IMPACT OF MEDICATION BURDEN ON ADHERENCE WITH ANTIHYPERTENSIVE DRUGS

by

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A Dissertation submitted to the

Graduate School-New Brunswick

Rutgers, The State University of New Jersey

in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

Graduate Program in Public Health

written under the direction of

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and approved by

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New Brunswick, New Jersey

October 2010

ABSTRACT OF THE DISSERTATION

Impact of Medication Burden on Adherence with Antihypertensive Drugs

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Antihypertensive drug adherence is key in achieving blood pressure control and preventing cardiovascular complications. The objective of this study was to understand how pill burden, age and comorbid conditions impact antihypertensive medication compliance. This retrospective study used MarketScan claims to identify continuously enrolled adults with newly diagnosed hypertension, follow-up ≥ 6-month pre- and 12–month post-index antihypertensive prescription. Pill burden was defined as total number of prescriptions per month and/or doses per day. Medication possession ratio (MPR), defined as total number of index antihypertensive days' supply divided by 365, was a proxy for compliance. MPR ≥ 0.80 was classified as high. Descriptive statistics were conducted for 27 variables including sociodemographic characteristics, comorbid conditions, health

care resource utilization and costs. Logistic regression analysis was run (SAS, version 8.2, Cary, NC).

Mean age was 53 years for 68,538 study subjects and 56% were female. Diabetes (18%) and other forms of heart disease (14%) were most prevalent. Most subjects were full-time employees (64%), working in manufacturing/durable goods (36%) or transportation/communications/utilities (21%), and residing in the South (41%) or North Central (28%) United States. Preferred provider organizations (41%) and comprehensive benefit plans (23%) provided coverage for most subjects. Approximately 25% of subjects received diuretics, 21% angiotensin-converting enzyme inhibitors, 20% beta-blockers, 17% fixed-dose combinations, 9% calcium-channel blockers, and 8% angiotensin receptor blockers (ARBs). Total index antihypertensive copay was lowest for diuretics ($48.71) and highest for ARBs ($98.12). Mean number of doses per day (excluding antihypertensive prescriptions) was 1.3 and number of prescriptions per month (excluding antihypertensive prescriptions) was 1.85. Mean MPR was 0.70 and 57% of subjects were highly compliant with antihypertensive medications. Likelihood of compliance decreased by 10% per additional dose per day, increased by 22.5% per additional prescription per month (excluding antihypertensive medications), decreased by 10% per additional comorbid conditions, increased by 0.6% per additional year of age, by 1.1% per dollar increase in total copay and was 9% greater for males ($p < 0.0001$). Increasing doses per day, comorbid conditions and being

female had a negative impact on compliance with antihypertensive medications and may assist in targeting populations for quality improvement initiatives.

ACKNOWLEDGEMENT AND DEDICATION

To my mother and sister Mary Jane who were most supportive and caring and to my children (Peter Fejry, Edward George and Soraya Ann) who inspired me to finish. A heartfelt thanks to Professor Schneider for her encouragement and guidance all the way.

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I. INTRODUCTION

"Drugs don't work in patients who don't take them."

C. Everett Koop,

Former U.S. Surgeon General

Compliance and persistence with prescribed antihypertensive therapy are key factors contributing to the achievement of blood pressure (BP) control and preventing cardiovascular complications. Hypertension is a highly prevalent disease and, with the aging population in the United States, its prevalence is expected to grow. Additionally, a higher proportion of seniors will likely bring a surge in prescription use, which may compromise compliance with antihypertensive therapies. Most patients will require at least two antihypertensive agents to achieve goal BP.[1] Understanding the impact of overall pill burden on compliance with antihypertensive therapy will assist in findings ways to enhance care and improve health in this patient population.

Scope of the problem

The American Society of Hypertension warned in their proposed new definition of hypertension that "progression of hypertension is strongly associated with function and structural cardiac and vascular abnormalities that damage the heart, kidneys, brain, vasculature, and other organs and lead to premature morbidity and death."[2] The currently accepted definition of hypertension, established in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure or the JNC 7 report,

is the presence of systolic blood pressure (SBP) ≥ 140 millimeters of mercury (mmHg), or diastolic blood pressure (DBP) ≥ 90 mmHg (derived from the mean of two or more properly measured seated BP readings on each of two or more office visits.[1] The JNC 7 report states that the relationship between blood pressure and risk of cardiovascular disease (CVD) events is continuous, consistent, and independent of other risk factors. The higher the BP, the greater the chance of myocardial infarction (MI), heart failure (HF), stroke and kidney disease. For individuals aged 40 to 70 years, each increment of 20 mmHg in SBP or 10 mmHg in DBP doubles the risk of CVD across the entire BP range (written as SBP/DBP) from 115/75 to 185/115 mmHg. Epidemiologic data from the Framingham Heart Study have shown that patients with hypertension had a 2- to 3-fold increase in the risk of congestive heart failure (CHF) and an approximately 1.5-fold increase in the risk of atrial fibrillation compared with normotensive individuals.[3, 4]

Hypertension affects approximately 72 million individuals in the United States (estimated prevalence of 33.6%[5]) and roughly one billion individuals worldwide.[6] The American Heart Association reports the prevalence of hypertension in the U.S. population 65 years and older well over 60% (63.6% and 73.9% among males and females ages 65-74 years old, and 69.5% and 83.8% among males and females age 75 years and older, respectively). [5]

Giles and colleagues reported data from the National Health and Nutrition Examination Survey (NHANES) 1999-2002 survey, confirming the well-established effects of age on hypertension and documenting BP control by age group.[7] They

showed prevalence increased with age while BP control decreased with age. The prevalence of hypertension in individuals ≥ 65 and ≥ 75 years of age was the highest (67.3% and 76.2%, respectively), but BP control among those receiving treatment was the lowest (48.4% and 38.8%, respectively). The prevalence of hypertension increased steadily from 11.0% to 29.7% and 50.2% in the 18-39, 40-54 and 55-64 year old age groups, respectively. BP control was 60.8%, 64.4% and 59.1% in those same age groups, respectively.

Prevalence and BP control statistics become more noteworthy when coupled with US Census Bureau's projections for our nation's population. The US Census Bureau projects that, in 2030, when the last of the baby boomers reaches age 65 years, nearly one in five Americans is expected to be 65 and older.[8] This age group is anticipated to increase to 88.5 million in 2050, more than doubling the number in 2008 (38.7 million).

The current public health objectives of the US Department of Health and Human Services, *Healthy People 2010*, stresses the crucial role of compliance in hypertension control.[9] Patients' ability and willingness to carry out a treatment program successfully are of critical importance in realizing its potential benefits. Efforts at the long-term management of asymptomatic coronary heart disease risk factors such as hypertension suggest that a sizable number of patients do not successfully carry out their prescribed treatment regimen for a variety of reasons, including not filling the initial prescription, lack of persistence, or partial compliance. *Healthy People 2010* notes the need for continued efforts to better

understand the determinants of adherence to ensure that patients stay with their prescribed therapy.

In 2007, the American Heart Association (AHA) estimated the direct and indirect costs of high blood pressure to total approximately $66.4 billion.[5] Direct costs take into account hospital, nursing home, physician/other professionals, drug/other medical durables, and home healthcare, amounting to $49.3 billion. Lost productivity due to morbidity and mortality comprise the indirect costs ($9.3 billion).

Hypertension was one of the 20 leading primary diagnosis groups in terms of the number and percent of office visits in the United States in 2006.[10] The National Ambulatory Medical Care Survey (NAMCS), which began in 1973, gathers information about the health care provided by office-based (non-federally employed) physicians. Each physician is randomly assigned to a 1-week reporting period to systematically record patients' symptoms, physicians' diagnoses, and medications ordered or provided for a random sample of visits on an encounter form provided for that purpose. The survey also provides statistics on the demographic characteristics of patients and services provided, including information on diagnostic procedures, patient management, and planned future treatment. The number of visits with essential hypertension (the International Classification of Diseases, 9th Revision, Clinical Modification or ICD-9-CM rubric 401) as primary diagnosis was 35.7 million.

The impact of hypertension extends far beyond the treatment of blood pressure. In 1998, the AHA reported the cost of treating hypertension-related complications being higher than that of treating the diagnosis ($29.7 billion and $22.8 billion, respectively).[5] Hypertension was the primary or contributing cause of an estimated 277,000 deaths in the United States in 2003 and, from 1993 to 2003, the actual number of deaths related to hypertension rose 56.1%.

Achieving BP control may reduce the burden of illness and may reduce the risk of cardiovascular complications and death. Antihypertensive therapy has been associated with a 35% to 40% mean reduction in stroke incidence, a 20% to 25% decrease in MI, and more than 50% reduction in HF.[1] In the Hypertension Optimal Treatment (HOT) trial, the subpopulation of patients with diabetes who had a lower target DBP experienced a reduced incidence in the number of major cardiovascular events compared with diabetic patients who had a higher target DBP.[11] In the Systolic Hypertension in the Elderly Program (SHEP study), patients >60 years of age with isolated systolic hypertension who were receiving antihypertensive therapy experienced a 36% reduction in the incidence of stroke.[12] Data from the NHANES III (1988-1994) showed that, compared with normotensive individuals, the relative risk of CVD mortality was 1.74 (95% CI, 1.28-2.49; p = 0.007) for patients with uncontrolled hypertension.[13] However, the relative risk of CVD mortality was not statistically significantly different between normotensive individuals and individuals with pre-hypertension or treated hypertensive patients

who had controlled BP (< 140/90 mm Hg or < 130/80 mm Hg for individuals with diabetes or chronic kidney disease).

Understanding factors impacting adherence with antihypertensive therapy is crucial in preventing cardiovascular complications and addressing the needs of the growing elderly population. To help reduce the health and economic burden we will face from hypertension alone, we need to find ways to improve compliance with disease treatment.

The objective of this study is to evaluate the impact of overall pill burden (number of medications and number of doses per day) on adherence with antihypertensive drugs. The hypothesis is that an increasing number of medications and doses per day decrease adherence with antihypertensive medications. To test the hypothesis, a retrospective study design will be employed, correlating the average compliance with antihypertensive drugs over the follow-up period to the pill burden observed during the same period, controlling for age, gender, and prevalence of pre-specified comorbid conditions. The study will use medical and pharmacy claims data from MarketScan to identify hypertensive subjects initiating treatment with thiazide diuretics, beta blockers (BBs), angiotensin-converting-enzyme (ACE) inhibitors, calcium channel blockers (CCBs), or angiotensin receptor blockers (ARBs) to evaluate how overall pill burden impact compliance with antihypertensive medication over a 12-month follow-up period. Chapter II will review the literature evaluating compliance in hypertension as well as the negative outcomes associated with decreased

compliance in general. This summary will identify gaps in the literature that this research project will attempt to address. Chapter III will present in detail the methods utilized in this study. The methods section will include a description of the database used to conduct the study, the inclusion/exclusion criteria for subject identification, the statistical analysis plan including the rationale for the definitions set forth for the study. Finally, this chapter will address the limitations of this research, given its observational nature. Chapter IV will present the results addressing the research questions and hypotheses in order. Chapter V will interpret the results in the previous chapter and will put the findings in context of the published literature. Appendices A and B will contain the tables and graphs illustrating the results. The appendices will be followed by the references and curriculum vitae.

II. Review of the literature

The American Heart Association (AHA) estimates that the number one problem in treating illness today is patients' failure to take prescription medications correctly, regardless of patient age.[14] Compliance involves taking medication as prescribed, on time, and in the correct dose. It also includes following any recommended lifestyle modifications such as diet or exercise. Compliance is critical for the 12% of Americans who don't fill their prescriptions at all, for the 12% who don't take medication at all after they buy the prescription, and the two-thirds who fail to take any or all of their prescriptions medicines.[14] Polypharmacy further compounds the problem, with 59% of people with ≥ 5 medications taking them improperly, irrespective of age.[14] Noncompliance is a serious issue that leads to both adverse patient and economic outcomes. The AHA estimates that 10% of all hospitalizations and 23% of all nursing home admissions are the result of patients failing to take prescription medications correctly.[14]

Patients with hypertension must comply with therapy to achieve and maintain blood pressure control. A recent retrospective study by Bramley and colleagues of 840 randomly selected hypertensive patients using antihypertensive monotherapy, conducted in 13 managed care organizations, assessed the relationship between medication compliance and blood pressure control (< 140/90 mmHg or < 130/85 mmHg for diabetic hypertensive patients).[15] Patients received monotherapy with an ACE inhibitor (27%), CCB (22%), BB (20%), or diuretic (11%) and were classified as having high (80–100%) medication compliance (75% of

patients), medium (50–79%) medication compliance (20% of patients), or low (< 50% compliance; 5% of patients) medication compliance. High-compliance patients were 45% more likely to achieve blood pressure control than those with medium or low compliance after controlling for age, gender, and comorbidities. Interestingly, a higher total number of nonhypertensive medications was associated with a lower rate of BP control (OR = 0.95; p = 0.007).

The long-term survival of treated hypertensive patients has been demonstrated to be dependent on the degree of compliance.[16] Perry and Camel followed 223 patients who began antihypertensive treatment under the supervision of physicians in the Hypertension Division at Washington University in St. Louis for 16 years. Mean age of the entire group was 46 years upon entry into the study and 115 were female. Patients were instructed to take and record his/her blood pressure four or five times per day and to bring all BP records to the next treatment visit. Patients were categorized as (1) non-compliant, (2) compliant but uncontrolled, or (3) controlled after the first year of follow-up. The researchers assumed that compliance with home BP monitoring (defined as at least 2 measurements per day) was indicative of compliance with antihypertensive drug therapy. There was a positive correlation between long-term survival and compliance. Mean survival times were 56.5, 134 and 153 months for 56 non-compliant, 60 compliant but uncontrolled and 107 controlled patients, respectively. Compliance, in this study, relied on self-reports of blood pressure readings rather than actual antihypertensive medication taking. Despite the study

limitations, Perry and Camel concluded that non-compliance is one of a constellation of characteristics associated with shortened survival but that this should not lessen the power of compliance as a predictor of longevity among treated hypertensive patients.

Noncompliance specifically with antihypertensive medication is well-recognized as a serious public health problem. Van Wijk and colleagues studied the relationship between noncompliance and discontinuation among patients starting to use antihypertensive monotherapy.[17] For this nested case-control study, Van Wijk and colleagues used the PHARMO database, a record linkage system in the Netherlands containing drug dispensing records from community pharmacies and linked hospital discharge records of approximately 950,000 subjects, for his logistic regression predicting discontinuation. The computerized drug-dispensing histories contain data on the drug dispensed, type of prescriber, dispensing date, dispensed amount, prescribed dose regimen and the prescription length for inhabitants of 33 medium-sized areas in the Netherlands and is estimated to include 95% of all prescriptions dispensed to a particular patient. Cases discontinued their use of antihypertensive monotherapy and were not switched to other antihypertensive treatment. Matched controls stayed on their initially prescribed monotherapy. The percentage of noncompliant patients (measured as the medication possession ratio or MPR < 80) among cases and controls was 14.0% and 5.8%, respectively (odds ratio 2.86; 95% confidence interval 2.52-3.24). MPR is calculated as the sum of days' supply for all prescription fills of the index

hypertension class during the follow-up period, divided by the duration of the follow-up period (365 days), multiplied by 100 to express as a percentage. The authors concluded that, in patients who start antihypertensive monotherapy, noncompliance is often followed by discontinuation of antihypertensive treatment.

A surprisingly high percentage of patients discontinue therapy within the first year of treatment.[18] Bernard Bloom used pharmacy records from a large pharmaceutical benefits management organization to retrospectively analyze the refill behavior of patients who had recently started antihypertensive drugs in the outpatient setting. Subjects were considered persistent users of an antihypertensive agent at 12 months if they had refilled their prescription on or within 3months after the 1-year anniversary of the initial prescription. Mean age of the study population (n=21,723) was 56 years and 55.9% were female. Most patients were on ACE inhibitors (26.9%) followed by thiazide diuretics (24.1%), CCBs (23.4%), BBs (23.0%), and angiotensin-receptor blockers (ARBs) (2.6%). The vast majority was taking their antihypertensive once a day (83.5%). At 12 months' follow-up, discontinuation ranged from 36% to 62%, depending on the drug class. While persistence with treatment is required to achieve BP control, discontinuation rates are very high in actual practice after only 1 year of therapy.

Van Wijk and colleagues conducted a study to assess the proportion of patients starting antihypertensive drug treatment who continued treatment for at least 10 years.[19] This retrospective cohort study was conducted using the PHARMO record linkage system, which contains drug dispensing records from

community pharmacies and is linked to hospital discharge records of approximately 950,000 subjects. New starts were defined as patients not receiving a prescription for any antihypertensive drug in the 365 days preceding the first prescription. Analysis of the 2,325 patients in the study showed that older patients were more persistent than younger patients:

Age group	**Odds ratio**	**95% confidence interval**
20-39 years	2.08	1.52-2.84
40-59 years	1.00 (reference group)	
≥ 60 years	0.69	0.54-0.89

Additionally, only 39% of patients used antihypertensive drugs continuously during 10 years of follow-up, while 22% temporarily discontinued and restarted treatment, and 39% discontinued treatment permanently.

Gregoire and colleagues conducted a prospective cohort study through a network of pharmacies across Canada to examine the effect of an array of potential predisposing, enabling and reinforcing factors on the discontinuation of newly prescribed antihypertensive medications.[20] Participants were interviewed by telephone four times to obtain information for a minimum duration of 18 months after entry into the cohort. Through a multivariate proportional hazard model, this study found that 43.3% of study subjects had discontinued their initial medication at the end of the observational period. Individuals more likely to

discontinue their initial medication were those who perceived side effects from this medication (hazard ratio = 1.91, 95% CI 1.47-2.47). Individuals with medication insurance coverage were less likely to discontinue (hazard ratio = 0.74, 95% CI 0.55-0.99).

Thomas Burke et al evaluated antihypertensive drug discontinuation among newly diagnosed hypertensive patients using the United Kingdom (UK) General Practice Research Database (GPRD).[21] The GPRRD contains computerized information entered by general practitioners in the UK for over 9 million patients (40 million patient years). Newly diagnosed was defined as lack of a hypertension diagnosis prior to the start of the follow-up period and ≥ 1 year of history prior to the date of their new hypertension diagnosis during which no antihypertensive prescription were recorded. Antihypertensive therapy was considered discontinued when no antihypertensive drug prescriptions were issued within 90 days following the end of the latest antihypertensive drug prescription. The discontinuation date was the date the last consecutive prescription expired. Researchers also determined if patients switched to a second antihypertensive drug class after discontinuing their first antihypertensive class. Switching was defined as a prescription from a second antihypertensive drug class within 90 days of the discontinuation date, excluding patients starting dual therapy and those with less than 90 days of follow-up after discontinuing their first therapy. Overall, 61.59% discontinued the first antihypertensive during the 10-year follow-up period. The median time to overall discontinuation was 3.07 years. The risk of

discontinuation was highest early in the course of treatment; one of every five patients in the study had discontinued therapy at 6 months.

What can be done to improve compliance with drug therapy?

