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A retrospective analysis to identify factors that predict adherence with HMG-CoA reductase inhibitors (statin) among University of Toledo employees with diabetes

Jinender Kumar
The University of Toledo

A Thesis

Entitled

A Retrospective Analysis to Identify Factors that Predict Adherence with HMG-CoA Reductase Inhibitors (Statin) among University of Toledo Employees with Diabetes

by

Jinender Kumar

Submitted to the Graduate Faculty as partial fulfillment of the requirements for the Masters of Science Degree in Pharmaceutical Sciences, Administrative Pharmacy Option

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Dr. Monica, Holiday-Goodman, Committee Chair

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College of Graduate Studies

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May 2010

An Abstract of

A Retrospective Analysis to Identify Factors that Predict Adherence with HMG-CoA Reductase Inhibitors (statins) among University of Toledo Employees with Diabetes

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Background: Diabetes patients are usually at increased risk of developing cardiovascular diseases (CVDs). The treatment with statins is known to reduce cardiovascular risk in the secondary prevention of CVDs. Several observational studies have shown that the patients on statin therapy have low adherence. Low adherence is an important issue which has serious health implications like increased morbidity and mortality.

Objectives: The main objectives of this study were to determine the adherence with statins among the University of Toledo (UT) employees and their dependents with diabetes and to study the effects of independent variables [age, co-payment, gender, location (main vs. health science campus), and adherence with the diabetes medications] on adherence with statins.

Methods: This study was a retrospective, longitudinal observational study. UT employees and their dependents pharmacy claims data was used for the study. Adherence with statins was determined in 180 day and one year observation periods for those patients who filled prescriptions for statins in addition to prescriptions for oral hypoglycemic drugs (OHDs) during the study period. Medication possession ratio (MPR) for statins was calculated and used as the dependent variable (MPR < 80% - non-adherent, MPR ≥ 80% - adherent). Descriptive statistics were used to describe the study population. Logistic regression was used to study the effects of independent variables on adherence with statins.

Results: One hundred and ninety-three patients were included in the 180 day analysis, while 150 patients were included in the one year analysis. The mean adherence with statins was 0.80 and 0.78 over the 180 day and one year observation periods, respectively. About 64% of patients were adherent to statin medications with MPR ≥ 80% during the 180 day observation period. This adherence rate decreased to 60% of patients at the end of one year. In the regression model, adherence with diabetes medications was significantly positively related with adherence with statin medications.

Conclusion: Adherence with statins was found to be suboptimal among the study population. This presents an increased risk of developing cardiovascular complications among this population, which can lead to increases in the healthcare costs for the university. The university should further investigate the reasons for non-adherence in this

population and interventions should be designed to improve adherence. Improved adherence can help in reducing overall healthcare cost for this self-insured organization.

I dedicate this thesis to

My parents – Pawan and Kamlesh Jain,

My wife – Ritika Jain,

My sisters – Rekha and Anu Jain,

My brother – Punit Jain,

My parents-in-law – Pawan and Sunil Jain

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Chapter-1

Introduction

Diabetes mellitus is one of the most common chronic diseases in the United States. In 2007, 246 million people worldwide had diabetes. By 2025, the figure is expected to rise to 380 million.[1] In 2007, approximately 17.5 million people in the U.S. had been diagnosed with diabetes.[2] The diagnosis of diabetes mainly falls into two categories: type-1 and type-2 diabetes.[3, 4] Type-1 diabetes typically strikes children and young adults at a higher rate than other age groups and is usually associated with the need for insulin use. Type-2 diabetes is usually associated with older age, obesity, impaired glucose metabolism, physical inactivity and/or race/ethnicity. It accounts for 90-95% of all diagnosed cases of diabetes. In type 2 diabetes, either the body does not produce enough insulin or the body cells ignore insulin. Type 2 diabetes leads to serious vascular, nephrologic, neurologic and ophthalmological complications.[5] The total estimated cost of diabetes in 2007 was $174 billion, including $116 billion in direct medical cost and $58 billion in reduced national productivity.[2]

Patients with diabetes are at a significantly increased risk of developing cardiovascular disease.[6,7] As per National Cholesterol Education Program Adult

treatment guidelines (NCEPATP-III), diabetes patients have the risk for coronary events equivalent to that of a history of cardiovascular disease.[8] The treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) is known to reduce cardiovascular risk in primary and secondary prevention of cardiovascular diseases (CVD).[9-13] The latest report from the NCEPATP-III guidelines advises healthcare professionals to use an intensive Low Density Lipoprotein-Cholesterol (LDL-C) lowering program for patients at high risk of developing, or patients with existing cardiovascular disease.[14] The recommendation from the report supports statins as first-line agents for reducing LDL-C levels.[14] The efficacy of statins to prevent CVD has also been well documented in several long term outcome trials involving patients with varying degrees of risk, including patients with type 2 diabetes.[15-21] American Diabetes Association (ADA) guidelines on prevention of CVD recommend statin therapy in diabetes patients 40 years of age and above, regardless of their low-density lipoprotein level.[22]

Previous studies assessing adherence with statin therapy have reported a lack of adherence with treatment.[9-11, 21] There is also an association between adherence with statin therapy and mortality.[13] Non adherence is an important issue which has serious health implications.[19, 20] Wei and colleagues found that in more than 5,500 patients who experienced a myocardial infarction (MI) there was a lower risk of MI recurrence when patients were >80% compliant with statin medications.[23] A subgroup analysis of the West of Scotland Coronary Prevention Study (WOSCOPS) showed that individuals taking 75% or more of their medications had a one-third greater reduction in mortality than those taking less than 75% .[9]

There is substantial but inconsistent literature regarding factors that can affect patients' adherence with statin therapy. Previous studies based on large medical and pharmacy claims databases have identified variables such as age, sex, number of medications, frequency of doctor visits, lipid testing, comorbidities, cost, and depression as predictors of poor statin adherence.[24-30] The aim of this study is to identify significant predictors of adherence with statin medications among University of Toledo employees and their dependents with diabetes.

The University of Toledo prescription program

The University of Toledo is one of 13 state universities in Ohio. The University of Toledo merged with the Medical University of Ohio on July 1, 2006 to form two campuses, the main campus and the health science campus. The main campus employees are faculty and staff in the colleges of Arts and Sciences, Business Administration, Education, Pharmacy, and Engineering, in addition to other university classified staff, and other non-college administrative staff. The health science campus employees include academic faculty and staff in the colleges of Medicine, Nursing, and Health and Human Services as well as physicians, nurses, and other paramedical/classified and administrative staff.

The time period for this study was January 1, 2006 to June 2, 2008. During this period, the prescription benefit program and the plan design for main and health science campus employees were different and managed by two different pharmacy benefit

management (PBM) companies. The PBM for main campus employees was Prescription Drug Management Insurance (PDMI). Express-Scripts (ES) served as the PBM for health science campus employees. After the merger, the prescription benefit plan design did not become uniform for main and health science campus employees until January 1, 2009. The University of Toledo changed its PBM companies from PDMI for main campus employees and ES for health science campus employees to SXC Health Solutions for both campus locations. These changes became effective from July 1, 2008 for main campus employees and January 1, 2009 for health science campus employees.

During the study period, the health insurance provided by the University of Toledo covered about 13,000 employees and their dependents on both campuses. Both campus plans had their own formulary system which contained mainly three tiers of drugs, Tier 1 (generic and selected OTC), Tier 2 (preferred brand), and Tier 3 (non-preferred brand). Beside these drugs, there were some specialty drugs which were reimbursed as per formulary. The prescription benefit plans for each campus are described below.

Main Campus prescription benefit plan

As per formulary, main campus employees had the option of filling their prescription at either a University of Toledo pharmacy or several participating retail network pharmacies. The University had two outpatient pharmacies where employees could fill their prescriptions, one on the main campus and the other on the health science campus. The participating retail network pharmacies included all national retail chain

pharmacies and the independent community pharmacies in the northwest Ohio area. Before the merger, main campus employees could fill their prescription at the main campus pharmacy or any of the retail network pharmacies. After the merger, the health science campus pharmacy became part of University of Toledo and therefore, main campus employees could fill their prescriptions at that pharmacy as well. Main campus employees were allowed to fill prescriptions for a 30 or less days supply from the retail network pharmacies. If a prescription was for more than a 30-day supply, it had to be filled at a University pharmacy. The copayment differed based on the type of pharmacy used (University pharmacy or network pharmacy). For example, the cost of filling a generic simvastatin for a 30-day supply was $6 at a university pharmacy and $11 at a network pharmacy.

Health Science Campus prescription benefit plan

As per formulary, health science campus employees had to fill their prescriptions for either a 30 or 90 days supply at a University pharmacy. Before the merger, they could fill their prescription at the health science campus pharmacy only. After the merger, they could fill their prescription at the main campus pharmacy as well. As before the merger, they have the option to fill an emergency 10-day supply at a retail network pharmacy.

During the study period, the copayment structure for main campus and health science campus plans were different. The copayments were based on contracts that were negotiated with each campus union group. The copayments for both main campus and

health science campus employees based on different tiers of drugs are shown in Table 1.1.

