Evaluation of Medication Therapy Management (MTM) Services for Patients with Cardiovascular Disease

by

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Abstract

Background: Medication therapy management (MTM) services are utilized to manage cardiovascular diseases.

Objectives: To 1.) compare economic outcomes between patients who received and those who did not receive MTM services and 2.) compare clinical outcomes before and after receiving MTM services from the self-insured employer perspective.

Methods: Retrospective designs: 1.) a cohort with comparison groups 2.) a pre-post cohort study

Results: MTM group had a statistically significant decrease in pharmacy and medical expenditures per patient compared with non-MTM group. MTM services provided cost-saving of $359.30 per patient and the return on investment of 1.67. No statistical differences were observed in clinical outcomes; however, the study demonstrated clinical significance by generating improvements in the proportion of patients at treatment goal and in the stages of hypertension and body mass index.

Conclusions: MTM services statistically reduced pharmacy and medical expenditures compared with the non-MTM group and demonstrated clinical significances in terms of achieving goals and improving disease stages.

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Chapter 1

Introduction

Background

Cardiovascular disease (CVD) is one of the major causes of mortality worldwide, as well as in the U.S., regardless of ethnicity and gender. Cardiovascular disease (CVD) as the underlying cause of death is associated with 813,804 deaths and accounted for an estimated 33.6 % of all deaths in the U.S. in 2007 (Xu, Kochanek, Murphy, & Tejada-Vera, 2010). The 2007 CVD mortality rate data revealed that there was approximately 1 CVD death every 39 seconds (Roger et al., 2011). Cardiovascular disease has continued to be one of the 15 leading causes of death in the United States since 1900. Particularly, heart disease and stroke ranked first and third, respectively, across all gender and races (Roger, et al., 2011; Xu, et al., 2010). An estimated prevalence of cardiovascular disease indicates that 82.6 million American adults have one or more types of cardiovascular disease and this prevalence has shown no improvement in the past decade. The prevalence increases with advancing age as approximately 46% of people with cardiovascular disease were aged 60 or older. In addition to advancing age, there are significant disparities among genders, races, ethnicities, geographic area, and socioeconomic status. The annual incidence of initial cardiovascular events is also substantial. For example, approximately 1,255,000 Americans experience a new or recurrent coronary heart disease attack each year, of which approximately 610,000 are new cases (Roger, et al., 2011).

In addition to adverse pattern in epidemiology of CVD, total expenditures, health utilization, and hospitalization can be used to demonstrate the impact of CVD to the U.S health care system. According to the Medical Expenditure Panel Survey (MEPS), in 2008 CVD represented the highest total expenditures among major leading health conditions (Agency for Healthcare Research and Quality, 2008). Further, total expenditures for cardiovascular diseases are projected to increase considerably in the future. Specifically, the annual expenditures of CVD in the United States were estimated at $444.2 billion in 2010 and projected to exceed $1 trillion ($1,093.9 billion) by 2030 (Heidenreich et al., 2011).Total direct costs of CVD for healthcare utilization were extrapolated to increase from $272.5 billion in 2010 to $818.1 billion in 2030. If this trend remains unchanged, the estimated amount in 2030 would rise three times higher than the amount in 2010 (Heidenreich, et al., 2011). Also, total indirect costs for all CVD are projected to increase from $171.7 billion in 2010 to $275.8 billion in the next 20 years. Moreover, health expenditures for CVD hospitalizations increased by 61% over 11-year time interval (1997-2008) (Healthcare Cost and Utilization Project [HCUP], 2010). Cardiovascular disease (CVD) accounted for the highest proportion of total hospitalization expenditure and the highest number of discharges in 2008. These conditions constituted 15% (5.9 million) of all hospital discharges and were responsible for 17% ($ 51.8 billion) of hospitalization expenditures in 2008 (Healthcare Cost and Utilization Project [HCUP], 2010).

Several guidelines and clinical practice recommendations on cardiovascular disease indicate that major risk factors of CVD are hypertension, dyslipidemia, overweight and obesity (body mass index (BMI) $\geq$30 kg/m^2), diabetes, physical

inactivity, smoking, and poor nutrition. Any major risk, if remained untreated for many years, is associated with an increasing risk for CVD and poorer outcomes in the presence of CVD (American Diabetes Association, 2009; Chobanian et al., 2003; Graham et al., 2007; National Cholesterol Education Program (NCEP) Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), 2002). According to the Framingham Heart Study endorsed by the National Heart, Lung, and Blood Institute (NHLBI), the existence of a greater number of risk factors and burden (i.e., hypertension, hypercholesterolemia, smoking, and diabetes) at age of 50 were highly associated with the lifetime risk for CVD and median survival (D. M. Lloyd-Jones et al., 2006). For example, according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7), hypertension was a strong independent risk factor of CVD regardless of existing heart disease. The risk of cardiovascular disease, particularly mortality from stroke and ischemic heart disease, increases two-fold for each 20 mmHg of systolic blood pressure and 10 mm Hg of diastolic blood pressure (20/10 mm Hg)(Chobanian, et al., 2003). In addition to hypertension, hyperlipidemia, particularly high serum concentration of LDL-C, is one of the crucial independent risk factors for coronary heart disease. According to the Adult Treatment Panel III (ATPIII) of the National Cholesterol Education Program (NCEP), LDL-C level is associated with relative risk for major coronary heart disease events (National Cholesterol Education Program (NCEP) Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), 2002).

As previously stated, total expenditures for cardiovascular diseases were projected to increase. In fact, in the next ten years, health spending is projected to grow at an average annual rate of 6.1% and reach $4,571.5 billion by 2019, accounting for 19.6% of gross domestic product (GDP) (Center for Medicare and Medicaid Services, 2010b; Truffer et al.). Rising health care costs attribute to an increase in health insurance cost, resulting in less affordable insurance for employers and employees. Due to continually rising health care costs and rapidly rising costs for employees, self-insured employers face challenges in terms of whether they can provide stable and sustainable health benefits (Joyce, Escarce, Solomon, & Goldman, 2002; National Center for Health Statistics, 2011). The burden in health care inflation causes employers to find practical strategies to reduce the costs of their health-care plans within their organization's budget. There are several strategies employers have implemented, such as changes in drug benefit designs (e.g., co-payments, coinsurance rates, generic substitution rules, a list of drug or therapeutic classes not covered by plan, and mail-order pharmacy service) and medical benefit design (e.g., deductibles, patient cost-sharing arrangement for inpatients and ambulatory setting) (Goldman et al., 2004).

However, these benefit designs also raise concerns regarding health outcomes. First, increases in copayments could prevent people from seeking necessary health services and, therefore, worsen their health conditions and lead to increase in health expenditures and adverse health consequences (Goldman, et al., 2004). Second, increased cost-sharing for prescription drugs could be associated with high morbidity and mortality in some high-risk population such as elderly people due to an increase in

serious adverse events and emergency department (ED) visits. This increase mainly resulted from reductions in utilization of essential drugs (Tamblyn et al., 2001).

Alternatively, some self-insured employers take a different approach in addressing rising health care costs. These employers have developed and adopted a variety of strategies to manage health care cost by providing the desired level of benefit coverage as well as improving employees' health outcomes and wellness (the Government Finance Officers Association, 2009). For example, they have implemented health promotion programs, wellness, disease management, medication therapy management (MTM), and care coordination programs (G. P. Mays, Claxton, & White, 2004). Research has found that these types of programs could help employees become healthier, leading to improvement in productivity, reduced absenteeism, and ultimately reduced health care expenditures (Baicker, Cutler, & Song, 2010; Meenan et al., 2010).

Research has consistently shown that incorporating pharmacists as members of the health care team improves outcomes among patients with chronic diseases such as cardiovascular diseases (Bodenheimer, Chen, & Bennett, 2009; Carter, Rogers, Daly, Zheng, & James, 2009). Pharmacists play an important role in enhancing drug therapy, improving adherence and resolving potential medication-related problems. Furthermore, pharmacist-provided interventions may considerably enhance surrogate endpoints and control other risk factors associated with cardiovascular diseases among patients at risk for cardiovascular events such as myocardial infarction (Bodenheimer, et al., 2009; Carter, et al., 2009). Therefore, third-party payers and self-insured employers have demonstrated interest in incorporating pharmacist-provided care as part of their benefits offered to their enrollees as a way to address the rising cost concern. This pharmacist-

provided care often falls under the umbrella term, Medication Therapy Management (MTM).

The American Pharmacist Association (APhA) has defined criteria of Medication Therapy Management (MTM) as "*a distinct service or group of services that optimize therapeutic outcomes for individual patients. MTM services are independent of, but can occur in conjunction with, the provision of a medication product. Medication Therapy Management encompasses a broad range of professional activities and responsibilities within the licensed pharmacist's, or other qualified healthcare provider's scope of practice.*" (American Pharmacists Association, 2004). After the first implementation of the Medicare Modernization Act (MMA) 2003 in January 2006, there has been an expansion of MTM programs to various groups of payers, particularly self-insured employers. Pharmacists are the leading provider of MTM services across all MTM programs (Center for Medicare and Medicaid Services, 2010a). Several studies support that pharmacist-provided MTM services improve health care quality in various aspects (see Appendix A, table A1). Medication therapy management (MTM) services seek to optimize therapeutic outcomes, maximize the benefit of medication therapy, and minimize the risk of adverse events that contribute to high expenditure, morbidity, or mortality (National Committee for Quality Assurance and Academy of Managed Care Pharmacy, 2006).

Despite the considerable benefit of pharmacist-provided MTM services, many issues still need to be addressed. For example, little is known about the impact of MTM services on patient outcomes and healthcare cost, quality improvement, and the value of MTM services (Glen P. Mays, Au, & Claxton, 2007). Until recently, few rigorous studies

have been conducted on this area. The majority of studies evaluating MTM programs have focused their evaluations from the health care providers, third-party payers, and insurers' perspectives, but have not fully investigated from the self-insured employer perspective where 60% of employees with workplace coverage were enrolled in self-insured plan, according to the Employer Health Benefits 2011 Annual Survey from the Kaiser Family foundation (The Kaiser Family Foundation and Health Research & Education Trust, 2011). Furthermore, the lack of appropriate comparison groups in this field might raise concerns regarding challenges in term of internal validity and confounding variables.

Problem Statement

1. Cardiovascular disease is the leading cause of mortality in the U.S. which constitutes the highest total health expenditures among major health conditions.
2. Rising healthcare expenditures have major effects on employer-sponsored insurance. Many sponsors have developed strategies and implemented various programs to reduce or contain costs while improving quality of care, but few programs have been evaluated.
3. Studies have shown that pharmacist-provided medication therapy management (MTM) services improved clinical, economic, and humanistic outcomes. However, few studies have evaluated MTM services from the self-insured employer perspective. Better understanding of the impact of MTM services may help self-insured employers effectively design their benefits to improve patient outcomes while containing costs.

Purpose

The primary goal of this study was to evaluate the impact of medication therapy management (MTM) services on economic and clinical outcomes among patients with cardiovascular diseases from the self-insured employer perspective. The first objective was to evaluate the impact of MTM services on economic outcomes among patients who received MTM services compared with those who did not receive MTM services (i.e. non-MTM services). The second objective was to evaluate the impact of MTM services on clinical outcomes among patients with cardiovascular diseases.

Research Questions and Hypotheses

Research question 1:

Was there a significant difference in economic outcomes between patients with cardiovascular diseases who received Medication Therapy Management (MTM) services and those who did not receive MTM services (i.e. non MTM services)?

H_{o1}: There was no difference in economic outcomes between patients with cardiovascular diseases who received Medication Therapy Management (MTM) services and patients who did not receive MTM service (i.e. non-MTM services).

H_{A1}: There was a difference in economic outcomes between patients with cardiovascular diseases who received Medication Therapy Management (MTM) services and patients with cardiovascular diseases who did not receive MTM services (i.e. non-MTM services).

Research question 2:

Research question 2 consisted of two parts. The first part was analytical and used for hypothesis testing. The second part was descriptive which identified types of

interventions implemented by pharmacists as part of Medication Therapy Management (MTM) services.

Part 1:

Was there any difference in clinical outcomes among patients with cardiovascular disease after receiving MTM services?

H_{o2}: There was no difference in clinical outcomes among patients with cardiovascular diseases after receiving MTM services.

H_{A2}: There was a difference in clinical outcomes among patients with cardiovascular diseases after receiving MTM services.

Part 2:

To explore types and frequency of drug-related problems identified and assessed by pharmacists during the MTM services.

Significance of the Study

A few studies have evaluated the effectiveness of medication therapy management (MTM) services from the self-insured employer perspective; however, appropriate comparison groups were not utilized (Bunting & Cranor, 2006; Bunting, Smith, & Sutherland, 2008; Cranor, Bunting, & Christensen, 2003). Also, while the existing studies focused on statistical significance of changes in clinical outcomes as a result of MTM services, none addressed clinical significance (e.g., identifying changes in stages of hypertension). For example, the Asheville project, which was conducted based on a self-insured perspective, did not assess changes in various stages of clinical outcomes. Therefore, the results obtained through this study may make a valuable contribution to self-insured employers, policy makers, and pharmacy practice. In terms of

self-insured employers, this study may have a great impact as 55.8% of health insurance coverage among non-elderly in the U.S. is provided by employers (National Center for Health Statistics, 2011). By providing information regarding the impact of MTM services on clinical and economic outcomes, employers may be able to make informed decisions regarding the inclusion of MTM services into the benefit programs.

This study could provide evidence to policy makers in order to endorse MTM program into public-sponsored benefit programs. Offering MTM services could help Americans achieve Healthy People 2020 objectives for cardiovascular disease. In terms of pharmacy practice, this study may give further insightful information to pharmacists regarding the impact of pharmacist-provided MTM services on outcomes compared with pharmacist-provided usual care. Moreover, a study that uses both statistical and clinical significance to assess the results would reflect clinically meaningful significance. This will not only indicate differences between variables after having intervention, but also present potential clinical benefits. Lastly, positive clinical and economic outcomes of MTM services could encourage pharmacists, especially community pharmacies to implement these services in their pharmacies. This study could lead to opportunities for community pharmacists in order to provide more comprehensive pharmaceutical care to patients.

Chapter 2

Literature Review

This chapter provides background information related to cardiovascular diseases, healthcare expenditures, roles of pharmacists in the U.S. healthcare system and the impact of medication therapy management (MTM) programs. Particularly, this chapter focuses on cardiovascular disease burden and the impact of these diseases on the U.S. healthcare system in the United States. Also, this chapter discusses the importance of pharmacist-provided interventions and identifies several key areas that need to be further explored.

This chapter organizes in the following way.

- Cardiovascular diseases: burden and trends in the United States
- An overview of the U.S. health care system and burden of expenditure and quality
- Cost containments strategies
- Roles of pharmacists in improving patient outcomes and reducing health services utilization
- Impact of pharmacist-provided interventions on improving cardiovascular diseases
- Medication therapy management (MTM): overview for Medicare Part D
- Medication therapy management (MTM): definition and framework for services

- Pharmacist's roles in medication therapy management (MTM)
- A systematic review of medication therapy management (MTM) services
- Gap in the literature and research opportunities

Cardiovascular Diseases: Burden and Trends in the United States

Epidemiology of cardiovascular diseases: Prevalence, incidence and mortality. Cardiovascular disease (CVD), defined as all diseases of the circulatory system, is one of the major causes of mortality globally and also in the United States regardless of ethnicity and gender. An estimated prevalence of cardiovascular disease indicates that 82.6 million American adults or more than 33% have one or more types of cardiovascular disease. Total cardiovascular disease (International Classification of Diseases, Ninth Revision, [ICD-9] 390-459, 745-747; Tenth Revision [ICD-10] I00-I99, Q20-Q28) ranked from high prevalence to low prevalence as follows: hypertension (76. 4 million), coronary heart disease (16.3 million), heart failure (5.7 million), stroke (7 million), and congenital cardiovascular defect (0.65-1.3 million). The prevalence increases with advancing age as approximately 46% of this population, or 40.4 million, are aged 60 or older. In addition to advancing age, there are significant disparities among genders, races, ethnicities, geographic areas, and socioeconomic status.

The annual incidence of initial cardiovascular events is also substantial, increasing in men from 3 per 1000 at age 35-44 to 74 per 1000 for those ages 85-94. The gap between women and men narrows with advancing age. Among adults free of CVD at the age of 50, the lifetime risk for developing CVD is higher for men than for women (51.7% vs. 39.2%) (National Institutes of Health, 2006). It was estimated that 1,255,000 Americans experience a new or recurrent coronary heart disease attack each year and

approximately 610,000 are new cases. On average, an American has coronary event every 25 seconds. In addition to coronary events, approximately 795,000 Americans will have a new or recurrent stroke.

Cardiovascular diseases have been one of the fifteen leading causes of death in the United States since 1900. Mortality data for 2007 from the National Heart, Lung, and Blood Institute and the National Center for Health Statistics identified CVD as the underlying cause of death (Xu, et al., 2010), specifically, it was associated with 813,804 deaths and accounted for an estimated 33.6 % of all 2,423,712 deaths in the U.S. in 2007 (Xu, et al., 2010). The 2007 mortality rate data further indicated that more than 2,200 Americans died of CVD every day or approximately 1 death every 39 seconds. Most of these deaths were attributed to coronary heart disease (CHD) (51% of total number of death) and stroke (17% of total number of deaths), respectively (D. Lloyd-Jones et al., 2010; Roger, et al., 2011; Xu, et al., 2010). Particularly, heart disease and stroke also ranked first (25.4%, 616,067 deaths) and third (5.6%, 135,952 deaths), respectively, across all gender and races among fifteen leading causes of death in the U.S. in 2007 (Roger, et al., 2011; Xu, et al., 2010). In the same year, CHD and stroke mortality rate were 406,351 and 795,000, respectively. Additionally, data have shown that CHD accounted for 1 of every 6 deaths whereas stroke accounted for 1 of every 18 deaths in the U.S. It is interesting that over 150,000 Americans die of CVD before the age of 65 years (Roger, et al., 2011).

Total expenditures, health utilization, and hospitalization for cardiovascular disease (CVD). Total expenditures, health utilization, and hospitalization can be used as measures of burden of cardiovascular disease (CVD). According to the Medical

Expenditure Panel Survey (MEPS), in 2008 the estimated health expenditure of CVD was greater than any other major leading health conditions on the MEPS list (Agency for Healthcare Research and Quality, 2008). Additionally, prevalence of heart diseases and stroke accounted for 39.1% and 22.3%, respectively among the most costly beneficiaries (Riley, 2007). Further, total expenditures of cardiovascular diseases accounted for 15% of Gross Domestic Product (GDP) in 2008 and were projected to increase considerably in the future. Specifically, the annual expenditures of CVD in the United States were estimated at $444.2 billion in 2010 and projected to exceed $1 trillion by 2030 (Heidenreich, et al., 2011).

Total direct costs of CVD for healthcare utilization including physician visits, other healthcare professional services, hospitalization, emergency room (ER) visits, laboratory testing, prescriptions, medical equipment, pharmaceutical care, nursing home services, and administrative services were extrapolated to increase from $272.5 billion in 2010 to $818.1 billion in 2030. If this trend remains true, the estimated amount in 2030 would triple the amount in 2010. Specifically, in this estimation, hypertension shared the highest proportion of CVD expenditures, and its direct costs were estimated to reach $130 billion in 2030 compared to $69.9 billion in 2010. Additionally, coronary heart disease, stroke, and heart failure expenditures in 2030 were projected to triple the amount in 2010, accounting for $106.4, $95.6, and $77.7 billion, respectively (Heidenreich, et al., 2011).

Total indirect costs, defined as cost of lost productivity are also a concern. The indirect cost for all CVD was projected to increase from $171.7 billion in 2010 to $275.8 billion by the next 20 years. This amount indicates 61% change from 2010. Particularly,

coronary heart disease was estimated to have the greatest proportion of CVD expenditures, accounting for 40% of all CVD indirect costs. The indirect costs of coronary heart disease were estimated to reach $112.3 billion in 2030 compared with $73.2 billion in 2010. Additionally, annual indirect costs attributable to hypertension, stroke, and heart failure in next 20 years were projected to increase more than two-thirds of indirect costs, accounting for $39.8, $44.4, and $17.4 billion, respectively (Heidenreich, et al., 2011).

Healthcare utilizations and hospitalizations can be used to demonstrate the problem of CVD. The total number of inpatient cardiovascular operations and procedures increased 27% from 5.3 million in 1997 to 6.8 million in 2007 (Roger, et al., 2011). Also, a primary diagnosis of CVD resulted in 79.7 million physician visits, ER visits, and outpatient visits (D. Lloyd-Jones, et al., 2010). In addition to healthcare utilization, health expenditures for hospitalizations increased by 61% from $227.2 to $364.7 billion over the 11-year time interval (1997-2008) (Healthcare Cost and Utilization Project [HCUP], 2010). Among these, the most frequent major cause of hospitalizations was due to circulatory conditions including coronary atherosclerosis, acute myocardial infarction, congestive heart failure, acute cerebrovascular disease, and cardiac dysrhythmias. Consequently, CVD established the highest proportion of total hospitalization expenditure and the highest number of discharge in 2008. These conditions constituted 15% (5.9 million) of all hospital discharges and were responsible for 17% ($ 51.8 billion) of hospitalization expenditures in 2008 (Healthcare Cost and Utilization Project [HCUP], 2010).

Major risk factors of cardiovascular disease (CVD). Several guidelines and clinical practice recommendations indicate that major risk factors of CVD are hypertension, dyslipidemia, overweight and obesity (body mass index (BMI) ≥30 kg/m^2), diabetes, physical inactivity, smoking, and poor nutrition. Any major risk, if remained untreated for many years, is associated with an increasing risk for CVD and poorer outcomes in the presence of CVD, (American Diabetes Association, 2009; Chobanian, et al., 2003; Graham, et al., 2007; National Cholesterol Education Program (NCEP) Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), 2002).

