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The Impact of Medicare Part D Coverage on Medication Adherence and Health Outcomes in End-stage Renal Disease (ESRD) Patients

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The Impact of Medicare Part D Coverage on Medication Adherence and Health Outcomes in End-stage Renal Disease (ESRD) Patients

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Dedication

For My Father and Mother

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The Impact of Medicare Part D Coverage on Medication Adherence and Health Outcomes in End-stage Renal Disease (ESRD) Patients

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The University of Texas at Austin, 2013

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The purpose of this study was to investigate the impact of Medicare Part D coverage on medication adherence and health outcomes in dialysis patients. A retrospective analysis (2006-2010) using the United States Renal Data System was conducted for Medicare-eligible dialysis patients. Cardiovascular disease morbidity, healthcare utilization and expenditures, medication adherence, and mortality rates were compared, categorized based on patients' Part D coverage in 2007 for those who: 1) did not reach the coverage gap (cohort 1); 2) reached the coverage gap but not catastrophic coverage (cohort 2); 3) reached catastrophic coverage (cohort 3); and 4) did not reach the coverage gap but received a low-income subsidy (cohort 4). Cox proportional hazards models, Kaplan-Meier methods, logistic regressions, generalized linear models, and generalized estimating equations were used.

A total of 11,732 patients were included as meeting inclusion criteria: 1) cohort 1: 3,678 patients had out-of-pocket drug costs <$799; 2) cohort 2: 4,349 patients had out-of-pocket drug costs between $799 and $3,850; 3) cohort 3: 1,310 patients had out-of-pocket

drug costs > $3,850; and 4) cohort 4: the remaining 2,395 patients had out-of-pocket drug costs <$799 but received a low-income subsidy. After adjusting for demographic and clinical factors, patients in cohort 2 and cohort 3 had 42 percent and 36 percent increased risk of cardiovascular disease (odds ratio (OR)=1.42, 95% confidence interval (CI):1.20-1.67; OR=1.38, 95% CI:1.10-1.72); and had 36 percent and 37 percent higher death rates compared to those in cohort 4, respectively (hazard ratio (HR)=1.36, 95% CI:1.27-1.44; HR=1.37, 95% CI:1.27-1.48). Patients in cohort 2 were more likely to be nonadherent to medications for diabetes (OR=1.72, 95% CI:1.48-1.99), hypertension (OR=1.69, 95% CI:1.54-1.85), hyperlipidemia (OR=2.01, 95% CI:1.76-2.29), hyperphosphatemia (OR=1.74, 95% CI:1.55-1.95), and hyperparathyroidism (OR=2.08, 95% CI:1.66-2.60) after reaching the coverage gap. These patients had total health care costs that were $2,644 higher due to increased rates of hospitalization and outpatient visits, despite $2,419 lower pharmacy costs compared to patients in cohort 4 after controlling for covariates ($p<0.0001$).

Reaching the Part D coverage gap was associated with decreased medication adherence and unfavorable clinical and economic outcomes in dialysis patients.

Table of Contents

List of Tables

List of Figures

List of Appendices

Chapter 1: Literature Review

1.1 Literature Review

This chapter is a review of the literature relevant to this dissertation. The following broad areas will be covered in the literature review:

- Epidemiology of end-stage renal disease (ESRD) in the United States;
- Cardiovascular disease in ESRD patients;
- Prescription medication and pill burden in ESRD patients;
- An overview of the Medicare Part D prescription drug benefit in ESRD patients;
- Discussion about the impact of cost sharing policies on health outcomes;
- Discussion about the impact of Part D on health outcomes; and
- Discussion about the impact of Part D on dialysis patients.

1.2 Section 1: End-stage Renal Disease (ESRD)

1.2.1 ESRD in the United States

End-stage renal disease (ESRD) patients are those who require renal replacement therapy, including hemodialysis, peritoneal dialysis or kidney transplantation as lifesaving measures. (National Kidney Foundation 2002)

Chronic Kidney Disease (CKD) is the standard term to describe the chronic renal dysfunction that occurs prior to ESRD. CKD is defined as the presence of either kidney damage or decreased kidney function as evidenced by a glomerulo-filtration rate (GFR) < 60mL/min/1.73 m^2 for 3 or more months. (National Kidney Foundation 2002) Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies. The CKD trajectory has five stages, based on the calculated GFR (Table 1.1).

Table 1.1 Definition and Stages of Chronic Kidney Disease (NKF, 2002)

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥ 90
2	Kidney damage with mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure	< 15 (or dialysis)

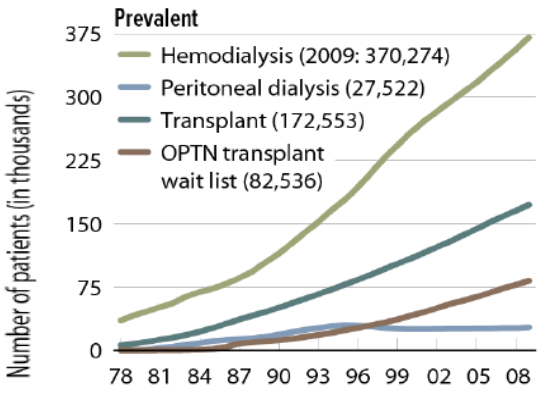
Source: The National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification

This CKD staging system was adapted by the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI). Stage 5 CKD is described as kidney failure. Kidney failure is not synonymous with ESRD, which is an administrative term in the United States (U.S.) based on eligibility for coverage by Medicare, specifically patients with kidney failure who require renal replacement therapy. (National Kidney Foundation 2002) Approximately 98 percent of patients with kidney failure in the U.S. are also ESRD patients.

1.2.1.1 Prevalence and Incidence

The number of U.S. patients with ESRD exceeded 570,000 in 2010. (US Renal Data System 2011) As of December 31, 2009, the prevalent population included 370,274 patients on hemodialysis and 27,522 on peritoneal dialysis, as well as 172,553 with a functioning kidney transplant (Figure 1.1). (US Renal Data System 2011) The rate of prevalent ESRD cases reached 1,738 per million. The prevalent dialysis population has grown to 397,796 patients, from 48,855 in 1980 and 110,656 in 1988. The transplant population has increased to 172,553 patients through 2009, from 10,138 in 1980 and 41,194 in 1988 (Figure 1.1). The prevalent population and the transplant population have doubled every 10 years. (Collins, Foley et al. 2009)

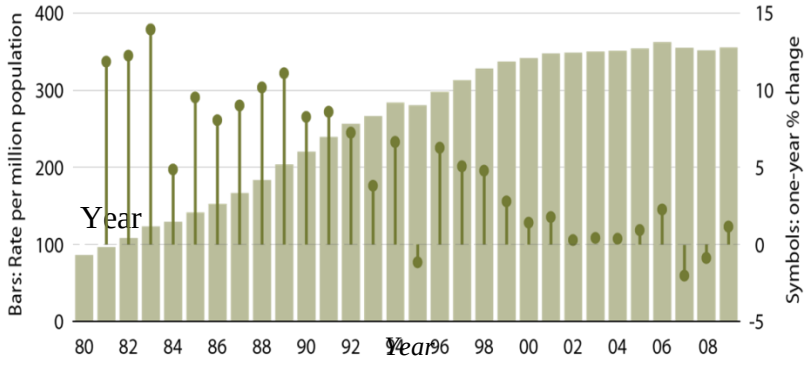
Figure 1.1 Prevalent Patient by Modality, 2009



Source: The United States Renal Data System (USRDS) 2011 Annual Report

The incident population growth has slowed significantly over the last 10 years, rising or decreasing one to two percent per year (Figure 1.2). (Collins, Foley et al. 2009) In 2009, 104,252 new patients began ESRD therapy on hemodialysis, 6,966 were placed on peritoneal dialysis, and 2,500 received a preemptive transplant.

Figure 1.2 Adjusted Incident Rates of ESRD & Annual Percent Change



Source: The United States Renal Data System (USRDS) 2011 Annual Report

1.2.1.2 Patient Characteristics and Treatment

According to United States Renal Data System (USRDS) Annual Reports, the adjusted rate of prevalent ESRD for patients age 65-75 has increased 28 percent (6,066 per million population) since 2000, while the rate among those age 75 and older has grown 37 percent (5,545 per million population). (US Renal Data System 2011) Among those ages 20-44 and 45-64, growth has been 13 and 20 percent, respectively. Although the rate of growth is relatively small, the total number of patients in the ESRD program appears to be driven by the group aged 45 to 64 years, accounting for 40 percent of the prevalent population (250,878 patients). (US Renal Data System 2011)

By race, rates of prevalent ESRD were higher in the African American and Native American populations, at 5,284 and 2,735 per million population in 2009, respectively, compared to 1,279 and 2,101 among whites and Asians, respectively. Hispanics reached 2,538 per million population in 2009, 1.5 times greater than the prevalence in the non-Hispanic population. (US Renal Data System 2011) In 2009, among 113,636 incident patients, the mean age was 62.6 years and 65.7 percent were white. Twenty-eight percent of patients were African American and the primary diagnosis of incident dialysis was diabetes (44.6%), which was followed by hypertension (28.9%), glomerulonephritis (9.5%), and cystic kidney disease (2.5%). (US Renal Data System 2011)

Diabetes remained the dominant primary cause of incident ESRD, with reported rates of 148.8 cases per million in 2009. Among younger adults (30-39 years), rates have declined in white individuals since the 1990s and remained constant in Asian and Hispanic populations, whereas rates have continued to rise among African American and Native American groups. Among older adults (60-69 years), rates seem to have stabilized in the past five years in all racial and ethnic groups, although disparities remain marked. (Foley and Collins 2007; Collins, Foley et al. 2009) For hypertension, the second most common cause of ESRD, incident rates remained considerably higher in African American individuals in all age groups.

The two major renal replacement therapies for ESRD are dialysis and kidney transplantation. Hemodialysis was the first widely available renal replacement therapy and is still the most common. Among US patients with ESRD, 66 percent receive hemodialysis. A hemodialysis regimen is based on two pillars: restriction of certain nutrients and removal of waste metabolites from the blood by regular dialysis. (Denhaerynck, Manhaeve et al. 2007) Successful hemodialysis depends on four factors: (1) fluid restrictions, (2) dietary guidelines, (3) prescription medications, and (4) attendance at hemodialysis sessions. (Denhaerynck, Manhaeve et al. 2007) Fluid restrictions can be as severe as a maximum of 500 mL of fluid intake daily, depending on the residual diuresis. Prescribed dietary restrictions limit sodium, potassium, and protein intake. The goals of the medication regimen are to treat or prevent

cardiovascular comorbid conditions and keep a stable mineral blood balance. Attendance at dialysis sessions implies both regular attendance (no skipping of sessions) and full completion of the sessions (no shortening of a session). (Denhaerynck, Manhaeve et al. 2007)

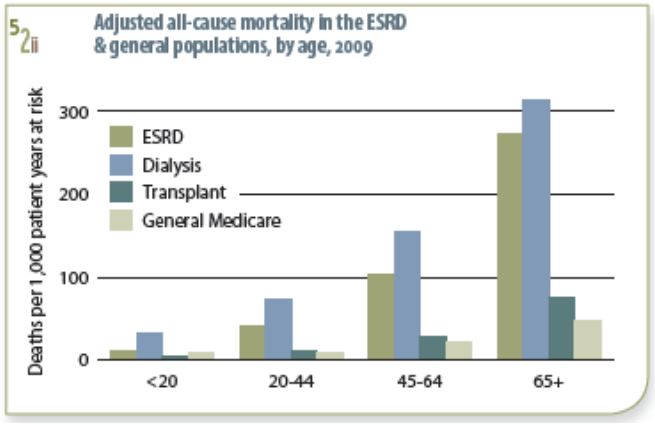
1.2.1.3 Mortality

Survival rates have improved steadily in the US ESRD population since the late 1980s, which is remarkable considering the ever-expanding burden of comorbidity in incident patients. (Foley and Collins 2007) However, although dialysis effectively contributes to long-term survival, morbidity and mortality of dialysis patients remains high, especially due to high cardiovascular morbidity and mortality. Every year, 10 to 20 percent of all patients on dialysis die. The average expected remaining lifetime for patients on dialysis is 5.9 years, compared with 16.4 years for kidney transplant recipients and 25.2 years for the general population. (US Renal Data System 2010) Approximately 20 percent of dialysis patients die within the first year of diagnosis. (US Renal Data System 2010) Only 33 percent of patients on hemodialysis survive to the fifth year of treatment, whereas 70 percent of patients who have kidney transplants are alive after 5 years. (US Renal Data System 2011)

In 2009, the adjusted rate of all-cause mortality was seven times greater for dialysis patients than for individuals in the general Medicare population (Figure 1.3). Rates rise

by age, reaching 274 per 1,000 patient-years at risk for ESRD patient age 65 and older, and 313 per 1,000 patient-years at risk for dialysis patients of the same age.

Figure 1.3 Adjusted All-cause Mortality in the ESRD & General Populations, by Age, 2009



Source: The United States Renal Data System (USRDS) 2011 Annual Report

Cardiovascular disease (CVD) is the leading cause of mortality in ESRD, accounting for about 45 percent of all deaths. (Wright and Hutchison 2009) Cardiovascular mortality is 10 to 30 times higher in patients treated by dialysis than in the general population, despite stratification by sex, race, and the presence of diabetes. (Meyer and Levey 1998) After adjustment for age, CVD mortality remains 5-folder higher in dialysis patients than in the general population. The high mortality rate is likely due to both a high case fatality rate and a high prevalence of CVD. (Levey, Beto et al. 1998; Sarnak, Levey et al. 2003)

1.2.2 Cardiovascular Events in Patients with ESRD

1.2.2.1 Cardiovascular Disease (CVD)

The incidence of CVD was estimated to be 11-16 percent in the dialysis population (Park, Rascati et al. 2011), which is five- to 15-fold higher than that seen in the general population. (Longenecker, Coresh et al. 2002) CVD accounted for approximately half of the deaths in ESRD and contributed to the extraordinarily high total annual mortality - 23 percent - observed in such patients. (US Renal Data System 2009)

In addition to an increased risk of death, CVD is associated with high rates of resource utilization. On average, dialysis patients are hospitalized between 1.8 and 2.4 times annually, with a mean length of stay of 13.7 days per patient per year. (US Renal Data System 2008) Approximately 19 to 33 percent of these hospitalizations are attributable to CVD. Once patients reach ESRD and enter dialysis programs, they have an alarmingly high rate of cardiovascular death - with those in the youngest age group of < 25 years having equivalent cardiovascular mortality rates compared to 75- to 85- year-olds in the general population. (Foley, Parfrey et al. 1998)

1.2.2.2 Risk Factors for CVD in Patients with ESRD

The Framingham Heart Study identified a set of individual biomarkers, behaviors, and demographic characteristics that are routinely used to predict the risk of CVD. (Wilson,

D'Agostino et al. 1998) These risk factors - which include age, gender, history of diabetes, total cholesterol, systolic blood pressure, and smoking status - have been extensively validated in multiple populations. (Grundy 2005)

However, the Framingham instrument has demonstrated poor overall accuracy in predicting cardiac events in individuals with CKD. (Weiner, Tighiouart et al. 2007) Patients with ESRD have higher rates of cardiovascular morbidity and mortality than would be predicted by Framingham models of cardiovascular risk. (McClellan and Chertow 2005) There are many reasons for this, including the confounding additional cardiovascular risk arising from malnutrition which occurs because kidney dysfunction leads to a catabolic state. This then promotes inflammation, a key trigger in the development of cardiovascular disease. (Bergstrom and Lindholm 1998)

The traditional risk factors for CVD such as hypertension, dyslipidemia, diabetes, and obesity are highly prevalent in ESRD populations. There are many other cardiovascular risk factors that are uremia-specific or much more common in patients with ESRD than in the general population. (Wright and Hutchison 2009) These factors include anemia, hyperparathyroidism, carnitine deficiency, hyperhomocysteinemia, low vitamin C, high lipoprotein levels and small apolipoprotein size. (Wright and Hutchison 2009) The presence of these risk factors in dialysis patients clearly enhances the incidence and severity of CVD and associated mortality. Therefore, the strategy to lower CVD

incidence and mortality should be a combined effort targeting potential risk factors including traditional (i.e., diabetes mellitus, hypertension, and hyperlipidemia) and dialysis-specific factors (i.e., phosphorous level and parathyroid level). (Cheigh and Kim 1999)

Understanding the literature on risk factors of CVD and current recommended guidelines to prevent CVD for ESRD are crucial. Although studies have shown the beneficial effects of several medication classes in decreasing CVD morbidity and mortality in the general population, information is limited for dialysis patients. In an effort to improve clinical outcomes among patients with ESRD, the National Kidney Foundation (NKF) launched the Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines in 1995. The KDOQI guidelines cover many aspects of care for hemodialysis patients including dialysis, anemia, diabetes mellitus (National Kidney Foundation 2007), cardiovascular disease (National Kidney Foundation 2005), dyslipidemia (National Kidney Foundation 2003), and bone and mineral metabolism. (Kidney Disease: Improving Global Outcomes (KDIGO) 2009)

1.2.2.3 Diabetes Mellitus and ESRD

Diabetes mellitus and CKD are potent independent risk factors for cardiovascular events and progression to ESRD. (Go, Chertow et al. 2004) Patients with both conditions are, therefore, at exceedingly high risk of CVD. Diabetic nephropathy is the most common

cause of ESRD in North America, accounting for approximately 44.6 percent of patients undergoing incident dialysis. (US Renal Data System 2011) Diabetes deteriorates kidney function through microvascular complications caused by chronic hyperglycemia.

The NKF and the American Heart Association (AHA) have recently issued guidelines and scientific statements recommending that people with both CKD and diabetes be considered in the highest risk category for CVD. Having CKD with diabetes mellitus is far worse than for either condition alone because the combination is one the most powerful predictors of major adverse cardiovascular events and death. (National Kidney Foundation 2007) Indeed, while current NKF KDOQI guidelines suggest a target HbA1c level of seven percent for all diabetic patients with or without chronic kidney disease, very little evidence supports this recommendation. Patients with chronic kidney disease and ESRD have not been included routinely in most studies, and the relation between markers of glycemic control and mortality is poorly defined in this population. (Shurraw, Majumdar et al. 2010)

There have been very few published studies that have examined the association between HbA1c and clinical outcomes in dialysis patients. A population-based cohort study was conducted in Canada to determine whether HbA1c levels were independently associated with important clinical outcomes, such as all-cause mortality, cardiovascular events, hospitalizations, and kidney failure, in patients with diabetes mellitus and stage 3 to 4

CKD. (Shurraw, Hemmelgarn et al. 2011) This study found that regardless of baseline GFR, a higher HbA1c level was strongly and independently associated with excess risk of all outcomes (P<.001 for all comparison). However, the association with mortality was U-shaped, which had increases in the risk of mortality apparent at HbA1c levels lower than 6.5 percent and higher than 8.0 percent. (Shurraw, Hemmelgarn et al. 2011)

Two retrospective cohort studies in patients undergoing hemodialysis reported little or no association between HbA1c level and all-cause mortality. (Shurraw, Majumdar et al. 2010; Williams, Lacson et al. 2010) Shurraw's population-based retrospective cohort study of all maintenance hemodialysis patients in the Northern Alberta Renal Program (Alberta, Canada) found that high HbA1c levels were not associated with mortality. (Shurraw, Majumdar et al. 2010) Another retrospective analysis used a time-dependent Cox model for patients treated in a large dialysis center, the Fresenius Medical Care-North America facilities, and reported that HbA1c categories <6.5% and >11% were associated with increased mortality risk. (Williams, Lacson et al. 2010)

These findings contrast with the largest observational study, which found that higher levels of HbA1c were incrementally associated with higher death risk in 23,618 patients undergoing hemodialysis in Davita outpatient clinics. (Kalantar-Zadeh, Kopple et al. 2007) Unadjusted survival analyses indicated paradoxically lower morality risk with higher HbA1c as previous studies reported. However, after controlling for potential

confounders including demographics, dialysis vintage, dose, comorbidity, anemia, malnutrition and inflammation compared with HbA1c in the 5-6% range, the adjusted all-cause and cardiovascular mortality risks for HbA1c ≥ 10% were 41 and 73 percent greater, respectively ($P<0.05$). (Kalantar-Zadeh, Kopple et al. 2007)

1.2.2.3.1 Treatment of Diabetes Mellitus in Dialysis Patients

In patients with ESRD, second-generation sulfonylureas, (such as glipizide) are recommended because metabolites are not active and there is less potential for the development of hypoglycemia compared to first-generation medications. (National Kidney Foundation 2007) Insulin and thiazolidinediones are suitable for patients with ESRD. Metformin is contraindicated in male patients with serum creatinine > 1.5mg/dL and in female patients with serum creatinine >1.4 mg/dL because it is cleared by the kidney and may build up with even modest impairment of kidney function, putting patients at risk of lactic acidosis (Table 1.2). (National Kidney Foundation 2007)

Table 1.2 Dosing Adjustments for Drugs Used to Treat Hyperglycemia in ESRD Patients

Class	Drug	Dosing recommendation for dialysis patients
First-generation sulfonylureas	Acetohexamide, Chlorpropamide, Tolazamide, Tolbutamide	Avoid
Second-generation sulfonylureas	Glipizide	Preferred sulfonylurea No dose adjustment necessary
	Gliclazide	Preferred sulfonylurea No dose adjustment necessary Not available in US
	Glyburide, Glimepiride	Avoid
Alpha-glucosidase inhibitors	Acarbose	Avoid
	Miglib	Avoid
Biguanides	Metformin	Avoid
Meglitinides	Repaglinide	No dose adjustment necessary
	Nateglinide	Avoid
Thiazolidinediones	Pioglitazone	No dose adjustment necessary
	Rosiglitazone	No dose adjustment necessary
Incretin minetic	Exenatide	No dose adjustment necessary
Amylin analog	Praminide	No data available
DPP-4 inhibitor	Sitagliptin	Reduce dose by 75% (25mg/day)

Source: The National Kidney Foundation KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease

1.2.2.4 Hypertension and ESRD

Hypertension is very prevalent among dialysis patients (50-60%) when hypertension is defined as blood pressure > 150/90 mm Hg for hemodialysis patients and contributes to increased cardiovascular morbidity in patients. (National Kidney Foundation 2005) While blood pressure control may improve cardiovascular outcomes in hemodialysis patients, the management of blood pressure in this population is challenging. Nonpharmacologic interventions to improve blood pressure include educating patients about limiting sodium intake, ensuring adequate sodium removal during hemodialysis, and achieving target dry weight. (Inrig 2010) However, most patients require antihypertensive medications to achieve an appropriate blood pressure.

It has long been believed that hypertension is a major cause of morbidity and mortality in dialysis patients, as is the case in the general population. (Charra, Calemard et al. 1996; Foley, Parfrey et al. 1996) Foley et al. conducted a prospective study with a cohort of 432 dialysis patients followed for an average of 41 months. After adjusting for age, diabetes, heart disease, and hemoglobin levels, each 10mmHg rise in mean arterial blood pressure was independently associated with the development of cardiac failure and ischemic heart disease. (Foley, Parfrey et al. 1996)

Several observational studies, however, have not shown a consistent association between blood pressure and mortality. Many of them have shown a U-shaped relationship with both low and high blood pressure being associated with an increased relative risk of death. (Zager, Nikolic et al. 1998; Foley, Herzog et al. 2002; Stidley, Hunt et al. 2006; Myers, Adams et al. 2010) Zagar et al. reported a U-shaped relationship to the pre-dialysis systolic blood pressure with the lowest mortality observed in the group being associated with blood pressure between 160 and 179 mmHg. (Zager, Nikolic et al. 1998). These observations were subsequently supported by other investigators. The USRDS Dialysis Morbidity and Mortality Waves 3 and 4 Study, a randomized generated sample of 11,142 subjects receiving hemodialysis was examined. (Foley, Herzog et al. 2002) In a comorbidity-adjusted model, low pre-dialysis diastolic, low post-dialysis diastolic, and high post-dialysis systolic blood pressure value were associated with higher mortality. Nonetheless, antihypertensive therapy, especially using beta-blockers, was statistically significantly associated with longer survival. (Foley, Herzog et al. 2002)

Recent studies explored further the relationship between blood pressure and mortality using stratification by time, age, race, and diabetes status. (Stidley, Hunt et al. 2006; Myers, Adams et al. 2010) Stidley et al. conducted a retrospective study to determine the relationship between blood pressure and mortality in 16,959 dialysis patients. (Stidley, Hunt et al. 2006) The results demonstrated that the relationship between baseline blood pressure and mortality changed over time; low systolic blood pressure

(<120 mmHg) was associated with increased mortality in year 1-2. (Stidley, Hunt et al. 2006) High systolic blood pressure (≥150 mmHg) was associated with increased mortality among patients who survived ≥3 years. (Stidley, Hunt et al. 2006) In addition, Myers et al. reported that low systolic blood pressure was associated with increased mortality, and the association was more pronounced among older patients and those with diabetes. However, higher systolic blood pressure was associated with increased mortality among younger patients, regardless of race or diabetes status. (Myers, Adams et al. 2010)

1.2.2.4.1 Treatment of Hypertension in Dialysis Patients

Blood pressure is usually raised in patients receiving dialysis, possibly because the role of the kidneys in blood pressure homoeostasis is impaired; chronic volume overload and a range of other factors might also contribute to high blood pressure. (Heerspink, Ninomiya et al. 2009)

The NKF KDOQI has recently recommend pre-dialysis (<140/90 mmHg) and post-dialysis (<130/80 mmHg) blood pressure goals. (National Kidney Foundation 2005) The supporting evidence was graded as weak because it was extrapolated from the general population. The KDOQI Clinical practice guidelines for CVD in dialysis patients recommends drugs that inhibit the renin-angiotensin system, such as angiotensin-converting-enzyme (ACE) inhibitors or angiotensin II-receptor blockers. These are

preferred because they cause greater regression of left ventricular hypertrophy, reduce sympathetic nerve activity, reduce pulse wave velocity, may improve endothelial function, and may reduce oxidative stress. (National Kidney Foundation 2005)

There was an important worldwide hemodialysis study, representing approximately 70 percent of the world's hemodialysis patient population, coordinated by the Arbor Research Collaborative for Health. (Health 2012) The Dialysis Outcomes and Practice Patterns Study (DOPPS) was an international, prospective, observational study of practice patterns and associated outcomes involving maintenance hemodialysis facilities and patients. (Pisoni, Gillespie et al. 2004) The DOPPS comprise three phases (DOPPS I-III). In DOPPS I (1996-2001), 17,034 patients were sampled from 308 dialysis facilities in France, Germany, Italy, Spain, the United Kingdom, Japan and the U.S. In DOPPS II (2002-2004), 12,839 patients were sampled from 322 facilities in 12 countries (the original 7 countries, with Australia, Belgium, Canada, New Zealand, and Sweden). In DOPPS III (2005-2007), more than 9,000 patients were sampled from 12 countries. Nationally representative samples of dialysis facilities were recruited in each country. Within each participating facility, study patients were randomly selected.