Table 1.1: Tiers of drugs and related copayments by location

	Main Campus Employee		**Health Science Campus Employees**
	Network Pharmacy (PDMI)	**UT Pharmacy (PDMI)**	**UT Pharmacy (ES)**
30 Days Supply	**30-Day Co-pay**	**30-Day Co-pay**	**30-Day Co-pay**
Tier 1 (generic & select OTC)	$11.00	$6.00	$10.00
Tier 2 (preferred brand)	$28.00	$12.00	22%AWP + $5.00
Tier 3 (non-preferred brand)	$45.00	$24.00	Difference between brand and generic
90 Days Supply		**90-Day Co-pay**	**90-Day Co-pay**
Tier 1 (generic & select OTC)		$15.00	$10.00
Tier 2 (preferred brand)		$22.50	22% AWP + 5.00
Tier 3 (non-preferred brand)		$45.00	Difference between brand and generic
Specialty Drugs	As per formulary	As per formulary	As per formulary

Need for the study

Patients with diabetes are at increased risk of developing cardiovascular diseases.[6,7] Statin therapy is recommended as a first line treatment to reduce cardiovascular risk in the secondary prevention of cardiovascular diseases.[10,11] Previous observational studies have shown that patients do not adhere with their statin therapy.[9-11] Through this study, the researchers hoped to determine the adherence to statin medications among the diabetes population on both campuses. The results are relevant to

the University because non-adherence to statins among diabetic employees can increase the risk for cardiovascular diseases, which can lead to an increase in healthcare costs for this self-insured organization. Diabetes patients with concomitant CVD incur annually 1.5 to 3.5 times more medical costs than patient with diabetes alone.[37] During the study period, the University had approximately 725 diabetes patients. These patients could be at risk of CVDs, especially if they are not on statin therapy or are non-adherent. Additional cardiovascular complications can lead to more outpatient and emergency room visits and hence, an increase in healthcare costs for The University of Toledo and its employees. There might also be an additional indirect cost burden on The University of Toledo due to decreases in work productivity and employee absenteeism.

Studies have looked for adherence to statin medications in non-diabetes populations and identified several factors that can predict adherence. [23, 33-36] However, to the best of the researchers' knowledge, there is only one study in the literature which has looked at adherence to statin medications among diabetes patients and tried to identify predictors to adherence with statin medications among these patients specifically.[32] This previous study tried to predict statin adherence based on age, gender, A1c levels, smoking status, presence of cardiovascular morbidity at baseline, history of stroke, history of myocardial infarction, and occurrence of cardiovascular disease and infarction after statin commencement.[32] The present study will attempt to predict adherence with statin medications by using three different variables which were not included in the previous study. These variables are copayment, location (main campus/health science campus), and adherence with diabetes medications.

Studies on factors affecting adherence to statin medications in non-diabetes population have shown that adherence differs by copayment.[33-35] The variable location was included because the university and the university PBM administrators were interested to determine if statin adherence differed by campus. The effect of adherence with diabetes medications on adherence with statin medications had not been studied before. The researchers' hypothesized that if a patient is adherent with diabetes medications, he/she will also be adherent with statin medications. The present study also included age and gender which were assessed in the previous study. Identifying additional variables to predict adherence with statin medications among the diabetes population will be an important addition to the current literature.

Significance of the study

In this study, the adherence with statin medications among diabetes patients at The University of Toledo was calculated. Additionally, the relationship between variables such as age, gender, copayment, location (main campus/health science campus), and adherence with diabetes medication with adherence with statin medications was determined. The determination of adherence rate and identifying predictors of adherence has many advantages. Once the major factors relating to poor adherence have been identified, interventions can be designed and implemented to improve adherence. These interventions can include, but are not limited to, patient education, intensified patient care (increased follow-up by health care providers, sending out reminders to fill prescription), and complex behavioral approaches (increasing motivation by arranging group sessions).

Findings from this study will help the University of Toledo to determine adherence patterns with statin medications among its diabetes population. If the adherence rate is found to be lower than optimal, interventions can be designed to improve adherence. The study of the effects of various factors mentioned in the previous paragraph will help in identifying risk factors associated with poor adherence. These risk factors will help in determining those employees more at risk of becoming non-adherent. For example, if the study findings show that younger patients, females or patients with more out of pocket costs are more at risk of becoming non-adherent, this population can be targeted for intervention. This study will also establish the need for conducting future studies which can look at other reasons (e.g. behavioral, emotional) for non-adherence in this population.

Research Goal: The main goal of this study was:

1) To determine the predictors of adherence with statin medications among The University of Toledo employees and their dependents with diabetes.

Research objectives: The research objectives addressed in this study were:

1) To determine the percentage of employees and their dependents with diabetes who have a concomitant prescription for statin medications.

2) To determine the adherence with statin medications as measured by Medication Possession Ratio (MPR) among the university of Toledo employees and their dependents with diabetes.
3) To determine the difference in patients' characteristics based on their adherence status and location.
4) To determine the effect of age, gender, copayment, location (main campus/health science campus), and adherence with diabetes medications on adherence with statin medications.

Research Questions: The research questions addressed in this study were:

1) What is the percentage of employees and their dependents with diabetes who have a concomitant prescription for statin medications?
2) What is adherence with statin medications as measured by Medication Possession Ratio (MPR) among the university of Toledo employees and their dependents with diabetes?
3) What are the differences in patients' characteristics based on their adherence status and location?
4) What is the effect of age, gender, copayment, location (main campus/health science campus), and adherence with diabetes medications on adherence with statin medications?

Chapter-2

Literature Review

This chapter includes a brief overview of the relevant topics related to the study and covers a review of the literature. This chapter is composed of the following sections. (1) Diabetes, (2) Cardiovascular risk among diabetes patients, (3) The role of statins in preventing cardiovascular risk, (4) Adherence and its importance, (6) Methods of measuring non-adherence, (7) Reason for non-adherence, (8) Adherence with statin medications, and (5) Previous studies identifying factors affecting adherence with statin medications.

Diabetes

Diabetes affects people throughout the world. In 2007, approximately 17.5 million people in the United States had been diagnosed with diabetes.[2] There are two common types of this disease: type-1 and type-2 diabetes.[3] Type-1 diabetes accounts for 5-10% of all diagnosed diabetes. This type of diabetes is developed when the body's immune system destroys the beta cells in the pancreas. Beta cells are responsible for making insulin, which regulates blood glucose. It is a serious disease that requires insulin

injections to control it. Type-2 diabetes is the most common type of diabetes. It accounts for 90-95% of all diagnosed cases of diabetes. This type of diabetes occurs when the body does not produce enough insulin or the cells in the body ignore the insulin produced. Many people with type-2 diabetes can control their blood glucose by following a healthy meal plan and exercise program, losing excess weight, and taking oral hypoglycemic medications. Some people with type-2 diabetes may also need insulin to control their blood glucose.

There are several co-morbidities associated with diabetes. Co-morbidities include obesity, high blood pressure, high triglycerides levels, high LDL or bad cholesterol levels, and low HDL or good cholesterol levels. Life style changes and the appropriate treatment can greatly reduce or delay the onset of these co-morbidities. For 2007, the total cost of treating diabetes in the United States was $174 billion.[5] The direct medical costs of treating diabetes accounted for $116 billion.[5] Direct medical costs include medical care, pharmaceutical drugs, insulin and other diabetes supplies, and cost to the healthcare sector, such as physician and hospital visits. The indirect medical costs of treating diabetes accounted for $58 billion. The indirect medical costs include cost of disability, work loss, and premature mortality. The cost of diabetes continues to grow each year. Hence, it is important that patients are adherent to their diabetes medications in order to reduce overall healthcare expenditures.

Cardiovascular risk among diabetes patients

People with diabetes are at a higher risk of developing cardiovascular diseases than people without diabetes due to a variety of risk factors including: poorly controlled blood glucose, high blood pressure, lipid disorders, smoking, obesity, and lack of physical activity. As per the American Diabetes Association (ADA), adults with diabetes have heart disease death rates about two to four times higher than adults without diabetes. [37] The risk of stroke is also two to four times higher than adults without diabetes. In 2004, 68% of diabetes-related deaths were due to heart diseases among people aged 65 years or older.[37] In the same year, 16% of diabetes-related deaths were due to stroke among people aged 65 years or older. Improved LDL control can reduce the cardiovascular risk to diabetes patients by 20-50%.[37]

The role of statins in preventing cardiovascular risk

Statins are a class of drugs that lower the level of cholesterol in the blood by reducing the production of cholesterol by the liver. Statins block the enzyme, 3-hydroxy-3-methylglutaryl-coenzyme A reductase, in the liver that is responsible for making cholesterol. Statins include well-known medications such as atorvastatin (Lipitor), simvastatin (Zocor), lovastatin (Mevacor), pravastatin (Pravachol), rosuvastatin (Crestor), fluvastatin (Lescol), and others.