According to the Framingham Heart Study, the existence of a greater number of risk factors and burden (i.e., hypertension, hypercholesterolemia, smoking, and diabetes) at age of 50 were highly associated with the lifetime risk for CVD and short median survival (D. M. Lloyd-Jones, et al., 2006). In contrast, the findings show that individuals with an absence of risk factor or optimal risk factor profiles, including blood pressure <120/80 mmHg, total cholesterol <180 mm/dL, no current smoking, and no history of diabetes, are associated with very low lifetime risk of CVD and considerably longer median survival. For example, men with optimal risk factor profiles had the lifetime risks lower than those with ≥2 major risk factors. (5.2% versus 68.9%) and also had a median survival more than 10 years longer than those with ≥2 major risk factors (>39 versus 28 years). In addition to middle age, a recent study conducted by Berry and colleagues reveals that even younger adults at an age below 50 with low lifetime risk for CVD also have substantially lower prevalence, less severity, and lower incidence of atherosclerotic progression compared with those with higher lifetime risk for CVD (Berry et al., 2009).

Higher risk factors were also associated with greater expenditures (Burton, Chen, Conti, Schultz, & Edington, 2003; Daviglus et al., 1998). For example, the Chicago Heart Association Detection Project in Industry found that the presence of unfavorable risk factors in the middle age was associated with lower quality of life and higher total average expenditures and higher cardiovascular disease-related expenditures. For example total annual costs were lower by $878 (21%) and cardiovascular-related costs were lower by $978 for the men at low risk than for those not at low risk. A Framingham Heart Study reported that high blood pressure at age 50 was related to shorter overall life expectancy and shorter life expectancy free of CVD regardless of gender. This means those with hypertension would have more years lived with CVD (Franco, Peeters, Bonneux, & de Laet, 2005). Also, according to the Seventh Report of Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7), hypertension was a strong independent risk factor of CVD regardless of existing heart disease. Cardiovascular disease risk increases two-fold for each increment of systolic blood pressure 20 mmHg and diastolic blood pressure 10 mmHg (20/10 mmHg). The initiation of antihypertensive agents is recommended at hypertension stage 1 and when blood pressure is more than 20/10 mmHg above goal, initiating therapy with two-drug combination should be considered (Chobanian, et al., 2003).

In addition to hypertension, hyperlipidemia, a particularly high serum concentration of LDL-C, is one of the crucial independent risk factors for coronary heart disease. According to the Adult Treatment Panel III (ATPIII) of the National Cholesterol Education Program (NCEP), one percent reduction of LDL-C levels results in one percent decrease in relative risk for major coronary heart disease events (National

Cholesterol Education Program (NCEP) Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), 2002). Also, the presence of hypercholesterolemia is a prerequisite of atherosclerotic vascular disease (Graham, et al., 2007). A meta analysis conducted by Linden and colleagues showed that a 10% reduction in total cholesterol is related to a 25% reduction in incidence of coronary artery disease after 5 years (Linden, Stossel, & Maurice, 1996).

Other modifiable risk factors are overweight (BMI =25.0-29.9 kg/m^2) and obesity (BMI $\geq$30 kg/m^2) (D. Lloyd-Jones, et al., 2010; Roger, et al., 2011). These two risk factors constituted approximately 45% of the increased risk of coronary heart disease regarding negative impact on blood pressure and cholesterol levels (Bogers et al., 2007). According to the Framingham Heart Study, the age-adjusted relative risk for CVD was considerably higher among obese people as the relative risk was increased by 46% in men and 64% in women, respectively (Wilson, D'Agostino, Sullivan, Parise, & Kannel, 2002). Moreover, overweight and obesity are related to increased risk for cardiovascular disease and increased other potential risk factors, including diabetes. In addition to obesity, patients with diabetes also have doubled risk of coronary heart disease and stroke compared with those who do not have diabetes (Wingard DL & Barrett-Connor E, 1995).

Modifiable Risk Factors and Importance of Primary and Secondary Prevention

Potential risk factors are considered to be modifiable risk factors, meaning that they can be modified, controlled and avoided through lifestyle changes. According to data from National Center for Health Statistics, life expectancy would increase by approximately seven years if all forms of major CVD were eliminated. (Anderson R. & DeTurk PB., 1999; Roger, et al., 2011). Therefore, many researchers have advocated for

primary and secondary prevention. Primary prevention targets reducing risk of cardiac events and lowering total mortality and morbidity by focusing on modifying risk factors, preventing, or delaying onset of CVD. Secondary prevention focuses on treating and decreasing mortality among those whose disease is already present and those who are at high risk of developing CVD. For example, findings from the Framingham Heart Study revealed that a 60% decrease in cardiovascular mortality may result from an improvement in potential modifiable risk factors (Sytkowski, Kannel, & D'Agostino, 1990). Therefore, therapeutic lifestyle change is essential and strongly recommended for a person at high-risk or moderately high-risk or a patient who has lifestyle-related risk factors (Chobanian, et al., 2003; Graham, et al., 2007; Grundy et al., 1998; National Cholesterol Education Program (NCEP) Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), 2002).

Recognizing the consequences of CVD in terms of health and economics, along with the importance of primary and secondary prevention, the U.S. Department of Health and Human Services has continued to include heart disease and stroke in Healthy People 2010 and 2020 (U.S. Department of Health and Human Services, 2010). The goal of Healthy People 2020 for CVD is to enhance overall cardiovascular-related outcomes and health-related quality of life by promoting primary and secondary prevention, early detection, and treatment of risk factors. New objectives that have been added to Healthy People 2020 documents the importance of cardiovascular health. For example, it identifies the need to a) reduce incidences and recurrence rates for heart disease and stroke and b) promote lifestyle modification. Particularly, new objectives focus on preventing and controlling CVD as follows: decreasing prevalence and premature death

of CVD, encouraging lifestyle changes, promoting early detection of hypertension and arthrosclerosis, preventing the initiation and progression of diseases, maintaining low risk of diseases, and controlling high risk of diseases, including modifiable risk factors as mentioned earlier (Nora L. Keenan & Kate M. Shaw, 2011).

An Overview of the U.S. Health Care

The U.S. health care system: burden of expenditure and quality. The U.S. health care system is complex, accounting for 17.9% of the gross domestic product (GDP) (Martin, Lassman, Washington, & Catlin, 2012) and the rising healthcare costs affect both public and private sectors. Health care expenditure projections during 2009-2019 are influenced by a variety of factors, including the economic recession, rising unemployment, changing demographics, and baby boomers aging into Medicare coverage (Truffer, et al., 2010). A small proportion of the population accounts for a remarkably large distribution of health spending in any year. An estimated 50% of all health care costs in 2006 came from five percent of the population who incurred health spending equal or greater than $14,601. This is due to an increase in chronic diseases prevalence (e.g., diabetes, heart disease), comprehensive technology, and time to treat. Moreover, elderly populations also have the highest health expenditures compared with other groups. In the next ten years, health spending is projected to grow at an average annual rate of 6.1 percent and reach $4,571.5 billion by 2019, accounting for 19.6% of gross domestic product (GDP) (Center for Medicare and Medicaid Services, 2010b; Truffer, et al., 2010). Expenditures in the U.S. on health care grew 4.0 percent to $2.5 trillion in 2009, more than three times the $714 billion spent in 1990 (2010). Health care expenditures as a percentage of GDP have grown considerably overtime in the U.S.

Specifically, in 2007; the U.S. spent approximately $2.2 trillion on health care and $7,421 per person annually, accounting for 16.2 % of the nation's total economic activity or gross domestic product (GDP).

This financial burden of health care is a major concern because the government, private business, and households increasingly struggle with the cost of care (National Health Care Expenditures Data Centers for Medicare and Medicaid Services, 2010; US Department of Health and Human Service & Centers for Medicare and Medicaid Services, 2010). Moreover, rising health care costs attribute to an increase in health insurance premiums which result in less affordable insurance for employers and employees. The growth in health insurance premiums has continued to increase since 2000; however, the share of employer-sponsored premiums paid by employers has decreased from 74.7 to 69.7 % in 2009 (US Department of Health and Human Service & Centers for Medicare and Medicaid Services, 2010). Consequently, employees have to spend more of their earnings per year on the premium in order to purchase and maintain coverage. Those who cannot afford the premium might become uninsured. This is a concern because uninsured people are more likely to delay needed medical care or preventive services compared with those with insurance (27.6% versus 4.0%) (Freeman, Kadiyala, Bell, & Martin, 2008; JB Fox, 2010). This delayed health care can eventually result in unhealthy conditions and likelihood of higher healthcare spending in the long-term (Hoffman & Schwartz, 2008; JB Fox, 2010).

Despite the relatively high healthcare spending, the United States falls behind other Organization for Economic Cooperation and Development (OECD) countries in terms of achieving better health benchmarks. In 2008, the U.S. spent 16% of its national

income on health which was the greatest share in the OECD and also higher than the average of OECD countries. However, those OECD countries had higher quality of care than the U.S. in many significant health indicators. For example, they had infant mortality rates below 5 deaths per 1,000 live births in 2006 while the United States had approximately 7 deaths per 1,000 live births in the same year. They also had higher life expectancy than the U.S. (79.1 versus 78.1). In terms of health promotion and prevention in the U.S., many hospital admissions for chronic conditions still occur even though these could have been avoided through appropriate primary and secondary prevention. For example, in 2009 the U.S. had the highest rate of asthma admission rates per 100,000 population of OECD countries (120 versus 51) (the Organisation for Economic Co-operation and Development (OECD), 2009). Further, health expenditures in the U.S. in 2008 were $7,538 per person and were $2,500 higher than the next highest spending country. It should be noted that U.S. health expenditure per individual was also approximately two-and-a-half times the $3,060 average of all OECD countries (the Organisation for Economic Co-operation and Development (OECD) 2010).

Cost Containments Strategies

Employer-sponsored insurance represents the most common source of health insurance coverage in the U.S., accounting for 55.8 % of health insurance coverage (National Center for Health Statistics, 2011). Due to continually rising health care cost and its effect on employees, self-insured employers face challenges in terms of whether they can provide stable and sustainable health benefits (Joyce, et al., 2002). The burden in health care inflation causes employers to find practical strategies to reduce the costs of their health-care plans. There are several strategies that employers have tried to

implement to address cost concerns such as changing drug benefit design (e.g., co-payments, coinsurance rates, generic substitution rules, a list of drug or therapeutic classes not covered by plan, and mail-order pharmacy service) and medical benefit design (e.g., deductibles, patient cost-sharing arrangement for inpatients and ambulatory setting) (Goldman, et al., 2004).

One of the common strategies is to shift the cost to employees by increasing employee's premiums and employee's cost sharing, including co-payments and deductibles. Additionally, some employers may require use of generics and mail-order services to discourage use of more expensive drugs and to reduce medical spending. Mandatory generic substitution (MGS) is another strategy, whereby enrollees who prefer brand names to generic equivalents will have to pay the full difference in cost between the brand and generic drugs including the generic co-payments. Next, some employers might establish highly restrictive drug formularies, sometimes disallowing coverage of some specific medications or specific therapeutic classes that were previously covered by the plan, to reduce pharmaceutical use and cost. Another strategy is incentive-based-formularies. Medications are classified into different tiers, normally 2-3 tiers which range from generic to nonformulary drugs. Then, beneficiaries have to pay differential co-payments or co-insurance rates based on which tier a medication is placed. Generally, generic drugs have the lowest differing co-payments and nonformulary drugs have highest differing co-payments. This approach encourages employees to use generic or preferred drugs while discouraging the use of nonformulary medication due to increasing patients cost-sharing for nonformulary drugs (Joyce, et al., 2002).

The above strategies that solely focus on cost raise a concern about their effects on health outcomes. First, copayment increases could prevent people from seeking necessary health services and, therefore, worsen their health conditions and lead to increase in health expenditures and adverse health consequences. A study by the RAND corporation found that copayments increased the use of ER visits by 17% and increased hospitalization by 10% among patients with diabetes, asthma, and gastric acid disease (Goldman, et al., 2004). Second, increased cost-sharing for prescriptions could be associated with increased morbidity and mortality in some high-risk population, such as elderly people, due to an increase in serious adverse events, and emergency department (ED) visits. Mainly resulted from reductions in utilization of essential drugs (Tamblyn, et al., 2001).

To address both cost and outcome concerns, self-insured employers have developed and adopted a variety of strategic plans. This is to manage health care cost at sustainable levels, provide the desired level of benefit coverage, and improve employees' health outcomes and wellness (the Government Finance Officers Association, 2009). Some visionary self-insured employers have explored an innovative approach to control health expenditures such as health promotion programs, wellness programs, disease management programs, medication therapy management (MTM) services, and related care coordination programs in conjunction with those mentioned benefit designs. These programs are advantageous as they can constrain healthcare expenditures without shifting cost to enrollees or put pressure on health care providers and their patients (G. P. Mays, et al., 2004). Also, research has consistently found that well-designed programs could help employees become healthier, leading to the improvement in productivity, reducing

absenteeism, and ultimately reducing health care expenditures (Baicker, et al., 2010; Meenan, et al.). These types of programs can address various aspects of care. For example, some programs promote health and prevent diseases through risk identification tools (e.g., establishing healthy risk assessments). Other programs may focus on behavior modification (e.g., enhancing physical activities, changing healthy habits, and modifiable health risk factors associated with an incidence of chronic disease), patient and provider education, and improving employees' work environment. In addition, health management programs such as wellness, disease management, utilization review, and medication therapy management can improve and modify employees' health behaviors and habits by providing educational program, offering web-based information regarding particular illness, and granting financial incentives which can lead to improvement in health care and subside costs.

Although, the rapid growth of programs that focus on patient outcomes is promising, many issues still need to be addressed and further explored. For example, little is known about the impact of MTM services on patient outcomes, healthcare cost, quality improvement, and the value of MTM services (Glen P. Mays, et al., 2007). However, until recently few rigorous studies have been conducted on this area. The majority of studies evaluating MTM programs have focused their evaluations on health care providers, third-party payers, and insurers' perspective, but have not fully investigated the self-insured employer perspective where the majority of employees receive their care in the US. Furthermore, the lack of appropriate comparison groups in this field might raise concern regarding challenges in term of internal validity and

confounding variables. Therefore, employers might be skeptical about implementing the programs due to uncertainty about return on investment (Glen P. Mays, et al., 2007).

Roles of Pharmacists in Patient Outcomes and Health Utilization

Pharmacists have played an important role in the U.S. healthcare system by assuring that drug therapy achieves desired health and economic outcomes. In the past, pharmacists have focused on a medication distribution function, including, preparing, distributing, and utilizing medications. Recently, pharmacists have expanded their roles from dispensing to pharmaceutical care. Pharmaceutical care is a patient-centered and outcomes-oriented pharmacy practice that requires pharmacists to work with their patients, address patient's drug-related needs, and collaborate with other health care professionals (Cipolle, 2004; Hepler & Strand, 1990).

The primary goals of pharmaceutical care are to improve patients' quality of life and medication-related therapeutic outcomes within practical economic constraints. To obtain such goals, pharmacists are responsible for promoting health, preventing disease, identifying, assessing, and monitoring drug-related problems, as well as modifying medication therapy for patients (American Pharmacists Association, 1995; American Society of Health-System Pharmacists, 1996). Research has consistently shown that pharmaceutical care can be applied in a variety of practices and settings to enhance patients' health status.

A substantial number of intervention studies (i.e., 298 studies) have emphasized the role of pharmacists in therapeutic management, patient counseling, and health care providers' education (M. A. Chisholm-Burns, J. Kim Lee, et al., 2010). The most common reported diseases being studied were hypertension, dyslipidemia, diabetes,

anticoagulation, asthma, infection, and psychiatric conditions, respectively. This might be because these diseases generally require multidrug regimens and therefore can greatly benefit from intensive monitoring. While specific strategies for each pharmacist-provided intervention varied from one research study to another, these interventions focused on the following areas. The most frequently reported areas in which pharmacist-provided interventions targeted, in order, were medication focused education, disease focused education, adherence education, prospective or retrospective drug utilization review, and chronic disease management (M. A. Chisholm-Burns, J. Kim Lee, et al., 2010). Research consistently found that pharmacist-provided interventions had a positive impact on economic, clinical, and humanistic outcomes across diverse health care settings.

Findings from prior systematic reviews on effects of pharmacists-provided interventions indicated positive effect on health services utilization and health outcomes (Bero, Mays, Barjesteh, & Bond, 2000; M. A. Chisholm-Burns, J. S. Graff Zivin, et al., 2010; Elliott, Barber, Clifford, Horne, & Hartley, 2008; Nkansah et al., 2010). That is, pharmacists' services or interventions reduced both direct and indirect health care costs. The first systematic review conducted by Bero and colleagues emphasized the impact of pharmacist-provided interventions on health services utilization and direct costs (Bero, et al., 2000). The results suggested that pharmacist-provided interventions reduced hospital admission per patient per study month (-67%), reduced total ambulatory care visits in the previous three months (-564%), and decreased cost-related to medication costs and numbers of prescriptions compared to no pharmacist service. This study further demonstrated that when comparing services provided by pharmacists and services provided by other health care providers, pharmacist services resulted in 16% decrease in

hospital admissions while achieving patient outcomes (e.g., improved adherence, reduced blood pressure level, and reduced blood sugar level) (Bero, et al., 2000).

Similarly, in a separate systematic review, Chisholm-Burns and colleagues found that pharmacist-provided interventions reduced direct costs. Specifically, they found a decrease in drug expenditures (-7.2%-8.2%), total hospital costs ($p < 0.05$), total mean direct medical cost $1,200-$1,872 per patient annually in outpatient setting, copayments per patient (-62%, $-145.29, and hospital charges for all readmissions during the first month ($p=0.01$) (Marie A. Chisholm-Burns et al., 2010). In addition to the direct costs, Chisholm-Burns and colleagues investigated the impact of pharmacist-provided interventions on indirect costs. The findings revealed that pharmacist-provided interventions increased productivity by $18,000 annually for employers' health plan by reducing absenteeism. Further, Chisholm-Burns and colleagues also highlighted an improvement in the average cost saving and the benefit-to-cost ratio (Marie A. Chisholm-Burns, et al., 2010). In terms of cost-effectiveness, Elliott and colleagues found that a pharmacist-provided telephone intervention was superior to the control group which received only usual care. Specifically, the intervention group had a mean incremental cost effectiveness ratio (ICER) of -£2,168 (approximately $3,941.81), had lower drug-related problems ($p = 0.021$), and had significant reduction in non-adherence ($p = 0.032$) (Elliott, et al., 2008).

Pharmacist-provided interventions have a favorable effect on clinical outcomes, safety outcomes, and disease-related resource consumption (Benavides, Rodriguez, & Maniscalco-Feichtl, 2009; M. A. Chisholm-Burns, J. Kim Lee, et al., 2010; Machado, Bajcar, Guzzo, & Einarson, 2007a). A comprehensive systematic review of pharmacist-

provided interventions with focused meta-analyses reports an improvement of disease parameters and disease severity including hemoglobin A1c (-1.8%), blood pressure ($p < 0.001$), and low density lipoprotein (LDL) cholesterol (-6.3 mg/dL) (M. A. Chisholm-Burns, J. Kim Lee, et al., 2010). Likewise, Machado and colleagues, through a meta-analysis, found a significant reduction in hemoglobin A1c levels among 2247 patients in 16 studies who received pharmacist-provided interventions (1.00±0.28%; $p < 0.001$), but the same is not true for the control group (0.28 +/- 0.29%; $p = 0.335$) (Machado, et al., 2007a).

In addition to clinical outcomes, research consistently supports a positive impact of pharmacists on patient safety, particularly adverse drug events and disease-related resource consumption (M. A. Chisholm-Burns, J. Kim Lee, et al., 2010; Saokaew, Permsuwan, Chaiyakunapruk, Nathisuwan, & Sukonthasarn, 2010). For example a systematic review and meta-analysis conducted by Saokaew and colleagues found that pharmacist-provided warfarin therapy management prevented total bleeding (RR, 0.51; 95% confidence interval 0.28-0.94). Similarly, the previous systematic reviews and meta-analysis from Chisholm-Burns and colleagues documented similar results, including 47% reduction in the odds of adverse drug events ($p =0.01$) among patients who received the pharmacist-provided interventions versus the comparison group (M. A. Chisholm-Burns, J. Kim Lee, et al., 2010). In addition to adverse drug events, a systematic review conducted by Chisholm-Burns and colleagues found a reduction in physician visits ($p < 0.05$), hospitalizations (40%), emergency department (ED) admissions (66.65%), and length of hospital stay (-5.9%--14.7%) (M. A. Chisholm-Burns, J. S. Graff Zivin, et al., 2010).

In terms of humanistic and adherence outcomes, previous systematic reviews establish a positive impact of pharmacist-provided interventions on improving quality of life, patient satisfaction, patient knowledge, and adherence to medication regimens ($p<0.05$) (Bero, et al., 2000; M. A. Chisholm-Burns, J. Kim Lee, et al.; Haynes, Ackloo, Sahota, McDonald, & Yao, 2008; Pickard & Hung, 2006). According to a Cochrane Database systematic review, there is sufficient evidence to support the impact of pharmacist-provided intervention. Specifically, through multiple approaches, including convenient care, information, counseling, reminders, self-monitoring, reinforcement, tailored intervention, and supportive care, pharmacists were able to modify patients' behavior and improve medical adherence (Bero, et al., 2000; Haynes, et al., 2008).

Impact of Pharmacist-Provided Interventions on Improving Cardiovascular Diseases

Research has consistently shown that incorporating pharmacists as a member of the health care team improves outcomes among patients with chronic diseases such as cardiovascular diseases. Furthermore, pharmacist-provided interventions may considerably enhance surrogate endpoints and control other risk factors associated with cardiovascular diseases among patients at risk for cardiovascular events such as myocardial infarction (Bodenheimer, et al., 2009; Carter, et al., 2009). The following paragraphs discuss the impact of pharmacist-provided interventions on patient outcomes among patients with heart failure, hypertension, and hyperlipidemia, respectively.