In over half of treatment failures, the problem is not an inadequate regimen, but suboptimal compliance with that prescribed regimen. A review article by Rudd summarized the principal findings of studies related to hypertension epidemiology, component behaviors contributing to suboptimal compliance with prescribed antihypertensive medications, the direct and indirect costs of nonadherent behaviors, and measures of pill-taking behavior, and made recommendations to improve pill taking among patients with hypertension.[22] While noting that current levels of hypertension detection, treatment, and control remain suboptimal, Rudd concludes that more than half of those patients failing to achieve goal blood pressure display suboptimal compliance rather than an inadequate regimen. Rudd points to patients frequently reporting a lack of understanding of the instructions provided by physicians, as well as adverse effects as their reason for noncompliance.

Delivering proper dosing instructions and patient counseling may be challenging for health care providers. A survey of patients discharged from an academic medical center in the United States found that while physicians believed 95% of patients understood the post-discharge plan, only 58% of patients reported that they understood the directions.[23] Patient understanding of and memory for

what they are told have a significant effect on compliance and patient satisfaction with recommended regimens.[24]

Noncompliance with antihypertensive therapy has been commonly attributed to tolerability issues. A study of 948 patients in the UK found that 42% of all changes in antihypertensive therapy were due to side effects.[25] Adverse effects associated with antihypertensive medications can include cough, fatigue, edema, and dizziness.[26] In a survey of 623 patients, patients reporting problems with their medications were 3.5 times more likely to titrate themselves down or discontinue therapy than were patients not reporting problems. It has been estimated that 36% of patients adjust their antihypertensive drug regimen due to side-effects.[27]

Several alternatives could be considered to improve compliance and persistence. Convenient dosing schedules present an opportunity to improve compliance. Greenberg reviewed the literature in an effort to relate frequency of dosing and other influences with patient compliance in medication taking. Once-a-day and twice-a-day regimens were associated with significantly better compliance (73% and 70%, respectively) than were three-times-daily (52%) and four-times-daily (42%) regimens.[28] Additionally, Greenberg estimated that unintentional errors in taking medication are made by 50% to 90% of patients. Even so, a 20-year review of the literature found only a 76% compliance rate for once-daily antihypertensive medication.[29] Specifically, Cramer reviewed patient compliance with once-daily antihypertensive medications and the impact of partial

compliance on healthcare outcomes. She conducted a MEDLINE search to identify articles that described patterns of compliance, including rates for differing dosing regimens. Thirteen reports met these criteria. In contrast with Greenberg's review, Cramer found that compliance for once-daily antihypertensive medications varied widely (53% to 85%), with only a partial relationship to dosing regimens. The studies in this review evaluated the use of CCBs (n=6), ACE inhibitors (n=3), diuretics (n=2), BBs (n=1) and a variety of antihypertensive medications. None of these studies evaluated the newer drug class angiotensin-receptor blockers, which have superior tolerability. Cramer concluded that it is necessary to couple once-daily dosing with selection of a drug with long duration of action to overcome problems of missed doses.

A common problem with hypertension is that agents which decrease blood pressure can cause adverse events in previously asymptomatic patients. This may lead to noncompliance and even to discontinuation of therapy. While ACE inhibitors are regarded as effective agents for the treatment of hypertension, the cough that often accompanies their use is difficult for some patients to tolerate. Likewise, dihydropyridine CCBs are associated with an increased incidence of edema. Patient adherence to therapy may be influenced by such factors as efficacy, tolerability, dosing, memory and motivation.

Patel and colleagues conducted a retrospective database study of compliance and persistence for antihypertensive medication classes was performed using the MedImpact database, a large pharmacy claims database for

approximately 27 million members.[30] Newly-treated patients older than 18 years of age and initiating monotherapy with ARBs, ACE inhibitors, CCBs, BBs, or diuretics were identified and included in the study. New to treatment was defined as lack of claims for any target antihypertensive medication during the 6 months before the index date, which was defined as the date when the first prescription for the study medication was filled. Participants were required to be continuously benefit-eligible for at least 6 months preceding and 12 months following the index date. Compliance was defined as the MPR. Persistence was measured at monthly intervals post-index fill date (i.e., month 2, 3, 4…) and for the 12 month study period overall and was defined as the percentage of individuals remaining on therapy who did not discontinue therapy with the index medication. To be defined as "remaining on therapy," participants could not have a gap of over 60 days after exhausting the supply from the prior prescription.

Patel and colleagues identified 242,882 patients who were new to one of the target antihypertensive medications, which comprised the final study cohort.[30] Mean cohort age was 54.5 years and 56.9% were female. Most patients started on BBs (34.1%), followed by ACE inhibitors (32.4%), CCBs (14.9%), diuretics (14.4%) and ARBs (4.2%). Patient copayment for ARBs was the highest, followed by CCBs, ACE inhibitors, BBs, and diuretics; the exact amounts are not provided in the publication. While mean MPR was similar for ACE inhibitor (59.2%) and ARB (58.9%) patients, ARB and ACE inhibitor users had significantly higher MPRs than

patients using BBs, CCBs, and diuretics, adjusted for covariates ($p < 0.0001$, all comparisons).

A higher proportion of ARB patients (51.9%) remained persistent at 12 months following the index date compared with ACE inhibitor (48.0%), BB (40.3%), CCB (38.3%) and diuretics (29.9%).[30] Patients who initiated hypertension monotherapy with ARBs (HR = 0.59, $p < 0.0001$), ACE inhibitors (HR = 0.64, $p < 0.0001$), CCBs (HR = 0.86, $p < 0.0001$), or BBs (HR = 0.82, $p < 0.0001$) were all significantly less likely to discontinue their index therapy compared to patients who initiated diuretic therapy.

Patel and colleagues point to diuretics being the consistent outlier in all of the outcome measures in the study, despite diuretics having the lowest average patient copayment. Although significant ($p = 0.009$), the magnitude of the effect of patient copayment as a predictor of therapy discontinuation in the Cox proportional hazards model was marginal. This study suggests that the potential impact of medication drug class on compliance and persistence should be considered when initiating therapy, regardless of copayment level.

While patient age, gender and insurance status have been shown to be associated with antihypertensive persistence, the influence of other patient demographics and socioeconomic factors on drug compliance and persistence is unclear. As a result, it may prove difficult to identify characteristics of those patients who are less likely to adhere to antihypertensive therapy.

Degli Esposti and colleagues investigated stay-on-therapy patterns over three years among patients prescribed different classes of antihypertensive drugs for the first time.[31] This retrospective analysis used information recorded in the drugs database of the Local Health Unit of Ravenna (Italy) and included 7,312 subjects receiving a first prescription for diuretics, BBs, CCBs, ACE inhibitors or ARBs. The researchers found that 57.9% of patients continued their initial treatment during the three years of follow-up, 34.5% discontinued the treatment, and 7.6% were restarted on a treatment in the third year. This study found that persistence with treatment was influenced by age (persistence rate increased proportionately with advancing age), type of drug first prescribed (highest persistence with ARBs followed by ACE inhibitors, BBs, CCBs, and diuretics), gender (persistence was better in males), age of general practitioners (the younger the general practitioner, the better the persistence rate) and gender of general practitioner (better stay-on-therapy rate with male general practitioner prescribing).

Another study by Schectman and colleagues evaluated the association of medication refill adherence with demographic and prescription characteristics to determine whether such factors could guide intervention strategies in an indigent rural population.[32] This study was conducted at a university-based internal medicine practice serving an indigent rural population. Refill data for diabetes, hypertension, and hypercholesterolemia drugs from a closed pharmacy system were used to calculate mean adherence (for all drugs taken by each patient) and

minimum adherence (that of the least adhered to drug) for 1,984 patients during a 9-month period. Adherence was defined as the number of days of therapy dispensed on all except the last refill divided by the interval between the first and last refills. Mean refill adherence was < 80% for 33% of the population and minimum refill adherence was < 80% for 55% of the patients. Increasing age, race (white) and prescription length were associated with higher mean and minimum adherence, independent of income, prescription copay and insurance status. Number of drugs taken had a positive mean but negative minimum adherence association. Gender, number of primary care visits and dosage schedule were not independently associated with adherence. The findings of this study support evidence in the literature; however, the setting in which the study was conducted make it challenging to extrapolate the findings to the general US population.

Gregoire et al examined the effect of an array of potential predisposing, enabling and reinforcing factors on the discontinuation of newly prescribed antihypertensive medications.[20] This prospective cohort study conducted through a network of 173 pharmacies across Canada identified individuals newly prescribed an antihypertensive monotherapy. Participants were interviewed by phone four times to obtain information for a minimum duration of 18 months after entry into the study. Of 682 eligible participants, 43.3% had discontinued their initial medication at the end of the observation period. Individuals more likely to discontinue their initial medication were those who perceived side effects from the medication (hazard ratio = 1.91; 95% CI 1.47-2.47). Individuals with medication

insurance coverage were less likely to discontinue (HR = 0.74, 95% CI 0.55-0.99). Gregoire and colleagues concluded that persistence with newly prescribed medications could be improved by selecting antihypertensive medications containing fewer side effects and by lifting economic barriers to drug treatment.

Greenberg reviewed the literature in an effort to relate frequency of dosing and other influences with patient compliance in medication taking.[28] Besides finding better compliance with once and twice a day regimens in general, Greenberg found that compliance is not related to income, social class, occupation, or educational background, and it cannot be accurately predicted by physicians.

Recent studies have found an association between copayment and medication use. Shrank and colleagues studied whether patients enrolled in 3-tier pharmacy benefit plans who receive generic or preferred brand-name agents when initiating chronic therapy were more adherent to treatment than those who received nonpreferred brand-name medications.[33] This study analyzed pharmacy claims from Anthem Blue Cross and Blue Shield and Anthem Prescription Management. Anthem Blue Cross and Blue Shield is a large managed care plan providing health insurance coverage to patients in Colorado and Nevada. This study focused on 6 classes of chronic medications: Statins (or HMG-CoA reductase inhibitors), CCBs, oral contraceptives, orally inhaled corticosteroids, ARBs, and ACE inhibitors. Researchers measured adherence as the proportion of days covered (PDC) in each drug class during the first year of therapy and evaluated

how the formulary status of the initial prescription (generic, preferred, or nonpreferred) influenced PDC and adequate adherence, defined as PDC >80%, over the subsequent year. The days' supply dispensed during the year was divided by 365 to calculate the proportion of days covered (PDC).

A total of 7,532 new prescriptions were filled in 1 of the classes evaluated by 6,755 patients, and written by 3,110 physicians: 1,747 (23.2%) for nonpreferred medications, 4,376 (58.1%) for preferred drugs, and 1,409 (18.7%) for generic drugs. Mean age was 42.2 years and 65.3% were female. The average number of prescriptions per month was 2.7. The distribution of patients among home zip codes with low (< $30,000), medium ($30,000-$60,000) and high (> $60,000) annual income levels was 10.3%, 68.9% and 21.8%, respectively. After controlling for patient sociodemographic characteristics and drug class, PDC was 12.6% greater for patients initiated on generic medications versus non-preferred medications (58.8% versus 52.2%; $p < 0.001$). The PDC was 8.8% greater for patients initiated on preferred versus non-preferred medications (56.8% versus 52.2%; $p < 0.001$). Patients initiated on generic and preferred medications had 62% and 30% greater odds, respectively, of achieving adequate adherence compared with those who received non-preferred medications. Based on these data, the authors concluded that, in 3-tier pharmacy benefit plans, prescribing generic or preferred medications within a therapeutic class is associated with improvements in adherence to therapy.

In another study, researchers concluded that changes in formulary administration may have dramatically different effects on utilization and spending and, in some instances, may lead enrollees to discontinue therapy.[34] Huskamp and his research team used claims data to compare the utilization of an spending on drugs in two employer-sponsored health plans that implemented changes in formulary administration with those in comparison groups of enrollees covered by the same insurers. One plan simultaneously switched from a one-tier to a three-tier formulary and increased all enrollee copayments for medications. The one-tier benefit required a $7 copayment for any 30-day supply of a generic or brand name medication in the retail setting and a $15 copayment for any 90-day supply of a generic or brand name medication obtained through mail order. The three-tier formulary established a list of preferred brand name products. The copayment structure changed as follows: (1) In the retail setting (30-day supply) - $8 copayment for generic, $15 for preferred brand name and $30 for non-preferred brand name medications; and, (2) in the mail order setting (90-day supply) - $16 for generic, $30 for preferred brand name and $60 for non-preferred brand name medications. The second switched from a two-tier to a three-tier formulary, changing only the copayments for tier-3 drugs. The two-tier benefit had differential copayments for generic and brand name medications regardless of retail or mail order ($6 and $12, respectively). The new three-tier benefit established a list of preferred brand name products that would be covered at the tier-2 level ($12) and a list of non-preferred brand name products that would be

covered after a $24 copayment, regardless of retail or mail order. This study examined specifically how these changes affected the utilization of ACE inhibitors, proton-pump inhibitors (for gastrointestinal disorders), and statins (to lower cholesterol). The analysis included enrollees who filled at least two prescriptions for a given class of drug during the six months before each employer's policy changes took effect and determined whether enrollees who used only tier-3 drugs (i.e., those facing the largest increases in cost sharing) continued to use tier-3 drugs, switched to drugs of a lower tier, or stopped using any medication in the particular class of drug during the 6 month period after the changes were adopted.

Among the enrollees who were initially taking tier-3 statins, more enrollees in the intervention group than in the comparison group switched to tier-1 or tier-2 medications (49% versus 17%, $p < 0.001$) or stopped taking statins entirely (21% versus 11%, $p = 0.04$). Patterns were similar for ACE inhibitors and proton-pump inhibitors. Huskamp and colleagues concluded that the discontinuation of the use of medications such as statins and ACE inhibitors that are needed for the treatment of chronic illnesses raises important questions about potentially harmful effects of formulary changes and the associated changes in copayments.

Further evidence of this association has been reported in the literature. For example, Landsman and colleagues compared a reference drug benefit program (i.e., one that undertook no changes) to plans that changed drug copayment levels as a result of changing from a two-tier to a three-tier formulary design.[35] A decline in the use of retail prescription medications within specific therapeutic classes was

found when copayment levels were increased. Monthly prescription fills per person decreased by 10% to 16% for ACE inhibitors, CCBs, and ARBs as copayments increased by 66% to 100%. Noncompliance involves a myriad of economic and provider/health care-related factors beyond the patient-related factors discussed previously. Patient out-of-pocket cost is certainly one of these factors, which is impacted most significantly by copayments. One study demonstrated that compliance was greatest and declined less rapidly among patients with copays from $0 to < $10 compared with patients with copay from $10 to < $20. In this analysis, researchers reported that compliance was lowest and declined most rapidly among patients with copays ≥ $20.

Sokol and colleagues evaluated the impact of medication noncompliance on total diabetes medical cost in a study of 3,260 patients.[36] For patients at 80-100% adherence, total medical costs were approximately $4,000 compared with approximately $9,000 for patients at 1-19% adherence. Although drug costs escalated, as expected, in the increasingly compliant groups, medical costs decreased, thus reducing the total cost of care in more compliant groups. This study, however, did not evaluate drug copayment issues.

Chapman et al analyzed various predictors, including copayment, of adherence with antihypertensive (AH) and lipid lowering (LL) agents among Medicare-eligible patients.[37] Adherence to AH and LL therapy is particularly important in older patients with concomitant hypertension and dyslipidemia because of its prevalence and high risk of adverse cardiovascular events. Enrollees

(n=4052) aged ≥ 65 years who initiated treatment with an AH and a LL agent within a 90-day period were included in this retrospective cohort study conducted in a US managed care organization. Adherence to both medications was measured as the proportion of days covered by any AH and/or LL medication in each 3-month interval, from the start of concomitant therapy for up to 36 months. In each interval, patients were considered 'adherent' if they had filled prescriptions sufficient to cover ≥ 80% of days with both medication classes. A multivariable regression model evaluated potential predictors of adherence to concomitant therapy, including patient demographics, clinical characteristics and health services use patterns at baseline. The percentage of patients adherent to both AH and LL therapy declined rapidly, before stabilizing, with 40.5%, 32.7% and 32.9% adherent at 3, 6 and 12 months, respectively. At each time point, an additional 27.8-35.0% of patients were adherent to either AH or LL therapy, but not both. Adherence was on average greater to AH than LL therapy. After adjusting for age, sex and other potential predictors, patients were more likely to be adherent if AH and LL therapies were initiated closer together in time (adjusted odds ratio [AOR] 1.13 for 0-30 days versus 61-90 days, $p = 0.0563$), had a history of cardiovascular disease (AOR 1.27, $p = 0.0004$), took fewer additional medications (AOR 0.43 for six or more medications versus zero or one medication, $p < 0.0001$) or had more outpatient physician visits in the prior year (AOR 1.26 for four to six visits versus zero to one visit, $p < 0.0027$). These results pointing to the number of other prescription drugs taken in the year before initiating concomitant therapy with an

antihypertensive and a lipid lowering agent as the strongest predictor of adherence substantiates the finding by Bramley and colleagues that increased pill burden may negatively impact adherence with prescription drugs.

Shalansky and Levy administered a survey to 367 patients who had taken an angiotensin-converting enzyme inhibitor or lipid-lowering medication for at least three consecutive months to evaluate the relationship between the number of medications dispensed and adherence with chronic cardiovascular regimens.[38] The questionnaire was composed of questions regarding patient characteristics potentially influencing adherence to chronic cardiovascular medication regimens, including prescription and nonprescription drug use, use of compliance aids, perceived need for medications, perceived health, demographics, living situation and adverse drug reactions. Also, prescription drug use data over the previous 12 months were obtained for each subject from the British Columbia prescription claims database. Adherence for each prescription medication was calculated based on prescription fill dates and number of days supplied. Forty-five subjects (or 12%) were categorized as non-adherent. Having a lower number of prescriptions medications was an independent predictor of non-adherence with cardiovascular medications after controlling for age, gender, reported adverse effects, use of compliance aids, over-the-counter medication use, complimentary or alternative medication use, and participation in outpatient clinics.

The impact of pill burden and dosing frequency, particularly among individuals on antihypertensive medication therapy has not been extensively

studied. The fact that hypertension is asymptomatic, that its complications tend to occur many years after its diagnosis, and that many antihypertensive drugs cause secondary effects make this condition particularly vulnerable to compliance issues.

With the aging of the American population and the improved access to medications provided by the new Medicare Part D provision, an increasing number of patients will likely be treated for multiple co-morbidities. Families USA, in conjunction with the PRIME Institute a the University of Minnesota, analyzed data from the most recent years' Medicare Current Beneficiary Survey as well as from the Health Care Financing Administration (HCFA), Office of the Actuary. This study examined seniors' prescription drug spending starting in 1992, the first year the MCBS was undertaken in the 1990s, and provided projections for seniors' drug spending through 2010. Although seniors constituted only 13 percent of the population (34.4 million out of 270.2 million) in 1998, they accounted for 34 percent of all prescriptions dispensed (932.7 million out of 2,732.7 million) and 42 cents of every dollar spent on prescription drugs ($42,899.20 out of $102,687.50). The average number of prescriptions per elderly person grew from 19.6 in 1992 to 28.5 in 2000, an increase of 45 percent. By 2010, the average number of prescriptions per elderly person is projected to grow to 38.5, an increase of 10 prescriptions, or 35 percent, per senior since 2000.[39]

The greater number of prescription drugs available coupled with increased awareness fueled by direct-to-consumer (DTC) advertising are complicating

factors in this equation. A study by researchers at Harvard University and the Massachusetts Institute of Technology investigated the effect of DTC advertising on spending for prescription drugs. The study found that, on average, a 10% increase in DTC advertising of drugs within a therapeutic drug class resulted in a 1% increase in sales of the drugs in that class. Applying this result to the 25 largest drug classes in 2000, the study found that DTC advertising was responsible for 12% of the increase in prescription drugs sales.[33]

Rationale for the study

The objective of this study is to evaluate the impact of overall pill burden (number of medications and number of doses per day) on adherence with antihypertensive drugs. The hypothesis is that an increasing number of medications and doses per day decrease adherence with antihypertensive medications. Improving our understanding of this relationship may provide the health care community with important insights on how to enhance adherence with prescription medications to improve patient outcomes.