The efficacy of statins in prevention of cardiovascular diseases in non-diabetes population has been well documented in major clinical trials.[15-21] Two major studies investigated the benefits of statins in preventing cardiovascular diseases among diabetes patients.[38-39] The first study was the Collaborative AtoRvastatin Diabetes Study (CARDS).[38] This study was the first large primary prevention study to focus specifically on the role of a statin in patients aged 40-75 years with type-2 diabetes. None of the participants had heart disease at the start of the trial, but they did have an extra risk factor for developing it, such as smoking, high blood pressure, or average or below average cholesterol levels. The trial was a prospective double-blind randomized trial with 2,383 type-2 diabetes patients randomized to either 10-mg atorvastatin daily or placebo. At study entry, more than 50% of patients had a LDL level below 3.3 mmol/l and about 25% had a LDL level below 2.6 mmol/l. Atorvastatin 10 mg reduced LDL-C by 40% (1.2 mmol/l) on average. At the end of four years, the risk of heart attack reduced by 37 % and stroke by 48 % in the atorvastatin group versus the placebo group. These benefits were seen regardless of age, sex or patients' LDL levels.

The second study was the Heart Protection Study (HPS).[39] This study involved 5,963 patients with diabetes aged 40-80 years. Patients were randomized to receive either 40-mg simvastatin daily or placebo. In this study, about 50% of patients had baseline cardiovascular diseases (CVDs). At the end of five years, the risk of first occurrence of any cardiovascular event among diabetes patients with no baseline CVDs reduced by 22% in the simvastatin group versus the placebo group. In the same period, the risk of any cardiovascular event reduced by 33% among diabetes patients with baseline CVDs.

These results were seen regardless of patient's cholesterol or glucose levels at baseline. The HPS study provided definitive evidence that statin treatment can produce a substantial reduction in the risk of cardiovascular diseases, such as heart attack and stroke, in people with diabetes.

Adherence and its importance

Adherence with a medication regimen is defined as the extent to which patients take medications as prescribed by their healthcare providers. In the literature, the terms adherence and compliance have been used interchangeably. The word "adherence" is preferred by many healthcare providers because "compliance" suggests that the patient is passively following the doctor's orders and that the treatment plan is not based on the therapeutic alliance or contract between the patient and the physician.[40] Adherence with medications is very important. The full benefits of many effective medications can be fully realized only if patients follow prescribed treatment regimens reasonably closely. Rates of adherence are usually reported as the percentage of the prescribed doses of medications actually taken by patients over a specified period.[40] Adherence rates are typically higher among patients with acute conditions, as compared with those with chronic conditions. Persistence has been defined as the continuation over time with long term drug therapy prescribed for the management of chronic conditions.[41] Persistence among patients with chronic conditions is low. For example, approximately 50% of patients receiving hydroxymehtylglutaryl – coenzyme A reductase inhibitors (statins) will discontinue their medications within six months of starting the therapy.[42]

In general, the average rates of adherence in clinical trials can be remarkably high. This is due to the attention study patients receive and to the selection of patients; yet, even clinical trials report average adherence rates of only 43-78%.[43-45] There is no consensus among healthcare providers on what constitutes adequate adherence. Some trials consider rates greater than 80% to be acceptable, whereas others consider rates of greater than 95% to be mandatory for adequate adherence, particularly among patients with serious conditions such as human immunodeficiency virus (HIV).[40] Adherence rates can vary from 0% to more than 100%, since patients sometimes take more than the prescribed amount of medication.[40, 46-48] Adherence rates are also reported as a categorical variable (adherence vs. non-adherence).

Adherence with medications is very important to reduce overall healthcare expenditures. Literature has shown that poor medication adherence has been associated with increased rates of hospitalization and total cost of care.[41] Of all the medication-related hospital admissions in the United States, 33 - 69 % are due to poor adherence, with a resultant cost of approximately $100 billion a year.[40]

Patients in clinical trials who are not adherent to medications or placebo have a poorer prognosis than patients in the respective group who do not.[41] Adherence with medication regimen, therefore, leads to better outcomes.[49-51] The collection of adherence data is now considered an essential part of clinical trials. Given the magnitude and importance of poor adherence with medication regimens, the World Health Organization

has published an evidence-based guide for clinicians, healthcare managers, and policy makers to improve strategies for medication adherence.[40, 52]

Methods for measuring non-adherence

Medication adherence can be measured in various ways, including direct and indirect techniques. Each method has advantages and disadvantages, and no method is considered the gold standard. Table 2.1 shows various direct and indirect methods of measuring adherence and the advantages and disadvantages of each method.

Table 2.1: Methods of measuring adherence, advantages and disadvantages of each method*

	Test	Advantages	Disadvantages
Direct Methods	Directly observed therapy	Most accurate	Patients can hide pills in the mouth and discard them; impractical for routine use
	Measuring of the level of drug or metabolite in blood	Objective	Variation in metabolism can give a false impression of adherence; expensive
	Measuring of the biological marker in blood	Objective	Requires expensive quantitative assays and collection of body fluids
Indirect Methods	Patient questionnaires and self reports	Simple, in expensive, most useful method in clinical settings	Susceptible to error with increase in time between visits; results are easily distorted by patients
	Pill counts	Easy, quantifiable	Data easily altered by patient
	Patient kept diary	Only self-report method with regimen data	Potential for overestimation, patient might not return diary
	Assessment of patient clinical response	Easy to perform	Factor other than medication adherence can affect clinical outcomes
	Electronic medication monitors	Precise, quantifiable results, track pattern of taking medication	Expensive, require return visits and downloading data from medication vials
	Measurement of physiological markers (e.g. heart rate in patients taking beta-blockers)	Easy to perform	Markers may be absent for other reasons (e.g. increased metabolism, poor absorption, lack of response)
	When the patient is a child, questioning the caregiver	Simple, objective	Susceptible to distortion
	Prescription record review, manual	Easy to perform	Limited to specific location
	Use of large claims data to determine prescription refill rates	Long term data, large population	Knowledge of database required, validity of variables, prescription refill is not equivalent to ingestion of medications

*- Information in this table was adopted from Osterberg and Blaschke,[40] and Karmer KC[52]

Direct methods provide proof that the drug has been taken by the patient. Direct methods include detection of drug or a metabolite in a biological fluid, usually blood or urine, detection of a biologic marker that is given with the drug (or placebo), and direct observation of the patient receiving the medication. Tests to detect the presence of the drug or drug markers can be conducted at specified intervals or randomly when feasible.[40] Direct methods are usually more accurate in measuring adherence than indirect methods. The direct methods are expensive to conduct and often not feasible. However, direct methods of measuring adherence are used for patients with serious conditions such as Tuberculosis. Khan et al. studied tuberculosis patient adherence by direct observation.[53] In this study, caregivers monitored the patients' adherence to therapy by direct observation and reported to the physician.

Most of the methods used to measure adherence are considered to be indirect methods. Examples include patient self-reporting, measuring physiological markers, third-party observation, medication measurement (pill count), use of electronic monitoring devices, prescription record review, and ascertaining rates of refilling prescription.[37] Questioning the patient (using a questionnaire), and patient-kept diaries are easy methods to use, but questioning the patient can be susceptible to misrepresentation and tends to result in overestimating the patient's adherence. Patients tend to over report their adherence with medication regimens. The most common method used to measure adherence, other than patient questioning, has been pill counts.[37] Pill counts can be defined as the number of pills that remain in the patient medication bottle or vials. This method has its flaws as patients might switch medicines between bottles

and may discard the pills before visiting the healthcare practitioner in order to appear adherent.[37] The other indirect methods used to measure adherence are electronic devices which are capable of recording and stamping the time of opening bottles, dispensing drops (as in case of glaucoma), or activating a canister (as in case of asthma). These devices provide detailed insight into patient's medication taking behavior.[37] This indirect method has its disadvantage in that it does not document whether the patient has actually ingested the correct drug or dose. The patient might open a container and not take the medication, take the wrong amount of medication, put the medication in another container, or take multiple doses out of the container at the same time.[37] There are many studies in the literature which have used these indirect methods and compared adherence rates calculated by the different indirect methods. For example, Grymonpre et al. measured and compared adherence to medications in the elderly using pills counts, self-report, and pharmacy claims.[54] Choo et al. validated patient-reported adherence, adherence from pharmacy records, and adherence using pill counts with electronic monitoring for antihypertensive drugs.[55]

In recent years, the use of administrative claims databases to measure medication adherence has gained importance. Andrade et al. conducted a systematic review of the literature on medication adherence using retrospective databases.[56] The authors included all studies published between January 1, 1980 and March 31, 2004 that evaluated adherence, compliance, persistence, switching, or discontinuation of medicines using automated dispensing data (pharmacy records). They identified 136 studies which used different methods of measuring adherence and compliance using retrospective claims

data. Of the 136 studies reviewed, 77 used Medication Possession Ratio (MPR) or related measures of medication availability to measure adherence. Twenty-one studies specifically used the term "MPR". Fifty-four studies used similar measures of medication availability using such terms as medication-total, proportion of days covered (PDC), adherence ratio, refill adherence, compliance rate, continuous multiple-refill interval measure of medication availability, adherence index, and compliance ratio or compliance index. Two studies reported total number of days supply dispensed during a specified time interval but did not express the value as a proportion or percentage.[56]

Forty-two studies calculated MPR by dividing the number of days supplied during the observation period by the number of days in the observation period. Thirty studies calculated MPR by dividing the number of days supplied including all but the last refill, by the number of days between the first and last dispensing date. The other methods used were to determine the number of days between the first prescription and the exhaustion of the last prescription (one study), or the number of days supply dispensed divided by the number of days until the next treatment episode (one study), or the number of days supply dispensed in one refill interval divided by the days in the refill interval (two studies). The adherence measure was dichotomized or categorized in 38 studies so that patients were considered adherent if a specific threshold was attained. Of the 32 studies for which the adherence measure was dichotomized, a MPR value of 80% or higher was considered adherent in 24 studies and a MPR value of 90% or higher was considered adherent in four studies. In eight studies, the adherence measure was categorized into three or more levels.

