EFFECT OF PRESCRIPTION COPAYMENTS ON MEDICATION COMPLIANCE AND
HOSPITALIZATIONS IN COMMERCIALLY INSURED PATIENTS WITH HEART
FAILURE

Mark Elliot Patterson, M.P.H.

A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctorate of Philosophy in the Division of Pharmaceutical Outcomes and Policy

Chapel Hill
2006

Approved by,

Michael Murray, Pharm.D.
Susan Blalock, Ph.D.
Richard Hansen, Ph.D.
Herb Patterson, Pharm.D.
David Ridley, Ph.D.

ABSTRACT

MARK ELLIOT PATTERSON: Effect of Prescription Copayments on Medication
Compliance and Hospitalizations in Commercially Insured Patients with Heart Failure
(Under the direction of Dr. Michael Murray)

While pharmaceutical copayments are effective in containing system-level
expenditures, the increased financial burden on patients may decrease medication
compliance. Though many studies have focused on the effects of copayments on utilization,
fewer have simultaneously examined copayments, compliance, and clinical outcomes,
especially within heart failure patients. The rising prevalence and economic burden of heart
disease underscores the need to research copayment effects on compliance and outcomes in
this population.

The primary objective of this research was to estimate the effects of angiotensin
converting enzyme (ACE) inhibitor, beta-adrenergic blocker and diuretic prescription
copayment levels on medication compliance and hospitalizations in commercially insured
heart failure patients. The secondary objective was to measure whether medication non-
compliance mediates the association between copayment levels and hospitalizations.

Heart failure patients were identified from the Integrated Health Care Information
Solutions, Inc. database, containing a sample of United States commercially insured
individuals between 1997 and 2005. Refill copayments were defined in categorical ranges,
medication compliance by the Medication Possession Ratio, and hospitalizations by the
presence of all-cause, cardiovascular specific or heart failure specific inpatient claims.

This retrospective cohort study used ordinary least squares, random effects, and fixed effects regressions to estimate the effect of copayment level on compliance and logistic regressions to estimate the risk of hospitalizations conditional upon prescription copayment level. Mediation models were used to explore causal pathways between copayment level, medication compliance, and hospitalization.

Beta blocker and diuretic refills with higher copayment levels were associated with up to a 9% and 21% decrease in medication compliance, respectively. In regards to clinical outcomes, higher diuretic copayments were associated with up to 1.4, 2.5, and 3.8 times the risk of all-cause, cardiovascular, or heart-failure specific hospitalization, respectively. Medication compliance did not mediate the association between copayment level and hospitalization.

Results suggest that higher beta blocker and diuretic copayments are associated with decreased compliance in privately insured heart failure patients. Furthermore, higher diuretic copayments are associated with increased risk of hospitalization. Estimates need to be interpreted with caution given the absence of a control group. Future studies need to be conducted to determine the true causal nature of these associations

ACKNOWLEDGEMENTS

This project has allowed me to integrate knowledge and skills learned across multiple disciplines during my doctoral student career. I consider it an honor to have worked with such a talented group of professors who were genuinely interested in my research topic. My committee's combined expertise in the areas of heart failure pharmacotherapy, pharmacy practice, health economics, pharmaceutical policy, and behavioral theories added a unique dimension to my learning experience.

I would first like to recognize my committee chairman and academic advisor, Dr. Michael Murray. Mick has skillfully coached me through daily dissertation challenges, providing insight that helped propel me forward. His practical advice helped keep me focused, and his genuine interest in my career development has kept my spirits high. For these examples and countless others, I extend my thank you and appreciation to Mick for being an outstanding mentor. I would also like to extend my deep appreciation to other members of my committee, Drs. Susan Blalock, Rick Hansen, Herb Patterson, and David Ridley. Our frequent meetings over the past two years have been informative and enjoyable, and I look forward to collaborating in the future. To my committee as a whole, I would like to thank all of you for being so approachable, helpful, and genuinely interested in my research topic. Your mentoring styles made my dissertation experience enjoyable.

In addition to extending gratitude to my professors, I also would like to recognize both Dr. Joseph Ober and Mr. Jonas Daugherty of GlaxoSmithKline in Research Triangle

Park, North Carolina for their instrumental support in helping me acquire and access my dissertation data. While Joe helped me acquire the data, Jonas helped arrange for on-site computer access. Beyond providing workspace, he has also taken an interest in my career development. As my mentor during two summer internships, Jonas has taught me important business aspects of the pharmaceutical industry, as well as an immense amount of data management skills, both of which will serve me well during my health services research career.

I would finally like to thank my parents for the moral support they have provided me throughout my entire graduate school career. From my M.P.H. through my Ph.D., their practical advice has helped me through stressful moments, their phone calls have kept my sense of humor in check, and their unconditional love has kept me grounded.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACE: Angiotensin converting enzyme

ACC / AHA: American College of Cardiologists / American Heart Association

ADHERE: Acute Decompensated Heart Failure National Registry

AMI: Acute myocardial infarction

ARB: Angiotensin receptor blocker

CAD: Coronary artery disease

CHF: Chronic heart failure

CMA: Continuous medication acquisition

CMG: Continuous medication gap

CVD: Cardiovascular disease

FE: Fixed effects

HFSA: Heart Failure Society of America

HMO: Health maintenance organization

HRS: Health and Retirement Survey

IHCIS: Integrated Health Care Information Solutions

IPA: Independent practice association

JCAHO: Joint Commission on Accreditation of Healthcare Organizations

MPR: Medication possession ratio

MSA: Metropolitan statistical area

NDC: National drug code

NYHA: New York Heart Association

OLS: Ordinary least squares

POS: Point-of-service

PPO: Preferred provider organization

RE: Random effects

S-HMO: Social health maintenance organization

CHAPTER I: INTRODUCTION

OVERVIEW

As health care and pharmaceutical expenditures escalate, health plans continue to adapt their formulary benefit packages in order to provide appropriate care and contain costs. Drug formularies incorporate cost-sharing in the form of copayments or coinsurance. Formularies may be quite diverse across plans. For example, a prescription benefit plan may have a closed or open formulary structure, may require prior authorization for particular drug classes, or have a tiered pharmacy benefit structure with different copayment levels for generics, non-preferred or preferred drug brands. The rationale of tiered benefit structures is to contain system-level expenditures by providing incentive to beneficiaries to use preferred brands or generics, also providing them a choice of non-preferred pharmaceuticals if they are willing to pay higher out-of-pocket costs.

Cost-sharing policies have advantages and disadvantages. First, cost-sharing policies have demonstrated effectiveness in decreasing pharmaceutical utilization (Foxman, Valdez et al. 1987; Harris, Stergachis et al. 1990; Motheral and Henderson 1999; Tamblyn, Laprise et al. 2001; Huskamp, Deverka et al. 2003; Goldman, Joyce et al. 2004; Huskamp, Deverka et al. 2005), increasing switching rates from non-preferred to preferred drugs (Motheral and Fairman 2001; Thomas, Wallack et al. 2002; Fairman, Motheral et al. 2003; Huskamp, Deverka et al. 2003; Nair, Wolfe et al. 2003; Rector, Finch et al. 2003) or generic drugs (Motheral and Henderson 1999; Thomas, Wallack et al. 2002; Nair, Wolfe et al. 2003;

Christian-Herman, Emons et al. 2004; Kamal-Bahl and Briesacher 2004) or decreasing plan

expenditures (Smith 1993; Johnson, Goodman et al. 1997; Motheral and Henderson 1999;

Motheral and Fairman 2001; Thomas, Wallack et al. 2002; Fairman, Motheral et al. 2003;

Nair, Wolfe et al. 2003; Christian-Herman, Emons et al. 2004; Meissner, Moore et al. 2004),

patient expenditures (Smith 1993; Johnson, Goodman et al. 1997; Motheral and Henderson

1999; Motheral and Fairman 2001; Joyce, Escarce et al. 2002; Thomas, Wallack et al. 2002;

Nair, Wolfe et al. 2003; Christian-Herman, Emons et al. 2004; Meissner, Moore et al. 2004),

or overall expenditures (Nelson, Reeder et al. 1984; Leibowitz, Manning et al. 1985;

Soumerai, Avorn et al. 1987; Harris, Stergachis et al. 1990; Soumerai, Ross-Degnan et al.

1991; Soumerai, McLaughlin et al. 1994; Motheral and Henderson 1999; Motheral and

Fairman 2001; Joyce, Escarce et al. 2002; Thomas, Wallack et al. 2002; Soumerai 2004).

Although financially beneficial, decreasing pharmaceutical utilization may result in

unintended adverse events. Studies examining decreased utilization as a result of restrictive

prescribing policies have also shown these decreases to be significantly associated with

increased rates of adverse events and emergency department visits (Soumerai, McLaughlin et

al. 1994; Tamblyn, Laprise et al. 2001) or increased nursing home admissions (Soumerai,

Ross-Degnan et al. 1991; Soumerai, McLaughlin et al. 1994). These studies demonstrate the

potential for adverse health effects due to decreased access to essential medications.

Focusing research on associations among prescription copayments, medication

compliance and hospitalizations within heart failure patients is important given the

prevalence of heart failure in the United States, the number of essential medications required

to treat heart failure patients, as well as the potentially severe clinical consequences of non-

compliance. Though many studies have demonstrated the effects of copayments on

utilization, none have focused on heart-failure specific populations. Furthermore, most studies finding significant effects of copayments on utilization within commercially insured populations have been limited to select groups of employers (Smith 1993; Motheral and Henderson 1999; Huskamp, Deverka et al. 2003; Huskamp, Deverka et al. 2005), or only one health plan, (Harris, Stergachis et al. 1990; Motheral and Fairman 2001; Thomas, Wallack et al. 2002; Fairman, Motheral et al. 2003; Nair, Wolfe et al. 2003; Rector, Finch et al. 2003; Meissner, Moore et al. 2004), decreasing generalizability to commercially insured patients across the United States. Past studies have established the following:

- Prescription drug cost-sharing effectively decreases medication utilization and system-level expenditures in commercially insured populations (Harris, Stergachis et al. 1990; Smith 1993; Motheral and Henderson 1999; Motheral and Fairman 2001; Joyce, Escarce et al. 2002; Thomas, Wallack et al. 2002; Fairman, Motheral et al. 2003; Huskamp, Deverka et al. 2003; Nair, Wolfe et al. 2003; Rector, Finch et al. 2003; Goldman, Joyce et al. 2004; Meissner, Moore et al. 2004; Huskamp, Deverka et al. 2005), Medicaid populations (Nelson, Reeder et al. 1984; Reeder and Nelson 1985; Soumerai, Avorn et al. 1987; Soumerai, Ross-Degnan et al. 1991; Soumerai, McLaughlin et al. 1994; Kamal-Bahl and Briesacher 2004; Soumerai 2004), managed Medicare beneficiaries (Johnson, Goodman et al. 1997; Johnson, Goodman et al. 1997; Christian-Herman, Emons et al. 2004) and Canadian elderly populations (Tamblyn, Laprise et al. 2001).

- Significantly different copayment effects have been found between drug classes (Reeder and Nelson 1985; Goldman, Joyce et al. 2004) in addition to between medications considered to have important effects on health status ('essential') versus those providing mostly symptomatic relief ('discretionary') (Harris, Stergachis et al. 1990; Motheral and Henderson 1999; Tamblyn, Laprise et al. 2001). In general, it has been found that compared to individuals taking 'discretionary' medications, those taking 'essential' medications are less responsive to copayment increases.

- Decreased medication utilization as a result of restrictive prescribing policies (e.g., 3 drug per month limit) has been associated with increased nursing home admissions or acute mental health service utilization in Medicaid beneficiaries (Soumerai, Ross-Degnan et al. 1991; Soumerai, McLaughlin et al. 1994).

- Decreased compliance with heart failure medications is associated with increased hospitalizations and expenditures (Stroupe, Teal et al. 2004).

Despite the vast number of studies examining copayment effects, fewer studies have focused on the following:

- Measuring individual level medication compliance instead of broad medication utilization.

- Exploring the causal mechanism between prescription copayment level, medication compliance, and clinical outcomes.

More studies need to be conducted examining prescription copayments, medication compliance, and clinical outcomes in heart failure patients. Although one study examined the effect of copayment increases on the utilization of ACE inhibitors, beta blockers and diuretics as well as hospital readmissions after acute myocardial infarction (Pilote, Beck et al. 2002), and several have examined either ACE inhibitor use in commercially insured populations (Huskamp, Deverka et al. 2003; Kamal-Bahl and Briesacher 2004), angiotensin II receptor blockers (Kamal-Bahl and Briesacher 2004), cardiovascular agents or diuretics in Medicaid populations (Reeder and Nelson 1985), studies examining copayment effects of ACE inhibitors, beta blockers or diuretics on compliance and hospitalizations in commercially insured heart failure patients have not been forthcoming.

This dissertation will add to the literature by: 1) being generalizable to a more diverse population of commercially insured beneficiaries residing in the United States, 2) being the first study to examine drug-specific copayment effects on compliance within a heart-failure specific cohort, and 3) being the first to use mediation modeling to explore causal pathways between prescription copayment levels, medication compliance, and heart failure specific clinical outcomes.

The primary aims are to examine:

- Whether ACE inhibitor, beta blocker, and diuretic copayment levels are associated with lower medication compliance.

- Whether individuals experiencing higher ACE inhibitor, beta blocker or diuretic copayment levels are at increased risk of hospitalization.

The secondary aim is to:

- Explore the extent to which data support that increased copayments result in hospitalizations due to decreased medication compliance.

The remainder of this chapter will review heart failure epidemiology in the United States, clinical recommendations for treatments of heart failure, and a detailed literature review of studies examining copayment effects on pharmaceutical utilization, medication compliance, and health outcomes.

HEART FAILURE EPIDEMIOLOGY

Heart failure affects approximately 5 million individuals in the United States (Hunt, Abraham et al. 2005; HFSA 2006). While the prevalence is 1% among those under 50 years of age, it is 10% in individuals older than 80 (Kannel and Belanger 1991). More than 550,000 new heart failure cases emerge each year (Hunt, Abraham et al. 2005; HFSA 2006). The incidence approaches 10 per 1,000 individuals after the age of 65 (Thom, Haase et al. 2006). Prevalence estimates from the Rochester Epidemiology project were 214 and 327 per 100,000 for women and men, respectively, demonstrating a higher prevalence of heart failure among men compared to women (Roger, Weston et al. 2004).

Coronary artery disease, hypertension and diabetes are risk factors for developing heart failure. Coronary artery disease is a risk factor associated with worsened outcomes in patients with pre-existing heart failure (Dei Cas, Metra et al. 2003). The presence of hypertension contributes to accelerated atherosclerosis as well as elevated stress on the left ventricular wall (Dei Cas, Metra et al. 2003) whereas the presence of diabetes contributes to increases in left ventricle mass and wall thickness (Devereux, Roman et al. 2000), all of which result in worsening heart failure. Other risk factors include chronic renal insufficiency (Krum and Gilbert 2003), smoking (Dei Cas, Metra et al. 2003), excessive alcohol use (Dei Cas, Metra et al. 2003), illicit drug use (Dei Cas, Metra et al. 2003), obesity (Dei Cas, Metra et al. 2003), male gender (Aronow 2003), and age (Aronow 2003).

As the population ages, heart failure will increasingly become an economic burden on the health care system. Heart failure is already the most frequent reason for hospitalization in the United States among Medicare beneficiaries aged 65 and over (Lee, Chavez et al. 2004). Furthermore, 80% of those patients hospitalized with heart failure are 65 years of age and older (Hunt, Abraham et al. 2005). Consequently, more Medicare funds are spent on heart failure than on any other diagnosis (Lee, Chavez et al. 2004). The cost of heart failure was estimated in 2006 to be $29.6 billion (Thom, Haase et al. 2006). The significant economic burden of heart failure underscores the need to improve treatment options and compliance in heart failure patients.

CLINICAL TREATMENT GUIDELINES

Clinically recommended first-line therapies for heart failure patients at all stages of severity include ACE inhibitors, diuretics, and beta-adrenergic antagonists (Hunt, Abraham et al. 2005; HFSA 2006). Some drugs such as angiotensin II receptor blockers or isosorbide

20

dinitrate hydralazine combination therapy may be appropriate for African-Americans and second line therapy for others including those unable to tolerate ACE inhibitors. Contraindicated therapies include calcium channel blockers, some anti-arrhythmic drugs, and some inotropic therapies except for digoxin, which may be appropriate for more severe heart failure patients (Hunt, Abraham et al. 2005). Pharmacotherapy generally commences when patients show clinical manifestations of heart disease such as shortness of breath or ankle edema. ACE inhibitors and beta blockers have demonstrated efficacy in decreasing morbidity and mortality across numerous clinical trials (CONCENSUS 1987; SOLVD 1991; Cohn, Johnson et al. 1991; Fonarow, Chelimsky-Fallick et al. 1992; Packer, Bristow et al. 1996; CIBIS-II 1999; MERIT-HF 1999).

In contrast to the amount of evidence favoring the efficacy of ACE inhibitors and beta blockers, mixed evidence is available supporting the efficacy of diuretics in decreasing morbidity and mortality. One meta-analysis of randomized clinical trials found decreased mortality in those using diuretics (Faris, Flather et al. 2002) and two observational studies found increased mortality (Domanski, Norman et al. 2003; Ahmed, Husain et al. 2006). Despite this mixed evidence of a mortality benefit, diuretics are very effective in decreasing the symptoms of heart failure, such as edema, by removing excess fluid from the body, and therefore are clinically recommended in treating edema in heart failure patients (Brater 1998).

ECONOMIC FACTORS

Over twenty studies between 1984 and 2006 have demonstrated significant associations between increased prescription copayments or other cost-sharing policies on decreased patient expenditures (Smith 1993; Johnson, Goodman et al. 1997; Motheral and

Henderson 1999; Motheral and Fairman 2001; Joyce, Escarce et al. 2002; Thomas, Wallack et al. 2002; Nair, Wolfe et al. 2003; Christian-Herman, Emons et al. 2004; Meissner, Moore et al. 2004), plan expenditures (Smith 1993; Johnson, Goodman et al. 1997; Motheral and Henderson 1999; Motheral and Fairman 2001; Thomas, Wallack et al. 2002; Fairman, Motheral et al. 2003; Nair, Wolfe et al. 2003; Christian-Herman, Emons et al. 2004; Meissner, Moore et al. 2004), overall expenditures (Nelson, Reeder et al. 1984; Leibowitz, Manning et al. 1985; Soumerai, Avorn et al. 1987; Harris, Stergachis et al. 1990; Soumerai, Ross-Degnan et al. 1991; Soumerai, McLaughlin et al. 1994; Motheral and Henderson 1999; Motheral and Fairman 2001; Joyce, Escarce et al. 2002; Thomas, Wallack et al. 2002; Soumerai 2004), pharmaceutical utilization (Foxman, Valdez et al. 1987; Harris, Stergachis et al. 1990; Motheral and Henderson 1999; Tamblyn, Laprise et al. 2001; Huskamp, Deverka et al. 2003; Goldman, Joyce et al. 2004; Huskamp, Deverka et al. 2005), switching from brand to generic (Motheral and Henderson 1999; Thomas, Wallack et al. 2002; Nair, Wolfe et al. 2003; Christian-Herman, Emons et al. 2004; Kamal-Bahl and Briesacher 2004), non-preferred to preferred drugs (Motheral and Fairman 2001; Thomas, Wallack et al. 2002; Fairman, Motheral et al. 2003; Huskamp, Deverka et al. 2003; Nair, Wolfe et al. 2003; Rector, Finch et al. 2003), prescription to over-the-counter drugs (Goldman, Joyce et al. 2004), and retail to mail-order pharmacy utilization (Thomas, Wallack et al. 2002). Fewer studies have examined the effects of copayments on medication compliance. Of the six studies examining the effect of copayments on medication compliance or medication continuation (Motheral and Henderson 1999; Coombs, Cornish et al. 2002; Huskamp, Deverka et al. 2003; Dor and Encinosa 2004; Ellis, Erickson et al. 2004; Huskamp, Deverka et al. 2005) (Table 1.1), three studies showed that increased copayments decreased

22

compliance either to statins (Coombs, Cornish et al. 2002; Ellis, Erickson et al. 2004) or oral

hypoglycemics (Dor and Encinosa 2004). The other three studies showed no difference in

chronic disease medication discontinuation rates in commercially insured patients (Motheral

and Henderson 1999), in attention deficit hyperactivity disorder medication use in children of

commercially insured beneficiaries (Huskamp, Deverka et al. 2005), or in utilization or

discontinuation rates of ACE inhibitors, proton-pump inhibitors or statins before and after a

copayment change (Huskamp, Deverka et al. 2003).

Few studies have simultaneously examined effects of copayments on both medication

compliance or utilization and health outcomes. Of the eight studies that examined all three

constructs, three used self-report surveys (Mojtabai and Olfson 2003; Heisler, Langa et al.

2004; Piette, Wagner et al. 2004) and five used claims data (Johnson, Goodman et al. 1997;

Motheral and Fairman 2001; Pilote, Beck et al. 2002; Fairman, Motheral et al. 2003;

Christian-Herman, Emons et al. 2004) (Table 1.2). The self-report studies found significant

associations between cost-related medication restriction and health decline within

respondents of the Health and Retirement Survey (Mojtabai and Olfson 2003; Heisler, Langa

et al. 2004) and diabetics seeking care at the Veterans Administration or county or university

hospital system (Piette, Wagner et al. 2004). The claims studies found a mixture of results.

While some found increased copayment levels to be associated with decreased health status

and decreased medication supply (Johnson, Goodman et al. 1997), other found higher

copayments to be associated with increased hospitalizations and no change in compliance

(Christian-Herman, Emons et al. 2004), no change in hospitalizations or compliance with the

exception of one drug class (Motheral and Fairman 2001; Fairman, Motheral et al. 2003), or

null results across both outcomes and medication persistence (Pilote, Beck et al. 2002).

Given the breadth of studies conducted, the following section categorizes the literature into four sections: a) copayment effects on pharmaceutical utilization, b) prescribing policy effects on health services utilization, c) copayment effects on medication compliance, and d) copayment effects on medication compliance and health outcomes.

COPAYMENT EFFECTS ON PHARMACEUTICAL UTILIZATION

It has been well established that copayments and other cost-sharing policies significantly reduce pharmaceutical utilization. Of these studies, most have focused on medication utilization as an outcome in either Medicaid, or privately insured individuals. Across studies, most results have been consistent.

Reeder and colleagues conducted one of the earlier studies examining pharmaceutical utilization in ten different therapeutic categories of drugs before and after a $0.50 copayment increase among South Carolina Medicaid beneficiaries in 1977 (Reeder and Nelson 1985). Using time-series analyses within the framework of a quasi-experimental design, they found that a $0.50 copayment increase significantly reduced pharmaceutical expenditures within multiple therapeutic classes, including antihistamines, anti-infective agents, cholinergic, adrenergic, cardiovascular agents, psychotherapeutics, diuretics, and gastrointestinal drugs. Compared to other drug classes studied, more significant long-term trends existed among cardiovascular, cholinergic, diuretic, and psychotherapeutic agents (Reeder and Nelson 1985). For example, compared to the control group with no copayment change, a $0.50 copayment increase for a 30-day supply of cardiovascular or diuretic medications led to statistically significant decreases of $0.18 and $0.13 in member-per-month expenditures for cardiovascular and diuretics, respectively (Reeder and Nelson 1985). These results suggest that increasing copayments decreases medication use, especially in medications essential in

maintaining health. Though outdated and not generalizable to privately insured beneficiaries, this study provides some of the earliest evidence supporting the hypothesis that increased copayment levels are associated with decreased utilization of drugs indicated for heart failure. Furthermore, it provides specific parameter estimates that differ between medication classes, suggesting differential price responses across drug classes.

In addition to Medicaid populations, differential price responses were found across essential versus discretionary drug utilization in a study examining commercially insured populations. Harris and colleagues conducted one of the earliest studies examining copayment effects within a managed care population, expanding past studies which had focused primarily on Medicaid beneficiaries. Investigators measured how pharmaceutical utilization and costs varied by drug copayment levels within a staff model HMO by comparing the mean change in system-level pharmaceutical utilization and expenditures between cohorts of individuals from Group Health Cooperative who either experienced a copayment change or did not (Harris, Stergachis et al. 1990). Introducing a $1.50 copayment significantly reduced overall drug utilization by 10.7% in the first year, with an additional 10.6% reduction in the second year upon introduction of a $3.00 copayment (Harris, Stergachis et al. 1990). Furthermore, utilization reductions differed depending upon whether the drug was considered 'essential' or 'discretionary'. For example, the $1.50 increase significantly reduced discretionary drugs (e.g., analgesics, non-steroidal anti-inflammatories, cough and cold products, or skeletal muscle relaxants) by 17.3%, but did not significantly reduce essential drug utilization (e.g., anti-hypertensives, cardiac drugs, oral hypoglycemics, or thyroid medications). Similarly, the $3.00 copayment reduced discretionary and essential medication utilization by 19.2% and 13%, respectively (Harris, Stergachis et al. 1990).

These results suggest that beneficiaries are less responsive to copayment increases of essential medications compared to discretionary drugs, implying that individuals are willing to pay more out-of-pocket for drugs that have a potentially greater impact on their health. This was the first study examining copayment effects on utilization within a managed care population, demonstrating that modest copayment increases can have significant effects on drug utilization. Despite this, results are generalizable only to beneficiaries enrolled in one staff-model HMO, limiting the external validity to more diverse commercially insured populations within the United States. Numerous other claims-based studies examining the association between copayments and utilization similarly only center on select employers or single regional health plans (Harris, Stergachis et al. 1990; Smith 1993; Motheral and Fairman 2001; Huskamp, Deverka et al. 2003), with the exception of two recent studies focusing on larger samples of privately insured individuals (Joyce, Escarce et al. 2002; Goldman, Joyce et al. 2004). The current research therefore contributes to the literature by examining copayment effects within a diverse managed care population enrolled in a variety of HMO, PPO, and other independent health plans. Studying copayment effects in a more diverse setting should obtain results more generalizable to commercially insured heart failure patients residing in the United States.

Though not focusing specifically on heart failure populations, several studies have examined effects of pharmacy benefit structures on drug expenditures within larger cohorts of beneficiaries numbering between 420,000 and 520,000. For example, Joyce et al. used data from a wide array of employers and benefit designs to assess the effects of copayments, tiered incentive-based formularies,[1] and generic substitution on drug utilization and patient

---

[1]Drug formularies are comprehensive lists of preferred generic and brand name drugs covered under a health plan's outpatient pharmaceutical benefit. Tiered incentive-based formularies set different copayment levels on

out-of-pocket drug expenditures in over 420,000 beneficiaries from 25 different employers and 55 unique pharmacy benefit packages (Joyce, Escarce et al. 2002), while Goldman et al. used a dataset of 30 large employers and 528,000 beneficiaries to examine the effects of copayment increases on utilization of chronic disease medications, conducting subgroup analyses in individuals diagnosed with different chronic conditions (Goldman, Joyce et al. 2004). Joyce et al. found that doubling copayments resulted in a 22% and 32% decrease in annual average drug expenditures in 1-tier, and 2-tier benefit plans, respectively (Joyce, Escarce et al. 2002). Goldman et al. found that doubling copayments resulted in significant reductions of days supply for eight different therapeutic classes, decreasing 45% for non-steroidal anti-inflammatory drugs, 44% for antihistamines, 34% for antihyperlipidemics, 33% for antiulcerants, 32% for antiasthmatics, 26% for antihypertensives and antidepressants, and 25% for antidiabetic agents (Goldman, Joyce et al. 2004). Furthermore, they found lower price responsiveness among subgroups of individuals taking these medications for ongoing chronic conditions. For example, doubling copayments was associated with a 26% decrease in antidepressant utilization in the full sample, including individuals with acute episodes of depression, but only an 8% decrease among a subgroup of chronically depressed beneficiaries (Goldman, Joyce et al. 2004). These results suggest that some chronically ill patients are less responsive to copayment increases compared to individuals taking medications on a temporary basis, but are affected nonetheless.

The Goldman et al. study is one of few conducting disease-specific subgroup analyses examining effects of copayment on drug utilization. While these studies focused on

---

medications depending upon whether they are generic, preferred brands, or non-preferred brands. For example, generic, preferred brands, and non-preferred brands are usually designated as 1st tier, 2nd tier, and 3rd tier drugs, respectively. Furthermore, copayments increase with higher tiered drugs in order to encourage enrollees to use generic or lower cost brand name medications.

hypertensive or depressed patients, the current analysis will contribute to the literature by focusing specifically on heart failure patients. Although heart failure is less common among privately insured populations compared to, for example, older Medicare fee-for-service beneficiaries, the source population of over 38 million individuals should provide a sufficient sample of heart failure patients to examine drug-class specific effects for ACE inhibitors, beta blockers, and diuretics.

A recent study examined the effects of copayment change magnitude on utilization of oral hypoglycemics (OH) in privately insured individuals diagnosed with type II diabetes (Roblin 2005). Since average daily doses were expected to increase over time to achieve optimal glucose levels, investigators used interrupted time-series analyses to examine if copayment increases interrupted the expected trend of increases in oral OH average daily dose. Results showed that compared to small copayment increases, defined as under $10 for a monthly supply, large copayment increases, defined as over $10, were associated with an immediate 3.6% decrease in monthly OH utilization within the same month of the copayment shift (Roblin 2005). Refills with large copayment increases resulted in a 2.6% *decrease* in monthly utilization compared to a 2.2% *increase* before the copayment change, resulting in a significant *net* decrease of 0.4% (Roblin 2005). In contrast, low copayment increases were not associated with decreases in monthly OH utilization trends (Roblin 2005), suggesting that copayment effects depend upon the magnitude of the cost shift. These results imply that increased copayments for OH medications result in decreased utilization in privately insured beneficiaries diagnosed with type II diabetes. Although decreased utilization of these essential medications may adversely affect clinical outcomes, this study did not measure this association. Given the importance of measuring copayment effects on clinical outcomes in

chronically ill populations, the current research will contribute to the literature by measuring the effects of copayment levels on both compliance and outcomes in heart failure patients.

In summary, the aforementioned studies examining effects of copayment changes on drug utilization and expenditures consistently show, either through quasi-experimental designs or interrupted time series analysis, that increased copayments are associated with decreased medication utilization. Different effects across 'essential' versus 'discretionary' medications suggest that utilization either depends upon the perception of need or the nature of the chronic disease. Considering that decreased utilization of essential drugs contributes to poor health status, it is reasonable to hypothesize that increased copayments may contribute to poor health outcomes by creating a financial barrier to optimal pharmaceutical care. These studies were therefore limited by not examining the downstream health effects of decreased medication utilization.

The current research in heart failure contributes to the literature by continuing to study privately insured beneficiaries, an important research area considering the recent increase in pharmaceutical coverage plans in the private sector upon the implementation of Medicare Part D. Furthermore, examining a large diverse sample of beneficiaries enrolled in different health plan types allows sufficient sample size and variation to study ACE inhibitor, beta blocker, and diuretic specific effects within heart failure patients. Additionally, measuring compliance instead of utilization increases the ability to examine more detailed individual level medication taking patterns which would otherwise be masked in more broad utilization metrics. Finally, simultaneously measuring associations among copayment levels, medication compliance, and clinical outcomes will provide insight into how copayments directly affect the health of heart failure patients.

PRESCRIBING POLICIES AND HEALTH SERVICES UTILIZATION

Several studies have examined the effect of limited capitation policies in Medicaid populations on medication utilization, in conjunction with the adverse events associated with this decreased use. Cost-containment during the 1980's by state Medicaid programs often imposed either copayments or monthly limits on medication use. An example of a monthly limit was a 3-drug limit policy enacted by the New Hampshire Medicaid program (Soumerai, Ross-Degnan et al. 1991). Given that restrictive cost-containment policies could potentially decrease access to essential medications, it was hypothesized that health services utilization such as nursing home admissions or hospitalizations, would increase due to decreased health status (Soumerai, Ross-Degnan et al. 1991). Soumerai et al. used interrupted time series analysis to compare rates of nursing home and hospital admissions before and after the enactment of a 3-drug limit policy in a New Hampshire Medicaid beneficiary population (Soumerai, Ross-Degnan et al. 1991). Compared to the New Jersey Medicaid beneficiary control group, New Hampshire beneficiaries had a 35% decrease in standardized monthly dosages of 26 medication classes indicated for chronic heart disease, chronic obstructive pulmonary disease, asthma, diabetes, depression, migraines, ulcers, or thyroid disorders (Soumerai, Ross-Degnan et al. 1991). Furthermore, compared to the control group, New Hampshire beneficiaries were at significantly greater risk of nursing home admission following implementation of the 3-drug limit policy (RR=1.8, 95% CI 1.2-2.6) (Soumerai, Ross-Degnan et al. 1991). In a separate study conducted within the same source populations, investigators examined the effect of this 3-drug limit on the utilization of psychotropics within patients diagnosed with schizophrenia (Soumerai, McLaughlin et al. 1994). Compared to the control group, New Hampshire beneficiaries had up to a 49% decrease in

the utilization of either antipsychotics, antidepressants, lithium, anxiolytics or hypnotic drugs (Soumerai, McLaughlin et al. 1994). These decreases in utilization were further associated with significant increases in outpatient mental health visits, and emergency mental health service use (Soumerai, McLaughlin et al. 1994). Another study conducted within elderly Canadians corroborated these results, finding copayment increases to be significantly associated with decreased utilization of essential medications, which was further associated with increased rates of adverse events (Tamblyn, Laprise et al. 2001).