Research Question 1

What is the impact of overall pill burden in terms of the total number of prescriptions per month and/or doses per day on adherence with antihypertensive drugs?

H1: There is a threshold effect for compliance with antihypertensive therapy that can be measured in total prescriptions per month.

Rationale: Compliance with antihypertensive drugs is important yet predictors of poor compliance are inadequate. The association of patient demographics and socioeconomic factors on drug compliance is inconclusive, making it difficult to identify patients at risk. The literature, however, provides evidence regarding the deleterious effect of complex medication regimes.[28, 29, 37, 38] A higher number of total prescriptions per month and doses per day may result in an increased incidence of secondary effects and extraordinary health care costs, as well as simply becoming more difficult for the patient to integrate into their lives. Thus, we would expect that there is a tipping point where medications become more burdensome than can be tolerated.

H2: There is a threshold effect for compliance with antihypertensive therapy that can be measured in total number of doses per day.

Rationale: Evidence exists of the negative effect of complex medication regimes on adherence to therapy. [28, 29, 37, 38] A higher number of total prescriptions per month and doses per day may result in an increased incidence of secondary effects and extraordinary health care costs, as well as simply becoming more difficult for the patient to integrate into their lives. Understanding the relationship between number of doses per day and adherence may provide important clues to practicing physicians of the need for additional attention to patients at risk.

Research Question 2

What patient characteristics influence adherence with antihypertensive drugs?

H1: Compliance with antihypertensive therapy increases with age.

Rationale: Hypertension is an asymptomatic condition associated with important complications in the long run. Unlike asthma and diabetes, the consequences of lack of blood pressure control are manifested as incident myocardial infarction, heart failure, and strokes, among others, many years later. Increasing age may bring about the feeling of vulnerability to these complications, either due to a better understanding of the condition, knowledge of a close relative/friend suffering from one such complication or other unknown reasons.

H2: Compliance with antihypertensive therapy increases with the presence of comorbid conditions.

Rationale: Hypertension is an asymptomatic condition associated with important complications in the long run. Unlike asthma and diabetes, the consequences of lack of blood pressure control are manifested as incident myocardial infarction, heart failure, and strokes, among others, many years later. Increasing age may bring about the feeling of vulnerability to these complications, either due to a better understanding of the condition, knowledge of a close relative/friend suffering from one such complication or other unknown reasons.

Chapter III will provide a detailed description of the database used in the study. The selection criteria will also be described. The outcome measures will be defined in detail as will the independent variables and potential confounders. The

reasoning behind each of these will be provided. The data analysis will be reviewed and justification for each of the procedures will be included.

III. Data and Method

Source of data

The source of patient information consisted of the de-identified, HIPAA-compliant MarketScan database, which allows for patient level analysis. The MarketScan database includes pharmacy and medical claims for over 40 million lives supplied by employers, health plans, Medicaid and Medicare supplemental plans. The database includes inpatient, outpatient, drug, lab, health risk assessment, and benefit design data from commercial, Medicare supplemental and Medicaid populations. Additionally, MarketScan provides fully integrated health and productivity data, which will not be used for this study.

The subset of the MarketScan database used for this study consisted of covered claims filed between January 2003 and December 2005, which included 21,462,013 unique subjects. All medical and pharmacy claims for patients meeting the inclusion/exclusion criteria were used to build the "study database" for the analysis. Medical claims for outpatient visits were identified as those with a "standard value for place of service" (STDPLAC) of 11 (meaning "office") or 22 (meaning "outpatient hospital"). Emergency room visits were those coded as 23 for STDPLAC (meaning "emergency room-hospital") and hospitalizations as 21 ("inpatient hospital"). The database included the first 3 International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes for all physician and ER visits as well as hospitalizations. A description of the Current Procedural Terminology (CPT) codes for physician and ER visits may be

found in Appendix A, Table 1. For all physician and ER visits, the dates of service were included and, for hospitalizations, admission date, and length of stay. The amount paid for each service was included for all medical claims.

All claims for mail order and retail prescriptions were included in the study database. The National Drug Code (NDC) for each medication, date the prescription was filled, days' supply and amount paid by the health insurance were included in the study database for analysis. Claims were flagged by place of service, retail versus mail order. All prescriptions of interest in the following drug classes for patients meeting the inclusion/exclusion criteria were included:

- Thiazide diuretics (DIU): Hydrochlorothiazide (HCTZ)
- Beta blockers (BBs): Acebutolol, atenolol, betaxolol, bisoprolol, carteolol, labetalol, metoprolol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, and timolol
- Angiotensin-converting-enzyme inhibitors (ACEIs): Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, prindopril, quinapril, ramipril, and trandolopril
- Calcium channel blockers (CCBs): Amlodipine, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, diltiazem, verapamil
- Angiotensin receptor blockers (ARBs): Candesartan, irbesartan, losartan, telmisartan, and valsartan
- Fixed dose combinations (FDCs):

- ACEI + CCBs: Amlodipine+benazepril, enalapril+felodipine, trandolapril+verapamil
- ACEIs + DIU: Benazepril+HCTZ, captopril+HCTZ, enalapril+HCTZ, fosinopril+HCTZ, lisinopril+HCTZ, moexipril+HCTZ, quinapril+HCTZ
- ARBs + DIU: Candesartan+HCTZ, eprosartan+HCTZ, irbesartan+HCTZ, losartan+HCTZ, olmesartan+HCTZ, telmisartan+HCTZ, valsartan+HCTZ
- BBs + DIU: Atenolol+chlorthalidone, bisoprolol+HCTZ, metoprolol+HCTZ, nadolol+bendroflumethiazide, propranolol LA+HCTZ, timolol+HCTZ

Using the Generic Indicator (GENIND) variable, generic versus brand drugs were classified as follows:

1. "Brands" were defined as those with values of 1 ("single source brand") or 3 ("brand name, generic available").
2. "Generics" were defined as those with values of 4 ("multi source generic") or 5 ("single source generic").
3. "Other/unavailable" were those coded with a 7 or reported as missing.

Values of 2 ("no longer used") and 6 ("over the counter") did not apply. Two participants receiving CCBs were coded as 2; this code was changed to "other/unavailable."

The following sociodemographic variables for each patient meeting the inclusion/exclusion criteria were also used to build the study database (variable names are in parenthesis):

- Age (AGE)
- Sex (SEX)
- Employment status of primary beneficiary (EESTATU)
- Employment classification of primary beneficiary (EECLASS)
- Industry classification of the employer responsible for payment of claim (INDSTRY)
- Geographic region of employee's residence (REGION)
- Metropolitan Statistical Area of primary beneficiary (MSA)
- Relationship of the patient to the primary beneficiary (EMPREL)
- Type of benefit plan (PLANTYP)

Specifics on the coding of the socioeconomic variables can be found in Appendix A, Table 2).

Study Population

Subjects with at least one of the following ICD-9-CM codes were identified using the medical claims:

401	Essential hypertension
402	Hypertensive heart disease
403	Hypertensive chronic kidney disease
404	Hypertensive heart and chronic kidney disease

To be included in the analysis, subjects needed to meet the following criteria:

- Have pharmacy and medical benefits (commercial, Medicare or other health insurance in MarketScan) for a minimum of 6 months before and 12 months after initiation of antihypertensive drug therapy.
- Be at least 18 years old.
- Have no pharmacy claims for an antihypertensive in the 6 months prior to initiation of therapy.
- Have no medical claims with a primary or secondary diagnosis code for any of the following cardiovascular conditions or complications in the 6 months prior to initiation of antihypertensive therapy:
    - hypertensive disease (ICD-9-CM 401-405)
        - 401 Essential hypertension
        - 402 Hypertensive heart disease
        - 403 Hypertensive chronic kidney disease
        - 404 Hypertensive heart and chronic kidney disease
        - 405 Secondary hypertension
    - ischemic heart disease (ICD-9-CM 410-414)
        - 410 Acute myocardial infarction
        - 411 Other acute and subacute forms of ischemic heart disease
        - 412 Old myocardial infarction
        - 413 Angina pectoris
        - 414 Other forms of chronic ischemic heart disease

- other forms of heart disease (ICD-9-CM 420-429)
    - 420 Acute pericarditis
    - 421 Acute and subacute endocarditis
    - 422 Acute myocarditis
    - 423 Other diseases of pericardium
    - 424 Other diseases of endocardium
    - 425 Cardiomyopathy
    - 426 Conduction disorders
    - 427 Cardiac dysrhythmias
    - 428 Heart failure
    - 429 Ill-defined descriptions and complications of heart disease
- cerebrovascular disease (ICD-9-CM 430-438)
    - 430 Subarachnoid hemorrhage
    - 431 Intracerebral hemorrhage
    - 432 Other and unspecified intracranial hemorrhage
    - 433 Occlusion and stenosis of precerebral arteries
    - 434 Occlusion of cerebral arteries
    - 435 Transient cerebral ischemia
    - 436 Acute, but ill-defined, cerebrovascular disease
    - 437 Other and ill-defined cerebrovascular disease
    - 438 Late effects of cerebrovascular disease

    - end-stage renal disease (ICD-9-CM 285.21: Anemia in chronic kidney disease)

- Be at least one pharmacy claim for any medication in the following drug classes:
    - DIU
    - BBs
    - ACEI
    - CCBs
    - ARBs
    - Fixed dose combinations of
        - ACEI + CCB,
        - ACEI + DIU,
        - ARB + DIU, or
        - BB + DIU
- Receive antihypertensive drug treatment with one agent only for the initial prescription.

The purpose of limiting the study to patients initiating antihypertensive therapy and without a recent history of a medical claim for the cardiovascular codes listed above was to minimize potential confounding by disease severity. Additionally, we excluded patients with ICD-9-CM code 405 (secondary hypertension) for the same purpose. More severe patients (especially those with a

recent cardiovascular event) may adhere to drug therapy differently than less compromised patients in the outpatient setting.

For the purposes of this study, a patient was considered as receiving monotherapy for their initial antihypertensive prescription if no prescriptions for other antihypertensive drugs were filled in the 30 days after the index prescription fill date. The index prescription fill date was defined as the date of service for the first pharmacy claim for an antihypertensive in any of the classes of interest (DUI, BBs, ACEIs, CCBs and ARBs) after 6 months of coverage showing no other antihypertensive prescription fill.

Outcome Measure

Adherence with antihypertensive drug therapy was defined as compliance based on prescription refill data. The medication possession ratio (MPR) was used as a proxy of compliance with antihypertensive drug therapy. The MPR was defined as the total number of days' supply divided by 365, which suited the required 12-month follow-up period. The number of days' supply was capped at 365. No MPR was calculated for drugs used prior to the index antihypertensive prescription. The MPR was calculated for the index antihypertensive drug for each patient and averages by drug class were calculated. The MPR measure was used as a continuous as well as a categorical variable.

To find the most appropriate categories for the study, the distribution using various definitions were evaluated. Initially, categories were investigated as follows:

- High MPR defined as ≥ 0.80 and low as < 0.80

- High MPR defined as ≥ 0.80, medium as 0.50-0.79 and low as < 0.50

Other dichotomous categories were also investigated, namely using ≥ 0.70, ≥ 0.75 and ≥ 0.90 as the high MPR. Besides evaluating the distribution of subjects, preliminary regression models were ran to fully consider the consequences of the various definitions.

The MPR does not provide information on the timeliness or appropriateness of taking medications on a daily basis. For instance, if the physician instructed the patient to take the medication at a certain time of the day, the MPR does not provide information on how closely these instructions were followed. Furthermore, the MPR provides insight into the availability of medication but not on the consistency of refilling the prescription over the follow-up period. Given the available data, the MPR was our best option for estimating compliance with antihypertensive medications. The main advantages of the MPR measurement are the ease of calculation, data is readily available and the avoidance of a potential Hawthorne effect.

Independent Variables

Overall pill burden was defined as the total number of medications and total number of doses per day, excluding antihypertensive prescriptions. Total number of medications was calculated monthly by adding the number of different agents for any disease or disorder filled during the calendar month, excluding antihypertensive prescriptions. The total number of doses per day was calculated

by dividing the number of tablets/capsules dispensed for any disease or disorder by the days' supply recorded by the pharmacy filling the prescription and by using prescribing information for the frequency of administration. The total number of doses per day excluded antihypertensive prescriptions. For example, a prescription for 60 tablets and a 30-day supply corresponded to 2 doses in the day. If the prescribing information suggested twice a day use, the frequency of administration was 2. For medications that were taken less than once per day, an estimation per day was used (e.g., once every 2 days; dosing frequency = 0.5 per day).

The MarketScan database is employer-based and should contain most, if not all, pharmacy records for individuals. However, the thoroughness and accuracy of these records were not and cannot be verified for the purposes of conducting the study.

The other two independent variables for research question 2 were age and comorbid conditions. Age was analyzed as a continuous as well as categorical variable and was measured at baseline. Pre-specified comorbid conditions included diabetes, heart failure, ischemic heart disease, cerebrovascular disease and end-stage renal disease, which were identified using ICD-9-CM codes as previously detailed. Diabetes was defined as the presence of ICD-9-CM codes 250 (Diabetes mellitus), 357.2 (Polyneuropathy in diabetes), 362.0 (Diabetic retinopathy), 366.41 (Diabetic cataract) or 648.0 (Diabetes mellitus) OR DRG 294 (Diabetes Age >35) or 295 (Diabetes Age 0-35).

Potential Confounders

Due to the observational nature of the study and the limitations in data availability, age, gender, and prevalence of relevant comorbid conditions as a proxy for overall severity were controlled for. Additionally, copayment and level of health care resource use were included as potential confounders. Level of copayment has been associated with compliance and level of health care resource use may be indicative of overall health status.

Data Analysis

Descriptive and chi-square analyses were conducted for the following variables: Age at baseline, gender, employment status, employee classification, industry of employment, region of employee's residence, relationship of the patient to the primary beneficiary, type of benefit plan, prevalence of comorbid conditions, total number of medications per month (excluding antihypertensive prescriptions), total number of doses per day (excluding antihypertensive prescriptions) and medication possession ratio, as appropriate. Pharmacy and medical resource utilization were also analyzed descriptively. Percent of patients receiving the target antihypertensive drug classes, copayment level, generic drug use, mail order prescription service use, and days' supply were estimated. Additionally, mean number of outpatient visits, emergency room visits, and hospitalizations were calculated in the pre- and post-index antihypertensive prescription periods. Health care resource use was categorized as well. For outpatient visits, emergency room visits and hospitalizations, percent of patients

with 0, 1 to 3, 4 to 6 and 7 or more visits were assessed. Descriptive analyses were repeated by index antihypertensive drug class.

Multivariate models were built in forward stepwise fashion to identify predictors of adherence with antihypertensive therapy; initial linear regression models proved futile as the MPR distribution was severely skewed (see Graph 1, Appendix B). The skewness to the right is very clearly illustrated by the graph. Subsequently, the MPR was categorized in two ways:

- High (MPR ≥ 0.80) and low (MPR < 0.80); and,

- High (MPR ≥ 0.80), medium (MPR ≥ 0.50 and < 0.80), and low (MPR < 0.50).

Separate logistic regression analyses run with the above MPR definitions yielded very similar results suggesting no gain drawn from the more distinct classification (see Appendix A, Table 3). The odds ratios and p values for each variable were very similar. Also, the variables removed due to redundancy or lack of significance were the same. Furthermore, the various dichotomous definitions previously listed yielded undistinguishable results using principal component regression. Therefore, the MPR was categorized as a dichotomous variable (high ≥0.80 and low < 0.80) for the remainder of the study.

Logistic regression analysis was conducted using the following variables: Number of doses per day (excluding antihypertensive prescriptions), number of prescriptions per month (excluding antihypertensive prescriptions), number of comorbid conditions, pharmacy expenses in the post-index period, age, male

gender and average copay. These variables were selected for their perceived likelihood of being good proxies within their categories and to address potential redundancies. For instance, age and male gender were selected as representative sociodemographic variables. Average copay and pharmacy expenses in the post-index period were identified as good proxies for health care costs. Number of doses per day (excluding antihypertensive prescriptions), number of prescriptions per month (excluding antihypertensive prescriptions), and number of comorbid conditions were included as they were part of the hypotheses for the study. The seven variables were used to build twelve models with various combinations of the variables. One model included all of the variables. Seven separate models included each variable individually and the rest of the models included combinations of variables.

Additional logistic regression models were run using dummy variables for the age, number of comorbid conditions, pharmacy expenses in the post-index prescription period (less than or equal to $500, greater than $500 but equal or lower than $1,500, and greater than $1,500).

To further address the potential redundancy among the variables, principal component analysis was conducted for its ability to transform a number of possibly correlated variables into a smaller number of uncorrelated variables or principal components. Principal component analysis seeks a linear combination of variables such that the maximum variance is extracted from the variables. After removing this variance, the procedure seeks a second linear combination which

explains the maximum proportion of the remaining variance, and so on. Thus, the first principal component accounts for the maximum possible variability in the data and the subsequent factors account for decreasing amounts of variability.

Principal component analysis first evaluated the correlation between the following 27 variables: Age as a continuous variable; gender; number of prescriptions per month (excluding antihypertensive prescriptions); number of doses per day (excluding antihypertensive prescriptions); use of ACEIs, ARBs, BBs, CCBs, DIUs or FDCs; presence of ischemic heart disease, other heart conditions, heart failure, cerebrovascular disease, and diabetes; number of comorbid conditions; mail order use; number of outpatient visits pre and post-index prescription; number of emergency room visits pre- and post-index prescription; occurrence of hospitalizations in the pre- and post-index prescription periods; medical expenses in the pre- and post-index periods; and, pharmacy expenses in the pre- and post-index prescription periods. Results pointed to significant correlations between multiple variables:

- Age was correlated with cerebrovascular, mail order and number of comorbid conditions.
- Gender (male) did not have significant correlations.
- The number of doses per day (excluding antihypertensive prescriptions) was correlated with prescriptions per month (excluding antihypertensive prescriptions).

- Number of prescriptions per month (excluding antihypertensive prescriptions) was correlated with doses per day (excluding antihypertensive prescriptions) and medical expenses (post). It was highly correlated with number of comorbid conditions, number of outpatient visits (pre and post), hospital stays (post), and pharmacy expenses (pre and post).
- Some drug classes were correlated at significant levels, in particular ACEI, diuretic, BB and fixed dose combinations.
- Comorbid conditions (ischemic heart disease, other heart disease, heart failure, cerebrovascular disease and diabetes) and number of comorbid conditions were correlated.
- Number of comorbid conditions, individual conditions (ischemic heart disease, other heart disease, heart failure, cerebrovascular disease and diabetes) and health care utilization variables (number of prescriptions per month (excluding antihypertensive prescriptions) and hospitalizations – post) were correlated.
- Health care utilization and health care costs were correlated. Office visits (pre) were highly correlated with number of prescriptions per moth, office visits (post) and pharmacy expenses (pre). Office visits (post) were highly correlated with number of prescriptions per month (excluding antihypertensive prescriptions), office visits (pre), medical

expenses (post) and pharmacy expenses (post). ER visits pre and post were highly correlated.