The other methods used were determining medication gaps (13 studies), medication persistence (58 studies), switching (34 studies), refill compliance (7 studies), and retentiveness/turbulence (4 studies).[56]

Reasons for non-adherence

The reasons for non-adherence to medications are complex and vary from patient to patient. Patients might not take their medications due to forgetfulness, other priorities, decisions to omit doses, lack of information, and emotional factors.[40] Some other reasons for non-adherence with medications are side effects, asymptomatic nature of disease (e.g. hyperlipidemia), amount of copayment, high number of medications, low socioeconomic status, lack of prescription drug coverage, complex treatment regimen, poor patient-provider relationship, and financial issues.[30, 57, 58] The knowledge of reasons for non-adherence can help identify necessary interventions to improve adherence.

Adherence with statin medications

Previous studies assessing adherence with statin therapy have reported a lack of adherence with treatment.[9-11, 21] In an analysis involving 6,462 diabetes patients, the mean proportion of days covered (PDC) for statin medications were 87% in the first year and 65% after 13 years. PDC was calculated by dividing the sum of total number of days of drug coverage (excluding the last prescription) to total number of days' follow-up in the study. Less than 50% of patients maintained a PDC > 80% after 13 years.[32] In another

study involving 34,501 elderly patients (23.5% with diabetes), the proportion of days covered by treatment was 79% during the first 3 months; thereafter, adherence fell dramatically to 56% after 6 months and to 42% after 120 months.[59] Wei et al. determined adherence with statins among myocardial infarction patients over a period of six years and reported that 69% of patients had > 80% adherence after a follow up periods of six years.[23] Adherence with statin medications may vary by the degree of cardiovascular risk. One particular study showed that two year adherence was 40.1% by patients prescribed a statin after an acute coronary event, 36.1% by patients with chronic heart disease, and 25.4% in patients being treated for primary hypertension.[60]

Factors affecting adherence with statin medications

Donelly and colleagues determined the patterns and predictors of long-term adherence with statin therapy among patients with diabetes in the community setting.[32] These researchers retrospectively analyzed the prescription database for patients with diabetes in Tayside, Scotland from January 1, 1989 to May 31, 2003. Percentage of days covered (PDC) was used as a dependent variable. PDC was calculated by dividing the sum of the total number of days of drug coverage (excluding the last prescription) by the total number of days' follow-up in the study. The patients with PDC < 80% were classified as non-adherent and PDC > 80% were classified as adherent to statin medication. They found that the predictors of poor long-term adherence with statin treatment among diabetes patients were younger age, higher HbA1c, no history of

smoking, no cardiovascular morbidity at baseline, and occurrence of cardiovascular disease after statin commencement.

Ye and colleagues determined the association between copayment and adherence with statin medications initiated after discharge from a coronary heart disease hospitalization.[33] The researchers retrospectively analyzed a database containing information on patient's inpatient admission, outpatient enrollment, and pharmacy claims from 1999 to 2003. In this study, about 61% of patients were adherent (MPR>80%) to statin treatment during a one year observation period. The adherence was measured as Medication Possession Ratio (MPR). MPR was calculated as the ratio of total days' supply of statins to total days during the one year observation period. Patients with an MPR of >80% were considered adherent. MPR was used both as a dichotomous and a continuous variable. Both multivariate logistic analysis and generalized least square regression analysis were conducted using MPR as a dependent variable. The results of both analyses were consistent. They found a reverse relationship between copayment and adherence with statins. Other relevant factors significantly associated with low adherence were younger age ($P < 0.001$), female sex ($P < 0.001$), absence of dyslipidemia diagnosis ($P <0.001$), presence of depression ($P = 0.010$), and concomitant use of nonstatin lipid-lowering drugs ($P < 0.001$).

Pedan and colleagues determined factors associated with statin adherence using a hierarchical model.[34] They used the time period of 30 days per refill within one year as the dependent variable. The patients with more than 11 refills were considered adherent.

They found that patients younger than 50 years had 13.6% fewer refills per year than did patients older than 70 years (P <0.001). This means that younger patients were less likely to be adherent than older patients. Women were 4.4% less adherent than men (p=0.041). Patients residing in southern states were significantly less adherent than were other patients; they had 19.4% fewer refills per year than did patients from western states (P<0.001). This variable showed that location also affects adherence with medications. Each prescription dispensed for co-morbid conditions increased adherence by 2.0% (P =0.002), and patients with a history of cardiovascular drug use were 14.1% more adherent than were other patients (P <0.001). Patients on a higher statin dose appeared to be 8.4% less adherent than were patients on a lower dose (P <0.001). Adherence was greater as the number of prescribed refills increased, with a rate of 2.1% per refill (P <0.001). Adherence was lower for patients with higher copayments, with a rate of 2.2% per each additional $10 of copayment (P <0.001).

Avorn and colleagues determined patients adherence with lipid lowering medications for one year and seven months in two different patient populations – the New Jersey Medicaid population (N=5,611) and the Quebec provincial medical care population (N=1,676).[24] Percentage of days covered (PDC) was used as a dependent variable. PDC was calculated by dividing the sum of total number of days of drug coverage to total number of days' follow-up in the study. The patients with PDC < 80% were classified as non-adherent and PDC > 80% were classified as adherent to statin medication. They found that the adherence with statins was 64.3% ± 29.8%. In their

study population, adherence did not differ by sex, decreased with increasing age, and decreased as the number of concomitant medications increased.

Benner and colleagues determined long-term adherence for the use of statin medications among elderly patients in New Jersey Medicaid and pharmaceutical assistance program.[26] Adherence was measured using percentage of days covered (PDC). The adherence was 79% in the first three months, 56% in the next quarter and then dropped to 42% at the end of three years. After five years, only 25% of the patients had a PDC of more than 80%. The researchers found that the predictors of poor long-term adherence were nonwhite race, lower income, older age, less cardiovascular morbidity at initiation of therapy, depression, dementia, and occurrence of coronary heart disease events after starting treatment.

Gibson and colleagues determined the impact of statin copayments on adherence with statin medications using the Medstat MarketScan database from 2000 to 2003.[35] The Medstat MarketScan database contains information on healthcare experiences of about 6 million enrollees with employer-sponsored health insurance each year. This database also contains information on Medicare patients with employer-sponsered supplemental medical benefits. Adherence was measured using Medication Possessions Ratio (MPR). MPR was calculated as the ratio of total days supply of statins to total days during the 18 month study observation period. Patients with an MPR of $\geq$ 80% were considered adherent. The researchers found that as cost sharing increased, statin adherence decreased. The researchers classified statin users as new and continuing users. A $10

dollar increase in copayment was associated with a 3 % point reduction in adherence among continuing users and a 1.8 % point reduction in adherence among new users. Female sex was associated with a lower level of adherence than males. As age increased towards 65 years, adherence increased, but as age exceeded 65 years, adherence declined. As number of medications increased, adherence decreased. The patients who filled their prescription by mail order in the past year for any prescription were more likely to be adherent to statins.

Caspard and colleagues determined compliance and risk factors for poor compliance in a Massachusettes health maintenance organization (HMO).[36] They found that those at risk for poor compliance were patients with age < 50, women, and patients with no previous hyperlipidemia treatment. About 64% of patients were adherent with MPR ≥ 80% at six months. This number decreased to 55% at year 1 to 53% at year 3. The average MPR the during first six months was 65%. In this population, 20% of population discontinued treatment within six months of start of therapy. About 74%, 65% and 61% were still on treatment after 1, 2 and 3 years of statin therapy respectively. The probability of resuming treatment was 51% within 24 months after the last prescription was filled.

Summary

Diabetes patients are at increased risk of developing cardiovascular diseases. Treatment with statins is effective in reducing this risk. Patients are usually non-adherent

with their statin treatment. Non-adherence with statins among diabetes patients can result in increased morbidity and mortality due to development of cardiovascular complications. This can lead to increase in healthcare expenditures for patients, insurance companies, self-insured employers, and the government. Thus, it is important to determine the adherence of patients with statins and the factors affecting adherence. The University of Toledo is a self-insured employer group which covers about 13,000 employees and their dependents. Currently, no study has measured adherence rate and identified factors affecting adherence with statins among the University of Toledo employees and their dependents with diabetes. This study will bridge this gap in the literature.