A systematic review of randomized trials performed by Koshman and colleagues indicates that pharmacist-provided interventions had a positive impact on patient outcomes among patients with heart failure. The findings established a significant

relationship between pharmacists' interventions and intermediate outcomes. That is, there were reductions in the rate of all-cause hospitalizations (OR, 0.71; 95% CI, 0.54-0.94) and heart failure hospitalizations (OR, 0.69; 95% CI, 0.51-0.94) were found. However, there was no statistically significant reduction in mortality (OR, 0.84; 95% CI, 0.61-1.15) (Koshman, Charrois, Simpson, McAlister, & Tsuyuki, 2008). A separate literature review conducted by Ponniah and colleagues also evaluated the impact of pharmacist-provided post-discharge services among patients with heart failure. In contrast to Koshman and colleagues' study, this study emphasized that pharmacists improved final outcomes by reducing morbidity and mortality associated with heart failure (Ponniah, Anderson, Shakib, Doecke, & Angley, 2007). Moreover, a study evaluated Clinical Pharmacy Cardiac Risk Service (CPCRS) has found that pharmacists involved in collaborative practice with physician and other health care professional, improved clinical outcomes (Sandhoff et al., 2007). The findings further indicated that pharmacy services such as medication management and patient education reduced coronary-related events and other cardiovascular risks in patients with coronary artery disease in the long-term (Sandhoff, et al., 2007).

Furthermore, epidemiological and patient-oriented clinical trials suggested that controlled blood pressure and LDL-cholesterol correlated with a reduction of major cardiovascular events (Stamler et al., 2000; Stamler, Dyer, Shekelle, Neaton, & Stamler, 1993). Therefore, incorporating healthy lifestyle and controlling major risk factors such as smoking, blood pressure, and serum cholesterol can prevent long-term mortality from coronary heart disease (Stamler, et al., 1993). Two separate meta-analysis studies consistently suggested that pharmacist-provided interventions significantly improved

blood pressure control (Carter, et al., 2009; Machado, Bajcar, Guzzo, & Einarson, 2007b). Specifically, Machado and colleagues conducted a meta-analysis of 13 studies with 2,246 hypertensive patients and found a significant effect in reducing systolic blood pressure (10.7 ± 11.6 mm Hg) among patients that received pharmacists' interventions compared with the control group (3.2 ± 12.1) (Machado, et al., 2007b). This finding is consistent with the other meta-analysis study; pharmacist-provided interventions in a team-based care resulted in a significant reduction of systolic blood pressure of 9.33 mm Hg. The results were similar across both primary clinics and community pharmacies settings (Carter, et al., 2009).

In terms of hyperlipidemia, a meta-analysis of 23 studies which consist of 2,084 patients with hyperlipidemia showed a significantly superior impact on a reduction of total cholesterol from baseline (mean ±SD; 34.3±10.3 mg/dL; $p < 0.001$) in patients who received pharmacist-provided interventions compared to the control group (mean ±SD; 22.0±10.4 mg/dL; $p <0.001$) (Machado, Nassor, Bajcar, Guzzo, & Einarson, 2008). Next, a Study of Cardiovascular Risk Intervention by Pharmacists (SCRIP-plus) using web-based education module and a workshop indicated positive outcomes. Specifically, the findings reported 13.4% reduction of LDL level (from 3.5 ± 0.7 mmol/L at baseline to 3.0 ± 0.9 mmol/L; $p<0.0001$) and 27% of patients met the NCEPIII target level of LDL cholesterol at 6 months (Tsuyuki, Olson, Dubyk, Schindel, & Johnson, 2004). A long-term follow-up result at 12 months showed that 38% of patients (61 out of 162 patients) were maintained at the target LDL level (< 96.7 mg/dl) (Yamada, Johnson, Robertson, Pearson, & Tsuyuki, 2005). Moreover, pharmacist-provided interventions also had a positive impact on secondary prevention among patient with coronary heart disease who

did not achieve LDL goal of treatment (Straka, Taheri, Cooper, & Smith, 2005). Specifically, Straka and colleagues found that pharmacist-provided interventions had a greater proportion of patients achieving goal LDL compared with the control group (usual care) and the results were sustainable even after the discharge from a program.

In addition to the above clinical outcomes, the impact of pharmacist-provided interventions on economic outcomes in patients with cardiovascular diseases and patients at high risk of cardiovascular events was also established in several studies (Cote, Gregoire, Moisan, Chabot, & Lacroix, 2003; Luzier, Forrest, Feuerstein, Schentag, & Izzo, 2000). Okamoto and colleague found that hypertensive patients who received pharmacist-provided interventions had higher significant reduction in blood pressure ($p<0.001$), higher patient satisfaction, and lower cost effectiveness ratio compared to the physician group in management of patients (systolic blood pressure: $27 vs. $193 per one mm Hg; diastolic blood pressure: $48 vs. $151 per one mm Hg)(Okamoto & Nakahiro, 2001). Likewise, Luzier and colleagues found that pharmacists improved rehospitalization rates and significantly reduced heart failure-related total by optimizing medication therapy (Luzier, et al., 2000).

Lastly, numerous studies have demonstrated the value of pharmacists in improving quality of life, adherence, and satisfaction in patients with cardiovascular disease in several settings (Hohmann, Klotz, Radziwill, Jacobs, & Kissel, 2009; Okamoto & Nakahiro, 2001; Sadik, Yousif, & McElnay, 2005). For example, Sadik and colleagues found that pharmacists-provided interventions in patients with heart failure resulted in significantly higher health-related quality of life compared with the control group which received standard care (463.5 vs. 637.5 unit) (Sadik, et al., 2005).

In conclusion, pharmacists have played an important role in enhancing drug therapy, improving adherence and resolving potential medication-related problems. Because pharmacists can be a viable solution to help improve economic, clinical and humanistic outcomes, third-party payers and self-insured employers are interested in incorporating pharmacist-provided care as part of their benefits offered to their enrollees as a way to address the rising cost concern. This pharmacist-provided care is often referred to as Medication Therapy Management (MTM) which will be discussed next.

Medication Therapy Management (MTM): Overview for Medicare Part D

Medication therapy management (MTM) was first introduced in 2003 by the federal government in Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA 2003) (Department of Health and Human Services Center for Medicare and Medicaid Services, 2005). The MMA 2003 adds a prescription drug benefit via Medicare Part D which is administered through Prescription Drug Plans (PDPs) and Medicare Advantage prescription drug plans (MA-PD). Because one of the goals of the Center for Medicare and Medicaid Services (CMS) is to optimize therapeutic outcomes for individual patients by improving medication use, reduce the risk of drug-related adverse events, and improve patient adherence, the requirement was established in 2006 for Part D sponsors to provide medication therapy management (MTM) programs (Center for Medicare and Medicaid Services, 2010c; Department of Health and Human Services Center for Medicare and Medicaid Services, 2005).

Initially, CMS regulation for MTM intentionally left enrollment criteria and details about MTM requirements broadly and flexibly in order to encourage each Part D sponsor to develop its innovation approaches and establish best practice that best suited

their landscape. Therefore, there has been a wide range of diverse MTM programs that have been developed under Part D sponsors (e.g., face-to-face or telephonic intervention; pharmacist-provided care or non-pharmacist-provided care). In 2010 MTM requirements were revised to improve consistency among MTM programs and expand requirements of MTM offered to eligible enrollees. The purpose of the revision was to increase the number of enrollee population, improve level of MTM interventions, and provide more quality of plan reported-data for evaluating outcomes(Center for Medicare and Medicaid Services, 2010a, 2010c).

Specifically, in 2010 the Center for Medicare and Medicaid Services (CMS) established the eligibility criteria that Medicare Part D plan sponsors will be required to provide MTM programs for eligible enrollees who have multiple chronic diseases, have several Part D covered medications (i.e., 2-8 covered Part D medication), and are likely to incur annual costs of at least $3,000 for all Part D-covered medication. The cost threshold has been reduced from $4,000 to $3,000 in 2010. Data from CMS in 2010 demonstrates that 72% and 66% of MTM contracts set their eligibility requirements by requiring at least three multiple chronic diseases and at least eight Part D medications, respectively. All plan sponsors are required to annually submit a MTM program description to CMS for review and approval for the next contract year (Center for Medicare and Medicaid Services, 2010a, 2010c).

Approximately, 95.5% of plan sponsors primarily target their MTM programs at specific diseases more than chronic diseases in general. Additionally, they are required to target at a minimum four of these following core chronic diseases: hypertension, heart failure, diabetes, dyslipidemia, respiratory disease (e.g., ashma, chronic obstructive

pulmonary disease (COPD), bone disease-arthritis (e.g., osteoporosis, rheumatoid arthritis), mental health (e.g., depression, schizophrenia). Specifically, cardiovascular diseases are targeted by 60% of MTM programs (Center for Medicare and Medicaid Services, 2010a).

Medication Therapy Management (MTM): Definition and Framework for Services

According to Medicare Prescription Drug, Improvement and Modernization Act of 2003(MMA), medication therapy management (MTM) service focuses on provision of education and counseling about patient's understanding of drug use, enhancement of medication adherence, and identification of adverse drug events and patterns of improper prescription medication use. Consistent with the MMA's goal, the American Pharmacist Association (APhA) has defined criteria of Medication therapy management (MTM) as "*a distinct service or group of services that optimize therapeutic outcomes for individual patients. MTM services are independent of, but can occur in conjunction with, the provision of a medication product. Medication Therapy Management encompasses a broad range of professional activities and responsibilities within the licensed pharmacist's, or other qualified healthcare provider's scope of practice*." (American Pharmacists Association, 2004).

Most of the MTM services reimburse health care professionals based on services rendered and some of them are paid by the intensity of services. In order to be considered as MTM services, the services must consist of a review of medication therapy, patient interaction (e.g., counseling), and a review of drug related-problems (e.g., medication over and underuse, suboptimal drug therapy and adverse drug events). Intervention can

be provided by pharmacists or other qualified providers (National Committee for Quality Assurance and Academy of Managed Care Pharmacy, 2006).

Pharmacist's Roles in Medication Therapy Management (MTM)

After the first implementation of MMA 2003 in January 2006, there has been an expansion of MTM programs to other payers, particularly self-insured employers. According to the Center for Medicare and Medicaid Services, pharmacists are the leading provider of MTM services across all MTM programs, accounting for 99.9% of providers of MTM services (Center for Medicare and Medicaid Services, 2010a). An establishment of medication therapy management (MTM) programs for Medicare part D beneficiaries and for private sector beneficiaries present great opportunities for pharmacists to provide direct patient care services to improve patients' therapeutic outcomes which eventually lead to a reduction of health care cost (Lewin group, 2005). Several studies support that pharmacist-provided MTM services improve health care quality in all aspects of outcomes including economic, clinical, and humanistic outcomes while decreasing health expenditures for patients with chronic diseases. Medication therapy management (MTM) services optimize therapeutic outcomes, maximize the benefit of medication therapy, and minimize the risk of adverse events that contribute to high expenditure, morbidity, or mortality (National Committee for Quality Assurance and Academy of Managed Care Pharmacy, 2006).

Medication therapy management (MTM) that are currently being provided by pharmacists can be categorized into the following five core elements model (American Pharmacists Association, 2010):

- Medication therapy review (MTR): a systematic process of gathering and assessing both information and medication therapies to identify new and ongoing medication-related problems and developing a plan for resolving each problem.
- Personal medication record (PMR): a comprehensive patient record (both prescription and nonprescription drugs) provided for each patient to use in overall medication therapy self-management.
- Medication-related action plan (MAP): a patient-centered document for assisting the patient achieve therapeutic goals. It consist of a list of actions that the patient can use as a guide to track one's progress.
- Intervention and/or referral: consultative services and interventions provided by pharmacists to address medication-related problems and a referral to a physician or other provider to optimize and enhance medication therapy.
- Documentation and follow-up: electronic or manual records in a standard format [e.g., SOAP (subjective observation, objective observation, assessment, and plan) note] which will help pharmacists communicate among healthcare team.

Service delivery methods may vary, but most MTM services are provided through face-to-face and telephone interactions. A desired approach for MTM is a faced-to-face interaction between pharmacist and patients in order to further strengthen pharmacist-patient relationships. However, alternative methods such as telephonic are acceptable if a face-to-face approach is not possible (Academy of Managed Care Pharmacy (AMCP),

2008; American Pharmacists Association and National Association of Chain Drug Stores Foundation, 2008). A survey conducted by the American Pharmacist Association in 2009 found that payers used both telephone and face-to face intervention as common delivery methods; however, a telephone intervention dominated frequency of use over a face-to-face intervention (American Pharmacists Association, 2010).

Medication therapy management (MTM) services have been distinguished from other pharmacist-provided services, including disease management and patient counseling. That is, MTM focuses on entire patient drug regimens and is personalized to a specific individual's drug therapy needs. Disease management, however, focuses on patient and disease by using population guidelines and does not individualize to patient needs (McGivney et al., 2007). Medication therapy management (MTM) also differs from patient counseling because MTM requires a two-way communication, focuses on an individual patient drug therapy regimen, is delivered independent of dispensing, requires follow-up, and involves collaboration with patients and healthcare providers (McGivney, et al., 2007; Pellegrino, Martin, Tilton, & Touchette, 2009).

A Systematic Review of Medication Therapy Management (MTM) Services

In order to inform self-insured employers regarding the value of MTM services, it is important to review pertinent studies in this area. Better understanding of the existing knowledge and gaps in the literature will help identify the areas in which future studies should address.

Search strategy. Eight electronic databases were searched for relevant research articles published between 2003 and March 2011. These included the Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Registry, MEDLINE/Pubmed,

CINAHL, EMBASE, International Pharmaceutical Abstracts (IPA), Academic Search Premier (EBSCO), and Dissertations & Theses (Proquest). The reference lists of articles, or handsearching, were also screened. Unpublished studies from ClinicalTrials.gov, meeting abstracts, poster presentations were reviewed. The search strategy used a combination of medical subject heading and general terms relating to the research of interest.

Search terms. Medication therapy management, pharmaceutical care, pharmacist provided care, intervention

Inclusion criteria. For inclusion in this review, the following criteria had to be met in the first and second tier screens:

1. Types of studies: In the first tier screen, randomized controlled trials (RCTs) were sought; since only one was detected, the search strategy expanded to include in the second tier screen cohort studies, case-control studies, observational studies, and quasi-experimental designs that conducted tests of pharmacist-provided medication therapy management (MTM). Descriptive studies, surveys, and single case studies were excluded.
2. Types of participants: Patients who received MTM services.
3. Types of interventions: Any method of intervention studied for at least 3-6 months for its affect on outcomes.
4. Types of outcomes measures: Types of outcomes measures included clinical, economic, and humanistic outcomes.
5. The definition of *medication therapy management* used in the studies had to comply with the American Pharmacist Association definition.

6. Studies were required to describe the details of their MTM services and intermediate or final outcomes.

Result. A total of 693 citations were initially retrieved. After a preliminary review of titles and abstracts, 672 citations were excluded because they failed to meet at least one of the inclusion criteria. Of the initial 21 studies, 3 studies were then excluded due to inadequate baseline patient data. Therefore, the remaining 18 studies were fully analyzed. Summary of general finding information, outcome measures, and finding are presented in Appendix A: TableA1, A2, and A3 respectively. The list of included studies are shown in Appendix B. Nine of the included studies were pre-post design. Among these, five studies were a pre-post design within group (Bunting & Cranor, 2006; Bunting, et al., 2008; Chisholm, Spivey, & Mulloy, 2007; Cranor, et al., 2003; Isetts et al., 2008) and four studies were a pre-post design with comparison group (Christensen, Roth, Trygstad, & Byrd, 2007; Hirsch, Rosenquist, Best, Miller, & Gilmer, 2009; Pindolia et al., 2009; Stockl et al., 2008). Two of the included studies were quasi-experimental design with comparison groups (Fox, Ried, Klein, Myers, & Foli, 2009; E. K. Welch, Delate, Chester, & Stubbings, 2009). Five of the included studies were observational studies (Barnett et al., 2009; Doucette, McDonough, Klepser, & McCarthy, 2005; Johannigman et al., 2010; Maack, Miller, Johnson, & Dewey, 2008; Ramalho de Oliveira, Brummel, & Miller, 2010). One study was a cross-sectional design (Moczygemba et al., 2010). Only one study is randomized-controlled trial (Planas, Crosby, Mitchell, & Farmer, 2009).

Discussion. Almost of included studies examined the effect of MTM services targeted at chronic diseases or patients who had more than four medications. The most frequently reported diseases were diabetes, hypertension, hyperlipidemia, cardiovascular

diseases, and asthma. Only two studies focused on HIV patients and renal transplantation recipients. Time periods for data collection of these 18 included studies varied from 6 months to 10 years. These studies primarily were conducted using the health care providers', third-party payers', and insurers' perspectives. Only three studies originated from the same project (i.e., the Asheville Project) evaluated from the self-insured employer perspective (Bunting & Cranor, 2006; Bunting, et al., 2008; Cranor, et al., 2003). Settings of included studies varied, including university hospital-based, managed care organizations, ambulatory clinics, state Medicaid programs, and community pharmacies. Medication therapy management (MTM) services, delivered by pharmacists, included providing patient counseling and educational materials; identifying and resolving drug-related problems; and reviewing medication therapy and drug utilization. All of these services are part of the core elements of MTM services mentioned in the previous section. Medication therapy management (MTM) services used by these studies were performed over a period of time (e.g., every 3-12 month) through face-to-face intervention, telephone, or mailing approach and each session lasted about 30 minutes. Clinical and economic outcomes were primarily evaluated in these included studies. In terms of humanistic outcomes, five studies measured patient satisfaction, while only two studies presented quality of life. Clinical outcomes used in the studies were based entirely on surrogate endpoints and intermediate outcomes [e.g., change in baseline values for HA1C, adherence rate, forced expiratory volume in 1 second (FEV1), mean systolic or diastolic blood pressure, mean lipid panels (LDL-C TG, HDL-C), number of disease-related hospitalization, and ER visits]. Economic outcomes being evaluated were direct cost (e.g., physician visits, hospitalizations, ER visits, medication costs, cost of laboratory

test and procedure, cost of medical supplies, health care provider visit, and co-payment wavier) and indirect cost (e.g., cost due to absenteeism or productivity cost). None of these studies investigated intangible cost (e.g., pain and suffering from disease).

Results favored MTM services in terms of clinical, economic, or humanistic outcomes in all included studies. Significant improvement in clinical outcomes was found in most studies. Some studies provided contradictory results in terms of medication adherence and number of ER visits. For example, Pindolia and colleagues presented that the MTM group had higher adherence compared with control group (Pindolia, et al., 2009); however, Planas and colleagues established that there was no statistically significant difference between MTM and control groups (Planas, et al., 2009). In general, the findings from all included studies supported the role of pharmacist-provided MTM services as MTM services: (a) improved clinical parameters (e.g., blood pressure level, lipid panels, mean HA1C, BMI); (b) achieved therapeutic goals; (c) improved disease functions; (d) improved adherence rate; (e) decreased disease severity; (f) decreased occurrence of opportunistic infections; (g) decreased number of ER visits and hospitalizations; (h) decreased mortality rates; (i) modified health behavior (e.g., smoking cessation); and (j) identified drug-related problems.

Studies evaluating economic outcomes suggested that MTM services had positive results on benefit-to cost-ratio and return on investment. Furthermore, MTM services established a reduction in medication costs and total health care expenditures, decreased overall disease-related cost, improved estimated costs avoidance related to coronary events, and improved direct and indirect cost saving. Although, Hirsch and colleagues had reported relatively higher average total costs per patient in the MTM group compared

with control group, the researchers claimed that the higher total costs mostly attributed to the medications used for treating side effects or other conditions (e.g., antiemetic for treating nausea condition from antiviral medications, anticonvulsants for treating drug-related toxicity or antidepressant medication for treating condition related disease) (Hirsch, et al., 2009). They further suggested that the MTM group may have more appropriate HIV treatment and comprehensive care than the control group. Similarly, Bunting and colleagues argued that while medication utilization increased three times after completing MTM services compared to baseline, cardiovascular-related medication costs and mean cost per cardiovascular event decreased significantly (Bunting, et al., 2008).

Gaps in the Literature and Research Opportunities

Gaps in the literature. In this section, gap in existing knowledge are identified.

1. There was a lack of randomized-controlled trials in the field. Research mainly performed pre-post analysis and had no comparison group. Only one included study was randomized-controlled trial. Without randomization, it could generate a potential selection bias because patients who opted into a medication therapy management program may have been more motivated to be engaged in the program and therefore lead to treatment success. Additionally, several factors that were different between the two groups may affect the results. These included patients' willingness to follow treatment protocols, possible physician referral of more complicated patients to MTM group, and possible same services provided by other pharmacies to control group.

2. There were few appropriate comparison groups in the field. A total of 11 had no comparison group or control group which did not receive MTM services. The lack of comparison group or appropriate comparison groups could generate challenges in term of internal validity and confounding variables.
3. There was a lack of terminal outcomes. Almost all studies focused on intermediate clinical outcomes; only one focused on terminal outcomes (e.g., mortality rate). Without examining terminal outcomes, we may not draw definitive conclusions whether or not the program can improve clinical outcomes. Hence, there is the need for research to identify causal association between intermediate outcomes and terminal outcomes.
4. There were few studies based on self-insured employer perspective. Only three studies that originated from the same project have been conducted based on the self-insured perspective. Because the majority of employees enroll in plans offered by self-insured employers, more studies from this perspective are needed.
5. There was an issue of clinical significance. All included studies provided statistical significance for evaluating mean values for the clinical indicators (e.g., mean difference of reduction in blood pressure between MTM group and control group). Nevertheless, statistical significance does not always provide clinically meaningful information about potential benefits regarding what occurs at a practical level. For example, some studies reported improvement in blood pressure after the intervention; however, they did not determine the proportion of patient who achieved therapeutic goals (Bunting, et al., 2008; Johannigman, et al., 2010; Pindolia, et al., 2009). Although, some studies represented the proportion of

patients who attained therapeutic goal, none of these quantified the degree to which patients had clinical significance such as improved severity from the previous state, remained at the same stage, or decline from the previous stage (e.g., proportion of patients who have an improvement of clinical parameter from severe hypertension to moderate hypertension).