Results from these three studies suggest that prescribing policies restricting access to essential medications contribute to adverse events. It is therefore reasonable to hypothesize that copayment policies restricting access to heart failure medications may also result in increased hospitalization rates in privately insured populations, especially given that decreased compliance to heart failure medications has been found to increase risk of hospitalization (Stroupe, Teal et al. 2004). Although these studies did find significant associations between prescribing policies and adverse events, they did not estimate the effects of specific copayment levels. The current research will contribute to the literature by using individual level claims data to study associations between specific copayment level categories, medication compliance, and clinical outcomes. Furthermore, results will be generalizable to privately insured populations, as opposed to Medicaid beneficiaries, the latter of whom may be more price responsive compared to privately insured individuals due to higher health risk or lower income (Motheral and Henderson 1999).

COPAYMENT EFFECTS ON MEDICATION COMPLIANCE

Few studies have examined the effect of cost-sharing on medication compliance, as opposed to medication utilization, especially within disease-specific groups. Relevant

31

studies were conducted within privately insured populations examining the effects of copayments on 1) compliance to oral hypoglycemics (Dor and Encinosa 2004); 2) compliance or discontinuation of statin therapy (Ellis, Erickson et al. 2004); 3) compliance to statins post-acute myocardial infarction (Coombs, Cornish et al. 2002); 4) chronic medication continuation rates (Motheral and Henderson 1999); 5) medication continuation rates of ACE inhibitors, proton pump inhibitors (PPIs), or statins within six months after a policy shift (Huskamp, Deverka et al. 2003); or 6) discontinuation of medications for attention deficit and hyperactivity disorder taken by children of beneficiaries (Huskamp, Deverka et al. 2005).

Dor and colleagues used MarketScan® data containing over 3 million lives with 40 different employer-based health plans between 1999 and 2000 to examine effects of both copayment and coinsurance levels on 90-day supply compliance levels to OH. Investigators used ordered logistic regression models to estimate the probability of full compliance, partial compliance, or non-compliance within 90-day periods conditional upon a particular copayment or coinsurance level. They found that a $6 to $10 increase in copayments resulted in a 6.2% increase and a 9% decrease in the number of non-compliers and fully-compliant individuals, respectively (Dor and Encinosa 2004), implying that increased copayments of OH significantly decreased medication compliance in privately insured beneficiaries diagnosed with diabetes. Given that decreased compliance to OH may result in suboptimal glycemic levels, and consequently, poorer clinical outcomes, future studies need to examine the clinical consequences of non-compliance due to prescription copayments. The current research is similar to Dor et al. in estimating the probability of non-compliance conditional upon copayment levels in commercially insured populations, yet contributes to the literature by targeting heart failure rather than type II diabetes. Additionally, it will

further contribute to past studies by estimating the effects of copayments on total, cardiovascular-specific, and heart failure specific hospitalizations.

Studies focusing on patient-level compliance measured it in different manners. While Dor et al. measured compliance based upon percent coverage of therapy within a 90-day interval, Motheral et al. measured compliance as a rate of medication continuation across a six month period following a copayment increase (Motheral and Henderson 1999). Using a comparison group that had no copayment changes, Motheral et al. examined the effect of a copayment increase from $15 to $20 for brand name drugs on treatment continuation within one large employer health plan. Compared to the control group, medication discontinuation rates in the copayment change group did not significantly differ, suggesting that copayment increases from $15 to $20 do not result in medication discontinuation. Despite the null findings, the authors suggest that the 6-month post-intervention time window was not sufficiently long to detect any true effects (Motheral and Henderson 1999). For example, Soumerai et al. suggests a minimum of two years of follow-up time following an intervention in order to detect utilization changes in response to a policy shift (Soumerai et al., 1993). Alternatively, authors suggest null results reflect the relatively lower price responsiveness of healthy, employed, continuously enrolled individuals compared to lower income or high risk individuals (Motheral and Henderson 1999). This implies that modest copayment increases may not be sufficient to change medication continuation rates of healthier, privately insured individuals even beyond a six month post-intervention period.

The conflicting results between Dor et al. and Motheral et al. could be attributed to the measurement definitions. For example, while copayments may be sufficient to change 90 day supply levels as measured by Dor et al., in contrast, copayments may not be sufficient to

have somebody stop medications completely, as measured in Motheral et al. The current research adds to literature by focusing on medication supply levels as the compliance metric instead of medication discontinuation. Furthermore, given the current study's focus on long-term, persistent utilizers of heart failure medications, it may be more appropriate to measure medication supplies as opposed to discontinuation, the latter of which may be less common in long-term chronic utilizers. Despite the relatively high medication persistence and compliance of heart failure patients, the clinical consequences of behaviors such as pill splitting, which can be detected in compliance metrics such as the Medication Possession Ratio, can be similarly detrimental to health status as abruptly stopping medications. The sufficient follow-up time in the current analysis will also help detect the health effects of decreased medication supply levels.

One study examined the predictors of statin non-compliance and discontinuation rates in 200,000 commercially insured beneficiaries taking statins for either primary or secondary prevention purposes using two different compliance measures (Ellis, Erickson et al. 2004). Compliance was first measured as a function of medication supply levels using the cumulative medication gap (CMG), a metric previously cited by Steiner et al. (Steiner, Koepsell et al. 1988) that indicates the proportion of missed therapy days across a pre-determined time interval. Compliance was also measured using therapy discontinuation, defined as time to discontinuation within the context of Cox proportional hazard analysis (Ellis, Erickson et al. 2004). Compared to those with a $10 average monthly copayment level for statins, individuals with average monthly copayment between $10 and $20, and above $20, were 45% more likely (OR=1.45, 95% CI 1.25-1.69), and 300% more likely (OR=3.23, 95% CI 2.55 – 4.10) to be non-adherent (CMG>10%) (Ellis, Erickson et al.

2004). Furthermore, medication discontinuation rates differed depending upon copayment

levels. Compared to those with $10 copayment levels, individuals with copayment between

$10 and $20, and above $20 were 39% more likely (HR=1.39, 95% CI 1.19 – 1.63) and

430% more likely (HR=4.30,. 3.39 – 5.44) to discontinue statin therapy during follow-up

(Ellis, Erickson et al. 2004). These results suggest that compared to statins with lower

copayment levels, those at higher copayment levels increase the probability of non-adherence

as well as the probability of treatment discontinuation. Since statins have established

efficacy in decreasing the risk of coronary events, higher copayment levels may also

contribute to adverse outcomes via medication non-compliance. In contrast to this study

which did not measure clinical outcomes, the current analysis contributes to the literature by

estimating the effects of ACE inhibitor, beta blocker, and diuretic copayments on

hospitalizations.

Another study measured predictors of compliance to statins, yet in this case focused

on commercially insured beneficiaries already having experienced either an acute myocardial

infarction or other atherosclerotic event (Coombs, Cornish et al. 2002). Coombs et al. used

regression analysis to measure predictors of statin non-compliance using the continuous

multiple-interval availability metric (CMA), validated by Steiner et al (Steiner, Koepsell et

al. 1988). CMA, mathematically equivalent to the Medication Possession Ratio (MPR),

captures the percentage of medication acquisition over a particular refill interval. Linear

regressions found that for each $1.00 copayment increment, statin CMA decreased

significantly by an average of 0.009 units (Coombs, Cornish et al. 2002), equivalent to a $10

increase in statin copayment level resulting in an average 0.09 decrease in CMA units. These

results imply that for every $10 increase in copayment, medication supply levels will

decrease by 9%. Given the possible clinical consequences of poor adherence to chronic disease pharmacotherapy, more studies need to examine disease-specific outcomes resulting from such decreased adherence. The current research is similar to past studies in focusing on associations between copayment levels and medication supply levels but adds to the literature by also measuring how these affect the risk of hospitalization.

In contrast to studying the effects of specific copayment levels on medication compliance, Huskamp et al. focused on measuring the copayment effects of a policy implementation on medication discontinuation. Investigators measured the effect of moving from a single tier to either a 2-tier or 3-tier formulary on utilization, switching, or discontinuation of ACE inhibitors, statins, or PPIs within two employer-based health plans (Huskamp, Deverka et al. 2003). Compared to the control group, employer health plans replacing a 1-tier with a 2-tier formulary had a 24%, 34%, and 24% decrease in the probability of ACE inhibitor, PPI, and statin utilization, respectively (Huskamp, Deverka et al. 2003). In contrast, compared to the control group, employer health plans replacing a 2-tier with a 3-tier formulary had no significant decreases in the probability of use. Investigators also estimated the effects of copayment policy shifts on medication discontinuation 6 months after the policy shift. Compared to the control group, employer plans replacing a 1-tier with a 3-tier formulary had approximately 10% higher discontinuation rates of ACE inhibitors, PPIs, and statins. In contrast, employers replacing a 2-tier with a 3-tier formulary did not have significant differences in discontinuation rates of PPIs or statins (Huskamp, Deverka et al. 2003). These results suggest that modest copayment increases occurring upon movement from a 2-tier to a 3-tier formulary are not sufficient in changing utilization patterns. In contrast, larger copayment increases occurring

36

upon movement from a 1-tier to a 3-tier are sufficient in decreasing medication use. If health plans are trying to achieve optimal essential medication utilization, adopting more modest copayment increases as opposed to higher copayment increases may sufficiently contain system level costs while minimizing the risk of medication discontinuation.

Potential adverse events associated with medication discontinuation motivate the need to measure the effects of copayment levels on clinical outcomes. The current research contributes to the literature by examining copayment effects on heart failure specific hospitalizations. Since ACE inhibitor, beta blocker, and diuretic copayment effects have not been previously studied in heart failure specific populations, results from this analysis will provide insight into how copayment policies have the potential to directly affect medication compliance and clinical outcomes in individuals with heart failure. The fact that more Medicare dollars are spent for the diagnosis and treatment of heart failure than any other diagnosis (Massie and Shah 1997) emphasizes the clinical and policy importance of examining the effects of prescription copayment levels on clinical outcomes in this high risk population.

Another study by Huskamp et al. measured the effect of implementing a 3-tier formulary structure on the utilization and continuation of medications indicated for attention deficit and hyperactivity disorder in children of beneficiaries enrolled in a managed care plan (Huskamp, Deverka et al. 2005). Using a quasi-experimental design, difference-in-difference estimates showed that compared to individuals in the control group, children of beneficiaries exposed to the 3-tier benefit shift had a decreased probability of medication utilization for attention deficit and hyperactivity disorder. In contrast, medication discontinuation rates 6 months after the policy shift were not significantly different (Huskamp, Deverka et al. 2005).

These results suggest that although increased copayments may decrease overall utilization in ADHD medications, those same increases may not sufficient to increase discontinuation rates.

In summary, most of the aforementioned studies found inverse associations between increased copayment levels and either medication compliance or medication discontinuation. Though all studies did focus on either medications indicated for chronic diseases, such as ACE inhibitors, oral hypoglycemics, or statins, no analysis focused specifically on heart failure patients. The null results found in individuals diagnosed with a previous myocardial infarction or atherosclerotic event suggests that the severity of the illness or the perceived essential nature of the medication may contribute to less price sensitivity. Furthermore, the null results found in the study using only a 6-month time window suggests more time may need to elapse after a policy shift before changes in medication taking behavior can be observed. The current study contributes to the literature by building upon past studies examining the effects of copayments on compliance, yet adds to the literature by estimating class specific copayment effects specifically in a cohort of heart failure patients. Furthermore, using the MPR instead of medication discontinuation rates as the compliance measure will increase the ability to detect levels of partial non-compliance which may not otherwise be captured in medication discontinuation measures. Drawing upon a very large sample of

Table 1.1: Studies examining effect of prescription copayments or policy shifts on chronic disease medication discontinuation or non-compliance

Study	Population	Sample Size	Copayment predictor	Compliance outcome	Null Results	Significant results	Study design	Drug class
(Ellis, Erickson et al. 2004)	Commercially insured adult beneficiaries taking statins for primary or secondary prevention purposes	2,258 (primary prevention) 2,544 (secondary prevention)	Average 30-day copayment level	1) Medication adherence using Continuous Medication Gap (CMG>10%); 2) time to treatment discontinuation		Increased copayments associated with non-compliance and discontinuation of therapy	Retrospective cohort with claims data	statins
(Dor and Encinosa 2004)	Commercially insured adult beneficiaries diagnosed with Type II diabetes	20,494 (copay cohort) 6,563 (coinsurance cohort)	Copayment and coinsurance levels	Non-compliance, partial compliance, full compliance within 90-day supply intervals		Increased copayments and coinsurance levels associated with increased probability of partial or non-compliance	Retrospective cohort with claims data	Oral hypoglycemics
(Coombs, Cornish et al. 2002)	Commercially insured adult beneficiaries within 1 health plan with a history of acute myocardial infarction	216	Copayment level	Cumulative Medication Acquisition (CMA)		Copayment level inversely associated with medication compliance; $1 copayment levels associated with 0.009 unit decrease in CMA	Retrospective cohort with claim data	statins
(Motheral and Henderson 1999)	Commercially insured adult beneficiaries enrolled in one of 2 employer health plans	1,112 (copay changers) 1,112 (matched)	Copay change from $10 to $15 for brand name drugs	Medication continuation rate	Increase in copayment not associated with decreased medication continuation rate		Retrospective cohort with quasi-experimental design	Prescriptions for chronic disease
(Huskamp, Deverka et al. 2003)	Beneficiaries enrolled in employer-based health plans; one implementing a 1 to 3 tier shift, the other a 2 to 3 tier shift.	55,000 (control) 56,000(treat) (employer 1) 11,000(control) 27,000(treat) (employer 2)	Copayment shifts associated with moving from a) 2-tier to 3 tier; b) 1 tier to 3-tier formulary benefit structure	Discontinuation of medications 6 months post policy shift	No significant differences in medication discontinuation in PPIs or statins moving from 2-tier to 3-tier benefit structure	Moving from 1-tier to 3-tier was significantly associated with increased discontinuation rates of ACE inhibitors, PPIs, and statins	Retrospective cohort with quasi-experimental design	ACE inhibitors, PPIs, and statins

Table 1.1: Studies examining effect of prescription copayments or policy shifts on chronic disease medication discontinuation or non-compliance (continued)

Study	Population	Sample Size	Copayment predictor	Compliance outcome	Null Results	Significant results	Study design	Drug class
(Huskamp, Deverka et al. 2005).	Children of beneficiaries enrolled in large employer with PPO and PPS plans using medication for ADHD	20,326 (intervention) 15,776 (control)	Copayment change	Medication continuation	Movement to a 3-tier benefit formulary plan does not result in decreased continuation of ADHD medications in children		Retrospective cohort with quasi-experimental design	Medications for ADHD

commercially insured individuals, this analysis also has sufficient follow-up time to measure the clinical effects of both copayment levels and medication non-compliance.

COPAYMENT EFFECTS ON MEDICATION COMPLIANCE AND HEALTH OUTCOMES

Studies simultaneously measuring associations among copayment changes, medication compliance and health outcomes have varied in their methodological approaches as well as their results. Out of the eight studies reviewed, five used claims data (Johnson, Goodman et al. 1997; Motheral and Fairman 2001; Pilote, Beck et al. 2002; Fairman, Motheral et al. 2003; Christian-Herman, Emons et al. 2004) while three used self-report survey designs (Mojtabai and Olfson 2003; Heisler, Langa et al. 2004; Piette, Wagner et al. 2004). Pilote et al. measured the effect of a copayment increase on the utilization of cardiac medications, outpatient visits, emergency room use, and mortality among an elderly Canadian population (Pilote, Beck et al. 2002). This retrospective cohort study used hospital discharge claims to examine if the implementation of a 5% coinsurance policy affected the utilization, persistence, and compliance of ACE inhibitors, beta blockers, lipid-lowering drugs, and aspirin after being discharged from the hospital following an acute myocardial infarction (AMI). Compared to the control group, the group exposed to the policy change had a similar proportion of patients receiving ACE inhibitors, beta blockers, lipid-lowering drugs, or aspirin within 30 days of discharge for AMI and similar medication persistence rates 1 year after discharge or until death. Furthermore, cardiac-related hospital readmission rates, outpatient visit rates, and emergency room visit rates did not significantly differ between pre and post-periods (Pilote, Beck et al. 2002). Results suggest that copayment changes are not associated with decreased utilization or persistence of ACE inhibitors, beta

41

blockers, lipid-lowering medications, or aspirin within 30 days of discharge in elderly

Canadians experiencing AMI. Additionally, policy shifts did not cause increased rates of

adverse events.

Although the null associations between copayments and health services utilization are

inconsistent with another past study finding copayment increase policies associated with

increased rates of adverse events in another Canadian population (Tamblyn, Laprise et al.

2001), authors propose the null results may be due to individuals' lower price sensitivity after

a recent serious health event (Pilote, Beck et al. 2002). For example, compared to an

individual who experienced an AMI several years in the past, an individual recently

experiencing an AMI may be less sensitive to beta blocker copayments due to the immediate

need to treat the condition. This explanation is consistent with past studies finding

individuals less sensitive to copayment increases in essential compared to discretionary

medications (Harris, Stergachis et al. 1990; Tamblyn, Laprise et al. 2001).

Although the Pilote study does provide insight into ACE inhibitor and beta blocker

copayment effects on clinical outcomes, the absence of a control group limits the ability to

infer causality. Furthermore, results cannot be generalized to commercially insured heart

failure patients. The current research will contribute to the literature by studying copayment

effects of ACE inhibitors and beta blockers within heart failure patients. Although it is

hypothesized that higher copayments will result in decreased compliance, null findings may

occur since individuals could be insensitive to copayment increases given the severity of

their illness.

Unlike the Pilote study which did not employ a comparison group, a study by

Motheral et al. used a quasi-experimental design to examine the effect of replacing a 2-tier

with a 3-tier benefit structure on the utilization and discontinuation of estrogen, oral contraceptives, antihypertensives, and antihyperlipidemics and on outpatient, inpatient, and emergency room rates 1 year after policy implementation in a cohort of PPO beneficiaries (Motheral and Fairman 2001). Compared to beneficiaries remaining in a 2-tier copayment design, those moving to a 3-tier system had significantly greater medication discontinuation of estrogens at 6 and 11 months after policy implementation. In contrast, no significant differences were found in inpatient, outpatient, or emergency room visit rates, or discontinuation of the other three drug classes (Motheral and Fairman 2001). Results suggest that copayment increases associated with moving from 2-tier to 3-tier formularies are not sufficient in causing medication discontinuation with exception of more discretionary drugs such as estrogen. Furthermore, the null associations found between the policy shifts and adverse events suggest that moving from a 2-tier to a 3-tier policy is not sufficient to cause increased inpatient, outpatient, or emergency room rates within the same year of policy implementation.

Since investigators only examined copayment effects within drug classes which had sufficient sample size to detect significant differences, more studies are needed to measure class-specific copayment effects within commercially insured populations. Furthermore, since this analysis only focused on PPO beneficiaries, results may not be generalizable across all managed care plan types. The current study adds to the already large body of literature examining copayment effects in commercially insured populations, but uniquely contributes by having sufficient power to examine ACE inhibitor, beta blocker, and diuretic specific copayment effects among heart failure beneficiaries enrolled across different health plan types.

43

While Motheral et al. measured health outcomes conditional upon copayment policy shifts after one year and found null associations, Fairman et al. conducted a follow-up study to examine whether lengthening the follow-up time improved detecting changes in health status. Fairman et al. used a quasi-experimental design to measure the effect of moving from a 2-tier to a 3-tier benefit structure on utilization and discontinuation of estrogens, oral contraceptives, anti-hypertensives, and antihyperlipidemics, as well as inpatient, outpatient, and emergency room visits at 6, 12, 18, 24, and 28 months post policy implementation (Fairman, Motheral et al. 2003). Compared to the control group, beneficiaries moving from the 2-tier to the 3-tier had modest decreases in medication utilization, but no significant decreases in medication discontinuation at month 12, 18, 24, or 28 with the exception of oral contraceptives at month six. Additionally, groups did not differ in terms of office visits, emergency room visits, or hospitalizations (Fairman, Motheral et al. 2003). These results suggest that replacing a 2-tier with a 3-tier benefit formulary does not result in increased medication discontinuation or adverse event rates, even after 30 months of observation. Although the current research does not have the ability to measure the effects of copayment changes because of data limitations, the analysis still follows individuals for a minimum of three years, increasing the probability of detecting hospitalization effects if they indeed exist.

Related to previous studies examining the effects of implementation of different tiered benefit policies, Christian-Herman et al. examined the effect of implementing a generic-only drug benefit on pharmaceutical utilization, compliance and hospitalization in a group of California HMO Medicare beneficiaries. Using a quasi-experimental design to measure changes, the study also conducted subgroup analyses among five chronic diseases: chronic heart failure, coronary artery disease, epilepsy, diabetes, and depression (Christian-

Herman, Emons et al. 2004). Compared to the control group who had equal access to both brand and generic products, beneficiaries exposed to the generic only policy had similar levels of medication compliance before and after the benefit change. In contrast, the subgroup analyses found that compared to heart failure patients in the control group, those with heart failure in the generic-only policy group had a decreased mean number of months of utilization of ACE inhibitors (Christian-Herman, Emons et al. 2004).

Similar to heart failure subgroup analyses, generic-only cases with cardiovascular disease had significantly decreased utilization of both ACE and statins, diabetics had significantly less utilization of insulin or oral hypoglycemics, and those diagnosed with depression had significantly less utilization of anti-depressants (Christian-Herman, Emons et al. 2004). Results suggest that implementing generic only substitution results in decreased utilization of essential medications for these high risk populations. Investigators also found that compared to individuals accessing both generics and brand name drugs, those in the generic only group had a significantly higher likelihood of hospitalization during the first year after policy implementation (Christian-Herman, Emons et al. 2004). These results suggest that restricting access to brand name drugs may increase the risk of hospitalization. If generics are in fact associated with higher hospitalization rates, the lower copayments may result in a negative association between copayment level and hospitalization, opposite of the hypothesized direction. While most studies theorize that higher copayments result in adverse events via restriction to essential medications, the use of lower copayment medications may result in adverse events via suboptimal efficacy, therefore suggesting an alternative causal pathway between copayments and adverse events. The current study contributes to the

45

literature by using mediation modeling to further explore the causal pathways among copayment levels, non-compliance and hospitalizations in heart failure patients.

While the aforementioned studies examining effects of copayment shifts on medication compliance and outcomes all used medical claims, a few studies have examined these associations using patient surveys. Mojtabai et al., for example, used data from the Health and Retirement Survey (HRS) to examine the association between self-reported medication restriction due to copayments and health status. Compared to respondents who did not report medication restriction due to cost, those who did report this had an increased likelihood of also reporting worsening health status (OR=1.75, p<0.001), worsening physical symptoms (β=0.82, p<0.001), and increased hospitalizations within the past 2 years (OR=1.49, p<0.001) (Mojtabai and Olfson 2003). Within HRS respondents being treated for heart disease, cost-related poor adherence was also significantly associated with worsening heart disease (OR=1.81, p<0.001) (Mojtabai and Olfson 2003). Results suggest that decreased compliance directly attributable to increased drug costs is associated with decreased health status. Despite these significant associations, the cross-sectional design limits the ability to infer causality between self-reported medication restriction due to cost and health status. The current study will contribute to the literature by using claims data to measure associations between copayment levels, non-compliance, and hospitalization. Although retrospective claims studies cannot attribute medication non-compliance to cost as well as a survey question, they do have advantages of increasing the ability to detect changes over time.

Heisler et al. also used data from the HRS to measure the effect of self-reported medication restriction due to cost on health outcomes, yet improved the previous study by

examining health outcomes for up to 2 to 3 years after baseline. Compared to respondents who did not report cost-related medication restriction, those who did report this had greater health status decline (OR=1.76, 95% CI 1.27 – 2.44) (Heisler, Langa et al. 2004). Furthermore, within the cohort of respondents reporting cardiovascular disease, those who did report medication restriction due to cost had higher self-reported rates of angina (OR=1.50, 95% CI 1.09 – 2.07) or non-fatal heart attacks or strokes (OR=1.51, 95% CI 1.02, 2.25) (Heisler, Langa et al. 2004). These results provide evidence that decreased medication compliance due to increased cost causes health decline. Despite the ability of this study to couple non-adherence with cost via a survey question and to measure trends over time, it still did not capture the magnitude of changes in either copayment levels or compliance. For example, individuals reporting cost-related non-adherence may have had a copayment threshold level at which this behavior change occurred. The current study contributes to the literature by examining the effects of specific copayment level ranges on both medication compliance and clinical outcomes. The use of claims data instead of self-report will also strengthen the validity of the outcome measures.

Another study used a combination of data from self-reported surveys and medical claims to examine associations between self-reported cost-related medication restriction and diabetes-specific health status among cohorts of Veterans Affairs, county clinic, and university clinic patients diagnosed with type II diabetes (Piette, Wagner et al. 2004). In addition to measuring self-reported diabetes and non-diabetes symptom levels and mental and physical composite scores of the SF-12, the study captured glycemic control by using glycosolated hemoglobin levels (A1C) from medical claims. The use of a diabetes-specific marker created an optimal, objective health status metric. Compared to individuals who did

not report cost-related medication restriction, those reporting it had significantly lower glycemic control, indicated by the 0.6% absolute increase in A1C levels (p=0.0005) (Piette, Wagner et al. 2004). Cost-related medication restriction was also significantly associated with increased symptoms and decreased scores on the SF-12. Compared to diabetics who did not report cost-related medication restriction, those reporting it had an average increase of 1.8 self-reported diabetes symptoms, as well as a 4.5 and 2.6 point decline in the physical and mental health scores, respectively, on the SF-12 (Piette, Wagner et al. 2004). These results suggest that decreased compliance due to cost is significantly associated with diabetes-related health decline as measured by A1C levels, self-reported symptoms, and the SF-12. Despite the strengths of using an objective marker of diabetes control, the cross-sectional design limits the ability to infer causality between cost-related medication non-compliance and diabetes-specific outcomes. The current study adds to the literature by using claims data to measure associations between copayment levels, compliance, and outcomes within a longitudinal setting. Instead of diabetes, this study focuses on heart failure, an equally important chronic disease contributing to rising health care costs in the United States.

While the aforementioned studies examined copayment effects on compliance and outcomes using either longitudinal or cross-sectional surveys, Johnson et al. used claims data to measure the impact of increased copayments on the utilization and health status of elderly individuals enrolled in a large Medicare HMO (Johnson, Goodman et al. 1997). Investigators used a series of quasi-experimental study designs to compare changes in mean utilization and health status as a function of copayment changes occurring within a Social HMO (S-HMO) or the Medicare Plus population, both subsidiary plans of Kaiser Permanente Northwest (Johnson, Goodman et al. 1997). Health status was measured using a per capita

index created by combining Chronic Disease Scores with Diagnostic Cost Groups. During one analysis period, compared to S-HMO beneficiaries experiencing no cost-sharing increases, Medicare Plus beneficiaries moving from a 50% to 70% coinsurance rate had significantly less total days of cardiac and diuretic agent utilization (Johnson, Goodman et al. 1997). During a second analysis period, compared to the Medicare Plus cohort experiencing a constant 50% coinsurance rate, S-HMO beneficiaries experiencing a copayment increase from $1 to $3 had significantly lower health status as indicated by the per-capita index score (Johnson, Goodman et al. 1997). Results of this study suggest that increased copayments or coinsurance results in decreased utilization of essential medications indicated for heart disease within an elderly group of Medicare HMO beneficiaries. Furthermore, those experiencing copayment increases have significantly lower health status, implying that copayment increases have a negative affect on health status.

Although being one of the few retrospective claims studies simultaneously measuring copayment change, utilization, and health status, inconsistent associations between cost-sharing changes and per-capita health status limited the ability to infer causality between decreased utilization and individual level health status. For example, in comparing two different analysis periods both having either a copayment or coinsurance change, one had significant effects on decreased health status while the other did not (Johnson, Goodman et al. 1997). These inconclusive findings motivate the need to conduct further research using pharmaceutical claims to estimate copayment effects on health status. The current analysis contributes to the literature by using individual level inpatient events as opposed to a per-capita disease index to measure health status. Furthermore, this remains the first claims-based study using individual level pharmaceutical and hospital claims to simultaneously

Table 1.2: Studies examining effect of prescription copayments or policy shifts on medication utilization or adherence and health outcomes.

Study	Population	Sample Size	Copayment Predictor	Compliance Outcome	Health Outcome	Null Results	Significant Results	Study Design	Drug classes of interest
(Heisler, Langa et al. 2004)	Respondents of Health Retirement Survey with self-reported heart disease	7,991	Self-reported medication restriction due to drug cost	Self-reported medication restriction due to drug cost	Self-reported health status; angina; stroke; non-fatal MI		CV specific health decline associated with cost-related medication restriction	Longitudinal	Any medications
(Mojtabai and Olfson 2003)	Respondents of Health Retirement Survey with self-reported heart disease	10,413	Self-reported medication restriction due to drug cost	Self-reported medication restriction due to drug cost	Self-reported health decline; physical and mental scores		Worsening CHD and physical symptoms associated with cost-related medication restriction	Cross sectional	Any medications
(Piette, Wagner et al. 2004)	Veteran Administration beneficiaries with diabetes	766	Self-reported medication restriction due to drug cost	Self-reported medication restriction due to drug cost	Hemoglobin levels (A1C); diabetes symptoms; SF-12 QOL		Increased A1C levels; more symptoms, and lower SF-12 scores associated with cost-related medication restriction	Cross sectional	Any medications
(Johnson, Goodman et al. 1997)	HMO Medicare beneficiaries of Kaiser Permanente Northwest	6,704 7,472 7,962 7,646 (4 cohorts)	Presence of copayment increase	Drug utilization; day supply	Per-capita health index using CDS/DCG algorithm	Copayment increase associated with decreasing trends in health status	Copayment increase associated with reduced day supply of cardiac and diuretic drugs.	Retrospective cohort with quasi-experimental design (pre/post)	Cardiac drugs Diuretics

Table 1.2: Studies examining effect of prescription copayments or policy shifts on medication utilization or adherence and health outcomes (continued)

Study	Population	Sample Size	Copayment Predictor	Compliance Outcome	Health Outcome	Null Results	Significant Results	Study Design	Drug classes of interest
(Pilote, Beck et al. 2002)	Elderly Canadians admitted to hospital for acute myocardial infarction	22,066	Movement from a $0 copayment or $2 copayment for welfare/low income, and all elderly, respectively to a 25% coinsurance rate.	1) Percentage of days covered by medication 1 year after hospital discharge	1) cardiac-related hospital readmissions. 2) Outpatient visits. 3) ER visits 4) mortality rates	No significant differences in medication utilization, medication persistence, readmissions, OP, ER, or mortality before and after copay change		Retrospective cohort with claims data	1) ACE inhibitors 2)beta blockers; 3)lipid lowering drugs; 4)aspirin
(Motheral and Fairman 2001)	Commercially insured beneficiaries of 1 Midwestern PPO	6,881 (intervention) 13,279 (control)	Movement from a 2-tier to 3-tier formulary	1) Medication discontinuation	1)Office visits, 2) inpatient visits 3) ER visits	Implementation of policy was not associated with increased rates of office visits, inpatient visits, or ER visits within 1 year post-policy	Intervention group had significantly higher discontinuation of estrogens at month 6, 11 post-policy	Retrospective cohort with claims data; quasi experimental design with valid comparison group	1) estrogens 2) oral contraceptives 3) antihypertensive 4) antihyperlipidemics

Table 1.2: Studies examining effect of prescription copayments or policy shifts on medication utilization or adherence and health outcomes (continued)

Study	Population	Sample Size	Copayment Predictor	Compliance Outcome	Health Outcome	Null Results	Significant Results	Study Design	Drug classes of interest
(Christian-Herman, Emons et al. 2004)	California Medicare HMO beneficiaries	310,132 (case: yr1) 210,299 (case: yr2) 238,639 (ctrl: yr1) 198,430 (ctrl: yr2)	Movement from standard tiered benefit formulary to generic only formulary	1) Physician adherence: class-specific utilization of clinically recommended medications for select chronic diseases Mean number of months with at least 1 day supply of a clinically recommended medications 2) patient adherence: mean % of days supply	1) total hospitalizations	Policy not associated with decreased patient adherence to class-specific drugs. Policy not associated with increased hospitalizations within chronic disease subgroups.	Policy associated with increased likelihood of any hospitalization with 1 year in overall sample. Policy associated with decreased physician adherence, or the utilization of Medications indicated for CHF, CAD, diabetes, and depression subgroups.	Retrospective cohort with quasi-experimental design, pre/post with valid comparison group.	Various medications indicated for: a) CHF b) CAD c) diabetes d) epilepsy e) depression
(Fairman, Motheral et al. 2003)	Commercially insured beneficiaries of 1 Midwestern PPO	4,132: control group 3,577:intervention group	Movement from a 2-tier to 3-tier formulary	Medication discontinuation	1)Office visits, 2) inpatient visits 3) ER visit s	Implementation of policy was not associated with increased rates of office visits, inpatient visits, or ER visits Implementation of policy not associated with medication discontinuation rates at 12, 18, 24, or 28 months	Implementation of policy associated with discontinuation of oral contraceptives 6 months after policy implementation.	Retrospective cohort with claims data; quasi experimental design with valid comparison group	1) estrogens 2) oral contraceptives 3) antihypertensive 4) anti-hyperlipidemics

measure associations between ACE, beta blocker, and diuretic copayments, medication compliance, and clinical outcomes in commercially insured heart failure patients.