The efficacy and safety of lowering blood pressure in dialysis patients are unknown as showned previously, however, but the benefits of antihypertensive agents have been

reported. (Lopes, Bragg-Gresham et al. 2009) Data from DOPPS I and DOPPS II were used to assess which classes of antihypertensive agents were associated with a lower risk of all-cause and cardiovascular-related mortalities. Despite large variations across countries in antihypertensive agents used for hemodialysis patients, significant associations with a reduction in cardiovascular mortality rates were observed for angiotensin receptor blockers and beta blockers. (Lopes, Bragg-Gresham et al. 2009)

Furthermore, two recent meta-analyses of randomized controlled trials revealed control of blood pressure in hemodialysis patients contributes to regression of left ventricular hypertrophy and improved cardiovascular morbidity and mortality rates. (Agarwal and Sinha 2009; Heerspink, Ninomiya et al. 2009) Agarwal et al. found that patients on antihypertensive therapy compared with the control group had a 38 percent reduced risk for cardiovascular events ($p<0.05$). In the eight evaluated studies by Heerspink et al., antihypertensive therapy was associated with a 29 percent lower relative risk of cardiovascular events ($p<0.05$), a 20 percent lower relative risk of all-cause mortality ($p<0.05$), and a 29 percent lower relative risk of cardiovascular mortality ($p<0.05$), even though the absolute reductions in blood pressure were small. (Heerspink, Ninomiya et al. 2009)

1.2.2.5 Hyperlipidemia and ESRD

Dyslipidemia is common in people with diabetes and CKD. Hypercholesterolemia has been established as one of the primary risk factors associated with CVD outcomes in the general population. However, the association between quantitative lipid abnormalities and outcomes in ESRD are inconsistent and counterintuitive. (Foley and Parfrey 1998)

Surprisingly, higher cholesterol levels have been associated with lower mortality in dialysis patients (Lowrie and Lew 1990), which stands in marked contrast to prospective studies and clinical trial findings in the general population. Lowrie et al. revealed that overall mortality in 12,000 ESRD patients increased exponentially when the serum total cholesterol decreased from a range of 200-250 to less than 100mg/dL. (Lowrie and Lew 1990) This prospective study in dialysis patients also found that hypocholesterolemia was an independent predictor of death in dialysis patients. A recent study has replicated this reverse epidemiology for lipid variables. Data revealed that lower levels of low-density lipoprotein (LDL) and total cholesterol were predictors of an increased mortality rate. (Bowden, La Bounty et al. 2011)

It has been suggested, but remains unproven, that this paradoxical U-shaped relationship between mortality and total cholesterol in ESRD may be explained partly by reverse causation, in which advanced CVD leads to inflammation and/or malnutrition and lower cholesterol levels, or a confounding effect of inflammation and/or lower cholesterol

levels and higher mortality rates. (Coresh, Longenecker et al. 1998; National Kidney Foundation 2003; Liu, Coresh et al. 2004) A prospective study revealed that there was a strong and positive association of serum cholesterol levels with overall and CVD mortality in the absence of inflammation/malnutrition, whereas an inverse association of cholesterol levels with all-cause mortality and a U-shaped relationship with CVD mortality in presence of inflammation/malnutrition was found. (Liu, Coresh et al. 2004) Other studies have suggested these same findings in dialysis patients who had inflammation and were malnourished. (Nurmohamed and Nube 2005; Diepeveen, Wetzels et al. 2008)

1.2.2.5.1 Treatment of Dyslipidemia in ESRD

Although the published data have yet to confirm the target of treatment for dyslipidemia in dialysis patients, the NKF KDOQI clinical practice guidelines for managing dyslipidemia were published in 2003. (National Kidney Foundation 2003)

> *4.1. For adults with stage 5 CKD and fasting triglycerides ≥ 500mg/dL (≥ 5.65mmol/L) that cannot be corrected by removing an underlying cause, treatment with therapeutic lifestyle changes and a triglyceride-lowering agent should be considered.*
>
> *4.2 For adults with stage 5 CKD and LDL ≥ 100mg/dL (≥ 2.59mmol/L), treatment should be considered to reduce LDL to <100mg/dL (< 2.59mmol/L).*
>
> *4.3 For adults with stage 5 CKD and LDL <100mg/dL (<2.59mmol/L), fasting triglycerides ≥ 200 mg/dL (≥ 2.26mmol/L), and non-high-density lipoprotein (HDL) cholesterol (total cholesterol minus HDL) ≥ 130 mg/dL (≥ 3.36mmol/L), treatment should be considered to reduce non-HDL cholesterol to < 130 md/dL (<3.36 mmol/L).*

Results from several randomized controlled trials (RCTs) in hemodialysis patients did not indicate significant improvements in reduction in CVD with the use of statins. (Wanner, Krane et al. 2005; Holdaas, Holme et al. 2011) The 4D trial (Die Detsche Diabetes Dialysis Studie) had a total of 1,200 type II diabetics undergoing hemodialysis who were randomized to atorvastatin 20mg/day or placebo for four years. This study found that atorvastatin had a non-significant eight percent relative risk reduction in cardiovascular events. (Wanner, Krane et al. 2005) Another randomized controlled trial, the AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: an Assessment of Survival and Cardiovascular Events), compared rosuvastatin 10mg/day with placebo in 2,700 hemodialysis patients. (Holdaas, Holme et al. 2011) Assignment to rosuvastatin was associated with a non-significant 16.2 percent reduction in risk for CVD and mortality with mean follow-up of 3.2 years. (Holdaas, Holme et al. 2011)

In contrast, a recent randomized clinical trial demonstrated favorable results of using statins on occurrence of a first major vascular event in patients with CKD. The SHARP (Study of Heart and Renal Protection) trial included 9,270 patients, who were randomly assigned to simvastatin 20mg plus ezetimibe 10mg versus matching placebo. (Baigent, Landray et al. 2011) During five years, allocation to simvastatin plus ezetimibe reduced LDL cholesterol by an average of 0.85 mmol/L, yielding a reduction of 17 percent in major atherosclerotic events but no benefit on survival. (Baigent, Landray et al. 2011)

There were observational studies suggesting a benefit from treating dyslipidemia in patients on hemodialysis. In the USRDS Dialysis Morbidity and Mortality Study, 3,700 patients on hemodialysis were followed for two years. Statin users had a 32 percent relative risk reduction in total mortality, whereas fibrate users had no reduction in cardiovascular or total mortality. (Seliger, Weiss et al. 2002) In the Dialysis Outcomes Practice Patterns Study (DOPPS), 9,800 hemodialysis patients were followed for five years, and statin users had a 31 percent relative risk reduction in total mortality compared with nonusers. (Andreucci, Fissell et al. 2004)

1.2.2.6 Mineral and Bone Disorder (MBD) and ESRD

Recently, the Kidney Disease Improving Global Outcomes (KDIGO) published clinical practice guidelines on the management of chronic kidney disease-mineral and bone disorder (CKD-MBD). (Kidney Disease: Improving Global Outcomes (KDIGO) 2009) CKD-MBD was defined as the broader clinical syndrome encompassing mineral, bone, and calcific cardiovascular abnormalities that develop as a complication of CKD. (Moe SM 2009) Disturbed mineral and bone metabolism is common in CKD patients, especially abnormalities in serum calcium, phosphorous, and parathyroid hormone levels. It is an important cause of morbidity and decreased health-related quality of life in CKD patients. (Moe, Drueke et al. 2006) Importantly, these disorders in mineral and bone metabolism have been associated with increased cardiovascular calcification, morbidity,

and mortality (Covic, Kothawala et al. 2009) and result in a high burden of economic costs. (Komaba, Moriwaki et al. 2009)

Specifically, high phosphorous levels have been associated with a greater risk for all-cause and cardiovascular mortality, as well as hospitalizations due to both cardiovascular events and fractures. (Block, Hulbert-Shearon et al. 1998; Block, Klassen et al. 2004; Kestenbaum, Sampson et al. 2005; Tentori, Blayney et al. 2008) Consequently, phosphate control has become an important therapeutic target in CKD, primarily to reduce the risk of vascular calcification and cardiovascular mortality. (Hutchison 2009)

In addition to high phosphorous levels, secondary hyperparathyroidism (sHPT) is common in patients with ESRD, affecting most of those who are receiving hemodialysis. This disorder is characterized by persistently elevated levels of parathyroid hormone and complicated by important disturbances in mineral metabolism. (Block, Martin et al. 2004) Bone disease is the most widely recognized consequence of sHPT. Several reports indicated, however, that alterations in calcium and phosphorus metabolism, partially as a result of sHPT contribute to soft-tissue and vascular calcification, cardiovascular disease, and risk of death. (Block and Port 2000)

1.2.2.6.1 Hyperphosphatemia

Treatment guidelines issued by the NKF KDOQI recommend that serum phosphorous levels should be maintained between 3.5 and 5.5 mg/dl for patients with ESRD. (Eknoyan 2003)

About 90 percent of dialysis patients continue to require oral phosphate binders (Mohammed and Hutchison 2008) due to limited effectiveness of dietary phosphate restriction (Uribarri 2007) and insufficiency of hemodialysis to maintain phosphate levels within recommended targets. (Hutchison 2009) The most commonly used phosphate binders are calcium salts. Calcium-based binders (calcium carbonate and calcium acetate) have been the standard of care in phosphate-binding therapy for almost 20 years and are relatively inexpensive. (Sprague 2007) However, calcium salts have been associated with an increased risk of hypercalcemia and vascular calcification, especially with long-term or high-dose use. (Chertow, Raggi et al. 2004) In addition, the KDOQI panel recommends that the daily calcium intake from phosphate binders should not exceed 1,500mg, which could limit the use of calcium-based binders. (Eknoyan 2003) Thus, there is significant interest in the optimal use of non-calcium binders to achieve and maintain KDOQI targets. (Barton Pai, Conner et al. 2009) Lanthanum carbonate, sevelamer hydrochloride, and sevelamer carbonate are non-calcium, non-aluminum binders available in the U.S. (Mohammed and Hutchison 2008)

Isakova noted longer survival for hemodialysis patients prescribed versus not prescribed phosphate binders even for patients with serum phosphorous levels within the recommended range (3.5-5.5 mg/dL). (Isakova, Gutierrez et al. 2009) Further evidence of association between prescribed phosphate binders and mortality was provided by the DOPPS, a prospective cohort study of 23,898 maintenance hemodialysis patients at 923 facilities in 12 countries. (Lopes A.A. 2012) This study found that patients prescribed phosphate binders had a 25 percent lower mortality rate (hazard ratio, 0.75; 95% CI, 0.68-0.83) when adjusted for serum phosphorus level and other covariates; further adjustment for nutritional indicators attenuated this association (hazard ratio, 0.88; 95% CI, 0.80-0.97). The improved patient survival in facilities with a higher percentage of patients prescribed phosphate binders was explained in part by the better nutritional status and more liberal dietary intake with phosphate binders. (Isakova, Gutierrez et al. 2009)

1.2.2.6.2 Secondary Hyperparathyroidism

Treatment guidelines issued by the NKF KDOQI recommend that patients be treated to achieve parathyroid hormone levels between 150 and 300 pg/ml. (Eknoyan 2003) Cinacalcet (Senipar®) is a first-in-class calciminetic used with other therapies such as phosphate binders and vitamin D sterols, for sHPT in patients on dialysis. Calciminetic acts directly on calcium-sensing receptors expressed in parathyroid glands, and reduces parathyroid hormone secretion by rendering parathyroid cells more sensitive to inhibitory actions of extracellular calcium. (Goodman, Hladik et al. 2002) Since cinacalcet

became commercially available in 2004, there were few studies that examined health outcomes associated with use of cinacalcet.

In a combined analysis of four randomized, double-blind, placebo-controlled clinical trials, Cunningham et al. found that randomization to cinacalcet led to significant reductions in the risk of parathyroidectomy, fracture, and cardiovascular hospitalization. (Cunningham, Danese et al. 2005)

Recently, an observational study examined the impact of cinacalcet treatment on all-cause and cardiovascular-related survival in hemodialysis patients. (Block, Zaun et al. 2010) This study found that the adjusted all-cause mortality rate for patients with cinacalcet prescriptions was 26 percent lower than for non-cinacalcet patients (hazard ratio, 0.74; 95% CI, 0.68-0.78). (Block, Zaun et al. 2010) In addition, the adjusted cardiovascular mortality rate was 24 percent lower in patients with cinacalcet compared to control patients (hazard ratio, 0.76; 95% CI, 0.66-0.86).

1.2.3 Prescription Medications, Pill Burden, and Adherence in ESRD Patients

Chronic dialysis patients face many health problems including chronic inflammatory state, malnutrition, increase risk for cardiovascular morbidity and mortality, phosphate retention, secondary hyperparathyroidism, diabetes and dyslipidemia as a result of incomplete replacement of kidney function. (Katzir, Boaz et al. 2010) Most patients therefore require polypharmacy which often includes phosphate binders, vitamin D or calcimimetic preparations, statin agents, erythropoietin, and iron supplements as well as medications for comorbidities.

Estimates of medication use among ESRD patients range from 10 to 14 medications per day in the U.S. (Manley, Bailie et al. 2000; Manley, Garvin et al. 2004) Manley et al. noted that patients were prescribed, on average, 12.3 ± 5.0 (median 12) different medications (2.6 ± 1.4 clinic medications and 10.0±4.5 home medications) in ambulatory hemodialysis patients within the Dialysis Clinic database. (Manley, Garvin et al. 2004) Upon further examination of home medications, researchers found that cardiac medications (any agent used for hypertension, congestive heart failure, coronary artery disease, arrhythmia, or hyperlipidemia), gastrointestinal medications, and phosphate binding agents accounted for 55 percent of medication expenditures. (Manley and Cannella 2005) Diabetes mellitus patients were prescribed more medications than non-diabetes mellitus patients (11.1±4.6 versus 9.6±4.8; $p<0.001$). Medication costs for

hemodialysis patients were estimated to be $16,000 per patient per year. (Manley and Cannella 2005)

Much of the more recent empirical literature on prescription drug adherence in dialysis has focused on phosphate binders and cinacalcet. (Chiu, Teitelbaum et al. 2009; Lee, Song et al. 2011) Recently, Chiu et al. assessed total pill burden, adherence to phosphate binders, and serum phosphorous levels in 253 prevalent chronic dialysis patients. (Chiu, Teitelbaum et al. 2009) The results showed that the median daily pill burden was 19; in addition, 25 percent of patients took more than 25 pills per day. Phosphate binders accounted for 50 percent of the daily pill burden; and only 38 percent of the patients were adherent to their phosphate binder therapy (≥ 80% pill consumption). (Chiu, Teitelbaum et al. 2009) Although there was no significant relationship between adherence and serum phosphorus levels, a significant inverse relationship between adherence to phosphate binders and pill burden from phosphate binders was observed ($p<0.05$). (Chiu, Teitelbaum et al. 2009)

Lee et al. conducted a retrospective cohort study of dialysis patients with an initial cinacalcet prescription to assess the relationship between cinacalcet adherence and healthcare costs. (Lee, Song et al. 2011) Medication possession ratio (MPR) was used to measure adherence. Patients were dichotomized as adherent (<180 days refill gap) or non-adherent (≥180 day refill gap). Researchers found that 30 percent of patients discontinued cinacalcet by the 6th month, and 46 percent by the 12th month post-index

date, respectively. (Lee, Song et al. 2011) Adherent patients at 12 months were further dichotomized as low adherent (<0.8 MPR) and high adherent (≥0.8 MPR). During 12 months, 27 percent were low adherent (i.e., without a 180-day gap but < 0.8 MPR), and 28 percent were high adherent (i.e., without a 180-day gap and ≥ 0.8 MPR). High cinacalcet adherence was associated with significantly lower inpatient costs with cost-savings of greater magnitude ($8,899) than the increased medication costs ($5,858). In another study of the assessment of adherence to cinacalcet in dialysis patients in a Missouri state-funded pharmacy program, Gincherman et al. found similar adherence rates, where 29 percent patients were highly adherent (≥ 0.8 MPR). (Gincherman, Moloney et al. 2010)

A recent systematic literature review of the Medline and Pubmed database (1971-2008) was conducted to quantify non-adherence in hemodialysis patients to certain oral medications and to raise awareness of factors that may cause problems in a patient's adherence to this treatment. (Schmid, Hartmann et al. 2009) A total of 19 studies were identified as reporting total rates of non-adherence to oral medication among adult hemodialysis patients: (1) 18/19 studies for phosphate binders, (2) 11/19 studies for antihypertensive drugs, and (3) 8/19 studies for oral calcium supplementation. Self-reports or structured interviews (patients self-reports, 16/19 studies) were the most frequently used tools to assess adherence rates.

Two studies by Curtin et al. used medication event monitoring devices (MEMS) to monitor adherence to antihypertensives and phosphate binders. (Curtin, Svarstad et al. 1997; Curtin, Svarstad et al. 1999). The first study found that almost 30 percent of older patients (> 65) and more than 32 percent of younger patients (≤ 65) missed their antihypertensives completely on 20 percent or more of the prescribed days. In addition, 18 percent of the older patients, but 33 percent of younger patients, missed their phosphate binders on 20 percent or more of prescribed days. (Curtin, Svarstad et al. 1997) Another study described the prevalence, severity, and patterns of non-compliance with prescribed medications among hemodialysis patients. (Curtin, Svarstad et al. 1999) The results demonstrated that 52 percent of patients monitored for antihypertensive use were repeatedly noncompliant according to the MEMS, whereas 42 percent were noncompliant based on the pill count over a six-weeks monitored period. For phosphate binders, 70 percent of patients were estimated to be repeatedly noncompliant both by MEMS measurement and pill count.

1.2.4 Summary of Section

The prevalence of ESRD is continuously increasing in the U.S. However, morbidity and mortality of maintenance of dialysis patients remain high and only about one-third of the US hemodialysis patients are alive after five years. CVD is the leading cause of mortality in ESRD. Notably, patients with ESRD have a very high prevalence of CVD risk factors such as diabetes, hyperlipidemia and hypertension, but they are also exposed

to other non-traditional, uremia-related cardiovascular disease factors (i.e., calcium and phosphate metabolism). Most dialysis patients therefore require many medications and have a high pill burden. Unfortunately, poor adherence with prescribed medication is a widely recognized problem in dialysis patients due to the complexity of the regimen and lifelong duration of therapy.

Most dialysis patients are eligible for Medicare benefits. The next chapter will review the Medicare Part D prescription drug benefit in ESRD patients. In addition, the next chapter will discuss the impact of cost-sharing policies on health outcomes, and the impact of Part D on health outcomes in general populations and dialysis patients.

1.3 Section 2: Medicare Part D

1.3.1 Medicare Overview

Established in 1965 under Title XVIII of the Social Security Act, Medicare was initially established to provide health insurance to individuals age 65 and older, regardless of income or medical history. (The Henry J. Kaiser Family Foundation 2010) The program was expanded in 1972 to include individuals under age 65 with permanent disabilities and people suffering from ESRD. In 2001, Medicare eligibility expanded further to cover people with amyotrophic lateral sclerosis (ALS, or Lou Gehring's disease). Individuals age 65 and over qualify for Medicare if they are U.S. citizens or permanent legal residents. (The Henry J. Kaiser Family Foundation 2010) Individuals qualify without regard to their medical history or preexisting conditions, and do not need to meet an income or asset test. Adults under age 65 with permanent disabilities are eligible for Medicare after receiving Social Security Disability Income (SSDI) payments for 24 months, even if they have not made payroll tax contributions for 40 quarters. (The Henry J. Kaiser Family Foundation 2010) People with ESRD or Lou Gehrig's disease are eligible for Medicare benefits as soon as they begin receiving SSDI payments, without having to wait 24 months. (The Henry J. Kaiser Family Foundation 2010)

In 2010, approximately 47 million Americans had Medicare coverage, including 39 million people aged 65 and older and another eight million younger adults with permanent disabilities. (The Henry J. Kaiser Family Foundation 2010) Medicare

spending was estimated to be $519 billion in 2010, nearly 25 percent of all spending on health in the U.S. (The Henry J. Kaiser Family Foundation 2010)

Medicare consists of four parts, each covering different benefits: Part A, Part B, Part C, and Part D. (The Henry J. Kaiser Family Foundation 2011)

Part A is known as the Hospital Insurance program which covers inpatient hospital services, skilled nursing facilities, home health, and hospice care. Individuals who are entitled to Part A do not pay premiums for covered services. Individuals aged 65 and over who are not entitled to Part A, such as those who did not pay enough Medicare taxes during their working years, can pay a monthly premium to receive Part A benefits. (The Henry J. Kaiser Family Foundation 2010) Part A benefits are subject to a deductible ($1,156 in 2012) and coinsurance. (Klees 2009) In 2011, Part A accounted for approximately 31 percent of Medicare benefit spending.

Part B is the Supplementary Medical Insurance program, and helps pay for physician, outpatient, home health, and preventive services. Part B is voluntary, but about 95 percent of beneficiaries with Part A are also enrolled in Part B. (The Henry J. Kaiser Family Foundation 2010) For most individuals who become entitled to Part A, enrollment in Part B is automatic unless the individual declines enrollment. Individuals who do not sign up for Part B when they are first eligible typically pay a penalty for late enrollment, in addition to the regular monthly premium ($110.50 in 2010) with the

exception of individuals if they receive employment-based coverage. (The Henry J. Kaiser Family Foundation 2010) Part B benefits are subject to an annual deductible ($155 in 2010), and 20 percent coinsurance generally applies for most Part B benefits. (Klees 2009) Part B accounted for 18 percent of benefit spending in 2011.

Medicare Parts A and B constitute the original fee-for-service Medicare program. Medicare Part C is an alternative to traditional Medicare. While all Medicare beneficiaries can receive their benefits through the traditional fee-for-service program, most beneficiaries enrolled in both Part A and Part B can choose to participate in a Part C program instead. (Klees 2009)

Part C refers to the Medicare Advantage program, which allows beneficiaries to enroll in a private plan, such as a health maintenance organization (HMO), preferred provider organization (PPO), or private fee-for-service (PFFS) plan. Beneficiaries may generally elect to enroll in a Medicare Advantage plan on an annual basis between October 15 and December 7 of each year during the annual election period. Nearly 12 million beneficiaries were enrolled in a Medicare Advantage Plan in 2011 (25% of all beneficiaries). (The Henry J. Kaiser Family Foundation 2011) Medicare Advantage accounted for 21 percent of benefit spending in 2011.

Part D is the voluntary, subsidized outpatient prescription drug benefit, with additional subsidies for beneficiaries with low incomes and modest assets. The Part D benefit is offered through private plans - either stand-alone prescription drug plans (PDPs) or Medicare Advantage prescription drug plans (MAPDs) - that contract with Medicare. (The Henry J. Kaiser Family Foundation 2009) Plans are required to provide a standard benefit or one that is actuarially equivalent, and may offer more generous benefits. Part D enrollees pay a monthly premium, along with cost-sharing amounts for each prescription. Part D is funded by general revenues, beneficiary premiums, and state payments, and it accounted for 12 percent of benefit spending in 2011. (The Henry J. Kaiser Family Foundation 2011) More than 29 million beneficiaries were enrolled in a Medicare Part D plan in 2011. (The Henry J. Kaiser Family Foundation 2011)

1.3.2 Medicare Part D

In 2006, the U.S. government expanded its Medicare health insurance program to offer a prescription drug insurance benefit, Medicare Part D, to improve affordability of essential medications for the beneficiaries. (Centers for Medicare and Medicaid Services 2005) Medicare beneficiaries have access to an outpatient prescription drug benefit (Part D) offered through private health plans: either stand-alone PDPs or MAPDs, as described above. In 2010, 1,576 PDPs were available nationwide, up from 1,429 in 2006.

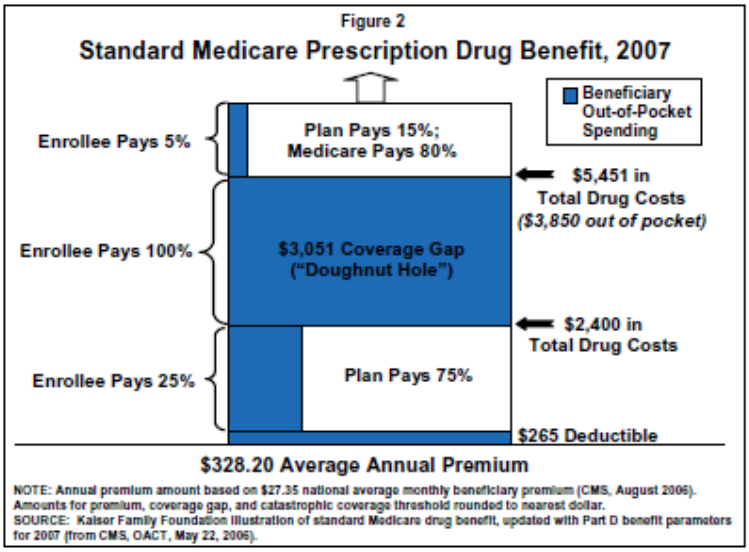
Beneficiaries in most states could choose from at least 45 stand-alone PDPs and multiple MAPDs. (The Henry J. Kaiser Family Foundation 2010)

To obtain Part D benefits, beneficiaries must enroll in a PDP or MAPD. The annual election period for Part D benefits runs from November 15 to December 31 of each year, until 2011, when the election period was changed to October 15 to December 7. Individuals who delay enrollment in Part D and are without creditable drug coverage, at least comparable to the Part D standard benefit, pay a permanent premium penalty for late enrollment. (The Henry J. Kaiser Family Foundation 2010) In 2010, the national average monthly Part D premium including PDPs and MAPDs was $31.94. Monthly Part D premiums and cost-sharing amounts are not uniform nationwide, but vary across plans and regions, ranging from a low of $8.80 in Oregon and Washington to a high of $120.20 in Delaware, Maryland, and Washington, D.C. (Foundation 2010)

Part D coverage includes most FDA-approved prescription drugs and biological products. However, plans may set up formularies for their prescription drug coverage, subject to certain statutory standards. Medicare excludes some drugs for anorexia, weight loss, weight gain, infertility, cosmetic purposes (e.g., hair growth), cold and cough medicines, nonprescription or over-the-counter products, barbiturates, benzodiazepines, and vitamins and minerals, except for active vitamin D analog. (Levinson 2006)

The Part D program differs significantly from the traditional Medicare program in that it relies on numerous private companies that offer plans with varying cost sharing structures and provisions to provide benefits. (Howell, Powers et al. 2012) The standard Part D benefit design includes a novel cost containment feature, the "coverage gap." (Neuman, Strollo et al. 2007) In 2007, patients with total Part D drug costs up to $2,400 fell into the initial coverage phase, while those with costs over that amount entered the coverage gap (also called the "donut hole"), in which they were responsible for 100 percent of drug costs. (US Renal Data System 2011) At the end of the gap, patients whose out-of-pocket costs reached $3,850 ($265 deductible + $600 out-of-pocket (25% of $2400) + $2985) then entered the catastrophic coverage phase, in which they paid only a fraction of overall drug costs (Figure 1.4). (US Renal Data System 2011) The Part D coverage gap involves substantial periods of uncovered drug use and may increase out-of-pocket spending for beneficiaries because they pay the full price of drugs filled during these periods. (Fung, Mangione et al. 2010)

Figure 1.4 Standard Medicare Prescription Drug Benefit, 2007



Source: The Henry J. Kaiser Family Foundation Medicare Fact Sheet

The Part D program offers a low-income subsidy (LIS) benefit to enrollees with limited assets ($12,510/individual; $25,010/couple in 2010) and income at or below 150 percent of the federal poverty level ($16,245 for an individual; $21,855 for a couple in 2010), including those who are dually-enrolled. (The Henry J. Kaiser Family Foundation 2011) The LIS provides full or partial waivers for many out-of-pocket cost sharing requirements, including premiums, deductibles, and copayments, and provides full or partial coverage during the coverage gap. (The Henry J. Kaiser Family Foundation 2011; US Renal Data System 2011) The Centers for Medicare & Medicaid (CMS) estimates

that 12.5 million beneficiaries were potentially eligible for the LIS as of February 2009. (Centers for Medicare & Medicaid Service 2012)

Among Part D enrollees who filled one or more prescriptions but did not receive the LIS in 2007, 26 percent had spending high enough to reach the coverage gap. (Hoadley J 2008) Fifteen percent of these Part D enrollees who reached the coverage gap ultimately had spending high enough to reach catastrophic coverage. (Hoadley J 2008) Applying this estimate to the entire population of Part D enrollees, the analysis suggested that about 3.4 million beneficiaries (14 percent of all Part D enrollees) reached the coverage gap and faced the full cost of their prescriptions. (The Henry J. Kaiser Family Foundation 2010)

1.3.3 Prescription Drug Cost Sharing

Prescription drug expenditures are one of the fastest growing components of national health expenditures. Over the past decade, the cost of prescription drugs has been rising at about 10 percent per year. (Smith, Cowan et al. 2005; Goldman 2009) In an attempt to control prescription drug costs, health plans and employers have increased prescription drug cost sharing amounts for patients. Cost sharing represents the price of the prescription drug to the insured patient, while insurance covers the remainder of the cost. (Gibson, Ozminkowski et al. 2005) The typical features are copayments, coinsurance,

deductibles, and upper limits on coverage. (Phelps 2010) An increase in the level of cost sharing specified in insurance policies may be implemented by raising copayments, adding a flat fee assessed per prescription (e.g., $10), or increasing the coinsurance ratio - a fixed fraction of each dollar of cost (e.g., 20%). (Phelps 2010)

Insurers call the change in behavior that occurs when a person becomes insured "moral hazard." Moral hazard occurs when an insured person makes extra purchases that he or she would not otherwise have purchased. (Nyman 2004) In theory, increasing the share of costs paid by patients creates an incentive for more efficient use of care. (Phelps 2010) Cost sharing can be advantageous when physician and patients collaborate on appropriate, cost-effective drug therapy decisions. (Hsu, Price et al. 2006) Conversely, the burden of cost sharing can create barriers to care, especially for patients requiring long-term drug therapy. (Piette, Heisler et al. 2006; Goldman, Joyce et al. 2004) It is widely accepted, based on considerable evidence accumulated over decades of study, that higher cost sharing will lead to reduced healthcare expenditures. (Chernew and Newhouse 2008) However, the impact of cost sharing on health status has been much more controversial.