Chapter-3

Methods

This chapter describes the methodology used in the study. It is divided into the following sections: study design, data source, inclusion criteria, exclusion criteria, study independent and dependent variables, and data analysis. The methodology is based on the research objectives of the study.

Study Design

This was a retrospective, longitudinal observational study. Pharmacy claims were used to identify diabetes patients using both diabetes and statin drugs during the study period between January 1, 2006 and June 2, 2008.

Data Source

The University of Toledo (UT) pharmacy administrative claims data was used for the study. This claims data was available for both main and health science campus employees and their dependents for the period between January 1, 2006 and June 2, 2008.

The data was provided to the researchers by the coordinator of managed care pharmacy services for the University of Toledo. The coordinator acquired this data from Prescription Drug Management Insurance (PDMI) for main campus employees and Express-Scripts (ES) for health science Campus employees. PDMI and ES were the pharmacy benefit management companies for the University of Toledo during the study period.

The coordinator de-identified the data by removing all non-essential identifiable variables, such as social security number (SSN), employees' names and addresses from the original prescription claims data. The Health information Portability and Accountability Act (HIPPA) guidelines "requirements for removing identifiers from research information/records/samples" were followed to remove all identifiable variables. After removing all non-essential identifiable variables, the coordinator assigned a unique, random member ID to each employee and replaced dates of birth with age for each prescription claim. This member ID could not be traced back to the specific patient. The key which linked the original member ID to the random ID was kept confidential by the coordinator. No employee was contacted for the purposes of this study.

The researchers received the data as four Microsoft Excel spread-sheets saved in a USB flash drive. The first two Excel spread sheets had observations on the prescription claims for OHDs and statin medications for main campus employees and their dependents. The other two files had observations on the prescription claims for OHDs

and statin medications for health campus employees and their dependents. The number of observations for each prescription claim file is shown in Table 3.1

Table 3.1: Prescription claims files and number of observations

	Prescription Claim File	Number of Observations
Main campus employees and their dependents	Oral Hypoglycemic Drugs	3955
	Statins	1227
Health science campus employees and their dependents	Oral Hypoglycemic Drugs	2893
	Statins	4267

Inclusion criteria

Patients included in the analysis were University of Toledo employees and their dependents with a diagnosis of diabetes. The patients were required to be at least 18 years of age at the start of study period. The patients should have a prescription claim for a statin in addition to the prescription claim for oral hypoglycemic drugs (OHDs) during the study period between January 1, 2006 and June 2, 2008. For this study, the researchers were interested to study the effect of adherence with OHDs on adherence with statins. To study this effect, it was necessary that patients should be filling their OHDs and statin prescriptions concurrently. To meet this requirement, patients should have evidence of filling at least one OHD prescription within 180 days of the index date of a statin prescription. The index date for each patient was defined as the date of his or her first statin medication prescription on or after January 1, 2006. Adherence with statins

was examined in the 180 day observation period following the index date. Only those patients were included who had at least 180 days of follow-up data. In a secondary analysis, patient adherence was evaluated for a subset of patients from the main analysis who had at least one full year (365 days) of follow-up data. The statin drugs included were atorvastatin, fluvastatin, lovastatin, rosuvastatin, provastatin, and simvastatin. All branded/generic formulations of these statin drugs were included. The oral hypoglycemic drugs belonged to the following categories: sulfonyl-urea, non-sulfonyl-urea, thiazolidinedione, alpha-glucosidase inhibitors, meglitinides, anti-diabetic combinations, and miscellaneous anti-diabetes drugs.

Exclusion Criteria

For this study purpose, the observations on the prescription claims for insulin preparations (injections as well as pumps) were excluded from the analysis. This data did not provide sufficient detail about each patients' insulin regimen to reliably estimate their adherence (e.g. the researchers did not know if the patients are on a sliding scale for insulin). Previous studies have also shown that there is a difference in patients' adherence to oral hypoglycemic drug therapy and insulin therapy.[61,62] The adherence with insulin is generally higher than that of oral hypoglycemic drugs. Therefore, the inclusion of patients with an insulin claim would have skewed the data towards greater adherence with diabetes medications than with statins.

Study independent variables

The independent variables available in the data were age, gender, and copayment for statins. The average copayment adjusted to a 30-day supply for statin prescriptions was calculated and included in the analysis. The variable "location" was created which determined whether patients were from the main campus or the health science campus. Location was included as an independent variable to determine if adherence with statins differed based on the campus of employment. The medication possession ratio (MPR) for diabetes medications was calculated and used as an independent variable. Diabetes medications MPR was also calculated by dividing the number of days supply of medications during the observation period by the number of days in the observation period. A single MPR was calculated if patients switched from one drug class to another during the study observation period. If patients had prescriptions filled for drugs in multiple classes simultaneously, then a separate MPR was calculated for each drug class, and the mean of all classes was calculated. Previous studies have adopted the same technique to calculate MPR for patients who were taking two or more drugs simultaneously.[63]

Dependent Variable

The dependent variable was Medication Possession Ratio (MPR) for statin medications. Statin medications MPR was calculated by dividing the number of days supply of medications during the observation period by the number of days in the

observation period (180 days). A single MPR was calculated if patients switched from one statin medication to another during the study observation period. If patients filled two statin medications simultaneously, then a separate MPR was calculated for each statin, and the mean of two statins was calculated. The MPR for statin medications was used as a discrete variable. Patients with MPR $\geq$ 80% were considered adherent and patients with MPR < 80% were considered non-adherent. About 75% of adherence studies using administrative databases used MPR to measure adherence and the majority of these studies used a cut off value of 80% for differentiating between adherence and non-adherence.[56]

Data Analysis

The statistical analyses were conducted using SAS software (version 9.1.3, SAS Institute Inc., Cary, NC, USA). Descriptive statistics were used to describe the study population. The mean MPR to statins and percentage of patients classified as adherent and non-adherent to statins were calculated. The mean MPR to OHDs was calculated and used as the independent variable. The percentage of patients classified as adherent and non-adherent to OHDs was also calculated. The difference in population characteristics (age, gender, location, copayment, and adherence with OHDs) was analyzed between the adherent and non-adherent groups using t-tests for continuous variables and chi square tests for categorical variables. All statistical values were considered significant at $p \leq 0.05$.

Multivariate logistic regression techniques were used to determine the effect of independent variables on adherence with statin medications among University of Toledo employees and their dependents with diabetes. In the logistic regression model, statin medications MPR was used as a dichotomous variable. Patients with MPR $\geq$ 80% were considered adherent and patients with MPR < 80% were considered non-adherent.

Chapter-4

Results

This chapter describes the study population, data analyses and results of the study. Characteristics of the study population will be presented. The differences in population characteristics (age, gender, location, copayment, and adherence with OHDs) between the adherent and non-adherent groups to statins will be presented, followed by the relationship between independent variables and adherence with statins.

Study Population

A total of 193 patients out of 667 diabetes patients (28.93%) met study criteria and were included in the primary data analysis. The criterion for study population selection is described in Figure 1 on the following page.