SUMMARY

Though increasing prescription copayments may benefit health plans by containing system-level expenditures, copayment increases may create financial barriers that increase the probability of medication non-compliance in heart failure patients. Since decreased medication supplies have been associated with increased risk of hospitalization in heart failure patients, non-compliance to ACE inhibitors, beta blocker, and diuretics is especially dangerous for heart failure patients. The current research will contribute to the literature by simultaneously measuring associations among ACE inhibitor, beta blocker, and diuretic copayment levels on medication compliance and hospitalizations. Though past studies have created a strong foundation of literature demonstrating the effects of copayment changes on decreased pharmaceutical utilization, fewer studies have focused on the effects of copayment levels on both medication compliance and health outcomes in privately insured individuals. The large study population and long follow-up time of the current analysis will provide sufficient power to measure drug class specific effects within a relatively low prevalence disease among privately insured populations. Results from this study will be relevant for clinicians and insurance payers interested in how copayments may affect the medication taking behavior or health of heart failure patients.

AIMS AND HYPOTHESES

PRIMARY AIMS

- To determine the effects of ACE inhibitor, beta blocker, and diuretic prescription copayment levels on medication compliance in commercially insured patients with heart failure.

- To determine the association between ACE inhibitor, beta blocker, and diuretic prescription copayment levels and risk of hospitalization in commercially insured patients with heart failure.

Given the most recent recommendations of the Heart Failure Society for America (HFSA) as well as the American College of Cardiologists / American Heart Association (ACC/AHA) clinical guidelines for heart failure pharmacotherapy (Hunt, Abraham et al. 2005; HFSA 2006), analyses will focus on ACE inhibitors, beta-adrenergic blockers, and diuretics. Because copayment levels are potential barriers to access to clinically recommended pharmacotherapy, it is hypothesized that increased copayment levels will be associated with decreased medication compliance within each respective medication class. Since decreased access to clinical recommended medications may result in adverse events, it is hypothesized that increased copayments will be associated with increased rates of all-cause, heart disease-specific, and heart failure-specific hospitalizations across all medication classes.

SECONDARY AIM

- Explore the extent to which medication compliance mediates the association between copayment levels and hospitalizations.

Medication non-compliance may be largely responsible for the association between increased copayments and increased hospitalizations. It is hypothesized that non-compliance will partially mediate the association between copayment levels and hospitalizations. The presence of mediation would imply a causal pathway between copayments, compliance, and hospitalizations.

CHAPTER II: CONCEPTUAL FRAMEWORK

OVERVIEW

Measuring associations among heart failure medication copayments, compliance, and hospitalizations requires incorporating conceptual and clinical frameworks to ensure adequate inputs for empirical models. It is hypothesized that copayments are a primary determinant of access to medications, creating a barrier to optimal heart failure medication compliance. Medication undersupplies can exacerbate symptoms, increase the risk of adverse events, and increase the use of emergency department visits in heart failure patients (Stroupe, Teal et al. 2004). Since current ACC/AHA and HFSA guidelines recommend that all heart failure patients take ACE inhibitors, beta-adrenergic antagonists and diuretics (Hunt, Abraham et al. 2005; HFSA 2006), decreased compliance to these medications could therefore increase the risk of hospitalization in heart failure patients.

Other individual, health system, and regional level factors associated with prescription copayments could also be associated with medication compliance or hospitalization. Omitting these variables from the empirical models would result in biased estimates. Consequently, the proposed conceptual framework identifies competing factors present in the claims dataset apart from prescription copayment levels that may contribute to variation in medication compliance or hospitalizations (Figure 2.1). Controlling for these potential confounders or effect modifiers will help isolate the

total effects of prescription copayments on either medication compliance or hospitalization.

Figure 2.1: Conceptual pathways between prescription copayments, medication compliance, and hospitalization with potentially competing individual, system, and regional level factors

INDIVIDUAL

```
  Demographics          Health Status        Drug Utilization

     Age               Co-morbidities           CHF Rx
    Gender            Disease Severity         Non-CHF Rx
                                                Rx brand


      COPAY  ───────▶  COMPLIANCE  ───────▶  HOSPITALIZATION


              Health Plan Type                   MSA
                                                Census

                  SYSTEM               REGIONAL
```
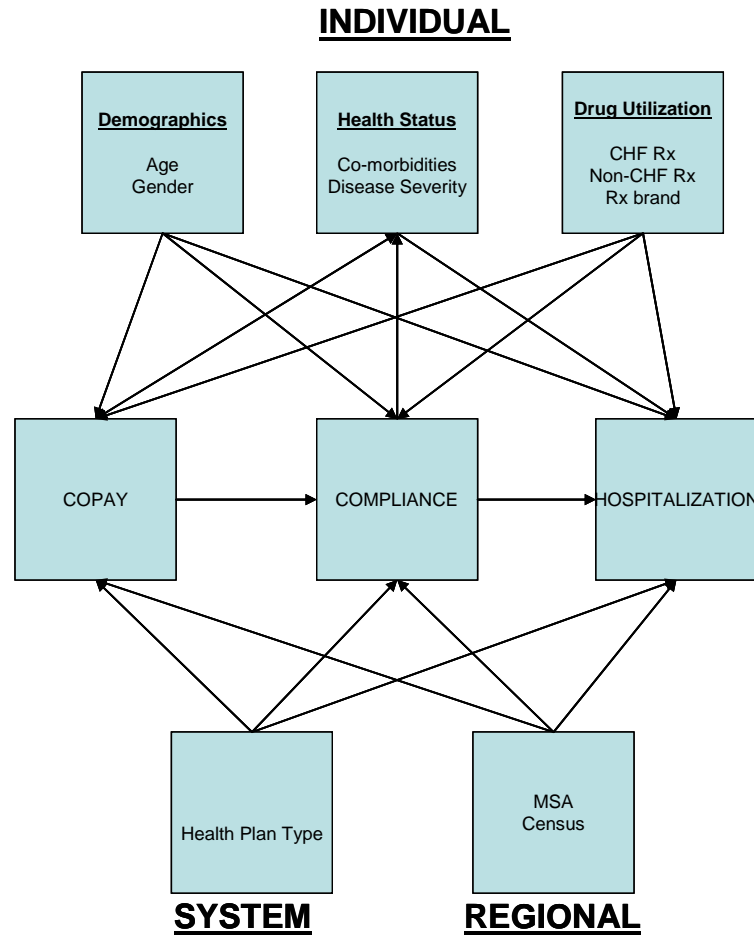
CLINICAL BACKGROUND

Clinically recommended therapies for heart failure patients at most stages of severity

include ACE inhibitors, diuretics, and beta blockers. Numerous clinical trials have

demonstrated the efficacy of ACE inhibitors in reducing morbidity and mortality in heart

failure patients of all severity levels (CONSENSUS 1987; SOLVD 1991; Cohn, Johnson et

al. 1991; Fonarow, Chelimsky-Fallick et al. 1992) while also improving symptoms, quality of

life, and increasing exercise tolerance (Andrews and Cowley 1995; Hunt, Abraham et al.

2005). Beta blockers have also demonstrated efficacy in decreasing hospitalizations, improving symptoms, and decreasing mortality in heart failure patients (Packer, Bristow et al. 1996; CIBIS-II 1999; MERIT-HF 1999). Diuretics are effective in decreasing symptoms of heart failure such as edema, but evidence is mixed in regards to mortality benefits.

Additional pharmacotherapy may be appropriate for treatment of heart failure. For example, aldosterone antagonists such as spironolactone indicated for class III / IV heart failure and eplerenone indicated for post-AMI left ventricular dysfunction have shown efficacy in improving survival rates in heart failure patients already taking ACE inhibitors (Pitt, Zannad et al. 1999; Hunt, Abraham et al. 2005). As a result, low doses of these medications in addition to ACE inhibitors, beta blockers, and diuretics are recommended to heart failure patients with New York Heart Association (NYHA) severity level III or IV (Hunt, Abraham et al. 2005; HFSA 2006). In the absence of detailed clinical information in the administrative claims data, it will be assumed that ACE inhibitors, beta blockers, and diuretics are clinically appropriate for all heart failure patients in the cohort regardless of severity level.

INDIVIDUAL LEVEL PATHWAYS

Individual level determinants such as age, gender, health status, or concomitant drug utilization may influence either physician prescribing patterns or the patient preference of a particular drug brand, therefore creating associations between these individual determinants and copayment levels. These factors may additionally influence medication compliance levels or hospitalizations, hence confounding the associations. As a result, these individual factors need to be included in the empirical models in order to prevent biased estimates.

DEMOGRAPHICS

Although associations between age, gender and medication compliance in the elderly have been inconsistent across numerous studies (Balkrishnan 1998), some disease specific analyses have found age and gender to be significantly associated with medication compliance. For example, Morris et al. found in a cross sectional analysis of baseline clinical trial data that increased age was associated with increased antihypertensive medication compliance (Morris, Li et al. 2006). Furthermore, Monane et al. found in a retrospective cohort analysis of New Jersey Medicaid beneficiaries diagnosed with heart failure that increased age, female gender and concomitant utilization of other medications indicated for heart failure were associated with higher medication compliance to digoxin (Monane, Bohn et al. 1994). Results from these studies imply that age and gender influence medication compliance in either hypertensive or heart failure patients.

In addition to age and gender being associated with medication compliance, they are also associated with heart failure risk. In a population cohort study affiliated with the Rochester Epidemiology Project in Olmstead County, Minnesota, results showed that compared to women, men had a higher risk of mortality during a four year follow-up period after heart failure onset (RR=1.33, 95% CI 1.24 – 1.43) (Roger, Weston et al. 2004). These results are further corroborated by the latest statistics compiled by the American Heart Association, showing that the rates of new and recurrent heart failure events increase with age, and are on average higher for men compared to women. More specifically, annual rates of new and recurrent heart failure events for non-black males is 21.5%, 43.3%, and 73.1% for the age categories 65-74, 75-84, and 85 and over. These rates are lower for non-black women, corresponding to annual rates of 11.2%, 26.3%, and 64.9% (Thom, Haase et al.

2006). These differences suggest that hospitalization rates increase with age, and are lower for women compared to men.

If age or gender is additionally associated with prescription copayment levels, omitting them from empirical models could result in biased estimates. For example, if older individuals, who are hypothetically more compliant compared to younger individuals, also select less expensive medications, omitting age from the models could result in overestimating (positively bias) the effects of copayments on compliance. Additionally, if older heart failure patients, who are hypothetically at higher risk of hospitalization compared to younger heart failure patients, also select less expensive medications, omitting age from the models could underestimate (negatively bias) the effect of copayments on hospitalizations. If gender differences also influence prescribing patterns, this same logic could extend to gender. Therefore, controlling for both age and gender in the empirical models will help attenuate possible bias due to confounding.

HEALTH STATUS

Although studies have found mixed results in terms of associations between number of co-morbidities and medication compliance (Balkrishnan 1998), the number of comorbidities is significantly associated with health outcomes. For example, hypertension and diabetes are significantly related to heart failure health outcomes. The Framingham study found that hypertension accounted for 39% and 49% of the risk of heart failure events in men and women, respectively. Additionally, diabetes increased the risk of heart failure 2-fold and 8-fold in men and women, respectively (Kannel and Belanger 1991). These results suggest that comorbidities present in heart failure patients may increase the risk of hospitalizations.

While health status determines the risk of hospitalization, the relationship between copayment level and health status is less clear. For example, if physicians selectively prescribe more expensive efficacious medications to more severe heart failure cases compared to mild cases, health status would determine copayment level. In contrast, if more expensive efficacious medications aid in decreasing heart failure severity more so than cheaper medications, copayment levels may help determine health status. These examples suggest that both prescription copayment levels and health status are endogenous, or can both *determine* or *be determined* by other variables already present in the empirical models. Because health status variables are conceptually associated with hospitalizations and copayment levels, they will be included in the empirical models.

<u>UTILIZATION</u>

Although the medication compliance literature consistently finds increased numbers of medications to be associated with poorer medication compliance (Balkrishnan 1998), one study examining compliance rates in heart failure patients initiating digoxin therapy found that compared to individuals taking fewer heart failure medications, those taking more heart failure medications had higher digoxin compliance rates (Monane, Bohn et al. 1994). In a separate study, Sharkness et al. conducted a survey to assess veterans' understanding of hypertension and pharmacy refills. Compared to those using one hypertensive drug, those using more than one hypertensive drug had greater overall compliance to hypertensive therapy (Sharkness and Snow 1992). Authors suggest that compared to patients taking only one medication for a particular chronic condition, patients taking more medications to treat one condition may have a greater perception of need to treat their condition, hence motivating them to comply better with their medications (Sharkness and Snow 1992).

Results of these studies imply that compared to heart failure patients taking only one required medication, such as ACE inhibitors, heart failure patients taking beta blockers and diuretics in addition to ACE inhibitors may be better compliers due to greater perception of need to treat their heart failure.

In addition to improving compliance, concomitant utilization of other heart failure medications improves health outcomes. As demonstrated in several landmark randomized clinical trials demonstrating the efficacy of beta blockers, the MERIT-HF, COPERNICUS, and CIBIS-II trials found that compared to individuals taking only diuretics and ACE inhibitors, those taking beta blockers in addition to these two medications had improved survival (1999; 1999; Fowler 2004) and reduced number of days spent in the hospital for any cause and for heart failure (1999; 1999; Fowler 2004). These results suggest that concomitant use of other heart failure medications may result in increased compliance as well as decreased hospitalizations. If concomitant utilization is also associated with the selection of less expensive medications, which could occur given the cumulative financial burden of three prescription copayments, omitting concomitant use from empirical models would bias parameter estimates.

Beyond concomitant use of other heart failure classes, medication selection within a class may also affect clinical outcomes. For example, although beta blockers as a whole are efficacious in improving morbidity and mortality among heart failure patients, only carvedilol, bisoprolol, and metoprolol succinate have had favorable effects in randomized clinical trials (Metra, Cas et al. 2004). Furthermore, in the COMET trial, carvedilol had greater efficacy in reducing mortality compared to metoprolol tartrate (Poole-Wilson, Swedberg et al. 2003). These results suggest that heart failure patients will have different

outcomes based upon the product. Since beta blockers also have different copayment levels, failing to control for drug product may contribute to spurious estimates of the association between copayment levels and hospitalizations.

The heterogeneity present in beta blockers is also present in the diuretics class, especially given that loop diuretics compared to thiazides have decreased effectiveness over time because of tolerance (Brater 1998). Furthermore, health outcomes may differ even between two types of loop diuretics. In a study examining hospitalization costs in heart failure patients, compared to those taking furosemide, those taking torsemide had significantly lower heart failure and cardiovascular specific hospitalization costs (Stroupe, Forthofer et al. 2000).

Results from both these studies suggest that intra-class differences in the efficacy of either beta blockers or diuretics may result in variation in hospitalizations, apart from the copayment level. Furthermore, if drug products also have different side effect profiles, compliance rates may also differ. The pooling of heterogeneous medications within the same class may be problematic in measuring effects of copayments on hospitalization. In order to capture these sources of bias, drug product fixed effects will be included in the empirical models.

In addition to the number of or the characteristics of heart failure medications affecting compliance, the total number of overall medications may also be associated with compliance, as established by the literature in this area (Balkrishnan 1998). In order to capture these potential effects, empirical models will also include measures for total unique medications as well as total out-of-pocket medication costs for all other medications beyond those indicated for heart failure.

In addition to individual level factors, the type of health plan may have a direct impact on medication utilization. For example, a survey conducted among elderly beneficiaries within a single health plan found differences in the probability of medication non-compliance based upon health plan type. Compared to PPO enrollees, more than twice as many Medicare enrollees reported occasionally or always skipping medications due to drug cost (Taira, Iwane et al. 2003). These results suggest that compared to beneficiaries enrolled in PPOs, those enrolled in Medicare managed care may be more sensitive to copayment increases. If faced with the same copayment level increase, Medicare managed care beneficiaries may be less compliant compared to PPO beneficiaries.

Although individual level case-mix partially explains the differences in prescription utilization in managed Medicare versus PPO beneficiaries, differing physician reimbursement incentives could also contribute to variation in prescription utilization. In a retrospective cohort study estimating the effect of prescription copayments on drug utilization and expenditures, Hillman et al. found that higher pharmacy copayments were associated with lower prescription drug spending in independent practice association (IPA) plans but with no change in prescription drug spending in staff HMO plans (Hillman, Pauly et al. 1999). These results suggest that the effect of prescription copayments on drug utilization depends upon health plan type. As proposed by the authors, these utilization differences may be due to physician reimbursement structures. For example, physicians under a staff-model HMO share less risk than those under an IPA HMO (Cangialose, Cary et al. 1997), implying that physicians bearing more risk in the care of their patient will prescribe less medications.

These results imply that increased financial risk is associated with decreased overall prescribing rates, and if these risk profiles differ between health plans, failing to measure system level differences may bias the true effects of copayments on medication use, especially if prescription copayment levels differ between health plan types. While controlling for health plan type within the empirical model may not capture differences in physician reimbursement incentives, it will at least capture some of the health plan level heterogeneity contributing to variation in prescription drug utilization. Furthermore, since health plans also have differing copayments, such as Medicaid versus commercial insurance, omitting plan type could result in spurious associations between copayment levels and medication compliance.

While type of managed care health plan may significantly affect prescribing rates via different physician reimbursement strategies, the associations between health plan type and clinical outcomes is less clear. Most of the literature in this area has examined these associations between managed care and fee-for-service plans. According to a systematic review article written in 1997 examining the impact of managed care on the quality of health care, although managed care plans often have lesser utilization rates compared to fee-for-service plans due to capitation, no systematic differences in clinical outcomes were found between fee-for-service plans and managed care plans (Cangialose, Cary et al. 1997).

Because these results only compare managed care versus fee-for-service, it is difficult to predict the impact of different subtypes of managed care on clinical outcomes. Similar to fee-for-service versus managed care plans, subtypes of managed care plans also have different risk-sharing structures. The amount of risk that the managed care organization bears depends upon the type of physician contract. In general, MCOs accept the least risk

with PPOs, and the most risk with staff-model HMOs (Cangialose, Cary et al. 1997). These contractual differences could translate into different physician practice styles due to financial incentives. For example, physicians employed by a staff-model HMO may be more encouraged to contain costs, given the increased risk to the insurer. In contrast, physicians under a PPO, most similar to the fee-for-service contractual agreement, assume more risk, and hence, may have be more liberal in their prescribing or ordering of services compared to their HMO counterparts.

These examples suggest that if reimbursement styles affect heart failure treatment, that plan type may affect heart failure medication prescribing rates, or even clinical outcomes depending upon how likely the physician will withhold or provide care as a function of financial incentives. Because differences in managed care plans may therefore affect the prescribing and quality of care received by heart failure patients, including health plan type in the empirical models will help control for these unobserved sources of heterogeneity.

REGIONAL LEVEL PATHWAYS

Geographical areas across the United States differ in their availability or quality of health resources. Access to quality heart failure management, for example, may be suboptimal in rural settings compared to urban settings, resulting in poorer outcomes and decreased adherence to clinically recommended medications. One study estimated differences in demographics, clinical severity, ACE inhibitor and beta blocker prescribing rates, and 1-year mortality rates in individuals discharged from rural versus urban health centers. Compared to individuals discharged alive from an urban health center, those discharged alive from a rural community health center had significantly higher NYHA severity levels, lower ACE inhibitor and beta blocker prescribing rates, and higher 1-year

66

mortality rates after discharge (Taubert, Bergmeier et al. 2001). This suggests rural disparities in the standard of care for heart failure patients could significantly contribute to the variation in compliance to heart failure medications and hospitalization. As a result, metropolitan statistical area (MSA) fixed effects will be included in empirical models to account for unobserved heterogeneity associated with geographical location.

While individuals' access to care potentially affects health outcomes, the market share of managed care services within a particular region may also affect health outcomes. One study measuring the associations between county-level managed market share levels and the utilization rates of beta blockers in elderly fee-for-service patients with myocardial infarction used managed market share levels as a proxy for managed care activity (Heidenreich, McClellan et al. 2002). Results showed that compared to areas with low managed care activity, areas with higher managed care activity had increased utilization of beta blockers and aspirin at discharge among fee-for-service elderly experiencing myocardial infarction. These results suggest that heart failure patients living in areas with high managed care activity may have a better standard of care.

In addition to differences in regional managed care activity, regional differences in heart failure specific standard of care may contribute to differences in prescribing patterns or hospitalization rates. In a study examining variation in heart failure care across US hospitals participating in the Acute Decompensated Heart Failure National Registry (ADHERE) (Fonarow, Yancy et al. 2005), 24%, 86%, 72%, and 43% of hospitals gave patients discharge instructions, assessed left ventricular function, prescribed ACE inhibitors, or gave smoking cessation counseling, respectively. Furthermore, the conformity of these four quality measures developed by the Joint Commission on Accreditation of Healthcare Organizations

(JCAHO) across hospitals was widely variable, ranging from 0% to 100%, with statistically significant differences occurring between academic and non-academic hospitals. Furthermore, the in-patient hospital mortality ranged between 0% and 11% (Fonarow, Yancy et al. 2005). These results suggest that significant differences in quality of heart failure care at the hospital level varies across geographical regions contribute to differences in ACE inhibitor prescribing patterns or hospitalization rates.

In addition to prescribing patterns and hospitalization rates, prescription copayment levels could also vary across geographic region. Since employers help determine cost-sharing levels during contract negotiations with health insurance providers, obtaining optimal copayments may also depend upon the ability of employers to effectively negotiate for the best health care premiums. Membership within employer health coalitions, for example, may help unite multiple employers into one purchasing alliance in order to negotiate one HMO rate for employees across all companies (Bodenheimer and Sullivan 1998). For example, one of the most influential employer health coalitions, Pacific Business Group on Health (PBGH), used a collective business strategy with great success in 1989 (Bodenheimer and Sullivan 1998). Regional differences in copayment levels could therefore be driven by certain MSAs having either a higher density of large employers or the presence of a health care coalition to help leverage more competitive premiums from health insurance companies.

If regional differences occur in prescription copayments, medication compliance, and hospitalizations, failing to control for region in the empirical models would result in biased estimates. Including MSA fixed effects or census region in the empirical models should capture the unmeasured heterogeneity contributing to regional variation in prescription

copayments, heart failure hospitalizations, or prescribing patterns, helping isolate the effects of copayment on medication compliance and hospitalizations.

PREDICTORS AND OUTCOMES

Health plans incur cost-sharing in the form of copayments in order to encourage individuals to select either preferred medications or less expensive medications on the formulary. Based upon economic theory, increased cost should result in decreased demand (Folland, Goodman et al. 2000), consistent with past literature demonstrating inverse relationships between copayment levels and medication utilization or medication compliance. If this decreased medication utilization is detrimental to health status, increased copayments may also be associated with increased hospitalizations or poor health status.

SUMMARY

The various individual, system, and regional level factors driven by clinical frameworks, behavioral theories, and consumer and market forces potentially confound associations among copayment levels, medication compliance, and hospitalizations. Accounting for these sources of variation should theoretically isolate the total copayment effects. The use of individual-level and regional-level fixed effects discussed more thoroughly in the methods chapter should additionally account for unobserved heterogeneity that would otherwise bias estimates found in traditional ordinary least squares empirical models.

CHAPTER III: METHODS

DATA SOURCE

Data originate from the Integrated Health Care Information Systems, Inc. (IHCIS) proprietary claims database containing de-identified inpatient, outpatient, and pharmacy claims representative of the United States commercial insurance carrying population. Claims are pooled from 30 different health plans in eight geographical census regions, are a balanced mixture of HMOs, PPOs, and POS plans, and contain over 38 million unique lives between December 1996 and May 2005 (IHCIS, 2005).

STUDY SAMPLE

Heart failure patients selected were those with either one inpatient claim or two outpatient claims with a primary diagnosis of chronic heart failure (ICD-9 code 428.x) in addition to at least one prescription claim of an ACE inhibitor, a beta adrenergic blocker (beta blocker) or a diuretic (Table 3.1). This combined disease and medication algorithm is a variation of one previously validated by Rector et al., finding a sensitivity of 49% and a specificity of 94% by using at least two heart failure claims (ICD-9 code 428.x) (Table 3.2) in addition to one beta blocker claim (e.g., carvedilol, metoprolol, or bisoprolol) over a 2-year follow-up period in order to identify heart failure cases (Rector, Wickstrom et al. 2004). Although Rector et al. found that adding pharmaceuticals indicated for other diseases increased the sensitivity of the algorithm (at the expense of decreasing the specificity)

(Rector, Wickstrom et al. 2004), the current analysis also included ACE inhibitors and diuretics in addition to beta blockers in the algorithm since all three medications are clinically recommended for heart failure.

Heart failure patients were 50 years of age or older and had three years of continuous prescription coverage and health insurance eligibility, the latter being defined as zero days between enrollment periods for a minimum of three years. Only individuals 50 years of age and above were included since chronic heart failure is most prevalent in older populations. This exclusion criterion was similarly applied to another study examining drug utilization in heart failure patients (Stroupe, Teal et al. 2004). Eligible heart failure patients were then divided into three non-mutually exclusive cohorts representing long-term ACE inhibitor, beta blocker, or diuretic utilizers. Long-term use was defined as individuals having used the medication for a minimum of three years from the date of the initial index drug prescription to either medication discontinuation or the last observed claim, whichever occurred first.

Medication discontinuation was defined as the date a prescription had a therapy gap greater than three times the days' supply; an adaptation of an algorithm used by Hamilton et al. defining a therapy gap as equivalent to two times the day supply (Hamilton and Briceland 1992). Re-defining therapy gaps with longer periods of time ensures that individuals have indeed discontinued therapy. For example, using the Hamilton et al. algorithm, individuals filling a 30-day supply of ACE inhibitors on July 1, 2002 and waiting until September 10, 2002 (more than 60 days later) for a subsequent prescription would be defined as discontinued on July 1, 2002. Though if temporary inter-class switching occurs, for example between ACE inhibitors and angiotensin receptor blockers, sixty days may be too soon to classify an individual as discontinued, especially if they temporarily shift out of the dataset to

71

use angiotensin receptor blockers (ARBs). Hence, extending the therapy gap requirement to 90 days in this case decreases the likelihood of mistakenly classifying non-discontinuers as discontinuers.

SAMPLE SIZE

The source population contained 38,373,738 individuals, 151,051 (0.4%) of whom had at least one inpatient or two outpatient claims with a primary diagnosis of heart failure occurring during any health insurance enrollment period between 1997 and 2005. Of these 151,051 individuals with heart failure diagnoses, 87,808 (58%) had at least one prescription claim for an ACE inhibitor, beta blocker, or diuretic (Table 3.3). These 87,808 (0.2%) individuals represent the prevalent heart failure cases in the IHCIS using the adapted algorithm by Rector et al. (Rector, Wickstrom et al. 2004).

Heart failure cases were further reduced to 77,098 after restricting to individuals aged 50 years and older with continuous pharmacy benefit throughout all enrollment periods. Only 11,944 (15%) of these 77,098 individuals, had three years of continuous health care coverage defined as zero days between eligibility periods for 1,095 consecutive days (e.g., 3 years).

This cohort of 11,944 continuously eligible heart failure patients were then divided into three non-mutually exclusive cohorts of 2,190, 4,409, and 5,918 (50%) ACE inhibitor, beta blocker, and diuretic utilizers, respectively, representing individuals having at least three years elapse between the index prescription date and the last observed drug-class specific claim. After excluding individuals with significant therapy gaps within this three year period, the final cohort was comprised of 1,172, 2,676, and 3,212 ACE inhibitor, beta blocker, and diuretic utilizers (Table 3.1).

Table 3.1: ACE inhibitors, beta adrenergic blockers and diuretics indicated for chronic heart failure

ACE Inhibitors	Beta adrenergic blockers	Diuretics
• Accupril®, quinipril • aceon • Ramipril®, altace • Capoten®, captopril, • Vasotec®, enalapril • Monopril®, fosinopril, • Lexxel® • Prinivil®, Zestril® lisinopril • Lotensin®, benazepril • Lotrel® • Mavik®, trandolapril • Tarka® • Univasc®	• Tenormin®, atenolol • Zebeta®, bisoprolol • Coreg®, carvedilol • Lopressor® Toprol®. Metoprolol	• Aldactazide®, spironolactone+HCTZ • Aldactone®, spironolactone • Bumex®, bumetanide, • Demadex®, torsemide • Lasix®, furosemide, • Hydrochlorothiazide (HCTZ), Microzide®, Hydrodiuril®, Esidrix®, Oretic® • Zaroxolyn®, metolozone

Table 3.2: Heart failure diagnoses included in (428.xx) (Adams, Fonarow et al. 2005)

ICD-9 Code	Disease Description
428.00	Heart failure, unspecified
428.10	Heart failure; left heart failure
428.90	Heart failure; unspecified
428.20	unspecified systolic heart failure
428.21	Acute systolic heart failure
428.22	Chronic systolic heart failure
428.23	Acute on chronic systolic heart failure
428.30	unspecified diastolic heart failure
428.31	Acute diastolic heart failure
428.32	Chronic diastolic heart failure
428.33	Acute on chronic diastolic heart failure
428.4	unspecified combined systolic and diastolic heart failure
428.41	Acute combined systolic and diastolic heart failure
428.42	Chronic combined systolic and diastolic heart failure
428.43	Acute on chronic combined systolic and diastolic heart failure

The final cohorts therefore represent select samples of continuously enrolled heart failure patients prescribed ACE inhibitor, beta blocker, or diuretic pharmacotherapy for at least three years.

Complete case analysis was performed in the final dataset, dropping an additional 11% of individuals from each of the cohorts due to missing information on Metropolitan Statistical Area (MSA). The final analytic samples contained 1,026, 2,345 and 2,812 individuals for the ACE, beta blocker, and diuretic analysis, respectively. Datasets contained 34,921, 77,571, and 96,588 refill observations for ACE, beta, and diuretics respectively, averaging approximately 33 refills of various day supply amounts per individual over an average of four years of follow-up. Individuals were followed for an average of 4 years including the baseline year.

DESIGN

A retrospective cohort was conducted to measure associations between prescription copayment levels and medication compliance at the refill and person-year level, as well as associations between copayment levels and hospitalizations at the person-year level. For the copayment and compliance regressions, the refill level design measured compliance levels associated with each unique prescription refill. In contrast, the person-year design averaged copayment levels and medication compliance over multiple refills at the annual level. For the copayment and hospitalization regressions, individuals were identified as having a hospitalization, a cardiovascular disease-specific (ICD-9 code 410.xx – 414.xx; 428.xx) or a heart failure specific hospitalization (ICD-9 code 428.x) anytime during a particular follow-up year, and prescription refill copayment medians were aggregated at the follow-up year level.

Three non-mutually exclusive cohorts were constructed, corresponding to each of the three heart failure classes examined: ACE inhibitors, beta blockers, and diuretics. Cohort datasets contained a minimum of three years of ACE inhibitor, beta blocker, or diuretic refills for each individual. Because individuals were often taking more than one heart failure medication, the cohorts were not mutually exclusive.

The date of heart failure diagnosis was defined as the date of the first heart failure prescription drug claim subsequent to the accumulation of either one inpatient or two outpatient heart. Each respective cohort defined the beginning of follow-up as the index prescription date following the heart failure diagnosis and the end of follow-up as the last index claim contained in the claims data or the last prescription before a significant therapy discontinuation gap. Given the staggered index dates for each individual, unique annual and monthly time periods were constructed to match control variables to the relative months and years following the index date. For example, all the claims occurring between February 15, 2003 and February 15, 2004 for an individual in the ACE inhibitor cohort with an index date of February 15, 2003 were considered baseline year level claims. Similarly, any claims occurring between February 15, 2004, and February 15, 2005 were considered the second year claims. This same logic was used in assigning monthly time periods. For example, any claims occurring between March 15, 2003 and April 15, 2003 were marked as month 2. Applying these time periods to inpatient, outpatient, and prescription claims allowed control variables to be merged into the appropriate person-year or person-month observation.

Table 3.3: Resulting sample sizes after applying exclusion criteria

Criteria	Sample size (N)
IHCIS source population	38,373,738
1 inpatient or 2 outpatient primary diagnoses for CHF (428.x)	151,051
1 heart failure drug claim (ACE inhibitor, beta blocker, or diuretic) subsequent to CHF diagnosis code accumulation	87,808
Continuous prescription drug coverage	86,409
Age 50 years and above	77,098
3 years of continuous enrollment in health plans	11,944
3 years between index drug and last observed claim	2,190 (ACE inhibitors) 4,409 (Beta blockers) 5,918 (Diuretics)
3 years between index drug and either discontinuation gap or last observed claim	1,172 (ACE inhibitors) 2,676 (Beta blockers) 3,212 (Diuretics)
No missing information on Metropolitan Statistical Area (MSA)	1,026 (ACE inhibitors) 2,345 (Beta blockers) 2,812 (Diuretics)
Total refill observations[1]	34,921 refills (ACE inhibitors) 77,571 refills (Beta blockers) 96,588 refills (Diuretics)

1: Before excluding refills with MPR outliers

MEASUREMENTS

COPAYMENT LEVELS

The original copayment code in the database corresponded to ten copayment

classifications, reflecting the total patient out-of-pocket expenses for a prescription refill

(Table 3.4). The prescription claims also have a range of values for days supply. In

addition to standard 30-day multiples, refills also had supply levels under 30 and over 90

days. In order to create comparable copayment levels between refills across individuals,

copayment levels were standardized to 30-day supply amounts. Because the copayment

in IHCIS was a categorical variable defining a particular range of copayment amounts, each refill was assigned the median copayment amount before transformation (Table 3.4).