1.3.3.1 The RAND Health Insurance Experiment

To date, the most comprehensive, 'gold standard' study to examine the impact of cost sharing on health utilization and outcomes has been the RAND Health Insurance

Experiment (HIE). (Brook, Ware et al. 1983; Manning, Newhouse et al. 1987) The RAND HIE was a randomized, controlled trial conducted by the federal government in the 1970s in which almost 6,000 enrollees were randomized to various insurance plans. (Phelps 2010)

The insurance plans differed by coinsurance rate and maximum out-of-pocket costs. The coinsurance rates were 0, 25, 50, or 95 percent. Each plan had maximum annual out-of-pocket expenses of 5, 10, 15 percent of family income, up to a maximum of $1,000. (Manning, Newhouse et al. 1987) Beyond the maximum out-of-pocket expenses, the insurance plan reimbursed all covered expenses in full. (Manning, Newhouse et al. 1987)

The RAND HIE revealed several important findings, one of which was that coinsurance rates influenced medical utilization and expenditures. (Manning, Newhouse et al. 1987) Coinsurance rates were inversely associated with the probability of receiving any medical care. The probability of receiving medical care in the free care cohort was significantly greater compared with the 95 percent coinsurance cohort (86.8% vs 67.7%; $p<0.001$). (Manning, Newhouse et al. 1987) Another analysis of the RAND data found that the cost sharing cohorts were nearly one-third less likely to see a physician when they had minor symptoms (e.g., cough, sneezing, allergies, or stomach flu) than the free care cohort (6.3% vs 9%; $p<0.04$). (Shapiro, Ware et al. 1986) The cost sharing cohorts and the free care cohort did not differ significantly in seeking care for serious symptoms (e.g.,

chest pain, bleeding, loss of consciousness, or shortness of breath) (17.9% vs 22.3%; p=0.095). (Shapiro, Ware et al. 1986) In addition, negative relationships were found between the coinsurance rate and total medical costs, although there was no difference in inpatient costs. Mean total cost for the free care cohort was significantly higher ($749) than the cost for the 95 percent insurance cohort ($518) ($p<0.001$).

Overall, an important finding was that although increased cost sharing was associated with decreased health care expenses, decreased health expenditures were not found to be associated with negative health consequences. (RAND Health 2006; Saverno K.R. 2011) Although the cost sharing cohorts used fewer services, their health outcomes did not differ from the free care cohort. Availability of the free care plan did not affect self-assessed health status, smoking habits, weight, or cholesterol. (Brook, Ware et al. 1983; Keeler, Sloss et al. 1987)

However, there were exceptions to this overall finding; especially among people who were less healthy and of lower socioeconomic status at the start of the experiment. They had better outcomes under the free care plan for four of the 30 conditions measured (e.g., hypertension, vision, dental care, and serious symptoms). (RAND Health 2006) For example, the free care cohort had greater reductions in blood pressure and better functional far vision than cost sharing cohorts. (Keeler, Sloss et al. 1987) In addition, for individuals with low socioeconomic status who began the study in poor health, the

prevalence of serious symptoms was higher in the cost sharing cohorts than the free care cohort (29.1% vs 23.8%; $p<0.004$). (Shapiro, Ware et al. 1986)

Upon further examination, among people under the age of 65 who were at risk for adverse health outcomes (a group defined as the least healthy 25 percent of those studied with respect to self-reported physiologic measures and health related habits), the free care cohort had a reduction in the estimated risk of death by 10 percent, as compared with the cost sharing cohorts. (Brook, Ware et al. 1983) Much of the more recent empirical literature on the impact of cost sharing on prescription utilization has come from observational research.

1.3.3.2 Observational Studies: Prescription Cost Sharing

Unlike RAND HIE where cost sharing changes occurred across nearly all health services, the post-RAND HIE literature on cost sharing has focused on prescription drug cost sharing. (Goldman, Joyce et al. 2004; Goldman, Joyce et al. 2007)

A retrospective study from 1997 to 2000 found that doubling co-payments was associated with a reduction in use by 25 to 45 percent across eight common drug classes. (Goldman, Joyce et al. 2004) The largest decreases occurred for nonsteroidal anti-inflammatory drugs (NSAIDs) (45%) and antihistamines (44%). Reductions in overall days supplied

of antihyperlipidemics (34%), antiulcerants (33%), antiasthmatics (32%), antihypertensives (26%), antidepressants (26%), and antidiabetics (25%) were also observed. (Goldman, Joyce et al. 2004)

Goodman et al. reviewed and summarized the 1985-2006 prescription drug cost sharing literature. (Goldman, Joyce et al. 2007) Researchers found that increased cost sharing was associated with lower rates of drug treatment, lower rates of adherence, and more frequent discontinuation of therapy. (Goldman, Joyce et al. 2007) On average, a 10 percent increase in drug cost sharing resulted in prescription drug spending decreases of two percent to six percent, depending on class of drug and condition of the patient. (Goldman, Joyce et al. 2007)

Out-of-pocket costs borne by patients usually are a major salient determinant of therapeutic adherence and, therefore, of the effectiveness of prescribed medications. (Hirth, Greer et al. 2008) Even small increases in these costs can lead to potentially important reductions in medication adherence, which, in turn, can have serious consequences for patients' health. (Goldman, Joyce et al. 2004)

Several studies have documented that higher out-of-pocket medication costs, lower patient incomes, and less generous prescription benefits are each associated with lower

rates of prescription drug use. (Federman, Adams et al. 2001; Goldman, Joyce et al. 2004; Piette, Heisler et al. 2004; Safran, Neuman et al. 2005) Safran et al. documented variations in prescription use and out-of-pocket spending by drug coverage, poverty, and disease burden. They examined cost-related nonadherence from 2003 national survey data in noninstitutionalized Medicare beneficiaries. (Safran, Neuman et al. 2005) The researchers found that three attributes including: no coverage, low income, and high disease burden, were significantly associated with higher cost-related non-adherence ($p<0.001$). (Safran, Neuman et al. 2005) Seniors without coverage reported significantly more cost-related non-adherence than those with coverage ($p<0.001$). More than 20 percent of seniors with congestive heart failure, diabetes, or multiple chronic conditions who lacked coverage reported that they did not fill at least one of their chronic disease medications in the past year because of costs. (Safran, Neuman et al. 2005)

A national survey examining the cost-related underuse of medications among chronically ill adults found that 18 percent of respondents cut back on medication use due to cost in the previous year. Although rates of underuse varied substantially across treatments, prescription coverage and out-of-pocket costs were determinants of underuse across medication types. (Piette, Heisler et al. 2004)

Federman et al. conducted a cross-sectional retrospective study using 1997 Medicare Current Beneficiary Survey (MCBS), a nationally representative survey of randomly sampled Medicare beneficiaries conducted by CMS. (Federman, Adams et al. 2001) The findings indicated that statin use ranged from four percent in Medicare patients without drug coverage to 27 percent in patients with employer-sponsored drug coverage ($P<0.001$). Another cross-sectional study reported that seniors in high-risk groups with no coverage had three to 15 times higher odds of medication restriction than others with partial or full coverage ($p<0.001$). (Steinman, Sands et al. 2001)

The negative unintended consequences of drug cost sharing - including increased emergency department visits and nursing home admission, as well as decreased health status - have been observed. (Soumerai, Ross-Degnan et al. 1991; Tamblyn, Laprise et al. 2001) A time-series analysis of New Hampshire Medicaid's implementation of a three prescription per month cap compared the rate of admission to nursing homes and hospitals for elderly patients in New Hampshire with a comparison cohort in a state without the cap (New Jersey). (Soumerai, Ross-Degnan et al. 1991) In New Hampshire, the 35 percent decline in the use of study drugs after the cap was applied was associated with an increase in rates of admission to nursing homes, whereas no changes were observed in the comparison cohort. (Soumerai, Ross-Degnan et al. 1991) When the cap was discontinued after 11 months, the use of medications returned nearly to baseline levels, and the excess risk of admission to nursing home vanished. (Soumerai, Ross-Degnan et al. 1991) Tamblyn et al. also demonstrated that increased cost sharing for

prescription drugs in elderly persons was followed by reductions in use of essential drugs and a higher rate of serious adverse events (i.e., the first occurrence of acute care hospitalization, long-term care admission, or death) or emergency department visits in Canada. (Tamblyn, Laprise et al. 2001)

1.3.4 Impact of Medicare Part D coverage on Health Outcomes: Evidence to Date

As mentioned earlier, a unique feature of the Medicare Part D drug benefit is the coverage gap, or so-called "doughnut hole," where Part D enrollees are required to pay 100 percent of total drug costs after their spending exceeds the initial coverage limit and before reaching the catastrophic coverage limit. (The Henry J. Kaiser Family Foundation 2010)

To date, researchers have observed reduced drug utilization among beneficiaries enrolled in Medicare Part D who reach the coverage gap spending threshold and have no financial assistance to pay for drugs. (Pedan, Lu et al. 2009; Schneeweiss, Patrick et al. 2009; Zhang, Donohue et al. 2009)

Zhang et al. examined how MAPD beneficiaries with hypertension and diabetes respond to the increase in out-of-pocket drug spending after reaching the doughnut hole. (Zhang, Donohue et al. 2009) Results indicated a 14 percent reduction in monthly prescriptions among beneficiaries who entered the coverage gap. A study of senior Medicare

beneficiaries found that patients reaching the coverage gap experienced a 10 percent decrease in obtaining essential medications. (Pedan, Lu et al. 2009) Nair et al. revealed that among patients with congestive heart failure, diabetes, dyslipidemia, or hypertension, 27 percent of patients reached the coverage gap in 2006, of which four percent passed through the gap (to catastrophic coverage). (Nair, Frech-Tamas et al. 2011) Patients < 65 years were more likely to reach the gap sooner as compared to older beneficiaries and those without diabetes. Beneficiaries took an average of 8.1 months to reach the gap and faced a 60 percent increase in out-of-pocket expenditures in the gap phase. (Nair, Frech-Tamas et al. 2011)

In a survey of Kaiser Permanente-Northern California patients in 2006, approximately 36 percent of Medicare Part D beneficiaries reported at least one of their responses to drug costs: cost-coping behavior (26%), reduced adherence (15%), or experiencing financial burden (7%). (Hsu, Fung et al. 2008) Beneficiaries with lower household income (< $ 40,000/year) more frequently reported cost responses. (Hsu, Fung et al. 2008) Further evidence of predictors of the increased risk of using cost-lowering strategies when beneficiaries reached the coverage gap was provided by an evaluation of Kaiser Permanente Colorado patients. (Cronk, Humphries et al. 2008) Results indicated that Medicare beneficiaries with a drug benefit threshold were three times more likely to adopt cost-lowering strategies (i.e., using less of a medication, discontinuing a

medication, or not filling a prescription) than beneficiaries who did not have a drug benefit threshold when entering the coverage gap.

Several other studies have demonstrated decreases in medication adherence and unintended health outcomes in Medicare Part D beneficiaries who entered the coverage gap phase. (Hsu, Price et al. 2006; Raebel, Delate et al. 2008; Fung, Mangione et al. 2010; Hales and George 2010; Polinski, Shrank et al. 2011) An analysis of stand-alone PDP beneficiaries - who were randomly selected, and who utilized at least one cardiovascular medication - reported that 17 percent delayed medication, 12 percent switched medication, 10 percent both delayed and stopped medication, and 10 percent stopped at least one medication within the coverage gap. (Hales and George 2010) In addition, Polinski et al. employed propensity-score matching to control for covariates in Medicare beneficiaries in 2006 and/or 2007. (Polinski, Shrank et al. 2011) After matching, coverage gap-exposed beneficiaries were twice as likely to discontinue but less likely to switch a drug after reaching their coverage gap (all $P<0.05$). (Polinski, Shrank et al. 2011) They were slightly more likely to have reduced adherence, defined as the proportion of days covered (PDC) $\geq 80\%$. More specifically, Fung et al. focused on the impact of the coverage gap among MAPD beneficiaries with diabetes. (Fung, Mangione et al. 2010) Researchers noted that out-of-pocket expenditures were 189 percent higher and adherence to three chronic medications - including oral diabetes, hypertension, and

lipid drugs - was significantly lower among beneficiaries with a coverage gap versus no gap. (Fung, Mangione et al. 2010)

Kaiser Permanente Colorado expanded upon previous adherence studies by investigating medical service utilization for Part D beneficiaries who reached the coverage gap. (Raebel, Delate et al. 2008) This analysis revealed that beneficiaries who reached the coverage gap were older, had greater comorbidity, received more medications, and had more medical visits than beneficiaries who did not reach the gap. (Raebel, Delate et al. 2008) After adjustment, those who reached the coverage gap had an 85 percent and a 60 percent greater incidence of inpatient and emergency department use, respectively, compared to the group with no threshold ($p<0.05$). Adherence to chronic medications declined over time in both groups, but the decline was greater for beneficiaries who reach the coverage gap.

A prospective cohort study examining medical service utilization, mortality rates and medical costs in 2003 was conducted by Kaiser Permanente-Northern California. Although the study was conducted before Part D was implemented, this study compared the clinical and economic outcomes between Medicare+Choice (now Medicare Advantage) beneficiaries whose annual drug benefits were capped at $1,000 and beneficiaries whose drug benefits were unlimited. (Hsu, Price et al. 2006) Hue et al. found that individuals whose benefits were capped had a 13 percent, nine percent, and 22

percent greater incidence of inpatient use, emergency department use, and death, respectively ($p<0.05$). (Hsu, Price et al. 2006) Those whose benefits were capped were 30 percent, 27 percent, and 33 percent more likely to be non-adherent to long-term drug therapy for hypertension, hyperlipidemia, and diabetes, respectively. (Hsu, Price et al. 2006) Furthermore, this study revealed that the physiological outcomes (e.g., blood pressure, cholesterol, and glycated hemoglobin level) were significantly worse for individuals whose benefits were capped than those whose benefits were not capped ($p<0.05$). (Hsu, Price et al. 2006) Authors highlighted the cap on drug benefits ($1,000) was associated with lower drug consumption and unfavorable clinical outcomes.

1.3.5 Medicare Part D in ESRD Patients

1.3.5.1 Medicare in ESRD Patients

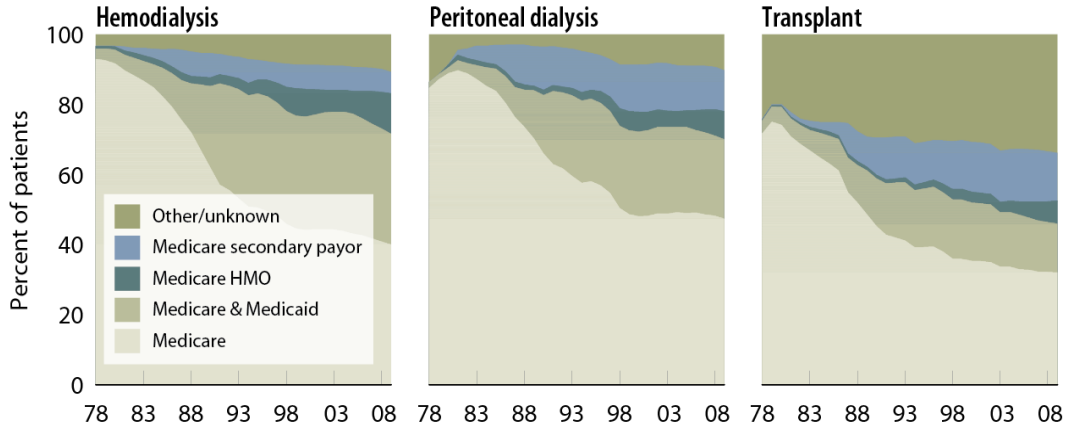
Since 1972, ESRD patients (dialysis and transplant) have been entitled to Medicare coverage through amendments to the Social Security Act. There are some unique features of Medicare for ESRD patients. Most dialysis and transplant patients are enrolled in the original fee-for-service Medicare (Part A and Part B). Under current Medicare legislation, new dialysis patients cannot enroll in a Medicare Advantage plan (Part C). (St Peter 2008) The only exception to this ban is that dialysis patients can enroll in a Medicare Advantage Special Needs Plan approved by CMS that accepts ESRD patients. (Centers for Medicare & Medicaid Service 2012) Patients who were already enrolled in a Medical Advantage plan when diagnosed with CKD can remain in their

plan. New kidney transplant patients can enroll in Medicare Advantage plans as long as they do not need dialysis and meet Medicare eligibility criteria. (St Peter 2007)

Regardless of age or disability, most patients are eligible for Medicare benefits beginning in the fourth month after diagnosis. (St Peter 2007) The exception is patients who undergo home (peritoneal) dialysis; patients who begin training for peritoneal dialysis can enroll in Medicare in the first month after ESRD diagnosis. (St Peter 2007) If individuals are eligible for Medicare only due to permanent kidney failure, their eligibility does not start until the fourth month of dialysis. When individuals have employer group health plans, that plan is the only payer for the first three months of dialysis. (Centers for Medicare & Medicaid Service 2012) Once individuals become eligible for Medicare at the fourth month of dialysis, there is another period of time, called a coordination period, when employer group health plans continue to pay health care bills. (Centers for Medicare & Medicaid Service 2012) However, the plans do not pay 100 percent of bills, as Medicare pays some of the remaining costs under Medicare 'secondary payer' rules. At the end of the 30-month coordination period, Medicare pays first for all Medicare-covered services. Employer group health plans can pay for services not covered by Medicare. (Centers for Medicare & Medicaid Service 2012)

The economic burden of ESRD on dialysis is substantial. The recent USRDS estimated that healthcare payers spend approximately $23 billion to treat ESRD annually. (US Renal Data System 2011) Dialysis patients, less than one percent of all Medicare beneficiaries, consumed 6.4 percent of the US Medicare budget in 2006. (US Renal Data System 2011) Nine in ten prevalent hemodialysis patients had some type of Medicare coverage in 2009, with 40 percent covered solely by Medicare, 32 percent under Medicare/Medicaid, 12 percent by Medicare HMO, six percent under Medicare as a secondary payer (Figure 1.5).

Figure 1.5 Incident Patient Distribution, by First Modality & Payer



Source: The United States Renal Data System (USRDS) 2011 Annual Report

1.3.5.2 Prescription Drug Coverage in ESRD Patients: Medicare Part D

Before 2006, Medicare enrolled patients accessed prescription drugs via other insurance plans with drug coverage, state Medicaid programs, pharmaceutical-assistance programs,

samples from physician, or out-of-pocket payment. Now, however, any patient enrolled in either Medicare Part A or Part B can enroll in a Part D plan. (St Peter 2007) Patients with both Medicare and Medicaid (dually eligible), who before 2006 received prescription benefits under state Medicaid programs, now obtain Part D covered drugs under Medicare Part D. (St Peter 2008)

In most cases, dialysis patients are allowed to join a stand-alone PDP, but not a MAPD. Exceptions can be made when patients enroll in a Medicare Advantage Special Needs Plan approved by CMS. In addition, patients who are already enrolled in an MAPD when diagnosed with CKD can remain in their plan. (St Peter 2008)

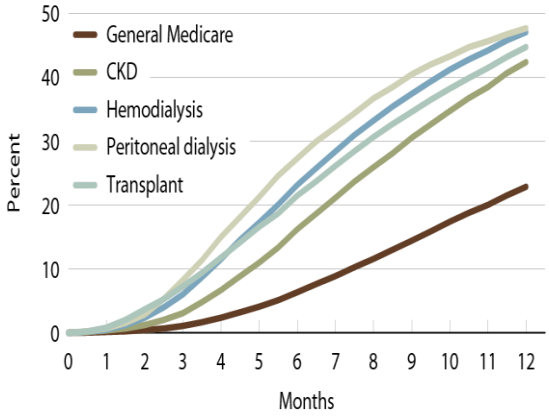
Dialysis patients dually-enrolled in Medicaid and Medicare qualify for low income subsidy (LIS), and, if they do not choose a plan, are automatically enrolled in a Medicare Part D plan. Sixty-five percent of hemodialysis patients with Part D coverage are dually-eligible LIS beneficiaries. (US Renal Data System 2011)

Medicare Part D covers most medications taken by ESRD patients at home, while Medicare Part B covers those administered during dialysis (e.g., erythropoiesis stimulating agents, IV vitamin D) as well as immunosuppressive medications for patients with Medicare-covered transplants. (US Renal Data System 2011) The USRDS estimated the per person per year (PPPY) total cost of medications covered by Medicare Part D to be $5,536 for dialysis patients and $6,183 for transplant patients; which is 2.3-2.5 times higher, respectively, than in the general Medicare population. (US Renal Data

System 2011) In 2008, Medicare Part D costs for ESRD patients reached $1.54 billion, while Medicare Part B costs were $1.87 billion. (US Renal Data System 2011) Total net Part D payment for patients with identified kidney disease (hemodialysis, peritoneal dialysis, and transplant patients, and CKD patients on dialysis) was $5 billion in 2008, which accounted for 10 percent of total Part D prescription drug costs. (US Renal Data System 2011)

In 2008, 42-48 percent of hemodialysis, peritoneal dialysis, and transplant patients reached the coverage gap, and 8-13 percent reached catastrophic coverage, compared to 23 percent and three percent, respectively, in the general Medicare program (Figure 1.6). (US Renal Data System 2011)

Figure 1.6 Cumulative Percent of Part D Non-LIS Enrollees who Reach the Coverage Gap, 2008



Source: The United States Renal Data System (USRDS) 2011 Annual Report

Not surprisingly, among those who reached the gap but did not reach catastrophic coverage, the number of prescription fills declined once the gap was reached (Table 1.3).

For example, hemodialysis patients who reached the coverage gap, but not catastrophic coverage, had 4.74 prescription fills per month during the initial coverage period but reduced their prescription fills to 4.42 during the coverage gap period. The authors attributed this to a reduction in medication adherence or to a decision to obtain medications outside the Part D plan. Interestingly, the reduction in prescription fills was not seen in patients who reached catastrophic coverage.

Table 1.3 Part-D Covered Prescription Fills per Person per Month in Part D Non-LIS Enrollees, by Modality, 2008

6 bii Part D-covered prescription fills per person per month in Part D non-LIS enrollees, by modality, 2008

	Hemodialysis	Peritoneal dialysis	Transplant
Patients who do not reach the coverage gap	2.41	2.58	2.55
Patients who reach coverage gap, but not catastrophic coverage			
During initial coverage period	4.74	4.63	5.43
During coverage gap	4.42	4.28	5.14
Patients who reach catastrophic coverage			
During initial coverage period	6.31	6.12	7.10
During coverage gap	6.70	6.39	7.48
During catastrophic coverage	7.44	7.46	8.03

Source: *The United States Renal Data System (USRDS) 2011 Annual Report*

1.3.5.3 Impact of Medicare Part D on Patients with ESRD: Evidence to Date

Patients with ESRD may benefit significantly from the Part D drug benefit, given their need for greater numbers of prescription drugs. (Patel and Davis 2006) This population, however, appears to be at a higher risk of falling into the coverage gap than other Medicare beneficiaries with Part D. Despite a rich body of literature on the negative

association between prescription drug cost sharing and medical/drug utilization and health outcomes in general populations, there is a paucity of empirical data focusing on these relationship among dialysis patients.

To date, several published studies, mainly survey data, reported higher cost-related non-adherence and higher out-of-pocket costs in patients with ESRD compared to patients without ESRD. (Hirth, Greer et al. 2008; Frankenfield, Howell et al. 2011; Smith, Witten et al. 2011) Hirth et al. examined out-of-pocket spending and cost-related non-adherence using samples of hemodialysis patients from 12 countries. (Hirth, Greer et al. 2008) Data were gathered from 2002 to 2004 as part of the Dialysis Outcomes and Practice Patterns Study (DOPPS), an observational study of hemodialysis practices and outcomes in 12 countries. Patient questionnaires were administered to a prevalent cross-section of patients (N=7,766). The proportion of patients reporting that they sometimes did not purchase medications because of cost varied widely across countries, ranging from three percent in Japan to 29 percent in the United States. However, the correlation between cost pressures and underuse was not consistent, which indicated that country-specific factors, other than health policies that determine out-of-pocket burdens, need to be considered. (Hirth, Greer et al. 2008)

Smith et al. conducted a study to investigate barriers with Medicare Part D medication access and changes in medication-taking behaviors observed while in the coverage gap among dialysis patients. (Smith, Witten et al. 2011) The survey was administered to

183 nephrology social workers in a variety of settings (e.g., dialysis organization, hospital-based dialysis units, and independent dialysis units). Results indicated that the most common problems seen for dialysis patients with their Medicare Part D plans were issues related to the coverage gap (donut hole). Fifty-five percent of respondents reported that over 80 percent of their patients experienced difficulties with the coverage gap. The most common patient behaviors included decreasing dosing frequency, spending less money on other basic needs, using other sources for their prescriptions, and using store discounts on generic medications once reaching the coverage gap. (Smith, Witten et al. 2011) Reflecting on the results of this survey, researchers noted that dialysis patients exhibited harmful medication-taking behavior during their coverage gap which led to a reduced use of medication, which may result in health care complications and increased use of medical services. (Smith, Witten et al. 2011)

Another recent survey assessed self-reported cost-related non-adherence (defined as delaying or not filling a prescription due to cost concerns) among Medicare Part D beneficiaries with ESRD. (Frankenfield, Howell et al. 2011) The 2007 Medicare Consumer Assessment of Health Provider and Systems (CAHPS) survey was administered by the CMS. Frankenfield et al. found that ESRD patients were significantly more likely than those without ESRD to report cost-related non-adherence. (Frankenfield, Howell et al. 2011) After controlling for potential confounding factors (e.g., age, gender, and chronic conditions), ESRD patients remained 23 percent more

likely than respondents without ESRD to report cost-related non-adherence. (Frankenfield, Howell et al. 2011)

A retrospective cohort study examining the potential impact of Medicare Part D on total and out-of-pocket expenditures also revealed substantial financial burden on ESRD beneficiaries compared with other Medicare beneficiaries. (Patel and Davis 2006) Patel et al. used the Medicare Current Beneficiary Survey (MCBS) Cost and Use data (1997-2001) to estimate the impact of the standard Part D benefit on drug expenditures. Total annual costs and out-of-pocket costs in 2006 were estimated to be more than two-fold higher for Medicare beneficiaries with ESRD compared with those without (total costs: $6,488 versus $2,705; out-of-pocket: $2,329 versus $1,311). (Patel and Davis 2006)

1.3.6 Summary of Section

Most dialysis patients are eligible for Medicare benefits; nine in 10 prevalent hemodialysis patients have some type of Medicare coverage. A unique feature of the Medicare Part D drug benefit is the coverage gap, where Part D enrollees are required to pay 100 percent of total drug costs. Several studies have demonstrated decreases in medication adherence and unintended health outcomes in Medicare Part D beneficiaries who entered the coverage gap phase in general populations. Beneficiaries with ESRD may be especially sensitive to coverage gap issues, given the large number of medications required to manage multiple comorbid conditions.

