycol</u> : Baycol 0.2mg tablet; Baycol 0.3mg tablet <u>Cholestyramine</u> : Cholestyramine light packet; Cholestyramine light powder; Cholestyramine powder; Questran light packet; Questran light powder; Questran packet; Questran powder <u>Colestid</u> : Colestid 1gm tablet; Colestid flavored granules; Colestid granules; Colestid	LIPIDCLASS 0 = Non-Statin bile acid sequestrant resins-cholestyramine, colestipol; fibrates-fenofibrozil, fenofibrate; nicotinic acid-niacin 1= Statin atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin

		granules packet	
		<u>Lopid</u> : Gemfibrozil 600mg tablet; Lopid 600mg tablet	
		<u>Lesol</u> : Lescol 20mg capsule; Lescol 40mg capsule	
		<u>Lipitor</u> : Lipitor 10mg tablet; Lipitor 20mg tablet; Lipitor 40mg tablet	
		<u>Mevacor</u> : Mevacor 10mg tablet; Mevacor 20mg tablet; Mevacor 40mg tablet	
		<u>Niacin</u> : Niacin 100mg tablet; Niacin 250mg capsule SA; Niacin 500mg tablet; Niaspan 500mg tablet SA; Niaspan 750mg tablet SA	
		<u>Pravachol</u> : Pravachol 10mg tablet; Pravachol 20mg tablet; Pravachol 40mg tablet	
		<u>Tricor</u> : Tricor 67mg capsule	
		<u>Zocor</u> : Zocor 10mg tablet; Zocor 20mg tablet; Zocor 40mg tablet; Zocor 5mg tablet; Zocor 80mg tablet	
Age	Age	Calculated as first transaction date minus date of birth (BDATE)	Continuous variable
Gender	Gender	Coded as M=male F=female	GENDER_RE 0 = Male 1 = Female

Health plan	Health plan used to acquire index lipid-lowering medication	Categorized as nurse-based diabetes management plan or other including local/state/federal programs or cash payments	HEALTHPLAN 0 = nurse-based diabetes management plan 1 = other
Number of Prescription Medications	Number of prescription medications within three months prior to index date	Medications other than lipid-lowering medication and antidiabetic supplies were counted as concomitant medication	Continuous variable
Antidiabetic Medication Regimen	Antidiabetic medication dispensed within 90 days of index date	Categorized as oral (patients dispensed oral antidiabetic medications) or insulin therapy (patients dispensed either insulin monotherapy or insulin in combination with oral antidiabetic medications)	ADREG 0 = oral medications 1 = insulin therapy

Table B-5. SAS procedures and their respective analytical measure

SAS Procedure	Analytical Measure
PROC FREQ	Frequency distribution of study variables
PROC FREQ with CHISQ option	Statistical comparison of categorical variables
PROC GLM	Multiple Regression Modeling
PROC LIFETEST	Nonparametric estimates of the survivor function either by the product-limit method (also called the Kaplan-Meier method).
PROC LOGISTIC	Logistic Regression Modeling
PROC MEANS	Descriptive statistics for variables across all observations and within groups of observations.
PROC NPAR1WAY	Statistical comparison for non-parametric variables
PROC PHREG	Performs regression analysis of survival data based on the Cox proportional hazards model.
PROC REG	Multiple Regression Modeling, assess collinearity of variables
PROC TRANSPOSE	Creates an output data set by restructuring the values in a SAS data set, transposing selected variables into observations.
PROC TTEST	t-test for comparison of means
PROC UNIVARIATE	Performs test for normality

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APPENDIX C

Confidentiality of Data

Data has been provided by CVS Pharmacies at no cost, through agreement and arrangement with the University of Rhode Island College of Pharmacy. All information will be held confidential, and results will not include any reference allowing for the identification of individuals in the data set. Patient name, address, telephone and social security number are not included in the data. Dates of birth included in the data set are not linked to any other identifying information. Thus, there is no identifying information that could link a patient's identity to the prescription claim.

The Institutional Review Board at the University of Rhode Island granted approval for this research project on November 20, 2002.

APPENDIX D

Overview of Major Findings

Since there is no standard measurement of medication adherence, the objective of the first study was to measure adherence with sulfonylureas based on continuous and dichotomous measures of medication availability, gaps, and surplus and evaluate the relationship between these measures. Patient-related and medication regimen complexity characteristics that may influence adherence with sulfonylureas in patients with diabetes mellitus were also examined.

A total of 988 patients were prescribed a sulfonylurea medication during the study period and included in the study analyses. The most commonly prescribed sulfonylureas were the second-generation sulfonylureas: glyburide (57%) and glipizide (35%); 7% of patients were prescribed glimepiride and 2% prescribed a first-generation sulfonylurea.