Table 3.4: Copayment level categories

Copayment Level	Range	Median Copayment
A	$0	$0
B	$1 - $5	$3
C	$6 - $10	$8
D	$11 - $15	$13
E	$16 - $20	$18
F	$21 - $25	$23
G	$26 - $30	$28
H	$31 - $35	$33
I	$36 - $50	$38
J	$50 +	$50*

*Assigned to the lower boundary given no information on upper boundary

A conversion factor was computed by dividing 30 by the observed refill day supply amount (Eq. 3.1).

Equation 3.1:
Conversion Factor = 30 / prescription refill day supply

The assigned copayment median was then multiplied by the conversion factor to obtain a standardized 30-day supply copayment amount (Eq. 3.2).

Equation 3.2:
*Standardized 30-day copayment = conversion factor * copayment median*

This calculation assumes a 90-day supply of medications to be three times as expensive as a 30-day supply, or a 10-day supply of medications to be one-third as expensive as a 30-day supply. Since these newly converted copayment values were not integers, they were reassigned to copayment categories based upon the original dataset, resulting in eight mutually exclusive categories after collapsing the highest three categories into one (Table 3.5).

77

Table 3.5: Newly converted copayment level categories

Newly assigned copayment category	Standardized 30-day copayment levels
A	$0
B	$1 - $5
C	$6 - $10
D	$11 - $15
E	$16 - $20
F	$21 - $25
G	$26 - $30
H I J	$31 +

MEDICATION COMPLIANCE

The Medication Possession Ratio (MPR) was used to capture ACE inhibitor, beta blocker, and diuretic medication compliance. The MPR captures the percentage of medication supply coverage within a defined interval of time, based upon the day supply of medication and the amount of calendar days elapsing between two refills. It is computed by dividing the total day supply of medications by the total number of days that elapse before an individual returns to the pharmacy for the next prescription refill (Eq. 3.3). This computation as well as other variations have been described and validated using managed care administrative claims data (Steiner, Koepsell et al. 1988).

Equation 3.3:
MPR = total days supply within interval A / calendar days elapsing during interval A

The MPR theoretically ranges from 0 to 1. For example, individuals filling a 30-day supply of ACE inhibitors on May 1, 2005 and picking up a subsequent refill on June 1, 2005 will have an MPR of 1, reflecting 100% compliance. In contrast, individuals filling a 30-day supply on June 1, 2005 and picking up a subsequent refill on August 1, 2005 will have an MPR of 0.5, reflecting 50% compliance. In practice, the MPR can be

above 1, reflecting an oversupply of medication. For example, individuals filling a 30-day supply on June 1, 2005, and picking up a subsequent refill on June 16, 2005, will have an MPR of 2, reflecting an over-consumption of 30 days of medication within 15 days. More extreme MPR values, though, are more likely to reflect intentional, clinically appropriate medication switching rather than over-consumption. For example, individuals filling a 90-day supply of hydrochlorothiazide on February 1st may switch doses on February 3rd, reflected as an MPR of 45. Since these extreme outliers probably are more reflective of switching rather than non-compliance, refills with associated MPR values over three standard deviations above the overall MPR mean were not included in the final analytic dataset.

The MPR was calculated at both the refill and the person-year level. At the refill level, the MPR was computed by dividing the days supply for refill *r* by the number of calendar days elapsing between the rth and the $(r+1)^{th}$ refill (Eq. 3.4). This required eliminating the final observed refill for each individual since subsequent refills are needed in order to compute the MPR.

Equation 3.4:
MPR $_{(refill\ r)}$ = total days supply $_{(refill\ r)}$ / [# of calendar days between (refill r) & (refill r+1)]

While measuring medication compliance at the refill level maximizes the degrees of freedom as well as the variability of the outcome, single interval compliance measures such as those computed over a 30-day period may be less reflective of true medication adherence compared to multiple interval measures computed over 90-day periods. In a study examining compliance to anti-hypertensive therapy, Christensen et al. found that observation periods less than 60 days may have introduced unobservable sources of bias, while measuring compliance over 90-day intervals or more was preferred (Christensen,

Williams et al. 1997). Therefore, to complement refill level analyses, medication

compliance was also measured at the person-year level by averaging refill MPR over 12-

month periods (Eq. 3.5).

Equation 3.5:
$MPR_{(person-year)} = Sum [MPR_{(refill)} (person-year level) / N_{(refills)} (person-year level)]$

HOSPITALIZATIONS

In the analyses measuring associations between copayment levels and

hospitalizations, hospitalizations were defined as annual level binary indicator variables,

capturing whether individuals did or did not have an inpatient claim during any particular

follow-up year. In models estimating probabilities of all-cause hospitalizations, any

inpatient encounter was considered a hospitalization. For models estimating probabilities

of disease-specific hospitalizations, individuals having hospitalizations coded with a

primary diagnosis (ICD-9 code 410.xx – 414.xx, 428.xx) or (ICD-9 code 428.xx) were

considered hospitalized for cardiovascular disease and heart failure disease, respectively.

CONTROL VARIABLES

OVERVIEW

Five sets of control variables were constructed depending upon the outcome, the

unit of analysis, or the requirements for testing mediation (Table 3.6). Common control

variables constructed similarly across all five sets included demographic variables such

as age, gender, and health plan type. Regional area effects were captured by using

metropolitan statistical area (MSA) and census region fixed effects for refill level and

person-year level analyses, respectively. Health status variables included total number of

annual comorbidities and total number of all-cause hospitalizations in the previous year,

the latter a proxy for heart failure severity in the absence of more detailed clinical information in administrative claims data. All refill-level analyses controlled for drug product brand within each analysis in order to capture brand-level effects. Other control variables included history of medication compliance, constructed as a continuous variable in compliance models. The mediation models, which test whether non-compliance (MPR<0.80) significantly contributes to the association between copayment level and hospitalizations, captured non-compliance as a binary indicator variable in select hospitalization outcome models. Heart failure specific medication use variables, total out-of-pocket prescription costs, and total number of unique drugs were constructed as monthly or annual binary indicator variables depending upon the unit of analysis. Time variables included total time of follow-up in addition to calendar year fixed effects.

DEMOGRAPHICS

Age, gender, and health plan type were constructed the same way for all models. Age was captured by subtracting the year of the prescription claim from the birth date year provided in plan eligibility file. Gender was a categorical variable present in the eligibility files. Health insurance type was captured during baseline year in two ways: one variable indicated whether the managed care plan was administered by the government or by a commercial entity, a second variable indicated the physician reimbursement type. The former was classified as a three level categorical variable of either commercial, Medicare, or Medicaid managed care, the latter classified as a five level categorical variables of HMO, PPO, POS, independent, or other health plan types.

81

Table 3.6: Control variable definitions within empirical models

	E(MPR)=f (copay)		Pr(MPR<0.8) = f(copay)	Pr(Hosp) = f(copay)	
	Refill Level	Person-Year Level	Person-Year Level	Person-Year Level	
				Direct Effect[1]	Total Effect[2]
Demographics					
Age	X	X	X	X	X
Gender	X	X	X	X	X
Insurance Payer	X	X	X	X	X
Health Insurance plan type	X	X	X	X	X
Metropolitan Statistical Area (MSA)	X	.	.	.	.
US Census Region	.	X	X	X	X
Health Status					
Charlson comorbidity index	X	X	X	X	X
Total number of hospitalizations in previous year	X	X	X	X	X
Medication Utilization					
Monthly non-index CHF drug utilization (yes/no)	X	.	.	.	.
Annual non-index CHF drug utilization (yes/no)	.	X	X	X	X
Monthly aldosterone antagonist utilization (yes/no)	X	.	.	.	.
Annual aldosterone antagonist utilization (yes/no)	.	X	X	X	X
Monthly sum of non-index prescription copayments	X	.	.	.	.
Annual average of monthly sum of non-index prescription copayments	.	X	X	X	X
Monthly count of non-index prescriptions	X	.	.	.	.
Annual average: monthly count of non-index prescriptions		X	X	X	X
Average annual index drug MPR during previous year	X	X	X	.	.
Annual average compliance level in current year (MPR<0.8)[3]	.	.	.	X	.
Drug product indicator	X	.	.	.	.
Time indicators					
Total number of follow-up days	X	X	X	X	X
Calendar year fixed effects	X	X	X	X	X

1)Direct effect models include potential mediator (MPR<0.80) as a control variable
2) Total effect models omit potential mediator as control variable
3) Potential mediator

Geographical region was defined as metropolitan statistical area (MSA) or census region in refill and person-year analysis, respectively. MSAs are defined as the regions corresponding to the first three digits of a United States postal code. Given the sufficient number of observations in the refill analyses, unique dummy variables for each MSA were included in the refill-level models in order to capture regional-level unobserved heterogeneity. The person-year level analyses used census region information, dividing the United States into Northeast/Atlantic, South, Midwest, West, and National, the latter category referring to individuals purposely censored from census classification by the data vendor given the presence a rare disease or procedure which could increase the probability of patient de-identification.

HEALTH STATUS

The number of co-morbidities was constructed using the Charlson comorbidity index (Charlson, Pompei et al. 1987) adapted to the most current ICD-9 CM codes based upon a study by Sundararajan et al (Table 3.7) (Sundararajan, Henderson et al. 2004). The Charlson index is comprised of fifteen categories of diagnoses ranging from diabetes to metastatic cancer, each contributing weight to the final index based upon the severity of the disease. In the current analysis, an individual was defined as having a diagnosis during baseline year based upon having at least one inpatient or outpatient claim with an ICD-9 code for a particular disease category. A summary index number was assigned to each individual based upon claims during the baseline year. In the absence of heart failure severity level information, total number of hospitalizations at baseline was used as a proxy for heart failure

severity by summing the total number of unique admissions dates per person per follow with
a one-year lag.

UTILIZATION

Concomitant heart failure drug utilization was captured at the monthly and annual
levels for the refill and person-year analysis, respectively, using binary indicator variables for
the non-index drugs. This vector included either monthly or annual indicators of the other
two classes of drugs required for heart failure. For example, models measuring the effect of
ACE refill copayment level on ACE inhibitor refill compliance had a separate monthly
binary indicator variables for beta blocker and diuretic utilization. These concomitant
utilization indicators were aggregated to the annual level for person-year level analyses. An
additional monthly or annual indicator variable for aldosterone antagonists was also included
in the models.

Table 3.7: Charlson Comorbidity Index Disease Categories (Sundararajan, Henderson et al.
2004)

Condition	ICD-9 Codes	Weight
Acute myocardial infarction	410.x, 412.x	1
Congestive heart failure	428.x	1
Peripheral vascular disease	441.x, 443.9, 785.4, V434	1
Cerebral vascular accident	430.x - 438.x	1
Dementia	290.x	1
Pulmonary disease	490 - 496; 500 -505	1
Peptic ulcer	531 – 534	1
Liver disease	571.2, 571.4, 571.5, 571.6	1
Diabetes	250.0, 250.1, 250.2, 250.3, 250.7	1

Table 3.7: Charlson Comorbidity Index Disease Categories (continued)

Condition	ICD-9 Codes	Weight
Diabetes complications	250.4, 250.5, 250.6	2
Paraplegia	342, 244.1	2
Renal disease	582, 583.0, 583.1, 583.2, 583.4, 583.5, 583.6, 583.7, 585.x, 586.x, 588.x	2
Cancer	140.x, 150.x, 160.x, 170.x, 171-172, 174-176, 179-180, 190-195	2
Metastatic cancer	196, 197, 198, 199.0, 199.1	3
Severe liver disease	572.2, 572.3, 572.4, 572.8	3
HIV	0.42, 0.43, 0.44	6

In addition to class-specific utilization variables, out-of-pocket prescription expenses as well as total number of unique drugs across all prescriptions besides the index drug of interest were captured as monthly average continuous variables. For the refill level analysis, total out-of-pocket prescription copayments were constructed at the monthly level by summing the medians of the copayment ranges of all non-index prescription within each respective month of follow-up. These sums were averaged at the annual level for the person-year analyses. In conjunction with total out-of-pocket expenses, the total number of unique non-index concomitant medications was constructed at the monthly level by summing the number of unique National Drug Codes (NDC) contained within each month of follow-up. These sums were averaged at the annual level for the person-year analyses. Since history of medication compliance is a significant predictor of future medication compliance, all models accounted for history of drug compliance at the refill and person-year analyses. This was constructed by averaging all refill MPRs at the person-year level and lagging this measure by one year. An additional binary indicator for non-compliance (MPR<0.8) was included as the

potential mediator in the logistic regressions estimating the probability of hospitalization conditional upon copayment level. Drug product fixed effects were captured by creating dummy variables for the drug product brand in the refill-level analyses in order to account for intra-class differences. In addition to medication utilization variables, total follow-up time was captured as the number of days elapsing since the index date, while annual trends were captured using calendar year fixed effects.

ANALYSIS

ECONOMETRIC TECHNIQUES DISCUSSION

Ordinary least squares (OLS) estimators using multivariate linear regression result in the best linear unbiased estimates if a) a linear relationship exists between the independent variable and the dependent variable; b) observations included in the analysis are a random sample from the source population; c) observations are independent; d) the error has an expected value of zero; e) there are no exact linear relationships among the independent variables, minimizing the presence of multicollinearity; and f) the variance of the error term is constant over all values of the outcome (resulting in homoskedastic errors) (Wooldridge 2003).

Since the current analysis uses a panel dataset consisting of multiple outpatient and inpatient encounters and prescription refills collected over time for the same individuals, it violates the assumption of independent observations. This violation is inevitable especially within panel because observations are not independently distributed over time (Wooldridge 2003). This non-independence occurs because of unobserved time-varying factors that affect the values of the outcome in both time periods. For example, unobserved income levels

affecting ACE inhibitor compliance in 1997 could also affect ACE inhibitor compliance in 1998, creating correlations between the outcome and the error term. Since OLS estimators in the context of panel data most likely result in biased estimates given this routine violation of non-independent observations, more advanced models such as fixed effects or random effects estimators must be used.

One of the main limitations of the OLS estimator is the creation of a common slope and intercept for all observations. This may be appropriate for cross-sectional data, but could limit the ability to account for inter-individual differences for longitudinal data (Ward and Leigh 1993). Similar to the OLS models, the FE model creates a common slope, but in contrast to OLS models, creates separate intercepts for each individual which helps account for idiosyncratic characteristics of individuals (Ward and Leigh 1993). Separate fixed effect intercepts therefore allow models to account for individual level differences otherwise lost in a single OLS intercept.

Fixed effects estimators divide the composite error (v_{it}) into unobserved time-varying factors (μ_{it}) and unobserved time-invariant factors (a_i), the latter of which are referred to as the fixed effects (Eq. 3.6). Examples of time-invariant factors at the individual level may be race, educational background, or genetic predisposition to cardiovascular risk factors. The fixed effects estimator uses a differencing technique to eliminate the unobserved time-invariant heterogeneity (a_i), (Wooldridge 2003) which would otherwise lead to biased OLS estimators. More specifically, fixed effects estimators subtract the overall group mean of a variable ($\mathbf{y_i}$) from each individual observation (y_{it}) creating a 'time-demeaned' data point ($\ddot{Y}_{it}$) (Wooldridge 2003) (Eq 3.7).

Equation 3.6:
$v_{it=}(a_i + \mu_{it})$

Equation 3.7:
$$\ddot{Y}_{it} = y_{it} - \mathbf{y_i}$$

Differencing values as well as errors across time periods within individuals eliminates

the heterogeneity of the time invariant unobserved variables (a_i). If these unobserved factors

(a_i) are indeed time-invariant, and are hypothetically correlated with the predictor ($\mathbf{X}_{it}$), the

fixed effects differencing technique successfully eliminates these factors as sources of bias

(Wooldridge 2003). For example, since race is unobserved and time-invariant, the variation

it contributes to copayment levels during 1999 and 2000 is also constant. The process of

differencing will not only subtract group means from individual observations (Eq. 3.6)

between the years 1999 and 2000 for observed variables, it will also difference the errors. If

time-invariant latent constructs such as race do not change between two particular years, the

differencing process rids the model of the unobserved heterogeneity due to race as well as

any other time-invariant omitted variable. Furthermore, if race is correlated with prescription

copayment levels, fixed effects models would in theory provide unbiased estimates when all

the other assumptions of linear models are met.

In certain cases, time-invariant unobservables may not be correlated with the

predictor, a scenario motivating the use of the more efficient alternative, the random effects

estimator. If time-invariant unobservables (a_i) are uncorrelated with the predictor (X_{it}), the

latent constructs contained within (a_i) become part of the random error term, and do not need

to be differenced in order to obtain unbiased estimates. Given this orthogonal relationship

between the time-invariant error (a_i) and the predictor ($\mathbf{X}_{it}$), using the OLS estimator would

seem like a viable option since OLS assumes no correlations between regressors and the error

term. Yet, because the panel data structure inherently creates serially correlated errors

through multiple observations per person, this violates the OLS assumptions of non-independent errors, and thus creates biased standard errors (Wooldridge 2003). To correct this, the RE estimator uses sophisticated matrix algebra to remove the effects of serially correlated errors, in essence creating a more efficient version of the OLS estimate (Wooldridge 2003). The efficiency advantage of RE over OLS is contingent upon the assumptions of the error structure, including homoskedastic errors, no autocorrelation within an individual, and no correlation across groups (Greene 2003). In summary, FE estimation techniques take advantage of repeated observations to adjust for time-invariant unobserved heterogeneity that would have otherwise led to biased estimates in standard OLS models. In situations where time invariant unobservables are orthogonal to the predictor, usually motivating the use of OLS estimators in cross-sectional analyses, the RE estimator can be used to obtain a more efficient version of the OLS estimator contingent upon the error structure satisfying strict assumptions.

Applying these concepts to an example, one may hypothesize that an individual's income level, an unobserved construct in the current analysis, is correlated with copayment level. If income is time-invariant, likely if elderly heart failure patients have fixed income levels, income becomes part of the time-invariant unobservable portion (a_i) of the composite error (ε_{it}), creating a correlation between the predictor and the error. Compared to individuals with low income, individuals with higher income may have an increased probability of selecting into a brand name drug over a generic, hypothetically creating a positive correlation between copayment level ($\mathbf{X}$) and the time-invariant portion (a_i) of the error term (ε_{it}). If income truly varies systematically with copayment levels, creating a positive correlation between copayment (X) and the time-invariant portion of the error term

$[(\mathbf{X}, a_i) \neq 0]$, FE would be an appropriate model. In contrast, if income varies randomly across different copayment levels, creating an orthogonal relationship between the copayment and (a_i), $[(\mathbf{X}, \mu_{it}) = 0]$, RE would be the more appropriate model.

Under either of these scenarios, OLS would have biased standard errors given the presence of serial correlation between repeated observations. Additionally, if time-invariant factors were correlated with the predictors, OLS would have biased parameter estimates in addition to biased standard errors compared to FE estimates. In all situations, if the unobserved income levels vary across time and were correlated with both copayment levels, all models would produce biased estimates.

Given the different error assumptions of OLS, FE, and RE, formal specification tests were performed in order to choose the best estimator. To test between the OLS and RE models, the Bruesch Pagan Lagrange Multiplier test (Bruesch and Pagan 1979) was used to test the null hypothesis that refills within an individual are independent. This was equivalent to testing the null that refills are not clustered within an individual. Rejecting the null hypothesis would favor the RE model over the OLS models, implying that refills are not independent observations within the individual, suggesting clustering of refills at the individual level. An example of a cluster may be a series of refills with high MPR values grouped within an individual because of an unobservable factor, such as titration of a new medication. If this requires a series of early refills, manifested as high MPR values in the datasets, this cluster of refills would be correlated with medication titration, a part of the error term. In summary, conducting the Bruesch Pagan test helps identify the presence of clustering, which gone undetected, would result in choosing an inappropriate estimator with biased standard errors.

To test between the FE and RE models, the Hausman test (Hausman 1978) was used to test the null hypothesis that the slopes of the RE and the FE do not differ significantly. When conducting the Hausman, one of the estimators must be used as a comparator. For example, it must be assumed that one estimator is always consistent (unbiased) yet may be inefficient, while another estimator maybe efficient yet inconsistent (biased). Under these circumstances, the FE would always be consistent, but may be inefficient compared to the RE model given the extra degrees of freedom needed to create 'time-demeaned' data points (Wooldridge 2003). In contrast, the RE would be more efficient compared to the FE, but may be inconsistent due to the presence of correlation between time-invariant unobservables and the predictor of interest. Rejecting the null hypothesis would favor the FE model over the RE model, implying that time-invariant unobservables are correlated with the regressors. This would most likely occur if race, education, or income influenced the choice of brands over generics, creating a correlation between the error term and copayment levels.

To test between OLS and FE models, an F-test was used to test the null that the fixed effect intercepts are equal to zero. Rejecting the null hypothesis would favor the FE model, implying that the fixed effects are significantly contributing to the fit of the model, and OLS or RE models would produce biased parameter estimates. This would provide evidence that separate intercepts for all observations, although using extra degrees of freedom, are helpful in capturing individual level unobserved heterogeneity.

In summary, standard linear regression of panel data can result in inefficient standard errors due to non-independent observations clustered within units of analyses. Using FE models may be advantageous in accounting for individual level differences as well as unobserved time-invariant factors. Using RE models may be advantageous in accounting for

91

serial correlation or clustering which would otherwise result in biased OLS standard errors. Though the structure of panel data allows for adjusting time-invariant errors in the FE models, these methodologies are not immune from omitting time-varying variables. For example, if modifiable heart failure risk factors such as smoking status are correlated with copayment levels, associations between copayments and hospitalizations would be biased.

Ordinary least squares (OLS), fixed effects (FE) and random effects (RE) models within the context of panel data were considered in estimating the expected value of MPR conditional upon copayment level for ACE inhibitors, beta blockers, and diuretics. Because OLS, RE, and FE each have their own set of error distribution assumptions, specification tests were performed to compare and choose the most efficient and unbiased parameter estimates. Ordinary least squares, random effects, and fixed effects models may be more or less appropriate depending upon the structure of the errors. Due to this, the Bruesch-Pagan, Hausman and F-tests were conducted to motivate the best estimator.

PRESCRIPTION COPAYMENTS AND MEDICATION COMPLIANCE

Ordinary least squares, individual random effects, and individual level fixed effect models were used to assess the effect of copayment level on compliance at the refill and person-year level, controlling for demographics, health status, drug utilization, time and metropolitan statistical area (MSA). Analyses conducted at the refill level measure associations between the copayment refill level and the refill's subsequent MPR. The short latency between the 'exposure' (the refill copayment) and the 'outcome' (the compliance level associated with that refill) may facilitate the ability to infer causality between

copayment levels and medication supply levels. Although the refill level analysis was helpful in determining the effects of copayment levels on the most proximal medication supply levels, the person-year analyses was helpful in aggregating refill-level MPR values, smoothing out relatively noisy single MPR measures which may not reflect true individual level compliance levels.

The final analytic dataset contained a minimum of two years of follow-up for each individual, using the observations in first year as baseline measurement for health status and medication compliance history. In the equations illustrated below (Eq. 3.10; 3.11) the vector **Copayment** includes dummy variables for the seven different copayment level categories, utilizing the $0 category as the reference: $1 to $5, $6 to $10, $11 to $15, $16 to $20, $21 to $25, $26 to $30, and $31 and above. These copayment categories corresponded to individual refills and annual averages across refills for the refill analysis, and person-year analyses, respectively. Given the low frequency of more expensive beta blockers and diuretics that resulted in small sample sizes and unstable estimates, upper copayment observations were collapsed. For example, the beta blocker analysis collapsed the upper two levels to create a copayment category of $26 and above, and the diuretic analysis collapsed the upper five levels to create a copayment category of $11 and above.

The vector **Demographics** includes individual age, health plan types, and gender. The vector **Health** includes the Charlson comorbidity score and total hospitalizations at baseline, the latter health status variable serving as a proxy for heart failure severity. The vector **Utilization** for the refill level analysis includes monthly utilization binary indicators for non-index heart failure medications (e.g., binary indicators for ACE inhibitors and diuretics for the beta blocker model; binary indicators for beta blockers and diuretics for the

ACE inhibitor model, etc), monthly count of unique non-index prescriptions, total monthly out-of-pocket prescription copayments for non-index prescriptions, and history of index-drug compliance captured by annual average MPR values in the previous year. In addition, the ACE, beta blocker, and diuretic refill analyses contain 15, 8, and 11-level drug product dummy variables respectively, each level corresponding to a different drug product contained within each medication class. For the person-year analysis, the utilization vector was collapsed to the person-year level, containing binary indicators for annual utilization of non-index chronic heart failure drugs, annual average monthly counts of unique drugs, and annual average monthly out-of-pocket copayments for non-index drugs. Drug product fixed effects were not included in these models given the frequent drug product switching.

Refill level models capture geographic fixed effects by including *N-1* dummy variables for *N* metropolitan statistical areas (MSA), designed to capture sources of copayment level and hospitalization rate variation at the metropolitan area. To preserve degrees of freedom, individual-level models captured geographic fixed effects using census regions instead of MSA regions. All models controlled for annual trends with calendar time fixed effects, constructing a dummy variable for each respective year of follow-up, as well as a variable capturing total study follow-up time.

Notations for the empirical models include subscripts referring to the level of variation of the variable (Eq. 3.10, 3.11). For example, baseline year demographics vary between individuals only, not across time, as indicated by subscript *i*. In refill analyses, MPR values vary by refill, individual, and time, indicated by the subscripts *r*, *i*, and *t*. In contrast, MPR varies only by individual and time in person-year analysis, indicated by subscripts *i* and *t*, given that individual refill observations are collapsed to the person-year

level. The errors are depicted as either ($\varepsilon_{(r, i, t)}$) or ($\varepsilon_{(i, t)}$) in the OLS refill and person-year

level analysis, respectively. The RE and FE models divide the error into individual level

time-invariant unobserved error ($a_{(i)}$) and random error, ($v_{(r, i, t)}$) and ($v_{(i, t)}$) for the refill and

person-year level analysis.

Equation 3.10: OLS, RE, and FE refill level analyses measuring associations between
prescription copayment levels and medication compliance using MPR.

OLS:
$E(MPR)_{(r,i,t)} = \beta_0 + \beta_1$ *Copayment* $_{(r,i,t)} + \beta_2$ *Demographics*$_{(i)} + \beta_3$ *Health* $_{(i)} + \beta_4$ *Utilization*$_{(i,t)}$
$+ \beta_5$ *MSA*$_{(i)} + \beta_6$ *Calendar_year*$_{(t)} + \beta_7$ *Follow_up_time*$_{(i)} + \varepsilon$ $_{(r,i,t)}$

FE and RE:
$E(MPR)_{(r,i,t)} = \beta_0 + \beta_1$ *Copayment* $_{(r,i,t)} + \beta_2$ *Demographics*$_{(i)} + \beta_3$ *Health* $_{(i)} + \beta_4$ *Utilization*$_{(i,t)}$
$+ \beta_5$ *MSA*$_{(i)} + \beta_6$ *Calendar_year*$_{(t)} + \beta_7$ *Follow_up_time*$_{(i)} + a_{(i)} + v_{(r,i,t)}$

Equation 3.11: OLS, RE, and FE person-year analysis of annual average prescription
copayment levels and annual average medication compliance.

OLS:
$E(Annual\ MPR)_{(i,t)} = \beta_0 + \beta_1$ *Copayment* $_{(i,t)} + \beta_2$ *Demographics*$_{(i)} + \beta_3$ *Health* $_{(i)}$
$+ \beta_4$ *Utilization*$_{(i,t)} + \beta_5$ *Census*$_{(i)} + \beta_6$ *Calendar_year*$_{(t)} + \beta_7$ *Follow_up_time*$_{(i)} + \varepsilon$ $_{(i,t)}$

RE or FE:
$E(Annual\ MPR)_{(i,t)} = \beta_0 + \beta_1$ *Copayment* $_{(i,t)} + \beta_2$ *Demographics*$_{(i)} + \beta_3$ *Health* $_{(i)}$
$+ \beta_4$ *Utilization*$_{(i,t)} + \beta_5$ *Region*$_{(i)} + \beta_6$ *Calendar_year*$_{(t)} + \beta_7$ *Follow_up_time*$_{(i)} + a_{(i)} + v_{(i,t)}$

<u>SPECIFICATION TESTS</u>

Specification tests were performed between OLS, FE, and RE estimators to determine

the best fit for the ACE inhibitor, beta blocker, and diuretic models. These included the

Bruesch-Pagan test, used to test the presence of clustered errors in OLS models; the

Hausman test, used to test the differences between the slopes of the RE and FE models, and

the F-test, used to test the joint significance of fixed effect intercepts.

Bruesch-Pagan Lagrange Multiplier Test

The Bruesch Pagan Lagrange Multiplier specification test tests the null hypothesis that the variance of the error is zero (Var (μ) = 0). Failing to reject the null would imply that refill observations are independent within the individual, motivating the use of the more efficient OLS model in the absence of individual level heterogeneity. Rejecting the null would imply the presence of clustering, motivating the use of RE given that clustering inflates the standard errors of OLS models. The null hypotheses across all medication class analyses were rejected, implying the presence of refill clusters at the individual level (Table 3.8). Under these circumstances, the RE is most appropriate contingent upon the error structures following the assumptions of the RE estimator.

Hausman Test

The Hausman test was performed to test the appropriateness of the RE versus the FE model. In order to conduct the Hausman, one must assume that one model has an unbiased, yet possibly inefficient estimator (in this case the FE) and the second model has an efficient, yet possibly biased estimator (in this case the RE). The null hypothesis assumes that the slope coefficients between the models do not differ significantly, implying that both models yield unbiased estimates. Failing to reject the null hypothesis would imply that unobserved heterogeneity (a_i) is randomly distributed among different copayment levels. Choosing the more efficient model would therefore be most appropriate. In contrast, rejecting the null hypothesis would favor the fixed effects model, implying that unobserved heterogeneity (a_i) is significantly correlated with copayment levels. The null hypothesis was rejected across all medication class analyses, favoring the FE over the RE, and implying that individual-level

unobserved heterogeneity (a_i) is significantly correlated with copayment level in all of the

models (Table 3.8).

F-Test

F-tests were performed between the OLS and FE models to test the joint significance

of the fixed effect intercepts, testing the null hypothesis that all G-1 fixed effect intercepts (g

= number of individuals) are zero. The F-test creates a ratio comparing the explained

variation in the restricted model (OLS) versus the unrestricted model (FE). Rejecting the

null hypothesis implies that the fixed effects intercepts contained in the unrestricted model

explain a significant amount of variation in the outcome compared to the restricted model

(OLS). The null hypothesis was rejected across all models, implying that the fixed effect

intercepts significantly contributed to the fit of the model compared to OLS (Table 3.8). This

also suggests the presence of individual level heterogeneity which would otherwise bias OLS

models only containing one intercept for all individuals. The results of the F-test in

conjunction with the Hausman suggest that individual level fixed effects models are the most

appropriate models to estimate the effect of copayment level on compliance using linear

regression.

Table 3.8: Results of the specification tests performed between OLS, RE, and FE estimators

	F-Test (OLS vs. FE)		Bruesch-Pagan (OLS vs. RE)		Hausman (FE vs. RE)		Overall Choice
	F-statistic	*Favors*	χ^2	*Favors*	χ^2	*Favors*	
Refill							
ACE	F(1037, 23806)=2.95; p<0.001	FE	875.23; p<0.001	RE	147.74; p<0.001	FE	FE
Beta	F(2359, 53273)=4.04; p<0.001	FE	8272.57; p<0.001	RE	525.29; p<0.001	FE	FE
Diuretic	F(2840, 67433)=3.48; p<0.001	FE	7498.2; p<0.001	RE	803.73; p<0.001	FE	FE
Person-Year							
ACE	F(1035, 2204)=2.23; p<0.001	FE	294.93; p<0.001	RE	92.53; p<0.001	FE	FE
Beta	F(2359, 5307)=2.33; p<0.001	FE	605.19; p<0.001	RE	433.09; p<0.001	FE	FE
Diuretic	F(2840, 6444)=2.45; p<0.001	FE	604.65; p<0.001	RE	546.28; p<0.001	FE	FE

PRESCRIPTION COPAYMENTS, MEDICATION COMPLIANCE, AND HOSPITALIZATIONS

Person-year level logistic regressions were used to model the probability of annual hospitalizations (e.g., all-cause, cardiovascular-specific, or heart failure specific) conditional upon annual average copayment levels within each of the three drug class categories (Eq. C). Additional logistic models were constructed to test the mediating properties of medication non-compliance. The first equation (Path A) measures the probability of non-compliance conditional upon medication copayment level.

Conceptually similar to the OLS models measuring the effect of copayment level on MPR levels, this adapts the linear models by dichotomizing the MPR outcome to above or below 0.8, a clinical meaningful threshold used in previous studies (Stroupe, Teal et al.