1.4 Section 3: Study Purpose, Objectives and Hypotheses

1.4.1 Statement of Problem

Patients with ESRD cope with a very complex and costly disease - often with multiple comorbidities: diabetes, hypertension, anemia, bone and mineral metabolism disorders, and cardiovascular disorders. (St Peter 2007) Notably, patients with ESRD have a very high prevalence of cardiovascular disease risk factors such as diabetes, hyperlipidemia, and hypertension, but they are also exposed to other non-traditional, uremia-related cardiovascular disease factors (e.g., calcium and phosphate metabolism). (Parfrey and Foley 1999; Covic, Kothawala et al. 2009) The management of ESRD requires adherence to dialysis treatments, dietary restrictions, and a drug regimen requiring patients to take multiple medications throughout the day. (Frankenfield, Howell et al. 2011) Estimates of medication use among ESRD patients range from 10 to 14 medications per day in the U.S. (Manley, Bailie et al. 2000; Manley, Garvin et al. 2004) A recent systematic literature review found that more than half of the included studies reported non-adherence rates of ≥ 50 percent in the ESRD population. (Schmid, Hartmann et al. 2009)

Most dialysis patients are eligible for Medicare benefits beginning in the fourth month after diagnosis. Nine in 10 prevalent hemodialysis patients had some type of Medicare coverage in 2009. Patients with ESRD may benefit significantly from the Part D drug

benefit, given their need for greater numbers of prescription drugs. (Patel and Davis 2006) This population, however, appears to be at a higher risk of falling into the coverage gap than other Medicare beneficiaries with Part D because of their need for chronic drug therapy and multiple drugs to treat comorbid conditions. (St Peter 2007) In 2008, 47 percent of dialysis patients reached the coverage gap, and 13 percent reached the catastrophic coverage phase, compared to 23 percent and three percent, respectively, in the general Medicare program. (US Renal Data System 2011) In 2007, patients with total Part D drug costs up to $2,400 fell into the initial coverage phase, while those with costs over that amount entered the coverage gap ("donut hole"), in which they were responsible for 100 percent of drug costs. (The Henry J. Kaiser Family Foundation 2010) The Part D coverage gap involves substantial periods of uncovered drug use and may increase out-of-pocket spending for beneficiaries because they pay the full price of medications filled during these periods.

Previous studies indicated that increasing out-of-pocket costs as patients entered the coverage gap resulted in adverse consequences. (Hsu, Price et al. 2006; Pedan, Lu et al. 2009; Zhang, Donohue et al. 2009; Nair, Frech-Tamas et al. 2011) Many studies have shown Medicare beneficiaries with a drug benefit threshold were significantly more likely to adopt cost-lowering strategies (e.g., using less of a medication, discontinuing a medication, or not filling a prescription) than beneficiaries who did not have a drug

benefit threshold when entering the coverage gap. (Cronk, Humphries et al. 2008; Pedan, Lu et al. 2009) Several studies have demonstrated the consequences of cost-related medication underuse, including increased emergency department visits, psychiatric admissions, and nursing home admissions, as well as decreased health status. (Soumerai, Ross-Degnan et al. 1991; Tamblyn, Laprise et al. 2001) Despite a rich body of literature on the association between Medicare Part D coverage and medical/drug utilization and health outcomes in general populations, (Hsu, Price et al. 2006; Raebel, Delate et al. 2008; Fung, Mangione et al. 2010; Hales and George 2010; Polinski, Shrank et al. 2011) there is a need for empirical data focusing on these relationships among dialysis patients. Information regarding how and to what extent this Part D coverage gap has affected prescription drug utilization and outcomes in dialysis patients is lacking. The impact of Part D coverage on health outcomes in dialysis patients warrants empirical evaluation.

1.4.2 Purpose of Study

This study aims to examine the consequences of Medicare Part D coverage in dialysis patients. The purpose of this study was to evaluate and compare A) medication adherence and costs, B) medical service utilization/costs, and C) mortality among Medicare beneficiaries with dialysis, categorized into four cohorts based on their Part D coverage.

The first objective was to compare characteristics among the four cohorts based on Part D coverage. Objective 2 was to examine medication-taking behaviors, defined in terms of medication adherence and persistence among Medicare beneficiaries with dialysis who received drug therapy for hypertension, hyperlipidemia, diabetes mellitus, hyperphosphatemia, and/or hyperparathyroidism. Objective 3 was to assess pharmacy utilization and costs. Objective 4 was to measure cardiovascular morbidity rates. Objective 5 was to assess the patterns of cardiovascular-related and all-cause medical service utilization and associated costs (e.g., hospitalization, outpatient, and skilled nursing home services). Objective 6 was to measure cardiovascular-related and all-cause mortality rates in Medicare beneficiaries with dialysis.

Specifically, the purpose was to compare the four cohorts of patients, categorized based on their Part D coverage in 2007:

1) cohort 1: patients who did not reach the coverage gap (out-of-pocket costs < $799; total drug costs < $2,400)
2) cohort 2: patients who reached the coverage gap but did not reach the point of receiving catastrophic coverage ($799 ≤ out-of-pocket costs < $3,850; $2,400 ≤ total drug costs <$5,451)
3) cohort 3: patients who reached catastrophic coverage ($3,850 ≤ out-of-pocket costs; $5451 ≤ total drug costs)

4) cohort 4: patients who did not reach the coverage gap and received the low-income subsidy - LIS (out-of-pocket costs < $799)

It is anticipated that findings from this study will add significant contributions to the empirical literature concerning the impact of Medicare Part D coverage on health outcomes in Medicare beneficiaries with dialysis. Below is a description of the study objectives and hypotheses.

1.4.3 Objectives and Hypotheses

1.4.3.1 Objective 1: Patient Characteristics

- To compare patient characteristics (age, gender, race, region of residence, primary disease causing ESRD, ESRD duration, and comorbidities) for Medicare beneficiaries with dialysis, by four Part D cohort categories.

$H_{0\ (1a)}$: Mean age will not differ significantly when categorized by Part D coverage.

$H_{0\ (1b)}$: The proportion of patients in each gender category will not differ significantly when categorized by Part D coverage.

$H_{0\ (1c)}$: The proportion of patients in each race category will not differ significantly when categorized by Part D coverage.

$H_{0\ (1d)}$: The proportion of patients in each region category will not differ significantly when categorized by Part D coverage.

$H_{0\ (1e)}$: The proportion of patients in each primary disease causing ESRD will not differ significantly when categorized by Part D coverage.

$H_{0\ (1f)}$: Mean ESRD duration will not differ significantly when categorized by Part D coverage.

$H_{0\ (1g)}$: Mean comorbidity score (Charlson Comorbidity Index (CCI) score) will not differ significantly when categorized by Part D coverage.

$H_{0\ (1h\text{-}1m)}$: The proportion of patients in the presence of cardiovascular disease [$H_{0(1h)}$], diabetes mellitus [$H_{0(1i)}$], hypertension [$H_{0(1j)}$], dyslipidemia [$H_{0(1k)}$], cancer [$H_{0(1l)}$], chronic lung disease [$H_{0(1m)}$]) will not differ significantly when categorized by Part D coverage.

1.4.3.2 Objective 2: Medication Utilization and Costs

- To determine whether the proportion and number of prescription medications and pharmacy costs (i.e., antihyperglycemics, antihypertensives, lipid-lowering drugs, phosphate binders, or cinacalcet) differ, by four Part D cohort categories.

$H_{0\ (2a\text{-}e)}$: The proportion of patients using antihyperglycemics [$H_{0(2a)}$], antihypertensives [$H_{0(2b)}$], lipid-lowering drugs [$H_{0(2c)}$], phosphate binders [$H_{0(2d)}$], or cinacalcet [$H_{0(2e)}$]) will not differ significantly when categorized by Part D coverage.

$H_{0\ (2f\text{-}j)}$: The mean number of antihyperglycemics [$H_{0(2f)}$], antihypertensives [$H_{0(2g)}$], lipid-lowering drugs [$H_{0(2h)}$], phosphate binders [$H_{0(2i)}$], or cinacalcet [$H_{0(2j)}$]) will not differ significantly when categorized by Part D coverage.

$H_{0\ (2k\text{-}p)}$: Mean pharmacy costs (i.e., antihyperglycemics [$H_{0(2k)}$], antihypertensives [$H_{0(2l)}$], lipid-lowering drugs [$H_{0(2m)}$], phosphate binders [$H_{0(2n)}$], cinacalcet [$H_{0(2o)}$] or all prescription $H_{0(2p)}$]) will not differ significantly when categorized by Part D coverage.

1.4.3.3 Objective 3: Medication Adherence and Persistence

- To determine whether medication adherence and persistence among patients receiving drug therapy for diabetes, hypertension, hyperlipidemia, hyperphosphatemia, or secondary parathyroid differ significantly, by four Part D cohort categories, while controlling for the following covariates: age, gender, race, region of residence, primary disease causing ESRD,

ESRD duration, CCI score, presence of chronic disease including diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease.

$H_{0\ (3a\text{-}e)}$: Medication adherence (i.e., antihyperglycemics [$H_{0(3a)}$], antihypertensives [$H_{0(3b)}$], lipid-lowering drugs [$H_{0(3c)}$], phosphate binders [$H_{0(3d)}$], or cinacalcet [$H_{0(3e)}$]) will not differ significantly when categorized by Part D coverage while controlling for covariates.

$H_{0\ (3f\text{-}j)}$: The proportion of patients who are adherent (MPR $\geq$ 80%) to antihyperglycemics [$H_{0(3f)}$], antihypertensives [$H_{0(3g)}$], lipid-lowering drugs [$H_{0(3h)}$], phosphate binders [$H_{0(3i)}$], or cinacalcet [$H_{0(3j)}$]) will not differ significantly when categorized by Part D coverage while controlling for covariates.

- To determine whether medication adherence differs before and after the coverage gap was exceeded among patients reaching the coverage gap, but not catastrophic coverage (**cohort 2**), while controlling for the following covariates: age, gender, race, region of residence, primary disease causing ESRD, ESRD duration, CCI score, presence of chronic disease including diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease and CVD.

$H_{0(3k-o)}$:Medication adherence with antihyperglycemics [$H_{0(3k)}$], antihypertensives [$H_{0(3l)}$], lipid-lowering drugs [$H_{0(3m)}$], phosphate binders [$H_{0(3n)}$], or cinacalcet [$H_{0(3o)}$]) will not differ significantly before and after reaching the gap while controlling for covariates.

$H_{0(3p-t)}$:The proportion of patients who are adherent (MPR ≥ 80%) to antihyperglycemics [$H_{0(3p)}$], antihypertensives [$H_{0(3q)}$], lipid-lowering drugs [$H_{0(3r)}$], phosphate binders [$H_{0(3s)}$], or cinacalcet [$H_{0(3t)}$]) will not differ significantly before and after reaching the gap while controlling for covariates.

$H_{0(3u-y)}$:Medication persistence with antihyperglycemics [$H_{0(3u)}$], antihypertensives [$H_{0(3v)}$], lipid-lowering drugs [$H_{0(3w)}$], phosphate binders [$H_{0(3x)}$], or cinacalcet [$H_{0(3y)}$]) will not differ significantly when categorized by Part D coverage while controlling for covariates.

$H_{0(3z-zd)}$: The proportion of patients who are persistent (until a 30-day gap) to antihyperglycemics [$H_{0(3z)}$], antihypertensives [$H_{0(3za)}$], lipid-lowering drugs [$H_{0(3zb)}$], phosphate binders [$H_{0(3zc)}$], or cinacalcet [$H_{0(3zd)}$]) will not differ significantly when categorized by Part D coverage while controlling for covariates.

1.4.3.4 Objective 4: Cardiovascular Disease Morbidity

- To determine whether cardiovascular morbidity rates among Medicare beneficiaries with dialysis differ, by the four Part D cohort categories while controlling for the following covariates: age, gender, race, region of residence, primary disease causing ESRD, ESRD duration, CCI score, presence of chronic disease including diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease.

$H_{0\ (4)}$: The incidence of cardiovascular disease will not differ significantly when categorized by Part D coverage, while controlling for covariates.

1.4.3.5 Objective 5: Cardiovascular-related and All-cause Medical Service Utilization/Costs

- To determine whether cardiovascular-related and all-cause medical service utilization (i.e., hospitalization, outpatient and other visits) and costs among Medicare beneficiaries with dialysis differ, by four Part D cohort categories, while controlling for the following covariates: age, gender, race, region of residence, primary disease causing ESRD, ESRD duration, CCI score, presence of chronic disease including diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease and CVD.

$H_{0\ (5a\text{-}c)}$: The proportion of patients who use any medical services including inpatient [$H_{0(5a)}$], outpatient [$H_{0(5b)}$], and other visits [$H_{0(5c)}$] will not differ significantly when categorized by Part D coverage, while controlling for covariates.

$H_{0\ (5d\text{-}f)}$: The mean number of medical service visits (i.e., inpatient [$H_{0(5d)}$], outpatient [$H_{0(5e)}$], and other visits [$H_{0(5f)}$]) will not differ significantly when categorized by Part D coverage, while controlling for covariates.

$H_{0\ (5g\text{-}i)}$: The proportion of patients who use medical services related to cardiovascular disease including inpatient [$H_{0(5g)}$], outpatient [$H_{0(5h)}$], and other visits [$H_{0(5i)}$], will not differ significantly when categorized by Part D coverage, while controlling for covariates.

$H_{0\ (5j\text{-}l)}$: The mean number of medical service visits (i.e., inpatient [$H_{0(5j)}$], outpatient [$H_{0(5k)}$], and other visits [$H_{0(5l)}$]) will not differ significantly when categorized by Part D coverage.

$H_{0\ (5m\text{-}t)}$: Mean all-cause medical care costs including inpatient [$H_{0(5m)}$], outpatient [$H_{0(5n)}$], physician/supplier [$H_{0(5o)}$], other visits [$H_{0(5p)}$], dialysis [$H_{0(5q)}$], total medical care costs [$H_{0(5r)}$], pharmacy costs [$H_{0(5s)}$], and all-cause total health care costs [$H_{0(5t)}$] will not differ significantly when categorized by Part D coverage, while controlling for covariates.

$H_{0\ (5u\text{-}y)}$: Mean cardiovascular disease-related medical care costs including inpatient [$H_{0(5u)}$], outpatient [$H_{0(5v)}$], and physician/supplier [$H_{0(5w)}$], and other visits [$H_{0(5x)}$], and total costs [$H_{0(5y)}$], will not differ significantly when categorized by Part D coverage, while controlling for covariates.

1.4.3.6 Objective 6: All-cause and Cardiovascular-related Mortality

- To determine whether cardiovascular-related and all-cause mortality rates among Medicare beneficiaries with dialysis differ, by four Part D cohort categories, while controlling for the following covariates: age, gender, race, region of residence, primary disease causing ESRD, ESRD duration, CCI score, presence of chronic disease including diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease, and CVD.

$H_{0\ (6a)}$: All-cause mortality rates will not differ when categorized by Part D coverage while controlling for covariates.

$H_{0\ (6b)}$: Cardiovascular-related mortality rates will not differ when categorized by Part D coverage while controlling for covariates.

Chapter 2: Methodology

2.1: Chapter Overview

This chapter provides a detailed description of the methodology used to evaluate the association between Part D coverage and various outcomes. The outcomes include medication-taking behaviors, patterns of cardiovascular-related and all-cause medical care utilization and associated costs, and cardiovascular-related and all-cause mortality rates in Medicare beneficiaries with dialysis. The data source and study design are described including study design structure, study population, inclusion, and exclusion criteria. Detailed descriptions of the study phases I-IV, study variables, and statistical analysis are also presented.

2.2: Data Source

The data for this analysis were provided by the United States Renal Data System (USRDS). The USRDS is a national data system that collects, analyzes, and distributes information about end-stage renal disease (ESRD) in the United States. The data for this study were obtained from the 2006-2010 USRDS.

The USRDS is funded directly by the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). (United States Renal Data System) The data used by the USRDS originate from the Centers for Medicare &

Medicaid Services (CMS), the United Network for Organ Sharing (UNOS), the ESRD Networks, and the USRDS special studies section. These data have been collected from all patients in the United States who have received Medicare-reimbursed maintenance renal replacement therapy since 1977. This database is estimated to include approximately 95 percent of the patients who receive renal replacement therapy in the United States. To be included in the database, patients must be receiving long-term dialysis therapy or have undergone renal transplantation. Patients are excluded if they received dialysis for acute renal failure only, died of renal failure before receiving dialysis or renal transplantation, or did not accept renal replacement therapy.

Data for input into the database that was utilized for this analysis was derived from the following sources that are summarized in the USRDS Researcher's Guide (2011). (US Renal Data System 2011) A quoted summary description of each from the guide follows:

PMMIS/REBUS/REMIS Database System

> The major source of ESRD patient information for the USRDS is the CMS Renal Beneficiary and Utilization System (REBUS), which was adopted in 1995 as the On-Line Transaction Processing system from its predecessor, the previous Program Management and Medical Information System (PMMIS) database. The PMMIS/REBUS database contains demographic, diagnosis, and treatment history information for all Medicare beneficiaries with ESRD. The database has been expanded to include non-Medicare patients.

CMS regularly updates the PMMIS/REBUS database, using the Medicare Enrollment Database (EDB), Medicare inpatient and outpatient claims, the UNOS transplant database, the ESRD Medical Evidence Report (form CMS-2728) provided by the ESRD Networks, the ESRD Death Notification (form CMS-2746) obtained from renal providers, and the ESRD Networks' Standard Information Management System database.

CMS Medical Evidence Report (Form CMS-2728)

The CMS Medical Evidence Report is completed by the renal provider for each new ESRD patient, and is sent to CMS through the ESRD Networks. It establishes Medicare eligibility for individuals who previously were not Medicare beneficiaries, reclassifies previously eligible Medicare beneficiaries as ESRD patients, and provides demographic and diagnostic information for all new ESRD patients regardless of Medicare entitlement. Since 1995, providers were required to file the Medical Evidence Report for all new ESRD patients regardless of Medicare eligibility status. The form includes comorbid conditions, employment status, expanded race categories, ethnicity, and biochemical data at ESRD onset.

The revision of the Medical Evidence Report was introduced in May 2005. It allows users to specify whether the Medicare registration is initial (new ESRD patient), re-entitlement (reinstating Medicare entitlement after a lapse due to no claims being filed for 12 or more months or a functioning graft for 36 or more months), or supplemental (updating missing or incorrect information). Data fields for nephrologist care, dietitian care, and access type were also added, with their respective time intervals relative to ESRD onset. Data on the laboratory values hematocrit, creatinine clearance, BUN, and urea clearance are no longer collected. Added laboratory values are HbA1c and lipid profiles (TC, LDL, and HDL cholesterol, and TG).

CMS ESRD Death Notification (Form CMS-2746)

Like the Medical Evidence Report, the Death Notification form is data rich, and CMS requires renal providers to complete it. Providers usually have 45 days to report ESRD death events to their respective ESRD Networks, including information about place, time, and cause of death.

CMS Medicare Enrollment Database (EDB)

The CMS Enrollment Database is the designated repository of all Medicare beneficiary enrollment and entitlement data, including current and historical information on beneficiary residence, Medicare as Secondary Payer (MSP) status, and Health Insurance Claim/ Beneficiary Identification Code cross-referencing.

CMS Paid Claims Records

Inpatient transplant and outpatient dialysis claims records are sometimes used to identify new ESRD patients for whom no Medical Evidence Report has been filed. These patients are most likely to be non-Medicare patients or beneficiaries already receiving Medicare because of age or disability. For patients without Medicare Evidence reports, these claims are the only reliable information from which to determine first ESRD service dates. Bills for some Medicare-eligible patients may not be submitted to or paid by Medicare. These patients are MSP patients covered by private insurance, HMOs, Medicaid, or the Department of Veterans Affairs.

CMS ESRD Standard Analytical Files (SAFs)

The CMS SAFs contain data from final action claims, submitted by Medicare beneficiaries, in which all adjustments have been resolved. For Part A institutional claims, the USRDS uses the following SAF claims:

- Inpatient
- Outpatient
- Skilled nursing facility
- Home health agency
- Hospice

For Part B physician/supplier SAF claims:

- Physician/supplier
- Durable medical equipment

CMS SAFs are updated each quarter through June of the next year, when the annual files are finalized. Datasets for the current year are created six months into the year and updated quarterly until finalized at 18 months, after which files

are frozen and will not include late arriving claims. Annual files are, thus, approximately 98 percent complete.

Medicare medical claims are of two types: (1) institutional claims primarily for Part A, and (2) physician/supplier claims for all of Medicare Part B. Some Part B claims, however, are institutional claims, notably those for outpatients. The institutional claims files contain data from final action claims submitted by Medicare beneficiaries

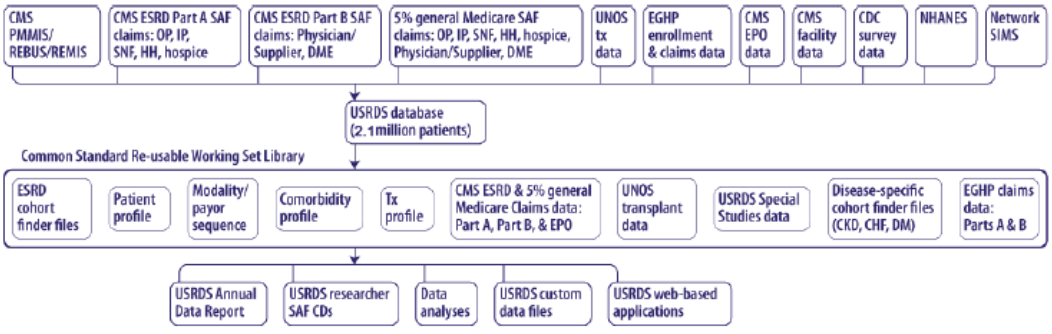
Medicare Prescription Drug Files

Effective January 1, 2006, Part D is an optional prescription drug benefit for individuals who are entitled to Medicare benefits under Part A or enrolled in Medicare benefits under Part B. Part D data are obtained from CMS annually with USRDS-provided Finder Files. Part D data are divided into two separate files: an annual enrollment file containing monthly indicators of enrollment in Part D, and a prescription drug event file (PDE) containing details of prescriptions filled by Part D beneficiaries.

Since the Part D benefit is voluntary, not all Medicare beneficiaries are enrolled in Part D. The annual enrollment file contains 12 monthly indicators that detail whether the beneficiary is enrolled in Part D, and if so, the type of plan. There are also monthly indicators for retiree drug subsidy and low income subsidy (LIS).

The structure of the USRDS data base is shown in Figure 2.1.

Figure 2.1 Structure of the USRDS Database



Reference: USRDS Researcher's Guide (2011)

Protection of Human Subjects

This study is a secondary data analysis of the USRDS database. Prior to obtaining any data from USRDS, approval from The University of Texas at Austin Institutional Review Board (IRB) was obtained.

2.3: Study Design

A cross-sectional retrospective design was employed for this study. This is a retrospective analysis using demographic data, Part D prescription claims, Part A & Part B medical claims, CMS medical evidence report, and mortality data for patients who were undergoing dialysis between January 1, 2006 and December 31, 2007. Outcomes were compared among the four cohorts: 1) patients who did not reach the coverage gap; 2) patients who reached the coverage gap but not catastrophic coverage; 3) patients who reached catastrophic coverage; and 4) patients who received LIS and do not reach the coverage gap.

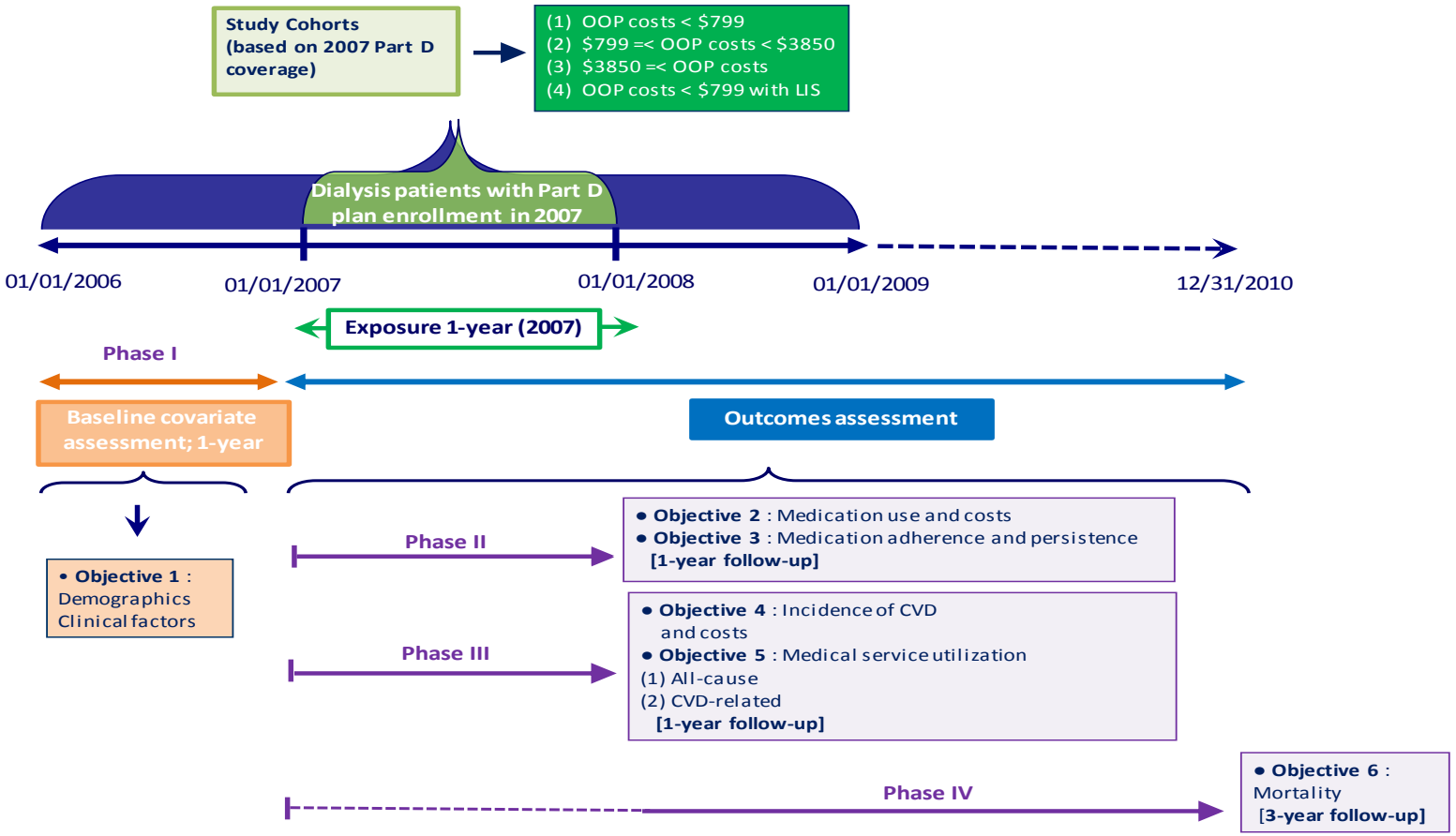
The study observation period consisted of a total of five years and the study outcomes were composed of four phases. The first period (phase I), January to December 2006, constituted the baseline covariate assessment period. In Phase I, the study sample was described with regard to demographic and clinical characteristics. January through December 2007 (phase II) is the one-year post-index Part D coverage exposure period.