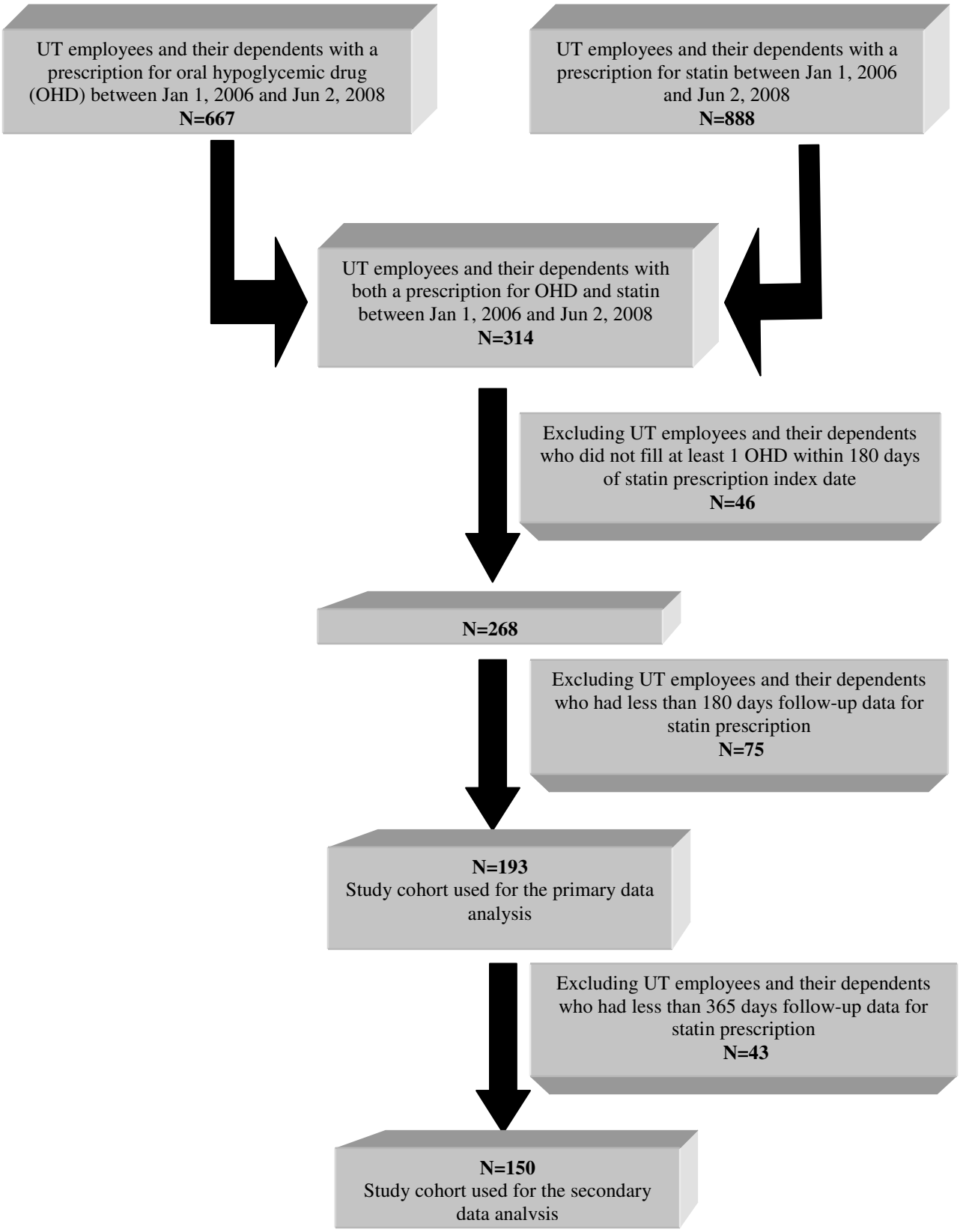

Figure 1: Study population selection criteria

There were 667 patients with a prescription claim for an oral hypoglycemic drug and 888 patients with a prescription claim for statin medications during the study period between January 1, 2006 and June 2, 2008. The patients on oral hypoglycemic drugs were matched with patients on statin medications using the unique member identifier for each patient. As a result, there were 314 diabetes patients who were on concomitant statin medications (atorvastatin. fluvastatin, lovastatin, rosuvastatin, pravastatin, or simvastatin). Out of these 314 patients, 75 patients were excluded as these patients did not fill at least one oral hypoglycemic drug prescription within 180 days of the statin prescription index date. An additional 45 patients were also excluded who did not have at least 180 days of follow-up data for statin medications. After excluding these patients, 193 patients were left which were used to determine adherence during the 180-day observation period following the statin prescription index date. Out of 193 patients, 43 patients did not have at least 1 year of follow-up data for statin medications. As a result, 150 patients were used to determine adherence over a one year period in the secondary analysis.

Table 4.1 and 4.1a show the characteristics of study population.

Table 4.1: Characteristics of study population, frequencies (N=193)

Characteristic	N (%)
Sex	
Male	142 (52.85)
Female	91 (47.15)
Location	
Main Campus	98 (50.78)
Health Science Campus	95 (49.22)
Oral Hypoglycemic Drugs MPR	
< 0.80	77 (39.90)
≥ 0.80	116 (60.10)
Statin Medications MPR	
< 0.80	70 (36.27)
≥ 0.80	123 (63.73)

Oral Hypoglycemic Drugs /Statin Medication MPR < .80 - Non adherent
Oral Hypoglycemic Drugs /Statin Medication MPR ≥ .80 – Adherent

Table 4.1a: Characteristics of study population, mean and standard deviation (N=193)

Characteristic	Mean ± SD
Age (years)	55.58 ± 9.31
Copayment ($)	10.04 ± 6.69
Oral Hypoglycemic Drugs MPR	0.78 ± 0.20
Statin Medications MPR	0.80 ± 0.20

As shown in Table 4.1, men accounted for approximately a little more than half of all study patients. The number of patients from each campus was fairly equal. About 60% of patients were adherent to oral hypoglycemic drugs with MPR ≥ 80%. Almost 64% of patients were adherent to statins with MPR ≥ 80%.

As shown in Table 4.1a, the mean age of the patients was almost 60 years old. The mean copayment of statin medications for 30-day supply was around $10. The mean adherence with oral hypoglycemic drugs was 0.72 while the mean adherence with statin medications was 0.80.

Patients' characteristics stratified by adherence status for overall sample:

Table 4.2 shows the patients' characteristics stratified by adherence status.

Table 4.2: Patients' characteristics stratified by adherence status for overall sample

Variable	Non-adherent Patients (N=70)	Adherent Patients (N=123)	P Value
Age*#	**53.80 (9.23)**	**56.59 (9.24)**	**0.05**
Oral Hypoglycemic Drugs MPR*#	**0.69 (0.21)**	**0.83 (0.17)**	**< 0.001**
Copayment *#	10.08 (7.34)	10.01 (6.78)	0.94
Sex, N (%)δ			
Female	36 (18.65%)	55 (28.50%)	0.36
Male	34 (17.62%)	68 (35.23%)	
Location, N (%)δ			
HSC	39 (20.21%)	56 (29.02%)	0.17
MC	31 (16.06%)	67 (34.72%)	

* - t- test, δ - chi square test, # - Mean (SD)

Results from t-tests showed that those patients who were adherent to statins were on average three years older than non-adherent patients. This difference in age was statistically significant. On average, patients who were adherent to statins had significantly higher MPR for OHDs compared with non-adherent patients. There was no statistically significant difference in mean copayment amounts between adherent and non-adherent patients. The results of chi-square tests showed that males were more adherent than females and a larger percentage of patients from the main campus were adherent than patients from the health science campus. However, these results were not statistically significant.

Patients' characteristics stratified by adherence status and location

Table 4.3 and 4.4 show the patients' characteristics stratified by adherence status and campus location. Table 4.3 shows the patients' characteristics stratified by adherence status for the main campus and Table 4.4 shows the patients' characteristics stratified by adherence status for the health science campus.

Table 4.3: Patients' characteristics stratified by adherence status for the main campus employees

Variable	Non-adherent Patients (N=31)	Adherent Patients (N=67)	P Value
Age*#	56.74 (8.15)	57.80 (8.77)	0.56
Oral Hypoglycemic Drugs MPR*#	**0.66 (0.21)**	**0.82 (0.16)**	**< 0.001**
Copayment*#	$14.11 ($6.70)	$11. 65 ($6.75)	0.09
Sex, N(%)δ			
Female	13 (13.27%)	25 (25.51%)	0.66
Male	18 (18.34%)	42 (42.86%)	

* - t-test, δ- chi square, # - Mean (SD)

On the main campus, patients who were adherent to statins were on average one year older than non-adherent patients. However, this difference in age was not statistically significant. On average, patients who were adherent to statins had a significantly higher MPR for OHDs compared with non-adherent patients. Non-adherent patients had on average $2.50 more mean copayment than adherent patients. This

difference in mean copayment was not statistically significant. Also, males were non-significantly more adherent than females ($\chi 2 = 0.191$; p=0.66)

Table 4.4: Patients' characteristics stratified by adherence status for the health science campus employees

Variable	Non adherent Patients (N=39)	Adherent Patients (N=56)	P Value
Age*#	51.46 (9.46)	55.13 (9.66)	0.06
Oral Hypoglycemic Drugs MPR*#	**0.72 (0.22)**	**0.86 (0.17)**	**0.00**
Copayment*#	6.89 (6.07)	8.05 (6.46)	0.37
Sex, N(%)δ			
Female	23 (24.21%)	30 (31.58%)	0.60
Male	16 (16.84%)	26 (27.37%)	

* - t test, δ - chi square test, # - Mean (SD)

On the health science campus, patients who were adherent to statins were on average four years older than non-adherent patients. This difference in age was statistically non-significant. On average, patients who were adherent to statins had significantly higher MPR for OHDs compared with non-adherent patients. Adherent patients had on average $1 more mean copayment than non-adherent patients. This difference in mean copayment was not statistically significant. Also, females were non-significantly more adherent than males ($\chi 2 = 0.271$; p=0.60)

Predictors of adherence with statin medications

This section presents the results of the logistic regression to determine the predictors of adherence with statin medications.

Table 4.5 shows the results of logistic regression. Statins MPR was used as a categorical variable for this regression analysis. Patients with MPR < 80% were considered non-adherent. Patients with MPR ≥ 80% were considered adherent. The chi-square likelihood ratio is 35.516 ($p<0.0001$). This ratio indicates that the model is significant.

Table 4.5: Results of logistic regression predicting adherence with statin medications (∑N=193)

Parameter	Odds ratio	95% Confidence Interval	P-Value
Age	1.030	0.994-1.067	0.103
Health Science Campus	0.617	0.306-1.246	0.179
Oral Hypoglycemic Drugs MPR	**1.042**	**1.025-1.061**	**<.0001**
Male	1.482	0.764-2.875	0.2459
Copayment	0.985	0.938-1.035	0.554

Age was positively associated with adherence with statin medications. The odds ratio with each 1 year increase in age was 1.03 (95% CI, 0.99-1.07) which means that

with every 1 year increase in age, the odds of being adherent with statin medications increased by 3%, holding all other variables constant. The health science campus employees had odds of being adherent with statins that are about 61.7% that of main campus employees, holding all other variables constant. The results of the effect of age and campus location on adherence with statins were not statistically significant.