2004). Though the OLS models provide insight on the effects of copayment categories on

medication supply units, the logistic models provided more insight on the effect of

copayment on compliance using a previously validated threshold.

The second equation (Path B) measures the probability of hospitalizations conditional

upon medication non-compliance (MPR<0.8). The third and fourth models (Path C, D)

measure the probability of hospitalization conditional upon copayment levels, the former

measuring the *direct effect* by including non-compliance in the empirical model, the latter

measuring the *total effect* by omitting non-compliance.

Equation A: Pr (MPR<0.8) = f (copayment level)

Equation B: Pr (hosp=1) = f (MPR<0.8)

Equation C: Pr (hosp =1) = f (copayment level, MPR<0.8)

Equation D: Pr (hosp = 1) = f (copayment level)

It is hypothesized that medication non-compliance partially explains the proportion of

the variation between copayments and hospitalizations, suggesting that higher copayment

levels contribute to higher risk of hospitalization partially due to medication non-compliance.

The objective of the mediation analysis was to test the extent to which non-compliance

mediated the association between copayment levels and hospitalizations. Baron and Kenny

(Baron and Kenny 1986) introduce a step-by-step approach to investigating the role of

intervening variables, a very common approach in the psychology literature (MacKinnon,

Lockwood et al. 2002). In this approach, hypothesis tests are applied to the collection of

empirical frameworks outlined in Equations A through D above in order to test the presence of mediation. More specifically, four conditions must apply for mediation to be supported:

1) *Copayment levels must be associated with medication non-adherence (Eq. A).*
2) *Medication non-adherence must be associated with hospitalization (Eq. B).*
3) *Copayment levels must be associated with hospitalizations in the absence of medication non-adherence (Eq. D) (total effect).*
4) *The effect of copayment on hospitalization (Eq. D) (total effect) must be attenuated when the mediator non-compliance is added to the model (Eq. C) (the direct effect).*

The pathway proposed in Equation D, or the probability of hospitalization conditional upon copayment level, is referred to as the *total effect* of copayment levels on hospitalization, while Equation C is referred to as the *direct effect* of copayment on hospitalization, controlling for medication non-adherence (Preacher and Hayes 2004). According to the Baron and Kenny definition, if the *direct effect* (Eq. C) drops to zero while the *total effect* (Eq. D) remains statistically significant, non-compliance would be considered a perfect mediator, in theory suggesting higher copayments result in hospitalizations *solely* because of non-compliance. In practice, perfect mediation does not occur due to many unobservable variables possibly contributing to the causal pathway. Given this, the attenuation of the *direct effect* (Equation C) in comparison to the *total effect* (Equation D) would be sufficient to conclude the presence of partial mediation (Preacher and Hayes 2004).

Figure 3.1: Proposed Mediation Pathways:

100
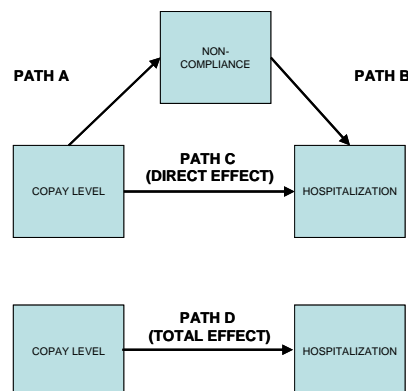
An alternative approach to testing mediation is to use the Sobel test, which tests the

null hypothesis that the *indirect effect* (mediation effect) of copayment on hospitalization is

zero. Mathematically, the indirect effect is calculated by multiplying parameters A*B, which

is theoretically equivalent to subtracting the *direct effect* from the *total effect* (Eq. 3.12).

Equation 3.12:
$$AB = (D-C)$$

The standard error of the *indirect effect* is calculated with the following formula (Sobel 1982)

(Eq. 3.13).

Equation 3.13:
$$s_{ab} = \sqrt{[(B^2 * s_a^2 + A^2 * s_b^2 + s_a^2 * s_b^2)]}$$

The Sobel tests the null hypothesis that $AB = 0$. The quotient $AB / (s_{ab})$ renders the critical

value which is then compared to the normal distribution (Preacher and Hayes 2004).

Rejecting the null hypothesis implies the presence of an indirect effect or that the intervening

variable is a mediator.

MEDIATION MODEL SPECIFICATION

The regressions outlined below were conducted for each medication class cohort, for

three different health outcomes: a) total hospitalizations; b) cardiovascular; and c) heart

failure hospitalizations. The direct effect (γ_2) (Path C) and total effect (δ_1) (Path D) of

copayment on the probability of hospitalizations were estimated using Equation C and D,

respectively, removing the potential mediator, non-compliance, in the latter model. The

effect of non-compliance on probability of hospitalization (γ_1) (Path B) was estimated in

Equation C, while the effect of copayment on the probability of non-compliance (β_1) (Path A)

was estimated in Equation A.

Equation A:
$Pr(MPR<0.8) = \alpha_0 + \boldsymbol{\beta_1 Copayment_{(i,t)}} + \boldsymbol{\beta_2 Demographics_{(i)}} + \boldsymbol{\beta_3 Health_{(i,t)}} + \boldsymbol{\beta_4 Utilization_{(i,t)}}$
$+ \boldsymbol{\beta_5 Census_{(i)}} + \boldsymbol{\beta_6 Calendar\_year_{(t)}} + \boldsymbol{\beta_7 Follow\_up\_time_{(i)}} + \varepsilon_{(i,t)}$

Equation C (Direct Effect):
$Pr(hosp=1) = \alpha_0 + \gamma_1(MPR<0.8)_{(i,t)} + \boldsymbol{\gamma_2 Copayment_{(i,t)}} + \boldsymbol{\gamma_3 Demographics_{(i)}} + \boldsymbol{\gamma_4 Health_{(i,t)}} + \boldsymbol{\gamma_5 Utilization_{(i,t)}} +$
$\boldsymbol{\gamma_6 Census_{(i)}} + \gamma_7\ \boldsymbol{Calendar\_year_{(t)}} + \boldsymbol{\gamma_7 Follow\_up\_time_{(i)}} + \varepsilon_{(i,t)}$

Equation D (Total Effect):
$Pr(hosp=1) = \alpha_{0\ +}\ \boldsymbol{\delta_1 Copayment_{(i,t)}} + \boldsymbol{\delta_2 Demographics_{(i)}} + \boldsymbol{\delta_3 Health_{(i,t)}} + \boldsymbol{\delta_4 Utilization_{(i,t)}} +$
$+ \boldsymbol{\delta_5 Census_{(i)}} + \boldsymbol{\delta_6 Calendar\_year_{(t)}} + \boldsymbol{\delta_7 Follow\_up\_time_{(i)}} + \varepsilon_{(i,t)}$

In the equations illustrated above, the vector **Copayment** includes dummy variables

for the seven different average annual copayment level categories, using $0 as the reference

category: $1 to $5, $6 to $10, $11 to $15, $16 to $20, $21 to $25, $26 to $30, and $31 and

above. Given the low frequency of more expensive beta blockers and diuretics that resulted

in small sample sizes and unstable estimates, upper copayment observations were collapsed.

For example, the beta blocker analysis collapsed the upper two levels to create a copayment

category of $26 and above, and the diuretic analysis collapsed the upper five levels to create

a copayment category of $11 and above.

The vector **Demographics** contain age, gender, health plan at baseline. The vector

Health includes the Charlson comorbidity score and total all-cause hospitalization count

during the baseline year, the latter serving as a proxy for heart failure severity. The vector

Utilization contains binary indicators for annual utilization of non-index chronic heart failure

drugs, annual average monthly counts of unique non-index drugs, and annual average

monthly out-of-pocket copayments for non-index drugs measured at the person-year level.

The vector **Census** represents the dummy variables indicating Northeast/Atlantic, South,

Midwest, West, and National. A vector of calendar year fixed effects was included in all analyses, as well as a variable indicating the total number of follow-up days.

SUMMARY

This retrospective cohort study used refill level and person-year level ordinary least squares (OLS), individual level fixed effects (FE) and random effects (RE) models to measure the associations between copayment levels and medication compliance. The specification tests comparing OLS, FE, and RE estimators found that the individual level fixed effects were the most appropriate models, suggesting the presence of unobserved individual level heterogeneity which would otherwise contribute to biased estimates in standard OLS models.

Person-year level logistic regressions were conducted to measure the probability of total, cardiovascular-specific and heart failure specific hospitalizations conditional upon annual average copayment levels. These models, technically measuring the direct effects of copayments on hospitalizations, were used in conjunction with models measuring the total effects in order to explore the role of non-compliance as a mediator. Sobel tests were used to test whether indirect effects were statistically significant, which would suggest medication non-adherence as a mediator.

CHAPTER IV: RESULTS

OVERVIEW

The chapter begins by reviewing descriptive statistics for ACE inhibitors, beta blocker, and diuretic refills, providing an overview of average copayment levels and distributions of brand versus generic products. Baseline descriptive statistics are presented for individuals within each of the drug cohorts, followed by results of the multivariate linear models measuring the associations between a) refill copayments and medication compliance; b) annual average copayment levels and annual average medication compliance; c) annual average copayment levels and annual hospitalizations. The chapter ends by reviewing results of the mediation models.

REFILL CHARACTERISTICS

The average MPR for all ACE inhibitors, beta blockers, or diuretic refills during follow-up was 0.98, 0.99, and 1.07, respectively, indicating an average 2% undersupply, 1% undersupply, and 7% oversupply of these medications during any one particular refill interval. After standardizing all ACE copayment levels to 30-day supply amounts, approximately 7%, 21%, 28%, and 16% fell into copayment categories $0, $1 to $5, $6 to $10, and $11 to $15, respectively (Table 4.1) (Figure 4.1), equivalent to an overall copayment median of $11.53 across all ACE inhibitor products. Compared to ACE inhibitors, beta blockers had a higher frequency of refills in the lower copayment category resulting in an overall copayment median of $7.42 across all products. For

example, approximately 19%, 37%, 15%, and 14% fell into copayment categories $0, $1 to $5, $6 to $10, and $11 to $15, respectively (Table 4.1) (Figure 4.2). Of the three drug classes examined, diuretics were the least expensive. Having an overall copayment median of $2.56 across all products, the distribution was heavily skewed to the lowest payment category with 46%, 42%, 9%, and 4% of the refills falling into the copayment categories $0, $1 to $5, $6 to $10, and $11 plus, respectively (Table 4.1) (Figure 4.3). The differences in average copayment levels across the drug classes parallel the differences in the proportion of brand to generics. For example, compared to ACE inhibitors having 63% brand name refills, beta blockers and diuretics had 48% and 8% brand name refill prescriptions (Table 4.1).

In addition to differences in brand versus generic, drug classes differed in the number of available products. For example, beta blocker refills were distributed approximately equally between four products, ranging between 23% and 28% for each (Figure 4.5). In contrast, diuretics were heavily distributed toward one generic product that dominated over 80% of the refills (Figure 4.6). Compared to beta blockers, ACE inhibitors have more product variety, although one brand still dominated almost one third of the refills (Figure 4.4).

REFILL COPAYMENT LEVELS AND MEDICATION COMPLIANCE

Ordinary least squares (OLS), individual level fixed effects (FE), and individual level random effects (RE) models were used to measure associations between refill copayment levels and refill compliance. Models right censored refill observations having a Medication Possession Ratio (MPR) exceeding 3 standard deviations above the mean MPR of all index prescription refills. Of the original 34,921, 77,571, and 96,588 refills

Table 4.1: ACE inhibitor, beta blocker, and diuretic prescription refill characteristics

	ACE Inhibitors (N=34,765)	Beta Blockers (N=77,185)	Diuretics (N=95,691)
Refill MPR	0.98 (sd=0.31)	0.99 (sd=0.39)	1.07 (sd=0.71)
30-day median copayment ($)	11.53 (sd=9.21)	7.42 (sd=8.11)	2.56 (sd=4.45)
30-day refill copayment level			
$0	7.0%	19.3%	45.8%
$1 to $5	21.4%	36.8%	41.5%
$6 to $10	28.3%	14.8%	8.7%
$11 to $15[1]	16.1%	13.7%	4%
$16 to $20	9.9%	8.1%	
$21 to $25	8.5%	5.0%	
$26 to $30[2]	3.8%	2.3%	
$30 and above	5.1%		
Brand Name	63.3%	47.5%	7.9%

1: $11 plus for diuretics
2: $26 plus for beta blockers

Figure 4.1: Frequency distribution of 30-day supply copayment levels of ACE inhibitor prescription refills during follow-up period (N=34,765)
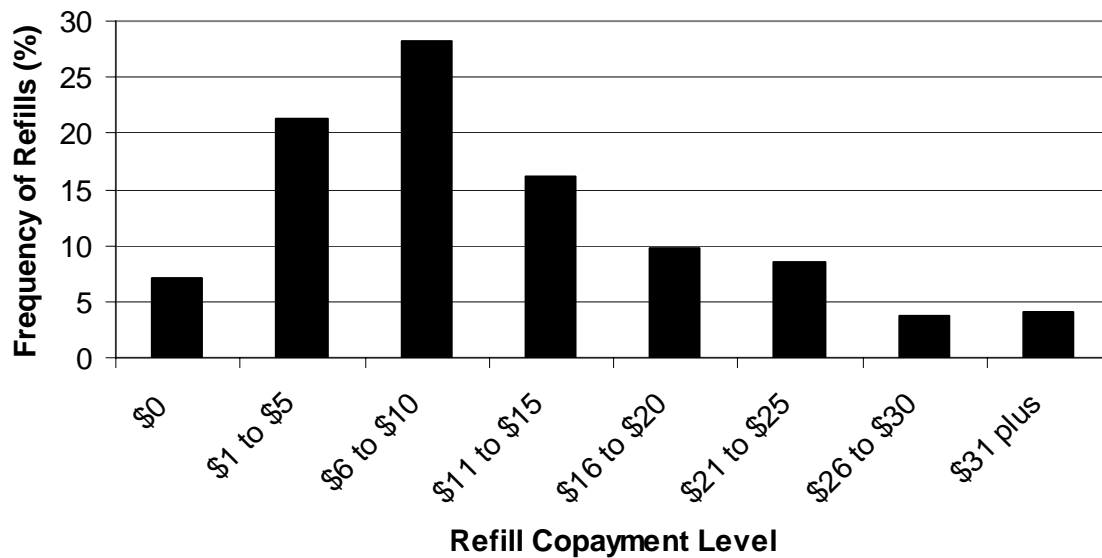
Figure 4.2: Frequency distribution of 30-day supply copayment levels of <u>beta blocker</u> prescription refills during follow-up period (N=77,185)
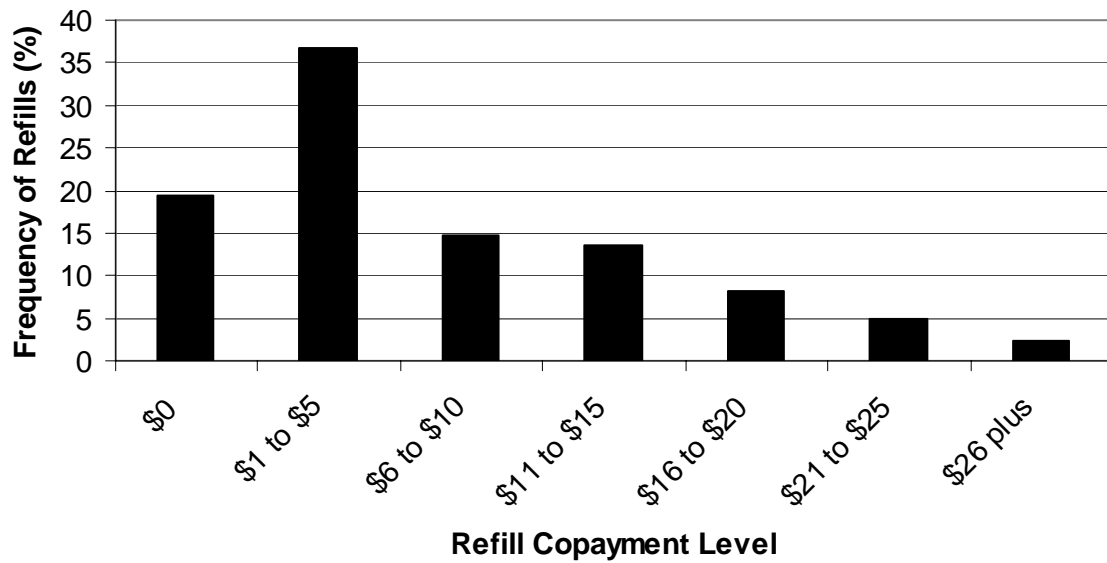
Figure 4.3: Frequency distribution of 30-day supply copayment levels of <u>diuretic</u> prescription refills during follow-up period (N=95,691)
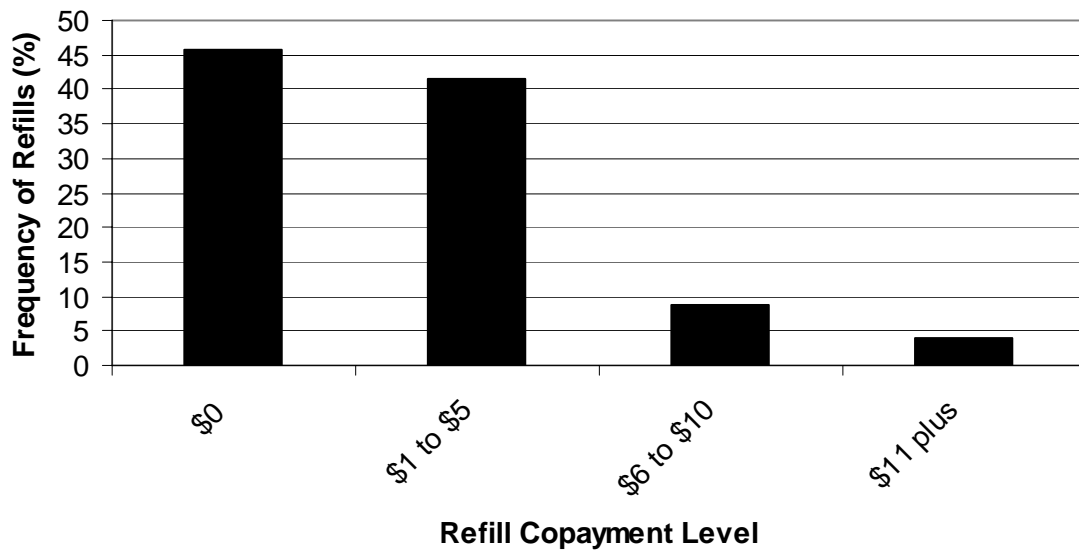
Figure 4.4: Frequency distribution of pharmaceutical products comprising <u>ACE inhibitor</u> refills during follow-up period (N=34,765)
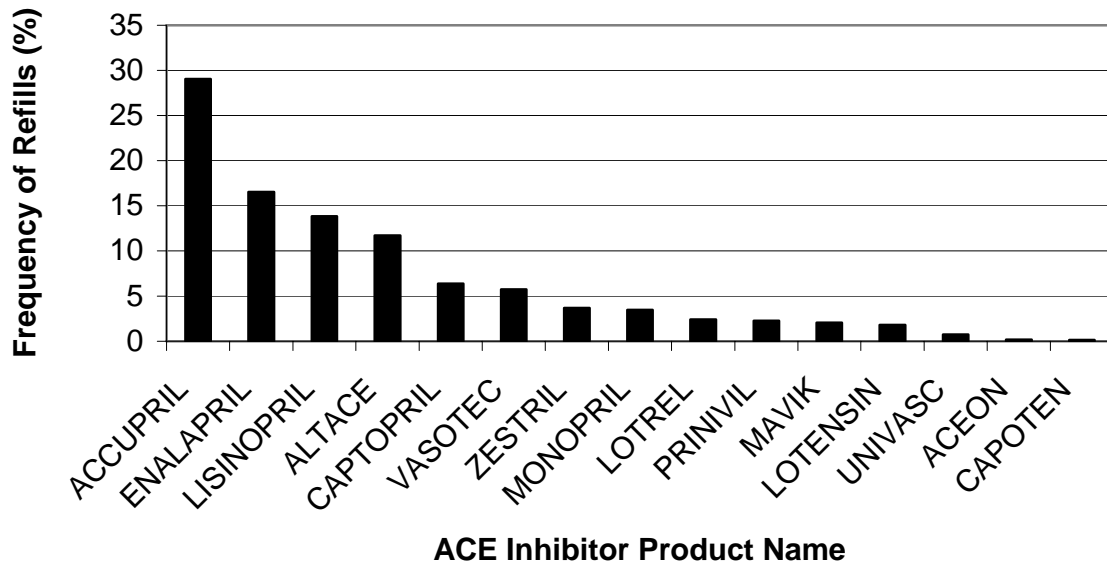
Figure 4.5: Frequency distribution of pharmaceutical products comprising <u>beta blocker</u> refills during follow-up period (N=77,185)
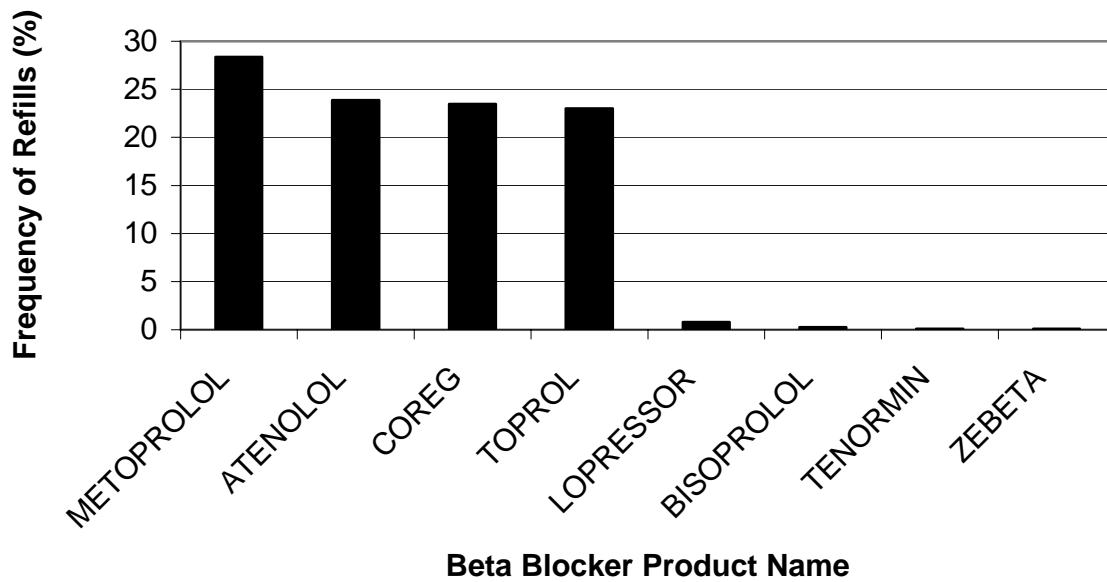
Figure 4.6: Frequency distribution of pharmaceutical products comprising <u>diuretic</u> refills during follow-up period (N=95,691)
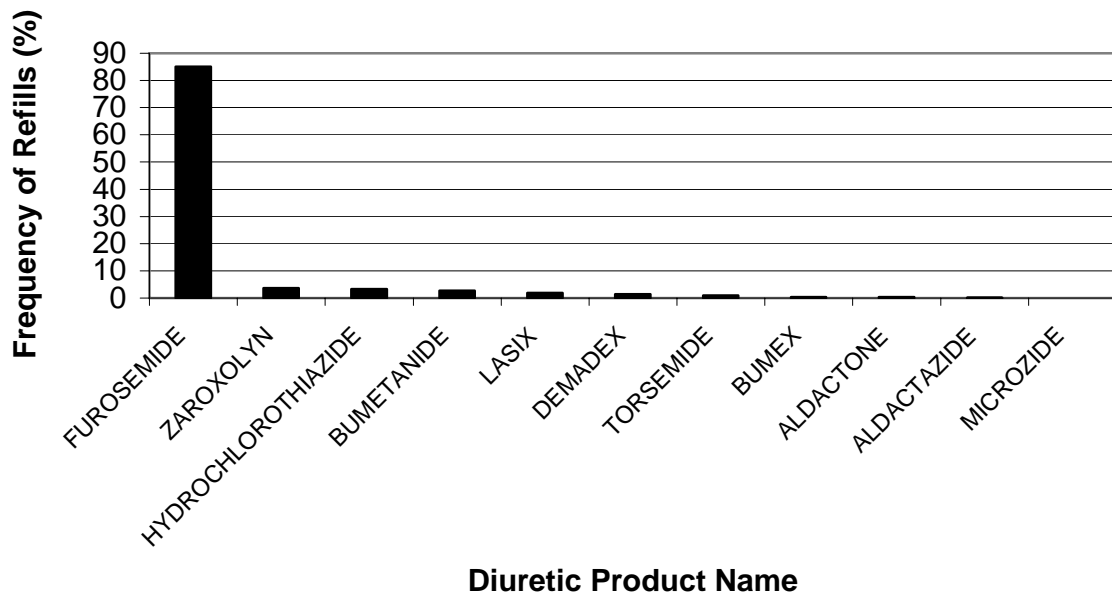
contained within the ACE inhibitor, beta blocker, and diuretic cohort, respectively, 0.45%, 0.5% and 0.9% of the ACE, beta blocker, and diuretic refills were considered outliers, resulting in final samples of 34,765, 77,185, and 95,691 refills for ACE inhibitor, beta blocker, and diuretic refill cohorts respectively. The mean MPR of the outlier observations were 16.8, 16.8, and 22.8 for ACE inhibitors, beta blockers, and diuretics, respectively, the minimum values being 5.6, 6.2 and 10, and the maximum being 90 for all three drug classes. Since extreme MPR values probably reflect switching as opposed to medication over-compliance, these were removed from the analysis, resulting in normally distributed MPR values for all three cohorts. Since analytic models used the first year of observations as baseline control variables, the analytic datasets contained 24,877, 56,109, and 70,299 refill observations for the ACE inhibitor, beta blocker, and diuretic models, respectively.

After performing specification tests to investigate whether OLS, FE, or RE models were favored in the refill level analyses, the collective results of the Bruesch-Pagan test, the Hausman test, and the F-test motivated the use of the individual fixed effects model (Table 3.8). As such, fixed effects parameter estimates were reported as the main results, yet all three parameter estimate types are presented in the result tables. Compared to ACE inhibitor refills with copayment levels of $0, ACE inhibitor refills having copayments between $26 and $30 were associated with an average 0.042 unit increase in the MPR during any particular refill interval (Table 4.2) (Figure 4.7).

In contrast to the ACE inhibitor analyses, beta blocker analyses produced results more consistent with the study hypotheses. Compared to beta blocker refills with copayment levels of $0, those refills with copayment levels between $1 and $5, $6 and $10, $11 to $15, $16 and $20, $21 and $26, and $26 and up were significantly associated with an average 0.02, 0.04, 0.03, 0.06, 0.04, and 0.09 unit decrease in MPR, respectively, in medication supply during any particular refill interval (Table 4.3) (Figure 4.8). Given that 0.5 MPR units reflect a 50% medication supply levels, these results correspond to a 2%, 4%, 3%, 6%, 4%, and 9% decrease in medication supply levels during any one refill interval.

Similar to beta blockers, diuretics had significant associations between copayment levels and medication supply levels. Compared to diuretic refills with copayments levels of $0, diuretics with copayment levels between $1 and $5, $6 and $10, and $11 plus were associated with a 9%, 21%, and 21% decrease respectively in medication supply levels (Table 4.4) (Figure 4.9).

In summary, beta blocker and diuretic refills with higher copayment levels were associated with decreased medication supply levels for the subsequent refill interval. In

contrast, ACE inhibitor refills with copayment levels between $26 and $30 were associated with increased medication supply levels. Because of the possible non-linear relationship between MPR and copayment levels, sensitivity analyses were conducted measuring the probability of non-compliance (MPR<0.8) as a function of copayment level. Results were consistent with FE estimates for beta blocker and diuretic refills, showing higher probabilities of non-compliance associated with higher levels of copayment levels (Table 4.5). Null associations found in the FE ACE inhibitor models were significant in the logistic models. Compared to ACE inhibitor refills costing $0, those refills costing $31 and over had a 55% increase in the probability of non-compliance (Table 4.5).

BASELINE CHARACTERISTICS OF HEART FAILURE PATIENTS

Average annual MPR values during baseline were 0.99, 0.98, and 1.03 for ACE inhibitor, beta blocker, and diuretic utilizers, reflecting an average undersupply of 1% and 2% for ACE inhibitors and beta blockers, and a 3% oversupply for diuretics (Table 4.6). Individuals had average annual copayments of $10, $6, and $2 for ACE inhibitors, beta blockers, and diuretics, respectively. Approximately 40% of each of the three drug cohorts was female, while average age at baseline was 67 years. Most individuals resided in the Northeastern or Mid-Atlantic regions of the United States. Between 21% and 27% of the individuals classified as 'National' had missing census region information due to procedures taken by the data vendor to protect patient confidentiality. In terms of government versus commercially sponsored managed care plans, between 62% and 70% were enrolled in commercial plans, the lowest percentage (62%) and highest percentage (70%) being in diuretic and beta blocker users, respectively (Table 4.6). In contrast, a greater percentage of diuretic users were enrolled in managed Medicare (37%) compared to beta blocker users

111

(30%). Enrollment in managed Medicaid ranged between 0.6% and 1.3% (Table 4.6). Compared to POS, PPO, independent and other unclassified plans, between 47% and 51% of ACE users, beta blocker users and diuretic users were enrolled in HMO plans. A majority of the remaining half of each sample were enrolled in either PPO or independent plans, while between 2% and 5% were enrolled in either POS or unclassified plans (Table 4.6).

Approximately 44%, 41% and 33% of ACE inhibitor, beta blocker, and diuretic cohorts, respectively, had a Charlson comorbidity index score ranging from 0 to 1. The proportion of individuals experiencing any hospitalization during the baseline was 25%, 31%, and 34% for ACE inhibitor, beta blocker, and diuretic utilizers, respectively. Proportions of those experiencing any cardiovascular disease hospitalizations during baseline was 8%, 12%, and 13%, and experiencing any heart failure hospitalizations was 5%, 7%, and 8%, for ACE inhibitor, beta blocker, and diuretic utilizers, respectively (Table 4.6). The average prescription out-of-pocket costs for non-index drugs was $43, $46, and $50 per month for ACE, beta blocker, and diuretic utilizers respectively, corresponding to an average of five unique monthly medications in addition to the index drug (Table 4.6).