In Phase II, medication utilization, costs, and medication adherence were measured for five therapeutic classes of outpatient prescription drugs including antihyperglycemic medications, antihypertensive medications, lipid-lowering medications, phosphate binders, and calcimimetic medications. The third period (phase III), January through December 2007, is a 1-year medical service follow-up period. In Phase III, the incidence of cardiovascular disease (CVD), medical resource utilization (i.e., inpatient and outpatient) and related costs were calculated for cardiovascular-related and all-cause medical services with adjustments for covariates. The fourth period (phase IV), January 2008 to December 2010 is a 3-year mortality rate follow-up period. In Phase IV, the time to occurrence of cardiovascular-related and all-cause death were examined. In order to be eligible for the study, patients were required to have been alive and enrolled in Part D throughout 2007. Thus, mortality was measured between January 2008 and December 2010.

2.3.1 Study Design Structure

The study design structure is depicted in Figure 2.2 below.

Figure 2.2 Study Design Structure



OOP : out of pocket ; LIS : low income subsidy; CVD : cardiovascular disease

2.3.2 Study Population

Four cohorts were created based on patients' Medicare Part D coverage in 2007. Before reaching the Part D coverage gap, the beneficiary usually pays a deductible and/or coinsurance up to the coverage gap. Once the threshold is reached, the beneficiary pays 100 percent of his or her drug costs out-of-pocket until a second threshold, the catastrophic coverage level, is reached. In 2007, the coverage gap and catastrophic coverage levels were reached when the beneficiary had spent $779 and $3850 out-of-pocket costs, respectively.

The first cohort was composed of patients who did not reach the coverage gap in 2007, paying out-of-pocket costs < $799. The second cohort was composed of patients who reached the coverage gap in 2007, paying $799 ≤ out-of-pocket costs < $3850. The third cohort was composed of patients who reached catastrophic coverage in 2007, paying $3850 ≤ out-of-pocket costs. The fourth cohort consisted of patients who received the LIS and paid out-of-pocket costs < $799. Medicare Part D prescription data, Part A and Part B medical service data, treatment modality history file, pay history file, medical evidence file, and demographic data were extracted for these patients from the appropriate databases and merged by patient USRDS ID. Individual entry and exit into the Medicare Part D coverage gap were determined by using 2007 Part D prescription claims data.

2.3.2.1 Inclusion Criteria

The current research is a cross-sectional retrospective study of all patients who experienced ESRD and received dialysis. The patients were identified using data acquired from the SAFs of USRDS. Patients were included in the study if they (1) were designated by CMS as having ESRD, (2) underwent dialysis from January 1, 2006 to December 31, 2007, (3) were at least 18 years old on January 1, 2006 and alive on December 31, 2007, (4) were continuously enrolled in a Medicare Part D plan in 2007, in order for complete 12 months of pharmacy data to be captured and (5) were enrolled in both Medicare Part A and Part B coverage from January 1, 2006 to December 31, 2007.

2.3.2.2 Exclusion Criteria

Patients were excluded if they (1) were Medicare/Medicaid dual-eligible beneficiaries for Part A and/or Part B or Part D plans, (2) received a kidney transplant between January 1, 2006 and December 31, 2007, or (3) were in an employer-sponsored health benefit plans. Because the inclusion criteria for the study required that individuals remain in Medicare plans throughout both years, beneficiaries who died in 2006 or 2007 were excluded.

The index date for patients in this study was defined as January 1, 2007. This study required patients to enroll in a Medicare Part D plan throughout 2007 to ensure that all patients had Part D during the exposure period.

2.4: Study Outcomes and Variables

As mentioned earlier, the study was composed of four phases. The following section describes the phases of the study in detail.

2.4.1 Phase I: Demographic and Clinical Characteristics (January to December 2006)

In Phase I, the study population was described and compared among Part D cohorts in terms of demographic characteristics (age, gender, race, and region of residence), primary disease causing ESRD, ESRD duration, CCI scores, and presence of chronic diseases (CVD, diabetes mellitus, hypertension, dyslipidemia, cancer, and chronic lung disease). Baseline covariates were assessed during the 1-year period prior to 2007.

2.4.2 Phase II: Medication Adherence and Costs (January to December 2007)

In Phase II, prescription drug utilization included five therapeutic classes of outpatient prescription drugs: (1) antihyperglycemic prescriptions, (2) antihypertensive prescriptions, (3) lipid-lowering prescriptions, (4) phosphate binder prescriptions, and (5) calcimimetic prescriptions. Medication use was identified from Part D prescription claims data. For each Medicare prescription claim, Medicare Part D data contains a de-identified beneficiary USRDS identification number, prescription characteristics (i.e., prescription service date, quantity dispensed, days of supply, national drug code (NDC), brand name, generic name), and coverage characteristics (patient pay amount, gross drug

cost). Pharmacy claims were identified by generic names. Section 2.5.2.4 describes generic names for outpatient prescription drugs in detail.

2.4.2.1 Medication Use and Costs

Medication use was defined as one or more prescription fills in any of the therapeutic classes for the period of January 1, 2007 through December 31, 2007. Medication use was measured by the percentage of patients who had any use of five therapeutic classes of outpatient prescription drugs and the mean numbers of medications. Medication costs were defined as total drug costs and out-of-pocket costs for each therapeutic class and all medications. Out-of-pocket costs for each prescription are equal to the amount paid directly by the patient. Total drug costs for each prescription are defined payments including the amount Medicare paid plus patient out-of-pocket costs.

2.4.2.2 Medication Adherence and Persistence

Medication adherence, treatment patterns, and persistence were calculated for each class of outpatient prescription drug separately. For this analysis, patients were included if they received at least two prescriptions in each therapeutics class of drugs.

Medication adherence

Before calculating medication adherence, medication treatment patterns were assessed (i.e., mono, dual, triple, or quad therapy). Monotherapy was defined as treatment with only one medication class within each therapeutic class (e.g., sulfonylureas, biguanides,

or thiazolidinediones in antihyperglycemic prescriptions). Dual therapy refers to a coadministration of 2 separate medication classes with at least 2 overlapping periods of 30 days or 1 overlapping period of 60 days (e.g., sulfonylureas and biguanides, or sulfonylureas and thiazolidinediones, etc.). Triple therapy was defined as a coadministration of 3 separate medication classes at least 2 overlapping periods of 30 days or 1 overlapping period of 60 days (e.g., sulfonylureas and biguanides and thiazolidinediones). Quad therapy refers to a coadministration of 4 separate medication classes with at least 2 overlapping periods of 30 days or 1 overlapping period of 60 days.

Medication adherence was defined using the medication possession ratio (MPR), which is the sum of total days' supply for all fills divided by the number of days during the study period. MPR for dual, triple, and quad therapies were determined by calculating the average of the MPRs of the individual medications that constituted the dual, triple, and quad therapies.

Formula for calculating MPR is shown below;

MPR (monotherapy) = $\frac{Sum\ of\ total\ days\ supply\ for\ all\ fills}{Number\ of\ days\ in\ the\ study\ period}$

MPR (dual therapy) = $\frac{Sum\ of\ total\ days\ supply\ for\ all\ fills/2}{Number\ of\ days\ in\ the\ study\ period}$

MPR (triple therapy) = $\frac{Sum\ of\ total\ days\ supply\ for\ all\ fills/3}{Number\ of\ days\ in\ the\ study\ period}$

MPR (quad therapy) = $\frac{Sum\ of\ total\ days\ supply\ for\ all\ fills/4}{Number\ of\ days\ in\ the\ study\ period}$

In addition MPR calculations were dichotomized, with adherence defined as MPR ≥ 80% and non-adherence defined as MPR < 80%. MPR values > 100% were truncated at 100% for the purpose of analyses. The number of days in the study period for mediation therapy was defined as the longest period among; 1) the number of days between first and last fills plus days supply of the last fill, 2) the number of days between first fill and Dec 31, 2007.

To increase our understanding of the temporal dynamics of drug adherence among the primary cohort (cohort 2) who reached the coverage gap but not catastrophic coverage, separate analyses were performed. Adherence before and after reaching the coverage gap were examined using generalized-estimating-equation (GEE) methods. This model allows each comparison group to have its own profile over time.

To examine drug adherence before and after the coverage gap was exceeded, the date in which a patient exceeds the $799 out-of-pocket costs was identified; and adherence before and after that date was examined. (Hsu, Price et al. 2006) If claims included the date which the patient exceeded the $799 out-of-pocket costs, the claim was separated into two claims; one before and one after that date. The first and second claims were included in calculating adherence before and after, respectively. Patients were included

if they received at least two prescriptions and at least one prescription before the coverage gap date in each of the therapeutic class of drugs.

The analysis was limited to prescriptions filled during 2007. Section 2.6.2.1 describes the GEE model in detail.

Medication persistence

Medication persistence is frequently computed alongside medication adherence to indicate how long patients remain on prescribed medications. Medication persistence was defined as the duration of therapy from the first fill date until discontinuation. (Cramer, Roy et al. 2008; McHorney, Victor Spain et al. 2009) Mean persistence to the index medication was calculated by summing the number of days from the filling of the first medication to the end date of the last medication claim (fill date plus days supply) prior to a 30-day gap (note: a 60-day gap was also used for a sensitivity analysis). Kaplan-Meier survival curves were used to depict the percentage of patients who remained persistent in the study period. Cox regression analyses by therapeutic class were used to measure the difference among the study cohorts while controlling for covariates. Section 2.6.6.1 describes the Kaplan-Meier method and the Cox proportional hazards regression model in detail.

2.4.3 Phase III: Medical Services and Costs (January to December 2007)

In Phase III, the incidence of CVD, medical service utilization, and related costs were examined. The data were obtained from Part A institutional claims and Part B physician/supplier claims. Each institutional medical claim (Part A) contains a de-identified beneficiary USRDS identification number, diagnostic and procedural codes, medical service characteristics (beginning and ending date of service), and coverage characteristics (total charges, Medicare payments). Each physician/supplier claim (Part B) includes a de-identified beneficiary USRDS identification number, diagnostic and healthcare common procedure coding system (HCPCS) codes, service characteristics (beginning and ending date of service) and coverage characteristics (submitted charges, allowed charges, claim payment amount).

2.4.3.1 Incidence of Cardiovascular Disease

The incidence of CVD was defined as the number of patients who were newly diagnosed with CVD during a 1-year follow-up between January 1, 2007 and December 31, 2007. CVD was defined as medical services (International Classification of Disease, Ninth Revision (ICD-9-CM) codes) for acute myocardial infarction (AMI), atrial fibrillation (AF), cerebrovascular accident/transient ischemic attack (CVA/TIA), congestive heart failure (CHF), and peripheral arterial disease (PAD).(US Renal Data System 2011) CVD-related treatments were identified by current procedural terminology (CPT) codes including percutaneous coronary interventions (PCI), coronary artery bypass graft

surgery (CABG), and use of an implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy with defibrillator (CRT-D) (Appendix B). (US Renal Data System 2011) Each of the eight events was defined on the date of the first appearance of a diagnosis or procedure code in the 2007 claims. The 2006 claims were used to ensure that no CVD events occurred in 2006.

2.4.3.2 Medical Service Utilization

Two medical utilization categories were assessed in the analysis: cardiovascular-related and all-cause medical service utilization. Cardiovascular-related resource use was defined as at least one medical service claim with a relevant ICD-9-CM code or CPT code. All-cause medical services were defined by medical service claims for any reason. Medical services consisted of inpatient, outpatient, and other (i.e., home health agency, skilled nursing facility, or hospice). Medical service utilization was measured by the percentage of patients who used these medical services for a 1-year follow-up period. The mean number of visits for medical services was also calculated.

2.4.3.3 Medical Service Costs

Medical costs per person per year were calculated for cardiovascular-related medical services and all-cause medical services. Medical costs were estimated from the Medicare perspective for a 1-year period between January 1, 2007 and December 31, 2007. Adjusted mean medical costs were estimated from two-part models which are

computed by multiplying the adjusted probability obtained from the logistic regression model (part 1) with predicted costs from the general linear model (part 2), as described in Section 2.5.5.2.1.

Costs were defined as payments made by Medicare for cardiovascular-related and all-cause medical service costs including inpatient, outpatient and other visits. Medical service costs per year per person were calculated for a 1-year follow-up period of January 1, 2007 through December 31, 2007.

2.4.4 Phase IV: Mortality Rates (January 2008 to December 2010)

To assess the effect of the coverage gap on mortality rates - including cardiovascular-related mortality and all-cause mortality - survival analysis was used. Cardiovascular causes of death were defined as those attributed to CVD. All-cause mortality included death from cardiovascular causes and non-cardiovascular causes. Because the inclusion criteria for the study required that individuals remain in Medicare plans throughout 2007, mortality in 2008-2010 was assessed. Survival analysis examined whether the 3-year survival rate was associated with Part D coverage groupings. Cox proportional hazards regression models estimated the hazard ratios of the association between Part D coverage cohorts and mortality; controlling for age, gender, race, region of residence, primary disease causing ESRD, ESRD duration, CCI score, presence of chronic disease including

cardiovascular disease, diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease.

Sensitivity analysis was also conducted for all of the covariates in the base case above as well as laboratory surrogates including GFR, BMI, serum creatinine, serum hematocrit, hemoglobin value (g/dl), serum albumin (g/dl), BUN, and ethnicity (Hispanic vs Non-Hispanic) and the receipt of transplant. Note: These laboratory data were obtained from the CMS End-Stage Renal Disease Medical Evidence Report (CMS-2728), which is used to register patients at the onset of ESRD. Thus, these laboratory data were recorded not during the same period of time but when patients began dialysis. Section 2.6.6.1 describes the Kaplan-Meier method and the Cox proportional hazards regression model in detail.

2.4.5 Independent Variables

2.4.5.1 Part D Coverage Variable

In this study, the four cohorts of Part D beneficiaries were categorized based on their Part D coverage in 2007. The first cohort consisted of patients who did not reach the coverage gap (cohort 1; out-of-pocket costs < $799). The second cohort was comprised of patients who reached the coverage gap but did not reach the point of receiving catastrophic coverage (cohort 2; $799 ≤ out-of-pocket costs < $3,850). The third cohort included patients who reached catastrophic coverage (cohort 3; $3,850 ≤ out-of-pocket costs). The fourth cohort was comprised of patients who did not reach the coverage gap

and receive the LIS (cohort 4; out-of-pocket costs < $799). Patients who received the LIS for their premium and copayment were included in cohort 4 because of their unique benefit structure.

2.4.5.2 Demographic and Clinical Variables

The following demographic and clinical variables were identified: age, gender, race, region of residence, primary disease causing ESRD, and ESRD duration (Table 2.1).

Table 2.1 Definitions of Demographic Variables

Name	Level	Definition
Age	Continuous	Age on January 1, 2007
Gender	Categorical	0: Female 1: Male
Race	Categorical	1: Black 2: White 3: Other – Native American, Asian, and other
Region of residence	Categorical	1: Midwest 2: Northeast 3: South 4: West
Primary disease causing ESRD	Categorical	1: Diabetes 2: Hypertension 3: Glomerulonephritis 4: Cystic kidney 5. Other
ESRD duration	Continuous	Disease duration on January 1, 2007

2.4.5.3 Comorbidity Variables

The CCI scores were used to calculate comorbidity severity scores. The presence of chronic diseases (CVD, diabetes mellitus, hypertension, and dyslipidemia) was also assessed (Table 2.2 and Table 2.3).

Table 2.2 Charlson Comorbidity Index (CCI)

Diagnoses	ICD-9 codes	Weight
Myocardial infarction	410.xx, 412	1
Congestive heart failure	428.x	1
Peripheral vascular disease	441.x, 443.9, 785.4, V43.4, 38.48(P)	1
Cerebrovascular disease	430-437.x, 438	1
Dementia	290.x	1
Chronic pulmonary disease	490-496, 500-505, 506.4	1
Ulcer disease	531.4x-531.7x, 532.4x-532.7x, 533.4x-533.7x, 534.4x-534.7x, 531.0x-531.3x, 532.0x-532.3x, 533.0x-533.0x, 534.0x-534.3x, 531.9, 532.9, 533.9, 534.9	1
Various cirrhosis	571.2, 571.4, 571.5, 571.6	1
Diabetes	250.0x-250.3x, 250.7x	1
Connective tissue disease	710.x, 714.x, 725.x	1
Hemiplegia	342.x, 344.1	2
Moderate or severe renal disease	582.x, 583.0-583.7, 585, 586, 588.x	2
Diabetes with complications	250.4x-250.6x	2
Various cancers	140.x-172.x, 174.x-195.x, 200.x-208.x	2
Moderate or severe liver disease	572.2-572.8	3
Metastatic cancers	196.x-199.9	6
HIV/AIDS	042.x-044.9	6
	Updated Charlson Codes (2008)	
Depression	296.2x-296.3	1
Use of warfarin	Used drug data	1
Hypertension	401.x-401.9	1
Skin ulcers/cellulitis	682.x-682.9, 707.x-707.9	2

Table 2.3 Presence of Chronic Disease

Name	Level	Definition
Cardiovascular disease	Categorical	0: No 1: Yes
Diabetes mellitus	Categorical	0: No 1: Yes
Hypertension	Categorical	0: No 1: Yes
Dyslipidemia	Categorical	0: No 1: Yes
Cancer	Categorical	0: No 1: Yes
Chronic lung disease	Categorical	0: No 1: Yes

2.4.5.4 Medication Variables

Use of antihyperglycemic drugs, antihypertensive drugs, lipid-lowering drugs, phosphate binders, and calcimimetic drugs were included (Tables 2.4 - 2.8).

Table 2.4 Antihyperglycemic Drugs

Drug Class	Generic Name
Sulfonylureas	Glipizide, Acetohexamide, Chlorpropamide, Tolazamide, Tolbutamide, Glyburide, Glimepiride, Glipizide/Metformin, Glyburide/Metformin
Alpha-glucosidase inhibitors	Acarbose, Miglib
Biguanides	Metformin HCl
Meglitinides	Repaglinide, Nateglinide
Thiazolidinediones	Pioglitazone, Pioglitazone/glimepiride, Pioglitazone/Metformin, Rosiglitazone, Rosiglitazone/Glimepiride, Rosiglitazone/Metformin
DPP-4 inhibitors	Sitagliptin, Sitagliptin/Metformin, Saxagliptin
GLP agonist	Exenatide, Pramlintide acetate
Insulin	Hum Insulin/Reg Insulin Hm, Insulin Aspart, Insulin Detemir, Insulin Glargine, Insulin Glulisine, Insulin Isophane, Insulin Lispro, Insulin Npl/Insulin Lispro, Insulin Regular, Human, Insulin Regular, Human&Rel.Unt, Insulin Zinc Extend Human Rec, Insulin Zinc Human Rec,Insuln Asp Prt/Insulin Aspart, Human Insulin Isophane, Reg Insulin Hm/Rlse/Chbr/Ihlr

Table 2.5 Antihypertensive Drugs

Drug Class	Generic Name
ACE Inhibitors	Benazepril, Benazepril/Hydrochlorothiazide, Captopril, Captopril/Hydrochlorothiazide, Enalapril Maleate, Enalapril Maleate/Felodipine, Enalapril/Hydrochlorothiazide, Enalaprilat Dihydrate, Fosinopril Sodium, Fosinopril/Hydrochlorothiazide, Lisinopril, Lisinopril/Hydrochlorothiazide, Moexipril HCl, Moexipril/Hydrochlorothiazide, Perindopril Erbumine, Quinapril HCl, Quinapril/Hydrochlorothiazide, Ramipril, Trandolapril, Trandolapril/Verapamil HCl
ARBs	Candesartan Cilexetil, Candesartan/Hydrochlorothiazide, Eprosartan Mesylate, Eprosartan/Hydrochlorothiazide, Irbesartan, Irbesartan/Hydrochlorothiazide, Losartan Potassium, Losartan/Hydrochlorothiazide, Olmesartan Medoxomil, Olmesartan/Hydrochlorothiazide, Telmisartan, Telmisartan/Hydrochlorothiazide, Valsartan, Valsartan/Hydrochlorothiazide
Calcium-channel Blockers	Amlodipine Besylate/Olmesartan, Amlodipine Besylate, Amlodipine Besylate/Benazepril, Amlodipine/Atorvast, Amlodipine/Valsartan, Diltiazem HCl, Felodipine, Isradipine, Nicardipine HCl, Nifedipine, Nimodipine, Nisoldipine, Verapamil HCl
Beta-blocker	Acebutolol HCl, Atenolol, Atenolol/Chlorthalidone, Betaxolol HCl, Bisoprolol Fumarate, Bisoprolol Fumarate/ Hydrochlorothiazide, Carteolol HCl, Carvedilol, Carvedilol Phosphate, Labetalol Hcl, Metoprolol Succinate, Metoprolol Tartrate, Metoprolol/Hydrochlorothiazide, Nadolol, Pindolol, Propranolol HCl, Propranolol/Hydrochlorothiazide, Timolol, Timolol Maleate

Table 2.5 (continued)

Alpha-Agonists	Clonidine HCl, Clonidine HCl/Chlorthalidone, Guanabenz Acetate, Guanfacine HCl, Methyldopa, Methyldopa/Hydrochlorothiazide
Alpha-Blockers	Doxazosin Mesylate, Prazosin HCl, Terazosin HCl
Aldosteron blocker	Eplerenone, Spironolact/Hydrochlorothiazid, Spironolactone, Spironolactone Micronized
Direct Renin Inhibitor	Aliskiren Hemifumarate
Diuretic	Indapamide, Hydrochlorothiazide, Torsemide, Chlorothiazide, Bumetanide, Hydrochlorothiazide, Furosemide, Chlorthalidone, Bumetanide, Amiloride Hcl, Triamterene, Triamterene/Hydrochlorothiazide
Vasodilator	Aspirin/Dipyridamole, Dipyridamole, Hydralazine HCl, Hydralazine/Hydrochlorothiazid, Isosorb Dinit/Hydralazine HCl, Isosorbide Dinitrate, Isosorbide Mononitrate, Minoxidil, Nitroglycerin,Nitroglycerin/D5W
Other	Reserpine

Table 2.6 Lipid-lowering Drugs

Drug Class	Generic Name
Statins	Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Simvastatin
Fibrate	Bezafibrate, Clofibrate, Ciprofibrate, Fenofibrate, Gemfibrozil
Niacin	Niacin
Bile acid sequestrants	Cholestyramine/Aspartame, Cholestyramine/Sucrose
Ezetimibe	Ezetimibe

Table 2.7 Phosphate Binders

Drug Class	Generic Name
Lanthanum	Lanthanum carbonate
Sevelamer	Sevelamer HCl, Sevelamer carbonate
Calcium	Calcium Acetate, Calcium Carbonate, Calcium Carbonate/Mag Carb/Fa, Calcium Carbonate/Vitamin D2, Calcium Carbonate/Vitamin D3

Table 2.8 Calcimimetic Drugs

Drug Class	Generic Name
Cinacalcet	Sensipar

2.5 Statistical Analysis

All data manipulation and statistical analyses were performed using SAS software (version 9.2; SAS Institute Inc., Cary, North Carolina) and Stata (version 11.1; Stata Corp, College Station, Texas). All statistical analyses were two-tailed, with significance

level set a priori at $\alpha = 0.05$. Descriptive statistics were conducted to compare the demographic and clinical variables. Categorical variables (e.g., gender, race, ethnicity and presence of chronic diseases) were examined using Pearson Chi-square tests. Continuous variables (e.g., age, CCI, and ESRD duration) were compared using one-way ANOVAs and the Kruskal-Wallis test, a nonparametric alternative to ANOVA. Normally distributed data were analyzed using ANOVA, whereas non-normally distributed data were analyzed using Kruskal-Wallis tests.

Adjusted regression models were built using GEE models, logistic regressions, GLMs, zero-inflated Poisson regression models, two-part models, and Cox proportional hazards regression models. Medication adherence and persistence were measured using logistic regression and Cox proportional hazards regression models, respectively. To examine differences in drug adherence before and after the coverage gap was exceeded, GEE models were used. Medical service utilization was estimated using zero-inflated Poisson regression models. Annual medical service costs for the cohorts were calculated using two-part models consisting of logistic regression of the probability of any costs and linear regression of costs for patients with costs. Logistic regression examined whether the 1-year incidence of CVD was associated with the level of Part D coverage. Survival analyses including Kaplan-Meier and Cox proportional hazards regressions examined whether the 3-year survival rates were associated with the Part D coverage gap.

All models to assess association between Part D coverage levels and outcomes were adjusted for age, gender, race, region of residence, primary disease causing ESRD, ESRD duration, CCI score, presence of chronic disease including cardiovascular disease, diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease. Cohort 4 served as the reference cohort, controlling for covariates.

2.5.1 Objective 1: Demographic Characteristics

For objective 1, Pearson Chi-square tests were conducted to compare the distribution of gender, race, presence of chronic diseases, and primary disease causing ESRD, categorized by Part D coverage levels. Mean age, the CCI score, and ESRD duration were compared using ANOVAs.

2.5.2 Objective 2: Medication Utilization and Costs

For objective 2, bivariate analyses (Pearson Chi-square and ANOVA or Kruskal-Wallis) were performed to compare the proportion and number of oral prescription drugs (i.e., antihyperglycemics, antihypertensives, lipid-lowering drugs, phosphate binders, or cinacalcet), categorized by the Part D coverage.

Pharmacy costs for each of the five therapeutic classes of outpatient prescription and all prescription drugs were compared across Part D coverage categories using one-way ANOVAs and Kruskal-Wallis tests.

2.5.3 Objective 3: Medication Adherence and Persistence

For objective 3, ANOVAs and Kruskal-Wallis tests were performed to compare mean MPR and persistence until the first 30-day gap (or 60-day gap for sensitivity analysis) in five therapeutic classes of outpatient prescription drugs, including antihyperglycemics, antihypertensives, lipid-lowering drugs, phosphate binders, or cinacalcet, categorized by Part D coverage. Medication adherence was dichotomized, with adherence defined as MPR $\geq$ 80 percent; and nonadherence defined as MPR < 80 percent. Pearson Chi-square tests were used to compare the proportions of patients who were adherent. Logistic regression was used to measure the proportion of patients who were adherent (MPR $\geq$ 80 %), controlling for of age, gender, race, region of residence, primary disease causing ESRD, ESRD duration, CCI score, presence of chronic disease including CVD, diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease. Kaplan-Meier survival curves were used to depict the percentage of patients who remained persistent among the cohorts. Cox proportional hazards regression was used to measure the difference in persistence among the cohorts with the same covariates used in the logistic regression. Adherence before and after the date in which patients who reached the coverage gap but did not reach the point of receiving catastrophic coverage (cohort 2: \$799 $\leq$ out-of-pocket costs < \$3,850) were compared using generalized estimating equations (GEE), controlling for the same covariates with logistic and Cox proportional hazards regressions.

2.5.3.1 Generalized Estimating Equations (GEE)

The GEE method, an extension of the quasi-likelihood approach, was used to analyze longitudinal and other correlated data. (Hanley, Negassa et al. 2003) While applications of generalized linear models are abundant, there are many situations in which repeated response measurements are made on the same unit, and, thus, this information forms a cluster of correlated observations. (Myers 2012) The advantage of GEE models is their control for correlation by incorporating the correlation structure into the regression model as a covariate.