Principal component analysis identified twelve factors with Eigenvalues greater than 1 with a final communality estimate of 18.33. However, considerable redundancy remained in the factors identified. Thus, the principal component regression, which uses principal component analysis when estimating regression coefficients, did not provide useful information

All analyses were run using SAS version 8.2 (Cary, NC).

Chapter IV provides details of the descriptive analysis conducted on variables that describe the study population. The results are presented as the analyses were conducted. The chapter includes the multivariate analyses run to better understand the impact of pill burden on compliance with antihypertensive medications, from the logistic regression to the principal component regression.

IV. RESULTS

Of the 21,462,013 unique subjects in the MarketScan database, 68,538 met the inclusion and exclusion criteria, and were included in the study. Most subjects were excluded for not having medical and pharmacy coverage between January 2003 and December 2005 (n=16,778,101), not using any of the study medications (n=2,844,714), or being < 18 years of age (n=970,033) (see Table 1).

Mean age of the study population was 53.47 years (see Table 2). The majority of subjects were 31-50 or 51-64 years old (25,065, 36.81% and 31,062, 45.62%, respectively). The majority was female (38,614, 56.34%). Most were full-time employees (43,751, 63.83%) and 33.21% (n=22,765) were retirees. The most frequent employee classifications were hourly (31,579, 31.48%) and salary (13,263, 19.35%), although classification was unknown for 25,422 or 37.09%. The three most common industries where study subjects worked were manufacturing, durable goods (15,241, 35.71%); transportation, communications, utilities (8,889, 20.83%); and, retail trade (6,001, 14.06%).

Table 1: Identification of patients for the study database

Patients	Number excluded	Number remaining
Total number of members with pharmacy and medical coverage between January 2003-December 2005	16,778,101	4,683,912
Total number of members ≥ 18 y/o	970,033	3,713,879
Total number with ≥ 1 pharmacy claim for any of the following antihypertensives between June 2003-December 2004: ✓ **thiazide diuretics** ✓ **BBs** ✓ **ACEIs** ✓ **CCBs** ✓ **ARBs** ✓ **FDCs**	2,844,714	869,165
Total number with none of the following ICD-9-CM codes in the 6 months prior to index prescription ("pre-index" period): 401-405; 410-414; 420-429; 430-438; 285.21	402,075	467,090
Total number of patients with no pharmacy claims for those antihypertensives in the pre-index period	310,329	156,761
Total number with ≥ 1 physician visit <u>or</u> hospitalizations for ICD-9-CM codes 401, 402, 403, <u>or</u> 404 in the 12 months after index prescription ("post-index" period)	88,223	68,538

Thiazide diuretics: Hydrochlorothiazide

BBs: Acebutolol, atenolol, betaxolol, bisoprolol, carteolol, labetalol, metoprolol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, timolol

ACEIs: Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, prindopril, quinapril, ramipril, trandolopril

CCBs: Amlodipine, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, diltiazem, verapamil

ARBs: Candesartan, irbesartan, losartan, telmisartan, and valsartan

FDCs: ACEI + CCBs, ACEIs + DIU, ARBs + DIU, BBs + DIU

Hypertensive disease (International Classification of Diseases, 9th Revision, Clinical Modification or ICD-9-CM 401-405):

- 401: Essential hypertension

- 402: Hypertensive heart disease
- 403: Hypertensive chronic kidney disease
- 404: Hypertensive heart and chronic kidney disease
- 405: Secondary hypertension

Ischemic heart disease (ICD-9-CM 410-414):

- 410 Acute myocardial infarction
- 411 Other acute and subacute forms of ischemic heart disease
- 412 Old myocardial infarction
- 413 Angina pectoris
- 414 Other forms of chronic ischemic heart disease

Other forms of heart disease (ICD-9-CM 420-429):

- 420 Acute pericarditis
- 421 Acute and subacute endocarditis
- 422 Acute myocarditis
- 423 Other diseases of pericardium
- 424 Other diseases of endocardium
- 425 Cardiomyopathy
- 426 Conduction disorders
- 427 Cardiac dysrhythmias
- 428 Heart failure
- 429 Ill-defined descriptions and complications of heart disease

Cerebrovascular disease (ICD-9-CM 430-438):

- 430 Subarachnoid hemorrhage
- 431 Intracerebral hemorrhage
- 432 Other and unspecified intracranial hemorrhage
- 433 Occlusion and stenosis of precerebral arteries
- 434 Occlusion of cerebral arteries
- 435 Transient cerebral ischemia
- 436 Acute, but ill-defined, cerebrovascular disease
- 437 Other and ill-defined cerebrovascular disease
- 438 Late effects of cerebrovascular disease

End-stage renal disease (ICD-9-CM 285.21: Anemia in chronic kidney disease)

The majority of subjects resided in the South (28,170, 41.10%), North Central (19,182, 27.99%) and West (16,160, 23.58%). Approximately one of every five

subjects resided outside of metropolitan statistical areas (22.49%). Of those in MSA's, Atlanta – Sandy Springs – Marietta, GA (2,631, 3.84%), Sacramento – Arden – Arcade – Roseville, CA (2,431 (3.55%), Los Angeles – Long Beach – Glendale, CA (2,002, 2.93%) and Warren – Farmington Hills – Troy, MI (1,858, 2.72%) had the widest representation. Approximately half of the study subjects resided in MSA's with less than 1% of the study population (34,841, 50.83%), not listed here.

The most common types of benefit plan were preferred provider organization (PPO) – 27,936, 40.77%, comprehensive – 16,092, 23.49%, and health maintenance organization (HMO) – 13,048, 19.04%. Over two-thirds of the study subjects were the primary beneficiaries (46,772, 68.24%) and 21,397 (or 31.22%) were spouses.

Table 2: Sociodemographic characteristics of the overall study population

Variable	Overall N=68,538
Gender	
- Female	38,614 (56.34%)
- Male	29,924 (43.66%)
Age	
- mean	53.47 years old
- median	53.0 years old
- % in each age group:	
18-30 years old	1,832 (2.69%)
31-50 years old	25,065 (36.81%)
51-64 years old	31,062 (45.62%)
65+ years old	10,127 (14.87%)
- Missing	452 (0.01%)
Employment status	
- Active full-time	43,751 (63.83%)
- Active part-time or seasonal	426 (0.62%)
- Early retiree	9,523 (13.89%)
- Medicare eligible retiree	7,781 (11.35%)
- Retiree (status unknown)	5,461 (7.97%)
- COBRA continuee	25 (0.04%)
- Long-term disability	210 (0.31%)
- Surviving spouse/dependent	990 (1.44%)
- Other/unknown	371 (0.54%)
Employee classification	
- Salary, non-union	9,016 (13.15%)
- Salary, union	2,804 (4.09%)
- Salary, other	1,443 (2.11%)
- Hourly, non-union	10,904 (15.91%)
- Hourly, union	10,364 (15.12%)
- Hourly, other	311 (0.45%)
- Non-union	7154 (10.44%)
- Union	1,120 (1.63%)
- Unknown	25,422 (37.09%)

Variable	Overall N=68,538
Industry	
- **Manufacturing, durable goods**	15,241 (35.71%)
- **Transportation, communications, utilities**	8,889 (20.83%)
- **Retail trade**	6,001 (14.06%)
- **Services**	4,847 (11.36%)
- **Manufacturing, nondurable goods**	4,511 (10.57%)
- **Finance, insurance, real estate**	2,901 (6.80%)
- **Oil & gas extraction, mining**	290 (0.68%)
Geographic region of employee residence	
- **Northeast**	4,878 (7.12%)
- **North Central**	19,182 (27.99%)
- **South**	28,170 (41.10%)
- **West**	16,160 (23.58%)
- **Unknown**	148 (0.22%)
Metropolitan Statistical Area of primary beneficiary	
- **Atlanta-Sandy Springs-Marietta, GA**	2,631 (3.84%)
- **Chicago – Naperville – Joliet, IL**	1,151 (1.68%)
- **Detroit – Livonia – Dearborn, MI**	929 (1.36%)
- **Flint, MI**	820 (1.20%)
- **Houston – Sugar Land – Baytown, TX**	778 (1.14%)
- **Jackson, MS**	764 (1.12%)
- **Los Angeles – Long Beach – Glendale, CA**	2,002 (2.93%)
- **Memphis, TN – MS – AR**	1,121 (1.64%)
- **Nashville – Davidson – Murfreesboro, TN**	743 (1.09%)
- **Oakland – Fremont – Hayward, CA**	1,336 (1.95%)
- **Peoria, IL**	737 (1.08%)
- **Riverside – San Bernardino – Ontario, CA**	1,354 (1.98%)
- **Sacramento – Arden – Arcade – Roseville, CA**	2,431 (3.55%)
- **Santa Ana – Anaheim – Irvine, CA**	689 (1.01%)
- **Warren – Farmington Hills – Troy, MI**	1,858 (2.72%)
- **MSA's with < 1.0%**	34,841 (50.83%)
- **Non-MSA**	15,390 (22.49%)
- **Missing**	107 (0.16%)
Relationship of the patient to the primary beneficiary	
- **Employee**	46,772 (68.24%)
- **Spouse**	21,397 (31.22%)
- **Child/other**	369 (0.54%)

Variable	Overall N=68,538
- **Dependent-relation unknown**	0 (0.00%)
Type of benefit plan	
- **PPO**	27,936 (40.77%)
- **Comprehensive**	16,092 (23.49%)
- **HMO**	13,048 (19.04%)
- **POS**	8,742 (12.76%)
- **POS with capitation**	2,533 (3.70%)
- **EPO**	165 (0.24%)
- **Missing**	22 (0.03%)

COBRA: Consolidated Omnibus Budget Reconciliation Act (of 1985)
MSA: Metropolitan Statistical Area
PPO: Preferred Provider Organization
HMO: Health Maintenance Organization
POS: Point Of Service
EPO: Exclusive Provider Organization

Diuretics were the most frequently prescribed antihypertensive in this study (17,029 or 24.85%), followed by ACEIs (14,477 or 21.12%) and BBs (13,987 or 20.41%) (see Table 3). More females received diuretics (68.02%), and more males received ACEIs (55.55%) compared to other drug classes. Mean age was similar across the groups as were medians and distribution within categories.

Full-time employment ranged from 59.60% in the CCB group to 67.45% in the FDC group (see Table 3). The highest percentages of retired subjects were in the CCB (36.95%) and ARB (36.32%) groups. Percentage in long-term disability was similar across groups, ranging from 0.25% in the diuretic group to 0.36% in the CCB group. Approximately 19 to 22% of subjects across drug groups were salaried (18.82% CCB to 21.91% ARB) versus 29 to 36% receiving hourly pay (28.62%

diuretic to 35.76% FDC). Percentage of subjects in the union employment classification was below 2% in all groups. These data were not available for 30 to 40% of study subjects. Additionally, there was slight variation in industry of employment. The more marked differences were in retail trade with a low of 11.08% among subjects receiving ARBs and a high of 16.99% among those receiving FDCs. Also, a noticeably lower percentage of subjects receiving FDCs worked in the service industry (8.68%).

Table 3: Sociodemographic characteristics by index drug class

Variable	ACEI n=14,477	ARB n=5,212	BB n=13,987	CCB n=6,351	DIU n=17,029	FDC n=11,482
Gender						
- Female	6,435 (44.45%)	2,643 (50.71%)	7,941 (56.77%)	3,637 (57.27%)	11,583 (68.02%)	6,375 (55.52%)
- Male	8,042 (55.55%)	2,569 (49.29%)	6,046 (43.23%)	2,714 (42.73%)	5,446 (31.98%)	5,107 (44.48%)
Age						
- Mean	53.35 y/o	54.62 y/o	53.81 y/o	54.58 y/o	53.27 y/o	52.40 y/o
- Median	53 y/o	55 y/o	54 y/o	55 y/o	53 y/o	52 y/o
- Age groups:						
18-30 years old	368 (2.56%)	104 (2.01%)	445 (3.20%)	183 (2.90%)	454 (2.68%)	278 (2.44%)
31-50 years old	5,281 (36.75%)	1,704 (32.86%)	4,934 (35.50%)	2,127 (33.75%)	6,399 (37.81%)	4,620 (40.50%)
50-64 years old	6,677 (46.46%)	2,530 (48.79%)	6,249 (44.97%)	2,829 (44.88%)	7,602 (44.92%)	5,175 (45.37%)
65+ years old	2,046 (14.24%)	847 (16.34%)	2,269 (16.33%)	1,164 (18.47%)	2,467 (14.58%)	1,334 (11.69%)
- Missing	105 (0.73%)	27 (0.52%)	90 (0.64%)	48 (0.76%)	107 (0.63%)	75 (0.63%)
Employment status						
- Active full-time	9,327 (64.43%)	3,151 (60.46%)	8,699 (62.19%)	3,785 (59.60%)	11,044 (64.85%)	7,745 (67.45%)
- Active part-time or seasonal	95 (0.66%)	23 (0.44%)	53 (0.38%)	38 (0.60%)	118 (0.69%)	99 (0.86%)
- Early retiree	1,961 (13.55%)	818 (15.69%)	1,887 (13.49%)	953 (15.01%)	2,213 (13.00%)	1,691 (14.73%)
- Medicare eligible retiree	1,468 (10.14%)	669 (12.84%)	1,803 (12.89%)	875 (13.78%)	1,857 (10.90%)	1,109 (9.66%)
- Retiree (status unknown)	1,329 (9.18%)	406 (7.79%)	1,194 (8.54%)	519 (8.17%)	1,436 (8.43%)	577 (5.03%)
- COBRA continuee	5 (0.03%)	1 (0.02%)	7 (0.05%)	1 (0.02%)	8 (0.05%)	3 (0.03%)
- Long-term disability	49 (0.34%)	18 (0.35%)	47 (0.34%)	23 (0.36%)	42 (0.25%)	31 (0.27%)

Variable	ACEI n=14,477	ARB n=5,212	BB n=13,987	CCB n=6,351	DIU n=17,029	FDC n=11,482
- Surviving spouse/dependent	171 (1.18%)	96 (1.84%)	230 (1.64%)	118 (1.86%)	221 (1.30%)	154 (1.34%)
- Other/unknown	72 (0.50%)	30 (0.58%)	67 (0.48%)	39 (0.61%)	90 (0.53%)	73 (0.64%)
Employee classification						
- Salary, non-union	1,807 (12.48%)					1,617 (14.08%)
- Salary, union	657 (4.54%)	801 (15.37%)	1,862 (13.31%)	808 (12.72%)	2,121 (12.46%)	418 (3.64%)
- Salary, other	267 (1.84%)	212 (4.07%)	629 (4.50%)	232 (3.65%)	656 (3.85%)	256 (2.23%)
- Hourly, non-union	2,271 (15.69%)	129 (2.48%)	319 (2.28%)	155 (2.44%)	317 (1.86%)	2,245 (19.55%)
- Hourly, union	2,151 (14.86%)	743 (14.26%)	2,126 (15.20%)	1,038 (16.34%)	2,481 (14.57%)	1,797 (15.65%)
- Hourly, other	69 (0.48%)	843 (16.17%)	2,134 (15.26%)	1,114 (17.54%)	2,325 (13.65%)	64 (0.56%)
- Non-union	1,282 (8.86%)	21 (0.40%)	66 (0.47%)	23 (0.36%)	68 (0.40%)	1,438 (12.52%)
- Union	221 (1.53%)	647 (12.41%)	1,159 (8.29%)	695 (10.94%)	1,933 (11.35%)	177 (1.54%)
- Unknown	5,752 (39.73%)	102 (1.96%)	221 (1.58%)	113 (1.78%)	286 (1.68%)	3,470 (30.22%)
		1,714 (32.89%)	5,471 (39.11%)	2,173 (34.22%)	6,842 (40.18%)	
Industry						
- Oil & gas extraction, mining	68 (0.77%)	18 (0.52%)	51 (0.58%)	29 (0.71%)	76 (0.77%)	48 (0.63%)
- Manufacturing, durable goods	3,152 (35.80%)	1,328 (38.43%)	3,135 (35.71%)	1,476 (35.98%)	3,453 (34.91%)	2,697 (35.27%)
- Manufacturing, nondurable goods	845 (9.60%)	454 (13.14%)	916 (10.43%)	447 (10.90%)	979 (9.90%)	870 (11.38%)
- Transportation, communications, utilities	1,898 (21.56%)	693 (20.05%)	1,794 (20.44%)	851 (20.75%)	2,081 (21.04%)	1,572 (20.56%)
- Retail trade	1,178 (13.38%)	383	1,179	582	1,380	1,299
- Finance, insurance,						

Variable	ACEI n=14,477	ARB n=5,212	BB n=13,987	CCB n=6,351	DIU n=17,029	FDC n=11,482
real estate	615 (11.08%)	(13.43%)	(14.19%)	(13.95%)	(16.99%)	
- Services	240 (6.94%)	596 (6.79%)	247 (6.02%)	706 (7.14%)	497 (6.50%)	
- Missing	1,049 (11.91%)	340 (9.84%)	1,108 (12.62%)	470 (11.46%)	1,216 (12.29%)	664 (8.68%)
	5,672 (39.18%)	1,756 (33.69%)	5,208 (37.23%)	2,249 (35.41%)	7,138 (41.92%)	3,835 (33.40%)
Region of employee residence						
- Northeast	1,049 (7.25%)	512 (9.82%)	1,098 (7.85%)	413 (6.50%)	1,046 (6.14%)	760 (6.62%)
- North Central	4,116 (28.43%)	1,373 (26.34%)	4,216 (30.14%)	1,811 (28.52%)	4,542 (26.67%)	3,124 (27.21%)
- South	5,037 (34.79%)	2,344 (44.97%)	4,872 (34.83%)	2,893 (45.55%)	7,041 (41.35%)	5,983 (52.11%)
- West	4,249 (29.35%)	967 (18.55%)	3,768 (26.94%)	1,218 (19.18%)	4,373 (25.68%)	1,585 (13.80%)
- Unknown	26 (0.18%)	16 (0.31%)	33 (0.24%)	16 (0.25%)	27 (0.16%)	30 (0.26%)
Relationship of the patient to the primary beneficiary						
- Employee	10,094 (69.72%)	3,545 (68.02%)	9,299 (66.48%)	4,327 (68.13%)	11,532 (67.72%)	7,975 (69.46%)
- Spouse	4,289 (29.63%)	1,642 (31.50%)	4,587 (32.79%)	1,982 (31.21%)	5,420 (31.83%)	3,477 (30.28%)
- Child/other	94 (0.65%)	25 (0.48%)	101 (0.72%)	42 (0.66%)	77 (0.45%)	30 (0.26%)
- Dependent-relation unknown	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Type of benefit plan						
- Comprehensive	3,263 (22.55%)	1,324 (25.41%)	3,501 (25.03%)	1,714 (27.00%)	3,783 (22.22%)	2,507 (21.85%)
- EPO	35	8	31	12 (0.19%)	39	40

Variable	ACEI n=14,477	ARB n=5,212	BB n=13,987	CCB n=6,351	DIU n=17,029	FDC n=11,482
- **HMO**	(0.24%)	(0.15%)	(0.22%)	932	(0.23%)	(0.35%)
	3,205	647	3,017	(14.68%)	3,810	1,410
- **POS**	(22.15%)	(12.93%)	(21.57%)	854	(22.38%)	(12.29%)
	1,662	691	1,512	(13.46%)	2,280	1,743
- **PPO**	(11.49%)	(13.26%)	(10.81%)	2,629	(13.39%)	(15.19%)
	5,745	2,278	5,431	(41.42%)	6,545	5,308
- **POS with capitation**	(39.70%)	(43.72%)	(38.83%)	206	(38.44%)	(46.25%)
- **Missing**	560	236	494	(3.26%)	569	468
	(3.87%)	(4.53%)	(3.53%)	4	(3.34%)	(4.08%)
	7	0	1	(0.06%)	3	6
	(0.05%)	(0.00%)	(0.01%)		(0.02%)	(0.05%)

Thiazide diuretics: Hydrochlorothiazide

BBs: Acebutolol, atenolol, betaxolol, bisoprolol, carteolol, labetalol, metoprolol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, timolol

ACEIs: Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, prindopril, quinapril, ramipril, trandolopril

CCBs: Amlodipine, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, diltiazem, verapamil

ARBs: Candesartan, irbesartan, losartan, telmisartan, and valsartan

FDCs: ACEI + CCBs, ACEIs + DIU, ARBs + DIU, BBs

COBRA: Consolidated Omnibus Budget Reconciliation Act (of 1985)

MSA: Metropolitan Statistical Area

PPO: Preferred Provider Organization

HMO: Health Maintenance Organization

POS: Point Of Service

EPO: Exclusive Provider Organization

Regional variation in medication utilization was observed. A higher percentage of subjects receiving ARBs resided in the Northeast and South. Lower percentages of subjects receiving ACEIs and BBs resided in the South while higher percentages of those receiving ARBs, CCBs and FDCs resided in this region. Drug

utilization in the West was markedly different, with lower rates of subjects receiving ARBs, CCBs and FDCs and higher rates of ACEIs, BBs and diuretics.