Research opportunities. Until recently, few studies evaluated medication therapy management services based on the self-insured employer perspective and none of these had a comparison group. Future studies should focus on the self-insured perspective as this perspective is very essential and could be a valuable contribution to the U.S. health care system. This is because approximately 55.8% of major population of health insurance coverage in the U.S. is attributed to employer-sponsored insurance. Also, 60% of employees with workplace coverage were enrolled in self-insured plans in 2011, according to the Employer Health Benefits 2011 Annual Survey from the Kaiser Family foundation (The Kaiser Family Foundation and Health Research & Education Trust, 2011). Furthermore, an evaluation of MTM services with comparison groups could provide precise information about the effect of MTM services on outcomes compared to the control group. Additionally, future studies should use both statistical and clinical significance to assess and interpret the results in order to present potential benefits that occur at the clinical level.

Consequently, this study will evaluate MTM services in patients with cardiovascular diseases in terms of clinical outcomes and economic outcomes based on the self-insured perspective. To be specific, this study will assess clinical outcomes using

both statistical and clinical significance. Also, this study will determine economic outcomes by using a comparison group.

In conclusion, this chapter elaborated background information on epidemiology of cardiovascular disease, the issues of employer-sponsored insurance and burden of rising health care expenditures, positive impact of MTM services on outcomes, and the need for rigorous studies that evaluate MTM services in term of clinically meaningful significance. The next chapter will specifically deal with the research method that will be applied in this study for the purpose of evaluating impact of MTM services in patients with cardiovascular disease in clinical and economic outcomes.

Chapter 3

Research Design and Methods

This study evaluated the impact of MTM services provided by pharmacists at a community-based setting from a self-insured employer perspective. This proposed study consisted of two retrospective cohort designs: a pre-post cohort study (Objective 1) and a cohort with comparison groups study (Objective 2). Data from medical claims, pharmacy claims and electronic medical records were used. The target population was the public university's health plan beneficiaries with cardiovascular diseases. The following sections describe the research questions and hypotheses, the study designs, the setting, the target population, timeline, inclusion/exclusion criteria, procedure of patient selection, and data analyses.

Research Questions and Hypotheses

Research question 1:

Was there a significant difference in economic outcomes between patients with cardiovascular diseases who received Medication Therapy Management (MTM) services and those who did not receive MTM services (i.e. non-MTM services)?

> H_{o1}: There was no difference in economic outcomes between patients with cardiovascular diseases who received Medication Therapy Management (MTM) services and patients with cardiovascular diseases who did not receive MTM services (non-MTM services).

H_{A1}: There was a difference in economic outcomes between patients with cardiovascular diseases who received Medication Therapy Management (MTM) services and patients who did not receive MTM services (non-MTM services).

Research question 2

Part 1:

Was there a difference in clinical outcomes among patients with cardiovascular disease after receiving Medication Therapy Management (MTM) services?

H_{o2}: There was no difference in clinical outcomes among patients with cardiovascular diseases after receiving MTM services.

H_{A2}: There was a difference in clinical outcomes among patients with cardiovascular diseases after receiving MTM services.

Part 2:

What are types and frequency of drug-related problems of identified and assessed by pharmacist-provided MTM services?

Study Design

This study consisted of two study designs. First, a retrospective cohort with comparison groups was used to answer research question 1. Second, a pre-post retrospective cohort design was used to answer research question 2.

Setting

This study was conducted based on the perspective of a self-insured employer. Data from medical and pharmacy claims were obtained from a public university with employer-sponsored insurance's health plan. Further, patient records and employer invoices (for billing purposes) for MTM services were obtained from a pharmacist-

provided pharmaceutical care clinic that is located in the university in which Medication Therapy Management (MTM) Services were provide. The pharmacist-provided pharmaceutical care clinic (PCC), located in a pharmacy school setting this public university, serves employees, their dependents and retirees. The PCC provides outpatient pharmacy services as well as pharmacist-provided health related services including Medication Therapy Management (e.g., acid reduction program, diabetes, respiratory, cardiovascular, medication review, wellness and disease prevention (e.g., healthy habits, women's health, tobacco cessation, immunizations, and health screening).

Population

The population was individuals covered by a public university's health plan. Specifically, for research question 1, the target population was patients with cardiovascular diseases who received MTM services at PCC and those patients who did not received MTM services (the non-MTM group). For research question 2, the target population was patients with cardiovascular disease who received MTM services at PCC.

Study Timeline

This study was a retrospective design

1. Enrollment period for this study was 36 months. We considered patients who began enrolling in January 1, 2008 through December 31, 2010. Patients who met the inclusion criteria were followed for 6 months.
2. The study period for this study was 42 months (January 1, 2008 to June 30, 2011). This time represented recent claims data set and clinical data available at the time of the analysis. Also, this period covered 6 months before and after the index date (the definition of index date is articulated in the patient selection section).

Inclusion Criteria and Exclusion Criteria

Inclusion criteria.

1. Patients who continuously enrolled in the public university's health plan, including employees, and their dependents during January 1, 2008 to December 31, 2010;
2. They must be 19 years of age or older;
3. They must be officially diagnosed with cardiovascular disease conditions including hypertension, hyperlipidemia, coronary heart disease, heart failure, stroke, and other form of heart disease. This information was obtained from the medical claims data, using International Classification of Diseases, Ninth Revision (ICD-9) codes. Specifically, 3 digit of ICD-9 codes were used to identify cardiovascular condition, including hypertension: ICD-9 codes: 401-405; coronary heart disease: ICD-9 codes : 410-414; heart failure: ICD-9 codes: 428; stroke: ICD-9 codes: 430, 431, 433, 434, 436, 438; disease of pulmonary circulation: ICD-9 codes: 415-417; other form of heart disease: ICD-9 codes: 420-429; cerebrovascular disease: ICD-9 codes: 430-438; disease of arteries, arterioles, and capillaries: ICD-9 codes: 440-448; disease of veins and lymphatics and other diseases: ICD-9 codes: 451-459; congenital cardiovascular anomalies: ICD-9 codes: 745-747; hyperlipidemia : ICD-9 codes: 272.
4. Patient must obtain prescriptions for cardiovascular conditions and their utilization must be reflected in the pharmacy claims. Specifically, National Drug Code (NDC) was used.
5. Patients were included in the economic analysis (research question 1) if

5.1 For MTM group, they had at least one MTM encounter during the study period between January 1, 2008 and December 31, 2010. The first MTM encounter was assigned as the index date.

5.2 Cardiovascular-related health care costs were available from pharmacy claims (or medical claims) for study period; and

5.3 They had at least one pharmacy claim during the pre-index date period and during the post- index date period (6 month pre- and post- the index date) during the study period.

6. Patients were included in the clinical analysis (research question 2) if

6.1 They had at least one MTM encounter and received MTM services at PCC during the study period between January 1, 2008 and December 31, 2010; and

6.2 Clinical data were available before and after MTM encounter (6 months before and at 6 months after first MTM encounter) for study period.

6.3 They were included in the economic analysis.

Exclusion criteria.

1. Patients who were not continuously enrolled with the public university's health plan 6 months before the index date and 6 months after the index date.

Procedure of Patient Selection and Data Analysis

A retrospective claims database analysis was conducted using medical claims, pharmacy claims, and eligibility data from the public university's Bluecross/Blueshield (BSBC) claims database. In addition, electronic medical record (EMR) data were retrieved from a pharmacist-provided pharmaceutical care clinic (PCC). The data used in

this study were from January 2008 to June 2011. The patient selection procedure is illustrated in Figure 3-1.

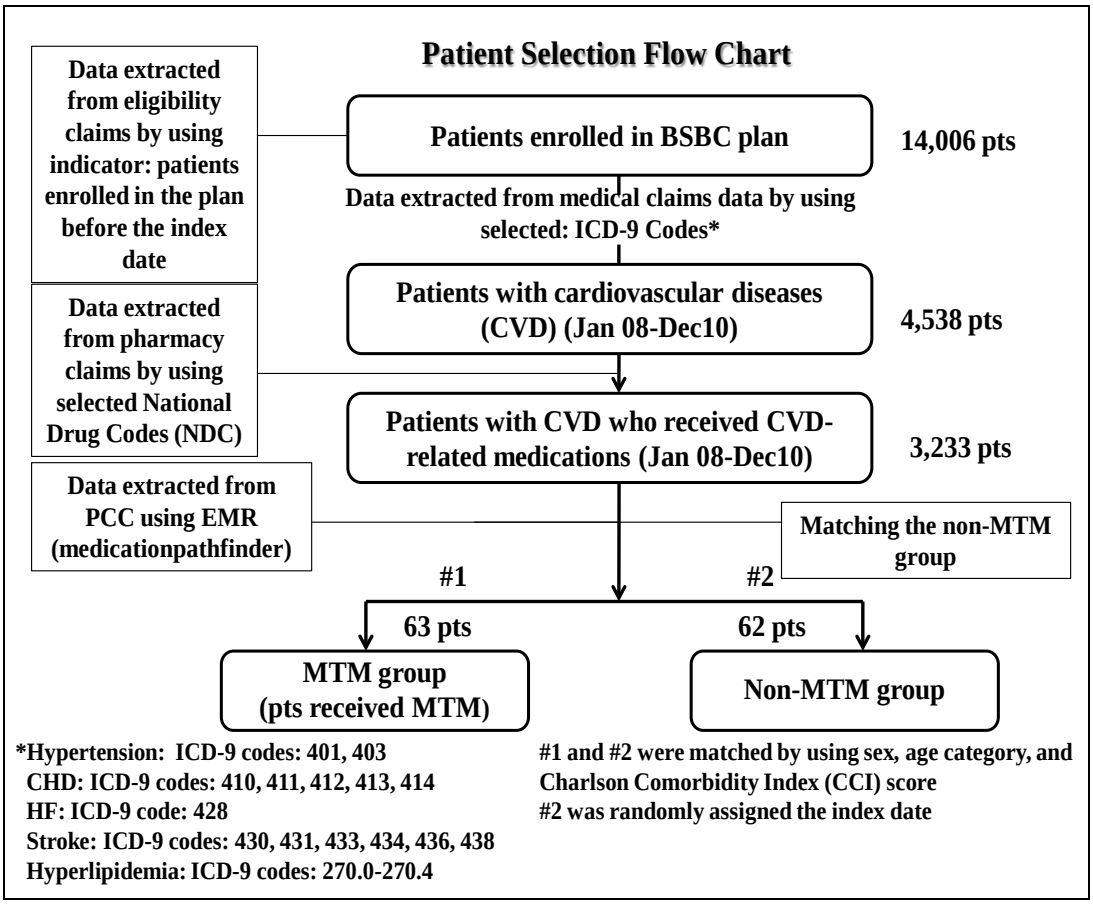

Figure 3-1

Flow Chart of Patient Selection [a]

Abbreviation: BSBC, the public university's Bluecross/Blueshield claims database; ICD-9 codes, the International Classification of Diseases, Ninth Revision; EMR, electronic medical record; pts, patients; MTM, medication therapy management; PCC, a pharmacist-provided pharmaceutical care clinic

[a] After screening patients for diagnoses and CVD medications, 3233 patients were eligible. Of these 63 met the criteria to be included in the MTM group and 62 match-paired patients were included in the non-MTM group.

Step 1. Patients included in the study were derived from AU's BSCB health plan. First, beneficiaries who enrolled in the AU's BSBC plan between January 1, 2008 and December 31, 2010 were identified. Then, the beneficiaries of the public university's health plan who had been diagnosed with cardiovascular diseases (CVD) as evidenced by at least one medical claim during January 1, 2008 and December 31, 2010 were identified using the International Classification of Diseases, Ninth Revision (ICD-9) codes. Further, patients from this population who also had CVD-related medications were identified from pharmacy claims data, using National Drug Code (NDC).

Step 2. Patients were classified into two groups, MTM group and non-MTM group. A unique patient ID was assigned to each patient. The MTM group was defined as patients who received MTM services from PCC between January 1, 2008 and December 31, 2010. The information regarding MTM encounter was retrieved from electronic medical record (EMR). The date of the first MTM services or MTM encounter was defined as *'index date'*. The MTM group was required to continuously enroll in the AU's BCBS plan for at least 6 months before and 6 months after the first MTM encounter (6 month pre- and post- the index date) and must have at least one refill of CVD-related medication during the 6-month prior and after the index date.

Step 3. The non-MTM group, defined as matched-pair patients who did not receive MTM services, but had CVD-related medications prescribed. First, patients who were retained from step 1 and did not receive MTM service were randomly matched to the MTM group based on age category, gender, and comorbidity level, using the Charlson Comorbidity Index (CCI) (see Appendix C6) (Charlson, Pompei, Ales, &

MacKenzie, 1987). Next, "*the index date*" of the non-MTM group was assigned to each patient by randomly selected the date between first enrollment date plus 6 months and last enrollment date minus 6 months of each patient. For example, if a patient in the non-MTM group had enrolled in the public university's health plan on August 1, 2009 and the last enrollment date was December 1, 2010 then this patient was randomly selected the index date based the period between August 1, 2009 and December 1, 2010. Similarly, individuals in the non-MTM group were required to continuously enroll for at least 6 months before and 6 months after their randomly assigned index date (6 month pre- and post- the index date) and must have at least one refill of CVD-related medication during the 6-month prior and after the assigned index date.

Measures and Data Sources

This section is divided into two parts. The first part addresses measures and data sources related to research question 1 while the second part addresses measures and data sources related to research question 2.

Research question 1: economic measures. Research question 1 seeks to address whether there was a difference between Medication Therapy Management (MTM) and non-MTM groups in terms of economic outcomes. The information was retrieved from two data sources (medical and pharmacy claims data) which were described in the data collection method. Both MTM and non-MTM groups must have at least two pharmacy claims. To be specific, patients must have at least one refill of CVD-related medication during the 6-month before and during the 6-month after the index date to determine economic outcomes regarding pharmacy expenditures. Should patients have any medical

claims 6 month pre- and post- the index date, those claims were included for analyzing medical expenditures. However, patients were not required to have a medical claim.

To answer this research question, this study compared economic outcomes between beneficiaries who received MTM services from PCC and those who did not receive MTM services. Economic outcomes that were compared included: pharmacy expenditures, medical expenditures and total health expenditures. Economic data were obtained from multiple sources (see Table 3-1).

1. Medical claims data from the public university's Bluecross/Blueshield database. The medical claims included cost of administering medical care and follow-up; cost of physician's visits, cost of hospitalization or emergency room (ER) visits, cost of laboratory test, cost of procedure;
2. Pharmacy claims data from the public university's Bluecross/Blueshield database. Pharmacy claims included cost of cardiovascular disease-related medications.
3. Cost of MTM services per visit. This billing record was obtained from PCC.

Table 3-1

Measures and data source for economic outcomes

Variables	Measures	Source of Data
1. Pharmacy expenditure (direct cost)	Costs of medications related to cardiovascular disease	Pharmacy claims
2. Medical expenditure (direct cost)	Total medical expenditures included: 1. Cost of administering medical care and follow-up treatment 2. Cost of laboratory tests 3. Cost of hospitalization 4. Cost of doctor's visits 5. Cost of emergency room (ER) visits 6. Cost of special diagnostic procedure	Medical claims
3. Total health expenditure (total direct cost)	Total health expenditure included pharmacy expenditures and total medical expenditures	Pharmacy and medical claims
4. Cost savings	Total health expenditures after the index date minus total health expenditures before the index date	Pharmacy and medical claims

Economic analysis. In addition to comparing economic outcomes, the return on investment was calculated. The following formulas were utilized.

$$\text{Return on Investment} = \frac{\text{Net benefit}^{a}}{\text{Average total cost of MTM services}^{b}}$$

[a] Net benefit = average total benefit – average total cost of MTM services

Average total benefits

Total benefits = average total benefits per person

$B_1 = [(Wa - Wb) - (Wc - Wd)]$
B_1 = average total benefits per person for MTM services
W_a =average total direct cost of MTM group per person after the index date
W_b =average total direct cost of MTM group per person before the index date
W_c = average total direct cost of non-MTM group per person after the index date
W_d =average total direct cost of non-MTM group per person before the index date

[b] Average total cost of MTM services was calculated from total cost of MTM services divided by total number of patients in the MTM group. Cost of MTM services for first initial encounter is $120 and subsequent visit is $40. Of 63 patients, 38 of them had one visit and the rest of them had two or more.

Therefore, the average total cost of MTM services $= \frac{\$8480}{63}$
$= \$134.60$

Definition of variables in research question 1.

Total health expenditure costs:	According to self-insured employer perspective, these costs were referred to the total direct costs per participant only. The total direct costs consisted of cost of administering medical care, follow-up treatment, laboratory test, hospitalization, doctor's visits, medications related-cardiovascular conditions, emergency room (ER) visits, and special diagnostic procedure.
Cost saving:	It was referred to as the average cost savings per patient. Cost savings were estimated as the mean difference in dollar amount between pre- and post-index date of MTM or the non-MTM group. Inflation rate was not adjusted.
Total benefits:	It was referred to as the average total benefits per patient. The total benefits were estimated as the mean difference in dollar amount between cost saving induced by the MTM group and cost saving induced by the non-MTM group (Cote, et al., 2003).
Cost of investment:	It was referred to the average cost of MTM services per patient (i.e., $134.60).
Net benefits:	It was refer to the average net benefit per patient. The net benefits were estimated as the difference in

dollar amount between the total benefits and cost of investment.

Research question 2: Clinical outcome measures. Research question 2 addressed whether there was a difference in clinical outcomes after patients received MTM services. The data source for research question 2 was obtained from an electronic medical record (EMR) database from PCC which provided patient records of those who received MTM services. Each patient record included patient demographic data (e.g., age, gender) and patient registry data (e.g., medical health, preventive health, labs and diagnostic tests, vitals, and medication list). The supplement part of research question 2 was to explore types and frequency of drug-related problems identified and assessed by pharmacist-provided MTM services. The data source was obtained from patient clinical assessment section which was part of the electronic medical record (EMR) database.

Clinical outcomes. Clinical data assessed in this study consisted of three clinical outcome parameters: 1.) lipid panel (high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, total cholesterol, and triglyceride), 2.) blood pressure (systolic blood pressure (SBP) and diastolic blood pressure (DBP)), and 3.) body mass index (BMI). Sources used for collecting information on clinical outcomes are in Appendix C, Table C1. Patients in the MTM group must have at least two laboratory measures of any parameters. To be specific, patients must have at least one laboratory measure during 6 months before and after the index date to obtain the baseline value and endpoint value.

Clinical outcomes before and after MTM intervention were compared. Baseline value was defined as the closest value measured before the index date. This value

represented patient's most recent condition before obtaining an MTM intervention. As for the value after the MTM intervention, the endpoint value was measured at 100-day interval after the index date. For each parameter, the endpoint value was defined as follows: 1.) if patients had only one measurement after the index date, their available laboratory value was used as the endpoint, assuming that the value remained static. This assumption was based on the last observation carried forward (Streiner, 2002) and 2.) if the patients had multiple parameter measurements during 100-day interval, the last available value was used.

It should be noted that there is no consensus regarding the endpoint value for follow-up measurement. Some study defined the follow-up value as the average of all available measurements during the follow-up period (L. K. Welch et al., 2011). Some study used the last available value measured during 90-day interval after the index date (Mosca et al., 2005). As stated before, the endpoint value in this study was based on the definition as mentioned earlier. In fact, the differences between this endpoint value (using the last available value definition) and the average endpoint value obtained during 100-day interval of follow-up were relatively small. For example, the endpoint value of systolic blood pressure based on definition in this study was 129.60 ± 15.92 mmHg while the average of systolic blood pressure measurements was 131.12 ± 16.08mmHg.

All The clinical outcomes are described in Table 3-2 in the following page.

Table 3-2

Measures and data source for clinical outcomes

Variables	Measures	Source of Data	Outcomes
1. A lipid panel (LDL-C, HDL-C, total cholesterol levels, and triglyceride)	A lipid panel level (mg/dL)	Electronic medical records (EMR)	Change in LDL-C, HDL-C, total cholesterol, and triglyceride levels between pre-and post-index date
2. Blood pressure (systolic and diastolic blood pressure)	2.1 Blood pressure level (mmHg) 2.2 Number of patients achieved their treatment goal 2.3 Number of patients in each hypertension stage	Electronic medical records (EMR)	2.1 Change in blood pressure between pre- and post-index date 2.2 Change in the proportion of patients achieved the treatment goal after the index date 2.3 Change in patient's disease stages based on JNC 7 classification (see Appendix C, Table C2)
3. Body mass index (BMI)	3.1 BMI level (kg/m^2) 3.2 Number of patients who have normal BMI 3.3 Number of patients in each BMI stage	Electronic medical records (EMR)	3.1 Change in BMI between pre-and post-index date

Table 3-2 (continued)

Variables	Measures	Source of Data	Outcomes
3. Body mass index (BMI)			3.2 Change in the proportion of patients who achieved the BMI of 18.5-24.9 kg/m^2 after the index date 3.3 Change in patient's BMI stages
4. Drug-related problems (see the complete list in Appendix C, Table C4)	Types and frequency of drug-related problems	Electronic medical records (EMR)	N/A

Data Analyses and Statistical Approaches

Characteristics of patients in MTM and non-MTM groups

All data extraction and analyses were performed using Statistical Analysis Software (SAS) version 9.2 (SAS institute Inc., Cary, NC). Descriptive statistics were used to describe patient baseline characteristics (before the index date) among patients in the MTM and non-MTM groups. Specifically, frequency distribution and Chi-square tests were used to describe and compare patients' characteristics between MTM and non-MTM groups for categorical variables including sex, age category, the Charlson Comorbidity Index Score, number of cardiovascular conditions, pharmacy claims category, medical claims category, and unique medications category. Means and standard deviations were used to describe continuous variables (e.g., age). Independent t-test was used to compare age between the two groups.