Single-interval measures of medication availability (CSA), gaps (CSG), and oversupply (CSOS) provide an accurate representation of adherence with sulfonylureas from fill to refill and allow an individual assessment of medication adherence and highlights particular times of non-adherence with medication, for example, patient-initiated medication holidays or dose reductions. In contrast, multiple-interval measures of medication availability (CMA), gaps (CMG), and oversupply (CMOS) provide a broad assessment of medication adherence over an extended period of time. The focus of the analysis was on the multiple-interval measures of adherence since they are more descriptive when evaluating overall adherence in patient populations.

Overall, patients had an average period of observation (i.e., date from first sulfonylurea dispensation to last fill in the study period) of 315 days (range, 32 to 364

days). Based on CMA, medication was available for an average ($\pm$ SD) of $89\% \pm 18\%$ of days during the 12-month study period. When CMA was dichotomized, 78% and 66% of patients had sufficient medication to cover at least 80% and 90% of days in the study period, respectively. An analysis of gaps in therapy supports the findings of medication availability. That is, patients had an average CMG of 47 days; only nine (1%) patients prescribed sulfonylureas had no gaps in therapy. Almost 1 in 4 patients had gaps in therapy for six or more days per month. The majority of patients (85%) had surplus sulfonylurea medication during the 12-month observation period: the average CMOS was 5% of days (range, 0 to 80%) among patients prescribed sulfonylurea medications. Dichotomous measures of adherence demonstrated that 46% and 15% of patients had $\geq 10\%$ of days during the study period with gaps or excess sulfonylurea medication, respectively. This study demonstrated that patients with diabetes obtained less sulfonylurea medication than prescribed over a 12-month period of observation.

Correlations for all continuous and dichotomous measures of adherence were statistically significant ($p < 0.0001$). Measures of medication availability were significantly correlated with measures of gaps in therapy ($r = -0.95$) and surplus medication ($r = 0.41$). Similarly, measures of gaps in therapy were significantly correlated with measures of surplus medication ($r = -0.20$). While the continuous measure of medication availability, CMA, was correlated with both dichotomous categorizations, the strongest relationship was observed between CMA and adherence dichotomized with the 80% level ($r = 0.82$). The continuous measure of gaps in therapy was strongly associated with the 20% level of dichotomization ($r = 0.84$) while the correlation between dichotomous categorizations and the continuous measure of surplus medication (CMOS) were similar ($r \leq 0.79$).

To evaluate the effect of observed time on the measures of adherence, subsequent analyses examined prescription claims for six and nine months. As the length of follow-up time increased, measures of available medication decreased while measures of gaps in therapy and oversupplies of medication increased. Based on CMA, the average proportion of days with available sulfonylurea medication was statistically significant using six, nine, and 12 months of observation; 92%, 90%, and 89%, respectively ($p=0.0137$). An average of 13% of days with gaps in therapy was observed during six months of observation while 15% of days had gaps when the observation time increased to nine and 12 months ($p=0.0195$). In contrast, CMOS did not seem to be affected by the amount of time under observation. These findings illustrate that a nine-month examination of prescription claims was adequate to assess adherence.

In a multiple regression model, no study factors significantly influenced adherence (i.e., availability of sulfonylurea medication) ($F_{5, 987} = 0.59$; $p=0.7065$). Although not a significant predictor of medication availability in this patient population, increasing age by one-year increments led to an increase in the rate of adherence of approximately 4.1%. An increase in the number of concomitantly prescribed medications had an inverse relationship with CMA. Higher rates of adherence were also observed for males, patients enrolled in a nurse-based diabetes management plan, and patients prescribed one sulfonylurea pill per day.

In summary, relying solely on a single measure of medication adherence, such as CMA, provides the health care provider one-dimension of information regarding appropriate and adequate use of a medication within a population. As illustrated in this study, by combining assessments of medication availability with analyses of gaps in therapy and surplus medication, the scope of the problems of non-adherence with medications is more defined.

The objective of the second study was to evaluate adherence with lipid-lowering medications in patients with diabetes mellitus. In addition, the effect of patient- and medication-related characteristics on adherence was examined.

A total of 90 patients were identified as new users of lipid-lowering therapy during a nine-month observation period. The majority of patients (91%) were prescribed a statin medication as their index lipid-lowering medication while eight patients were prescribed a non-statin medication.