Relationship of the patient to the primary beneficiary was similar across groups. Drug utilization varied by type of benefit plan. Rates of ARB, BB and CCB use were much higher for subjects with comprehensive benefit plans and lower for FDC use. Wide variation was observed for subjects with HMO coverage. Rates of ARB, CCB and FDC use were markedly lower while rates of ACEI, BB and diuretic use were higher. ARB and FDC use was also higher among subjects in PPO's.

Diabetes was the most prevalent comorbid condition (18.41%) followed by other forms of heart disease (13.54%) and ischemic heart disease (10.22%) (see Table 4). Overall mean number of relevant comorbid conditions was 0.51 and 1.40 for subjects with at least one comorbid condition.

Table 4: Clinical characteristics of the overall study population

Variable	Overall N=68,538
Prevalence of hypertensive disease (after index prescription fill)[1]	68,536 (100%)
Prevalence of ischemic heart disease (after index prescription fill)[2]	7,007 (10.22%)
Prevalence of other forms of heart disease (after index prescription fill)[3]	9,282 (13.54%)
Prevalence of heart failure (after index prescription fill)[4]	1,716 (2.50%)
Prevalence of cerebrovascular disease (after index prescription fill)[5]	4,119 (6.01%)
Prevalence of end-stage renal disease (after index prescription fill)[6]	0 (0.00%)
Prevalence of diabetes mellitus (at any time)[7]	12,621 (18.41%)
Number of comorbid conditions:	
– **Mean (SD) in overall population**	0.51 (0.79)
– **Mean (SD) among patients with at least 1 comorbid condition**	1.40 (0.70)

[1] Hypertensive disease (International Classification of Diseases, 9th Revision, Clinical Modification or ICD-9-CM 401-405):

- 401: Essential hypertension
- 402: Hypertensive heart disease
- 403: Hypertensive chronic kidney disease
- 404: Hypertensive heart and chronic kidney disease
- 405: Secondary hypertension

[2] Ischemic heart disease (ICD-9-CM 410-414):

- 410 Acute myocardial infarction
- 411 Other acute and subacute forms of ischemic heart disease
- 412 Old myocardial infarction
- 413 Angina pectoris
- 414 Other forms of chronic ischemic heart disease

[3] Other forms of heart disease (ICD-9-CM 420-429):

- 420 Acute pericarditis
- 421 Acute and subacute endocarditis
- 422 Acute myocarditis
- 423 Other diseases of pericardium
- 424 Other diseases of endocardium
- 425 Cardiomyopathy
- 426 Conduction disorders
- 427 Cardiac dysrhythmias

- 428 Heart failure
- 429 Ill-defined descriptions and complications of heart disease

[4] ICD-9-CM 428: Heart failure (already included under "other forms of heart disease" but important enough to separate)

[5] Cerebrovascular disease (ICD-9-CM 430-438):

- 430 Subarachnoid hemorrhage
- 431 Intracerebral hemorrhage
- 432 Other and unspecified intracranial hemorrhage
- 433 Occlusion and stenosis of precerebral arteries
- 434 Occlusion of cerebral arteries
- 435 Transient cerebral ischemia
- 436 Acute, but ill-defined, cerebrovascular disease
- 437 Other and ill-defined cerebrovascular disease
- 438 Late effects of cerebrovascular disease

[6] End-stage renal disease (ICD-9-CM 285.21: Anemia in chronic kidney disease)

[7] Diabetes was defined as the presence of ICD-9-CM codes 250 (Diabetes mellitus), 357.2 (Polyneuropathy in diabetes), 362.0 (Diabetic retinopathy), 366.41 (Diabetic cataract) or 648.0 (Diabetes mellitus) OR DRG 294 (Diabetes Age >35) or 295 (Diabetes Age 0-35)

SD: Standard Deviation

The prevalence of comorbid conditions varied by drug class (see Table 5). Higher percentages of BB and CCB users had ischemic heart disease and other forms of heart disease compared to lower percentages of those receiving diuretics and FDCs. A higher percentage of ACEI, CCB, BB and ARB users had heart failure compared to fixed dose combinations and diuretics (3.49%, 3.37%, 3.13% and 3.11% compared to 1.37% and 1.41%, respectively). The prevalence of cerebrovascular disease was highest among CCB users (8.03%) followed by BB and ARB users (7.67% and 7.43%, respectively). The prevalence of diabetes mellitus was the highest among ACEI and ARB users (30.91% and 28.86%, respectively). Overall, the number of comorbid conditions was also highest in these two drug classes

(overall mean = 0.64) and lowest among diuretic and fixed dose combination users (overall mean = 0.33 and 0.42, respectively). In contrast, the highest mean number of comorbid conditions as a percentage of patients with at least one comorbid condition was BB and CCB users (1.53 and 1.47, respectively).

Table 5: Clinical characteristics by index drug class

Variable	ACEI n=14,477	ARB n=5,212	BB n=13,987	CCB n=6,351	DIU n=17,029	FDC n=11,482
Prevalence of hypertensive disease (after index prescription fill) [1]	14,477 (100%)	5,212 (100%)	13,987 (100%)	6,349 (99.97%)	17,029 (100%)	11,482 (100%)
Prevalence of ischemic heart disease (after index prescription fill) [2]	1,535 (10.60%)	537 (10.30%)	2,269 (16.22%)	771 (12.14%)	1,035 (6.08%)	860 (7.49%)
Prevalence of other forms of heart disease (after index prescription fill) [3]	1,870 (12.92%)	735 (14.10%)	2,685 (19.20%)	1,143 (18.00%)	1,643 (9.65%)	1,206 (10.50%)
Prevalence of heart failure (after index prescription fill) [4]	505 (3.49%)	162 (3.11%)	438 (3.13%)	214 (3.37%)	240 (1.41%)	157 (1.37%)
Prevalence of cerebrovascular disease (after index prescription fill) [5]	904 (6.24%)	387 (7.43%)	1,073 (7.67%)	510 (8.03%)	721 (4.23%)	524 (4.56%)
Prevalence of end-stage renal disease (after index prescription fill) [6]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Prevalence of diabetes mellitus (at any time) [7]	4,475 (30.91%)	1,504 (28.86%)	1,798 (12.85%)	897 (14.12%)	1,913 (11.23%)	2,034 (17.71%)
Number of comorbid conditions:						
– **mean (SD) in overall population**	0.64 (0.85)	0.64 (0.84)	0.59 (0.88)	0.56 (0.85)	0.33 (0.63)	0.42 (0.70)
– **mean (SD) among patients with at least 1 comorbid condition**	1.40 (0.72)	1.39 (0.71)	1.53 (0.77)	1.47 (0.74)	1.28 (0.57)	1.31 (0.61)

Thiazide diuretics: Hydrochlorothiazide

BBs: Acebutolol, atenolol, betaxolol, bisoprolol, carteolol, labetalol, metoprolol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, timolol

ACEIs: Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, prindopril, quinapril, ramipril, trandolopril

CCBs: Amlodipine, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, diltiazem, verapamil

ARBs: Candesartan, irbesartan, losartan, telmisartan, and valsartan

FDCs: ACEI + CCBs, ACEIs + DIU, ARBs + DIU, BBs

[1] Hypertensive disease (International Classification of Diseases, 9th Revision, Clinical Modification or ICD-9-CM 401-405):

- 401: Essential hypertension
- 402: Hypertensive heart disease
- 403: Hypertensive chronic kidney disease
- 404: Hypertensive heart and chronic kidney disease
- 405: Secondary hypertension

[2] Ischemic heart disease (ICD-9-CM 410-414):

- 410 Acute myocardial infarction
- 411 Other acute and subacute forms of ischemic heart disease
- 412 Old myocardial infarction
- 413 Angina pectoris
- 414 Other forms of chronic ischemic heart disease

[3] Other forms of heart disease (ICD-9-CM 420-429):

- 420 Acute pericarditis
- 421 Acute and subacute endocarditis
- 422 Acute myocarditis
- 423 Other diseases of pericardium
- 424 Other diseases of endocardium
- 425 Cardiomyopathy
- 426 Conduction disorders
- 427 Cardiac dysrhythmias
- 428 Heart failure
- 429 Ill-defined descriptions and complications of heart disease

[4] ICD-9-CM 428: Heart failure (already included under “other forms of heart disease” but important enough to separate)

[5] Cerebrovascular disease (ICD-9-CM 430-438):

- 430 Subarachnoid hemorrhage
- 431 Intracerebral hemorrhage
- 432 Other and unspecified intracranial hemorrhage
- 433 Occlusion and stenosis of precerebral arteries

- 434 Occlusion of cerebral arteries
- 435 Transient cerebral ischemia
- 436 Acute, but ill-defined, cerebrovascular disease
- 437 Other and ill-defined cerebrovascular disease
- 438 Late effects of cerebrovascular disease

[6] End-stage renal disease (ICD-9-CM 285.21: Anemia in chronic kidney disease)

[7] Diabetes was defined as the presence of ICD-9-CM codes 250 (Diabetes mellitus), 357.2 (Polyneuropathy in diabetes), 362.0 (Diabetic retinopathy), 366.41 (Diabetic cataract) or 648.0 (Diabetes mellitus) OR DRG 294 (Diabetes Age >35) or 295 (Diabetes Age 0-35)

SD: Standard Deviation

Index antihypertensive drug utilization was as follows (see Table 6): 24.85% received a thiazide diuretic, 21.12% an ACEI, 20.41% a BB, 16.75% a fixed dose combination, 9.27% a CCB and 7.60% an ARB. Mean copay of index prescription fill was $13.09. Mean copay was highest for ARBs ($18.41) followed by fixed dose combinations ($15.73) and CCBs ($15.39) (see Table 8); mean copay was the lowest for diuretics ($10.06). Mean total copay of index prescription was $66.13 over the follow-up period (see Table 6). Mean total copayments were again highest for ARBs ($98.12) and lowest for diuretics ($48.71). The median copay for ARBs was also the highest ($50) (see Table 8). The vast majority of patients receiving thiazide diuretics and ACEIs were using generic equivalents (90.29% and 82.88%, respectively) (see Table 8). Generic use was also prevalent among patients receiving BBs (63.36%). None of the patients receiving ARBs was using generic equivalents as none are available in the US market.

Over one-third of patients (34.06%) received mail order services for their antihypertensive prescriptions (see Table 6). This percentage was the highest

among ARB users (42.33%) and lowest among diuretic users (29.66%) (see Table 8). The mean number of days' supply received was as follows: BBs – 44.10, ARBs – 44.09, ACEIs – 43.76, diuretics – 43.13, CCBs – 40.72 and fixed dose combinations – 39.83 (see Table 8). The median number of days' supply was 30.00 days, regardless of drug class.

Table 6: Pharmacy utilization for the overall study population

Variable	Overall N=68,538
Receiving a thiazide diuretic as index prescription	17,029 (24.85%)
Receiving a beta blocker (BB) as index prescription	13,987 (20.41%)
Receiving an angiotensin-converting-enzyme inhibitor (ACEI) as index prescription	14,477 (21.12%)
Receiving a calcium channel blocker (CCB) as index prescription	6,351 (9.27%)
Receiving an angiotensin-receptor blocker (ARB) as index prescription	5,212 (7.60%)
Receiving a fixed dose combination (FDC) as index prescription	11,482 (16.75%)
Mean copay of index prescription fill:	$13.09
Mean total copay of index prescription:	$66.13
% with any mail-order prescriptions	23,346 (34.06%)
Mean number of doses/day (SD) ♣	1.30 (0.65)
Mean number of prescriptions/month (SD) ♣	1.85 (1.50)
Mean MPR (SD)	0.70 (0.36)

Thiazide diuretics: Hydrochlorothiazide

BBs: Acebutolol, atenolol, betaxolol, bisoprolol, carteolol, labetalol, metoprolol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, timolol

ACEIs: Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, prindopril, quinapril, ramipril, trandolopril

CCBs: Amlodipine, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, diltiazem, verapamil

ARBs: Candesartan, irbesartan, losartan, telmisartan, and valsartan

FDCs: ACEI + CCBs, ACEIs + DIU, ARBs + DIU, BBs + DIU

SD: Standard Deviation

MPR: Medication Possession Ratio defined as the total number of days' supply divided by 365.

* Calculation of mean number of doses/day and mean number of prescriptions/month excluded antihypertensive medications.

The mean number of doses per day used by study subjects was 1.30 (SD 0.65) (see Table 6). The mean number of prescriptions per month was 1.85 (SD 1.50). Both of these measures (mean number of doses per day and mean number of prescriptions per month) exclude antihypertensive prescriptions. Mean MPR for antihypertensive medications was 0.70 (SD 0.36).

In terms of medical services utilization for the overall study population (see Table 7), the mean number of outpatient visits during the pre- and post-index prescription periods were 3.79 and 6.32, respectively. Approximately one of every three subjects had no visits in the pre-index period while 17.53% had 7 or more visits. The distribution was very different in the post-index period with only 2.60% having no visits and 37.20% having 7 or more. Mean emergency room visits were 0.31 and 0.38 in the pre- and post-index periods. More than twice as many study participants had at least one emergency room visit in the post-index compared to the pre-index period (22.23% versus 10.69%, respectively). The mean rate of hospitalizations was almost twice as high in the post- as in the pre-index period (0.15 and 0.08, respectively). The percent of study participants being hospitalized in the post-index compared to the pre-index period was over three times as high (11.99% versus 3.46%, respectively). Also, the number of study participants hospitalized 7 or more times rose from 13 in the pre-index period to 24 in the post-index period.

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Table 7: Medical services utilization for the overall study population

Variable	Overall N=68,538
Mean outpatient visits pre-index prescription	3.79
- 0 visits	22,981 (33.53%)
- 1 to 3 visits	16.083 (23.47%)
- 4 to 6 visits	17,456 (25.47%)
- 7 or more visits	12,018 (17.53%)
Mean outpatient visits post-index prescription	6.32
- 0 visits	1,780 (2.60%)
- 1 to 3 visits	19,280 (28.13%)
- 4 to 6 visits	21,985 (32.08%)
- 7 or more visits	25,493 (37.20%)
Mean emergency room visits pre-index prescription	0.31
- 0 visits	61,210 (89.31%)
- 1 to 3 visits	5,809 (8.48%)
- 4 to 6 visits	1,257 (1.83%)
- 7 or more visits	262 (0.38%)
Mean emergency room visits post-index prescription	0.38
- 0 visits	53,301 (77.77%)
- 1 to 3 visits	14,222 (20.75%)
- 4 to 6 visits	692 (1.01%)
- 7 or more visits	323 (0.47%)
Mean hospitalizations pre-index prescription	0.08
- 0 visits	66,164 (96.54%)
- 1 to 3 visits	2,151 (3.14%)
- 4 to 6 visits	210 (0.31%)
- 7 or more visits	13 (0.02%)
Mean hospitalizations post-index prescription	0.15
- 0 visits	60,319 (88.01%)
- 1 to 3 visits	8,064 (11.77%)
- 4 to 6 visits	131 (0.19%)
- 7 or more visits	24 (0.04%)
Mean medical expenses pre-index prescription	$2,988.63
Mean medical expenses post-index prescription	$5,640.38
Mean pharmacy expenses pre-index prescription	$1,113.05
Mean medical expenses post-index prescription	$1,724.21

Mean medical expenses were $2,988.63 per study participant in the pre-index period and $5,640.38 per study participant in the post-index period (see Table 7). Mean pharmacy expenses were $1,113.05 per study participant in the pre-index period and $1,724.21 per study participant in the post-index period.

The mean number of doses per day (excluding antihypertensive prescriptions) varied little by drug class (from 1.25 for diuretic users to 1.35 for beta blocker users) (see Table 8). The mean number of medications per month (excluding antihypertensive prescriptions) varied from 1.69 and 1.75 among diuretic and FDC users, respectively, to 1.99 and 2.09 among CCB and ARB users, respectively. FDC users had the lowest mean MPR (0.64) and ACEI users had the highest (0.76).

In the pre-index period, the mean number of office visits was lowest for FDC users (3.25) and highest for ARB users (4.33) (see Table 8). The median number of office visits was 2.00, regardless of index drug class. The percent of subjects with at least 1 office visit ranged from a low of 61.77% among FDC users to a high of 71.78% among ARB users. Similarly, the percentage with 7 or more office visits ranged from 14.13% among FDC users to 20.91% among ARB users.

In the post-index period, the mean number of office visits was lowest for FDC users (5.79) and highest for CCB users (6.84) (see Table 8). The median number of office visits was 5.00 for all subjects except ARB users, who had a median of 6.00. The vast majority of subjects had at least 1 office visit and the

percentage with 7 or more office visits ranged from 33.70% among FDC users to 40.64% among CCB users.

In the pre-index period, the mean number of ER visits was ranged from 0.26 for FDC users and 0.37 for BB users (see Table 8). The median number of office visits was 0.00, regardless of index drug class. The percent of subjects with at least 1 office visit was lowest among FDC users (9.36%) and highest among BB users (12.26%).