Each 1% increase in oral hypoglycemic drugs MPR increased the odds of being adherent with statins by 4.2%, holding all other variables constant. This result was statistically significant. Males were 48% more likely than females to be adherent with statins, holding all other variables constant. Each $1 increase in copayment decreased the odds of being adherent with statin medications by 1.5%. The results of the effect of gender and copayment on adherence with statins were not statistically significant.

In the above logistic regression model, the effects of independent variables age, gender, location, and copayment were not statistically significant. The researchers hypothesized that the patients who were adherent with OHDs would also be adherent with statins. So, there was a possibility of adherence with OHDs overcontrolling other independent variables. To counteract this problem, another regression model was analyzed in which adherence with statins was predicted excluding adherence with OHDs. The results of this regression model are shown in Table 4.6.

Table 4.6: Results of logistic regression predicting adherence with statin medications excluding adherence with OHDs (∑N=193)

Parameter	Odds ratio	95% Confidence Interval	P-Value
Age	**1.034**	**1.000-1.070**	**0.049**
Health Science Campus	**0.273**	**0.088-0.846**	**0.024**
Male	1.275	0.883-1.002	0.245
Copayment	0.940	0.883-1.002	0.058

After excluding adherence with OHDs, age and location were statistically significant which means that the effects of age and location might have worked through the effect of adherence with OHDs on adherence with statins. In other regression models, the interaction between adherence with OHDs and age, and the interaction variable between adherence with OHDs and location were analyzed. These interactions were statistically significant at p value of less than 0.05, which means that the effect of age and location on adherence with statins differed based on adherence with OHDs.

Adherence at one year follow-up

In a subset analysis, patients' adherence was evaluated over a one year observation period among patients whose prescription claims data was available for an additional six months (N=150). The patient characteristics for this subset of population are shown in Table 4.7 and Table 4.7a, and are comparable to the overall patient

population. The mean age was 55.69 years vs. 55.58 years in the original cohort. The mean copayment for statins was $10.68 vs. $10.04 in the original cohort. About 52% of patients were males in both populations. About 55% of patients were from main campus comparable to 51% in the original cohort.

At the end of one year, 59.33% of patients were still adherent to statins with MPR ≥ 0.80 compared with 63.73% of patients at the end of 180 days. There was a drastic decrease in the number of patients who were adherent to OHDs. At the end of one year, only 41.33% of patients were adherent to OHDs compared with 60.10% of patients at the end of 180 days. The mean adherence also decreased from 0.80 to 0.78 for statin drugs and from 0.78 to 0.72 for OHDs.

Table 4.7: Characteristics of subset of study population at one year, frequencies (N=150)

Characteristic	N (%)
Sex	
Male	79 (52.67)
Female	71 (47.33)
Location	
Main Campus	83 (55.33)
Health Science Campus	67 (44.67)
Oral Hypoglycemic Drugs MPR	
< 0.80	88 (58.67)
≥ 0.80	62 (41.33)
Statin Drugs MPR, N (%)	
< 0.80	61 (40.67)
≥ 0.80	89 (59.33)

Oral Hypoglycemic Drugs /Statin Medication MPR < .80 - Non adherent
Oral Hypoglycemic Drugs /Statin Medication MPR ≥ .80 - Adherent

Table 4.7a: Characteristics of subset of study population at one year, mean and standard deviation (N=150)

Characteristic	Mean ± SD
Age (years)	55.69 ± 8.65
Copayment for Statin Drugs ($)	10.68 ± 7.14
Oral Hypoglycemic Drugs MPR	0.72 ± 0.21
Statin Drugs MPR, Mean	0.77 ± 0.23

Summary

About 47% of diabetes patients had at least one statin prescription during the study period. Men accounted for approximately a little more than half of the all study patients. About 50% of patients were from main campus. The mean age of the patients was 55.58 ± 9.31 years. The mean copayment of statins for 30 day supply was $10.04 ± $6.69.

The mean adherence with statins was 0.80 in the 180 day observation period, which decreased to 0.78 at the end of one year. At the end of one year, 59.33% of patients were still adherent to statins with MPR ≥ 0.80 compared with 63.73% of patients at the end of 180 days. The mean adherence with OHDs was 0.78 in the 180 day observation period, which decreased to 0.72 at the end of one year. There was a drastic decrease in the number of patients who were adherent to OHDs after one year. At the end of one year, only 41.33% of patients were adherent compared with 60.10% of patients at the end of 180 days.

In the regression model, only adherence with OHDs was found to be the significant predictor of adherence with statins among diabetes patients. However, when adherence with OHDs was excluded from the model, age and location were significant predictors as well. Males showed higher adherence than females. Copayment was negatively related with adherence with statins among diabetes patients.

Chapter-5

Discussion and Conclusion

This chapter covers the discussion and conclusions based on the study results. It is divided into the following sections: adherence with statin medications among The University of Toledo diabetes population, effects of age, copayment, location (main/health science campus), gender and adherence with diabetes medications on adherence with statin medications, implication of the findings, study limitations, future research, and conclusion.

Adherence with statin medications among The University of Toledo diabetes population

Diabetes patients are at increased risk of developing primary and secondary cardiovascular diseases. [6,7] The clinical benefit of statin therapy as first line therapy in reducing this risk is well established in several clinical trials.[15-21] American Diabetes Association (ADA) guidelines on prevention of CVD recommend statin therapy in every patient 40 years and over with diabetes. [22] Maintaining adherence with statin treatment has been recommended as a critical strategy to achieve long term cholesterol control.[14] Adherence with statin treatment has consistently been reported as high in clinical trials.

This is likely due to the attention study patients receive and to the selection of patients.[40-42] The studies based on retrospective claims databases provides a more accurate estimate of adherence in real life settings. The studies using retrospective claims data suggest that adherence with statin might be an issue for many patients.[9-11, 21]

In the present study, the adherence with statins was assessed among diabetes patients who were concomitantly taking a statin medication. The results showed that about 47% of diabetes patients insured by the University of Toledo had at least one statin prescription during the study period. This percentage is really low considering the fact that diabetes is an independent risk factor for developing cardiovascular disease, with up to 80% of type-2 diabetes patients dying from cardiovascular complications.[32] The efficacy of statins in reducing the cardiovascular risk in patients with or without diabetes is well established.[15-21] Recent ADA guidelines even suggest that diabetes patients above 40 years of age should be on statin therapy irrespective of their lipid levels.[22]

In the present study, more than 90% of patients in the study population were above 40 years of age. As per the ADA guidelines, these patients should have been on a statin medication irrespective of their lipid levels. The low percentage (47%) of University of Toledo employees and their dependents with diabetes on a statin medication indicates that this population may be at increased risk of developing cardiovascular complications. This presents a significant risk of increased hospitalization, outpatient visits, emergency room visits, and mortality among this population. This additional risk can lead to an increase in healthcare expenditures for The University of

Toledo. There might also be additional cost burden due to decreased work productivity and absenteeism. Diabetes patients with concomitant cardiovascular diseases incur annually 1.5 to 3.5 times more medical costs than patients with diabetes alone.[63] Farqhar et al. used 1996 Medical Expenditure Claims Data (MEPS) to determine cost of concomitant illnesses among patients with diabetes.[63] Patients with diabetes with any concurrent cardiovascular disease incurred annual average medical costs ranging from $2,000 to $48,100, which was 1.5 to 3.5 times-fold higher than estimated average medical cost for patient with diabetes alone.[64] Treatment with statins is also cost-effective in diabetes patients without dyslipidemia.[65] Grover et al. developed a cardiovascular disease life expectancy model which showed that treatment with statins is cost effective among diabetes patients, with estimates ranging from $5,063 to $23,792 per year of life saved.[65]

In the present study, about 64% of the diabetes patients were adherent to statin medications, with an MPR value of greater than 80% during the 180 day observation period. The percentage of adherent patients dropped to 60% at the end of one year. These results are similar to adherence rates reported in a previous observational study to measure adherence with statin medications. The study by Caspard et al who analyzed a Massachusetts health maintenance organization's (HMO) drug-dispensing data found that about 64% of patients were adherent to statin medications with MPR $\geq$ 80% in a one year period compared to 53% of patients in a three year period.[36] The present study was a short-term study which looked at adherence with statins over a period of one year. A study by Donnelly et al. was a long-term study (13 years) and they reported that patients'

adherence with statins decreased sharply within the first six months, followed by a more gradual decline over time. Less than 50% of patients remained adherent with MPR > 80% after 13 years. Therefore, it is likely that adherence to statins among The University of Toledo population will continue to decline.