The average number of days of observation was 225 days (range, 59 to 270 days). Overall, mean ($\pm$ SD) CMA was $82.8\% \pm 23.4\%$. Adherence differed by class of lipid-lowering medication prescribed at the index date: patients prescribed statin and non-statin medications had a mean ($\pm$ SD) CMA of $84.1\% \pm 22.3\%$ and $70.0\% \pm 31.7\%$, respectively ($p=0.2627$).

Two-thirds of the patients (66%) had sufficient lipid-lowering medication to cover 80% or more days in a nine-month observation period; these patients were classified as adherent. Adherent patients were less frequently prescribed insulin therapy than non-adherent patients ($p=0.0297$). Additionally, adherent patients were more frequently prescribed a statin medication than a non-statin although this proportion was not statistically significant ($p=0.0802$).

A logistic regression model of adherence ($\geq 80\%$) incorporated significant covariates from the bivariate and multivariate models. The likelihood of patients achieving adherence with lipid-lowering medication was lower for patients prescribed insulin therapy (OR= 0.304, 95% CI=0.114, 0.815, $p=0.0180$) compared with patients prescribed only oral antidiabetic medications. Compared with patients prescribed non-statin medications, patients prescribed a statin medication were four times more

likely to be adherent with treatment (OR=4.709, 95% CI=0.996, 22.268, $p=0.0506$); this parameter was close to statistical significance in the final model.

Results of a sensitivity analyses (adherence defined as having adequate lipid-lowering medication to cover at least 90% or more days) found that only 46% of patients were adherent with lipid-lowering therapy. No study factors significantly influenced adherence in the bivariate or multivariate logistic regression model this level of adherence.

The observations of this study indicate that adherence with lipid-lowering therapy in patients with diabetes mellitus was less than optimal. Patients prescribed a statin medication as their initial lipid-lowering medication exhibited greater adherence compared with patients prescribed non-statin medications. Non-adherence was associated with insulin therapy and non-statin medications.

The objective of the third study was to assess persistence with lipid-lowering medications and evaluate patient- and medication-related characteristics that may influence discontinuation of lipid-lowering treatment in patients with diabetes mellitus.

A total of 190 patients were identified as new users of lipid-lowering therapy; these patients were followed for a total of 47,372 person-days, an average of 248 person-days. Statins were the most frequently (87%) prescribed lipid-lowering medication at the index date.

Overall, 58% of patients persisted with lipid-lowering medication. Patients prescribed statins were more likely to be persistent than patients prescribed non-statin medications ($p=0.0176$). Of the 165 patients prescribed statin medications, 74% persisted with treatment over six months, 59% over 12 months, and 46% over 18 months of observation. At six months, 60% of patients in the non-statin group persisted with treatment while only 26% of patients were persistent over 12 and 18

months of observation. Kaplan-Meier curves of non-persistence statistically differed for patients prescribed statin and non-statin therapy (Log-rank $\chi^2=7.9101$; $p=0.0049$).

Among the 87 patients who discontinued treatment, 23 (26%) patients interrupted treatment after a single prescription. Twenty-eight (28, 32%) restarted lipid-lowering medication during the observation period with the median time to re-initiation of 63 days; 43% of patients restarted therapy after the initial lipid-lowering medication prescription was not refilled.

Overall, 19 (10%) of patients switched to another lipid-lowering medication other than the index medication. The majority (84%) of the patients who switched medication changed to another medication in the same class as the lipid-lowering medication prescribed at the index date.

A Cox regression model showed that discontinuation with lipid-lowering therapy was related to the class of lipid-lowering medication prescribed at the index date. Compared with patients prescribed statin medications, patients prescribed non-statin medications were more than twice as likely to discontinue lipid-lowering therapy (HR=2.240; 95% CI= 1.260, 3.982; $p=0.0060$). Inclusion of other study factors or interaction terms into the Cox regression model did not significantly influence non-persistence with lipid-lowering therapy.

The observations of this study indicate that persistence with lipid-lowering therapy in patients with diabetes mellitus was sub-optimal. Patients prescribed a statin medication as their initial lipid-lowering medication exhibited greater persistence compared with those patients prescribed non-statin medications. These findings highlight the need for health care providers to manage persistence with lipid-lowering medications that may reduce the risk of major cardiovascular events in patients with diabetes mellitus.

APPENDIX E

Interventions to Improve Adherence with Prescribed Medication Regimens for Patients with Diabetes Mellitus

C Everett Koop, former US surgeon general, observed “Drugs don’t work in patients who don’t take them.”^{1, 2} This statement is reinforced by the findings of a recent World Health Organization (WHO) report on adherence to long-term therapy which concluded that improving adherence required multidisciplinary and multilevel interventions that take individual patients’ experiences of illness seriously.² The ability of patients to follow treatment plans in an optimal manner is complex and is frequently compromised by more than one barrier. Five dimensions have been identified as barriers to adherence: social and economic factors; health care system; characteristics of the disease; treatment-related factors; and patient-related factors.² Solving the problem related to each of these dimensions is necessary if patients’ adherence and persistence with prescribed medication regimens is to be improved.