In the post-index period, the mean number of ER visits ranged from 0.33 for diuretic and FDC users to 0.49 for CCB users (see Table 8). Again, the median number of office visits was 0.00 for all subjects, regardless of index drug class. The percent of subjects with at least 1 office visit was lowest among FDC users (19.84%) and highest among CCB users (26.47%).

Table 8: Pharmacy and medical services utilization by index drug class

Variable	ACEI n=14,477	ARB n=5,212	BB n=13,987	CCB n=6,351	DIU n=17,029	FDC n=11,482
Copay of index prescription fill:						
- mean	$12.52	$18.42	$12.19	$15.39	$10.06	$15.73
- median	8.33	15.00	7.68	11.40	5.00	10.72
- standard deviation	12.43	15.50	12.38	13.70	11.16	14.51
Total copay of index prescription:						
- mean	$65.06	$98.12	$60.65	$76.51	$48.71	$79.74
- median	38.05	50.00	30.00	36.00	25.00	40.00
- standard deviation	79.49	112.46	80.66	95.57	69.39	98.21
Number (and %) receiving a generic drug as index prescription	11,998 (82.88%)	0 (0.00%)	8,862 (63.36%)	2,404 (37.85%)	15,376 (90.29%)	4,816 (41.94%)
- Missing	5	0	93	10	37	47
% with any mail-order prescriptions	5,154 (35.60%)	2,206 (42.33%)	4,854 (34.70%)	2,194 (34.55%)	5,050 (29.66%)	3,888 (33.86%)
Number of days' supply per prescription fill:						
- mean	43.76	44.09	44.10	40.72	43.13	39.83
- median	30	30	30	30	30	30
- standard deviation	26.19	25.31	27.35	24.31	27.08	23.37
Mean number of doses/day (SD)♣	1.33 (0.55)	1.31 (0.52)	1.35 (0.76)	1.34 (0.77)	1.25 (0.73)	1.27 (0.49)
Mean number of medications/month (SD) ♣	1.93 (1.52)	2.09 (1.63)	1.91 (1.57)	1.99 (1.66)	1.69 (1.37)	1.75 (1.36)
Mean MPR (SD)	0.76 (0.34)	0.66 (0.37)	0.72 (0.36)	0.65 (0.37)	0.70 (0.36)	0.64 (0.37)
Office visits (any						

Variable	ACEI n=14,477	ARB n=5,212	BB n=13,987	CCB n=6,351	DIU n=17,029	FDC n=11,482
ICD-9 CM) pre-index prescription:						
- mean	3.71	4.33	4.02	4.02	3.78	3.25
- median	2.00	2.00	2.00	2.00	2.00	2.00
- standard deviation	5.39	5.06	5.16	5.52	4.62	4.30
- % with 0 visits	33.52%	28.22%	32.82%	34.66%	32.16%	38.23%
- % with 1-3 visits	24.51%	22.06%	22.79%	21.81%	24.22%	23.42%
- % with 4-6 visits	25.18%	28.80%	25.45%	24.07%	26.07%	24.23%
- % with 7 or more visits	16.79%	20.91%	18.95%	19.46%	17.55%	14.13%
Office visits (any ICD-9 CM) post-index prescription:						
- mean	6.22	6.67	6.71	6.84	6.14	5.79
- median	5.00	6.00	5.00	5.00	5.00	5.00
- standard deviation	5.17	5.19	5.41	5.70	4.62	4.43
- % with 0 visits	2.50%	2.49%	2.51%	3.29%	2.41%	2.76%
- % with 1-3 visits	28.94%	25.36%	26.40%	26.30%	28.51%	30.93%
- % with 4-6 visits	32.64%	31.52%	30.92%	29.77%	33.21%	32.62%
- % with 7 or more visits	35.93%	40.62%	40.17%	40.64%	35.86%	33.70%
ER visits (any ICD-9 CM) pre-index prescription:						
- mean	0.30	0.28	0.37	0.36	0.29	0.26
- median	0.00	0.00	0.00	0.00	0.00	0.00
- standard deviation	1.73	1.46	1.67	1.48	1.30	1.22
- % with 0 visits	89.43%	90.04%	87.74%	88.35%	89.73%	90.64%
- % with 1-3 visits	8.47%	8.00%	9.54%	8.64%	8.20%	7.73%
- % with 4-6 visits	1.78%	1.69%	2.24%	2.49%	1.69%	1.32%
- % with 7 or more visits	0.32%	0.27%	0.48%	0.52%	0.38%	0.32%
ER visits (any ICD-9 CM) post-index						

Variable	ACEI n=14,477	ARB n=5,212	BB n=13,987	CCB n=6,351	DIU n=17,029	FDC n=11,482
prescription:						
- mean	0.36	0.39	0.47	0.49	0.33	0.33
- median	0.00	0.00	0.00	0.00	0.00	0.00
- standard deviation	1.13	1.39	1.72	1.49	1.08	1.07
- % with 0 visits	78.23%	77.78%	74.52%	73.53%	80.00%	80.16%
- % with 1-3 visits	20.43%	20.64%	23.56%	24.31%	18.90%	18.56%
- % with 4-6 visits	0.93%	1.11%	1.33%	1.48%	0.69%	0.89%
- % with 7 or more visits	0.40%	0.46%	0.59%	0.68%	0.41%	0.39%
Hospitalization visits (any ICD-9 CM) pre-index prescription:						
- mean	0.07	0.07	0.10	0.11	0.07	0.06
- median	0.00	0.00	0.00	0.00	0.00	0.00
- standard deviation	0.42	0.41	0.48	0.54	0.41	0.38
- % with 0 visits	96.84%	96.93%	95.73%	95.06%	96.88%	97.26%
- % with 1-3 visits	2.84%	2.80%	3.83%	4.52%	2.81%	2.54%
- % with 4-6 visits	0.30%	0.25%	0.41%	0.35%	0.31%	0.19%
- % with 7 or more visits	0.02%	0.02%	0.02%	0.08%	0.00%	0.01%
Hospitalization visits (any ICD-9 CM) post-index prescription:						
- mean	0.17	0.16	0.22	0.21	0.11	0.10
- median	0.00	0.00	0.00	0.00	0.00	0.00
- standard deviation	0.53	0.51	0.57	0.61	0.38	0.39
- % with 0 visits	87.17%	87.66%	83.63%	84.95%	91.05%	91.73%
- % with 1-3 visits	12.57%	11.97%	16.03%	14.56%	8.89%	8.18%
- % with 4-6 visits	0.19%	0.29%	0.30%	0.46%	0.05%	0.08%
- % with 7 or more visits	0.06%	0.08%	0.04%	0.03%	0.01%	0.02%
Medical expenses						

Variable	ACEI n=14,477	ARB n=5,212	BB n=13,987	CCB n=6,351	DIU n=17,029	FDC n=11,482
pre-index prescription:						
- mean	$2,734.76	$3,088.94	$3,491.82	$4,088.01	$2,710.10	$2,455.26
- median	$533.64	$728.94	$656.00	$599.10	$591.32	$434.91
- standard deviation	$17.445.05	$9,329.38	$16,740.90	$20,095.19	$14,150.30	$14,138.58
Medical expenses post-index prescription:						
- mean	$5,903.77	$5,856.69	$7,020.08	$7,080.51	$4,522.13	$4,391.32
- median	$1,766.91	$2,065.03	$2,312.02	$2,225.06	$1,706.33	$1,488.00
- standard deviation	$22,878.52	$14,198.51	$16,050.32	$19,854.62	$9,780.13	$12,032.57
Pharmacy expenses pre-index prescription:						
- mean	$1,141.76	$1,473.84	$1,163.27	$1,224.53	$995.03	$965.30
- median	$0.00	$108.32	$16.32	$0.00	$0.00	$0.00
- standard deviation	$2,924.00	$3,276.34	$3,196.33	$3,210.24	$2,539.99	$2,525.94
Pharmacy expenses post-index prescription:						
- mean	$1,784.62	$2,375.10	$1,712.73	$2,067.39	$1,389.32	$1,673.43
- median	$1,079.73	$1,629.33	$962.25	$1,194.88	$734.98	$1,056.55
- standard deviation	$2,434.00	$2,904.30	$2,563.99	$3,082.45	$2,146.59	$2,086.37

Thiazide diuretics: Hydrochlorothiazide

BBs: Acebutolol, atenolol, betaxolol, bisoprolol, carteolol, labetalol, metoprolol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, timolol

ACEIs: Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, prindopril, quinapril, ramipril, trandolopril

CCBs: Amlodipine, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, diltiazem, verapamil

ARBs: Candesartan, irbesartan, losartan, telmisartan, and valsartan

FDCs: ACEI + CCBs, ACEIs + DIU, ARBs + DIU, BBs + DIU

ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification

MPR: Medication Possession Ratio, defined as the total number of days' supply divided by 365.

ER: Emergency Room

♣ Calculation of mean number of doses/day and mean number of medications/month excluded antihypertensive medications

In general, hospitalization rates were very low in the pre- and post-index periods (mean ranging from 0.06 to 0.22). The rate varied by index drug class. In the pre-index period, the lowest percentage of subjects with at least 1 hospitalization ranged from 2.74% for FDC users to 4.94% for CCB users. In the post-index period, the lowest percentage of subjects with at least 1 hospitalization ranged from 8.27% for FDC users to 16.37% for BB users.

Mean medical expenses ranged from $2,455.26 per study participant using FDCs to $4,088.01 per study participant using CCBs in the pre-index period (see Table 8). Mean medical expenses ranged from $4,391.32 per study participant using FDCs to $7,080.51 per study participant using CCBs in the post-index period (see Table 8).

Mean pharmacy expenses were lowest for diuretics and FDCs ($995.03 and 965.30 in the pre-index and $1,389.32 and $1,673.43 in the post-index periods, respectively). Mean pharmacy expenses were highest for ARBs in the pre- and post-index periods ($1,473.84 and $2,375.10, respectively).

Mean MPR was 0.70 (SD 0.36) (see Table 9). The MPR was also categorized as high/low and high/medium/low. Regardless of categorization, most subjects (57.12%) were highly compliant and the middle category did not have an effect in the results obtained from the regression models. The dichotomous MPR

classification was then used for the remainder of the study.

Table 9: Medication Possession Ratio (MPR)

Variable	Overall N=68,538
Mean MPR (SD)	0.70 (0.36)
Categorical MPR (dichotomous)	
- High (≥ 0.80)	39,149 (57.12%)
- Low (< 0.80)	29,389 (42.88%)
Categorical MPR	
- High (≥ 0.80)	39,149(57.12%)
- Medium (50-79)	6,222 (9.08%)
- Low (< 50)	23,167 (33.80%)

MPR: Medication Possession Ratio, defined as the total number of days' supply divided by 365.
SD: Standard Deviation

Focused on searching for the most appropriate break-down, the following definitions of the high MPR category were also evaluated:

Table 10: Additional MPR Definitions

MPR	0.70	0.75	0.80	0.90
High ≥ …	59.99%	57.51%	57.12%	54.11%
Low < …	40.01%	42.49%	42.88%	45.89%

MPR: Medication Possession Ratio defined as the total number of days' supply divided by 365.

The percentages of subjects in the high MPR category definitions were not meaningfully different, with a 5.88% difference at the extremes. Additionally, there was no impact on the regression models using the various definitions above. Besides the small difference between the different definitions, it is important to consider that the overall population for the study is substantial and may be driving the results. Thus, the MPR definition of ≥ 0.80 for high, which has been widely used in the literature, was chosen for the rest of the analysis.

Using Chi square tests, the relationship between the following variables and MPR were found to be significant to the $p < 0.05$ level: Age, gender, other heart disease, heart failure, cerebrovascular disease, diabetes, mail order, number of doses per day (excluding antihypertensive prescriptions), number of prescriptions per month (excluding antihypertensive prescriptions), average copay and total copay (see Tables 11). The relationship between MPR and number of comorbid conditions was not significant ($p < 0.1324$) and neither was the relationship with ischemic heart disease ($p < 0.6210$).

Table 11: Relationship between individual variables and compliance (MPR)

Table 11A: Dichotomous compliance and categorical age

Compliance	18-30 years	31-50 years	51-64 years	> 65 years	Totals
Yes	636 (33.7%)	13,205 (51.9%)	19,644 61.7%)	5,664 (60.5%)	39,149
No	1,251 (66.3%)	12,257 (48.1%)	12,189 (38.3%)	3,692 (39.5%)	29,389
Totals	1,887	25,462	31,833	9,356	68,538

$p < 0.0001$

Compliance was defined as an MPR, or Medication Possession Ratio, of 0.80 or greater.

Table 11B: Dichotomous compliance and gender

Compliance	Female	Male	Totals
Yes	21,769 (56.4%)	17,380 (58.1%)	39,149
No	16,845 (43.6%)	12,544 (41.9%)	29,389
Totals	38,614	29,924	68,538

$p < 0.0001$

Compliance was defined as an MPR, or Medication Possession Ratio, of 0.80 or greater.

Table 11C: Dichotomous compliance and number of comorbid conditions

Compliance	0	1	≥ 2	Totals
Yes	25,025 (57.2%)	9,977 (57.3%)	4,147 (56.0%)	39,149
No	18,716 (42.8%)	7,420 (42.7%)	3,253 (44.0%)	29,389
Totals	43,741	17,397	7,400	68,538

p < 0.1324

Compliance was defined as an MPR, or Medication Possession Ratio, of 0.80 or greater.

Table 11D: Dichotomous compliance and ischemic heart disease

Compliance	No	Yes	Totals
Yes	35,166 (57.2%)	3,983 (56.8%)	39,149
No	26,365 (42.8%)	3,024 (43.2%)	29,389
Totals	61,531	7,007	68,538

p < 0.6210

Compliance was defined as an MPR, or Medication Possession Ratio, of 0.80 or greater.

Table 11E: Dichotomous compliance and other heart disease

Compliance	No	Yes	Totals
Yes	34,028 (57.4%)	5,121 (55.2%)	39,149
No	25,228 (42.6%)	4,161 (44.8%)	29,389
Totals	59,256	9,282	68,538

p < 0.0001

Compliance was defined as an MPR, or Medication Possession Ratio, of 0.80 or greater.

Table 11F: Dichotomous compliance and heart failure

Compliance	No	Yes	Totals
Yes	38,245 (57.2%)	904 (52.7%)	39,149
No	28,577 (42.8%)	812 (47.3%)	29,389
Totals	66,822	1,716	68,538

p < 0.0002

Compliance was defined as an MPR, or Medication Possession Ratio, of 0.80 or greater.

Table 11G: Dichotomous compliance and cerebrovascular disease

Compliance	No	Yes	Totals
Yes	36,866 (57.2%)	2,283 (55.4%)	39,149
No	27,553 (42.8%)	1,836 (44.6%)	29,389
Totals	64,419	4,119	68,538

p < 0.0235

Compliance was defined as an MPR, or Medication Possession Ratio, of 0.80 or greater.

Table 11H: Dichotomous compliance and diabetes

Compliance	No	Yes	Totals
Yes	31,787 (56.8%)	7,362 (58.3%)	39,149
No	24,130 (43.2%)	5,259 (41.7%)	29,389
Totals	55,917	12,621	68,538

p < 0.0023

Compliance was defined as an MPR, or Medication Possession Ratio, of 0.80 or greater.

Table 11I: Dichotomous compliance and mail order

Compliance	No	Yes	Totals
Yes	23,116 (51.2%)	16,033 (68.7%)	39,149
No	22,076 (48.8%)	7,313 (31.3%)	29,389
Totals	45,192	23,346	68,538

$p < 0.0001$

Compliance was defined as an MPR, or Medication Possession Ratio, of 0.80 or greater.

Table 11J: Dichotomous compliance and number of daily doses

Compliance	< 1/day	1-3/day	> 3/day	Totals
Yes	3,766 (42.8%)	34,999 (59.6%)	384 (39.0%)	39,149
No	5,034 (57.2%)	23,754 (40.4%)	601 (61.0%)	29,389
Totals	8,800	58,753	985	68,538

$p < 0.0001$

Compliance was defined as an MPR, or Medication Possession Ratio, of 0.80 or greater.

Table 11K: Dichotomous compliance and number of prescriptions per month (excluding antihypertensive prescriptions)

Compliance	< 1/mo	1-5/mo	> 5/mo	Totals
Yes	8,018 (40.2%)	29,326 (64.0%)	1,805 (64.7%)	39,149
No	11,940 (59.8%)	16,466 (36.0%)	983 (35.3%)	29,389
Totals	19,958	45,792	2,788	68,538

$p < 0.0001$

Compliance was defined as an MPR, or Medication Possession Ratio, of 0.80 or greater.

Table 11L: Dichotomous compliance and average copay

Compliance	$0-30	$31-50	>$50	Totals
Yes	20,196 (46.3%)	4,229 (71.2%)	14,324 (78.0%)	38,749
No	23,409 (53.7%)	1,710 (28.8%)	4,039 (22.0%)	29,158
Totals	43,605	5,939	18,363	67,907

$p < 0.0001$

Compliance was defined as an MPR, or Medication Possession Ratio, of 0.80 or greater.

Table 11M: Dichotomous compliance and total copay

Compliance	$0-50	$51-150	>$151-300	>$300	Totals
Yes	4,058 (27.5%)	4,060 (24.8%)	9,900 (64.5%)	21,131 (95.9%)	39,149
No	10,721 (72.5%)	12,310 (75.2%)	5,445 (35.5%)	913 (4.1%)	29,389
Totals	14,779	16,370	15,345	22,044	68,538

$p < 0.0001$

Compliance was defined as an MPR, or Medication Possession Ratio, of 0.80 or greater.

Table 12 presents the odds ratios from twelve different logistic regression models using the dichotomous MPR definition. The models used different combinations of the following independent variables: Number of doses per day (excluding antihypertensive prescriptions), number of prescriptions per month (excluding antihypertensive prescriptions), number of comorbid conditions, pharmacy costs in the post-index prescription period, age, male gender and copay. Regardless of the model's components, the probability of being compliant decreases with increasing doses per day (10-20% decreased likelihood of compliance with every additional dose per day) (models 1, 2 and 9 in Table 12). Model 1 controlled for the rest of the variables listed above; model 2 incorporated doses per day (excluding antihypertensive prescriptions) only; and, model 9 controlled for age and male gender.

The likelihood of compliance increased 22-26% with every additional prescription per month (excluding antihypertensive prescriptions) in the 3 models (numbers 1, 3 and 10) that included prescriptions per month (excluding antihypertensive prescriptions) as an independent variable (see Table 12). Model 1 controlled for the rest of the variables listed above; model 3 incorporated prescriptions per month (excluding antihypertensive prescriptions) only; and, model 10 controlled for age and male gender.

Increased number of comorbid conditions was associated with a decreased likelihood of compliance in models 1 and 11 but not in model 4 (see Table 12). Model results suggest a ten percent decrease in compliance for every additional comorbid condition. Model 1 controlled for the rest of the variables listed above; model 4 included number of comorbid conditions only; and, model 11 controlled for age and male gender. Pharmacy cost in the post-index period did not have an effect on compliance (although the odds ratios of 1.00 in both models – 1 and 5 – were significant to the $p < 0.0001$ level).

Every additional year in the patient's age had a positive effect on compliance (0.6 to 2% increase in MPR) (see Table 12). Age was included in models 1, 6 and 9-12). Model 1 controlled for the rest of the variables listed above; model 6 included age only; model 9 controlled for doses per day and male gender; model 10 controlled for prescriptions per month (excluding antihypertensive prescriptions) and male gender; model 11 controlled for number of comorbid conditions and male gender; and, model 12 controlled for male gender and copay.