Research question 1: Economic Outcomes. After checking for normality (Kolmogorov-Smirnov tests, Q-Q plots, and histograms), the expenditures data (pharmacy, medical, and total expenditures) were skewed and the assumption of normality was violated. This was because the expenditures data contained some extremely high cost values whereas majority of costs cluster around a certain range of values. However, those extreme values were not considered as outliers. Therefore, the transformation of data was performed in attempt to correct the problem by taking logarithm, reciprocal, reciprocal square root of sample values. However, this approach still failed to create a symmetric cost distribution.

Another option was to conduct a nonparametric test because it did not require parametric assumptions. However, since it did not consider the impact of extreme values,

patients who had relatively high or low expenditures would be omitted and, hence, may influence the precision of the data (Rascati, Smith, & Neilands, 2001; Whitley & Ball, 2002). Also, this method may have an issue of low statistical power when the sample size is small (Whitley & Ball, 2002). Because of the stated reasons, a nonparametric test was not performed.

Instead, a 1000 bootstrap replication of the original data was conducted to deal with small sample sizes with skewed cost data (Briggs, Wonderling, & Mooney, 1997; Rascati, et al., 2001). The bootstrap method was a simulation of repeated random sampling of the original data. It replicated samples of the original data with each sampled item replaced after each random draw (Efron B. & Tibshirani R., 1993). The advantage of the bootstrap method was that it did not require a normal distribution assumption or theoretical models. Also, it was a recommended approach when dealing with small sample sizes (Briggs, et al., 1997; Committee for Medicinal Products for Human Use (CPMP), 2006; Fiellin & Feinstein, 1998).

To determine if there was a difference in economic outcomes, paired-t tests were used to compare the mean cost difference before and after the index date within groups (within MTM and non-MTM group) and independent t-tests were used to compare between-group cost difference (between MTM and non-MTM groups) before and after the index date. Comparisons were 2-sided and performed at a 0.05 level of significance.

Research question 2: clinical outcomes. As for clinical parameters, an assumption of normality was not violated after checking for normality (Kolmogorov-Smirnov tests, Q-Q plots, and histograms). Therefore, paired-t tests were used to compare mean difference between the baseline and endpoint values of clinical parameters (i.e.,

blood pressure and body mass index (BMI)). Comparisons were 2-sided and performed at a 0.05 level of significance.

To determine if there was an improvement in hypertension stages and body mass index stages, Generalization of the McNemar's test (Bhapkar's test) was used. In this study, this method was applied to test clinical outcomes that were classified into multiple categories or 4x4 contingency tables as follows: 1.) Hypertension stages: normal hypertension; pre-hypertension; hypertension stage 1; hypertension stage 2, 2.) Body mass index stages: underweight; normal; overweight; obese.

This McNemar test was conducted to test whether there was marginal homogeneity among hypertension stages or body mass index stages between pre- and post- the index date. In other words, whether the distribution of patients in four hypertension stages (or body mass index stages) before the index date differed from the distribution of patients after the index date. Differences were considered statistically significant when the χ^2 value was less than 0.05. The statistical hypotheses are enumerated in Table 3-3.

As for part 2, descriptive statistics were used to report for types and number of drug-related problems identified by pharmacists when they conducted MTM services (see Appendix C, table C4 for drug-related problem category).

Table 3-3

Statistical approaches to test hypotheses

Research question	Testing Group	H_o/H_A	Details	Statistical design
Research question 1 Was there a difference in economic outcomes between patients with cardiovascular diseases who received MTM services and patients who did not receive MTM service?	Within groups (within MTM and non-MTM groups)	H_{o1-1} H_{A1-1}	The mean cost difference (pharmacy, medical, or total health expenditures) between pre- and post- the index date of MTM and the non-MTM groups was not different The mean cost difference between pre- and post- the index date of MTM and the non-MTM groups was different	Comparison within group: paired-t tests
Research question 1 Was there a difference in economic outcomes between patients with cardiovascular diseases who received MTM services and patients who did not receive MTM service?	Between-group difference (between MTM and the non-MTM groups)	H_{o1-2} H_{A1-2}	The between-group cost difference (cost difference of pharmacy, medical, or total expenditures) between MTM and non-MTM groups was not different The between-group cost difference between MTM and the non-MTM groups was different	Comparison between MTM and the non-MTM groups: independent t-tests

Table 3-3 (continued)

Research question	Testing Group	H_o/H_A	Details	Statistical design
Research question 2 Was there a difference in clinical outcomes among patients with cardiovascular disease after receiving MTM services?	Within the MTM group	H_{o2-1} H_{A2-1}	The mean difference between the baseline and endpoint values for each clinical parameter was not different The mean difference between the baseline and endpoint values for each clinical parameter was different	Comparison within group: paired-t tests
Research question 2 Was there a difference in clinical outcomes among patients with cardiovascular disease after receiving MTM services?	Within the MTM group	H_{o2-2} H_{A2-2}	The distribution of patients before the index date was not different from the distribution of patients after the index date in terms of hypertension and BMI stages The distribution of patients before the index date was different from the distribution of patients after the index date in terms of hypertension and BMI stages	Generalization of the McNemar's test (Bhapkar's test)

Chapter 4

Results

This chapter reports the results from the analyses and addresses study objective 1 and 2. First, patient demographic data at baseline are described. Then, the results regarding economic outcomes are presented. Next, the results regarding clinical outcomes are reported. Finally, the findings of drug-related problems identified by pharmacists are summarized.

Descriptive Results

After excluding beneficiaries who did not meet the inclusion criteria 63 patients were included in the MTM group and 62 match-paired patients were included in the non-MTM group.

Baseline characteristics of patients in MTM and the non-MTM groups

Baseline characteristics of patients in the MTM group and the non-MTM group are displayed in Table 4-1. The first set of baseline characteristics was related to general demographic characteristics including sex, age, age category, comorbidity, and CVD conditions. The majority of patients were male (61.90% for the MTM group, and 61.29% for the non-MTM group). The average age was 56.77 ±9.31 and 56.91±9.63 for the MTM and non-MTM group, respectively. Specifically, more than 60% of patients in MTM and the non-MTM group were age 51-65 and only approximately 12% were age 65 and older.

In terms of comorbidity, the CCI scores were 1.00 and 0.90 for the MTM and non-MTM group, respectively. The majority of patients were diagnosed with hypertension and dyslipidemia (61.90% vs. 51.61%). When compared, chi-square analyses and independent t-test did not indicate any statistically significant difference between the MTM and the non-MTM groups. In other words, both groups were similar with respect to sex, age, age category, Charlson Comorbidity Index (CCI) score, and their CVD conditions.

Table 4-1

Baseline characteristics of patients in MTM and the non-MTM groups

Variable	MTM n=63	Non-MTM n=62	P Value
GENERAL CHARACTERISTICS [a]			
Sex			0.943 *(df=1)*
Male	39 (61.90%)	38 (61.29%)	
Female	24 (38.10%)	24 (38.71%)	
Age			
Mean age in years (Mean±SD)	56.77±9.31	56.91±9.63	0.933
Age category			0.999 *(df=3)*
21-35	0	0	
36-50	16	15	
51-65	39	39	
66-80	6	6	
81+	2	2	
The Charlson Comorbidity Index (CCI) Score	1.00 (0-7)	0.90 (0-5)	0.986 *(df=6)*
0	29	29	
1	19	19	
2	8	8	
3	4	4	
4	1	1	
5	1	1	
7	1	0	
Cardiovascular conditions			0.386 *(df=2)*
Hypertension	16 (25.40%)	17 (27.42%)	
Dyslipidemia	8 (12.70%)	13 (20.97%)	
Hypertension with Dyslipidemia	39 (61.90%)	32 (51.61%)	
PHARMACY CLAIMS			
Number of CVD-related medications (Mean±SD) [b]	1.95±0.97	1.75±1.13	
CVD-related Medications [b]			0.979 *(df=2)*
1-3 medications	58 (92.06%)	57 (91.94%)	
4-6 medications	5 (7.94%)	5 (8.06%)	
Number of pharmacy claims (Mean±SD)	2.97±2.12	2.47±2.00	
Pharmacy claims			0.505 *(df=3)*
1-3 claims	45 (71.43%)	51 (82.26%)	
4-6 claims	14 (22.22%)	8 (12.90%)	
7-9 claims	2 (3.17%)	2 (3.23%)	
10 claims or more	2 (3.17%)	1 (1.61%)	

Table 4.1 (continued)

Variable	MTM n=63	Non-MTM n=62	p Value
PHARMACY CLAIMS (continued)			
Total number of pharmacy claims	187	153	
Total number of generic medications	111	80	
Total number of brand medications	50	62	
MEDICAL CLAIMS			
Number of medical claims (Mean±SD)	5.19±6.11	4.45±3.08	
Medical claims			0.359*(df=4)*
None	32 (50.79%)	31 (50.00%)	
1-3 claims	16 (25.40%)	16 (25.81%)	
4-6 claims	8 (12.70%)	6 (9.68%)	
7-9 claims	2 (3.17%)	7 (11.29%)	
10 claims or more	5 (7.94%)	2 (3.23%)	
Total number of medical claims	161	138	
Hospitalizations	0	4	
Emergency Room (ER) visits	0	2	

a chi-square tests had been performed for categorical variables and independent t- test had been performed for continuous variables
b count CVD-related medication prescribed only once, regardless number of refills

The second set of baseline characteristics was related to pharmacy claims, medical claims, and health care utilizations. Generally, results have shown that patients in MTM and non-MTM group were not statistically significantly different regarding number of pharmacy claims (χ^2= 2.336; *df* = 3; *p* =0.505), number of CVD-related medications (χ^2= 0.001; *df* = 1; *p* =0.979), and number of medical claims (χ^2= 4.356; *df* = 4; *p* =0.359). Patients in the MTM group had a slightly higher mean ±SD number of cardiovascular disease (CVD)-related medications, compared with the non-MTM group (1.92±0.97 vs. 1.75±1.13, respectively). When categorized by number of medications or pharmacy claims, the majority of patients had 1-3 CVD-related medications and had pharmacy claims between 1-3 claims. Approximately 50% of patients in both groups did not have medical claims. Small percentages of MTM patients and the non-MTM patients had greater than 10 pharmacy claims (3.17% vs. 1.61 %) and greater than 10 medical claims (7.94% vs. 3.23%). Examination of utilization revealed that MTM group had lower incidence of hospitalization and emergency room visits, compared with the non-MTM group.

Economic outcomes

Table 4-2 summarized cardiovascular-related pharmacy, medical, and total direct expenditures for the 6 month pre- and post- the index date among the MTM and the non-MTM group. Before the index date, pharmacy expenditure was slightly lower in the MTM group ($8011.26), compared with the non-MTM group ($8297.67). The same is not true for the medical expenditure and the total direct expenditures, the MTM group generated greater medical and total direct expenditures than the non MTM group. When comparing expenditures between the pre- and post-index date in the MTM group, the

expenditures were reduced by 17.65% ($1,414.53) in pharmacy expenditure, 32.72% ($ 4,585.72) in medical expenditure, and 27.24% ($6,000.25) in total expenditures. In contrast, when comparing expenditures between the pre- and post-index date in the non-MTM group, the expenditures were increased by 7.40% ($663.30) in pharmacy expenditure, 63.73% ($ 13,701.41) in medical expenditure, and 41.15% ($14,364.61) in total expenditures.

Table 4-3 presents the mean direct costs for pharmacy, medical, and total expenditures for the 6 month pre- and post- index date for both MTM and the non-MTM groups. Compared with the 6 month prior to the index date, the mean cost of pharmacy expenditures in the MTM group decreased ($126.80±20.33 vs. $104.80±17.77, $p<0.05$). Similarly, the mean cost of medical expenditures expenditure ($235.80 ± 108.80 vs. $156.60 ± 89.41, $p<0.05$) and total direct cost ($481.20±137.00 vs. $406.10 ± 135.30, $p<0.05$) at the post- index date were lower than the expenditures measured 6 months prior to the index date. On the contrary, the mean cost of pharmacy, medical, and total direct cost for the non-MTM group statistically significant increased after the index date.

In terms of cost savings, the MTM group had a statistical significant decrease in mean cost of pharmacy (difference of -$22.03±19.104 vs. $10.73±24.20, $p<0.05$), medical expenditure (difference of-$79.20± 99.55 vs. $246.40 ± 248.40, $p<0.05$), and total expenditure (difference of-$75.09±136.20 vs. $289.00±269.5, $p<0.05$), per patient compared with the increase in these expenditures in the non-MTM group.

Furthermore, the MTM group had statistical significance in mean cost differences of pharmacy (difference of -$31.98±25.07, $p<0.05$), medical expenditure (difference of

-$325.60 ± 271.20, $p<0.05$), and total direct expenditure (difference of-$359.30± 219.20, $p<0.05$), per patient compared with the non-MTM group. Negative mean cost differences indicated cost saving. In order to evaluate the return on investment, the mean cost difference of total direct expenditure between two groups was referred to the average total benefit per patient (i.e., $359.30).

The average net benefit per patient attributable to MTM services was calculated by subtracting average MTM services per patient described in chapter 3 ($134.60) from the average total benefit per patient (i.e., $359.30-$134.60=$224.70). This average net benefit per patient was divided by the average cost of MTM services per patient (i.e., $224.70 divided by $134.60=1.67), resulting in a return on investment of $1.67 per $1 in MTM costs per patient.

$$\text{Return on Investment} = \frac{\text{average net benefit (average total benefit-average cost of MTM services)}}{\text{Average cost of MTM services}}$$

$$= \frac{\$359.30-\$134.60}{\$134.60}$$

$$= 1.67$$

Table 4-2

Summary of cardiovascular-related total expenditures (pharmacy, medical, and total direct expenditures) for 6 month pre- and post- the index date among MTM and the non-MTM groups

Study group and type of claims	MTM group (n=63)			Non-MTM group (n=62)		
	Pre- the index date ($)	Post- the index date ($)	Change (%)[a]	Pre- the index date ($)	Post- the index date ($)	Change (%)
Pharmacy claims	8011.26	6596.73	-17.65	8297.67	8960.87	7.40
Medical claims	14015.69	9429.97	-32.71	7797.68	21499.09	63.73
Total	22026.95	16026.7	-27.24	16095.35	30459.96	47.15

[a] Negative percentage indicated cost saving during the intervention period

Table 4-3

Mean direct cost (pharmacy, medical, and total direct cost) of cardiovascular disease-related expenditures for pre-and post-the index date per MTM patient (n=63) and the non-MTM patient (n=62)

Category of cost	MTM participants (n=63)			Non-MTM participants (n=62)			Between group difference of mean cost variation (p value)[b]
	mean cost (± SD)		mean within group cost difference (p value)[a]	mean cost (± SD)		mean within group cost difference (p value)	
Direct cost	Pre-index date	Post-index date		Pre-index date	Post-index date		
Pharmacy claims	126.80 (±20.33)	104.80 (±17.79)	-22.029 (±19.10) (p<0.05)	133.7 (±23.79)	144.4 (±24.60)	10.73 (±24.20) (p<0.05)	- 31.98 (±25.07) (p<0.05)
Medical claims	235.80(±108.80)	156.60 (± 89.41)	-79.20 (± 99.55) (p<0.05)	148.30 (± 48.96)	394.70 (±347.90)	246.40 (± 248.40) (p<0.05)	-325.60 (± 271.20) (p <0.05)
Total direct cost	481.20 (± 137.00)	406.10 (± 135.30)	-75.09 (± 136.20) (p<0.05)	291.30 (± 288.30)	580.30 (± 561.00)	289.00 (± 269.50) (p<0.05)	-359.30 (± 219.20) (p<0.05)

[a] Negative mean within group cost differences indicated cost saving during the intervention period
[b] Negative mean between groups cost differences indicated cost saving associated with the MTM group

Clinical outcomes

Out of the 63 patients in the MTM group (described previously in the economic analyses), only a portion of them were included in the clinical cohort. Patients were excluded because they failed to have clinical measurements before and after the index date. Specifically, a total of 14 patients were included in the total cholesterol analysis; 12 were included in the HDL cholesterol analysis; 8 were included in the LDL cholesterol analysis; and 8 were included in the triglycerides analysis. Forty patients were included in the blood pressure analysis, and, lastly, 23 patients were included in the body mass index analysis.

Table 4-4 summarizes changes in values of clinical parameters for patients remaining in the clinical cohort. The values included mean baseline and endpoint values of the lipid panel, systolic and diastolic blood pressure and body mass index.

Lipid panel. The mean difference between baseline and endpoint values of total cholesterol and HDL cholesterol levels were 3.71±24.73 mg/dL and 2.17±7.41 mg/dL, respectively. These changes indicated increase in total cholesterol and HDL cholesterol levels compared with the baseline values. Also, the mean difference between baseline and endpoint values of LDL cholesterol and triglyceride levels were -5.88±38.77 mg/dL and -20.00±119.90 mg/dL, respectively. These changes demonstrated a reduction in LDL cholesterol and triglyceride levels compared with the baseline. However, since the lipid panel analysis had a relatively small sample size, only descriptive analyses were conducted. The study was not able to assess if these differences were statistically significant.

Blood pressure. Table 4-4 illustrates that the mean systolic and diastolic blood pressure values at endpoints decreased from the baseline values (-3.35±17.54 mmHg and -1.62±8.35 mmHg, respectively). However, the magnitude of the changes was small and the mean systolic and diastolic at endpoint were not statistically different from the baseline ($p \geq 0.05$).

In addition to the mean differences, the study examined the change in the proportion of patients who achieved a treatment goal for BP (see Figure 4-1). Using the JNC 7 classification, treatment goals were individualized for each patient. For instance, patient with diabetes or chronic kidney disease was assigned a blood pressure goal at < 130/80 mmHg and those without diabetes or chronic kidney disease were assigned a blood pressure goal < 140/90 mmHg. More information about the goals can be found in appendix C, table C2.2. As shown in Figure 4-1, the percentage of patients at their goal increased from 55.00% to 70.00% compared to the baseline.

This study also categorized blood pressure readings into four stages: normal, pre-hypertension, hypertension stage I, and hypertension stage II. Figure 4-2 illustrates the change in the distribution of patients in various stages of blood pressure from the baseline values. The results indicated that 12 patients (30%) had an improvement in their blood pressure. To be specific, an improvement in two and one stages were found in 2 patients and 10 patients, respectively. A total of 25 remained in the same stage and 3 patients resulted in a more progressive stage of hypertension.

While the above data provided an overview of the changes in hypertension stages, it did not illustrate the change in hypertension stages for patients at each stage of

hypertension. Therefore, this study compared the distribution of patients by stages of hypertension between the baseline values and the end-point values (Table 4-5). Using generalization of the McNemar's (Bhapkar's test) to test homogeneity, the distributions of patients after the index date were statistically significant different from the distributions of those at the baseline in terms of stages of hypertension (χ^2 =12.77, p=0.01), indicating that the stages of hypertension have changed over the study period. For instance, of 16 patients that had prehypertension at baseline, 13 (81.25%) remained at their current stage while 3 (18.75%) had improved to the normal stage at post-the index date. Further, 50% of patients with stage 1 hypertension at the baseline had improved at least 1 stage. Specifically, one patient had improved to the normal stage and 7 patients had improved to the prehypertension stage.

Body mass index (BMI). Table 4-4 illustrates the mean difference in BMI. Mean BMI value at endpoint decreased compared with the baseline value (-0.43±1.21 km/m^2). Nevertheless, no statistically significant difference was reported between BMI value measured at the baseline and endpoint (p=0.10).

In addition to the mean differences, the study examined the change in the proportion of patients who achieved a normal BMI (see Figure 4-1). The percentage of patients at a body mass index goal increased from 13.04% to 21.74% compared to the baseline.

Similar to the analysis conducted with blood pressure, body mass index was classified into four stages: underweight, normal, overweight and obese. This study examined the extent of an improvement in stages of BMI (Figure 4-3) A total of 5

patients (22 %) had an improvement in the stages of body mass index at the endpoint from the baseline values. To be specific, this improvement was for one stage. It is important to note that, while 18 remained unchanged in their BMI, none had declined to a progressive BMI stage.

To track an improvement in BMI stages, the study used a similar approach to the approach used for tracking changes in blood pressure stages. Table 4-6 presented the distribution of patients by BMI stages between at baseline and at post-the index. The results indicated that the distributions of patients after the index date were statistically significant different from the distributions of those at the baseline in terms of body mass index stages (χ^2 =6.39, p=0.04), indicating that the stages of body mass index have changed over the study period. For instance, of the 11 patients that were classified as overweight at baseline, 9 (81.82%) remained overweight while 2 (18.18%) had improved to a normal category at the post-the index date. Similarly, 3 patients (33.33%) who were classified as obese at baseline had improved one stage to the overweight category at the post-index date.