The basic structure of the GEE model with within-subject correlation is shown below (Twisk 2003):

$$Y_{it} = B_o + \sum_{j=1}^{j} B_{ij} X_{itj} + B_2 t + \cdots + CORR_{it} + \varepsilon_{it}$$

Where Y_{it} = observations for subject *i* at time *t*;

B_o = intercept;

X_{itj} = independent variable *j* for subject *i* at time *t*;

B_{ij} = regression coefficient for independent variable *j*;

J = number of independent variables;

t = time;

β_2 = regression coefficient for time;

$CORR_{it}$ = working correlation structure; and

ε_{it} = error for subject *i* at time *t.*

2.5.4 Objective 4: Cardiovascular Disease Morbidity

For objective 4, the incidence of CVD was compared among the study cohorts, categorized by Part D coverage. Logistic regression was used to examine whether the 1-year cardiovascular incidence rates were associated with Part D coverage. The following variables were controlled for in the Cox regression: age, gender, race, region of residence, primary disease causing ESRD, ESRD duration, CCI score, presence of chronic disease including cardiovascular disease, diabetes mellitus, hypertension, dyslipidemia, cancer, and chronic lung disease.

2.5.5 Objective 5: Cardiovascular-related and All-cause Medical Service Utilization and Costs

2.5.5.1 Medical Service Utilization

For objective 5, cardiovascular-related and all-cause medical service utilization rates were defined by inpatient, outpatient or other claims having an ICD-9-CM code or CPT code of interest. Medical service utilization was measured by the percentage of patients who had medical services (i.e., inpatient, outpatient or other visits) for the 1-year follow-up period. The mean numbers of visits for medical services were also estimated. The inferential analysis estimated unadjusted differences in the percentage of patients and the mean number of cardiovascular-related medical services among the study cohorts, with statistical significance determined using chi-square, ANOVA, or the Kruskal-Wallis tests. Zero-inflated Poisson regression was used to calculate the adjusted mean utilization rates,

adjusting for age, gender, race, region of residence, primary disease causing ESRD, ESRD duration, CCI score, presence of chronic disease including cardiovascular disease, diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease.

2.5.5.1.1 Zero-inflated Poisson Regression

In many cases of medical service utilization, the data exhibit an excessively large proportion of zeros that is significantly larger than that expected in the Poisson distribution. To accommodate zero inflation, Mullahy proposed a zero-inflated Poisson model that assumes a two-state process. (Mullahy 1986) The zero-inflated Poisson regression has two equations, one is a logit specification that separates the excess of zeros from the rest, (i.e., those patients that have no medical service utilization from the others), and the other equation is a Poisson specification that counts the number of medical services. (Sole-Auro, Guillen et al. 2012) The Vuong test was used to test whether the zero-inflated Poisson regression was a better fit than the standard Poisson regression.

The basic structure of the zero-inflated Poisson regression model is shown below (Mullahy 1998; Lee, Wang et al. 2006):

$$P(Y = 0) = \phi + (1 - \phi)e^{-\lambda}$$

$$P(Y = y) = (1 - \phi)\frac{\lambda^y e^{-\lambda}}{y!}, \quad y = 1, 2, \ldots$$

Where $0 < Ø < 1$ so that it incorporates more zeros than those permitted under the Poisson assumption ($Ø=0$). It was assumed that a discrete count response variable Y follows a zero-inflated Poisson distribution.

2.5.5.2 Medical Service Costs

Medical service costs per year per person were calculated for cardiovascular-related and all-cause medical services, defined by medical claims. Cost differences among the study cohorts were calculated using both descriptive analysis and multivariate regression. The inferential analysis estimated the unadjusted differences in the mean annual medical service costs among the study cohorts, with statistical significance determined using one-way ANOVA and Kruskal-Wallis tests. The adjusted mean costs for medical services were estimated from two-part models, which are computed by multiplying the adjusted probability obtained from the logistic regression model (part 1) with predicted costs from the general linear model (part 2).

2.5.5.2.1 Two-part Models

Annual medical service costs for the four cohorts were calculated using a two-part model. (Mullahy 1998) Two-part models are often used to model cost data that include many zero observations. (Buntin and Zaslavsky 2004) In the first part, logistic regression was used to predict the likelihood of having cost greater than zero. A generalized linear model (GLM) with log link function was used in the second part to estimate the mean

annual healthcare costs for patients with positive health care costs. The adjusted mean costs estimated from two-part models were computed by multiplying the adjusted probability obtained from the logistic regression model (part 1) with the predicted cost from the GLM model (part 2).

Cohort 4 (out-of-pocket < $799 with LIS) served as the reference cohort, controlling for baseline covariates. A bootstrap resampling method was used to estimate the 95% confidence intervals of the healthcare cost differences among the study cohorts.

The basic structure of the two-part model is shown below (Mullahy 1998):

$$E(Y \mid X) = P(Y > 0 \mid X)\, E(Y \mid Y > 0, X)$$

- Part 1: $P(Y > 0 \mid X)$

The first part of the model predicts the probability of any use, specified as a probit.

- Part 2: $E(Y \mid Y > 0, X)$

The second part of the model predicts costs conditional on nonzero costs. To obtain unconditional predicted costs, the probabilities of use from the first part are multiplied by expected levels from the second part of the model.

2.5.6 Objective 6: All-cause and Cardiovascular-related Mortality

For objective 6, the associations between Part D coverage levels and 3-year mortality rates were assessed using survival analyses. Survival curves were calculated using the Kaplan-Meier method. Cox proportional hazards regression models estimated the hazard ratios of the association between Part D coverage levels and mortality. Cardiovascular causes of death were defined as those attributed to CVD. All-cause mortality included death from cardiovascular causes and non-cardiovascular causes.

2.5.6.1 Survival Analysis

Survival analysis is a technique used to make comparisons of the time to occurrence of events of interests in two or more treatment groups. Survival analysis has become a popular tool in observational and experimental studies involving follow-up study participants over time. The most commonly used survival analysis methods include the Kaplan-Meier survival function and the Cox proportional hazards function. This study used the Kaplan-Meier survival function to plot survival curves and the Cox proportional hazards regression model to quantify the hazards ratios for Part D coverage levels and other covariates.

2.5.6.1.1 Kaplan-Meier Method

The Kaplan-Meier method is frequently used to estimate survival functions. This method can depict the percentage of patients surviving at intervals and test the

differences between survival functions of two or more treatment groups. Kaplan-Meier curves were generated for the 3-year overall and cardiovascular event-free survival among the study cohorts.

The equation used to calculate the Kaplan-Meier function is (Allison PD 1995):

$$\widehat{S}(t) = \prod_{j:t_j \leq t} \left[1 - \frac{d_j}{n_j}\right]$$

S(t) = the survival function (proportion of patients surviving after time t or proportion of patients with survival time greater than t) at time t

t_j = the time at which one or more individuals experience the event of interest

d_j = the number of individuals who experience the event of interest at t_j

n_j =the number of individuals at risk at time t_j

the quantity in the brackets is the conditional probability of surviving to time t_j +1, given that one survived to time t_j. (Allison PD 1995)

However, the Kaplan-Meier method is limited to calculating the survival probability involving a single categorical predictor and cannot quantify the effect of individual variables on survival time while controlling for other covariates. When multiple predictors are involved to explain an event, the Cox proportional hazards regression model is preferred.

2.5.6.1.2 The Cox Proportional Hazards Regression Model

The Cox proportional hazard models belong to the family of survival analyses. This model has become popular because it easily incorporates time-dependent covariates and is effective at controlling for multiple covariates, and can easily accommodate discrete and continuous measurement of event times. (Allison PD 1995)

The basic structure of the Cox proportional hazard regression model is shown below (Cox 1972):

$$\log_e \left\{ \frac{h_i(t)}{h_0(t)} \right\} = \beta_1 X_{i1} + \beta_2 X_{i2} + \cdots + \beta_k X_{ik}$$

h_i (t): the hazard at time t

h_0 (t): the baseline hazard

X: an independent variable in the model

β: the regression coefficient for the corresponding independent variable.

Table 2.9 provides a summary of study hypotheses and statistical techniques.

Table 2.9 Summary of Objectives, Hypotheses Tested, Study Variable(s), and Statistical Tests

Objective/Hypothesis	Study Phase	Dependent Variable	Independent Variable	Test
Objective 1 To compare patient characteristics for Medicare beneficiaries with dialysis, categorized into four cohorts based on their Part D coverage.	Phase I			
$H_{0\ (1a)}$: Mean age will not differ significantly when categorized by Part D coverage.		Age	Part D coverage	ANOVA, Kruskal-Wallis test
$H_{0\ (1b)}$: The proportion of patients in each gender category will not differ significantly when categorized by Part D coverage.		Gender	Part D coverage	Pearson Chi-square (x^2)
$H_{0\ (1c)}$: The proportion of patients in each race category will not differ significantly when categorized by Part D coverage.		Race	Part D coverage	Pearson Chi-square (x^2)
$H_{0\ (1d)}$: The proportion of patients in each region category will not differ significantly when categorized by Part D coverage.		Region of residence	Part D coverage	Pearson Chi-square (x^2)
$H_{0\ (1e)}$: The proportion of patients in primary disease causing ESRD will not differ significantly when categorized by Part D coverage.		Primary disease causing ESRD	Part D coverage	Pearson Chi-square (x^2)
$H_{0\ (1f)}$: Mean ESRD duration will not differ significantly when categorized by Part D coverage.		ESRD duration	Part D coverage	ANOVA, Kruskal-Wallis test
$H_{0\ (1g)}$: Mean comorbidity score will not differ significantly when categorized by Part D coverage.		Charlson Comorbidity Index (CCI) scores	Part D coverage	ANOVA, Kruskal-Wallis test

Table 2.9 (continued)

$H_{0\ (1h-\ 1m)}$: The proportion of patients in each presence of chronic diseases (cardiovascular disease [$H_{0(1h)}$], diabetes mellitus [$H_{0(1i)}$], hypertension [$H_{0(1j)}$], dyslipidemia [$H_{0(1k)}$], cancer [$H_{0(1l)}$], chronic lung disease [$H_{0(1m)}$]) will not differ significantly when categorized by Part D coverage.		Cardiovascular disease, diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease	Part D coverage	Pearson Chi-square (x^2)
Objective 2 To determine whether the proportion and number of oral prescription medications and pharmacy costs differ when categorized by Part D coverage.	Phase II			
$H_{0\ (2a-e)}$: The proportion of patients using antihyperglycemics [$H_{0(2a)}$], antihypertensives [$H_{0(2b)}$], lipid-lowering drugs [$H_{0(2c)}$], phosphate binders [$H_{0(2d)}$], or cinacalcet [$H_{0(2e)}$]) will not differ significantly when categorized by Part D coverage.		Proportion of patients using antihyperglycemics, antihypertensives, lipid-lowering drugs, phosphate binders, cinacalcet	Part D coverage	Pearson Chi-square (x^2)
$H_{0\ (2f-j)}$: The mean number of antihyperglycemics [$H_{0(2f)}$], antihypertensives [$H_{0(2g)}$], lipid-lowering drugs [$H_{0(2h)}$], phosphate binders [$H_{0(2i)}$], or cinacalcet [$H_{0(2j)}$]) will not differ significantly when categorized by Part D coverage.		Number of antihyperglycemics, antihypertensives, lipid-lowering drugs, phosphate binders, cinacalcet	Part D coverage	ANOVA Kruskal-Wallis test

Table 2.9 (continued)

$H_{0\ (2k\text{-}p)}$: Pharmacy costs (i.e., antihyperglycemics [$H_{0(2k)}$], antihypertensives [$H_{0(2l)}$], lipid-lowering drugs [$H_{0(2m)}$], phosphate binders [$H_{0(2n)}$], cinacalcet [$H_{0(2o)}$] or all [$H_{0(2p)}$]) will not differ significantly when categorized by Part D coverage.		Total pharmacy costs, out-of-pocket costs	Part D coverage	ANOVA Kruskal-Wallis test
Objective 3 To determine whether medication adherence and persistence among patients receiving drug therapy for diabetes, hypertension, hyperlipidemia, hyperphosphatemia or secondary parathyroid differ when categorized by Part D coverage.	Phase II			
$H_{0\ (3a\text{-}e)}$: Medication adherence (i.e., antihyperglycemics [$H_{0(3a)}$], antihypertensives [$H_{0(3b)}$], lipid-lowering drugs [$H_{0(3c)}$], phosphate binders [$H_{0(3d)}$], or cinacalcet [$H_{0(3e)}$]) will not differ significantly when categorized by Part D coverage.		MPR	Part D coverage	ANOVA Kruskal-Wallis test
$H_{0\ (3f\text{-}j)}$: The proportion of patients who are adherent (MPR $\geq$ 80%) to antihyperglycemics [$H_{0(3f)}$], antihypertensives [$H_{0(3g)}$], lipid-lowering drugs [$H_{0(3h)}$], phosphate binders [$H_{0(3i)}$], or cinacalcet [$H_{0(3j)}$] will not differ significantly when categorized by Part D coverage.		Proportion adherent	Part D coverage	Pearson Chi-square (x^2) Logistic regression*

Table 2.9 (continued)

To determine whether medication adherence differs before and after the coverage gap is exceed among patients receiving drug therapy in our primary cohort (**cohort 2**) who reach coverage gap but not catastrophic coverage.				
$H_{0\ (3k\text{-}o)}$: Medication adherence with antihyperglycemics [$H_{0(3k)}$], antihypertensives [$H_{0(3l)}$], lipid-lowering drugs [$H_{0(3m)}$], phosphate binders [$H_{0(3n)}$], or cinacalcet [$H_{0(3o)}$] will not differ significantly before and after reaching the gap.		MPR	Before and after reaching coverage gap (month 0)	Paired t-test
$H_{0\ (3p\text{-}t)}$: The proportion of patients who are adherent (MPR ≥ 80%) to antihyperglycemics [$H_{0(3p)}$], antihypertensives [$H_{0(3q)}$], lipid-lowering drugs [$H_{0(3r)}$], phosphate binders [$H_{0(3s)}$], or cinacalcet [$H_{0(3t)}$] will not differ significantly before and after reaching the gap.		Proportion adherent	Part D coverage	McNemar's test Generalized estimating equation model (GEE)*
$H_{0\ (3u\text{-}y)}$: Medication persistence with antihyperglycemics [$H_{0(3u)}$], antihypertensives [$H_{0(3v)}$], lipid-lowering drugs [$H_{0(3w)}$], phosphate binders [$H_{0(3x)}$], or cinacalcet [$H_{0(3y)}$] will not differ significantly when categorized by Part D coverage.		Persistence	Part D coverage	ANOVA Kruskal-Wallis test
$H_{0\ (3z\text{-}zd)}$: The proportion of patients who are persistent (until 30days gap) to antihyperglycemics [$H_{0(3z)}$], antihypertensives [$H_{0(3za)}$], lipid-lowering drugs [$H_{0(3zb)}$], phosphate binders [$H_{0(3zc)}$], or cinacalcet [$H_{0(3zd)}$] will not differ significantly when categorized by Part D coverage.		Proportion persistent		Kaplan-Meier curves Cox proportional regression*

Table 2.9 (continued)

Objective 4 To determine whether cardiovascular morbidity rates differ when categorized by Part D coverage.	Phase III			
$H_{0\ (4)}$: Incidence of cardiovascular disease will not differ significantly when categorized by Part D coverage		Incidence of cardiovascular disease	Part D coverage	Logistic regression*
Objective 5 To determine whether all-cause and cardiovascular-related medical service utilization (i.e, inpatient, outpatient, and other visits) and costs differ when categorized by Part D coverage.	Phase III			
$H_{0\ (5a\text{-}c)}$: The proportion of patients used all-cause medical services including inpatient [$H_{0(5a)}$], outpatient [$H_{0(5b)}$], and other visits [$H_{0(5c)}$] will not differ significantly when categorized by Part D coverage.		Proportion of patients with all-cause inpatient, outpatient, other visits	Part D coverage	Pearson Chi-square (x^2)
$H_{0\ (5d\text{-}f)}$: Mean numbers of medical service visits (i.e., inpatient [$H_{0(5d)}$], outpatient [$H_{0(5e)}$], and other visits [$H_{0(5f)}$],) will not differ significantly when categorized by Part D coverage.		Mean numbers of all-cause inpatient, outpatient, other visits	Part D coverage	Kruskal-Wallis test Poisson regression* Zero-inflated Poisson regression*
$H_{0\ (5g\text{-}i)}$: The proportion of patients used medical services related to cardiovascular disease including inpatient [$H_{0(5g)}$], outpatient [$H_{0(5h)}$], and other visits [$H_{0(5i)}$], will not differ significantly when categorized by Part D coverage.		Proportion of patients with cardiovascular-related inpatient, outpatient, other visits	Part D coverage	Pearson Chi-square (x^2)

Table 2.9 (continued)

$H_{0\ (5j\text{-}l)}$: Mean numbers of cardiovascular-related medical service visits (i.e., inpatient [$H_{0(5j)}$], outpatient [$H_{0(5k)}$], and other visits [$H_{0(5l)}$]) will not differ significantly when categorized by Part D coverage.		Mean numbers of cardiovascular-related inpatient, outpatient, other visits	Part D coverage	Kruskal-Wallis test Poisson regression* Zero-inflated Poisson regression*
$H_{0\ (5m\text{-}t)}$: All-cause medical care costs including inpatient [$H_{0(5m)}$], outpatient [$H_{0(5n)}$], physician/supplier [$H_{0(5o)}$], other visits [$H_{0(5p)}$], dialysis [$H_{0(5q)}$], and total medical costs [$H_{0(5r)}$], pharmacy costs [$H_{0(5s)}$] and total health care costs [$H_{0(5t)}$] will not differ significantly when categorized by Part D coverage.		All-cause medical care costs	Part D coverage	Kruskal-Wallis test Generalized linear model (GLM)* Two-part model*
$H_{0\ (5u\text{-}y)}$: Cardiovascular disease-related medical care costs including inpatient [$H_{0(5u)}$], outpatient [$H_{0(5v)}$], physician/supplier [$H_{0(5w)}$], other visits [$H_{0(5x)}$], and total medical service costs [$H_{0(5y)}$], will not differ significantly when categorized by Part D coverage.		Cardiovascular-related medical care costs	Part D coverage	Kruskal-Wallis test Generalized linear model (GLM)* Two-part model*
Objective 6 To determine whether cardiovascular-related and all-cause mortality rates differ when categorized by Part D coverage.	Phase IV			
$H_{0\ (6a)}$: All-cause mortality rates will not differ when categorized by Part D coverage.		All-cause mortality rates	Part D coverage	Kaplan-Meier curves Cox proportional regression*
$H_{0\ (6b)}$: Cardiovascular-related mortality rates will not differ when categorized by Part D coverage.		Cardiovascular-related mortality rates	Part D coverage	Kaplan-Meier curves Cox proportional regression*

2.6 Sample Size Calculations

This section discussed sample size calculations for the statistical analyses used for this study. Sample size calculations conducted for statistical tests under objectives 2-6 including multiple regression, logistic regression, and Cox proportional hazards regression. Sample size calculations were performed using PASS (Power Analysis & Sample Size) software (version 12; NCSS Statistical Software, Kaysville, Utah). Using the PASS 12 software and varying the parameter required for sample size calculations over a range of values, the largest sample size obtained was chosen as the required sample size for each regression.

2.6.1 Multiple Regression Analysis

Given 15 independent variables, an alpha of 0.05 and power equal to 0.8, the estimated total sample size of 205 patients were required for multiple regressions as shown in Table 2.10. (Cohen 1988)

2.6.2 Logistic Regression Analysis

Table 2.11 presents the estimates of sample sizes required for the logistic regression analysis. Based on the estimates of sample size obtained, an estimated total sample size of 7714 patients was required for the logistic regression ($\alpha = 0.05$; power=0.8). (Hsieh, Bloch et al. 1998)

Table 2.10 Estimates of Sample Size for Multiple Regression Analysis

N	Alpha	Ind. Variables Tested [a]	R^2 [b]	Ind. Variables Controlled [c]	R^2 [b]
186	0.05	20	0.1	15	0.1
94	0.05	20	0.2	15	0.1
66	0.05	20	0.3	15	0.1
53	0.05	20	0.4	15	0.1
47	0.05	20	0.5	15	0.1
205	0.05	20	0.1	15	0.01
103	0.05	20	0.2	15	0.01
71	0.05	20	0.3	15	0.01
57	0.05	20	0.4	15	0.01
49	0.05	20	0.5	15	0.01

[a] Ind. Variables Tested are those variables whose regression coefficients are tested against zero.
[b] R^2 is the amount that is added to the overall R-Squared value by these variables.
[c] Ind. Variables Controlled are those variables whose influence is removed from experimental error.

Table 2.11 Estimates of Sample Size for Logistic Regression Analysis

N	P_0 [a]	P_1 [b]	Odds Ratio [c]	R-Squared [d]
4571	0.3	0.320	1.1	0.1
603	0.3	0.358	1.3	0.1
252	0.3	0.391	1.5	0.1
147	0.3	0.421	1.7	0.1
100	0.3	0.449	1.9	0.1
5877	0.3	0.320	1.1	0.3
775	0.3	0.358	1.3	0.3
324	0.3	0.391	1.5	0.3
189	0.3	0.421	1.7	0.3
129	0.3	0.449	1.9	0.3
6000	0.2	0.216	1.1	0.1
791	0.2	0.245	1.3	0.1
331	0.2	0.273	1.5	0.1
193	0.2	0.298	1.7	0.1
132	0.2	0.322	1.9	0.1
7714	0.2	0.216	1.1	0.3
1018	0.2	0.245	1.3	0.3
426	0.2	0.273	1.5	0.3
248	0.2	0.298	1.7	0.3
170	0.2	0.322	1.9	0.3

[a] P0 is the response probability at the mean of X.
[b] P1 is the response probability when X is increased to one standard deviation above the mean.
[c] Odds Ratio is the odds ratio when P1 is on top. That is, it is [P1/(1-P1)]/[P0/(1-P0)].
[d] R-Squared is the R^2 achieved when X is regressed on the other independent variables in the regression.

2.6.3 Cox Proportional Hazards Regression Analysis

Table 2.12 presents the estimates of sample size required for the Cox proportional hazards regression analysis. Based on the estimates of sample size obtained, an estimated total sample size of 599 patients was required for the Cox proportional hazards regression ($\alpha = 0.05$; power=0.8). (Schoenfeld 1983; Hsieh and Lavori 2000)

Table 2.12 Estimates of Sample Size for Cox Proportional Hazards Regression Analysis

Sample Size (N)	Reg. Coef. (B) [a]	Event Rate (P) [b]	R-Squared X1 vs Other X's (R^2) [c]
466	0.5	0.3	0.1
117	1	0.3	0.1
52	1.5	0.3	0.1
30	2	0.3	0.1
599	0.5	0.3	0.3
150	1	0.3	0.3
67	1.5	0.3	0.3
38	2	0.3	0.3
280	0.5	0.5	0.1
70	1	0.5	0.1
32	1.5	0.5	0.1
18	2	0.5	0.1
359	0.5	0.5	0.3
90	1	0.5	0.3
40	1.5	0.5	0.3
23	2	0.5	0.3

[a] B is the size of the regression coefficient to be detected
[b] P is the event rate.
[c] R^2 is the R-squared achieved when X1 is regressed on the other covariates.

Chapter 3: Results

3.1 Chapter Overview

This chapter provides a detailed description of the results of the study.

Study results presentation

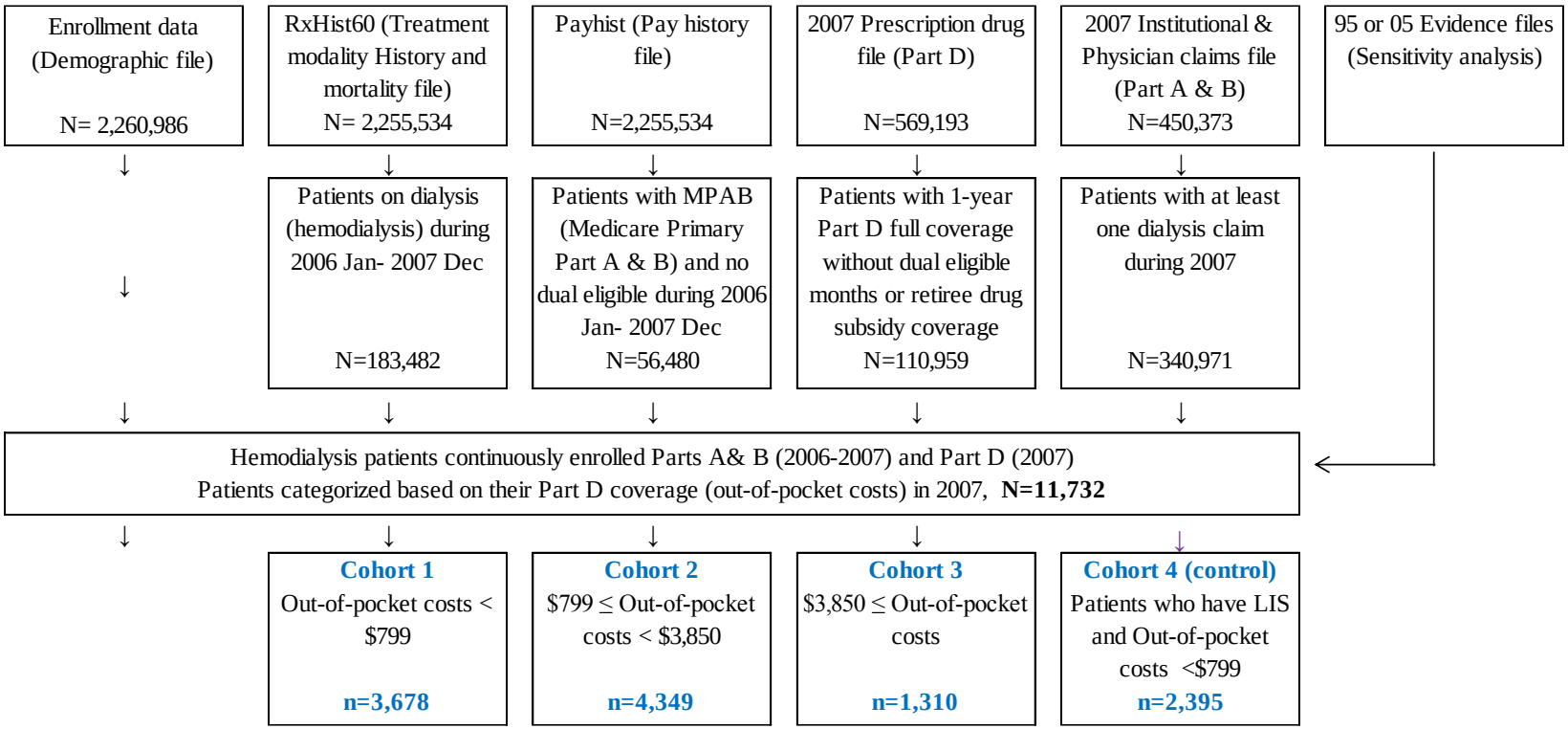
The results of the study are presented in order of the study objectives and corresponding hypotheses in accordance with the four study phases, i.e.:

- Phase I: Demographic and Clinical Characteristics (Objective 1)
- Phase II: Medication Adherence and Costs (Objectives 2-3)
- Phase III: Medical Services and Costs (Objectives 4-5)
- Phase IV: Mortality Rates (Objective 6)

Sample Selection

A total of 11732 patients were included as meeting inclusion criteria: 1) cohort 1: 3678 patients (31.4%) had out-of-pocket drug costs <$799; 2) cohort 2: 4349 patients (37.1%) had out-of-pocket drug costs between $799 and $3850; 3) cohort 3: 1310 patients (11.2%) had out-of-pocket drug costs > $3850; and 4) cohort 4: the remaining 2395 patients (20.4%) had out-of-pocket drug costs <$799 but received a low income subsidy. Fig 3.1 depicts the flow of sample selection process.