Table 4.2: Ordinary least squares (OLS), fixed effects (FE) and random effects (RE) models measuring associations between <u>ACE inhibitor</u> refill copayment levels and refill compliance in heart failure patients (N=24,877)

	OLS		RE		FE	
	Beta	SE	Beta	SE	Beta	SE
Refill Copayment Level[1]						
$1 to $5	0.008	(0.02)	0.006	(0.01)	-0.007	(0.01)
$6 to $10	-0.019	(0.02)	-0.017	(0.01)	-0.02	(0.01)
$11 to $15	-0.028	(0.02)	-0.02	(0.01)	-0.02	(0.01)
$16 to $20	-0.038**	(0.02)	-0.019	(0.01)	-0.003	(0.02)
$21 to $25	-0.040**	(0.02)	-0.01	(0.02)	0.009	(0.02)
$26 to $30	-0.006	(0.02)	0.022	(0.02)	0.042**	(0.02)
$31 and up	-0.069*	(0.02)	-0.042*	(0.02)	-0.023	(0.02)
Age	0.001**	(0.0005)	0.001	(0.0003)	-0.002	(0.003)
Female	0.005	(0.01)	0.003	(0.01)	.	.
Health Plan Level 1[2]						
Medicaid	-0.008	(0.04)	0.045	(0.07)	.	.
Medicare	-0.050*	(0.01)	-0.057*	(0.02)	.	.
Health Plan Level 2[3]						
Independent	-0.007	(0.01)	0.002	(0.02)	.	.
PPO	-0.018	(0.01)	-0.009	(0.01)	.	.
POS or Other	0.002	(0.02)	0.003	(0.03)	.	.
Charlson Index[4]						
1	-0.009	(0.01)	-0.006	(0.01)	.	.
2	-0.006	(0.01)	-0.002	(0.01)	.	.
3	-0.02	(0.01)	-0.014	(0.02)	.	.
4 and over	-0.024	(0.01)	-0.019	(0.02)	.	.
Number of hospitalizations in previous year	0.002	(0.003)	0.004	(0.001)	0.005	(0.003)
Average ACE inhibitor MPR in previous year	0.028*	(0.01)	0.009*	(0.0001)	-0.002	(0.004)
Concomitant Monthly Drug Utilization						
Beta blockers	0.008	(0.01)	0.004	(0.01)	.	.
Diuretics	-0.002	(0.01)	-0.002	(0.01)	.	.
Aldosterone Antagonists	-0.018	(0.01)	-0.011	(0.01)	.	.
Monthly drug count	-0.001	(0.002)	-0.037	(0.04)	-0.004**	(0.002)
Monthly total OOP Rx ($)	0.0003*	(0.0001)	-0.013	(0.02)	0.0003*	(0.0001)
Number of follow-up days	-0.00001	(0.00001)	-0.009	(0.02)	.	.
Drug Product[5]						
Aceon	0.112	(0.08)	0.001	(0.07)	-0.244**	(0.11)
Altace	0.017	(0.01)	0.024	(0.01)	0.070**	(0.03)
Capoten	-0.017	(0.06)	-0.065	(0.10)	-0.149	(0.17)
Captopril	-0.062*	(0.02)	-0.033**	(0.02)	0.048	(0.04)
Enalapril	-0.019	(0.01)	-0.002	(0.01)	0.058**	(0.03)
Lisinopril	-0.038*	(0.01)	-0.009	(0.01)	0.108*	(0.03)
Lotensin	-0.027	(0.03)	-0.086*	(0.03)	-0.186*	(0.07)
Lotrel	-0.017	(0.02)	0.02	(0.02)	0.070	(0.04)
Mavik	0.008	(0.02)	0.028	(0.03)	0.114**	(0.05)
Monopril	-0.011	(0.02)	0.003	(0.02)	0.116*	(0.04)
Prinivil	-0.024	(0.02)	0.001	(0.02)	0.115*	(0.04)
Univasc	-0.043	(0.03)	0.001	(0.07)	0.035	(0.10)
Vasotec	-0.006	(0.02)	0.024	(0.01)	0.026	(0.03)
Zestril	-0.009	(0.02)	-0.065	(0.10)	0.083*	(0.03)

Robust standard errors in parentheses
** significant at 5%; * significant at 1%
Reference groups: 1: $0; 2: commercial; 3: HMO; 4: 0; 5: Accupril

Table 4.3: Ordinary least squares (OLS), fixed effects (FE) and random effects (RE) models measuring associations between <u>beta blocker</u> refill copayment levels on refill compliance in heart failure patients (N=56,109)

	OLS		RE		FE	
	Beta	SE	Beta	SE	Beta	SE
Refill Copayment Level[1]						
$1 to $5	0.009	(0.01)	-0.008	(0.01)	-0.023*	(0.01)
$6 to $10	-0.001	(0.01)	-0.028*	(0.01)	-0.043*	(0.01)
$11 to $15	-0.014	(0.01)	-0.025*	(0.01)	-0.029*	(0.01)
$16 to $20	-0.030**	(0.01)	-0.055*	(0.01)	-0.061*	(0.01)
$21 to $25	-0.049*	(0.02)	-0.050*	(0.01)	-0.042*	(0.01)
$26 to $30	-0.072*	(0.02)	-0.088*	(0.02)	-0.089*	(0.02)
Age	0.0001	(0.0005)	10x10e-6	(0.0005)	0.008	(0.04)
Female	-0.001	(0.01)	-0.002	(0.01)	.	.
Health Plan Level 1[2]						
Medicaid	-0.046	(0.05)	-0.074	(0.06)	.	.
Medicare	-0.030*	(0.01)	-0.034*	(0.01)	.	.
Health Plan Level 2[3]						
Independent	0.002	(0.01)	0.003	(0.01)	.	.
PPO	-0.015	(0.01)	-0.004	(0.01)	.	.
POS or Other	-0.030	(0.02)	-0.023	(0.02)	.	.
Charlson Index[4]						
1	0.005	(0.01)	0.01	(0.01)	.	.
2	0.009	(0.01)	0.017	(0.01)	.	.
3	-0.002	(0.01)	0.006	(0.01)	.	.
4 and over	-0.01	(0.01)	-0.005	(0.01)	.	.
Number of hospitalizations in previous year	-0.002	(0.00)	0.00005	(0.002)	0.001	(0.002)
Average beta blocker MPR in previous year	0.087*	(0.02)	0.027*	(0.003)	-0.002	(0.004)
Concomitant Monthly Drug Utilization						
ACE inhibitors	0.007	(0.01)	0.001	(0.01)	-0.003	(0.01)
Diuretics	0.007	(0.01)	0.007	(0.004)	0.005	(0.01)
Aldosterone Antagonists	0.001	(0.01)	0.008	(0.01)	0.01	(0.01)
Monthly drug count	0.003	(0.001)	0.001	(0.001)	0.001	(0.001)
Monthly total OOP Rx ($)	0.0003*	(0.0001)	0.0003*	(0.0001)	0.0003*	(0.0001)
Number of follow-up days	-0.00002	9x10e-6	0.00002	(0.00001)	.	.
Drug Product[5]						
Bisoprolol	-0.023	(0.04)	-0.02	(0.05)	0.018	(0.08)
Coreg	0.032*	(0.01)	0.027*	(0.01)	0.038**	(0.02)
Lopressor	-0.014	(0.03)	-0.001	(0.03)	0.071	(0.04)
Metoprolol	-0.014**	(0.01)	-0.005	(0.01)	0.065*	(0.02)
Tenormin	0.041	(0.10)	0.126	(0.14)	0.503**	(0.24)
Toprol	0.032*	(0.01)	0.040*	(0.01)	0.099*	(0.02)
Zebeta	-0.190	(0.10)	-0.107	(0.09)	0.025	(0.12)

Robust standard errors in parentheses
** significant at 5%; * significant at 1%
Reference groups: 1: $0; 2: commercial; 3: HMO; 4: 0; 5: Atenolol

Table 4.4: Ordinary least squares (OLS), fixed effects (FE) and random effects (RE) models measuring associations between <u>diuretic</u> refill copayment levels on refill compliance in heart failure patients (N=70,299)

	OLS		RE		FE	
	Beta	SE	Beta	SE	Beta	SE
Refill Copayment Level[1]						
$1 to $5	-0.002	(0.01)	-0.035*	(0.01)	-0.093*	(0.01)
$6 to $10	-0.066*	(0.02)	-0.129*	(0.01)	-0.211*	(0.02)
$11 and up	-0.036	(0.05)	-0.124*	(0.02)	-0.206*	(0.02)
Age	-0.001	(0.001)	-0.002**	(0.00)	0.007	(0.06)
Female	-0.004	(0.01)	-0.01	(0.01)	.	.
Health Plan Level 1[2]						
Medicaid	-0.104	(0.06)	-0.103	(0.07)	.	.
Medicare	-0.028	(0.02)	-0.038**	(0.02)	.	.
Health Plan Level 2[3]						
Independent	0.036	(0.02)	0.023	(0.02)	.	.
PPO	0.014	(0.02)	0.015	(0.02)	.	.
POS or Other	0.008	(0.03)	0.025	(0.03)	.	.
Charlson Index[4]						
1	-0.037	(0.02)	-0.025	(0.02)	.	.
2	-0.005	(0.02)	0.004	(0.02)	.	.
3	-0.028	(0.03)	-0.011	(0.02)	.	.
4 and over	0.024	(0.03)	0.049**	(0.02)	.	.
Number of hospitalizations in previous year	0.013*	(0.004)	0.008*	(0.003)	0.001	(0.003)
Average diuretics MPR in previous year	0.091*	(0.01)	0.034*	(0.003)	-0.008**	(0.004)
Concomitant Monthly Drug Utilization						
ACE inhibitors	-0.023**	(0.01)	-0.027*	(0.01)	-0.022**	(0.01)
Beta blockers	-0.033*	(0.01)	-0.027*	(0.01)	-0.011	(0.01)
Aldosterone Antagonists	-0.024	(0.02)	-0.020	(0.01)	-0.025	(0.01)
Monthly drug count	0.011*	(0.002)	0.007*	(0.001)	0.001	(0.002)
Monthly total OOP Rx ($)	0.002	(0.0001)	0.0004*	(0.0001)	0.000*	(0.0001)
Number of follow-up days	-0.00002	(0.00001)	1x10e-6	(0.00001)	.	.
Drug Product[5]						
Aldactone	0.388	(0.35)	0.405**	(0.17)	0.651*	(0.24)
Bumetanide	-0.083	(0.25)	-0.054	(0.16)	0.177	(0.24)
Bumex	-0.158	(0.27)	-0.047	(0.17)	0.276	(0.25)
Demadex	-0.156	(0.25)	-0.089	(0.16)	0.168	(0.24)
Furosemide	-0.164	(0.25)	-0.128	(0.16)	0.14	(0.24)
Hydrochlorothiazide	-0.057	(0.25)	-0.032	(0.16)	0.248	(0.24)
Lasix	-0.069	(0.25)	-0.037	(0.16)	0.226	(0.24)
Microzide	.	.			.	.
Torsemide	-0.133	(0.25)	-0.06	(0.16)	0.211	(0.24)
Zaroxolyn	0.409	(0.25)	0.352**	(0.16)	0.542**	(0.23)

Robust standard errors in parentheses
** significant at 5%; * significant at 1%
Ref groups: 1: $0; 2: commercial; 3: HMO; 4: 0; 5: Aldactazide

Figure 4.7: Fixed effects (FE) parameter estimates measuring associations between ACE inhibitor refill copayment levels and refill compliance.
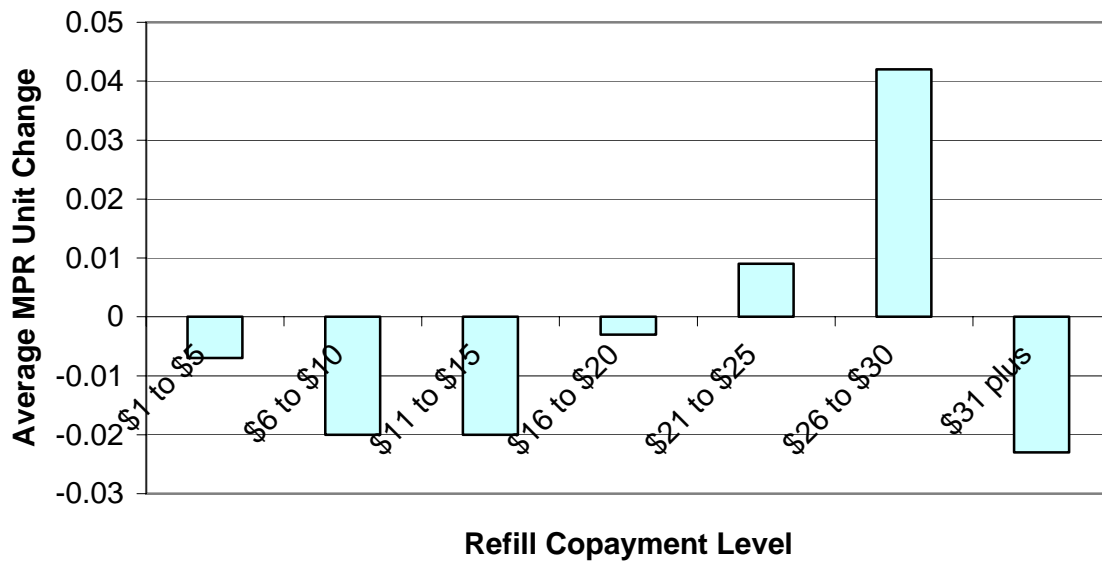
Figure 4.8: Fixed effects (FE) parameter estimates measuring associations between beta blocker refill copayment levels and refill compliance
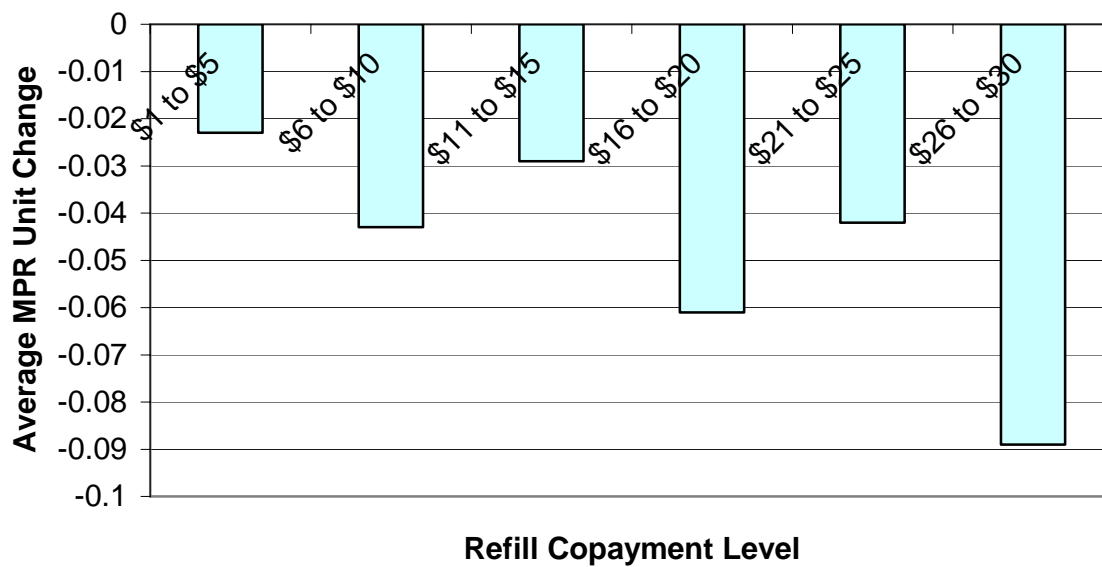
Figure 4.9: Fixed effects (FE) parameter estimates measuring associations between diuretic inhibitor copayment levels and refill compliance
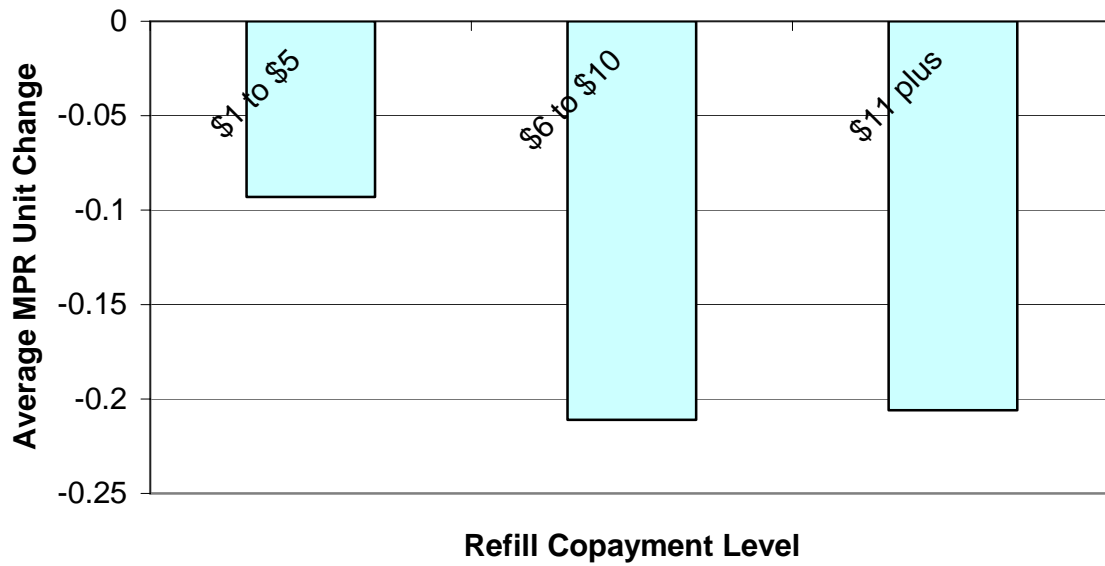
Table 4.5: Probability of refill non-compliance conditional upon ACE inhibitor, beta blocker, or diuretic refill copayment levels

	ACE		Beta Blockers		Diuretics	
	Parameter (β)	SE	Parameter (β)	SE	Parameter (β)	SE
Refill Copayment Level[1]						
$1 to $5	0.149	(0.17)	0.200*	(0.06)	0.299*	(0.06)
$6 to $10	0.322**	(0.16)	0.282*	(0.08)	0.685*	(0.08)
$11 to $15[2]	0.304	(0.18)	0.199**	(0.10)	0.714*	(0.10)
$16 to $20	0.219	(0.20)	0.299*	(0.11)		
$21 to $25	0.171	(0.22)	0.451*	(0.14)		
$26 to $30[3]	-0.017	(0.27)	0.922*	(0.16)		
$31 plus	0.548**	(0.23)				

1: $0 reference group
2: $11 plus for diuretics
3: $26 plus for beta blockers

Table 4.6: Baseline characteristics of commercially insured heart failure patients regularly using ACE inhibitors, beta blockers, or diuretics

	ACE Users (N=1,026)	Beta Blockers (N=2,345)	Diuretics (N=2,812)
Annual MPR	0.99 (sd=0.18)	0.98 (sd=0.21)	1.03 (sd=0.34)
Annual Refill Copayment Median			
$0	3.1%	14.9%	44.2%
$1 to $5	29.9%	49.4%	48.3%
$6 to $10	28.1%	15.5%	5.3%
$11 to $15[1]	17.2%	11.8%	2.2%
$16 to $20	9.3%	5.3%	
$21 to $25	8.3%	2.1%	
$26 to $30[2]	2.4%	1.1%	
$31 and up	1.8%		
Mean Annual Copayment ($)	10.4 (sd=7.7)	5.9 (sd=6.3)	2.1 (sd=3.2)
Age	66.8 (sd=8.6)	67.0 (sd=8.5)	68.3 (sd=8.3)
Gender			
Male	59.8%	59.6%	52.8%
Female	40.2%	40.4%	47.2%
Census			
Northeast/Mid-Atlantic	70.6%	64.3%	65.9%
South	2.1%	2.5%	2.2%
Midwest	3.7%	2.9%	3.4%
Pacific/Mountain	2.9%	3.4%	3.6%
National[3]	20.8%	27.0%	24.9%
Health Plan Level 1			
Commercial	64.4%	69.9%	61.6%
Medicare	34.4%	29.5%	37.2%
Medicaid	1.3%	0.6%	1.3%
Health Plan Level 2			
HMO	48.8%	46.6%	51.5%
Independent	15.8%	21.7%	21.4%
PPO	30.3%	25.1%	20.7%
POS	2.9%	4.5%	3.9%
Other	2.1%	2.1%	2.5%
Charlson Comorbidity Index			
0	10.9%	10.4%	5.4%
1	33.2%	30.6%	28.0%
2	27.6%	24.9%	27.7%
3	13.3%	13.8%	16.3%
Over 3	15%	20.3%	22.7%
Any hospitalizations			
All-type	25.2%	31.3%	33.7%
CAD-specific	8.4%	12.3%	12.9%
CHF-specific	4.7%	6.6%	8.4%
Any concomitant drug utilization			
ACE inhibitors		43.8%	44.3%
Beta blockers	55.5%		55.9%
Diuretics	72.9%	72.8%	.
Aldosterone antagonists	11.1%	13.1%	14.8%
Number of monthly non-index prescriptions	4.7 (sd=2.4)	4.9 (sd=2.2)	5.1 (sd=2.3)
Monthly out-of-pocket non-index drug expenses ($)	42.5 (sd=33.2)	46.4 (sd=33.4)	50.2 (sd=37.58)
Total number of days during follow-up	1455 (sd=305)	1524 (sd=329)	1550 (sd=351)
Censored at medication discontinuation[4]	9.0%	7.2%	8.2%

1:$11 plus for diuretics
2:$26 plus for beta blockers
3:Missing census region information to preserve patient confidentiality
4:After a minimum of 3 years follow-up

Average total follow-up times including baseline year were similar across drug cohorts, averaging 1455 days (3.9 years), 1524 days (4.1 years), and 1550 days (4.2 years) for ACE inhibitor, beta blocker, and diuretic cohorts respectively. Approximately 9%, 7% and 8% of the ACE inhibitor, beta blocker, and diuretic cohort were right censored due to a significant gap of therapy at least three years after the beginning of follow-up, implying that over 90% of the final cohorts were followed until the last prescription claim record.

PATIENT COPAYMENT LEVELS AND MEDICATION COMPLIANCE

Individual fixed effects models were favored over the OLS and RE in the person-year level analyses measuring associations between average annual copayment levels and average medication supply levels (Table 3.8). Average annual copayment levels for ACE inhibitors were not significantly associated with annual average medication supply levels (Table 4.7). In contrast, significant associations were found in beta blocker and diuretic cohorts. Compared to individuals filling prescriptions for beta blockers having annual average annual copayments under $1, those with annual copayments $26 and above had an average 0.098 unit decrease in MPR, reflecting an average 9.8% decrease in annual beta blocker medication supply levels for beta blockers (Table 4.8), similar to the 8.9% decrease in the refill level analysis (Table 4.3). While annual compliance and annual copayments were negatively associated in beta blockers, they were positively associated in the diuretic users. Compared to individuals with annual diuretic copayments under $1, those with copayments $11 and up had a 0.10 unit increase in annual average MPR, reflecting an average 10% increase in medication supply level (Table 4.9). Person-year logistic models estimating the probability of annual non-compliance (annual average

Table 4.7: Ordinary least squares (OLS), fixed effects (FE) and random effects (RE) models measuring associations between annual average <u>ACE inhibitor</u> copayment levels on annual average compliance in heart failure patients (N=3,259 person-years)

	OLS		RE		FE	
	Beta	SE	Beta	SE	Beta	SE
Annual Refill Copayment Median[1]						
$1 to $5	0.046**	(0.02)	0.042	(0.02)	0.041	(0.03)
$6 to $10	0.026	(0.02)	0.027	(0.03)	0.037	(0.03)
$11 to $15	0.03	(0.03)	0.031	(0.03)	0.041	(0.04)
$16 to $20	0.031	(0.03)	0.032	(0.03)	0.045	(0.04)
$21 to $25	0.024	(0.03)	0.033	(0.03)	0.065	(0.04)
$26 to $30	0.034	(0.03)	0.036	(0.03)	0.057	(0.04)
$31 plus	-0.017	(0.03)	-0.012	(0.03)	0.017	(0.04)
Age	0.001	(0.001)	0.001	(0.001)	0.003	(0.004)
Female	-0.005	(0.01)	-0.006	(0.01)	.	.
Census[2]						
South	0.052**	(0.03)	0.059**	(0.03)	.	.
Midwest	-0.038	(0.02)	-0.039	(0.02)	.	.
West	0.014	(0.02)	0.015	(0.03)	.	.
National Mix	0.003	(0.01)	0.005	(0.01)	.	.
Health Plan Level 1[3]						
Medicaid	0.06	(0.04)	0.061	(0.05)	.	.
Medicare	-0.043*	(0.01)	-0.047*	(0.01)	.	.
Health Plan Level 2[4]						
Independent	0.01	(0.02)	0.011	(0.02)	.	.
PPO	0.003	(0.01)	0.003	(0.01)	.	.
POS and other	-0.011	(0.02)	-0.01	(0.02)	.	.
Charlson Comorbidity Index[5]						
1	-0.001	(0.01)	0	(0.01)	.	.
2	0.01	(0.01)	0.009	(0.01)	.	.
3	-0.007	(0.02)	-0.007	(0.02)	.	.
4 plus	-0.011	(0.02)	-0.012	(0.02)	.	.
Number of hospitalizations in previous year	0.002	(0.004)	0.004	(0.004)	0.005	(0.004)
Average ACE inhibitor MPR in previous year	0.033*	(0.01)	0.020*	(0.004)	0.004	(0.004)
Any concomitant drug utilization						
Beta blockers	0.00003	(0.01)	-0.001	(0.01)	-0.004	(0.01)
Diuretics	-0.006	(0.01)	-0.006	(0.01)	-0.013	(0.02)
Aldosterone antagonists	-0.011	(0.01)	-0.007	(0.01)	0.01	(0.02)
Average monthly unique drug utilization	0.0003	(0.002)	-0.0001	(0.002)	-0.006	(0.004)
Average monthly OOP Rx ($)	0.0003*	(0.0001)	0.0003**	(0.0001)	0.0003	(0.0002)
Number of follow-up days	-0.00001	(0.00001)	-0.00002	(0.00001)	.	.

Robust standard errors in parentheses
** significant at 5%; * significant at 1%
Ref groups: 1: $0 - $1; 2: Northeast/Atlantic; 3: commercial; 4: HMO; 5: 0

Table 4.8: Ordinary least squares (OLS), fixed effects (FE) and random effects (RE) models measuring associations between annual average <u>beta blocker</u> copayment levels on annual average compliance in heart failure patients (N=7,686 person-years)

	OLS		*RE*		*FE*	
	Beta	SE	Beta	SE	Beta	SE
Annual Refill Copayment Median[1]						
$1 to $5	0.019**	(0.01)	0.013	(0.01)	-0.005	(0.01)
$6 to $10	0.035*	(0.01)	0.030**	(0.01)	0.019	(0.02)
$11 to $15	0.01	(0.01)	0.011	(0.01)	0.019	(0.02)
$16 to $20	0.015	(0.02)	0.008	(0.02)	0.006	(0.02)
$21 to $25	-0.029	(0.02)	-0.03	(0.02)	-0.018	(0.03)
$26 plus	-0.067*	(0.02)	-0.078*	(0.02)	-0.094**	(0.04)
Age	-0.0001	(0.0005)	-0.0001	(0.0005)	0.063	(0.04)
Female	0.008	(0.01)	0.008	(0.01)	.	.
Census[2]						
South	0.026	(0.03)	0.032	(0.02)	.	.
Midwest	-0.029	(0.02)	-0.03	(0.02)	.	.
West	-0.024	(0.02)	-0.025	(0.02)	.	.
National Mix	-0.011	(0.01)	-0.011	(0.01)	.	.
Health Plan Level 1[3]						
Medicaid	0.003	(0.04)	-0.006	(0.05)	.	.
Medicare	-0.037*	(0.01)	-0.039*	(0.01)	.	.
Health Plan Level 2[4]						
Independent	0.017	(0.01)	0.019	(0.01)	.	.
PPO	-0.007	(0.01)	-0.009	(0.01)	.	.
POS and other	-0.035	(0.02)	-0.032	(0.02)	.	.
Charlson Comorbidity Index[5]						
1	0.005	(0.01)	0.003	(0.01)	.	.
2	0.001	(0.01)	0	(0.01)	.	.
3	-0.002	(0.02)	-0.004	(0.02)	.	.
4 plus	-0.016	(0.02)	-0.018	(0.01)	.	.
Number of hospitalizations in previous year	-0.004	(0.004)	-0.003	(0.003)	-0.002	(0.003)
Average beta blocker MPR in previous year	0.048**	(0.02)	0.023*	(0.004)	-0.011*	(0.004)
Any concomitant drug utilization						
ACE Inhibitors	0.011	(0.01)	0.009	(0.01)	0.005	(0.01)
Diuretics	0.008	(0.01)	0.006	(0.01)	-0.004	(0.01)
Aldosterone antagonists	0.006	(0.01)	0.011	(0.01)	0.033**	(0.02)
Average monthly unique drug utilization	0.004**	(0.002)	0.004**	(0.002)	0.006	(0.003)
Average monthly OOP Rx ($)	0.0004*	(0.0001)	0.0004*	(0.0001)	0.0004**	(0.0002)
Number of follow-up days	0.00001	(0.00001)	0.00001	(0.00001)	.	.

Robust standard errors in parentheses
** significant at 5%; * significant at 1%
Ref groups: 1: $0 - $1; 2: Northeast/Atlantic; 3: commercial; 4: HMO; 5: 0

Table 4.9: Ordinary least squares (OLS), fixed effects (FE) and random effects (RE) models measuring associations between annual average <u>diuretic</u> copayment levels on annual average compliance in heart failure patients (N=9,301 person-years)

	OLS		RE		FE	
	Beta	SE	Beta	SE	Beta	SE
Annual Refill Copayment Median[1]						
$1 to $5	0.047*	(0.01)	0.033*	(0.01)	-0.02	(0.01)
$6 to $10	0.060*	(0.02)	0.049*	(0.02)	-0.023	(0.02)
$11 plus	0.182*	(0.05)	0.173*	(0.03)	0.099*	(0.04)
Age	0	(0.00)	0	(0.00)	-0.018	(0.06)
Female	-0.006	(0.01)	-0.008	(0.01)	0	0.00
Census[2]						
South	0.015	(0.04)	0.019	(0.04)	0	0.00
Midwest	-0.009	(0.03)	-0.014	(0.03)	0	0.00
West	0.002	(0.04)	0.009	(0.03)	0	0.00
National Mix	0.023	(0.01)	0.029**	(0.01)	0	0.00
Health Insurance Type[3]						
Medicaid	0.023	(0.06)	0.017	(0.06)	0	0.00
Medicare	-0.027	(0.02)	-0.032	(0.02)	0	0.00
Plan type[4]						
Independent	0.022	(0.02)	0.021	(0.02)	0	0.00
PPO	0.004	(0.02)	0.004	(0.02)	0	0.00
POS and other	-0.004	(0.02)	-0.001	(0.03)	0	0.00
Charlson Comorbidity index[5]						
1	-0.063*	(0.02)	-0.062*	(0.02)	0	0.00
2	-0.032	(0.02)	-0.029	(0.02)	0	0.00
3	-0.066*	(0.02)	-0.064**	(0.03)	0	0.00
4 plus	-0.015	(0.03)	-0.009	(0.03)	0	0.00
Number of hospitalizations in previous year	0.005	(0.00)	0.003	(0.00)	-0.001	(0.00)
Average diuretics MPR in previous year	0.060*	(0.01)	0.029*	(0.00)	-0.013*	(0.00)
Any concomitant drug utilization						
ACE Inhibitors	-0.006	(0.01)	-0.006	(0.01)	-0.003	(0.01)
Beta Blockers	-0.014	(0.01)	-0.015	(0.01)	-0.011	(0.02)
Aldosterone antagonists	0.01	(0.02)	0.009	(0.01)	-0.002	(0.02)
Average monthly unique drug utilization	0.015*	(0.00)	0.014*	(0.00)	0.010**	(0.00)
Average monthly OOP Rx ($)	0	0.00	0	0.00	0	0.00
Number of follow-up months	0	0.00	0	0.00	0	0.00

Robust standard errors in parentheses
** significant at 5%; * significant at 1%
Ref groups: 1: $0 - $1; 2: Northeast/Atlantic; 3: commercial; 4: HMO; 5: 0

Figure 4.10: Fixed effects (FE) parameter estimates measuring associations between annual average <u>beta blocker</u> copayment levels and annual average compliance.
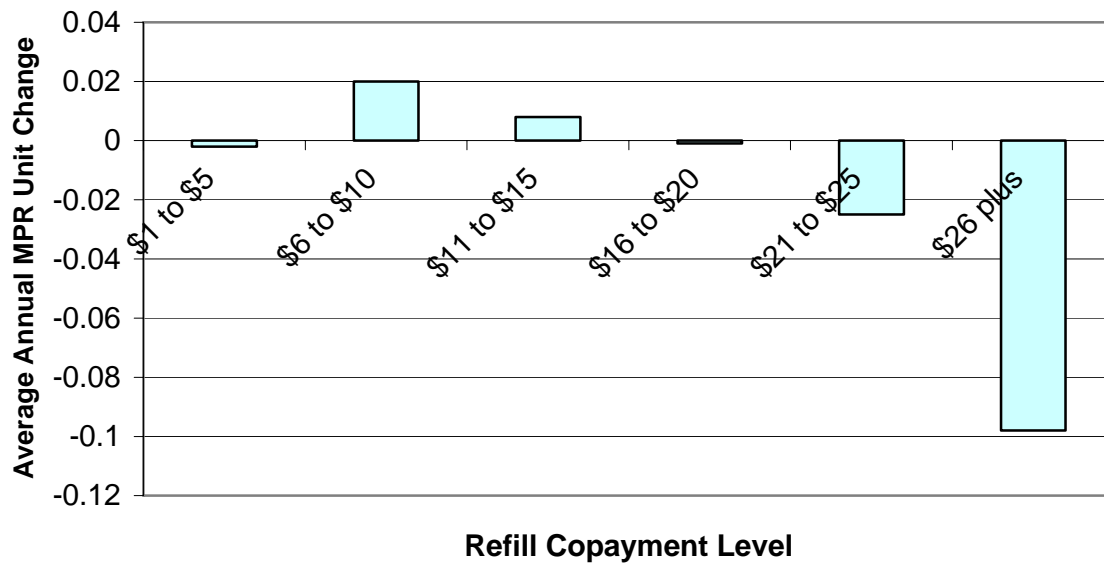

Figure 4.11: Fixed effects (FE) parameter estimates measuring associations between annual average <u>diuretic</u> copayment levels and annual average compliance

Table 4.10: Probability of non-compliance (MPR<0.8) conditional upon annual average copayment levels in ACE inhibitor, beta blocker, and diuretic utilizers with heart failure.