Male gender and copay also had a positive effect on compliance (7.2 to 9.3% and 1.1%, respectively) (see Table 12). Male gender was included in models 1, 7 and 9-12). Model 1 controlled for the rest of the variables listed above; model 7 included male gender only; model 9 controlled for doses per day and age; model 10 controlled for prescriptions per month (excluding antihypertensive prescriptions) and age; model 11 controlled for number of comorbid conditions and age; and, model 12 controlled for age and copay.

The odds ratios calculated by the different models remained similar. The variability in the estimate did not change the direction of the relationship of each variable with the MPR. The level of significance was changed only twice. In model 4, which considered number of comorbid conditions by itself, the relationship became non-significant. In model 12, which included age, male gender and copay, male gender became non-significant. Finally, the models run using dummy variables for the age, number of comorbid conditions and pharmacy expenses in the post-index prescription period did not further inform the results.

Table 12: Odds Ratios (and 95% Wald confidence limits) from logistic regression models

Model #	Doses/day♣	Rx/month♣	# comorbid conditions	Rx cost post	Age	Male	Copay
1	0.90 (0.867, 0.934)	1.225 (1.203, 1.247)	0.905 (0.882, 0.93)	1.000 (1.000, 1.000)	1.006 (1.005, 1.008)	1.090 (1.047, 1.134)	1.011 (1.011, 1.011)
2	0.804 (0.782, 0.827)						
3		1.258 (1.243, 1.273)					
4			0.982 (0.963, 1.001)♣				
5				1.000 (1.000, 1.000)			
6					1.019 (1.018, 1.020)		
7						1.072 (1.040, 1.105)	
8							1.011 (1.011, 1.012)
9	0.821 (0.799, 0.845)				1.019 (1.017, 1.020)	1.093 (1.060, 1.128)	
10		1.244 (1.230, 1.259)			1.016 (1.015, 1.017)	1.184 (1.147, 1.222)	
11			0.907 (0.890, 0.926)		1.021 (1.019, 1.022)	1.104 (1.071, 1.139)	
12					1.007 (1.005, 1.009)	1.011 (0.973, 1.052)❖	1.011 (1.011, 1.012)

Model #	Doses/day♣	Rx/month♣	# comorbid conditions	Rx cost post	Age	Male	Copay

p < 0.0001

♣ p < 0.0594

❖ p < 0.5690

Rx/month: Number of prescriptions per month

Rx cost post: Pharmacy costs in the post-index period

♣ Calculation of mean number of doses/day and mean number of prescriptions/month excluded antihypertensive medications.

Summary

Almost one of every four adults (23.40%) with pharmacy and medical claims in the MarketScan database received at least one prescription for the antihypertensive drugs in the study.

Mean age was 53 years and 46% of subjects were 51-64 years of age.

A majority of the subjects, or 56%, were female.

Diabetes mellitus (18%) and other forms of heart disease (14%) were the most prevalent comorbid conditions. Additionally, a high percent of ACEI and ARB users had diabetes.

The vast majority of study subjects were full-time employees (64%) with the most common industries represented were (1) manufacturing, durable goods (36%); (2) transportation, communications and utilities (21%); and, retail trade (14%). Sixty-eight percent of study subjects were employees and 31% spouses.

Most of the study subjects resided in the South (41%) or North Central (28%) regions of the US.

Preferred provider organizations, or PPOs, (41%) and comprehensive benefit plans (23%) were the most common type of health insurance coverage.

Antihypertensive drug class use was as follows: 25% of study subjects received diuretics, 21% ACEIs, 20% BBs, 17% fixed dose combinations, 9% CCBs and 8% ARBs.

Gender differences in the type of antihypertensive treatment received were noted. More females received diuretics (68% versus 32% males) and more males received ACEIs (56% versus 44% female).

Regional differences in the type of antihypertensive treatment received were also noted. Low ARB use was registered in the West and highest fixed dose combination use in the South.

The total copay of the index antihypertensive was lowest for study subjects receiving diuretics ($48.71) and highest for those receiving ARBs ($98.12). Furthermore, ninety percent of diuretic users were receiving generics versus zero percent of ARB users (generic ARBs are not available yet).

The mean number of doses per day was 1.3, with the lowest for subjects receiving diuretics (1.25) and the highest for subjects receiving BBs (1.35).

The mean number of prescriptions per month (excluding antihypertensive prescriptions) was 1.85, with the lowest for subjects receiving diuretics (1.69) and the highest for subjects receiving ARBs (2.09).

The mean MPR was 0.70 and 57% had a high level of compliance (MPR ≥ 0.80). The MPR was clearly skewed, which made a logistic regression a more appropriate option for the analysis.

Age, gender, other heart disease, heart failure, cerebrovascular disease, diabetes, mail order, number of doses per day (excluding antihypertensive prescriptions), number of prescriptions per month (excluding antihypertensive prescriptions), average copay and total copay had statistically significant independent relationships with the MPR ($p < 0.05$). The relationship between MPR and number of comorbid conditions was not significant ($p < 0.1324$) and neither was the relationship with ischemic heart disease ($p < 0.6210$).

The probability of being compliant decreased by 10% for every additional dose per day, controlling for the number of prescriptions per month (excluding antihypertensive medications), number of comorbid conditions, pharmacy costs in the follow-up period, age, gender and copay. In the same logistic regression model, the likelihood of compliance increased by 22.5% with every additional prescription per month (excluding antihypertensive medications), and decreased by 10% for every additional comorbid conditions. The probability of compliance increased by 0.6% for every additional year of age and by 1.1% for every dollar increase in copay. The likelihood of increased compliance is 9% greater for males versus females. P value was < 0.0001 for all of these associations.

V. Discussion

Increasing doses per day and number of comorbid conditions significantly decreased the likelihood of being compliant with the index antihypertensive medication, controlling for potential confounders. Furthermore, increasing number of total prescriptions per month (excluding antihypertensive medications), age, copay and male gender were associated with greater likelihood of compliance with the index antihypertensive medication. Adherence with antihypertensive medications is a key factor in the achievement of blood pressure control and favorable clinical outcomes in patients with hypertension. Adherence is a challenge for the health care system because it is complex and multifactorial, as supported by the findings of this study.

The present study was an attempt to better understand factors impacting adherence with antihypertensive therapy. Simplifying drug therapy, by decreasing the number of doses per day has been shown to improve compliance with antihypertensive medications. Schroeder, Fahey and Ebrahim conducted a systematic review of randomized controlled trials searching for all-language publications in the Cochrane Controlled Trials Register, MEDLINE, EMBASE, and CINAHL.[48] After screening 1,929 citations, they included 38 studies involving a total of 15,519 patients and testing 58 different interventions. All studies involved adult patients with essential hypertension in a primary care, outpatient, or community setting. The interventions were aimed to increase adherence to antihypertensive medications and the intervention group was compared with

either no intervention or usual care. Adherence to medication was reported in the 38 studies and the follow-up ranged from 2 to 60 months. Simplifying dosing regimens increased adherence in 7 of 9 studies, with a relative increase in adherence of 8% to 19.6%. Motivational strategies and complex interventions were partly successful in 10 of 24 and 8 of 18 studies, with increases in adherence of up to 23% and 41%, both respectively. Patient education alone was largely unsuccessful. The authors concluded that reducing the number of daily doses should be tried as a first-line strategy when developing programs to improve adherence with antihypertensive medications.

Iskedjian and colleagues found that with antihypertensive medications, once-daily dosing regimens are associated with higher rates of adherence than either twice daily or multiple daily dosing regimens.[49] MEDLINE, Embase, and the International Pharmaceutical Abstracts (IPA) databases were searched for articles published in English or French between 1980 and 1998 using the key words *compliance, non-compliance, adherence, nonadherence, drug, drug therapy, drug treatment, hypertension, blood pressure* and *study* or *trial*. A manual search was also performed on all references from retrieved articles and from review articles identified in the initial literature search, as well as textbooks on the topic. The eight studies in the meta-analysis reported adherence rates to chronically administered medications (≥ 10 weeks' duration) in solid, oral formulations (tablets or capsules) to treat essential hypertension in adults ≥ 18 years of age. Adherence was defined as the proportion of patients who had taken ≥ 80% of

doses; if this outcome measure was not available, the main adherence outcome as reported by the authors was used in the primary analysis. The overall total number of observations was 11,485: 1,830 for once-daily, 4,405 for twice-daily, 4,147 for greater than twice-daily, and 9,655 for multiple daily dosing regimens. The average adherence rate for once-daily dosing, 91.4%, was significantly higher than for multiple daily dosing (83.2%, $p < 0.001$). The meta-analytic difference between adherence rates for once-daily (92.7%) and twice-daily dosing (87.1%) was also statistically significant ($p = 0.026$). The difference in adherence rates between twice-daily (90.8%) and greater than twice-daily dosing (86.3%) was not statistically significant ($p = 0.069$).

Claxton, Cramer and Pierce conducted a systematic review of the associations between dose regimens and medication compliance by searching MEDLINE, PsychInfo, HealthStar, Health & Psychosocial Instruments, and the Cochrane Library using the terms *patient compliance, patient adherence, electronic monitoring, and MEMS* (medication event monitoring systems).[50] The review was limited to studies reporting compliance measured by electronic monitoring devices, considered by the authors to be the most accurate compliance assessment method to date. Data were pooled from 76 studies to calculate mean compliance with once-daily, twice-daily, 3-times-daily, and 4-times-daily dosing regimens. Twenty-six studies were in cardiovascular disease (17 of them in hypertension only), ten in respiratory disease, and the rest in infectious disease, cancer, fertility, psychiatry, epilepsy, and general medical disorders (diabetes = 3). Because of

heterogeneity in definitions of compliance, two major categories of compliance rates were defined: (1) dose taking (or taking the prescribed number of pills each day), and (2) dose-timing (or taking pills within the prescribed time frame). Mean dose-taking compliance was 71% and declined as the number of daily doses increased: 79% for once-daily, 69% for twice-daily, 65% for 3-times-daily and 51% for 4-times-daily ($p < 0.001$ among dose schedules). Compliance was significantly higher for once-daily versus 3-times-daily ($p = 0.008$), once-daily versus 4-times-daily ($p < 0.001$), and twice-daily versus 4-times-daily regimens ($p = 0.001$). The average dose-timing compliance from a subset of 14 studies was 59%. Patients were better able to comply with once-daily regimens (mean 74% of doses taken within 24-hour interval) than with regimens requiring multiple daily doses. Fifty-eight percent of patients prescribed 2 doses per day took them within 12-hour intervals, and 46% took 3 doses per day within 8-hour intervals.

More recently, Saini and colleagues published a systematic review of relevant literature published between January 1986 and August 2007 to evaluate the evidence on the effect of daily medication dosing frequency on medication adherence in chronic disease states, as assessed by precise medication event monitoring systems (MEMS).[51] Twenty articles were identified using the MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, and the Cochrane Library covering various disease conditions, including hypertension (6 studies), stable angina (4 studies), type 2 diabetes mellitus (4 studies), epilepsy (2 studies), congestive heart failure (1 study), migraine headaches (1 study),

cardiovascular disease (1 study), and multiple different disease conditions (1 study). Focusing on the hypertension-specific data gathered from 6 studies, the adherence rate for once-daily dosing regimens ranged from 49% to 94% and the adherence rate for twice-daily regimens ranged from 5% to 82%. The lower end of the range for both dosing regimens was markedly skewed by a single outlier study. The within-study differences in adherence for once-daily versus twice-daily dosing regimens ranged from 5% to 44%, with 4 studies of 6 reporting the differences to be statistically significant.

With more than half of all hypertensive patients not achieving BP control to the currently recommended target of < 140/90 mm Hg with a single antihypertensive agent,[11, 40, 41] a large percentage of high-risk patients with hypertension require 2 or more drugs to control BP to the more stringent goal of < 130/80 mm Hg.[42] Fixed dose combinations for the treatment of hypertension are abundant and recommended as another way of simplifying drug regimen to improve adherence with therapy. A recent American Society of Hypertension (ASH) position article on the use of combination therapy in hypertension emphasized the importance of abolishing the risks associated with blood pressure elevation without affecting patients' quality of life.[43] Recognizing that at least 75% of patients will require combination therapy to achieve contemporary BP targets, the position article suggests practical tasks involved in consistently achieving and maintaining goal BP in clinical practice. While acknowledging how combination regimens reduce the number of medications and dosing frequency, balancing cost

of therapy is identified as a critical issue for patients. With this in mind, the American Society of Hypertension recommends the use of fixed dose combination products rather than separate individual agents in circumstances where convenience outweighs other considerations.

Taylor and Shoheiber found a relationship between antihypertensive pill burden and compliance.[44] Using pharmacy and medical claims data from a managed care organization, they investigated whether medication adherence was superior, and cost benefits accrued, in subjects who received a once-daily, single-capsule, fixed-dose combination product for BP control, compared with subjects who received a similar regimen of separate components. Group 1 included subjects who had been prescribed the single-capsule, fixed-dose combination of amlodipine besylate/benazepril HCl; Group 2 comprised subjects who had been prescribed a regimen including an angiotensin-converting enzyme (ACE) inhibitor and a dihydropyridine calcium channel blocker (DHP CCB) as separate drugs. The medication possession ratio (MPR), calculated as the sum of the total days' supply across prescriptions divided by the total number of days from the first prescription fill date to the first day of the last prescription fill date, was used to assess compliance. Medical resource utilization by the 2 groups was assessed during the study period. The study cohorts (2,754 subjects in Group 1 and 2,978 in Group 2) were balanced with regard to age (mean, 53 years) and gender (women, 50%). The overall MPR for Group 1 was significantly higher than that for Group 2 (80.8% vs 73.8%; $p < 0.001$). The average annual cost of cardiovascular-related care per

subject was significantly lower in Group 1 ($726) compared with Group 2 ($1,600) ($p < 0.001$).

Vicki Fung and colleagues found that adherence with antihypertensive medications was inversely related to the number of antihypertensive medications prescribed.[45] This study identified Medicare+Choice beneficiaries (aged ≥ 65 years) who were members of the Kaiser Permanente's Northern California hypertension registry and who had received ≥ 1 antihypertensive medication (ACEI/ARB, BB, CCB, or diuretic) in 2002. The study used the proportion of days covered (PDC) to measure adherence. The PDC was defined as the total days of supply of all hypertension drug classes, divided by 365 days. To be considered adherent, the PDC had to be ≥ 80%. Additionally, blood pressure levels were gathered from outpatient records to evaluate the association between adherence and systolic blood pressure control, defined as < 140 mmHg. Systolic blood pressure was the clinical measure as it is a stronger predictor of cardiovascular risk in the elderly compared with diastolic blood pressure and the majority of elderly patients with hypertension have isolated systolic hypertension. The percent of subjects who were adherent to their full treatment regimen decreased as the number of drug s included in the regimen increased (adherence levels were 77.2%, 69.7%, 62.9%, and 55.5% of subjects with a 1-, 2-, 3-, and 4-drug regimen respectively). The logistic regression model using a repeated-measures generalized estimating equation approach showed that as the number of drugs in the regimen increased, subjects were less likely to be adherent to the complete

treatment regimen. The model was adjusted for sex, age, race/ethnicity, neighborhood socioeconomic status, comorbidity score, presence of chronic diseases, $1,000 drug cap, and medical center. The odds ratios were 0.75 and 0.52 for subjects with a 2- and 3-/4-drug regimen versus subjects with a 1-drug regimen (95% confidence intervals were 0.73-0.78 and 0.50-0.54, respectively).

To evaluate the impact of pill burden (fixed-dose combination versus separate agents) on adherence and ultimately clinical outcomes, a team of researchers lead by Richard Chapman studied the association between adherence to calcium-channel blocker and statin medications and the likelihood of cardiovascular events among managed care enrollees in the United States.[46] Using administrative claims data from the IMS LifeLink, they retrospectively identified adults taking a CCB or statin (but not both), who either initiated treatment with a single-pill amlodipine/atorvastatin or added a CCB to a statin (or vice versa). The proportion of days covered, calculated as the total days supplied of index drug divided by the number of days in the follow-up period (in this case, a denominator of 180 days), was used to assess compliance. They found that compliance was significantly better among those with a simplified treatment regimen. Of the 1,537 subjects receiving single-pill amlodipine/atorvastatin, 56.5% were compliant at 6 months compared with 21.4% of the 17,910 CCB/statin subjects ($p < 0.001$). Furthermore, multivariate analyses showed that single-pill amlodipine/atorvastatin patients were 4.7 times more likely to be compliant ($p <$

0.001) than CCB/statin patients and that being adherent to either regimen significantly lowered the risk of a CV event (hazard ratio = 0.77, p = 0.003).

A meta-analysis of compliance studies in hypertension among other conditions concluded that the use of fixed-dose combination regimens improves patient's medication compliance compared with free-drug regimens.[47] Four hypertension-specific studies were identified from a MEDLINE search using the words fixed-dose combinations, compliance and/or adherence. Studies which (1) involved fixed-dose combination versus free-drug components of the regimen given separately, and (2) reported patient's compliance were included in the meta-analysis. All hypertension-specific studies were retrospective and used three different measures of compliance. One used the medication possession ratio (defined as the sum of total days supply across prescriptions divided by the total number of days from the first prescription fill date to the first day of the last prescription fill date) and three used two distinct definitions of persistence (1. if patients renewed their prescription within 3 times the number of days supplied by the previous prescription, which was used by 2 of the studies; and, 2. percent of patients taking the same drug in the first year compared with the second year of treatment). The fixed-dose combination products in the 4 studies were amlodipine/benazepril, lisinopril/HCTZ, enalapril/HCTZ and ARB/diuretic. Follow-up was 1 year for 2 of the studies, and 2 years for the other 2. In the hypertensive cohort, fixed-dose combination regimens reduced the risk of non-compliance by 24% compared with free-drug combination regimens (non-

compliance rate: 35.7% versus 37.9%, p < 0.0001). The other conditions included in the meta-analysis were tuberculosis, human immunodeficiency virus (HIV) disease and diabetes. Overall, fixed-dose combination resulted in a 26% decrease in the risk of non-compliance compared with free-drug component regimen (pooled relative risk 0.74; 95% confidence interval 0.69-0.80; p < 0.0001).

Contrary to evidence in the literature, this study found a likelihood of improved compliance with antihypertensive medication with increasing total copay for prescriptions. Multiple studies, including some previously reviewed,[35, 36] have documented a negative impact of prescription cost on adherence. A retrospective pharmacy claims data from January 1999 to June 2004, the impact of copayment on patient adherence with antihypertensive drugs was analyzed in a large health plan in Hawaii.[52] Tiered formularies are designed to increase consumer cost sharing and provide incentives for the health plan member to choose medications on lower tiers. The health plan in Hawaii had a 3-tier pharmacy benefit design and the higher tier drugs had lower adherence rates across all drug classes. Adherence rates for ACEIs were 68%, 61% and 50% for agents in the tier-1, tier-2 and tier-3 categories, respectively. Similar results were observed in the ARB class, where adherence rates were 71% and 58% in tier-2 and tier-3 categories, respectively (there were no ARBs in tier-1). Patients taking medications listed on tier-2 were 24% more likely to be nonadherent compared to those who were prescribed tier-1 drugs. Furthermore, patients taking medications listed on tier-3 were 52% more likely to be nonadherent compared to those taking

tier-1 medications. Increasing copayment levels through different tiers of medication significantly decreased patients' adherence to antihypertensive therapy. A difference in copayment levels may result in patients exhibiting drug-sparing behavior and, thus, may have a negative impact on compliance. In this dissertation study, the total copay of the index antihypertensive was lowest for study subjects receiving diuretics ($48.71) and highest for those receiving ARBs ($98.12). Furthermore, ninety percent of diuretic users were receiving generics, which are most commonly placed in tier-1 of managed care formularies, versus zero percent of ARB users (generic ARBs are not available yet).