Figure 3.1 Diagram of the Selection of the Study Sample



Patients' out-of-pocket drug cost spending in 2007 was used to categorize patients into four cohorts. To show the changes of out-of-pocket and total drug costs as patients reached coverage gap or catastrophic coverage phases, the number of pharmacy claims, total pharmacy costs and out-of-pocket costs by coverage phase (initial, coverage cap and catastrophic coverage phases) are listed in Table 3.1.

Table 3.1 Number of Pharmacy Claims, Total Pharmacy Costs, Out-of-pocket Costs, and Ratio of Out-of-pocket Costs to Total Pharmacy Costs among Study Cohorts (N=11732)

	Cohort 1 (n=3678)		Cohort 2 (n=4349)		Cohort 3 (n=1310)		Cohort 4 (n=2395)	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Initial phase								
No. of pharmacy claims	32.4	20.0	36.7	16.0	25.1	11.9	53.5	32.3
Total pharmacy costs	$1,820	$1,618	$2,617	$1,599	$2,375	$542	$5,312	$4,869
Out-of-pocket costs	$423	$217	$736	$94	$677	$149	$192	$157
Out-of-pocket/total costs	23.25%		28.12%		28.50%		3.62%	
Coverage gap phase								
No. of pharmacy claims			24.3	19.6	32.9	18.1		
Total pharmacy costs			$1,814	$1,811	$3,375	$1,075		
Out-of-pocket costs			$1,118	$843	$2,974	$288		
Out-of-pocket/total costs			61.64%		88.14%			
Catastrophic coverage phase								
No. of pharmacy claims					30.4	25.9		
Total pharmacy costs					$4,935	$7,218		
Out-of-pocket costs					$520	$952		
Out-of-pocket/total costs					10.53%			
Total								
No. of pharmacy claims	32.4	20.0	61.0	26.6	88.1	36.8	53.5	32.3
Total pharmacy costs	$1,820	$1,618	$4,431	$2,614	$10,659	$7,112	$5,312	$4,869
Out-of-pocket costs	$423	$217	$1,854	$827	$4,153	$780	$192	$157
Out-of-pocket/total costs	23.25%		41.85%		38.96%		3.62%	

3.2 Phase I: Demographic and Clinical Characteristics

3.2.1 Objective 1: Demographic Characteristics

Table 3.2 presents the demographic and clinical characteristics of the study sample.

Age

$H_{0\ (1a)}$: Mean age will not differ significantly when categorized by Part D coverage. The mean ages of patients were 69.76 years (SD=12.67) in cohort 1, 72.54 years (SD=10.76) in cohort 2, 71.69 years (SD=10.88) in cohort 3, and 61.83 years (SD=13.84) in cohort 4, respectively. A one-way ANOVA revealed that patient age differed significantly among cohorts (F=429.64; d.f.=3 ; p<.0001). Patients in cohort 4 were more likely to be younger than other cohorts.

$H_{0\ (1a)}$: Rejected.

Gender

$H_{0\ (1b)}$: The proportion of patients in each gender category will not differ significantly when categorized by Part D coverage.

Sixty-two percent of patients (n=2272) in cohort 1, 55.3 percent of patients (n=2404) in cohort 2, 50 percent of patients (n=655) in cohort 3, and 52.5 percent of patients (n=1258) in cohort 4 were male, respectively. A chi-square test showed that patient gender differed significantly among the cohorts (χ^2=81.47; d.f.=3; p<.0001). Patients in cohort 1 were more likely to be male compared to other cohorts. **$H_{0\ (1b)}$: Rejected.**

Race

$H_{0\ (1c)}$: The proportion of patients in each race category will not differ significantly when categorized by Part D coverage.

Sixty-two percent of patients in cohort 1, 76 percent of patients in cohort 2, and 80 percent patients in cohort 3 were white compared to 46 percent of patients in cohort 4. A chi-square test showed that patient race differed significantly among the cohorts (χ^2=776.14; d.f.=6; p<.0001).

$H_{0\ (1c)}$: Rejected.

Region of residence

$H_{0\ (1d)}$: The proportion of patients in each region category will not differ significantly when categorized by Part D coverage.

Thirty-nine percent of patients (n=1422) in cohort 1, 34.1 percent of patients (n=1484) in cohort 2, 32 of percent patients (n=421) in cohort 3, and 59.5 percent of patients (n=1425) in cohort 4 resided in the South, respectively. A chi-square test showed that patient geographic region differed significantly among the cohorts (χ^2=528.21; d.f.=3; p<.0001). Patients in cohort 4 were more likely to live in the southern region compared to other cohorts.

$H_{0\ (1d)}$: Rejected.

Primary disease causing ESRD

$H_{0\ (1e)}$: The proportion of patients in primary disease causing ESRD will not differ significantly when categorized by Part D coverage.

For patients in cohort 1, the proportion of ESRD due to diabetes and hypertension were 39.8 percent and 32.7 percent, respectively. For patients in cohorts 2 through 4, the proportion of ESRD caused by diabetes and hypertension ranged from 43.3 to 45.0 percent and from 28.5 percent to 31.1 percent, respectively. A chi-square test showed that the primary disease causing ESRD differed significantly among the cohorts (χ^2=45.74; d.f.=12; p<.0001).

$H_{0\ (1e)}$: Rejected.

ESRD duration

$H_{0\ (1f)}$: Mean ESRD duration will not differ significantly when categorized by Part D coverage.

The mean ESRD durations of patients were 5.40 years (SD=4.30) in cohort 1, 4.77 years (SD=3.58) in cohort 2, 5.20 years (SD=4.06) in cohort 3, and 5.91 years (SD=4.48) in cohort 4. A one-way ANOVA revealed that the mean ESRD duration differed significantly among the cohorts (χ^2=147.82; d.f.=3 ; p<.0001). Patients in cohort 2 were more likely to have shorter ESRD duration compared to other cohorts.

$H_{0\ (1f)}$: Rejected.

Charlson Comorbidity Index (CCI) scores

$H_{0\ (1g)}$: Mean comorbidity scores will not differ significantly when categorized by Part D coverage.

The mean CCI scores of patients were 1.97 (SD=1.75) in cohort 1, 2.26 (SD=1.83) in cohort 2, 2.36 (SD=1.83) in cohort 3, and 1.93 (SD=1.72) in cohort 4. A one-way ANOVA revealed that the mean CCI scores differed significantly among cohorts (F=103.70; d.f.=3; p<.0001). Patients in cohort 1 or cohort 4 were more likely to have lower CCI scores than those in cohort 2 or cohort 3.

$H_{0\ (1d)}$: Rejected.

Presence of chronic disease

$H_{0\ (1h-\ 1m)}$: The proportion of patients with chronic diseases (cardiovascular disease [$H_{0(1h)}$], diabetes mellitus [$H_{0(1i)}$], hypertension [$H_{0(1j)}$], dyslipidemia [$H_{0(1k)}$], cancer [$H_{0(1l)}$], chronic lung disease [$H_{0(1m)}$]) will not differ significantly when categorized by Part D coverage.

Fifty-two percent of patients (n=1917) in cohort 1, 58.9 percent of patients (n=2562) in cohort 2, 60.8 percent of patients (n=797) in cohort 3, and 50.2 percent of patients (n=1202) in cohort 4 had a diagnosis of CVD, respectively. A chi-square test showed that the proportion of patients with CVD differed significantly among the cohorts

(χ^2=79.49; d.f.=3; p<.0001). Patients in cohort 3 were more likely to have a diagnosis of CVD relative to the other 3 cohorts.

$H_{0\ (1h)}$: Rejected.

Fifty percent of patients (n=1819) in cohort 1, 54.5 percent of patients (n=2372) in cohort 2, 54.1 percent of patients (n=709) in cohort 3, and 53.2 percent of patients (n=1273) in cohort 4 had a diagnosis of diabetes mellitus, respectively. A chi-square test showed that the proportion of patients with diabetes mellitus differed significantly among the cohorts (χ^2=22.66; d.f.=3; p<.0001).

$H_{0\ (1i)}$: Rejected.

Thirty-five percent of patients (n=1282) in cohort 1, 39.6 percent of patients (n=1722) in cohort 2, 41.1 percent of patients (n=538) in cohort 3, and 38.8 percent of patients (n=930) in cohort 4 had a diagnosis of hypertension, respectively. A chi-square test showed that the proportion of patients with hypertension differed significantly among the cohorts (χ^2=25.97; d.f.=3; p<.0001).

$H_{0\ (1j)}$: Rejected.

Twelve percent of patients (n=431) in cohort 1, 14.4 percent of patients (n=628) in cohort 2, 15.3 percent of patients (n=201) in cohort 3, and 10.5 percent of patients (n=251) in cohort 4 had a diagnosis of dyslipidemia, respectively. A chi-square test showed that

the proportion of patients with dyslipidemia differed significantly among the cohorts (χ^2=33.24; d.f.=3; p<.0001).

$H_{0\ (1k)}$: Rejected.

Seven percent of patients (n=259) in cohort 1, 8.1 percent of patients (n=353) in cohort 2, 9.4 percent of patients (n=123) in cohort 3, and 4.7 percent of patients (n=112) in cohort 4 had a diagnosis of cancer, respectively. A chi-square test showed that the proportion of patients with cancer differed significantly among the cohorts (χ^2=37.73; d.f.=3; p<.0001).

$H_{0\ (1l)}$: Rejected.

Nineteen percent of patients (n=684) in cohort 1, 22.4 percent of patients (n=974) in cohort 2, 24.5 percent of patients (n=321) in cohort 3, and 18.1 percent of patients (n=433) in cohort 4 had a diagnosis of chronic lung disease, respectively. A chi-square test showed that the proportion of patients with chronic lung disease differed significantly among the cohorts (χ^2=39.15; d.f.=3; p<.0001).

$H_{0\ (1m)}$: Rejected.

Table 3.2 Demographic and Clinical Characteristics in Study Cohorts (N= 11732)

	Cohort 1 (n=3678)		Cohort 2 (n=4349)		Cohort 3 (n=1310)		Cohort 4 (n=2395)		Test-statistic	p-value
Age [a]	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**		
	69.76	12.67	72.54	10.76	71.69	10.88	61.83	13.84	1018.55	<.0001
Gender [b]	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**		
Male	2272	61.77	2404	55.28	655	50.00	1258	52.53	81.47	<.0001
Female	1406	38.23	1945	44.72	655	50.00	1137	47.47		
Race [b]	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**		
Black	1233	33.52	912	20.97	220	16.79	1187	49.56	776.14	<.0001
White	2302	62.59	3304	75.97	1055	80.53	1106	46.18		
Other	143	3.89	133	3.06	35	2.67	102	4.26		
Region of residence [b]	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**		
Midwest	806	21.91	1169	26.88	320	24.43	300	12.53	528.21	<.0001
Northeast	975	26.51	1162	26.72	386	29.47	521	21.75		
South	1422	38.66	1484	34.12	421	32.14	1425	59.50		
West	475	12.91	534	12.28	183	13.97	149	6.22		
Primary disease causing ESRD [b]	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**		
Diabetes	1463	39.78	1958	45.02	567	43.28	1063	44.38	45.74	<.0001
Hypertension	1202	32.68	1292	29.71	373	28.47	744	31.06		
Glomerulonephritis	415	11.28	433	9.96	118	9.01	253	10.56		
Cystic Kidney	108	2.94	128	2.94	47	3.59	54	2.25		
Other	490	13.32	538	12.37	205	15.65	281	11.73		
ESRD duration [a]	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**		
	5.40	4.30	4.77	3.58	5.20	4.06	5.91	4.48	147.82	<.0001

Table 3.2 (continued)

Comorbidity [a]	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Charlson Comorbidity Index (CCI)	1.97	1.75	2.26	1.83	2.36	1.83	1.93	1.72	103.70	<.0001
Presence of chronic disease [b]	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**		
Cardiovascular disease	1917	52.12	2562	58.91	797	60.84	1202	50.19	79.49	<.0001
Diabetes mellitus	1819	49.46	2372	54.54	709	54.12	1273	53.15	22.66	<.0001
Hypertension	1282	34.86	1722	39.60	538	41.07	930	38.83	25.97	<.0001
Dyslipidemia	431	11.72	628	14.44	201	15.34	251	10.48	33.24	<.0001
Cancer	259	7.04	353	8.12	123	9.39	112	4.68	37.73	<.0001
Chronic lung disease	684	18.60	974	22.4	321	24.50	433	18.08	39.15	<.0001

a ANOVA test

b chi-square test

3.3 Phase II: Medication Adherence and Costs

3.3.1 Objective 2: Medication Utilization and Costs

To determine whether the proportion and number of prescription medications and pharmacy costs differ when categorized by Part D coverage.

3.3.1.1 Use of Oral Prescription Medications

$H_{0\ (2a\text{-}e)}$: The proportion of patients using antihyperglycemics [$H_{0(2a)}$], antihypertensives [$H_{0(2b)}$], lipid-lowering drugs [$H_{0(2c)}$], phosphate binders [$H_{0(2d)}$], or cinacalcet [$H_{0(2e)}$]) will not differ significantly when categorized by Part D coverage.

Table 3.3 shows the proportion of patients who had outpatient prescriptions for diabetes mellitus, hypertension, dyslipidemia, hyperphosphatemia, or hyperparathroidism.

Twenty-eight percent of patients (n=1027) in cohort 1, 41.37 percent of patients (n=1799) in cohort 2, 42.44 percent of patients (n=556) in cohort 3, and 37.83 percent of patients (n=906) in cohort 4 had at least one claim for antihyperglycemic drugs, respectively. A chi-square test showed that the proportion of patients with antihyperglycemic drugs differed significantly among the cohorts (χ^2=182.83; d.f.=3; p<.0001).

$H_{0\ (2a)}$: Rejected.

Eight-one percent of patients (n=2975) in cohort 1, 91.42 percent of patients (n=3976) in cohort 2, 90.76 percent of patients (n=1189) in cohort 3, and 89.06 percent of patients (n=2133) in cohort 4 had at least one claim for antihypertensive drugs, respectively. A chi-square test showed that the proportion of patients with antihypertensive drugs differed significantly among the cohorts (χ^2=227.33; d.f.=3; p<.0001).

$H_{0\ (2b)}$: Rejected.

Thirty-two percent of patients (n=1160) in cohort 1, 53.16 percent of patients (n=2312) in cohort 2, 60.53 percent of patients (n=793) in cohort 3, and 38.66 percent of patients (n=926) in cohort 4 had at least one claim for lipid-lowering drugs, respectively. A chi-square test showed that the proportion of patients with lipid-lowering drugs differed significantly among the cohorts (χ^2=552.02; d.f.=3; p<.0001).

$H_{0\ (2c)}$: Rejected.

Sixty percent of patients (n=2194) in cohort 1, 81.49 percent of patients (n=3544) in cohort 2, 91.60 percent of patients (n=1200) in cohort 3, and 80.33 percent of patients (n=1924) in cohort 4 had at least one claim for phosphate binders, respectively. A chi-square test showed that the proportion of patients with phosphate binders differed significantly among the cohorts (χ^2=798.46; d.f.=3; p<.0001).

$H_{0\ (2d)}$: Rejected.

Twelve percent of patients (n=439) in cohort 1, 24.76 percent of patients (n=1077) in cohort 2, 49.39 percent of patients (n=647) in cohort 3, and 35.70 percent of patients (n=855) in cohort 4 had at least one claim for calcimimetics, respectively. A chi-square test showed that the proportion of patients with calcimimetics differed significantly among the cohorts (χ^2=876.76; d.f.=3; p<.0001).

$H_{0\ (2e)}$: Rejected.

Note: Cinacalcet (Sensipar®) is the only available drug in calcimimetics in the United States so the generic name of cinacalcet will be used for calciminetics from this point forward.

Table 3.3 Proportion of Patients with Antihyperglycemics, Antihypertensives, Lipid-lowering Drugs, Phosphate Binders, or Cinacalcet among Cohorts (N=11732)

	Cohort 1 (n=3678)		Cohort 2 (n=4349)		Cohort 3 (n=1310)		Cohort 4 (n=2395)			
	N	%	N	%	N	%	N	%	χ^2	p-value
Antihyperglycemic drugs	1027	27.92	1799	41.37	556	42.44	906	37.83	182.83	<.0001
Antihypertensive drugs	2975	80.89	3976	91.42	1189	90.76	2133	89.06	227.33	<.0001
Lipid-lowering drugs	1160	31.54	2312	53.16	793	60.53	926	38.66	552.02	<.0001
Phosphate binders	2194	59.65	3544	81.49	1200	91.60	1924	80.33	798.46	<.0001
Cinacalcet	439	11.94	1077	24.76	647	49.39	855	35.70	876.76	<.0001

Note: Degrees of freedom equal 3 for all chi-square tests

$H_{0\ (2f\text{-}j)}$: The mean number of antihyperglycemics [$H_{0(2f)}$], antihypertensives [$H_{0(2g)}$], lipid-lowering drugs [$H_{0(2h)}$], phosphate binders [$H_{0(2i)}$], or cinacalcet [$H_{0(2j)}$]) will not differ significantly when categorized by Part D coverage.

Table 3.4 showed the mean numbers of prescriptions by five therapeutic classes of outpatient prescription drugs among cohorts.

A one-way ANOVA revealed that the mean number of **antihyperglycemic drugs** differed significantly when categorized by Part D coverage ($F=92.95$; d.f.=3; $p<.0001$). The mean number of antihypertensive drugs was 9.70 for patients in cohort 3 (SD=6.64), higher than the means for patients in cohort 2 (Mean= 7.21; SD=5.35) and cohort 4 (Mean=7.20; SD=5.36), respectively. Patients in cohort 1 (Mean= 5.16; SD= 3.90) had the least number of antihypertensive drugs compared to the other 3 cohorts. A Kruskal-Wallis test also showed a statistically significant difference among the cohorts ($\chi^2=237.65$; d.f.=3; $p<.0001$).

$H_{0\ (2f)}$: Rejected.

A one-way ANOVA revealed that the mean number of **antihypertensive drugs** differed significantly when categorized by Part D coverage ($F=255.54$; d.f.=3; $p<.0001$). The mean number of antihypertensive drugs was 23.08 (SD=15.78) for patients in cohort 3, which was higher than the means for patients in cohort 2 (Mean= 18.86; SD=12.98) and cohort 4 (Mean= 18.63; SD=13.64), respectively. Patients in cohort 1 (Mean= 12.37;

SD= 10.30) had the least number of antihypertensive drugs compared to the other 3 cohorts. A Kruskal-Wallis test also showed a statistically significant difference among the cohorts (χ^2=754.76; d.f.=3; p<.0001).

$H_{0\ (2g)}$: Rejected.

A one-way ANOVA revealed that the mean number of **lipid-lowering drugs** differed significantly when categorized by Part D coverage (F=113.76; d.f.=3; p<.0001). The mean number of lipid-lowering drugs was 8.70 (SD=4.74) for patients in cohort 3, higher than the means of 7.07 (SD=4.14) and 6.89 (SD=4.54) for patients in cohort 2 and cohort 4, respectively. Patients in cohort 1 (Mean= 5.09; SD= 3.71) had the least number of lipid-lowering drugs compared to other cohorts. A Kruskal-Wallis test also showed a statistically significant difference among the cohorts (χ^2=340.30; d.f.=3; p<.0001).

$H_{0\ (2h)}$: Rejected.

A one-way ANOVA revealed that the mean number of **phosphate binders** differed significantly when categorized by Part D coverage (F=314.44; d.f.=3; p<.0001). The mean number of phosphate binders was 8.20 for patients in cohort 3 (SD=4.65), higher than the means for patients in cohort 2 (Mean= 5.74; SD=3.88) and cohort 4 (Mean= 5.65; SD=3.85), respectively. Patients in cohort 1 (Mean= 4.03; SD= 2.99) had the least number of phosphate binders compared to the other 3 cohorts. A Kruskal-Wallis test

also showed a statistically significant difference among the cohorts (χ^2=869.73; d.f.=3; p<.0001).

$H_{0\ (2i)}$: Rejected.

A one-way ANOVA revealed that the mean number of **cinacalcet** prescriptions differed significantly when categorized by Part D coverage (F=190.9; d.f.=3; p<.0001). The mean number of cinacalcet prescriptions was 7.40 for patients in cohort 3 (SD=3.74), higher than the means for patients in cohort 2 (Mean= 4.42; SD=3.15) and cohort 4 (Mean= 5.45; SD=3.67), respectively. Patients in cohort 1 had the least number of cinacalcet prescriptions compared to other cohorts (Mean= 2.77; SD= 2.42). A Kruskal-Wallis test also showed a statistically significant difference among the cohorts (χ^2=1856.81; d.f.=3; p<.0001).

$H_{0\ (2j)}$: Rejected.

Table 3.4 Number of Prescriptions by Five Therapeutic Classes of Outpatient Prescription Drugs among Cohorts (N=11732)

	Cohort 1 (n=3678)		Cohort 2 (n=4349)		Cohort 3 (n=1310)		Cohort 4 (n=2395)			
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**F-value**	**p-value**
Antihyperglycemic drugs (n)	1027		1799		556		906			
No. of prescriptions	5.16	3.90	7.21	5.35	9.70	6.64	7.20	5.36	92.95	<.0001
Antihypertensive drugs (n)	2975		3976		1189		2133			
No. of prescriptions	12.37	10.30	18.86	12.98	23.08	15.78	18.63	13.64	255.54	<.0001
Lipid-lowering drugs (n)	1160		2312		793		926			
No. of prescriptions	5.09	3.71	7.07	4.41	8.70	4.74	6.89	4.54	113.76	<.0001
Phosphate binders (n)	2194		3544		1200		1924			
No. of prescriptions	4.03	2.99	5.74	3.88	8.20	4.65	5.65	3.85	314.44	<.0001
Cinacalcet (n)	439		1077		647		855			
No. of prescriptions	2.77	2.42	4.42	3.15	7.40	3.74	5.45	3.67	190.90	<.0001

Note: Degree of freedom equal 3 for all one-way ANOVAs

3.3.1.2 Costs of Prescription Medications

$H_{0\,(2k\text{-}p)}$: Pharmacy costs (i.e., antihyperglycemics [$H_{0(2k)}$], antihypertensives [$H_{0(2l)}$], lipid-lowering drugs [$H_{0(2m)}$], phosphate binders [$H_{0(2n)}$], cinacalcet [$H_{0(2o)}$], or all medication [$H_{0(2p)}$]) will not differ significantly when categorized by Part D coverage.

Table 3.5 shows total pharmacy costs and out-of-pocket costs by five therapeutic classes of outpatient prescription drugs during 2007.

One-way ANOVA revealed that mean total pharmacy costs including total and out-of-pocket costs for **antihyperglycemic drugs** were significantly different among the cohorts (F=106.79; d.f.=3; p<.0001 and F=411.33; d.f.=3; p<.0001, respectively). The mean total antihyperglycemic drug costs were $927 (SD=897) for patients in cohort 3, higher than the costs for patients in cohort 2 (Mean= $585; SD= 607) and cohort 4 (Mean=$608; SD=741); patients in cohort 1 had the lowest total cost compared to the other 3 cohorts (Mean=$327; SD=412). The mean out-of pocket cost was $287 [SD=307] for patients in cohort 2, $141 lower than the cost for patients in cohort 3 (Mean=$428; SD=402), but $185 higher than the costs for cohort 1 (Mean=$102; SD=97) and cohort 4 (Mean=$32; SD=35). A Kruskal-Wallis test also showed that pharmacy costs including total and out-of-pocket costs for antihyperglycemic drugs were significantly different among the cohorts (χ^2=313.00; d.f.=3; p<.0001 and χ^2=1540.16; d.f.=3; p<.0001, respectively).

$H_{0\,(2k)}$: Rejected.

One-way ANOVA revealed that pharmacy costs including total and out-of-pocket costs for **antihypertensive drugs** were significantly different among the cohorts (F=325.66; d.f.=3; p<.0001 and F=1173.42; d.f.=3; p<.0001, respectively). The mean total antihypertensive drug costs were higher for patients in cohort 3 (Mean= $1056; SD=972) than the means for patients in cohort 2 (Mean= $758; SD= 640) and cohort 4 (Mean=$785; SD=790); patients in cohort 1 (Mean=$405; SD=420) had the lowest mean total cost compared to the other 3 cohorts. The mean out-of pocket cost was $365 (SD=339) for patients in cohort 2, $153 lower than the cost for patients in cohort 3 (Mean=$518; SD=496), but higher than the costs for those in cohort 1 (Mean=$120; SD=118) and cohort 4 (Mean=$51; SD=52). A Kruskal-Wallis test also showed that pharmacy costs including total and out-of-pocket costs for antihypertensive drugs were significantly different among cohorts (χ^2=903.43; d.f.=3; p<.0001 and χ^2=3395.69; d.f.=3; p<.0001, respectively).

$H_{0\ (2l)}$: Rejected.

One-way ANOVA revealed that pharmacy costs including total and out-of-pocket costs for **lipid-lowering drugs** were significantly different among cohorts (F=154.35; d.f.=3; p<.0001 and F=525.68; d.f.=3; p<.0001, respectively). The mean total lipid-lowering drug cost was $733 for patients in cohort 3 (Mean= $733; SD=520), higher than the costs for patients in cohort 2 (Mean= $517; SD= 453) and cohort 4 (Mean=$525; SD=452);

mean total cost for patients in cohort 1 (Mean=$304; SD=314) was the lowest among the cohorts. The mean out-of pocket costs were $240 (SD=242) for patients in cohort 2, $106 lower than the cost for patients in cohort 3 (Mean=$346; SD=274), but higher than the costs for cohort 1 (Mean=$82; SD=90) and cohort 4 (Mean=$29; SD=33). A Kruskal-Wallis test also showed that pharmacy costs including total and out-of-pocket costs for lipid-lowering drugs were significantly different among cohorts (χ^2=446.59; d.f.=3; p<.0001 and χ^2=1747.61; d.f.=3; p<.0001, respectively).

$H_{0\ (2m)}$: Rejected.

One-way ANOVA revealed that pharmacy costs including total and out-of-pocket costs for **phosphate binders** were significantly different among cohorts (F=502.82; d.f.=3; p<.0001 and F=1959.13; d.f.=3; p<.0001, respectively). The mean total phosphate binder cost was $2,922 for patients in cohort 3 (SD=2301), higher than the costs for patients in cohort 2 (Mean= $1291; SD= 1288) and cohort 4 (Mean=$1877; SD=2151); patients in cohort 1 (Mean=$810; SD=898) had the lowest total cost among the cohorts. The mean out-of pocket costs were $454 [SD=455] for patients in cohort 2, $856 lower than the cost for patients in cohort 3 (Mean=$1130; SD=824), but higher than the costs for cohort 1 (Mean=$133; SD=109) and cohort 4 (Mean=$42; SD=59). A Kruskal-Wallis test also showed that pharmacy costs including total and out-of-pocket costs for

phosphate binders were significantly different among cohorts (χ^2=1266.36; d.f.=3; p<.0001 and χ^2=4816.94; d.f.=3; p<.0001, respectively).

$H_{0\ (2n)}$: Rejected.