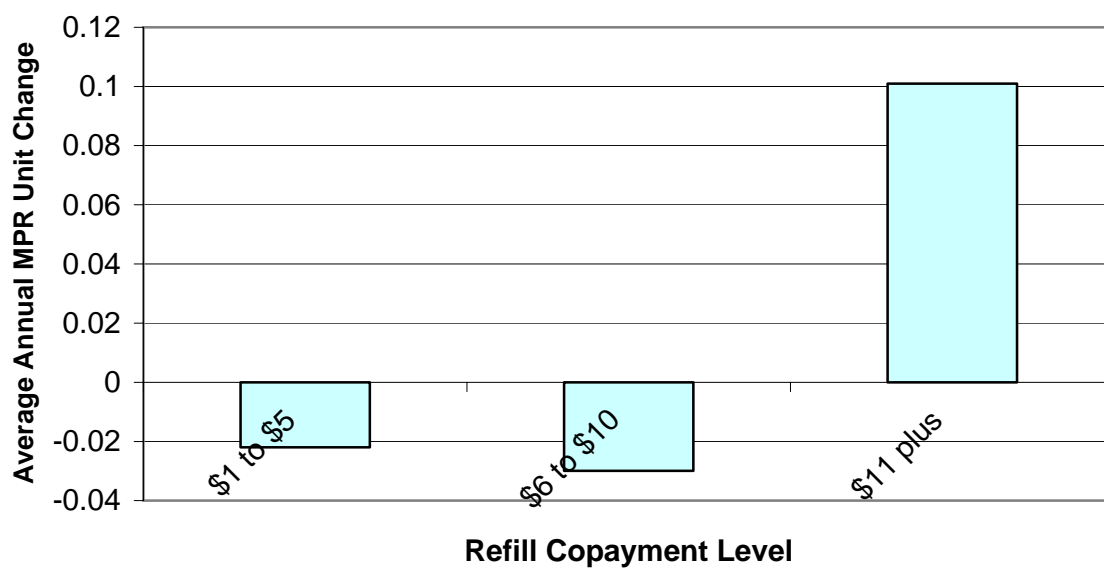|	ACE Inhibitors (N=3,256)		Beta Blockers (N=7,690)		Diuretics (N=9,305)	
	OR	95% CI	OR	95% CI	OR	95% CI
Annual Refill Copayment Median[1]						
$1 to $5	0.972	(0.316 - 2.984)	1.01	(0.792 - 1.288)	1.251*	(1.070 - 1.463)
$6 to $10	0.921	(0.293 - 2.891)	0.999	(0.747 - 1.338)	2.098*	(1.668 - 2.639)
$11 to $15	0.962	(0.299 - 3.089)	0.994	(0.722 - 1.368)	1.933*	(1.297 - 2.881)
$16 to $20	0.773	(0.237 - 2.515)	1.055	(0.725 - 1.533)		
$21 to $25	0.764	(0.226 - 2.590)	1.644**	(1.117 - 2.420)		
$26 to $30	0.745	(0.196 - 2.828)	2.539*	(1.611 - 4.003)		
$31 plus	1.909	(0.523 - 6.976)				
Age	0.987	(0.968 - 1.008)	0.999	(0.987 - 1.011)	0.996	(0.985 - 1.007)
Female	1.082	(0.818 - 1.432)	0.956	(0.814 - 1.123)	0.967	(0.836 - 1.120)
Census[2]						
South	0.176+	(0.027 - 1.153)	1.13	(0.709 - 1.800)	1.022	(0.597 - 1.747)
Midwest	2.182**	(1.151 - 4.137)	1.274	(0.811 - 1.999)	0.91	(0.595 - 1.391)
West	0.647	(0.266 - 1.577)	1.138	(0.745 - 1.738)	1.082	(0.678 - 1.729)
National Mix	1.036	(0.717 - 1.497)	1.094	(0.904 - 1.324)	0.929	(0.774 - 1.114)
Health Plan Level[3]						
Medicaid	1.378	(0.242 - 7.836)	0.532	(0.182 - 1.552)	0.907	(0.349 - 2.355)
Medicare	1.806**	(1.056 - 3.086)	1.371**	(1.051 - 1.787)	1.270+	(0.989 - 1.632)
Health Plan Level[4]						
Independent	1.148	(0.627 - 2.099)	1.049	(0.790 - 1.392)	1.063	(0.815 - 1.386)
PPO	1.436	(0.900 - 2.292)	1.173	(0.918 - 1.500)	1.173	(0.911 - 1.509)
POS and other	1.017	(0.461 - 2.246)	1.632*	(1.156 - 2.304)	0.879	(0.589 - 1.312)
Charlson Comorbidity index[5]						
1	1.101	(0.668 - 1.812)	0.977	(0.737 - 1.295)	1.09	(0.765 - 1.553)
2	1.055	(0.634 - 1.757)	1.099	(0.819 - 1.475)	1.059	(0.741 - 1.514)
3	1.333	(0.743 - 2.389)	1.004	(0.729 - 1.381)	1.346	(0.921 - 1.966)
4 plus	1.487	(0.851 - 2.601)	1.311+	(0.960 - 1.791)	1.275	(0.884 - 1.838)
Number of hospitalizations in previous year	1.06	(0.929 - 1.209)	1.103*	(1.037 - 1.173)	1.068**	(1.014 - 1.125)
Average index drug MPR in previous year	0.013*	(0.001 - 0.129)	0.017*	(0.006 - 0.046)	0.351*	(0.182 - 0.678)

(continued)

Table 4.10: Probability of non-compliance (MPR<0.8) conditional upon annual average copayment levels in ACE inhibitor, beta blocker, and diuretic utilizers with heart failure *(continued)*

	ACE Inhibitors (N=3,256)		Beta Blockers (N=7,690)		Diuretics (N=9,305)	
	OR	95% CI	OR	95% CI	OR	95% CI
Annual Concomitant Drug Use (yes/no)						
ACE inhibitors	.	.	0.940	(0.806 – 1.097)	1.028	(0.894 – 1.183)
Beta blockers	1.023	(0.781 - 1.338)	.	.	0.971	(0.843 - 1.120)
Diuretics	1.429**	(1.054 - 1.936)	1.003	(0.848 - 1.185)	.	.
Aldosterone antagonists	0.88	(0.579 - 1.337)	0.988	(0.792 - 1.231)	1.066	(0.878 - 1.293)
Average monthly unique drug utilization	0.94	(0.864 - 1.023)	0.950**	(0.909 - 0.993)	0.920*	(0.883 - 0.958)
Average monthly OOP Rx ($)	0.999	(0.994 - 1.003)	0.997**	(0.994 - 0.999)	0.998**	(0.995 - 1.000)
Number of follow-up months (ACE)	1	(1.000 - 1.000)	.	.	.	.
Number of follow-up months (Beta blockers)	.	.	1	(1.000 - 1.000)	.	.
Number of follow-up months (Diuretics)	.	.	.	.	1	(1.000 - 1.000)

Robust 95% confidence intervals in parentheses
** significant at 5%; * significant at 1%
Ref groups: 1: $0 - $1; 2: Northeast/Atlantic; 3: commercial; 4: HMO; 5: 0

MPR<0.80) as a function of copayment level were conducted for mediation models, and found consistent results (Table 4.10).

COPAYMENT LEVELS AND HOSPITALIZATIONS

In ACE inhibitor users, annual average copayment levels were not associated with increased probability of total hospitalizations, cardiovascular hospitalizations, or heart failure hospitalizations (Table 4.11). In beta blocker users, compared to those individuals with average annual copayments between $0 and $1, those averaging between $16 and $20 had a decreased probability of hospitalization, or a 30% decreased odds in having any hospitalization during the year (OR = 0.73, 95% CI 0.55 – 0.98) (Table 4.12).

In contrast, higher copayments were associated with increased hospitalizations in diuretic users. Compared to individuals with average annual diuretic copayments between $0 and $1, those with average annual copayments between $1 and $5, $6 and $10, and $11 plus had 1.2, 1.4, and 1.4 times the risk of any hospitalization (OR=1.2, 95% CI 1.1 – 1.3; OR=1.4, 95% CI 1.1 – 1.6; OR=1.4, 95% CI 1.01- 1.8) (Table 4.13). These associations were also present in cardiovascular and heart failure hospitalizations, but at higher magnitudes. Those with average copayments between $1 and $5, $6 and $10, and $11 plus had 1.6, 2.4, and 2.4 times the risk of cardiovascular hospitalizations (OR=1.6, 95% CI 1.3-1.9; OR=2.4, 95% CI 1.9 – 3.2; OR=2.4, 95% CI 1.6 – 3.6) (Table 4.13); and 1.9, 3.3, and 3.5 times the risk of heart failure specific hospitalizations (OR=1.9, 95% CI 1.6 – 2.3; OR=3.3, 95% CI 2.5 – 4.4; OR=3.5, 95% CI 2.2 – 5.4) (Table 4.13).

Table 4.11: Logistic regression models measuring odds of total hospitalizations, cardiovascular disease-specific hospitalizations, and heart-failure specific hospitalizations across annual average <u>ACE inhibitor</u> copayment levels (N=3,256 person-years)

	Any Hospitalization		Cardiovascular hospitalizations		Heart Failure Hospitalizations	
	OR	95% CI	OR	95% CI	OR	95% CI
Annual Refill Copayment Median[1]						
$1 to $5	1.245	(0.680 - 2.279)	1.345	(0.515 - 3.515)	2.539	(0.629 - 10.244)
$6 to $10	0.958	(0.513 - 1.791)	1.155	(0.428 - 3.114)	1.691	(0.404 - 7.067)
$11 to $15	1	(0.525 - 1.906)	1.243	(0.442 - 3.498)	2.231	(0.503 - 9.899)
$16 to $20	0.928	(0.476 - 1.807)	1.315	(0.450 - 3.839)	3.341	(0.751 - 14.859)
$21 to $25	0.86	(0.428 - 1.729)	1.089	(0.360 - 3.290)	1.979	(0.419 - 9.340)
$26 to $30	1.051	(0.494 - 2.239)	0.736	(0.205 - 2.638)	1.467	(0.268 - 8.016)
$31 plus	0.979	(0.460 - 2.085)	0.625	(0.183 - 2.137)	1.504	(0.279 - 8.103)
Non-compliance (MPR<0.80)	1.784*	(1.383 - 2.300)	1.495**	(1.013 - 2.206)	1.107	(0.667 - 1.838)
Age	1.034*	(1.020 - 1.049)	1.008	(0.987 - 1.029)	1.026+	(0.999 - 1.054)
Female	1	(0.832 - 1.201)	1.112	(0.830 - 1.489)	1.285	(0.894 - 1.847)
Census[2]						
South	1.376	(0.775 - 2.445)	0.638	(0.181 - 2.256)	0.865	(0.154 - 4.849)
Midwest	1.089	(0.699 - 1.698)	0.813	(0.363 - 1.819)	1.045	(0.391 - 2.795)
West	0.419**	(0.203 - 0.864)	0.378+	(0.139 - 1.030)	0.664	(0.181 - 2.434)
National Mix	1.600*	(1.262 - 2.028)	1.106	(0.759 - 1.613)	1.281	(0.799 - 2.054)
Health Plan Level 1[3]						
Medicaid	0.994	(0.325 - 3.040)	0.943	(0.168 - 5.281)	1.241	(0.110 - 13.954)
Medicare	1.261	(0.915 - 1.738)	1.747**	(1.006 - 3.033)	1.973+	(0.939 - 4.146)
Health Plan Level 2[4]						
Independent	0.852	(0.609 - 1.192)	1.304	(0.739 - 2.301)	1.21	(0.579 - 2.528)
PPO	1.185	(0.896 - 1.567)	1.709**	(1.056 - 2.765)	1.723+	(0.907 - 3.273)
POS and other	1.488	(0.900 - 2.459)	2.156+	(0.875 - 5.313)	1.879	(0.510 - 6.924)
Charlson Comorbidity index[5]						
1	1.601**	(1.092 - 2.347)	1.343	(0.722 - 2.500)	1.95	(0.802 - 4.738)
2	1.616**	(1.098 - 2.378)	1.585	(0.851 - 2.952)	1.805	(0.735 - 4.433)
3	1.847*	(1.211 - 2.817)	1.902+	(0.985 - 3.673)	2.117	(0.817 - 5.482)
4 plus	1.898*	(1.241 - 2.904)	1.759	(0.881 - 3.513)	2.647**	(1.005 - 6.969)
Number of hospitalizations in previous year	1.293*	(1.163 - 1.437)	1.324*	(1.159 - 1.514)	1.413*	(1.249 - 1.599)

(continued)

Table 4.11: Logistic regression models measuring odds of total hospitalizations, cardiovascular disease-specific hospitalizations, and heart-failure specific hospitalizations across annual average <u>ACE inhibitor</u> copayment levels (N=3,256 person-years) *(continued)*

	Any Hospitalization		Cardiovascular hospitalizations		Heart Failure Hospitalizations	
	OR	95% CI	OR	95% CI	OR	95% CI
Average ACE inhibitor MPR in previous year	1.039	(0.941 - 1.147)	1.043	(0.921 - 1.180)	1.023	(0.855 - 1.223)
Any concomitant drug utilization						
Beta blockers	1.13	(0.942 - 1.356)	1.814*	(1.318 - 2.498)	1.815*	(1.198 - 2.752)
Diuretics	1.285**	(1.028 - 1.607)	2.446*	(1.541 - 3.884)	9.061*	(2.447 - 33.548)
Aldosterone antagonists	1.373**	(1.046 - 1.802)	1.777*	(1.224 - 2.581)	2.154*	(1.392 - 3.331)
Average monthly unique drug utilization	1.131*	(1.079 - 1.187)	1.106*	(1.029 - 1.189)	1.116**	(1.024 - 1.217)
Average monthly OOP Rx ($)	1.001	(0.999 - 1.004)	1.001	(0.997 - 1.005)	1.001	(0.995 - 1.006)
Number of follow-up months	1	(1.000 - 1.001)	1.000+	(1.000 - 1.001)	1.001**	(1.000 - 1.001)

Robust 95% confidence intervals in parentheses
** significant at 5%; * significant at 1%
Ref groups: 1: $0 - $1; 2: Northeast/Atlantic; 3: commercial; 4: HMO; 5: 0

Table 4.12: Logistic regression models measuring probability of total hospitalizations, cardiovascular disease-specific hospitalizations, and heart-failure specific hospitalizations across annual average <u>beta blocker</u> copayment levels (N=7,690 person-years)

	Any Hospitalization		Cardiovascular hospitalizations		Heart Failure Hospitalizations	
	OR	95% CI	OR	95% CI	OR	95% CI
Annual Refill Copayment Median[1]						
$1 to $5	0.851+	(0.707 - 1.025)	0.95	(0.704 - 1.283)	0.94	(0.646 - 1.367)
$6 to $10	0.941	(0.756 - 1.170)	1.14	(0.802 - 1.620)	1.267	(0.816 - 1.969)
$11 to $15	0.887	(0.698 - 1.128)	1.283	(0.876 - 1.879)	1.540+	(0.960 - 2.471)
$16 to $20	0.728**	(0.543 - 0.975)	0.958	(0.605 - 1.517)	1.064	(0.602 - 1.880)
$21 to $25	0.747+	(0.533 - 1.048)	1.187	(0.733 - 1.923)	1.488	(0.824 - 2.688)
$26 plus	0.986	(0.664 - 1.465)	1.131	(0.639 - 2.001)	1.401	(0.663 - 2.958)
Non-compliance (MPR<0.80)	1.402*	(1.210 - 1.625)	1.315**	(1.041 - 1.661)	1.152	(0.847 - 1.567)
Age	1.025*	(1.017 - 1.034)	1.011	(0.998 - 1.024)	1.023*	(1.006 - 1.040)
Female	0.896+	(0.794 - 1.012)	0.686*	(0.558 - 0.842)	0.819	(0.638 - 1.049)
Census[2]						
South	1.094	(0.814 - 1.471)	1.231	(0.711 - 2.130)	1.178	(0.635 - 2.185)
Midwest	1.431+	(0.998 - 2.052)	1.680+	(0.983 - 2.870)	1.58	(0.816 - 3.057)
West	0.522*	(0.338 - 0.805)	0.537	(0.246 - 1.172)	0.454	(0.175 - 1.180)
National Mix	1.680*	(1.463 - 1.928)	1.623*	(1.308 - 2.015)	1.758*	(1.331 - 2.322)
Health Plan Level 1[3]						
Medicaid	0.538+	(0.269 - 1.074)	0.688	(0.146 - 3.230)	0.791	(0.138 - 4.544)
Medicare	1.264**	(1.030 - 1.551)	1.370+	(0.993 - 1.891)	1.184	(0.773 - 1.812)
Health Plan Level 2[4]						
Independent	1.492*	(1.215 - 1.834)	1.17	(0.845 - 1.620)	1.052	(0.705 - 1.568)
PPO	1.151	(0.953 - 1.390)	1.052	(0.792 - 1.396)	0.919	(0.633 - 1.332)
POS and other	1.345**	(1.028 - 1.760)	1.431	(0.914 - 2.240)	1.278	(0.725 - 2.253)
Charlson Comorbidity index[5]						
1	1.019	(0.815 - 1.275)	1.119	(0.742 - 1.687)	1.379	(0.786 - 2.419)
2	1.122	(0.894 - 1.408)	1.582**	(1.056 - 2.368)	1.799**	(1.034 - 3.127)
3	1.21	(0.941 - 1.556)	1.747**	(1.139 - 2.680)	1.757+	(0.962 - 3.209)
4 plus	1.301**	(1.024 - 1.654)	1.833*	(1.209 - 2.779)	2.332*	(1.327 - 4.098)
Number of hospitalizations in previous year	1.265*	(1.189 - 1.345)	1.218*	(1.139 - 1.301)	1.239*	(1.141 - 1.346)

(continued)

Table 4.12: Logistic regression models measuring probability of total hospitalizations, cardiovascular disease-specific hospitalizations, and heart-failure specific hospitalizations across annual average <u>beta blocker</u> copayment levels (N=7,360 person-years) *(continued)*

	Any Hospitalization		Cardiovascular hospitalizations		Heart Failure Hospitalizations	
	OR	95% CI	OR	95% CI	OR	95% CI
Average beta blocker MPR in previous year	1.033	(0.974 - 1.095)	0.981	(0.865 - 1.113)	0.959	(0.788 - 1.167)
Any concomitant drug utilization						
ACE Inhibitors	1.109+	(0.988 - 1.245)	1.416*	(1.189 - 1.686)	1.345*	(1.081 - 1.673)
Diuretics	1.363*	(1.191 - 1.560)	2.250*	(1.757 - 2.882)	4.260*	(2.828 - 6.419)
Aldosterone antagonists	1.209**	(1.028 - 1.421)	1.476*	(1.181 - 1.844)	1.778*	(1.359 - 2.326)
Average monthly unique drug utilization	1.156*	(1.121 - 1.192)	1.108*	(1.059 - 1.160)	1.107*	(1.047 - 1.171)
Average monthly OOP Rx ($)	1.002	(1.000 - 1.003)	1	(0.997 - 1.002)	0.998	(0.995 - 1.001)
Number of follow-up months	1	(1.000 - 1.000)	1.000*	(1.000 - 1.001)	1.000**	(1.000 - 1.001)

Robust 95% confidence intervals in parentheses
*** significant at 5%; * significant at 1%*
Ref groups: 1: $0 - $1; 2: Northeast/Atlantic; 3: commercial; 4: HMO; 5: 0

Table 4.13: Logistic regression models measuring probability of total hospitalizations, cardiovascular disease-specific hospitalizations, and heart-failure specific hospitalizations across annual average <u>diuretic</u> copayment levels (N=9,305 person-years)

	Any Hospitalization		Cardiovascular hospitalizations		Heart Failure Hospitalizations	
	OR	95% CI	OR	95% CI	OR	95% CI
Annual Refill Copayment Median[1]						
$1 to $5	1.198*	(1.069 - 1.343)	1.601*	(1.344 - 1.908)	1.932*	(1.573 - 2.373)
$6 to $10	1.346*	(1.124 - 1.612)	2.416*	(1.876 - 3.112)	3.283*	(2.471 - 4.363)
$11 plus	1.405**	(1.059 - 1.865)	2.537*	(1.713 - 3.759)	3.789*	(2.459 - 5.839)
Non-compliance (MPR<0.80)	1.159**	(1.019 - 1.320)	0.916	(0.754 - 1.112)	0.904	(0.726 - 1.127)
Age	1.031*	(1.023 - 1.039)	1.017*	(1.005 - 1.029)	1.026*	(1.012 - 1.041)
Female	0.941	(0.849 - 1.043)	0.93	(0.793 - 1.091)	1.005	(0.835 - 1.209)
Census[2]						
South	1.138	(0.820 - 1.580)	1.074	(0.637 - 1.811)	0.923	(0.511 - 1.670)
Midwest	1.18	(0.872 - 1.596)	0.801	(0.484 - 1.325)	0.7	(0.367 - 1.335)
West	0.669**	(0.455 - 0.984)	0.79	(0.446 - 1.400)	0.659	(0.354 - 1.230)
National Mix	1.542*	(1.360 - 1.747)	1.186+	(0.991 - 1.419)	1.141	(0.921 - 1.414)
Health Plan Level 1[3]						
Medicaid	1.195	(0.638 - 2.237)	0.778	(0.360 - 1.679)	1.156	(0.495 - 2.702)
Medicare	1.216**	(1.018 - 1.454)	1.517*	(1.168 - 1.970)	1.454**	(1.063 - 1.987)
Health Plan Level 2[4]						
Independent	1.102	(0.915 - 1.327)	1.035	(0.792 - 1.353)	1.066	(0.775 - 1.468)
PPO	1.06	(0.890 - 1.263)	1.133	(0.868 - 1.477)	1.156	(0.836 - 1.600)
POS and other	1.054	(0.799 - 1.390)	1.315	(0.882 - 1.960)	1.267	(0.780 - 2.058)
Charlson Comorbidity index[5]						
1	1.119	(0.857 - 1.460)	1.489+	(0.959 - 2.313)	1.319	(0.813 - 2.141)
2	1.242	(0.951 - 1.622)	1.634**	(1.051 - 2.542)	1.272	(0.784 - 2.064)
3	1.613*	(1.225 - 2.125)	2.193*	(1.392 - 3.456)	1.786**	(1.081 - 2.950)
4 plus	1.509*	(1.149 - 1.983)	1.866*	(1.194 - 2.916)	1.563+	(0.959 - 2.547)
Number of hospitalizations in previous year	1.303*	(1.239 - 1.371)	1.292*	(1.226 - 1.362)	1.329*	(1.256 - 1.407)

(continued)

Table 4.13: Logistic regression models measuring probability of total hospitalizations, cardiovascular disease-specific hospitalizations, and heart-failure specific hospitalizations across annual average <u>diuretic</u> copayment levels (N=9,305 person-years) *(continued)*

|	Any Hospitalization		Cardiovascular hospitalizations		Heart Failure Hospitalizations	
	OR	95% CI	OR	95% CI	OR	95% CI
Average diuretic MPR in previous year	1.019	(0.983 - 1.055)	1.043**	(1.003 - 1.085)	1.066*	(1.024 - 1.110)
Any concomitant drug utilization						
ACE Inhibitors	1.148*	(1.037 - 1.273)	1.589*	(1.375 - 1.838)	1.581*	(1.335 - 1.873)
Beta Blockers	1.378*	(1.245 - 1.526)	2.163*	(1.854 - 2.524)	1.876*	(1.570 - 2.242)
Aldosterone antagonists	1.315*	(1.148 - 1.507)	1.702*	(1.433 - 2.020)	1.993*	(1.638 - 2.425)
Average monthly unique drug utilization	1.174*	(1.143 - 1.206)	1.149*	(1.108 - 1.191)	1.157*	(1.108 - 1.208)
Average monthly OOP Rx ($)	0.998**	(0.997 - 1.000)	0.995*	(0.993 - 0.997)	0.993*	(0.991 - 0.996)
Number of follow-up months	1.000+	(1.000 - 1.000)	1.000**	(1.000 - 1.000)	1.000**	(1.000 - 1.001)

Robust 95% confidence intervals in parentheses
** significant at 5%; * significant at 1%
Ref groups: 1: $0 - $1; 2: Northeast/Atlantic; 3: commercial; 4: HMO; 5: 0

Mediation models used logistic regression to estimate the a) probability of non-compliance conditional upon copayment levels (Path A); b) the probability of hospitalization conditional upon non-compliance (Path B); c) the probability of hospitalization conditional upon copayment level controlling for non-compliance (Path C)(direct effect); d) the probability of hospitalization conditional upon copayment level omitting non-compliance (Path D)(total effect). Indirect effects were computed by multiplying the coefficients from Path A and Path B, and using the Sobel test in order to test the presence of mediation.

Figure 4.12: Mediation Model Pathway
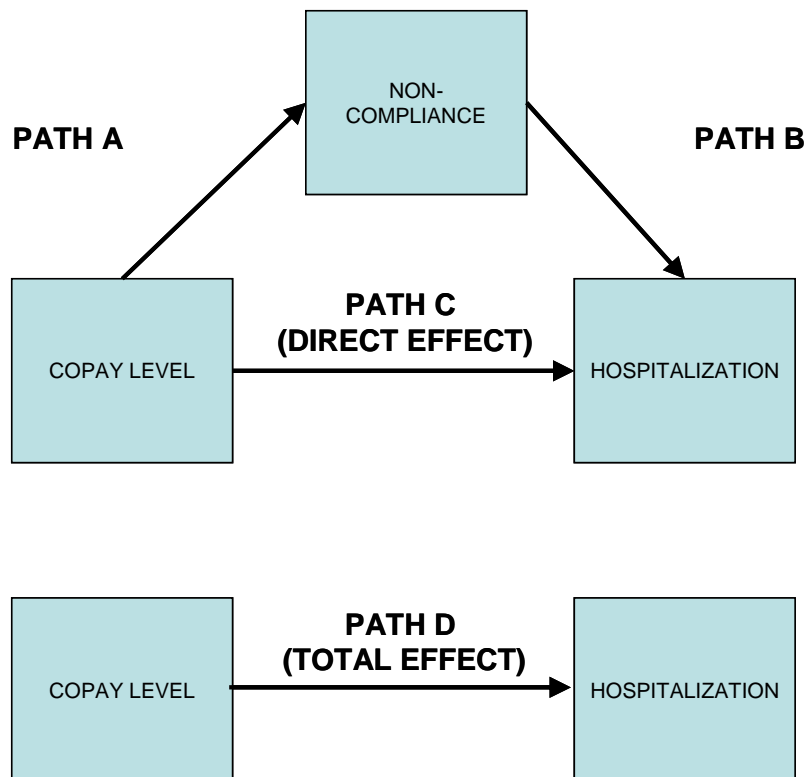
A prerequisite for non-compliance to be a mediator of hospitalization requires a total effect between the copayment and hospitalizations; otherwise there is no pathway upon

which the proposed mediator, non-compliance, can act. Since increased copayment levels were not significantly associated with increased risk of hospitalization in ACE inhibitor or beta blocker cohorts, testing the mediating properties of medication non-compliance for these cohorts became irrelevant. In contrast, the significant associations found between diuretic copayment levels and hospitalizations provided an opportunity to test the indirect effect.

In the diuretic models, indirect effects were not statistically significant at any copayment level, in comparison to the reference group, according to the Sobel test (Table 4.14). This suggests that factors besides non-compliance contribute to the relationship between diuretic copayment levels and risk of hospitalizations.

Table 4.14: Sobel test calculations of the indirect effects of non-compliance on copayment and hospitalizations

	Total Hospitalizations				
	Path A (β)	Path B (β)	Path AB (β)	$S_{(AB)}$[1]	Crit[2]
Refill Copayment Level					
$1 to $5	0.22	0.14	0.03	0.02	1.55
$6 to $10	0.75	0.14	0.10	0.06	1.88
$11 to $15	0.48	0.14	0.09	0.06	1.66
	Cardiovascular Hospitalizations				
	Path A (β)	Path B (β)	Path AB (β)	$S_{(AB)}$[1]	Crit[2]
Refill Copayment Level					
$1 to $5	0.22	-0.09	-0.02	0.09	-0.79
$6 to $10	0.75	-0.09	-0.07	0.13	-0.86
$11 to $15	0.48	-0.09	-0.06	0.17	-0.82
	Heart Failure Hospitalizations				
	Path A (β)	Path B (β)	Path AB (β)	$S_{(AB)}$[1]	Crit[2]
Refill Copayment Level					
$1 to $5	0.22	-0.10	-0.02	0.10	-0.82
$6 to $10	0.75	-0.10	-0.08	0.14	-0.90
$11 to $15	0.48	-0.10	-0.07	0.18	-0.85

1: Sobel Test $S_{ab}=\sqrt{[(B^2 * s_a^2 + A^2 * s_b^2 + s_a^2 * s_b^2)]}$
2: Critical value calculation: Path AB (β)/ $S_{ab;}$ *compare to normal distribution as a z-score*

PATHWAY A: COPAYMENT AND NON-COMPLIANCE

Deconstructing the indirect effect into the separate pathways provided additional insight into the relationship between copayment level and compliance; and compliance and

hospitalizations. Unlike the linear models that measured compliance as a continuous variable, the mediation models measured it as a dichotomous outcome (MPR<0.80). Compared to beta blocker users with annual average copayment levels between $0 and $1, those with average annual copayments levels of $20 to $25 and $26 upwards had 1.6 and 2.5 times the risk, respectively, of medication non-compliance (OR=1.6, 95% CI 1.12 - 2.42; OR=2.5, 95% CI 1.6 – 4.0) (Table 4.10). Similarly, compared to diuretic users with annual copayments averaging $0 to $1, those with annual copayment levels $1 to $5, $6 to $10, and $11 upwards had 1.3, 2.1, and 1.9 times the risk, respectively, of medication non-medication (OR=1.3, 95% CI 1.1 – 1.5; OR=2.1, 95%CI 1.7 – 2.6; OR=1.3 – 2.9) (Table 4.10).

PATHWAY B: COMPLIANCE AND HOSPITALIZATION

Additional associations found between compliance and hospitalizations corroborate past studies demonstrating that medication non-compliance increases the risk of hospitalizations. Compared to compliant ACE inhibitor users with an annual MPR above 0.8, non-compliant ACE inhibitor users had 1.8 and 1.5 times the risk of any hospitalization and any CAD-specific hospitalization, respectively (OR=1.79, 95% CI (1.38 – 2.3);OR=1.50, 95% CI (1.01 – 2.21)(Table 4.11). Similarly, non-compliance beta blocker users had 1.4, and 1.3 times the risk of any hospitalization or cardiovascular specific hospitalization (OR=1.40, 95% CI (1.21 – 1.63); OR=1.31, 95% CI (1.04 – 1.66) (Table 4.12), and non-compliance diuretic users had 1.2 times the risk of any hospitalization (OR=1.16, 95% CI (1.02 – 1.32) (Table 4.13).

SUMMARY

In summary, compared to refills in the lowest copayment category, refills in the higher copayment categories were associated with decreased medication supply levels for beta blockers and diuretics. These associations remained in the person-year level regressions, finding higher annual copayment levels associated with decreased annual medication supply levels.

Of all three drug classes, diuretics were the only category which showed significant associations between copayment levels and hospitalizations. Compared to individuals taking the lowest copayment level diuretic, those with higher copayment levels had increasingly more risk of all hospitalization outcomes examined, a statistically significant total effect which according to the Sobel statistic was not mediated by non-compliance. Consistent with past studies examining associations of medication non-compliance on hospitalizations, ACE inhibitor, beta blocker, and diuretic non-compliance was associated with increased risk of hospitalizations.

CHAPTER V: DISCUSSION

OVERVIEW

This dissertation's objectives were to a) estimate the effects of copayment levels on ACE inhibitor, beta blocker, and diuretic compliance; b) estimate the probability of all-cause, cardiovascular-specific, and heart-failure specific hospitalizations conditional upon ACE inhibitor, beta blocker, and diuretic copayment levels; and c) explore the mediation properties of medication non-compliance to assess the causal pathway between copayments, compliance and hospitalizations, all within a sample of commercially insured heart failure patients.

First, it was hypothesized that increased copayment levels would be associated with decreased compliance across all medication classes. Fixed-effects models found no association between ACE inhibitor copayments levels and MPR (Table 4.2, 4.7) with the exception of copayment levels ($26 to $30) that exhibited an unexpected positive correlation with MPR in the refill-level analysis (Table 4.2). In contrast, both refill-level and person-year models found higher beta blocker or diuretic copayment levels to be significantly associated with decreased MPR (Table 4.3, 4.4, 4.8, 4.9) with the exception of annual diuretic copayments ($11 and up) that exhibited unexpected positive correlations in the person-year analysis (Table 4.9).

Second, it was hypothesized that increased copayment levels would be associated with increased risk of all-cause, cardiovascular, and heart failure specific hospitalizations across all medication classes. Logistic regressions showed increased copayment levels associated with increased risk of hospitalizations in the diuretic cohort (Table 4.13), with the exception of the beta blocker cohort showing average annual copayments between ($16 and 20) significantly associated with decreased risk of hospitalization (Table 4.12).

Third, it was hypothesized that medication non-compliance would mediate the association between copayments and hospitalizations. Diuretic non-compliance did not mediate the significant associations found between average annual diuretic copayments and hospitalizations (Table 4.14).

CONCLUSIONS

Significant associations between beta blocker and diuretic copayment levels and the MPR suggest that higher copayments cause decreased compliance to beta blockers or diuretics in privately insured heart failure patients. Although the study design did not include a control group or estimate the effect of copayment changes, the dose-response relationship suggests a causal relationship (Figure 4.8; 4.9). The inverse associations found are also consistent with retrospective claims studies demonstrating that increased copayment levels are associated with either decreased medication utilization (Harris, Stergachis et al. 1990; Johnson, Goodman et al. 1997; Johnson, Goodman et al. 1997; Joyce, Escarce et al. 2002; Huskamp, Deverka et al. 2003; Goldman, Joyce et al. 2004) or compliance (Coombs, Cornish et al. 2002; Dor and Encinosa 2004; Ellis, Erickson et al. 2004).

138

The validity of these estimates was strengthened by the use of either fixed-effect estimators that captured individual-level time-invariant sources of heterogeneity, or random effects estimators that accounted for clustering of refills within individuals. Conducting specification tests to compare OLS, RE and FE estimators provided insight into how unobserved heterogeneity or clustering may bias the results if not accounted for in the analyses. For example, the Bruesch-Pagan test, favoring the RE over the OLS, demonstrated the likely presence of clustering, which gone unaccounted for, would result in inflated standard errors and consequently less efficient estimators. Additionally, the Hausman test, favoring the FE over the RE, demonstrated the likely presence of individual level time-invariant unobserved heterogeneity that would have caused biased parameter estimates in either the RE or OLS models. The use of more sophisticated estimators in this analysis therefore accounted for sources of bias that standard OLS models would be unable to detect.