Table 4-4

Comparison of a lipid panel, blood pressure, and body mass index between baseline and endpoint values of the MTM group

Outcome parameters	Baseline value [a]	Endpoint value [a]	Mean differences	p value
	Mean±SD	**Mean±SD**	**Mean±SD**	
Lipid panel (mg/dL) [b]				
Total cholesterol, n=14	153.28±33.98	155±27.73	3.71±24.73	N/A
HDL Cholesterol, n=12	42.33±16.46	44.50±16.82	2.17±7.41	N/A
LDL Cholesterol, n=8	89.38±41.54	83.50±19.12	-5.88±38.77	N/A
Triglycerides, n=8	171.38±111.34	151.38±70.61	-20.00±119.90	N/A
Blood pressure (mm Hg), n=40 [c]				
Systolic blood pressure (SBP)	132.95±19.02	129.6±15.91	-3.35±17.54	0.16
Diastolic blood pressure (DBP)	80.57±8.56	78.95±7.21	-1.62±8.35	0.23
Body mass index (BMI) (kg/m2), n=23 [c]	30.12±6.85	29.69±6.57	-0.43±1.21	0.10

[a] Baseline value represents value before the index date and endpoint value represents value after the index date.
[b] Statistical tests cannot be performed due to small sample size.
[c] Were not significantly different from baseline ($p \geq 0.05$), using paired t-test.

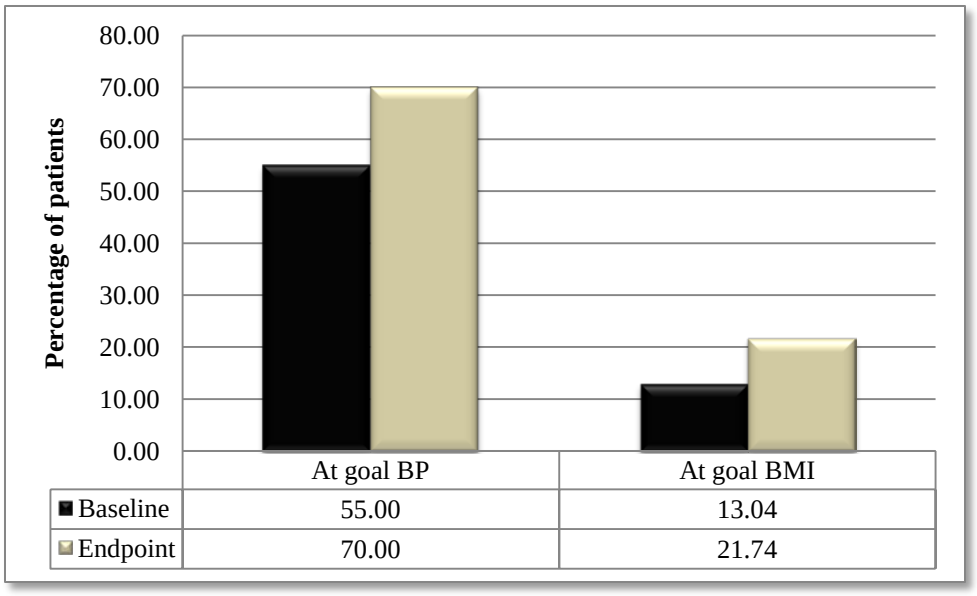

Figure 4-1

Change in the percentage of patients in MTM group who achieved the blood pressure and body mass index treatment goal at baseline and endpoint (using JNC 7 classification)[a,b]

Abbreviations: BMI, body mass index; BP, blood pressure; JNC 7, **The Seventh Report of the Joint National Committee on** Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

[a] Goals individualized for each patient based on the JNC

[b] Number of patients for BP analysis=40; number of patients for BMI analysis=23

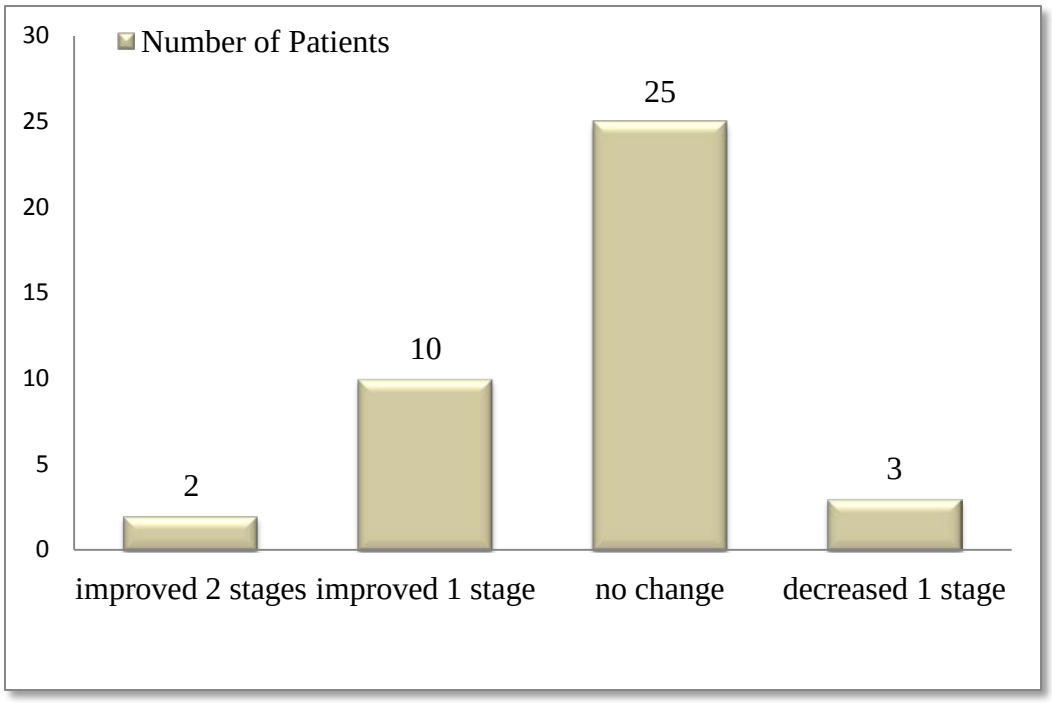

Figure 4-2

Number of patients whose stages of hypertension have changed from baseline at endpoint (n=40)

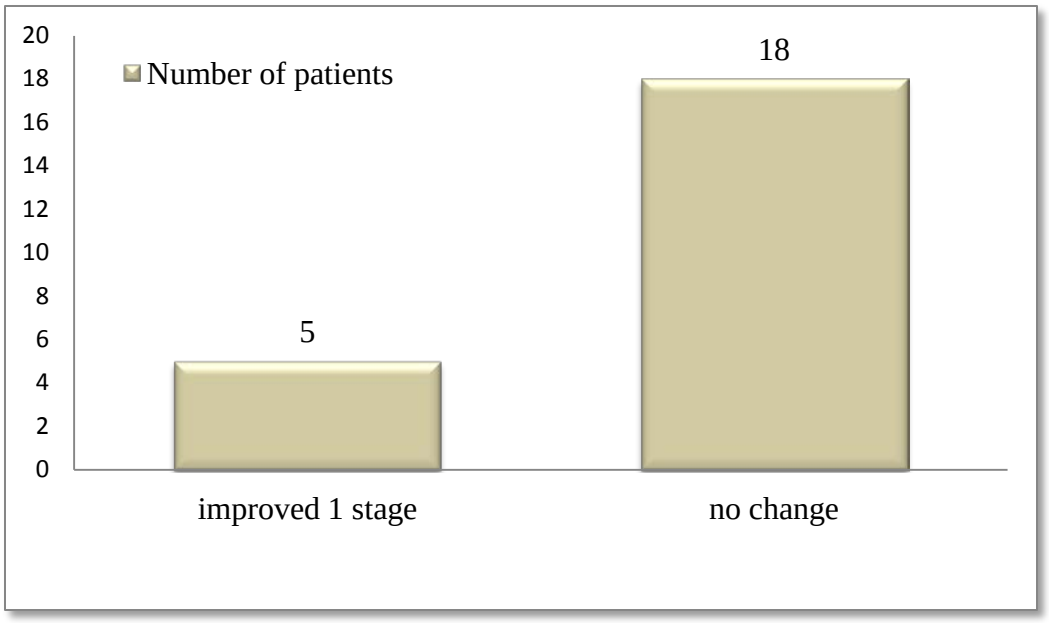

Figure 4-3

Number of patients whose stages of BMI have changed from baseline at endpoint (n=23)

Table 4-5

Cross-tabulation of number of patients by stages of hypertension between baseline and endpoint

Stages of BP	Definition		At baseline	At endpoint				Changes	P value [a] (χ^2)
	SBP	DBP		Normal	Pre hypertension	Hypertension stage 1	Hypertension stage 2		
			n (%)	n (%)	n (%)	n (%)	n (%)	(%)	
Normal	<120	<80	5 (12.50)	3 (60.00)	2 (40.00)			40.00	12.77
Prehypertension	120-139	80-89	16 (40.00)	3 (18.75)	13 (81.25)			43.75	
Hypertension stage 1	140-159	90-99	16 (40.00)	1 (6.25)	7 (43.75)	7 (43.75)	1 (6.25)	-56.25	
Hypertension stage 2	≥160	≥100	3 (7.50)	0 (0.00)	1 (33.33)	0 (0.00)	2 (66.67)	0.00	
Total			40 (100.00)	7	23	7	3		

Abbreviation BP, blood pressure; SBP systolic blood pressure, DBP diastolic blood pressure.

[a] Statistically significant difference at p=0.01, using generalization of the McNemar's chi-sqaure (Bhapkar's test) for the marginal homogeneity testing.

Table 4-6

Cross-tabulation of number of patients by stages of body mass index between baseline and endpoint

Stages of body mass index (BMI)	Definition	At baseline	At endpoint				Changes	P value [a] (χ^2)
			Underweight	Normal	Overweight	Obese		
	kg/m^2	n (%)	n (%)	n (%)	n (%)	n (%)	(%)	
Underweight	<18.5	0 (0.00)					0.00	6.39
Normal	18.5-24.9	3 (13.04)		3 (100)			66.67	
Overweight	25.0-29.9	11 (47.83)		2 (18.18)	9 (81.82)		9.09	
Obese	≥30.0	9 (39.13)			3 (33.33)	6 (66.67)	-33.33	
Total		23 (100.00)	0	5	12	6		

[a] Statistically significant difference at p=0.04, using generalization of the McNemar's chi-sqaure (Bhapkar's test) for the marginal homogeneity testing.

Drug related problem

Medication therapy management (MTM) services in a pharmacist-provided pharmaceutical care clinic (PCC) were provided to patients via face-to-face consultation for 30-60 minutes per encounter. A total of 92 MTM encounters were provided to 63 patients, accounting for an average of 1.46 encounters per patient. These encounters also included follow-up to assess patient response to drug therapy. A total sample of 63 patient electronic medication records from medication pathfinder software were reviewed by the researcher to classify the problems identified and resolved by pharmacists. The "patient assessments" section in the medication pathfinder was the source used to identify and categorize drug-related problems.

The pharmacist-provided pharmaceutical care clinic (PCC) pharmacists identified and resolved the problems based on the PCC guideline which was modified from the drug-related problems classification system established by Helper and Strand (Cipolle RJ, Strand LM, & Morley PC, 2004; Hepler & Strand, 1990). Drug-related problems were classified by the researcher into 12 categories (Table 4-6). Overall, the 63 patients in MTM group had a total of 143 drug-related problems identified and resolved by pharmacists. Furthermore, approximately two thirds of MTM patients had more than one drug-related problem (42 patients, 66.67%). Specifically, an average of 2.26±1.23 (mean±SD) medication problems per patient (range: 1-6) was identified. The most commonly identified drug-related problem was in the lifestyle modification required category (24.48%). The second most common category was patient recommendation required (23.78%). The next most commonly identified categories were needing

additional drug therapy (16.78%) and cost effectiveness alert (15.38%), respectively. Other categories (less than 10%) were adverse drug reaction/side effect, dosage too high, dosage too low, adherence, unnecessary drug therapy, and drug interaction, respectively. None of wrong drug or miscellaneous category was reported.

Table 4-7

Drug-related problems (DRPs) identified and assessed of patients in MTM group by category [a] (n=63)

Category and type of drug-related problem	Number problem identified (%)	Example
Lifestyle modification required	35 (24.48)	Recommend consistent diet and moderate level aerobic exercise 15-30 minutes 2-3 times a week.
Patient care recommendation	34 (23.78)	Patient education for disease information, self-care, and initiation of new drug therapy, to maximize efficacy and minimize risk of adverse drug events.
Need additional drug therapy	24 (16.78)	Patient with diagnosis of hypertension and recently started on enalapril 20mg. Blood pressure has remained elevated outside goal range (<140/90) on this visit and the last visit. Patient would benefit from additional therapy with a different class of blood pressure lowering medication (e.g. HCTZ)
Cost-effectiveness alert	22 (15.38)	Patient is currently taking spironolactone, metoprolol tatrate, and Crestor (rosuvastatin)for hypertenstion and hyperlipidemia. Due to cost savings the patient would benefit from switching from Crestor to generic simvastatin.
Adverse drug reaction/Side effect	7 (4.90)	Patient currently controlled (goal <140/90) on hypertension medications. Atenolol and amlodipine are appropriate treatment options following discontinuation of enalapril due to cough.
Dosage too high	6 (4.20)	Patient on warfarin with INR 4.2 and sign of bruising

Table 4-6 (continued)

Category and type of drug-related problem [b]	Number problem identified (%)	Example
Dosage too low	5 (3.50)	Increase warfarin dose to 2.5 mg daily except 5 mg on Tue/Thur (or 22.5 mg/week) to reach patient's INR goal of 1.9-2.5.
Adherence	5 (3.50)	Patient stopped taking atrovastatin due to muscle pain, consult physician for stoping current medication and restarting simvastatin because patient has no issue while taking simvastatin
Unnecessary drug therapy	3 (2.10)	Patient is taking both Clonazepam and Lorazepam for restless legs sysdrome. Duplicate therapy not necessary and a safety concern due to patient's age.
Interaction	2 (1.40)	Patient had elevation of liver function test because A drug interaction between terbinafine and rosuvastatin
Wrong drug	0	N/A
Other	0	N/A
Total drug-related problems (DRP)	143 (100)	

[a] Drug-related problems were identified and resolved among the 63 patients who received MTM services
[b] Drug-related problems were classified into 12 categories using the pharmacist-provided pharmaceutical care clinic (PCC) guideline and Helpler and Strand classification system

Chapter 5

Discussion and Conclusions

Study Overview

Cardiovascular disease (CVD) is one of the major causes of mortality worldwide. In the U.S., CVD had continued to be one of the 15 leading causes of death. Also, CVD represented the highest total expenditures among major leading health conditions and total expenditures of CVD were projected to exceed $1 trillion by 2030. Further, CVD established the highest proportion of total hospitalization expenditure and the highest number of discharge in 2008.

Due to continually rising health care costs for employees, third-party payers and self-insured employers have utilized various strategies to help address this problem. Since pharmacists can be a viable solution to help improve health outcomes while controlling healthcare expenditures, third-party payers and self-insured employers have offered pharmacist provided-medication therapy management (MTM) services as their healthcare benefits.

The primary purpose of the study was to evaluate the impact of medication therapy management (MTM) services among patients with cardiovascular diseases from the self-insured employer perspective. Specifically, the first objective was to evaluate the impact of MTM services on economic outcomes among patients who received MTM services compared to those who did not receive MTM services (i.e. non-MTM services). The economic outcomes examined in this study were direct healthcare expenditures

including pharmacy, medical and total expenditures. Cost savings and return on investment of MTM services were also evaluated. The second objective was to evaluate the impact of MTM services on clinical outcomes among patients with cardiovascular diseases. Clinical outcomes, in this study, included clinical parameters (lipid panel, blood pressure, and body mass index levels); the proportion of patients who achieved treatment goals for hypertension or body mass index; and the proportion of patients whose hypertension or body mass index stages have changed. In addition, to provide insights regarding specific interventions offered by pharmacists, this study explored types and frequencies of drug-related problems identified and assessed by pharmacists.

This chapter discusses the study's findings, limitations, and the implications of the findings as well as provides recommendations for future research.

Overview finding for economic outcomes

As hypothesized, the results suggest that there was a difference in economic outcomes among patients with cardiovascular disease who received MTM services and those who did not receive MTM services. In terms of difference within group, the mean direct cost (pharmacy, medical, and total expenditures) of the MTM group decreased statistically significant after the index date. Contradictory, the non-MTM group had a significant increase in the mean direct cost after the index date. The study also demonstrated consistent results across difference between groups. Compared with the non-MTM group, the MTM group had a significant decline in mean direct cost after the index date, indicating positive cost-saving. In addition to positive cost-saving, the results showed that the MTM services generated positive return on investment.

Overview finding for clinical outcomes

Although statistically significant improvements in both blood pressure and body mass index (BMI) were not found during the study period, participants in the MTM group demonstrated clinical significance in improving clinical outcomes on aspects of 1.) improving blood pressure and BMI at goal and 2.) positive changes in disease stages. In terms of improving blood pressure and BMI at goal, the proportions of participants at individualized blood pressure goal had been increased from 55% to 70% after being in the MTM program for 6 months. Similarly, 21.74 % of participants had their body mass index at goal (normal BMI), compared with 13.04% at baseline. Next, the MTM program demonstrated a positive trend of changes in disease stages. For instance, 30% of patients improved at least one stage of hypertension (e.g., from stage II to stage I). These findings were consistent with BMI. That is, approximately 22% of patients experienced improvements for one stage of BMI over baseline. Ultimately, none of them had declined to a progressive BMI stage.

To gain more insight into changes in disease stages, the study also examined changes by comparing the distribution of patients by stages of disease between the baseline and endpoint values. The results revealed that the stages of hypertension have changed statistically significant over the study period, indicating positive trend in improvement of disease stages.

The study also explored frequency of drug-related problem identified and resolved by pharmacists to characterize the nature of the problems in the MTM group. The majority was devoted to lifestyle modification required, patient recommendation required, need additional drug therapy, and cost effectiveness alert, respectively

Discussion and implications

In brief, the results of this study were consistent with previous studies in which comprehensive MTM services were provided. Also, the findings supported an impact of pharmacist-provided MTM services on improvements in economic and clinical outcomes.

One strength of this study was that it had an appropriate comparison group. The baseline characteristics of the two groups demonstrated no significant difference in age, diseases, the Charlson comorbidity index (CCI) scores, and number of medications by category. With respect to patient characteristics, the population in the MTM and the non-MTM groups were similar to the characteristics of the cardiovascular disease population of previous studies (Barnett, et al., 2009; Planas, et al., 2009). In this study, 87% of participants were aged less than 65 years with the mean age of 55.67 years, which represented a population focused on the middle age. For instance 86% of participants in the Minnesota Experience were age less than 65 (Isetts, et al., 2008). Also, participants in the Asheville project had the mean age of 50.4 years.

In terms of comorbidity, only a few studies take comorbidity into consideration or used comorbidity score when matching between the MTM and the non-MTM groups.(Stockl, et al., 2008) That is, they did not compare comorbidity scores between two groups nor control for its effects. Also, some study did not provide adequate information such as disease or medical condition (Barnett, et al., 2009; Chrischilles et al., 2004) or patient characteristics at baseline. (Isetts, et al., 2008)

Turning to sample size, while this study had a relatively small sample size (63 patients for the MTM and 62 patients for the non-MTM groups), it should be recognized that small sample size is quite common especially among studies that evaluated clinical

outcomes. Several studied had small sample size and less than 100 participants (Chrischilles, et al., 2004; Christensen, et al., 2007; Maack, et al., 2008; Planas, et al., 2009).

Discussion economic outcomes

The decrease in pharmacy, medical, and total expenditures from this study was similar to those previous studies regarding pharmacists-provided MTM services or health promotion programs, including the Asheville Project and the Minnesota Experience. (Bunting, et al., 2008; Isetts, et al., 2008) Generally, few studies have been performed pre-post design with comparison groups (i.e., the MTM and the non-MTM groups). Economic analyses were conducted among people with chronic diseases, including asthma, diabetes mellitus, or cardiovascular diseases. Pharmacists-provided MTM services resulted in statistically significant declines in pharmacy and/or medical expenditures compared with the non-MTM group (Bunting, et al., 2008; Maack, et al., 2008; Pindolia, et al., 2009) or compared with the pre-intervention period in the same group. (Isetts, et al., 2008)

The findings from the study revealed that total expenditures (pharmacy and medical claims) were reduced by 27.24% after the index date. When examined by type of claims, expenditures for patients in the MTM group were decreased 32.71% for medical expenditures. In contrast, medical expenditures of the non-MTM group increased by 63.73 %, resulting in an increase of 47.15% of total expenditures after the post-index date. However, it should be noted that the non-MTM group had demonstrated greater number of hospitalizations and emergency room visits than those in the MTM group at baseline (before the index date). Therefore, the increase in pharmacy, medical, and total

expenditures in the non-MTM group after the index date could be a result of worsening of medical conditions during the study period. However, both groups were similar in terms of comorbidity at baseline.

On the contrary, some studies with comparison groups indicated no significant differences observed in health care utilization or pharmacy expenditures among the MTM group between pre and post intervention. (Chrischilles, et al., 2004; Christensen, et al., 2007; Hirsch, et al., 2009) For example, a prospective cohort design of the Iowa Medicaid Pharmaceutical Case Management program with a comparison group and a 9-month follow-up period revealed no significant differences in terms of health care utilization or expenditures between two groups.(Chrischilles, et al., 2004) Another HIV/AID pharmacy MTM pilot program also reported increase in total mean annual health care cost (medical and pharmacy expenditures) and a greater number of refilled prescriptions in pilot MTM pharmacies compared with other pharmacies. These finding suggested that patients in MTM group may have received more comprehensive treatment and care such as treating side effects of medications or other conditions, resulting in higher expenditures after post-intervention period.(Hirsch, et al., 2009)

Turning to cost-saving, the study demonstrates the impact of pharmacist-provided MTM services on positive direct cost saving ($359.30 per person) and a net cost savings. This study also established results similar to previous studies. (Cote, et al., 2003; Johannigman, et al., 2010; Maack, et al., 2008; Pindolia, et al., 2009) Direct cost saving per patient ranged from $71.21-$290.60 and the duration of the studies were between 6 months to 12 months. The cost-saving from the MTM program is impressive considering that pharmacists did not just target toward the provision of generic substitution or

therapeutic alternatives, as is the approach of many MTM programs. In fact, more than one-fourth of the drug-related problems identified and resolved by pharmacists were related to needing additional medications.