The importance of patient medication adherence in chronic diseases and how lowering copayment can have a positive effect was illustrated in a program initiated in 2002 by Pitney Bowes.[53] Pitney Bowes modified their pharmacy benefit plan for participants with diabetes, asthma, or hypertension, allowing them to pay for brand-name medications at their tier-1 rates. The change in their pharmacy benefit plan reduced a potential barrier to care for these chronic diseases by improving access. For the average plan member with diabetes, the average cost of a 30-day prescription fill dropped by 50%. As a result, the rates of adherence with all medications that were previously in higher tiers increased significantly. Likewise, the percent of patients with suboptimal adherence with insulin decreased by two-thirds. The change to a less restrictive plan by Pitney Bowes also had a positive financial impact. For example, despite a small increase in the company's total annual pharmacy costs per covered person, pharmacy costs for

employees with diabetes decreased by 7%, which was attributed to a reduction in diabetes complications and the avoidance of more intensive (and more costly) diabetes drug therapy. Additionally, the rate of emergency department visits decreased by 26%, and the per patient cost of care decreased by 6% from 2001 to 2003. Also during this timeframe, the annual increase in employee health cost for Pitney Bowes was 8.1% compared with 12% to 15% increases for comparison companies. In the case of Pitney Bowes, the removal of barriers to care, such as those created by formulary restrictions, appears to have increased medication adherence, and provided financial gains to the payer.

Increasing age was associated with greater likelihood of compliance with antihypertensive medications. However, no age categories were investigated, which may have uncovered a ceiling in this effect. The elderly are considered especially vulnerable to compliance issues. A combination of their health status, which requires multiple drug treatments, along with restricted income may increase their risk of compliance with prescription medications, in general. The avrage number of prescriptions per elderly person is projected to reach 38.5 by 2010.[39] At the same time, Social Security was the largest source of income for the elderly (65 years and older) in 2005, accounting for 40.1% of their income on average.[54] The median income level of the elderly population was $15,422 and the average income $24,418 in 2005. Age is a very easily identifiable risk factor to be considered when developing medication therapy management initiatives.

To evaluate the generalizability of the study findings, it is important to compare the study population to the general population. The percent of adults 18 years or older in the MarketScan database affected by high blood pressure is similar to published estimates. Approximately one of every four adults (23.4%) in the MarketScan database received at least one of the antihypertensive drugs being studied. Data from the CDC's Behavioral Risk Factor Surveillance System (BRFSS), a state-based telephone survey of adults 18 years or older, showed that, in 2005, 25.5% of respondents had been told they had high blood pressure (http://apps.nccd.cdc.gov/brfss/index.asp). The BRFSS is the world's largest, on-going telephone health survey system, tracking health conditions and risk behaviors in the United States yearly since 1984. Additionally, data from NHANES 1999-2004 showed that of those with hypertension age 18 and older, 71.8% were aware of their condition, 61.4% were under current treatment, 35.1% had it under control, and 64.9% did not have it controlled.[5] The Framingham Heart Study, which evaluated 10,333 participants who were 45 to 74 years of age, reported the rate of use of antihypertensive medications increasing from 2.3 percent to 24.6 percent among men and from 5.7 percent to 27.7 percent among women, from 1950 to 1989.[55]

Hypertension is an extremely common comorbid condition in diabetes, affecting 20–60% of patients with diabetes. Because hypertension substantially increases the risk of both macrovascular and microvascular complications, including stroke, coronary artery disease, and peripheral vascular disease,

retinopathy, nephropathy, and possibly neuropathy, it is an important condition to monitor, treat and control.[56] The prevalence of diabetes among subjects in this study was 18%. A retrospective, time series analysis conducted by James Jackson and colleagues reported similar estimates.[57] Jackson and his team identified patients with hypertension being treated by more than 4,000 physicians from 27 provider groups and managed care organizations between 1998 and 2006. The study was conducted to assess improvements in blood pressure control since the publication of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, 7th Report (JNC-7) guidelines and to examine patterns of drug therapy regarding recommended best practices within JNC guidelines. Trained pharmacists and nurses conducted medical chart abstractions for 500 randomly selected subjects from each provider group or managed care organization with a hypertension-related medical claim (International Classification of Disease, 9th Revision, Clinical Modification, codes 401-404) or a pharmacy claim for an antihypertensive medication. Data collected included age, gender, hypertension diagnosis, cardiovascular risk factors, relevant comorbidities, blood pressure measurements and prescribing patterns. The prevalence rates of diabetes among the cohorts before and after the JNC-7 release (15,258 and 4,000 patients with hypertension, respectively) were 22.1 and 37.0%, correspondingly. It is important to note that the latter estimate was generated using a much smaller sample.

A high percent of ACEI and ARB users in this study had diabetes (30.91% and 28.86%, respectively). A total of 5,979 subjects received an ACEI (n=4,475) or an ARB (n=1,504), which is 47.37% of the 12,621 subjects with comorbid diabetes. Jackson and colleagues found slightly higher percentages, 60.6% to 75.6% before and after the release of the JNC-7 guidelines. Use of these antihypertensive drug classes for blood pressure management of patients with diabetes is consistent with the American Diabetes Association recommendations, based on their proven benefits of reducing CVD events during the treatment of uncomplicated hypertension.[58] Treatment with ACEIs or ARBs is also recommended by the JNC 7 Guidelines.[1]

The most frequently used antihypertensives in this study were diuretics (24.85%), ACEIs (21.12%) and BBs (20.41%). The extensive use of diuretics as well as the other drug classes are in line with the JNC-7 recommendations.[1] The guidelines, released in 2003, recommend the use of thiazide-type diuretics as initial therapy for most patients with hypertension, either alone or in combination with one of the other classes (ACEIs, ARBs, BBs, CCBs) demonstrated to be beneficial in randomized controlled outcome trials. Furthermore, multiple studies conducted in managed care have published similar findings. Godley and colleagues analyzed medical and pharmacy claims in a group-model managed care organization as part of their evaluation of the effectiveness of a quality improvement program for hypertension management practices and patient health outcomes.[59] Of the 30,721 hypertensive patients, chart reviews were performed on

a random sample of 417 patients. Pharmacy claims revealed a total of 193,311 antihypertensive prescriptions. Approximately 47% of all hypertensive patients were managed with monotherapy, while 24% received dual therapy, and 11% were taking three or more antihypertensive medications per day. Of the patients on monotherapy, 93% received an angiotensin-converting-enzyme inhibitor (27.3%), diuretic (26.6%), beta-blocker (23.4%), or calcium channel blocker (15.4%). Jackson and colleagues found a similar antihypertensive utilization. In the cohort evaluated before the JNC-7 guidelines were released, 31% received diuretics, 33.4% ACEIs and 29.4% BBs. Utilization of diuretics (40.6%) and BBs (35.7%) was higher in the after JNC-7 cohort. Interestingly, Jackson et al also evaluated the use of fixed dose combination agents. Their study showed an increase in utilization from 11.9% to 20.8% after the release of the guidelines, which support the use of fixed dose combinations to improve the convenience for patients and to simplify treatment regimens.

It is important to recognize study limitations as the data source relied solely on administrative pharmacy and medical claims data. This study utilized prescription refill patterns to assess compliance and did not ascertain whether the medication was actually taken by the patient. However, a number of studies suggest a good correlation between pharmacy dispensing records and cumulative drug exposure and gaps in medication supply.[60, 61, 62] Additionally, some of the medications evaluated have approved indications for hypertension as well as other conditions. Information on patient diagnosis relied on medical claims rather than

patients' clinical records and disease severity was not available from pharmacy claims data. These data did not suffice to determine the indication for which these medications were prescribed. Some of these drugs may have been used by subjects in the study to manage more symptomatic diseases, such as congestive heart failure or angina. Subjects suffering from these conditions may have had better compliance with the study medications and, therefore, biased the study. However, information is not available to determine whether such bias took place and medical claims for these conditions in the pre-index period were listed as exclusion criteria. 'This study did not include measures of clinical effectiveness (blood pressure control) or outcomes (morbidity and mortality). It was not possible to determine whether clinical effectiveness or outcomes influenced or were related to compliance. Finally, the study population included only persons with health plan benefits coverage, and these study results may not reflect the drug-taking behavior of patients without some form of insurance for prescription medications.

In conclusion, the number of doses per day, presence of comorbid conditions and female gender are significantly associated with compromised adherence with antihypertensive drug therapy. Health care professionals have an opportunity to impact adherence by simplifying treatment regimens using once daily agents. The presence of comorbid conditions and female gender are not modifiable. However, both of these risk factors for nonadherence with

antihypertensive medications may be used to identify target populations and tailoring medication therapy management initiatives accordingly.

VI. Appendix A: Tables

Table 1: CPT codes for outpatient physician and ER visits

CPT codes	Description
99281.	Emergency department **visit** for the evaluation and management of a patient, which requires these three key components: A problem focused history; A problem focused examination; and Straightforward medical decision making. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are self limited or minor.
99282.	Emergency department **visit** for the evaluation and management of a patient, which requires these three key components: An expanded problem focused history; An expanded problem focused examination; and Medical decision making of low complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of low to moderate severity.
99283.	Emergency department **visit** for the evaluation and management of a patient, which requires these three key components: An expanded problem focused history; An expanded problem focused examination; and Medical decision making of moderate complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate severity.
99284.	Emergency department **visit** for the evaluation and management of a patient, which requires these three key components: A detailed history; A detailed examination; and Medical decision making of moderate complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of high severity, and require urgent evaluation by the

CPT codes	Description
	physician but do not pose an immediate significant threat to life or physiologic function.
99285	Emergency department **visit** for the evaluation and management of a patient, which requires these three key components within the constraints imposed by the urgency of the patient's clinical condition and/or mental status: A comprehensive history; A comprehensive examination; and Medical decision making of high complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of high severity and pose an immediate significant threat to life or physiologic function.
99201.	Office or other outpatient **visit** for the evaluation and management of a new patient, which requires these three key components: A problem focused history; A problem focused examination; Straightforward medical decision making. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are self limited or minor. Physicians typically spend 10 minutes face-to-face with the patient and/or family.
99202.	Office or other outpatient **visit** for the evaluation and management of a new patient, which requires these three key components: An expanded problem focused history; An expanded problem focused examination; Straightforward medical decision making. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of low to moderate severity. Physicians typically spend 20 minutes face-to-face with the patient and/or family.
99203.	Office or other outpatient **visit** for the evaluation and management of a new patient, which requires these three key components: A detailed history; A detailed examination; Medical decision making of low complexity. Counseling and/or

CPT codes	Description
	coordination of care with other providers or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate severity. Physicians typically spend 30 minutes face-to-face with the patient and/or family.
99204.	Office or other outpatient **visit** for the evaluation and management of a new patient, which requires these three key components: A comprehensive history; A comprehensive examination; Medical decision making of moderate complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Physicians typically spend 45 minutes face-to-face with the patient and/or family.
99205.	Office or other outpatient **visit** for the evaluation and management of a new patient, which requires these three key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Physicians typically spend 60 minutes face-to-face with the patient and/or family.
99211.	Office or other outpatient **visit** for the evaluation and management of an established patient that may not require the presence of a physician. Usually, the presenting problem(s) are minimal. Typically, 5 minutes are spent performing or supervising these services.
99212.	Office or other outpatient **visit** for the evaluation and management of an established patient, which requires at least two of these three key components: A problem focused history; A problem focused examination; Straightforward medical decision making. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are self limited or minor.

CPT codes	Description
	Physicians typically spend 10 minutes face-to-face with the patient and/or family.
99213.	Office or other outpatient **visit** for the evaluation and management of an established patient, which requires at least two of these three key components: An expanded problem focused history; An expanded problem focused examination; Medical decision making of low complexity. Counseling and coordination of care with other providers or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of low to moderate severity. Physicians typically spend 15 minutes face-to-face with the patient and/or family.
99214.	Office or other outpatient **visit** for the evaluation and management of an established patient, which requires at least two of these three key components: A detailed history; A detailed examination; Medical decision making of moderate complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Physicians typically spend 25 minutes face-to-face with the patient and/or family.
99215.	Office or other outpatient **visit** for the evaluation and management of an established patient, which requires at least two of these three key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Physicians typically spend 40 minutes face-to-face with the patient and/or family.

Table 2: Names and codes for sociodemographic variables

Description of Variable	Variable Names and Code
Age	AGE (continuous and categorical: 18-30, 31-50, 51-64 and 65+ y/o)
Gender	SEX 1. Male 2. Female
Employment status of primary beneficiary	EESTATU 1. Active full time 2. Active part time or seasonal 3. Early retiree 4. Medicare eligible retiree 5. Retiree (status unknown) 6. COBRA continue 7. Long term disability 8. Surviving spouse/depend 9. Other/unknown
Employment classification of primary beneficiary	EECLASS 1. Salary non-union 2. Salary union 3. Salary other 4. Hourly non-union 5. Hourly union 6. Hourly other 7. Non-union 8. Union 9. Unknown
Industry classification of the employer responsible for payment of claim	INDSTRY 1. Oil & gas extraction, mining 2. Manufacturing, durable goods 3. Manufacturing, nondurable goods 4. Transportation, communications, utilities 5. Retail trade 6. Finance, insurance, real estate

Description of Variable	Variable Names and Code
	7. Services
Geographic region of employee residence	REGION 1. Northeast 2. North Central 3. South 4. West 5. Unknown
Metropolitan Statistical Area (MSA) of primary beneficiary	MSA (mapped from 5 digit employee ZIP code)
Relationship of the patient to the primary beneficiary	EMPREL 1. Employee 2. Spouse 3. Child/other 4. Dependent-relation unknown
Type of benefit plan	PLANTYP 1. Comprehensive 2. Exclusive Provider Organization (EPO) 3. Health Maintenance Organization (HMO) 4. Point Of Service (POS) 5. Preferred Provider Organization (PPO) 6. POS with capitation

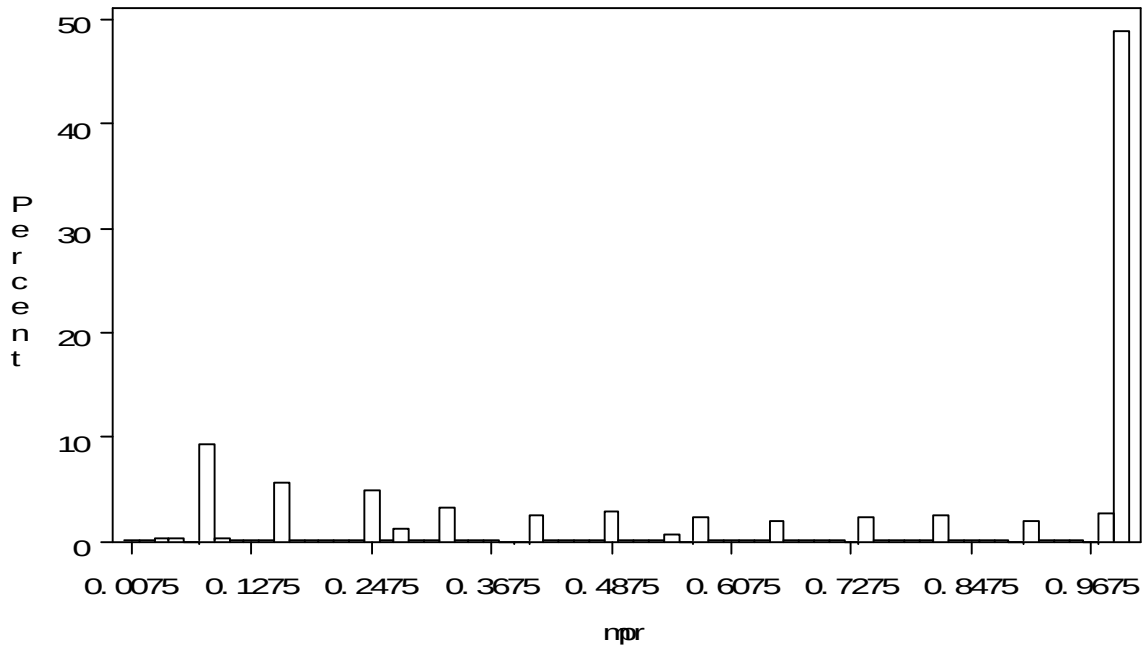
Table 3: Odds ratios from logistic regression models using two MPR classifications

	MPR – high/low[1]		MPR – high/medium/low[1]	
Variables	Odds ratio	P value	Odds ratio	P value
Age	1.007	< 0.0001	1.007	< 0.0001
Male	1.167	< 0.0001	1.155	< 0.0001
Doses per day	0.786	< 0.0001	0.809	< 0.0001
Medications per month	1.765	< 0.0001	1.773	< 0.0001
Ischemic heart disease	0.906	0.0010	0.899	0.0002
Other heart disease	0.897	< 0.0001	0.895	< 0.0001
Heart failure	0.724	< 0.0001	0.754	< 0.0001
Cerebrovascular	0.812	< 0.0001	0.836	< 0.0001
Diabetes	0.899	< 0.0001	0.901	< 0.0001
Mail order	1.657	< 0.0001	1.596	< 0.0001
Outpatient visits - pre	0.976	< 0.0001	0.976	< 0.0001
Outpatient visits – post	0.963	< 0.0001	0.965	< 0.0001
ER visits – pre	0.972	< 0.0001	0.977	0.0002
ER visits - post	0.931	< 0.0001	0.933	< 0.0001
Hospital stays – pre	0.899	< 0.0001	0.892	< 0.0001
Hospital stays - post	0.809	< 0.0001	0.824	< 0.0001
Medical expenses – post	1.000	0.0105	1.000	0.0133
Pharmacy expenses - pre	1.000	0.0014	1.000	< 0.0001
Pharmacy expenses – post	1.000	< 0.0001	1.000	< 0.0001
Average copay	1.024	< 0.0001	1.025	< 0.0001

[1] The following variables were removed because of redundancy: angiotensin-converting enzyme inhibitor drug class (ACEI), angiotensin receptor blocker drug class (ARB), beta blocker drug class (BB), calcium channel blocker drug class (CCB), diuretic drug class, fixed-dose combination drug class (FDC), end stage renal disease and number of comorbid conditions. Medical expenses – pre was removed at step 1.

VII. APPENDIX B: GRAPHS

Graph 1 : Histogram of MPR measure



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IX. CURRICULUM VITA

EDUCATION

- DOCTOR OF PHILOSOPHY IN EPIDEMIOLOGY AND QUANTITATIVE METHODS

  University of Medicine and Dentistry of New Jersey, 2010

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EXPERIENCE

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PUBLICATIONS

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