Effects of age, copayment, location (main/health science campus), gender, and adherence with diabetes medications on adherence with statin medications

In the present study, age was found to be non-significantly positively associated with adherence with statin medications. Most of the previous studies based on adherence have found that age has a significant positive relationship with adherence with statin medications.[32-34] In previous studies, Donnelly et al. reported that older diabetes patients adhered better with statin medications compared with younger patients.[32] Ye et al. also reported that patients older in age were significantly more likely to be adherent to statin medications. The odds ratio associated with each one year increase in age was 1.01 (95% CI, 1.01-1.02).[33] In the present study, the odds ratio associated with each 1 year increase in age was 1.03 (95% CI 0.99-1.06). However, in the present study, the presence of adherence with oral hypoglycemic drugs might have confounded the effect of age on adherence with statins. After adherence with oral hypoglycemic drugs was removed from the model, age was significantly positively associated with adherence with statins.

There was one study in the literature which specifically looked at the relationship between age and adherence with statin medications in patients over 65 years of age.[24]

They found that adherence with statins decreased with increasing age. Yet another study reported that as age increased towards 65 years, adherence with statin medications increased, but as age exceeded 65 years, adherence declined.[35] The present study did not find any negative relationship between age and adherence with statin medications in patients above 65 years of age. In the present study, there was a non-significant positive relationship between age and adherence with statin medications in patients above 65 years of age. This might be due to the small number of patients above 65 years of age in this study (< 15%).

In previous studies, higher copayment was found to be associated with lower adherence with statin therapy. [33-35] Ye et al. reported a significant negative relationship between copayment and adherence with statin medications.[33] Pedan et al. and Gibson et al. also reported that adherence with statin medications was significantly lower for patients with higher copayments.[34-35] The present study found a non-significant negative relationship between copayment and adherence with statin medications. However, the present study looked at the relationship between copayment and adherence for two different populations with different copayment structures. For a 30-day supply, the main campus employees had to pay $6 for a generic, $12 for preferred brand and $24 for non-preferred brand at any UT pharmacy. This copayment amount increased to $11 for a generic, $28 for preferred brand, and $45 for non-preferred brand at any other network pharmacy. Main campus employees could fill a 90-day prescription only at a UT pharmacy. For a 90-day supply, they had to pay $15 for a generic, $22.50 for preferred brand and $45 for a non-preferred brand. In comparison to the main campus, there was

less variation in copayment amounts for health science campus employees. For both 30 and 90 days' supply, health science campus employees had to pay a flat copayment of $10 for generic, 22% of average wholesale price (AWP) plus $5 dispensing fee for preferred brand, and the difference between brand and generic drug cost for non-preferred brand. The small population and the wide variation in the copayment structures might have prevented finding statistically significant differences in adherence with statin medications based on copayment in this study.

In the present study, males were more likely to be adherent than females. However, this result was not statistically significant. Previous studies have also found that the women are less likely to be adherent than males.[33-35] Pedan et al. reported that women are 4.4% less adherent than males.[34] Ye et al and Gibson et al also reported the female sex was associated with lower levels of adherence with statin medications compared to males.[33,35] The small sample size in the present study might have prevented finding significant differences related to gender.

Adherence with OHDs was found to be significantly associated with adherence with statins. Adherence with diabetes medications as a variable has not been studied as such in any previous study. This finding was anticipated as in the present study, the researchers hypothesized that patients who are adherent with OHDs would also be adherent with statin medications.

Implications of the study findings

The main objective of the present study was to determine the adherence with statin medications among The University of Toledo employees and their dependents with diabetes and to determine the factors which can affect the adherence. This study found that at The University of Toledo, a low percentage (47%) of the diabetes population is taking concomitant statin medications. To counteract this problem, awareness should be created among the area physicians who treat University of Toledo employees and their dependents with diabetes to prescribe statins.

About 36% of diabetes patients taking statins were non-adherent with statin medications over the 180 day observation period. This percentage increased to 40% over the one year follow-up period. This presents a significant risk of increased morbidity and mortality due to cardiovascular complications and significant health care cost to University of Toledo in the long run. Additionally, about 40% of patients were not adherent with their diabetes medications over the one year follow-up period. This can lead to increased outpatient and emergency room visits due to hyperglycemia and other complications, and further add to the healthcare cost for The University of Toledo and its employees. To counteract the problem of non-adherence, physicians should be encouraged to provide interventions, such as increased follow-up, to their patients who have problems with adherence. Physicians may not always have time to provide these interventions. Therefore, an alternative approach could be interventions provided by the university and network pharmacies and other healthcare providers such as pharmacists.

Pharmacies could assist by sending reminders to the patients to refill their prescriptions. Pharmacists can also conduct patient education programs to make them aware of the benefits of statin therapy and adherence. Patient group sessions can be conducted to enhance motivation.

The present study also looked at the effects of age, gender, copayment, location (main campus/health science campus), and adherence with diabetes medications on adherence with statins. Younger patients and females were more at risk of becoming non-adherent with their statin medications. Various interventions as mentioned in the above paragraph can be targeted to these specific populations to maximize the benefits of the interventions. Patients with more out of pocket costs tended to be more non-adherent with statins. Patients should be provided incentives to fill generic statin prescriptions which will lower the cost and possibly improve adherence.

Study Limitations

The small population size available for the study was a limitation. The small population size might not have allowed estimating significant effects of age, gender, location, and copayment on adherence with statin medications in this study. Non-availability of medical claims data did not allow following the patients adherence right from the start of therapy. Most previous studies followed patients from their first diagnosis and first prescription refill. [33-36] In the present study, we do not know whether the patients were newly diagnosed or taking medication for many years. Due to this

limitation, the researchers could not account for the effect of number of years patients were taking their medications on adherence with statin medications. Previous studies have shown that adherence differs based on the number of years patients were taking their medications.[33,34] Also, the non-availability of inpatient claims and cost data did not allow researchers to study the cost burden in this population due to diabetes and cardiovascular diseases.

Medication Possession Ratio (MPR) is only a surrogate measure of adherence. The actual consumption of medications cannot be measured using claims data. Also, the 80% cut off level is the most commonly used measure to determine adherence, albeit somewhat arbitratry. Some variables which might play an important role in explaining adherence could not be included in the study due to the retrospective nature of the data collection, e.g. A1c levels, blood pressure and lipid levels, presence or severity of cardiovascular disease at baseline. Finally, the results cannot be generalized beyond the population of University of Toledo employees and their dependents with diabetes.

Future Research

Future research on this population should be focused on determining the cost burden in this population due to the presence of diabetes and concomitant cardiovascular diseases. Studies should be designed to compare costs between diabetes patients who are on statins versus patients who are not on statins. Future studies can also include prospective studies to determine the reasons for non-adherence in this population. In

these studies, questionnaires can be collected either at the clinic or by mail from patients, to determine their reasons for non-adherence. Future research can also include other direct and indirect methods to measure non-adherence in this population such as measuring drug level in the blood or metabolite, pills counts, patient-kept diaries to record their medication taking behavior, and electronic monitoring.

Future research using administrative claims database on this topic should be conducted using a large claims database which has a much larger sample size, more independent variables, availability of both medical and pharmacy claims data, and eligibility data.

Conclusion

Adherence with statin medications among the diabetes population is very important because low adherence can result in increased outpatient and emergency room visits due to development of cardiovascular diseases. This can lead to increase in healthcare costs for the University of Toledo and its employees. The determination of adherence patterns and risk factors for non-adherence can provide evidence to design and implement interventions to improve adherence.

The researchers concluded that adherence with statin medication was suboptimal among this study population. Adherence was lower among younger patients, females, and patients with more out of pocket costs. Main campus patients were more likely to be

adherent than the health science campus patients. If patients were adherent with their OHDs, they tended to be more adherent with statins. Based on these findings, The University of Toledo should investigate the reasons for non-adherence in this population. The University of Toledo should also design and implement interventions which can improve adherence and potentially lower the healthcare costs for this self-insured organization.

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Appendix: Institutional Review Board Approval Letter

THE UNIVERSITY OF TOLEDO
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The University of Toledo
Department for Human Research Protections
Social, Behavioral & Educational Institutional Review Board
Office of Research, Rm. 2300, University Hall
2801 West Bancroft Street, Mail Stop 944
Toledo, Ohio 43606-3390
Phone: 419-530-2844 Fax: 419-530-2841
(FWA00010686)

To: Monica Holiday-Goodman, Ph.D. and Jinender Kumar
Department of Pharmacy Practice

From: Barbara K. Chesney, PhD., Chair
Wesley A. Bullock Ph.D., Vice Chair

Signed: _ **Date:** 02/02/09

Subject: IRB #106320

Protocol Title: *A Retrospective Analysis to Identify Factors that can Predict Adherence to HMG-CoA Reductase Inhibitors (Statins) among University of Toledo Employees with Diabetes*

On 02/02/09, the Protocol listed below was reviewed and approved by the Chair and the Chair Designee of the University of Toledo (UT) **Social Behavioral & Educational** Institutional Review Board (IRB) via the expedited process. You have also been granted a waiver from the requirements of a written consent form. This action will be reported to the committee at its next scheduled meeting.

Items Reviewed:

- IRB Application Requesting Expedited Review

This protocol approval is in effect until the expiration date listed below, unless the IRB notifies you otherwise.

Approval Date: 02/02/09 **Expiration Date: 02/01/10**

Number of Subjects Approved: 700

Please read the following attachment detailing Principal Investigator responsibilities.