The results in positive direct cost savings led to a positive return on investment (ROI) of the MTM program. The return on investment was used evaluate the efficiency of the MTM program. In this study, the ROI for the MTM services was 1.67, resulting in a return on investment of $1.67 per $1 in MTM cost per patient. The ROI exceeding one suggested that MTM services offer a positive financial benefit and are worthwhile to implementation. The findings from this study were consistent with previous studies which ranged from 0.12- 2.21. (Bunting, et al., 2008; Isetts, et al., 2008; Johannigman, et al., 2010; Maack, et al., 2008) However, one study conducted by Isetts and colleagues had been reported the ROI of 12.15 in the MTM group.(Isetts, et al., 2008)

Ultimately, the return on investment of 1.67 from this study also supported the need of providing health promotion and disease management program to employees. According to U.S. Department of Health and Human Services, these programs have generated a significant return on investment ranging from $1.49-4.91 in benefits. (U.S. Department of Health and Human Services, 2003)

Discussion clinical outcomes

This is the first study to measure body mass index as a clinical outcome parameter. According to the American Heart Association (AHA), body mass index is one of major risk factors of cardiovascular disease.(Roger et al., 2012). Therefore, it is important to take body mass index into consideration. Next, this study was the first

identifiable study to gain insight into changes in disease stages between pre-intervention and post-intervention by identifying number of patients and changes in disease stages compared with baseline value. Additionally, this study illustrated the changes in disease stages by comparing the distribution of patients by stages of disease between baseline and endpoint values.

Typically, it seems that existing studies with relatively larger sample size had demonstrated statistically significant reduction in some outcome parameters, including lipid panel (HDL, LDL, triglyceride, cholesterol), HbA_{1c}, blood pressure, and body fat. Although the differences between baseline and follow-up values of blood pressure and body mass index in this study were not statistically significant, the magnitude of differences appeared to be clinically significant in terms of achieving individualized goal and changes in disease stages.

In general, the population in the MTM and the non-MTM groups were similar to the cardiovascular disease populations of the previous studies. That is, the participants were derived from a general population of patients and did not specifically focus on patients with poorly controlled condition. In this study, 55% of participant in the MTM group had their blood pressure controlled at baseline (i.e., SBP/DBP < 140/90 mmHg for those with hypertension and SBP/DBP<130/80 mmHg for those with hypertension and diabetes or chronic kidney disease). Similarly, the Minnesota experience study conducted by Isetts and colleagues reported that 59% of individuals with hypertension had their blood pressure under control at baseline (Isetts, et al., 2008). Also, the results from the Asheville project indicated that 40.2 % of patients had blood pressure at goal before the study intervention.(Bunting, et al., 2008) Similarly, the percentage of patients with

overweight and obese was approximately 90% at baseline which was consistent with the previous study conducted by Planas and colleages (Planas, et al., 2009)

In terms of attaining blood pressure goal, the results demonstrated that after participating in the MTM program, 70% of patients had their blood pressure under control (compared to 55% at baseline). These MTM services offered by PCC were remarkably successful in achieving the Healthy People 2020 objectives and better than the national average.(Roger, et al., 2012) According to Healthy People 2020, one of the objectives for heart disease and stroke is to increase the proportion of U.S. adults with hypertension whose blood pressure is under control from 43.7% to 61.2%.(the U.S. Department of Health and Human Services, 2010) In addition, only 48% U.S. adults with hypertension have achieved optimum blood pressure control.(Roger, et al., 2012)

With respect to changes in disease stages, this study was consistent with previous studies which demonstrated a positive trend toward changes in disease stages for blood pressure. For example, this study is comparable with the results found in the Asheville project by Bunting and colleagues who reported improvement in percentages of patients with blood pressure reading in the hypertension stage I and II. (Bunting, et al., 2008).

Departing from previous MTM studies, this study also identified number of patients and changes in disease stages from baseline (i.e., improved 1 stage, improved 2 stage, no change, decreased 1 stage) to examine the impact of pharmacist-provided MTM services on improvements in blood pressure and body mass index stages. In addition to changes in disease stages, this study illustrated the changes by comparing the distribution of patients by stages of disease between the baseline values and the end-point values. The

findings from the study supported improvements in disease stages for blood pressure and body mass index, after 6-month follow-up of MTM program.

As mentioned earlier, this study also measured body mass index as one of clinical outcome parameters. This MTM program was remarkably successful in achieving the Healthy People 2020 objectives and better than the national average.(Roger, et al., 2012) According to healthy people 2020, one of the objectives for nutrition and weight status is to decrease the proportion of U.S. adults who are obese to 30.6 %.(the U.S. Department of Health and Human Services, 2010) In this study, 26% of patients were obese after being in the MTM program (compared to 39.13% before the MTM program).

Turning to drug-related problems, pharmacists identified and assessed a total of 143 drug-related problems during 6-month follow-up period with an average of 2.26±1.23 (mean±SD) per patient. Typically, the frequency and type of drug-related problems reported in this study were consistent with the previous studies in which comprehensive MTM services were provided within the practice of pharmaceutical care. That is, the previous studies had ranged from 0.8-3.9 per patient for the 6-24 month follow-up period and conducted in community-based pharmacies, ambulatory clinics, or hospital-based settings. (Barnett, et al., 2009; Christensen, et al., 2007; Doucette, et al., 2005; Isetts, et al., 2008; Maack, et al., 2008).

Some MTM studies targeted at medication safety and health care utilization have demonstrated no significant differences in health care utilization and expenditures between the MTM and the control groups. (Chrischilles, et al., 2004; Christensen, et al., 2007). Nevertheless, the types of intervention included in MTM in this study were

consistent with those reported in several previous studies in terms of 1.) providing patient education and self-care, 2.) ascertaining patient's goal of treatment, and 3.) identifying and assessing the most common drug-related problems identified by pharmacists during MTM services, including underuse of medication (i.e. need additional drug therapy), the available of a more cost-effectiveness medication (i.e. cost effectiveness alert) and suboptimal drug use due to side effects. (Barnett, et al., 2009; Christensen, et al., 2007; Maack, et al., 2008; Pindolia, et al., 2009)

As a result, the findings from this study support the evidence that pharmacist-provided intervention have a potential impact on health expenditures by identifying and assessing drug-related problems. According to an Omnibus Budget Reconciliation Act of 1990 demonstration project, community-based pharmacist interventions generated drug therapy changes in 28% of the identified drug-related problems, resulting in drug cost savings. (Smith, Fassett, & Christensen, 1999) Also, Barnett and colleagues indicated that pharmacist-provided MTM services could prevent drug related problems and resulted in significant cost-saving by ensuring that patients have other options such as appropriate generic substitution or therapeutic alternatives.(Barnett, et al., 2009)

Ultimately, the findings supported the impact of pharmacist-provided MTM services proposed by the American Pharmacist Association (APhA) in that the MTM program will help improve therapeutic outcomes, reduce drug-related problems, and reduce healthcare costs.(American Pharmacists Association, 2004).

Implication of the study

This study examined economic outcomes and clinical outcomes in order to evaluate the impact of MTM services in patients with cardiovascular disease. This study was the first known study to examine changes in disease stages in the aspects of improvements and distribution of changes between pre-intervention and post-intervention in addition to measuring the proportion of patients who achieved blood pressure and body mass index goal. This thesis makes significant contributions to three main areas: 1.) self-insured employers, 2.) policy makers, and 3.) pharmacy practice. This section discusses study finding and implication in each of these specific areas.

Self-insured employers

Employer-based insurance accounts for 55.8% of major population of health insurance coverage in the U.S. (National Center for Health Statistics, 2011). Continually rising healthcare spending causes concerns to self-insured employers. The findings from this study can inform self-insured employers of the value of pharmacist-provided MTM. Self-insured employers may use this information to justify why pharmacist-provided MTM services should be part of their healthcare benefits to their enrollees as a way to address the rising cost concern.

For instance, self-insured employers may use the results regarding cost-saving and the positive return on investment from implementing the MTM and make informed decisions regarding the inclusion of MTM services in their benefits. That is, they will assure that they could utilize financial resource and generate benefits through the investment in MTM programs. Additionally, positive impact of pharmacist-provided MTM services may impact self-insured employers' perceptions of indirect cost-saving

advantages in a manner that could help employees become healthier, improve productivity and reduce absenteeism.

Policy makers

This study emphasized consistency and benefits of pharmacist-provided MTM services to patients. The study provided a framework for optimizing patient therapeutic outcomes while assuring cost-saving of the treatment through the MTM program. Currently, policy makers often have a few clearly defined standards of practice, service level expectations, and limited data on outcomes derived from MTM programs. The findings from this study were meaningful as they show positive impact of pharmacist-run MTM services in improving patient outcomes.

For instance, the findings from this study successfully achieved beyond national objectives with respect to improving the proportion of patients at blood pressure goal and reducing the proportion of U.S. adults with obesity. Further, drug-related problems assessed by pharmacists were an example of how pharmacists can provide a rational medication use system for health care setting. Consequently, this study could provide significant evidence to policy makers in order to endorse the use of MTM programs as part of various public-sponsored benefit programs. This will be one of crucial factors for achieving the National Healthy People 2020 objectives for cardiovascular disease.

Pharmacy practice

Recently accountable care organizations have shifted payment incentive to value-based reimbursement. In other words, compensation is based on performance benchmarks. Consequently, health care providers need to start improving care with lower costs and receive shared savings payment incentives, accordingly. Therefore, pharmacy

managers or practitioners may use this evidence to assist them in the development of plans that will integrate pharmacists' role into MTM services and be recognized by other health care professionals as well as patients. For example, pharmacy managers may choose to use the information in terms of positive impact on economic and clinical outcomes to encourage community pharmacists and/or ambulatory pharmacists to participate in MTM services. That is, pharmacists could help reduce health care expenditures and promote patient achieved goal of therapy. Further, practitioners may use changes in disease stages to evaluate clinically meaningful significance regarding improvement in disease stages of hypertension or body mass index and present potential clinical benefits to patients or physicians.

Turning to impact of pharmacist on medication safety and rational medication use, pharmacy managers or practitioners can use the findings of drug-related problems assessed by pharmacists to determine drug therapy problems or cost-effectiveness alert in their community-based or ambulatory-based settings. This is important because several studies on drug-related problems have been conducted in hospital settings.

It is anticipated that the number of pharmacists needed to provide medication therapy management will range from 30,000 to 100,000 to serve the U.S. population. (Isetts, 2012). Therefore, schools and colleges of pharmacy may use data and information on the outcomes of MTM services provided in this study to support a necessity to offer a continuing education program or a certificate training program in delivering MTM services, which may help to facilitate post-graduated pharmacists in providing MTM as a systematic patient care process. Therefore, those post-graduated pharmacists will have opportunities to acquire more in-depth information and rigorous core elements of MTM

programs. Eventually, those consequences could enhance pharmacists' clinical expertise and provide more comprehensive pharmaceutical care to patients in long term with confidence.

Future research

Further study is needed to evaluate the impact of drug therapy changes suggested by pharmacists on clinical outcomes or economic outcomes, particularly indirect cost. Additionally, although a 6-month timeframe provides a reasonable length of time to determine a trend of an impact of an MTM program on economic and clinical outcomes, future research may consider using longitudinal design to demonstrate whether this trend is sustainable or not. Further, future research needs to demonstrate humanistic outcomes, including quality of life of employees. Finally, further studies of pharmacist-provided MTM services are required to determine the impact of this program on patient adherence.

Limitations

A number of limitations in this study should be noted. The following section describes these limitations with respect to the study design, data collection methods, and generalizability of the findings.

Study design and data collection method issues

The first limitation of the study design was that it was a non-randomized control study. Patients' self-selection to participate in the MTM program could increase the potential for selection bias. That is, patients who were more proactive and engaged in their own health might tend to seek MTM services compared with those in the non-MTM group. Also, physicians may have induced a selection bias because they may have

encouraged patients who had complex drug regimens to receive MTM services from the PCC clinic. This selection bias may affect the results in a favorable way for the MTM group. To minimize a potential selection bias, the researcher randomly selected the comparison group using matched-pair method based on sex, age category, and the Charlson Comorbidity Index (CCI) score. Using this technique, characteristics of the two groups were generally comparable. However, it should be noted that there was a slightly difference in the CCI scores between MTM and the non-MTM groups (1 vs. 0.90). Therefore, the MTM group, which had higher CCI score, may have different co-morbid conditions compared with the non-MTM group. This issue may influence health care expenditures in the MTM group.

The next limitation was inherent in the nature of retrospective analyses. The accuracy of pharmacy and medical expenditures used in the analysis depend on how claims and codes were billed for each patient. In order to mitigate this problem, the researcher had verified for the accuracy of data by sampling some claims from enrollees. For example, the researcher corrected the actual decimal point of dollar amount in pharmacy claims, eliminated duplicate medical and pharmacy claims data, and adjusted some missing data in eligibility claims data by writing a program to make the corrections in the SAS data set.

Another limitation was related to the lack of data when physicians dispensed drug samples to patients in the physician office. The use of drug samples may affect pharmacy expenditures because patients received drug samples to help decrease their financial burden instead of filling their prescriptions. Further, we were unable to track those

patients who bought their medications over-the-counter (OTC) such as aspirin. Therefore, these limitations might underestimate pharmacy expenditures.

The next limitation was related to missing data and a small sample size for both MTM and the non-MTM groups. Of 122 MTM patients, only 63 patients met the inclusion criteria for the economic analysis and only a small portion of them were included for further clinical outcomes analysis. This issue raises potential concern because of a small sample size may reduce the power to detect a statistically significant outcome. Consequently, statistical analysis for lipid panel variables (HDL, LDL, TG, and cholesterol) could not be performed because relatively small sample size.

In addition to the economic analysis, the clinical analysis was subject to some limitations. Because clinical data were retrieved from an electronic medical record (EMR) database, we were unable to use other sources of patient records (e.g., paper form) to gain additional information about any missing clinical parameters for any patients. Attempts had been made to retrieve patient information from supplemental documents that had been scanned and attached on the patient profile. However, only few patients had those scanned document on their profiles.

Also, an adjustment for baseline covariates such as demographic variables (e.g., age, CCI score) was not included in the clinical analysis. This issue may have an influence on outcomes in terms of the association between the covariate and clinical outcome variables. As a result, a study with unadjusted covariates may provide less efficient estimates of treatment effects and result in different interpretations or conclusions compared with a study with adjusted covariates.

Further, one possible issue which may have contributed to the bias is that MTM services may not be the same across all pharmacists and all patients included in the analyses. This is because the pharmacy residents might have different experience in performing a medication review or interviewing skills compared with the staff pharmacists. Therefore, there might be some variation in terms of the detection and assessing of drug-related problems between pharmacy residents and staff pharmacists. For instance, some pharmacists might detect more drug-related problems than others.

Finally, an issue of judgmental bias from reviewing cases to determine the type and frequency of specific interventions might be a concern. Although pharmacy residents and staff pharmacists had identified and reported drug-related problems in patient assessments, this information was narrative report. In other words, the patient assessments did not clearly define the type of drug-related problems when they described patients' problems. Therefore, the identification of drug-related problems was based on judgment or clinical experience of the researcher who reviewed patient records. The researcher minimized this potential bias by utilizing a structured guideline which provides comprehensive definitions of drug-related problems.

Generalizability

The study population was employees and their dependents who enrolled in a university-based insurance plan which may limit the generalizability of the study findings to other populations, other setting, or other MTM services. Fist, the findings of MTM services were reflective of characteristics of patients such as their disease status, age, comorbidity, or number of medication regimen. Therefore, this study may not be generalizable to other populations that have differences in the characteristics of patients.

For instance, the mean age of patients in this study was 56 years, which resulted in a population focused on the middle age. Hence, results of this study may not be generalized to elderly patients

Another potential issue is related to the setting. The population, particularly the MTM group, received MTM services from staff pharmacists and residents at a clinic in a pharmacy school setting. As a consequence, this setting has already been affiliated with advanced pharmacy practice skills and experience. Also, these health care professionals are available to provide their effort and time in assessing patient medication regimen. Also, these findings reflect the pharmaceutical practice provided by one pharmacy. It is more likely that different findings could be identified from a broader set of practices. In other words, differences in pharmacy practices, health system effects, or collaboration with physicians could generate different results.

Further, the accessibility to the setting or to the service may be one of barriers if patients have to travel for a certain time to receive MTM service. The PCC clinic is located on campus so it is convenient for patients to access the service. Therefore, generalizing the study findings to other self-insured employers or other community pharmacies where accessibility to the service is an issue would be limited.

Next, the findings of this study were based on a face-to-face MTM service personally delivered by pharmacists. It may not be generalized to 1.) MTM services for cardiovascular disease with different delivery methods (e.g., telephonic interaction, mail intervention, or interactive video) and/or 2.) a face-to-face MTM service for cardiovascular disease with other qualified health care practitioners (e.g., nurses). For example, a study using telephonic approach revealed no statistically significant difference

between the MTM and the control groups in terms of pharmacy expenditures, compared with the baseline. (Moczygemba et al., 2011)

Finally, generalizing the findings to other MTM services (e.g., asthma disease) should be made carefully. The reason is because different diseases might require distinct sets of services in terms of patient education and information activities. Hence, generalizability of the findings beyond a similar setting or different type of population should be done cautiously.

Conclusions

This study was the first known study to examine the aspects of changes in disease stages of hypertension and body mass index. This study evaluated impact of MTM services on economic and clinical outcomes. The findings provided evidence that MTM services statistically reduced pharmacy and medical expenditures compared with the non-MTM group. Further, MTM services demonstrated clinical significances in terms of achieving goals and improving disease stages. Finally, this study supported the role of pharmacists in identifying and addressing drug-related problems which leads to patient medication safety as well as effective and appropriate use of medication.

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Appendix A

Table A1.

General study information of the included studies

Author	Patient population	Perspective	Design	Setting	Intervention	Data source	Time horizon
1. (Cranor, et al., 2003)	Diabetes	Payer: Self-insurer	Pre-post study	Self-insured Community pharmacy	Consultation, education, physical assessment, lipid management	1.Demographic data: -enrollment questionnaire -medical record 2.Clinical data: -lab reports 3. Direct cost : -insurance, medication record, medical claim, employer records	4 years and 9 months
2. (Doucette, et al., 2005)	Taking ≥4 medications, targeted diseases	Payer: Medicaid	Retrospective Observational study	Medicaid pharmaceutical case management (state level)	MTM services face-to-face (encounter ≥ 1 time in 2 years otherwise every 3 months)	1.Patient record 2. Database	2 years

3. (Bunting & Cranor, 2006)	Asthma	Payer: Self-insurer	Pre-post study	Self-insured Community pharmacy and hospital clinic	MTM services face-to-face ~ 30 min every 3 months	1.Demographic data: -enrollment questionnaire -medical record 2. Clinical data and humanistic data: -lab, questionnaire 3. Direct cost: -Medical record, insurance, prescription claim, employer records 4. Indirect cost: -calculation based on self-report data	5 years
4. (Chisholm, et al., 2007)	Renal transplantation	Health care providers	Pre-post study	University hospital-based	MTM services face-to-face	1.Demographic data: -medical and pharmacy records 2.Clinical data: patients' medical records 3.Humanistic data: Questionnaire, SF-12 Health Study, version 2.0	2 years (before and after enrollment)

5. (Christensen, et al., 2007)	HTN, diabetes, cardiovascular disease, and lipid disorder	3rd payer: State health plan	Prospective, Pre-post design with comparison groups (MTM and control)	Community pharmacies and an ambulatory care clinic	MTM services: Face-to-face 30-60 mins	1.Demographic data -Medical claim 2.Drug therapy problem -Medical and pharmacy claims -Pharmacy medication review 3.Change in the cost of drug therapy associated with MTM - Medical and pharmacy claims -Pharmacy medication review 3.Patient satisfaction -survey	
6. (Bunting, et al., 2008)	HTN and or dyslipidemia	Payer: Self-insurer	Pre-post study	Self-insured Community pharmacy and hospital clinic	MTM services face-to-face ~ 30 min every 3 months	1.Demographic data: -enrollment questionnaire -medical record 2. Clinical data and humanistic data: -lab, questionnaire 3. Direct cost: -medical record, insurance,	6 years

						prescription claim, employer records 4. Indirect cost: calculation based on self-report data	
7. (Isetts, et al., 2008)	HTN and or dyslipidemia	3rd -party payer: BlueCross BlueShield	Retrospective, Pre-post study	Primary care clinics	MTM services face-to-face group vs. non MTM group Initial and one or more follow-up	1.Patient medication record 2.Database	1 year
8. (Maack, et al., 2008)	-Chronic diseases, 50.9% are cardiac disorder -Elderly patients	Health care provider	Prospective, observational study	Living facility-based	MTM services: Face-to-face~30-60 mins	1.Direct saving from recommendation made by pharmacy residents -patient's medical record -online prescription drug pricing database 2. Recommendation acceptance data –data collection sheet	6 months

9. (Stockl, et al., 2008)	Patients with diabetes or coronary artery disease	3rd party payer: pharmacy benefit management (PBM)	Prospective with comparison groups (MTM and control)	Pharmacy benefit management (PBM)	Mailing method (educational booklet)	1.Demographic data: -medical claims data -member-reported questionnaire 2.Major cardiovascular events and the coronary events cost avoidance: -medical and pharmacy claims data	1 year
10. (Fox, et al., 2009)	Diabetes	3rd party payer: Health maintenance organization (HMO)	Retrospective, quasi-experimental study with comparison groups (MTM and control)	Health maintenance organization (HMO)	MTM services: Telephone 10-30 mins (~3 times/year)	1.Demographic data: -pharmacy and claims data 2.Clinical indicators -health plan's vendor 3.Cost -Plan's pharmacy database	21 months
11. (Hirsch, et al., 2009)	HIV	Health care providers	Cohort study Pre-post with comparison group (MTM and non MTM)	Community pharmacy (pilot pharmacy VS. others)	pilot (MTM services face-to-face) vs. other pharmacy	1.Medi-Cal pharmacy 2.Medical claims data	2 years (pre=1, intervention=1)