In contrast to the significant associations found in the beta blocker and diuretic cohorts, null associations found between ACE inhibitor copayments and MPR suggest that ACE inhibitor compliance is unaffected by copayment level. These results are consistent with a study finding no associations between copayment change and ACE inhibitor use (Pilote, Beck et al. 2002). Pilote et al. speculated that individuals with a severe condition may be insensitive to copayment changes given the essential nature of the medication (Pilote, Beck et al. 2002). If so, heart failure patients may perceive that ACE inhibitors as more essential compared to beta blockers or diuretics, causing them to remain relatively price insensitive.

Although the significant associations found between diuretic copayment levels and hospitalization risk suggest that higher diuretic copayments increase the risk of all-cause,

cardiovascular, or heart-failure specific hospitalizations, the absence of a control group makes it difficult to infer causality. Furthermore, since these person-year level models did not control for drug-product heterogeneity, associations could be due to drug product effects. For example, physicians may be prescribing higher cost diuretics to more severe patients already at higher risk of hospitalization, causing a positive correlation between copayment level and hospitalization risk. One scenario could be the case of Zaroxolyn, a higher cost diuretic indicated for heart failure patients with renal failure (Wolters-Kluwer Health, 2006). Given that almost 50% of the diuretics in the $11 plus category prescribed were Zaroxolyn (Table 5.1), the increased risk of hospitalization associated with ($11 plus) diuretics may be attributed to physicians prescribing more Zaroxolyn to severe patients versus non-severe patients, creating a positive correlation between copayment level and hospitalization (Table 4.13).

Table 5.1: Frequency of diuretic product brands by copayment category

Diuretic Brand	$0 (%)	$1 to $5(%)	$6 to $10 (%)	$11 plus (%)
Furosemide	93.17	89.82	56.66	5.76
hydrochlorothiazide	4.56	2.76	0.61	0
Zaroxolyn®	0.72	1.14	11.39	47.49
Bumetanide	0.65	2.89	12.45	3.82
Lasix®	0.29	1.95	6.77	9.63
Demadex®	0.28	0.49	2.86	21.59
Bumex®	0.19	0.18	0.69	4.19
Torsemide	0.1	0.66	6.89	1.73
Aldactone®	0.04	0.1	1.3	4.89
Aldactazide®	0	0	0.37	0.76
Microzide®	0	0	0	0.16

Furthermore, if this select group of patients taking diuretics averaging $11 and above is on average more compliant to Zaroxolyn due to a perceived need to be extra compliant, this could explain the positive association found between copayment level and compliance in the person-year diuretic models (Figure 4.16). These unobserved factors motivate the need

to examine the causal mechanism existing between higher diuretic copayments and increased hospitalization risk more closely, providing rationale for the use of mediation models to explore causal pathways among copayments, compliance, and hospitalizations.

Although it was hypothesized that copayments cause increase hospitalizations due to medication non-compliance, the null indirect effects found using mediation models suggest that the effect of increased copayments on hospitalizations is not caused by non-compliance. This suggests that other unobserved mediators may be part of the causal pathway. Future studies therefore need to further explore the causal mechanism underlying the associations between diuretic copayment levels and hospitalizations.

LIMITATIONS

The absence of more detailed clinical information prevented classifying heart failure patients into alternative heart failure regimens. Since this analysis assumed that all individuals diagnosed with heart failure need to be compliant to ACE inhibitors, beta blockers, and diuretics, it did not account for the possibility of individuals switching to clinically appropriate alternatives such as ACE inhibitors to angiotensin receptor blockers (ARBs). Consequently, if individuals appropriately switch from ACE to ARBs, they would be misclassified as being non-compliant to ACE inhibitors. As a result, these results are most generalizable to heart failure patients who are chronic long term users of ACE inhibitors, beta blockers, or diuretics, and less so to heart failure patients who switch to 2nd line therapy classes not captured in this analysis.

One of the consequences of restricting this analysis to long-term utilizers is that it did not have the ability to test the marginal effects of copayment on compliance for extreme non-compliers. More specifically, because the existence of a pharmaceutical claim was required

141

in order to measure copayment levels, the existence of an observed copayment level depended upon the utilization level of the individual. Ideally, if the dataset had plan-level formulary benefit descriptions attributed to each individual, copayment exposures could have been assigned to individuals based upon the policy change dates instead of the copayment level associated with each of the observed refills. Consequently, the existence of the copayment measure was dependent upon a minimum amount of pharmaceutical claims, inevitably resulting in selection bias. As a result, the analysis excluded low compliers and focused primarily on patients with regular use of ACE inhibitors, beta blockers, or diuretics, respectively, over a three year period. Although this restricts the external validity to a select group of heart failure patients, it was the best solution in the absence of plan-level copayment information. Omitting less compliant heart failure patients from the sample may have attenuated the estimates, especially if the extreme non-compliers were more sensitive to higher copayment levels compared to chronic long term utilizers.

If plan-level indicator variables containing formulary benefit descriptions and change dates were present in the data, assigning copayment levels and change dates would have been possible even to the least compliant individuals. In addition, this information would have facilitated matching control groups to those individuals having copayment changes. Although significant associations were found between copayments, compliance, and hospitalizations, the absence of a control group makes it difficult to infer causality from the study results. Despite these limitations, the multiple copayment levels present in the claims data created an opportunity to estimate effects of multiple copayment levels on compliance, as opposed to the effects of just one policy shift, the latter being most common in quasi-experimental designs.

Even with the ability to construct a control group, this would not have prevented bias resulting from the endogenous relationship between copayment and health outcomes. For example, while increased diuretic copayments may increase the risk of hospitalizations, current models cannot account for the degree of bias resulting from physicians selectively prescribing diuretics in certain copayment levels due to the health status of an individual. In this example, the presence of reverse causality, one form of endogeneity, results in biased estimates. The bias created from endogeneity may be attenuated by using instrumental variables in conjunction with two stage least squares estimates (Wooldridge 2003). This requires choosing a variable as an instrument that is highly correlated with the predictor (copayment), yet orthogonal to the outcome (hospitalizations, or compliance). Since employers are a large influence in setting copayment levels when contracting with managed care organizations, some type of employer characteristic that is correlated with prescription copayments and unrelated to individual-level outcomes might have potential as an instrument. Assuming prescription copayment is endogenous, future studies might therefore employ instrumental variables to measure copayment effects on health outcomes.

Beyond the design, this study contained limitations universal to retrospective studies using administrative claims data. For example, information was missing from administrative claims on educational level, income, and racial background.
If these factors are systematically associated with copayment levels, as well as medication compliance or health status, biased estimates may have occurred. In a study examining low income cohorts of elderly respondents from the Aging and Health Dynamics (AHEAD) study, Moran et al. found significant inverse correlations between income level and prescription drug use (Moran and Simon December 2004). These results imply that lower

income heart failure patients may also take fewer medications, and failing to account for income level could bias the associations between copayment level and probability of hospitalizations. Yet, since all of these factors are arguably time-invariant, including income if individuals are retirees on fixed income, the use of individual fixed effects models accounts for these unobserved sources of heterogeneity.

In contrast to demographic characteristics which may be time-invariant, cardiovascular risk factors such as smoking status, BMI, or exercise levels may vary over time. These potentially omitted variables may have biased the estimates, especially if they are correlated with copayment levels. For example, if there were reason to believe that physicians would prescribe a higher costing beta blocker to a smoker versus a non-smoker, or to an avid exerciser versus a less active adult, failing to account for these factors may result in biased copayment estimates on hospitalizations. In addition to risk factor information, the lack of clinical information regarding heart failure severity levels also compromised the accuracy of risk adjustment. For example, classifying individuals into NYHA severity levels I, II, III, and IV would have improved the risk adjustment compared to the proxy measurement of total hospitalizations at baseline.

Finally, although claims-based adherence metrics such as the MPR have been cited as valid and reliable estimates of actual medication taking behavior (Steiner, Koepsell et al. 1988), it technically still reflects medication supply levels (Stroupe, Teal et al. 2004). Despite this, the MPR in certain cases may greatly diverge from actual medication taking behavior. For example, heart failure patients being titrated for diuretics may end up having a series of early refills, which mostly likely reflects dose switches as opposed to over-consumption. Given that early refills often manifest themselves as large MPR values in the

claims data (Grymonpre, Didur et al. 1998), the current analysis eliminated individual refills with outlier MPRs arguably because the refills associated with these MPR values were a reflection of early refills as opposed to true medication taking behavior of a stable regimen. Despite the limitations associated with MPR as a proxy of actual compliance, proxies with measurement error tend to bias estimates toward the null (Greene 2003), implying that this proxy would at worst underestimate the effect of copayments on compliance.

STRENGTHS

This study contributes to the literature by being the first to simultaneously measure drug-class specific associations among copayment levels, medication compliance, and clinical outcomes within a commercially insured heart failure population. Although prior studies established inverse correlations between prescription copayments and utilization, few studies have focused on medication compliance. Furthermore, although studies have examined drug class specific copayment effects, none have focused on ACE inhibitors, beta blockers, or diuretics in privately insured heart failure patients.

The main strengths of this analysis include the large number of claims, the diversity of the included plan types, the longitudinal nature of the data, and the use of mediation models to explore the causal pathway among copayments, non-compliance, and hospitalizations. The large number of claims facilitated the ability to conduct class-specific analyses within a subgroup of heart failure patients, a relatively rare but costly condition especially in healthier, privately insured beneficiaries. The diversity of plan type enrollees also increase the external validity of the results to a larger cross section of commercially insured populations in the United States. In contrast, many past studies measuring

145

copayment change effects on utilization or compliance have focused only in one type of managed care organization (Harris, Stergachis et al. 1990; Motheral and Fairman 2001; Huskamp, Deverka et al. 2003).

In addition to the large sample size and diverse source population, the panel data structure facilitated the use of fixed effects and random effects models. The use of specification tests to compare OLS, FE, and RE models demonstrates how pharmaceutical claims data is prone to serial correlation and unobserved heterogeneity, sometimes correctable using these more advanced error component models. Finally, simultaneous measurement of copayment levels, medication compliance, and hospitalizations enabled the use of mediation models to explore causal pathways among them. Although this mediation modeling is prevalent in the psychology and sociology literature, no current studies have used this method to explore the effects of copayments on compliance or hospitalization.

POLICY AND CLINICAL IMPLICATIONS

If increased beta blocker or diuretic copayments are associated with decreased compliance, this creates a challenge for policy makers whose goal is to contain system level costs concurrently with maintaining the health of health plan enrollees. For example, should managed care organizations or hospitals provide free diuretics for heart failure patients to encourage optimal compliance? Under this scenario, health plan administers would have to demonstrate that the cost of providing free diuretics would be less than or equal to the costs associated with diuretic non-compliance-related hospitalizations.

The current formulary decision process involves gathering information on safety, efficacy, and cost. The decision process made by hospitals and health plans often relies upon pharmacy and therapeutic (P&T) committees to gather information from case reports in the

literature, randomized clinical trials and anecdotes from clinicians to help guide their

decisions. While the formulary decision process is not currently standardized across health

care organizations, it is more recently becoming transparent after the introduction of the

Academy of Managed Care Pharmacy (AMCP) Format for Formulary Submission in 2000,

which urges committees to request formalized dossiers from pharmaceutical companies that

include the drug's safety, efficacy, and cost data in addition to unpublished studies, off label

indications, and disease management strategies (Neumann 2004). As more managed care

organizations outsource to pharmacy benefit management companies (PBMs) to design and

administer pharmacy benefits to their enrollee population, the PBMs have also evolved as

important decision-makers in the formulary process (Grabowski and Mullins 1997). In

addition to being influenced by P&T committees' expert opinions on safety, efficacy, and

cost, PBMs are also influenced by the rebates offered by pharmaceutical companies to

classify drugs as preferred products (Grabowski and Mullins 1997).

In summary, the medication's safety, efficacy, and cost profile in addition to volume

discounts offered to MCOs or PBMs by pharmaceutical companies influence the assignment

of a drug to a particular copayment level. Currently absent in this decision process is the

consideration of patient compliance based upon medication copayment level. Incorporating

class-specific effects of medication copayment levels on compliance into the formulary

decision process could improve the ability of P&T committees and PBMs to design

formularies sensitive to the medication-taking habits of chronically ill patients. Results from

this study are therefore helpful to pharmacy benefit managers or prescription policy designers

interested in assessing the effects of their formulary design on utilization of heart failure

medications in privately insured heart failure patients. Furthermore, given the trend of

pharmacy benefit management companies (PBMs) investing more in disease management, and their growing interest in outcomes research (Grabowski and Mullins 1997), they would have incentive to design unique disease-specific formularies based upon medication compliance levels in order to contain long-term system-level expenditures.

While cost-related medication adherence may be modified at the formulary level, communication between physicians and patients regarding drug costs could increase patient awareness of equivalent, cheaper therapies. In a nationwide study surveying over 600 adults reporting medication underutilization due to cost, approximately two-thirds of the respondents did not tell a clinician in advance that they planned to underutilize the medication because of cost (Piette, Heisler et al. 2004). In terms of physician communication, the same survey found that only 28% of respondents reported that their doctor or nurse asked whether they could afford the medication, only 69% reported the physician changing more expensive medications to cheaper alternatives, and 59% reported that physicians talked to them about which medications they should not skip (Piette, Heisler et al. 2004). Results from these studies imply a significant gap between patients and providers in terms of communication about medication cost issues. Furthermore, if physicians do not address the patients about medication non-compliance due to cost, the medications which should not be skipped, generic alternatives, physicians' own prescribing patterns could contribute to suboptimal medication compliance of heart failure medications. Clinicians therefore need to increase their awareness of medication cost and how medication cost barriers result in suboptimal mediation compliance to heart failure medications especially in the most vulnerable populations with multiple comorbidities and lower socioeconomic status.

FUTURE INVESTIGATIONS

The significant associations found between diuretic copayment levels and hospitalizations needs to be further investigated in order to elucidate the causal nature of these associations. More rigorous methods such as quasi-experimental designs or instrumental variables could help account for the role of selection bias or endogeneity. Using data with copayment policy change dates would facilitate assigning a control group, as well as measuring the effects of a change in copayments with changes in compliance and clinical outcomes. The use of instrumental variables could help account for whether copayments are causing decreased health status, or whether physicians are selectively prescribing medications with higher copayments to higher-risk patients.

Finally, future studies should account for unobserved heterogeneity due to specific drug products as well as different managed care firms. Although the present research did account for drug brand in the refill-level analyses, high drug switching rates made it difficult to assign drug brands at the person-year level. Although the presence research did account for health plan payer and physician reimbursement type, using MCO firm fixed effects could have better controlled for some of the unobserved firm-level differences such as quality of care and incentives affecting prescribing patterns.

Due to the increasing prevalence and economic burden of heart failure in the United States in conjunction with an aging population enrolling into managed care plans for the new Medicare drug benefit, the effects of copayments on compliance and hospitalizations need further study. The ever increasing economic burden of heart disease in the United States provides an impetus to continue studying the effects of copayment policies on medication adherence and hospitalizations, especially given the significant associations found in diuretic

users. Direct costs of treating heart failure have been estimated at $20 billion, or 1.5% of the total United States health care expenditures for hospitalization, outpatient visits, nursing home care and pharmaceuticals (Berry, Murdoch et al. 2001). More importantly, given this disease is most prevalent in individuals 65 and above, more Medicare funds are spent toward heart failure treatment than in any other diagnosis. For example, compared to all cancer treatments, Medicare spent twice as much for heart failure hospitalizations (Lee, Chavez et al. 2004). Since decreased medication compliance to clinically recommended heart failure medications increase the risk of hospitalizations (Stroupe, Teal et al. 2004), cost-sharing polices which potentially discourage optimal compliance to heart failure medications should be critically examined. Creating formularies which encourage optimal use of essential medications continues to be important, especially if these policies decrease the economic burden of heart failure.

REFERENCES

(1987). "Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group." N Engl J Med **316**(23): 1429-35.

(1991). "Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators." N Engl J Med **325**(5): 293-302.

(1999). "The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial." Lancet **353**(9146): 9-13.

(1999). "Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)." Lancet **353**(9169): 2001-7.

(2005). IHCIS Data Code Book, Integrated Healthcare Information Systems, Inc.

(2006). Facts and Comparisons Online v4.0, Wolters Kluwer Health, Inc.

Adams, K. F., Jr., G. C. Fonarow, et al. (2005). "Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE)." Am Heart J **149**(2): 209-16.

Ahmed, A., A. Husain, et al. (2006). "Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods." Eur Heart J **27**(12): 1431-1439.

Heart Failure Society of America (2006). "HFSA 2006 Comprehensive Heart Failure Practice Guideline." J Card Fail **12**(1): e1-122.

Andrews, R. and A. J. Cowley (1995). "Clinical and economic factors in the treatment of congestive heart failure." Pharmacoeconomics **7**(2): 119-27.

Aronow, W. S. (2003). "Epidemiology, pathophysiology, prognosis, and treatment of systolic and diastolic heart failure in elderly patients." Heart Dis **5**(4): 279-94.

Balkrishnan, R. (1998). "Predictors of medication adherence in the elderly." Clin Ther **20**(4): 764-71.

Baron, R. M. and D. A. Kenny (1986). "The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations." J Pers Soc Psychol **51**(6): 1173-82.

Berry, C., D. R. Murdoch, et al. (2001). "Economics of chronic heart failure." <u>Eur J Heart Fail</u> **3**(3): 283-91.

Bodenheimer, T. and K. Sullivan (1998). "How large employers are shaping the health care marketplace. First of two parts." <u>N Engl J Med</u> **338**(14): 1003-7.

Brater, D. C. (1998). "Diuretic therapy." <u>N Engl J Med</u> **339**(6): 387-95.

Bruesch, T. and A. Pagan (1979). "A simple test for heteroskedasticity and random coefficient variation." <u>Econometrika</u> **47**: 1287-94.

Cangialose, C. B., S. J. Cary, et al. (1997). "Impact of managed care on quality of healthcare: theory and evidence." <u>Am J Manag Care</u> **3**(8): 1153-70.

Charlson, M. E., P. Pompei, et al. (1987). "A new method of classifying prognostic comorbidity in longitudinal studies: development and validation." <u>J Chronic Dis</u> **40**(5): 373-83.

Christensen, D. B., B. Williams, et al. (1997). "Assessing compliance to antihypertensive medications using computer-based pharmacy records." <u>Med Care</u> **35**(11): 1164-70.

Christian-Herman, J., M. Emons, et al. (2004). "Effects of generic-only drug coverage in a Medicare HMO." <u>Health Aff (Millwood)</u> **Suppl Web Exclusives**: W4-455-68.

Cohn, J. N., G. Johnson, et al. (1991). "A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure." <u>N Engl J Med</u> **325**(5): 303-10.

Coombs, J. H., L. Cornish, et al. (2002). "Compliance and refill pattern behavior with HMG-CoA reductase inhibitors after acute myocardial infarction." <u>Manag Care Interface</u> **15**(1): 54-8, 60.

Dei Cas, L., M. Metra, et al. (2003). "Prevention and management of chronic heart failure in patients at risk." <u>Am J Cardiol</u> **91**(9A): 10F-17F.

Devereux, R. B., M. J. Roman, et al. (2000). "Impact of diabetes on cardiac structure and function: the strong heart study." <u>Circulation</u> **101**(19): 2271-6
.
Domanski, M., J. Norman, et al. (2003). "Diuretic use, progressive heart failure, and death in patients in the Studies Of Left Ventricular Dysfunction (SOLVD)." <u>J Am Coll Cardiol</u> **42**(4): 705-8.

Dor, A. and W. Encinosa (2004). Does cost sharing affect compliance? The case of prescription drugs. <u>NBER Working Paper</u>, National Bureau of Economic Research.

Ellis, J. J., S. R. Erickson, et al. (2004). "Suboptimal statin adherence and discontinuation in primary and secondary prevention populations." J Gen Intern Med **19**(6): 638-45.

Fairman, K. A., B. R. Motheral, et al. (2003). "Retrospective, long-term follow-up study of the effect of a three-tier prescription drug copayment system on pharmaceutical and other medical utilization and costs." Clin Ther **25**(12): 3147-61; discussion 3144-6.

Faris, R., M. Flather, et al. (2002). "Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials." Int J Cardiol **82**(2): 149-58.

Folland, S., A. C. Goodman, et al. (2000). The Economics of Health and Healthcare. Upper Saddle River, NJ, Prentice-Hall.

Fonarow, G. C., C. Chelimsky-Fallick, et al. (1992). "Effect of direct vasodilation with hydralazine versus angiotensin-converting enzyme inhibition with captopril on mortality in advanced heart failure: the Hy-C trial." J Am Coll Cardiol **19**(4): 842-50.

Fonarow, G. C., C. W. Yancy, et al. (2005). "Adherence to heart failure quality-of-care indicators in US hospitals: analysis of the ADHERE Registry." Arch Intern Med **165**(13): 1469-77.

Fowler, M. B. (2004). "Carvedilol prospective randomized cumulative survival (COPERNICUS) trial: carvedilol in severe heart failure." Am J Cardiol **93**(9A): 35B-9B
.

Foxman, B., R. B. Valdez, et al. (1987). "The effect of cost sharing on the use of antibiotics in ambulatory care: results from a population-based randomized controlled trial." J Chronic Dis **40**(5): 429-37.

Goldman, D. P., G. F. Joyce, et al. (2004). "Pharmacy benefits and the use of drugs by the chronically ill." Jama **291**(19): 2344-50.

Grabowski, H. and C. D. Mullins (1997). "Pharmacy benefit management, cost-effectiveness analysis and drug formulary decisions." Soc Sci Med **45**(4): 535-44.

Greene, W. H. (2003). Large-sample properties of least squares and instrumental variable estimators. Econometric Analysis. Upper Saddle River, NJ, Prentice-Hall: 65-92.

Grymonpre, R. E., C. D. Didur, et al. (1998). "Pill count, self-report, and pharmacy claims data to measure medication adherence in the elderly." Ann Pharmacother **32**(7-8): 749-54.

Hamilton, R. A. and L. L. Briceland (1992). "Use of prescription-refill records to assess patient compliance." Am J Hosp Pharm **49**(7): 1691-6.

Harris, B. L., A. Stergachis, et al. (1990). "The effect of drug co-payments on utilization and cost of pharmaceuticals in a health maintenance organization." Med Care **28**(10): 907-17.

Hausman, J. (1978). "Specification Tests in Econometrics." Econometrika **46**: 1251-71.

Heidenreich, P. A., M. McClellan, et al. (2002). "The relation between managed care market share and the treatment of elderly fee-for-service patients with myocardial infarction." Am J Med **112**(3): 176-82.

Heisler, M., K. M. Langa, et al. (2004). "The health effects of restricting prescription medication use because of cost." Med Care **42**(7): 626-34.

Hillman, A. L., M. V. Pauly, et al. (1999). "Financial incentives and drug spending in managed care." Health Aff (Millwood) **18**(2): 189-200.

Hunt, S. A., W. T. Abraham, et al. (2005). "ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society." Circulation **112**(12): e154-235.

Huskamp, H. A., P. A. Deverka, et al. (2003). "The effect of incentive-based formularies on prescription-drug utilization and spending." N Engl J Med **349**(23): 2224-32.

Huskamp, H. A., P. A. Deverka, et al. (2005). "Impact of 3-tier formularies on drug treatment of attention-deficit/hyperactivity disorder in children." Arch Gen Psychiatry **62**(4): 435-41.

Johnson, R. E., M. J. Goodman, et al. (1997). "The effect of increased prescription drug cost-sharing on medical care utilization and expenses of elderly health maintenance organization members." Med Care **35**(11): 1119-31.

Johnson, R. E., M. J. Goodman, et al. (1997). "The impact of increasing patient prescription drug cost sharing on therapeutic classes of drugs received and on the health status of elderly HMO members." Health Serv Res **32**(1): 103-22.

Joyce, G. F., J. J. Escarce, et al. (2002). "Employer drug benefit plans and spending on prescription drugs." Jama **288**(14): 1733-9.

Kamal-Bahl, S. and B. Briesacher (2004). "How do incentive-based formularies influence drug selection and spending for hypertension?" Health Aff (Millwood) **23**(1): 227-36.

Kannel, W. B. and A. J. Belanger (1991). "Epidemiology of heart failure." <u>Am Heart J</u> **121**(3 Pt 1): 951-7.

Krum, H. and R. E. Gilbert (2003). "Demographics and concomitant disorders in heart failure." <u>Lancet</u> **362**(9378): 147-58.

Lee, W., Y. Chavez, et al. (2004). "Economic burden of heart failure: a summary of recent literature." <u>Heart and Lung</u>.

Leibowitz, A., W. G. Manning, et al. (1985). "The demand for prescription drugs as a function of cost-sharing." <u>Soc Sci Med</u> **21**(10): 1063-9.

MacKinnon, D. P., C. M. Lockwood, et al. (2002). "A comparison of methods to test mediation and other intervening variable effects." <u>Psychol Methods</u> **7**(1): 83-104.

Massie, B. M. and N. B. Shah (1997). "Evolving trends in the epidemiologic factors of heart failure: rationale for preventive strategies and comprehensive disease management." <u>Am Heart J</u> **133**(6): 703-12.

Meissner, B. L., W. M. Moore, et al. (2004). "Effects of an increase in prescription copayment on utilization of low-sedating antihistamines and nasal steroids." <u>J Manag Care Pharm</u> **10**(3): 226-33.

Metra, M., L. D. Cas, et al. (2004). "Beta-blockers in heart failure: are pharmacological differences clinically important?" <u>Heart Fail Rev</u> **9**(2): 123-30.

Mojtabai, R. and M. Olfson (2003). "Medication costs, adherence, and health outcomes among Medicare beneficiaries." <u>Health Aff (Millwood)</u> **22**(4): 220-9.

Monane, M., R. L. Bohn, et al. (1994). "Noncompliance with congestive heart failure therapy in the elderly." <u>Arch Intern Med</u> **154**(4): 433-7.

Moran, J. R. and K. I. Simon (December 2004). Income and use of prescription drugs by the elderly: evidence from the notch cohorts. Working Paper 66, Syracuse Center for Policy Research.

Morris, A. B., J. Li, et al. (2006). "Factors associated with drug adherence and blood pressure control in patients with hypertension." <u>Pharmacotherapy</u> **26**(4): 483-92.

Motheral, B. and K. A. Fairman (2001). "Effect of a three-tier prescription copay on pharmaceutical and other medical utilization." <u>Med Care</u> **39**(12): 1293-304.

Motheral, B. R. and R. Henderson (1999). "The effect of a copay increase on pharmaceutical utilization, expenditures, and treatment continuation." <u>Am J Manag Care</u> **5**(11): 1383-94.

Nair, K. V., P. Wolfe, et al. (2003). "Effects of a 3-tier pharmacy benefit design on the prescription purchasing behavior of individuals with chronic disease." J Manag Care Pharm **9**(2): 123-33.

Nelson, A. A., Jr., C. E. Reeder, et al. (1984). "The effect of a Medicaid drug copayment program on the utilization and cost of prescription services." Med Care **22**(8): 724-36.

Neumann, P. J. (2004). "Evidence-based and value-based formulary guidelines." Health Aff (Millwood) **23**(1): 124-34.

Packer, M., M. R. Bristow, et al. (1996). "The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group." N Engl J Med **334**(21): 1349-55.

Piette, J. D., M. Heisler, et al. (2004). "Cost-related medication underuse: do patients with chronic illnesses tell their doctors?" Arch Intern Med **164**(16): 1749-55.

Piette, J. D., T. H. Wagner, et al. (2004). "Health insurance status, cost-related medication underuse, and outcomes among diabetes patients in three systems of care." Med Care **42**(2): 102-9.

Pilote, L., C. Beck, et al. (2002). "The effects of cost-sharing on essential drug prescriptions, utilization of medical care and outcomes after acute myocardial infarction in elderly patients." Cmaj **167**(3): 246-52.

Pitt, B., F. Zannad, et al. (1999). "The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators." N Engl J Med **341**(10): 709-17.

Poole-Wilson, P. A., K. Swedberg, et al. (2003). "Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial." Lancet **362**(9377): 7-13.

Preacher, K. J. and A. F. Hayes (2004). "SPSS and SAS procedures for estimating indirect effects in simple mediation models." Behav Res Methods Instrum Comput **36**(4): 717-31.

Rector, T. S., M. D. Finch, et al. (2003). "Effect of tiered prescription copayments on the use of preferred brand medications." Med Care **41**(3): 398-406.

Rector, T. S., S. L. Wickstrom, et al. (2004). "Specificity and sensitivity of claims-based algorithms for identifying members of Medicare+Choice health plans that have chronic medical conditions." Health Serv Res **39**(6 Pt 1): 1839-57.

Reeder, C. E. and A. A. Nelson (1985). "The differential impact of copayment on drug use in a Medicaid population." <u>Inquiry</u> **22**(4): 396-403.

Roblin (2005). "Effect of increased cost-sharing on oral hypoglycemic use in five managed care organiations: how much is too much?" <u>Medical Care</u> **43**(10): 951-9.

Roger, V., S. Weston, et al. (2004). "Trends in heart failure incidence and survival in a community-based population." <u>JAMA</u> **292**(3): 344-50.

Sharkness, C. M. and D. A. Snow (1992). "The patient's view of hypertension and compliance." <u>Am J Prev Med</u> **8**(3): 141-6.

Smith, D. G. (1993). "The effects of copayments and generic substitution on the use and costs of prescription drugs." <u>Inquiry</u> **30**(2): 189-98.

Sobel, M. E. (1982). Asymptotic confidence intervals for indirect effects in structural equation models. <u>Sociological methodology 1982</u>. S. Leinhart. San Francisco, Jossey-Bass**:** 290-312.

Soumerai, S.B. (1993). "A critical analysis of studies of state drug reimbursement policies: research in need of discipline." <u>Millbank Quarterly</u> **71**(2): 217-52

Soumerai, S. B. (2004). "Benefits and risks of increasing restrictions on access to costly drugs in Medicaid." <u>Health Aff (Millwood)</u> **23**(1): 135-46.

Soumerai, S. B., J. Avorn, et al. (1987). "Payment restrictions for prescription drugs under Medicaid. Effects on therapy, cost, and equity." <u>N Engl J Med</u> **317**(9): 550-6.

Soumerai, S. B., T. J. McLaughlin, et al. (1994). "Effects of a limit on Medicaid drug-reimbursement benefits on the use of psychotropic agents and acute mental health services by patients with schizophrenia." <u>N Engl J Med</u> **331**(10): 650-5.

Soumerai, S. B., D. Ross-Degnan, et al. (1991). "Effects of Medicaid drug-payment limits on admission to hospitals and nursing homes." <u>N Engl J Med</u> **325**(15): 1072-7.

Steiner, J. F., T. D. Koepsell, et al. (1988). "A general method of compliance assessment using centralized pharmacy records. Description and validation." <u>Med Care</u> **26**(8): 814-23.

Stroupe, K. T., M. M. Forthofer, et al. (2000). "Healthcare costs of patients with heart failure treated with torasemide or furosemide." <u>Pharmacoeconomics</u> **17**(5): 429-40.

Stroupe, K. T., E. Y. Teal, et al. (2004). "Health care and medication costs and use among older adults with heart failure." <u>Am J Med</u> **116**(7): 443-50.

Sundararajan, V., T. Henderson, et al. (2004). "New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality." J Clin Epidemiol **57**(12): 1288-94.

Taira, D. A., K. A. Iwane, et al. (2003). "Prescription drugs: elderly enrollee reports of financial access, receipt of free samples, and discussion of generic equivalents related to type of coverage." Am J Manag Care **9**(4): 305-12.

Tamblyn, R., R. Laprise, et al. (2001). "Adverse events associated with prescription drug cost-sharing among poor and elderly persons." Jama **285**(4): 421-9.

Taubert, G., C. Bergmeier, et al. (2001). "Clinical profile and management of heart failure: rural community hospital vs. metropolitan heart center." Eur J Heart Fail **3**(5): 611-7.

Thom, T., N. Haase, et al. (2006). "Heart disease and stroke statistics--2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee." Circulation **113**(6): e85-151.

Thomas, C. P., S. S. Wallack, et al. (2002). "Impact of health plan design and management on retirees' prescription drug use and spending, 2001." Health Aff (Millwood) **Suppl Web Exclusives**: W408-19.

Ward, M. M. and J. P. Leigh (1993). "Pooled time series regression analysis in longitudinal studies." J Clin Epidemiol **46**(7): 645-59.

Wooldridge, J. (2003). Instrumental Variables Estimation and Two Stage Least Squares. Introductory Econometrics: A Modern Approach. J. W. Calhoun, Thomson: South-Western**: 484-524.

Wooldridge, J. M. (2003). Advanced Panel Data Methods. Introductory Econometrics: A Modern Approach. J. W. Calhoun, Thomson: South-Western**: 461-483.

Wooldridge, J. M. (2003). Pooling cross sections across time. Simple Panel Data Methods. Introductory Econometrics: A Modern Approach. J. W. Calhoun, Thomson: South-Western**: 426-460.