A review of the literature demonstrates that no single intervention strategy will assure adherence with prescribed therapy.²⁻⁶ Rather, adherence and persistence with medications require a multifaceted approach, encompassing behavioral, cognitive, and social strategies.^{4, 7} Interventions that target adherence must be tailored to the particular illness-related demands experienced by the patient. To accomplish this, health care systems and providers need to develop means of accurately assessing not only adherence and persistence, but also those factors that influence it. As we have shown in this research, adherence and persistence with prescribed medication varies across all age groups and disease entities and can be influenced by many factors including tolerability of the medication, complexity of the medication regimen,

cost and convenience of the therapy, as well as characteristics of the patient, medical system and physician.

Providing access to clear information about health care options is especially important in improving patients' adherence to treatment. When patients are prescribed medication regimens, they should be able to obtain easily understandable information about the expected benefits and potential outcomes, any risks, interactions and adverse events associated with the prescribed medication. A combination of keeping the medication regimen as simple as possible, negotiating priorities with the patient, providing clear verbal and written instructions for the patient, family intervention, monitoring adherence with treatments and appointments, appointment and prescription refill reminders, and reinforcing the importance of high adherence or rewards for improved adherence and treatment response with prescribed therapy at each visit will provide practical and effective help for many patients with diabetes to follow prescribed regimens.⁸⁻¹⁰ In addition, counseling and continuing support from other health care professionals and patients affected with the same disorder are key to improving medication adherence with prescribed therapy among patients with diabetes mellitus.

Interventions directly focused on enhancing patients' participation in diabetes care have been proven to be the most powerful in improvement of glycemic control and quality of life for patients with diabetes: automated telephone diabetes management programs including personal nursing support, patient empowerment education, interactive group education/peer support meetings and family-oriented disease management therapy.¹¹⁻¹⁹ For example, Skaer and colleagues observed that patients who received mailed prescription-refill reminders, special medication packaging, or a combination of both interventions achieved a significant ($p \leq 0.05$) increase in adherence with sulfonylurea therapy compared with patients who received

standard pharmaceutical care.²⁰ Anderson and colleagues observed that a patient empowerment program designed to improve psychosocial self-efficacy and attitudes towards diabetes was an effective approach to developing educational interventions to address the psychosocial aspects of living with diabetes.¹⁴ This study also observed an improvement in glycemic control in patients assigned to the intervention group compared with the control group.¹⁴

Beyond interventions focusing on the patient, interventions that target health care providers can be used to improve self-management of diabetes and its co-morbid conditions. Patient-provider communication is essential to support diabetes self-care^{21, 22} and is associated with patients' glycemic control.²³ Pharmacist-intervention programs have proven beneficial in the management of diabetes²⁴⁻²⁶ and increased medication compliance and reductions of low-density lipoprotein cholesterol (LDL-C) levels in patients with dyslipidemia.^{27, 28} For example, enhanced pharmacist intervention (i.e., educational module including recommendations for therapeutic interventions and follow-up telephone calls) reduced LDL-C levels about 18 mg/dL during a six-month period with an adherence rate of 84% in patients receiving lipid-lowering medication; 31% of patients achieved National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III)²⁹ recommended target levels (≤ 100 mg/dL).²⁸

Adherence to prescribed medications is one of the many challenges in managing diabetes. Thus, it is important for health care providers to be able to appreciate the complexity of a diabetics' treatment regimen and understand the psychological, physiological, environmental, and regimen-specific factors that affect a patient's adherence to treatment regimens. Clearly the solution to the problem of poor adherence with diabetes self management, including medication adherence and

persistence, must involve a combination of approaches that include intensive efforts to modify the behavior of patients with diabetes together with efforts to make changes in the health care system and larger environment that shape and modify behaviors.³⁰ The International Pharmaceutical Federation Statement on Professional Standards³¹ has listed the following steps as building blocks for adherence with medication regimens:

- Training and supporting health care providers in different styles of consultation;
- Including cultural beliefs, patients' beliefs, lifestyle priorities, and medicine-taking issues of the patients;
- Sharing information among physicians, pharmacists, nurses and patients;
- Extending the educational role of physicians, pharmacists, and nurses;
- Creating and using all available opportunities to discuss issues related to the prescribed medication;
- Providing high quality tailored information for patients when medication regimen is prescribed.

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