12. (Pindolia, et al., 2009)	≥2-3 chronic diseases , ≥4 part D covered medications, tend to incur≥$4,000 in total cost	Plan sponsor	Retrospective Cohort study with comparison group (MTM and control)	Plan sponsor	MTM services: Telephone call ~45 minutes	1.Demographic data -medical record -prescription claims database -primary care physician's office 2.Adherence -prescription claims database 3.Cost-saving analysis -medical record -prescription claims database	2 years
13. (Planas, et al., 2009)	Hypertension and diabetes	Health care provider	Prospective, Randomized controlled trial	Community pharmacies	MTM services: Face-to-face	1.Demographic data -MCO database 2.Blood pressure -during patients received care at community pharmacies 3. Medication adherence -pharmacy claims data	9 months

14. (E. K. Welch, et al., 2009)	≥2 chronic diseases , ≥5 part D medications, incur≥$4,000 in total cost	3rd party payer: Health maintenance organization (HMO)	Quasi-experimental with comparison group (MTM and control)	Health maintenance organization (HMO)	MTM services: Telephone management group	1.Electronic medical databases 2.pharmacy and administrative databases 3.Manual medical chart reviews	6 months
15. (Barnett, et al., 2009)	General	Payer: Plan sponsor	Retrospective Observational study	Community pharmacy that have contracted with drug plan sponsors	MTM services: Face-to-face	1.Demographic data 2.Descriptive data (e.g, no. of MTM, characteristic of intervention) 3.drug and type(drug therapy problems) 4. Estimated Cost Avoidance [ECA]) Extracted from: MTM claim database from multi state MTM administrative service company	7 years
16. (Johannigman, et al., 2010)	Diabetes, hypertension, asthma, hyperlipidemia	Health care provider	Observational study	Community-based employer	MTM services face-to-face~30 min up to 4 sessions/year	1.Database: -demographic data -medical record -lab reports 2.Pharmacy Intervention	1 year

						Software 3.Published reference Indirect cost	
17. (Moczygemba, et al., 2010)	Beneficiaries ≥ 2 medications, ≥ chronic diseases, Part D medication costs ≥$1,000 per quarter	Plan sponsor	Cross-sectional study	Plan sponsor	MTM services Telephone intervention	1.Demographic data: -patient's electronic chart -during the MTM consultation - questionnaire 2.Patient satisfaction -mail survey questionnaire	N/A
18. (Ramalho de Oliveira, et al., 2010)	General (but mainly focus on diabetes)	Payer: Medicare	Retrospective Observational study	Network of hospitals, primary care clinics, specialty clinics, community pharmacies	MTM services face-to-face 60 mins (initial) then 30 mins (follow-up)	1.Demographic data 2.Descriptive data (e.g, , no of medication) 3.Types of drug therapy problems 4.Types of interventions 4.1change in clinical status 4.2pharmacist-estimated health	10 years

						care saving Extracted from: MTM documentation system (Assurance System)	

Table A2.

Outcome measures

Author	Clinical	Economic	Cost elements	Humanistic	
				Patient satisfaction	**Quality of life**
1. (Cranor, et al., 2003)	1.Change from baseline values for HbA1c, LDL-C(<100mg/dl), HDL-C(>45mg/dl), (measure at based line and follow up every 6 months) 2.Adherence (questionnaire)	Cost of saving	Direct cost: Amount paid by employer for 1. Physician visit 2. Hospitalization 3. ER visits 4. Lab testing 5. Prescription drug 6. Diabetes supplies 7. Cognitive pharmaceutical care service 8. Educator fees 9. Co-payment wavier	No	No
2. (Doucette, et al., 2005)	Resolves in Drug-related problem (% physician acceptance) Adherence Indication (need for additional therapy, unnecessary therapy) Safety (ADR, dose too high) Effectiveness	No	No	No	No

	(wrong drug, dose too low)				
3. (Bunting & Cranor, 2006)	1. Changes in forced expiratory volume in 1 second(FEV1), asthma severity, symptom frequency, proportion of patients with asthma action plan 2.Changes in Asthma care events (ER visit, hospitalization)	Cost of saving	Direct cost: Amount paid by employer for 1.Physician visit 2.Hospitalization 3.ER visits 4.Lab testing 5.Prescription drug 6.Pharmaceutical care service 7.Educator fees 8.Co-payment wavier Indirect cost: Cost to the employer of lost work hours due to absenteeism and presenteeism	No	YES (functional status)
4. (Chisholm, et al., 2007)	1.Change in mean ± SD of number medication use: antidiabetic, antihypertensive, antilipemic 2.Change in mean ± SD of -FBG -HbA1c -LDL-C -Total cholesterol -TG -SBP/DBP -Achieved target serum tacrolimus level and	No	No	No	YES Questionnaire regarding functional status, well-being, perception of health status SF-12 Health Study, version 2.0

	cyclosporine level -Graft rejection				
5. (Christensen, et al., 2007)	Potential drug therapy problems: Types, frequency, service performed	1.Difference in number of prescriptions 2.Difference in number of drug costs	Change in cost and number of drug therapy associated with MTM	YES	No
6. (Bunting, et al., 2008)	1.Hypertention : change in mean blood pressure 2.Dyslipidemia :change in -mean total cholesterol -mean LDL-C -mean TG (measure at based line and follow up every 6-12 months) 3.%patients at the goal of each parameter 4. CV events (pre-post) -MIs, non-MI acute coronary syndrome, hypertensive crisis, acute heart failure, coronary artery bypass grafts, transient ischemic attack and other	Cost of saving	Direct cost: amount paid by employers' health plan for 1.CV-related medical costs, procedure or services 2.Doctor-fee 3.ER visits 4.Hospitalization 5.Prescription 6.MTM services 7.Lab testing 8.Educator fees 9.Co-pay waiver	No	No

7.	(Isetts, et al., 2008)	1.% patients achieving goals of therapy 2. % number of drug therapy problems resolved 3.% quality-of-care performance	Cost-Benefit Analysis (ROI)	1.Professional(medical) claim 2.Prescription claim -facility claim	No	No
8.	(Maack, et al., 2008)	No	1.Direct cost saving 2. Cost-benefit analysis 3.Return on investment	Direct cost saving recommendation = difference in dollar amount between the original drug therapy and the recommended drug therapy	No	No
9.	(Stockl, et al., 2008)	No	Cost-avoidance	1.The number of patients interventions necessary to prevent 1 major cardiovascular events 2. The coronary event costs avoided by the intervention	No	No
10.	(Fox, et al., 2009)	1.LDL-leve 2.LDL-C at goal (<100mg/dL)	1.Difference in Number of prescriptions per month 2.Difference in total cost expenditures (2006 vs. 2007)	Cost expenditures: 1.Total Medicare Part D drug cost (copay + insurance drug costs + dispensing fee) 2.Enrollee out-of-pocket costs 3. Total medication copayment (PartD and non-PartD)	No	No

11. (Hirsch, et al., 2009)	1.ART regimen strategies 2.Rates of adherence and excessive fills 3.Use of contraindicated ART regimens 4.Occurrence of opportunistic infections 5.Pharmacy and medical cost	Compare total cost	1.Total medication cost 2.ART medication cost 3.Non-ART medication cost (1-2) 4.Medication costs: -hospitalization -ER visits -Mental health -Lab testing -AIDS Waiver program	No	No
12. (Pindolia, et al., 2009)	Clinical indicators: 1.Gastrointestinal 2.LDL-C<100mg/dL 3.Adherence to ACEI 4.Adherence to β-blocker 5.HbA1c<7% 6.Insulin use	Cost-saving analysis	1.Medical cost 2.Drug cost	YES (mail survey questionnaire)	No
13. (Planas, et al., 2009)	1.Difference in blood pressure between MTM and control: -SBP levels -percentage of patients at goal blood pressure 2.Differece in antihypertensive medication adherence between MTM and control	No	No	No	No

14. (E. K. Welch, et al., 2009)	1.Primary outcome: all cause mortality 2.Secondary outcomes: %of hospitalizations, ED visits, potential drug related problems	Secondary outcome: cost of Part D covered medication	-medication cost per day	No	No
15. (Barnett, et al., 2009)	No	Cost of saving (based on self-report)*	Estimate Cost Avoidance (ECA) derived from average national health care utilization costs -cost of avoided physician visit -cost of avoided emergency room -cost of avoided hospital admission	No	No
16. (Johannigman, et al., 2010)	% Change in -mean LDL-C -mean HDL -mean TG -mean HbA1c -%patients at HbA1c goal(<7%) -body fat -% patients who lost weight	Cost-Benefit Analysis (ROI)	Direct cost saving: 1.Medication therapy changes recommended by pharmacists (brand-to generic; conversion within therapeutic classes; brand-to-brand conversion) 2.Reduce co-pay Indirect cost saving: Estimated from pharmacy intervention software and published reference	YES (on-site questionnaire)	No
17. (Moczygemba, et al., 2010)	No	No	No	YES (mail survey questionnaire)	No

18. (Ramalho de Oliveira, et al., 2010)	1.% patients reaching treatment goal - HbA1c <7% -mean blood pressure<130/80mmHg -mean LDL-C<100 mg/dl -daily aspirin use -tobacco-free status	Cost-Benefit Analysis (ROI)	<u>Direct saving:</u> medical service avoided (from intervention) As following: -clinic outpatient visit avoided -Specialty office visit avoided -Employee work days saved ($30*8) -Laboratory service avoided -ER visit avoided -Hospitalization avoided -Nursing home admission -Home health visit -Total health visit	YES(mail survey questionnaire)	No

Table A3.
Results

Author	Clinical outcomes	Economic outcomes	Humanistic outcomes	Note
1. (Cranor, et al., 2003)	1.Improved in mean HA1c 2.Patients reach therapeutic goals (HbA1c, lipid panel levels)	1. Cost shifted from services to medication(Decrease in cost of services but increase in cost of medication) 2. Reduce in total mean direct medical costs (decrease by $1,200 to $1,872) 3. Increase in estimated productivity $18,000 per year	No	Found relationship between outcomes improvements (clinical and economics) and MTM
2. (Doucette, et al., 2005)	1. Total 886 of drug-related problems were identified. 2. Physicians accepted pharmacists' intervention 47.4% of the recommendations.	No	No	MTM program address drug-related issues and may enhance drug therapy in patients with chronic diseases in ambulatory setting via collaboration between pharmacists an physicians.
3. (Bunting & Cranor, 2006)	1.Improved asthma severity (70%) 2.Decrease in asthma events (decrease in ER visits from 9.9 to 1.3%; hospitalization from 4.0 to 1.9%	1.Decrease overall asthma-related costs 2.Direct/indirect cost saving were $725/$1,230 per patient per year 3. Indirect cost due to absenteeism decrease from 10.8 to 2.6days	Improve quality of life	No

4. (Chisholm, et al., 2007)	1.Significantly increased in numbers of medication use compared with pre-enrollment 2. Improved in overall clinical indicators: Reduction in FBG, HbA1c, LDL cholesterol, total cholesterol, triglycerides, blood pressure, and number of graft rejections compared with pre-enrollment ($p < 0.01$) 3.Improved in number of patients achieved target serum cyclosporine level compared with pre-enrollment ($p = 0.008$)	No	Improvement in Health related quality of life after one year post-enrollment ($p < 0.01$).	-Continuing treatment of hypertension, dyslipidemia, and diabetes is essential for patient survival -Lack of comparison groups due to study design (retrospective)
5. (Christensen, et al., 2007)	For MTM group only 1.Pharmacists identified an average of 3.6 potential drug therapy problems per patient 2. Most common potential drug therapy problems are potential	1. There is no significant difference in reduction in number of prescriptions in MTM group after post intervention. In contrast, control group has shown statistical significant results. 2. There is no significant	>90% of respondents agreed or strongly agreed with MTM services	The only one study that uses propensity scores among included studies.

	under use and more cost-effective available 3.An estimated 50% of patients with drug therapy problems had a change in drug therapy recommended by pharmacists	difference in reduction in prescription costs in pre and post index (both MTM and control groups)		
6. (Bunting, et al., 2008)	1.Improved in cardiovascular indicators (BP, lipid panel levels) 2.Reduction in cardiovascular rates from 77 to 38 per 1,000 person-year 3. Decrease in cardiovascular-related ER visits and hospitalizations	1.Increase in medication usage three times 2Cardiovascular-related medication costs decrease from 30.6 to 19% 3.Mean cost per cardiovascular event decrease from $14,343 to $9,931	No	-Medication usage increase three times but, cardiovascular/cerebrovascular medical-related cost decreased by 46.5% -There was no comparison group to compare trends in utilization against MTM group
7. (Isetts, et al., 2008)	1.%Patients'goals of therapy achieved increased from 76 to 90% 2.637 drug therapy problems (DRPs) were resolved 3. Improved in quality-of-care performance (intervention group compared with control):	1.Total health expenditures decrease from $11,965 to $8,197 2.A return on investment (ROI) of $12.15 per1$ in MTM group	No	-MTM groups were more likely to achieve treatment goals of hypertension and hyperlipidemia -Although expenditure decreased in MTM group, it is doubtful if the decrease was higher than a comparison group

	-hypertension: 71 vs 59% -hyperlipidemia: 52 vs 30%			
8. (Maack, et al., 2008)	No	1.Direct cost saving total=$3774 2.Net cost-benefit=$1550 3.Benefit-to-cost ratio 1.7 4. ROI=70%	No	1.The study indicates the positive drug-related cost-benefit 2.The study also shows the promising drug therapy acceptance by primary provider 3. There was no comparison group
9. (Stockl, et al., 2008)	No	1.Intervetnion members had higher number of statin initiation compared with control group (12.1vs.7.3%), p<0.001 2.The estimated coronary event costs avoidance is $12,323 per 220 intervention members	No	1.Study focused on economic outcomes only 2. Study measure cost of statins only but not other actual costs (e.g., medical costs/lab test) 2. Study did not have a similar comparison group in term of demographic data
10. (Fox, et al., 2009)	1.MTM group has a higher proportion of LDL<100 mg/dL compared with control group (p<0.001)	1.MTM group has greater percentage cost reduction than control group	No	1.The study only described changes in the economic indicators (costs and number of prescriptions) without evaluating cost-benefit analysis 2.The study is lack of baseline of the clinical outcomes indicators

11. (Hirsch, et al., 2009)	1. Maintain protease-inhibitor-based ART medication regimen (MTM vs. control:63.8 vs. 54.8%) 2. Improved in adherence rate (56.8 vs. 34.2%) 3.Fewer used contraindication regimen (11.6 vs. 16.6%) 4.Fewer excess refill in MTM group	1. 10% higher total mean annual health care cost in MTM pharmacy compared with control ($40,596 vs. 36,937)	No	1.Rising in total cost originated mainly from non-ART medication and mental health service 2.Patients received more appropriate HIV treatment in the pilot pharmacy compared with control
12. (Pindolia, et al., 2009)	1.MTM group had higher adherence rate, improve in clinical indicator, and lower gastrointestinal bleed (p=0.001)	1.A greater reduction in total prescription per patient per month (MTM vs. non-MTM: 17.2% vs. 7%), (p=0.001)	High patient satisfaction (>95%)	1.MTM group demonstrated a sustained positive effect in reducing drug cost, but not medical cost in 2007 2.Study did not clearly define what medical costs are
13. (Planas, et al., 2009)	1.MTM group has higher reduction in mean systolic blood pressure than control group (17.32 vs. 2.73 mm Hg, p=0.003) 2.MTM group has 12 times higher percentage patients achieved goal than control group	No	No	Only one study using RCT

	(p=0.021) 3.There is no statistically significant difference between MTM and control group in term of medication adherence			
14. (E. K. Welch, et al., 2009)	1.MTM group had a lower mortality compared with control group: (OR 0.5 vs.1.4) 2.MTM group had an increase in hospitalization events> control group (OR 1.4) 3.No relationship between MTM and control group vs. ED visits	1.MTM group tended to have a %increase in medication costs > control group(OR 1.4) 2.No difference in medication cost/day between group (MTM or control) 3. No relationship between group (MTM or control) and medication cost/day	No	1.The reduction in mortality of MTM group may resulted from -the identification and resolution of potential DRPs from pharmacists -patients have better understanding
15. (Barnett, et al., 2009)	No	1.Mean pharmacist-estimated cost avoidance (ECA) over 7 years was $93.78 per claim (increase from $24.18 to $429 from 2000 to 2006) 2. Mean pharmacy reimbursement over 7 years was $8.44 per claim	No	Mean estimated cost avoidance higher than the pharmacist reimbursement for MTM

16. (Johannigman, et al., 2010)	1.Improved in overall clinical indicators (reduction in LDL level, reach HbA1c goal, reduction in% body fat)	1.Total cost saving to companies averaged$1011 per patient per year 2. .ROI was $2.21 every $1 invest	High patient satisfaction (4.8 of 5.0)	Indicated sustainable business model due to favorable total net revenue and gained margin
17. (Moczygemba, et al., 2010)	No	No	High patient satisfaction (4.0 of 5.0)	-Most of participants were satisfied with pharmacist-provided telephone MTM
18. (Ramalho de Oliveira, et al., 2010)	1.Improved in % patients achieving clinical goal (55% improvement)	1.Pharmacist-estimated cost savings were$ 2,913,850 ($ 86 per encounter) 2. Total cost of MTM services was $2,258,302 ($ 67 per encounter) 3.Return on investment (ROI)of $1.29 per $1 in MTM administrative costs	95.3%patients agree or strongly agreed regarding MTM improve their health	Pharmacist-estimated cost saving exceeded cost of MTM per encounter

Appendix B

List of the Included Studies

Barnett, M. J., Frank, J., Wehring, H., Newland, B., VonMuenster, S., Kumbera, P., et al. (2009). Analysis of pharmacist-provided medication therapy management (MTM) services in community pharmacies over 7 years. *J Manag Care Pharm, 15*(1), 18-31.

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Welch, E. K., Delate, T., Chester, E. A., & Stubbings, T. (2009). Assessment of the impact of medication therapy management delivered to home-based Medicare beneficiaries. *Ann Pharmacother, 43*(4), 603-610.

Appendix C

Table C1.

Sources Used for Collecting Information on Clinical Outcomes.

Factors	Factor values obtained from
Guideline for cardiovascular health for each metric	PCC guideline which is modified from 1. Third Report of the Expert Panel on Detection, Evaluation, and Treatment of the High Blood Cholesterol in Adults (Adult Treatment Panel III, APTIII) 2. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)
Drug-related problems category	PCC guideline which is modified from Drug-related problems classification system established by Strand

Table C2.1.

Changes in Blood Pressure Classification

Systolic blood pressure/Diastolic blood pressure (mmHg)	JNC 7 Category
<120/80	Normal
120-129/80-84 130-139/85-89	Prehypertension
≥140/90 140-159/90-99 ≥160/100	Hypertension Stage 1 Stage 2

Table C2.2.

Goal Blood Pressure

Patients without diabetes or chronic kidney disease.	<140/90 mmHg
Patients with diabetes or chronic kidney disease.	<130/80 mmHg

Table C3.

Change in Lipid panel classification

Lipid panels	APTIII category
LDL cholesterol (mg/dL)	
<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-180	High
≥190	Very high
Total Cholesterol (mg/dL)	
<200	Desirable
200-239	Borderline high
≥240	High
HDL Cholesterol (mg/dL)	
<40	Low
≥60	High
Triglycerides (mg/dL)	
<150	Normal
150-199	Borderline high
240-499	High
≥500	Very high

Table C4.

Drug-Related Problem by Category

Category	Details
1. Need additional drug therapy	• Additional drug needed • Change of condition • Lab test needed • Patient monitoring required
2. Unnecessary drug therapy	• Change of condition • Excessive duration alert • Excessive quantity • Ingredient duplication • No recommendation required • Therapeutic duplication • Unnecessary drug
3. Wrong drug	• Misuse precaution
4. Dosage too low	• Gradual dose reduction • Low dose alert • Suboptimal regimen/therapy • Underuse precaution
5. Adverse drug reaction/Side effect	• Additive toxicity • Adverse drug reaction noted • BEERS list precaution • Prior adverse drug reaction • Side effect
6. Dosage too high	• High dose alert • Overuse precaution • Therapeutic duplication
7. Compliance	Non-adherence from: • Directions not understood

	• Drug expired • Drug product not available • Drug product too expensive • Non-specific • Patient cant' swallow or administer • Patient forgets to take • Patient prefers not to take
8. Interaction	• Drug-age precaution • Drug-disease precaution • Drug-drug interaction
9. Lifestyle modification required	• Lifestyle modification required
10. Patient care recommendation	• Patient care recommendation required
11. Cost-effectiveness alert	• Cost-effectiveness alert
12. Other	• Pharmacy restriction • Non formulary • Patient complaint/symptom • Provider consultation required • Product selection • Missing disease diagnosis • Missing information/classification

Table C5.

Charlson Comorbidity Index (CCI)(Charlson, et al., 1987)

Assigned weights for disease	Disease
1	• Myocardial infraction • Congestive heart failure • Peripheral vascular disease • Cerebrovascular accident • Dementia • Chronic pulmonary disease • Connective tissue disease • Gastrointestinal ulcer disease • Mild liver disease • Diabetes mellitus
2	• Hemiplegia • Moderate to severe renal disease • Diabetes with end-organ damage • Any tumor • Leukemia • Lymphoma
3	• Moderate or severe liver disease
6	• Autoimmune deficiency syndrome • Metastatic solid tumor