One-way ANOVA revealed that pharmacy costs including total and out-of-pocket costs for **cinacalcet** were significantly different among the cohorts (F=115.25; d.f.=3; p<.0001 and F=663.31; d.f.=3; p<.0001, respectively). The mean total cinacalcet cost for patients in cohort 3 (Mean= $3925; SD=3129) was higher than the costs for patients in cohort 2 (Mean= $2044; SD= 2076) and cohort 4 (Mean=$3109; SD=3012); for patients in cohort 1 had the lowest mean total costs (Mean=$1385; SD=1906) among the cohorts. The mean out-of pocket costs were$674 [SD=626] for patients in cohort 2, $807 lower than the cost for patients in cohort 3 (Mean=$1481; SD=1159), but higher than costs for cohort 1 (Mean=$152; SD=134) and cohort 4 (Mean=$44; SD=83). A Kruskal-Wallis test also showed that total and out-of-pocket pharmacy costs for **cinacalcet** were significantly different among the cohorts (χ^2=481.27; d.f.=3; p<.0001 and χ^2=1856.81; d.f.=3; p<.0001, respectively).

$H_{0\ (2o)}$: Rejected.

One-way ANOVA revealed that pharmacy costs including total and out-of-pocket costs for all prescription drugs were significantly different among the cohorts (F=6151.80;

d.f.=3; p<.0001 and F=9910.60; d.f.=3; p<.0001, respectively). The mean total drug cost for patients in cohort 3 (Mean= $10659; SD=7112) was higher than the costs for patients in cohort 2 (Mean= $4431; SD= 2614) and cohort 4 (Mean=$5312; SD=4869); patients in cohort 1 had the lowest total drug cost (Mean=$1820; SD=1618) among the cohorts. The mean out-of pocket costs were $1854 (SD=827) for patients in cohort 2, $2299 lower than the cost for patients in cohort 3 (Mean=$4153; SD=780), but higher than the costs for cohort 1 (Mean=$423; SD=217) and cohort 4 (Mean=$192; SD=157). A Kruskal-Wallis test also showed that total and out-of-pocket pharmacy costs for all prescription drugs were significantly different among cohort (χ^2=6151.80; d.f.=3; p<.0001 and χ^2=9910.60; d.f.=3; p<.0001, respectively).

$H_{0\ (2p)}$: Rejected.

Table 3.5 Total Pharmacy Costs and Out-of-pocket Costs by Five Therapeutic Classes of Outpatient Prescription Drugs and Total Prescription Drugs among Cohorts (N=11732)

	Cohort 1 (n=3678)		Cohort 2 (n=4349)		Cohort 3 (n=1310)		Cohort 4 (n=2395)			
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	F-value	p-value
Antidiabetic drugs (n=4288)	1027		1799		556		906			
Total costs	$327	412	$585	607	$927	897	$608	741	106.79	<.0001
Out-of-pocket costs	$102	97	$287	307	$428	402	$32	35	411.33	<.0001
Antihypertensive drugs (n=10273)	2975		3976		1189		2133			
Total costs	$405	420	$758	640	$1,056	972	$785	790	325.66	<.0001
Out-of-pocket costs	$120	118	$365	339	$518	496	$51	52	1173.42	<.0001
Lipid-lowering drugs (n=5191)	1160		2312		793		926			
Total costs	$304	314	$517	453	$733	520	$525	452	154.35	<.0001
Out-of-pocket costs	$82	90	$240	242	$346	274	$29	33	525.68	<.0001
Phosphate binders (n=8862)	2194		3544		1200		1924			
Total costs	$810	898	$1,291	1,288	$2,922	2,301	$1,877	2,151	502.82	<.0001
Out-of-pocket costs	$133	109	$454	455	$1,130	824	$42	59	1959.13	<.0001
Cinacalcet (n=3018)	439		1077		647		855			
Total costs	$1,385	1,906	$2,044	2,076	$3,925	3,129	$3,109	3,012	115.25	<.0001
Out-of-pocket costs	$152	134	$674	626	$1,481	1,159	$44	83	663.31	<.0001
All prescription drugs (N=11732)	3678		4349		1310		2395			
Total costs	$1,820	1,618	$4,431	2,614	$10,659	7,112	$5,312	4,869	1871.87	<.0001
Out-of-pocket costs	$423	217	$1,854	827	$4,153	780	$192	157	17354.60	<.0001

Note: Degrees of freedom equal 3 for all one-way ANOVAs

3.3.2 Objective 3: Medication Adherence and Persistence

To determine whether medication adherence and persistence among patients receiving drug therapy for diabetes, hypertension, hyperlipidemia, hyperphosphatemia or secondary parathyroid differ when categorized by Part D coverage.

Medication adherence and persistence were measured using both descriptive statistics and regression models. One-way ANOVAs and Kruskal-Wallis tests were performed to compare mean MPR and persistence until the first 30-day gap. Patients with an adherence (MPR) of less than 80 percent were assigned a value of 0 while 1 was assigned to those with MPR greater than or equal to 80 percent. Pearson Chi-square tests was used to compare the proportions of patients who were adherent. Logistic regression was employed to determine if adherence is associated with Part D coverage gap while controlling for age, gender, race, region of residence, primary disease causing ESRD, ESRD duration, CCI score, and presence of chronic disease including CVD, diabetes mellitus, hypertension, dyslipidemia, cancer, and chronic lung disease. A generalized estimating equation model was used to determine if adherence was associated with pre- and post- Part D coverage gap while controlling for covariates. Kaplan-Meier survival curves were used to depict the percentage of patients who remain persistent in the study period. A Cox regression model was used to determine if persistence is associated with Part D coverage while controlling for covariates.

3.3.2.1 Mean Medication Possession Ratio (MPR)

$H_{0\ (3a\text{-}e)}$: Medication adherence (i.e., antihyperglycemics [$H_{0(3a)}$], antihypertensives [$H_{0(3b)}$], lipid-lowering drugs [$H_{0(3c)}$], phosphate binders [$H_{0(3d)}$], or cinacalcet [$H_{0(3e)}$]) will not differ significantly when categorized by Part D coverage.

Table 3.6 shows the mean MPRs by five therapeutic classes of outpatient prescription drugs among cohorts. One-way ANOVAs revealed that mean MPR differed significantly among cohorts across all five therapeutic classes of outpatient prescription medications.

Regarding **antihyperglycemic drug therapies**, the mean MPR was 75.48 percent (SD=24.78) for patients in cohort 3, higher than the means for those in cohort 2 (Mean=65.74%; SD=26.99) and cohort 4 (Mean=67.80%; SD=26.79). The mean MPR was lowest for patients in cohort 1 (Mean=59.47%; SD=27.46) compared to the other 3 cohorts. A one-way ANOVA revealed that mean MPR differed significantly among cohorts ($F=40.03$; d.f.=3; $p<.0001$). A Kruskal-Wallis test also showed a statistically significant difference among the cohorts ($\chi^2=118.82$; d.f.=3; $p<.0001$).

$H_{0\ (3a)}$: Rejected.

Regarding **antihypertensive drug therapies**, the mean MPR for patients in cohort 3 was 86.83 percent (SD=17.82), higher than the means for those in cohort 2 (Mean=82.38%; SD=19.85) and cohort 4 (Mean=79.08%; SD=22.27). The mean MPR was lowest for

patients in cohort 1 (Mean=73.65%; SD=24.19). A one-way ANOVA revealed that mean MPR differed significantly among the cohorts (F=137.03; d.f.=3; p<.0001). A Kruskal-Wallis test also showed a statistically significant difference among the cohorts (χ^2=362.69; d.f.=3; p<.0001).

$H_{0\ (3b)}$: Rejected.

Regarding **lipid-lowering drug therapies**, the mean MPR for patients in cohort 3 was 84.15 percent (SD=18.05), higher than the MPRs for those in cohort 2 (Mean=75.33%; SD=23.32) and cohort 4 (Mean=74.49%; SD=23.41). The mean MPR was lowest for patients in cohort 1 (Mean=67.81%; SD=26.23) compared to the other 3 cohorts. A one-way ANOVA revealed that mean MPR differed significantly among cohorts (F=68.44; d.f.=3; p<.0001). A Kruskal-Wallis test also showed a statistically significant difference among the cohorts (χ^2=172.34; d.f.=3; p<.0001).

$H_{0\ (3c)}$: Rejected.

Regarding **phosphate binder therapies**, the mean MPR for patients in cohort 3 was 70.84 percent (SD=22.64), higher than the means for those in cohort 2 (Mean=57.02%; SD=23.74) and cohort 4 (Mean=57.23%; SD=24.16). The mean MPR was lowest for patients in cohort 1 (Mean=48.72%; SD=23.35) compared to the other 3 cohorts. A one-way ANOVA revealed that mean MPR differed significantly among cohorts

(F=203.05; d.f.=3; p<.0001). A Kruskal-Wallis test also showed a statistically significant difference among the cohorts (χ^2=563.63; d.f.=3; p<.0001).

$H_{0\ (3d)}$: Rejected.

Regarding **cinacalcet therapies**, the mean MPR for patients in cohort 3 was 77.22 percent (SD=22.12), higher than the means for those in cohort 2 (Mean=56.81%; SD=25.79) and cohort 4 (Mean=65.05%; SD=25.74). The mean MPR was the lowest for patients in cohort 1 (Mean=48.66%; SD=3.98) compared to the other 3 cohorts. A one-way ANOVA revealed that mean MPR differed significantly among cohorts (F=112.62; d.f.=3; p<.0001). A Kruskal-Wallis test also showed a statistically significant difference among the cohorts (χ^2=295.50; d.f.=3; p<.0001).

$H_{0\ (3e)}$: Rejected.

Table 3.6 Mean MPR by Five Therapeutic Classes of Outpatient Prescription Drugs among Cohorts (N=11732)

	Cohort 1 (n=3678)		Cohort 2 (n=4349)		Cohort 3 (n=1310)		Cohort 4 (n=2395)			
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	F-value	p-value
Antihyperglycemic drugs (n=3819)	851		1630	42.68	523	13.69	815	21.34		
MPR (Mean, SD)	59.47	27.46	65.74	26.99	75.48	24.78	67.80	26.79	40.03	<.0001
Antihypertensive drugs (n=9863)	2772		3863		1167		2061			
MPR (Mean, SD)	73.65	24.19	82.38	19.85	86.83	17.82	79.08	22.27	137.03	<.0001
Lipid-lowering drugs (n=4607)	922		2119		746		820			
MPR (Mean, SD)	67.81	26.23	75.33	23.32	84.15	18.05	74.49	23.41	68.44	<.0001
Phosphate binders (n=7753)	1729		3185		1151		1688			
MPR (Mean, SD)	48.72	23.35	57.02	23.74	70.84	22.64	57.23	24.16	203.05	<.0001
Cinacalcet (n=2436)	261		854		606		718			
MPR (Mean, SD)	48.66	3.98	56.81	25.79	77.22	22.12	65.05	25.74	112.62	<.0001

Note: Degrees of freedom equal 3 for all one-way ANOVAs

3.3.2.2 Proportion of Patients with MPR ≥ 80%

$H_{0\ (3f\text{-}j)}$: The proportion of patients who are adherent (MPR ≥ 80%) to antihyperglycemics [$H_{0(3f)}$], antihypertensives [$H_{0(3g)}$], lipid-lowering drugs [$H_{0(3h)}$], phosphate binders [$H_{0(3i)}$], or cinacalcet [$H_{0(3j)}$]) will not differ significantly when categorized by Part D coverage.

Table 3.7 shows the chi-square comparison of MPR≥80% by five therapeutic classes of outpatient prescription drugs. A chi-square analysis of MPR revealed that the proportion of patients with MPR ≥ 80% differed significantly among the cohorts for all five therapeutic classes of outpatient prescription medications.

Among patients on **antihyperglycemic drugs** (n=3918), 29.4 percent of patients in cohort 1, 38.2 percent patients in cohort 2, 52.6 percent patients in cohort 3, and 41.0 percent patients were adherent (MPR≥ 80%) to antihyperglycemic drugs (χ^2=75.58; d.f.=3; p<.0001).

Among patients on **antihypertensives** (n=9863), 47.3 percent of patients in cohort 1, 62.9 percent patients in cohort 2, 72.8 percent patients in cohort 3, and 57.0 percent patients were adherent (MPR≥ 80%) to antihypertensive drugs (χ^2=274.12; d.f.=3; p<.0001).

Among patients on **lipid-lowering drugs** (n=4607), 47.7 percent of patients in cohort 1, 54.0 percent patients in cohort 2, 70.9 percent patients in cohort 3, and 51.5 percent

patients were adherent (MPR≥ 80%) to lipid-lowering drugs (χ^2=135.14; d.f.=3; p<.0001).

Among patients on **phosphate binders** (n=7753), 12.6 percent of patients in cohort 1, 20.6 percent patients in cohort 2, 39.7 percent patients in cohort 3, and 21.0 percent patients were adherent (MPR≥ 80%) to phosphate binders (χ^2=306.22; d.f.=3; p<.0001).

Among patients on **cinacalcet** (n=2436), 17.2 percent of patients in cohort 1, 23.9 percent patients in cohort 2, 55.1 percent patients in cohort 3, and 37.1 percent patients were adherent (MPR≥ 80%) to cinacalcet (χ^2=192.09; d.f.=3; p<.0001).

Patients in cohort 3 were more likely to achieve adherence rates of ≥ 80 percent to antihyperglycemics, antihypertensives, lipid-lowering drugs, phosphate binders, and cinacalcet relative to those in cohort 2 or cohort 4, while patients in cohort 1 were less likely to be adherent to these drugs.

Table 3.7 Treatment Patterns and Proportion of Patients with MPR ≥ 80% in Patients by Five Therapeutic Classes of Outpatient Prescription Drugs among Cohorts (N=11732)

	Cohort 1 (n=3678)		Cohort 2 (n=4349)		Cohort 3 (n=1310)		Cohort 4 (n=2395)		χ^2	p-value
	N	%	N	%	N	%	N	%		
Antihyperglycemic drugs (n=3819)	851	22.28	1630	42.68	523	13.69	815	21.34		
Mono	835	98.12	1532	93.99	458	87.57	760	93.25		
Dual	15	1.76	96	5.89	63	12.05	54	6.63		
Triple	1	0.12	2	0.38	2	0.38	1	0.12		
MPR > 80%	**250**	**29.38**	**622**	**38.16**	**275**	**52.58**	**334**	**40.98**	**75.58**	**<.0001**
Antihypertensive drugs (n=9863)	2772	28.11	3863	39.17	1167	11.83	2061	20.9		
Mono	1522	54.91	1359	35.18	361	30.93	746	36.2		
Dual	819	29.55	1289	33.37	369	31.62	695	33.72		
Triple	431	15.55	1190	30.81	433	37.1	612	29.69		
Quad	0	0	25	0.65	4	0.34	8	0.39		
MPR > 80%	**1311**	**47.29**	**2431**	**62.93**	**849**	**72.75**	**1174**	**56.96**	**274.12**	**<.0001**
Lipid-lowering drugs (n=4607)	922	20.01	2119	46	746	16.19	820	17.8		
Mono	911	98.81	2011	94.9	680	91.15	790	96.34		
Dual	11	1.19	106	5	62	8.31	29	3.54		
Triple	0	0	2	0.09	4	0.54	1	0.12		
MPR > 80%	**394**	**42.73**	**1144**	**53.99**	**529**	**70.91**	**422**	**51.46**	**135.14**	**<.0001**
Phosphate binders (n=7753)	1729	22.3	3185	41.08	1151	14.85	1688	21.77		
Mono	1709	98.84	3103	97.43	1087	94.44	1629	96.50		
Dual	20	1.16	80	2.51	62	5.39	59	3.5		
Triple	0	0	2	0.06	2	0.17	0	0		
MPR > 80%	**218**	**12.61**	**655**	**20.57**	**457**	**39.7**	**355**	**21.03**	**306.22**	**<.0001**
Cinacalcet (n=2436)	261	7.1	854	19.64	606	46.26	718	29.98		
MPR > 80%	**45**	**17.24**	**204**	**23.89**	**334**	**55.12**	**266**	**37.05**	**192.09**	**<.0001**

Antihyperglycemics

Table 3.8 shows the results of the logistic regression model comparing the proportion of patients with MPR≥ 80% in patients receiving antihyperglycemic drugs among cohorts, while controlling for covariates. The overall statistics for the model testing the null hypothesis that all parameter estimates are equal to zero indicated that the null hypothesis was rejected ($p<0.001$). In addition, the Hosmer-Lemeshow test indicated that the model was of good fit ($\chi^2=6.78$; d.f.=8; $p=0.5602$).

This model indicated that patients in cohort 1 and cohort 2 were 47.7 percent and 23.8 percent less likely to be adherent to antihyperglycemic drugs compared to patients in cohort 4, respectively (Odds Ratio (OR) =0.523; 95% CI= 0.422 – 0.647; OR=0.762; 95% CI= 0.632 – 0.918). However, patients in cohort 3 were 40.2 percent more likely to be adherent to antihyperglycemic drugs compared to those in cohort 4 after controlling for covariates (OR= 1.402; 95% CI= 1.109 – 1.771).

Significant predictors of adherence to antihyperglycemic drugs were gender, race, ESRD duration, primary disease causing ESRD (hypertension), CCI score, and the presence of cancer. Female gender was associated with a 12.8 percent decrease in the odds of adherence to antihyperglycemic drugs compared with male gender (OR = 0.872; 95% CI: 0.761 – 0.998). Being white and other were 51.9 percent and 50.6 percent more likely to be adherent to antihyperglycemic drugs compared with being black (OR= 1.519; 95% CI: 1.289 – 1.792; OR=1.506; 95% CI: 1.029 – 2.204). Each year increase in ESRD

duration was associated with a 4.1 percent decrease in the odds of adherence to antihyperglycemic drugs (OR=0.959; 95% CI = 0.934-0.984). Hypertension as the primary disease causing ESRD was associated with a 32.9 percent increase in the odds of being adherent to antihyperglycemic drugs compared with diabetes mellitus (OR=1.329; 95% CI= 1.078 – 1.638). Each unit increase in CCI score was associated with a 12.8 percent decrease in the odds of being adherent to antihyperglycemic drugs (OR=0.872; 95% CI = 0.808-0.941). The presence of cancer was associated with a 44.7 percent increase in the odds of being adherent to antihyperglycemic drugs (OR=1.447; 95% CI= 1.017 – 2.059).

$H_{0\ (3f)}$: Rejected.

Table 3.8 Logistic Regression Model Comparing the Proportion of Patients with MPR ≥ 80% in Patients Receiving Antihyperglycemic Drugs while Controlling for Covariates (N= 3918)

Variable		Parameter Estimate	Standard Error	Wald Chi-Square	p-value	Odds Ratio	95% Confidence Interval
Intercept		-0.472	0.276	2.914	0.088		
Cohort [a]	1	-0.649	0.109	35.239	<.0001	0.523	0.422 - 0.647
	2	-0.272	0.095	8.195	0.004	0.762	0.632 - 0.918
	3	0.338	0.119	8.010	0.005	1.402	1.109 - 1.771
Age		0.005	0.003	2.176	0.140	1.005	0.998 - 1.012
Gender [b]	Female	-0.137	0.069	3.928	0.048	0.872	0.761 - 0.998
Race [c]	White	0.418	0.084	24.817	<.0001	1.519	1.289 - 1.791
	Other	0.409	0.194	4.432	0.035	1.506	1.029 - 2.204
Region of residence [d]	Northeast	0.084	0.100	0.707	0.400	1.087	0.894 - 1.322
	South	-0.084	0.093	0.820	0.365	0.92	0.767 - 1.103
	West	0.015	0.126	0.014	0.907	1.015	0.793 - 1.299
ESRD duration		-0.042	0.013	9.976	0.002	0.959	0.934 - 0.984
Primary disease causing ESRD [e]	Hypertension	0.284	0.107	7.115	0.008	1.329	1.078 - 1.638
	Glomerulonephritis	0.065	0.268	0.059	0.808	1.067	0.631 -1.805
	Cystic Kidney	0.253	0.518	0.239	0.625	1.288	0.467 - 3.557
	Other	0.002	0.168	0.000	0.991	1.002	0.722 - 1.391
Charlson Comorbidity Index (CCI) score		-0.137	0.039	12.555	0.000	0.872	0.808 - 0.941
Presence of chronic disease	Diabetes mellitus	0.145	0.130	1.243	0.265	1.156	0.896 - 1.491
	Hypertension	0.063	0.074	0.737	0.391	1.065	0.922 - 1.231
	Dyslipidemia	0.017	0.096	0.033	0.856	1.018	0.843 - 1.228
	Cancer	0.369	0.180	4.208	0.040	1.447	1.017 - 2.059
	Chronic lung disease	0.013	0.104	0.016	0.899	1.013	0.827 - 1.241
	Cardiovascular disease	-0.047	0.097	0.239	0.625	0.954	0.788 - 1.154

Model parameters: *Likelihood Ratio* = 170.27; *d.f.*=22; $p<0.0001$; *Score* = 166.13; *d.f.*=22; $p<0.0001$; *Wald* = 158.76; *d.f.*=22; $p< 0.0001$.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Antihypertensives

Table 3.9 shows the results of the logistic regression model comparing the proportion of patients with MPR≥ 80% in patients receiving antihypertensive drugs among cohorts, while controlling for covariates. The overall statistics for the model testing the null hypothesis that all parameter estimates are equal to zero indicated that the null hypothesis was rejected ($p<0.001$). In addition, the Hosmer-Lemeshow test indicated that the model was of good fit ($\chi^2=4.89$; d.f.=8; $p=0.7694$).

This model indicated that patients in cohort 1 were 41.1 percent less likely to be adherent (OR= 0.589; 95% CI= 0.522 – 0.665) but patients in cohort 3 were 68.1 percent more likely to be adherent to antihypertensive drugs (OR= 1.681; 95% CI= 1.428 – 1.978) compared to patients in cohort 4 after controlling for covariates. There was no significant differences between patients with MPR≥ 80% in cohort 2 and cohort 4 (OR=1.055; 95% CI=0.937 – 1.188).

Significant predictors of adherence to antihypertensive drugs were age, gender, race, ESRD duration, and CCI score. Each year increase in age was associated with a 1.1 percent increase in the odds of being adherent to antihypertensive drugs (OR=1.011; 95% CI= 1.007 – 1.015). Female gender was associated with a 12.0 percent increase in the odds of adherence to antihypertensive drugs compared with male gender (OR = 1.120; 95% CI: 1.030 - 1.218). Being white were 21.1 percent more likely to be adherent to antihypertensive drugs compared with being black (OR=1.211; 95% CI=1.097 - 1.335).

Each unit increase in the year of ESRD duration was associated with a 2.2 percent decrease in the odds of being adherent to antihypertensive drugs (OR=0.978; 95% CI=0.967 - 0.989). Each unit increase in CCI score was associated with a 7.2 percent decrease in the odds of adherence to antihypertensive drugs (OR=0.928; 95% CI = 0.885 -0.972).

$H_{0\ (3g)}$: Rejected.

Table 3.9 Logistic Regression Model Comparing the Proportion of Patients with MPR ≥ 80% in Patients Receiving Antihypertensive Drugs while Controlling for Covariates (N=9863)

Variable		Parameter Estimate	Standard Error	Wald Chi-Square	p-value	Odds Ratio	95% Confidence Interval
Intercept		-0.277	0.153	3.292	0.070		
Cohort [a]	1	-0.529	0.062	73.514	<.0001	0.589	0.522 - 0.665
	2	0.054	0.060	0.785	0.376	1.055	0.937 - 1.188
	3	0.519	0.083	39.111	<.0001	1.681	1.428 - 1.978
Age		0.011	0.002	33.301	<.0001	1.011	1.007 - 1.015
Gender [b]	Female	0.113	0.043	7.018	0.008	1.120	1.030 - 1.218
Race [c]	White	0.191	0.050	14.545	0.000	1.211	1.097 - 1.335
	Other	0.015	0.122	0.015	0.902	1.015	0.799 - 1.290
Region of residence [d]	Northeast	-0.079	0.062	1.655	0.198	0.924	0.819 - 1.042
	South	-0.088	0.058	2.317	0.128	0.916	0.817 - 1.026
	West	0.023	0.080	0.081	0.776	1.023	0.875 - 1.196
ESRD duration		-0.022	0.006	15.081	0.000	0.978	0.967 - 0.989
Primary disease causing ESRD [e]	Hypertension	0.033	0.059	0.320	0.572	1.034	0.921 - 1.160
	Glomerulonephritis	0.011	0.083	0.016	0.898	1.011	0.859 - 1.189
	Cystic Kidney	-0.176	0.137	1.649	0.199	0.839	0.642 - 1.097
	Other	-0.045	0.077	0.341	0.559	0.956	0.823 - 1.111
Charlson Comorbidity Index (CCI) score		-0.075	0.024	9.817	0.002	0.928	0.885 - 0.972
Presence of chronic disease	Diabetes mellitus	-0.015	0.066	0.051	0.821	0.985	0.865 - 1.122
	Hypertension	0.086	0.045	3.590	0.058	1.089	0.997 - 1.190
	Dyslipidemia	0.032	0.063	0.264	0.608	1.033	0.913 - 1.169
	Cancer	0.162	0.103	2.494	0.114	1.176	0.962 - 1.439
	Chronic lung disease	0.003	0.061	0.002	0.966	1.003	0.890 - 1.130
	Cardiovascular disease	0.086	0.058	2.217	0.137	1.090	0.973 - 1.220

Model parameters: Likelihood Ratio = 423.50; d.f.=22; p<0.0001; Score = 1416.46; d.f.=22; p<0.0001; Wald = 400.49; d.f.=22; p<0.0001

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Lipid-lowering drugs

Table 3.10 shows the results of the logistic regression model comparing the proportion of patients with MPR≥ 80% in patients receiving lipid-lowering drugs among cohorts, while controlling for covariates. The overall statistics for the model testing the null hypothesis that all parameter estimates are equal to zero indicated that the null hypothesis was rejected ($p<0.001$). In addition, the Hosmer-Lemeshow test indicated that the model was of good fit ($\chi^2=4.75$; d.f.=8; $p=0.7836$).

This model indicated that patients in cohort 1 and cohort 2 were 49.0 percent and 20.2 percent less likely to be adherent to lipid-lowering drugs compared to those in cohort 4, respectively (OR=0.510; 95% CI= 0.416 – 0.625; OR=0.798; 95% CI= 0.669 – 0.951). However, patients in cohort 3 were 70.9 percent more likely to be adherent to lipid-lowering drugs compared to those in cohort 4 after controlling for covariates (OR= 1.709; 95% CI= 1.372 – 2.130).

Significant predictors of adherence to lipid-lowering drugs were age, race, primary disease causing ESRD (hypertension or glomerulonephritis), and the presence of CVD. Each year increase in age was associated with a 2.3 percent increase in the odds of being adherent to lipid-lowering drugs (OR=1.023; 95% CI= 1.017 – 1.030). Being white and other were 55.3 percent and 51.2 percent more likely to be adherent to lipid-lowering drugs compared with being black (OR=1.553; 95% CI=1.334 – 1.808; OR=1.512; 95% CI= 1.053 – 2.172). Hypertension and glomerulonephritis as the primary disease causing ESRD were 20.4 percent and 31.4 percent more likely to be adherent to lipid-

lowering drugs compared with diabetes mellitus (OR=1.204; 95% CI= 1.018 – 1.426; OR= 1.314; 95% CI=1.015 – 1.700). The presence of CVD was associated with a 16.7 percent decrease in the odds of being adherent to lipid-lowering drugs (OR=0.833; 95% CI= 0.705 – 0.985).

$H_{0\ (3h)}$: Rejected.

Table 3.10 Logistic Regression Model Comparing the Proportion of Patients with MPR ≥ 80% in Patients Receiving Lipid-lowering Drugs while Controlling for Covariates (N=4607)

Variable		Parameter Estimate	Standard Error	Wald Chi-Square	p-value	Odds Ratio	95% Confidence Interval
Intercept		-1.639	0.259	40.125	<.0001		
Cohort [a]	1	-0.673	0.104	42.291	<.0001	0.510	0.416 - 0.625
	2	-0.226	0.090	6.349	0.012	0.798	0.669 - 0.951
	3	0.536	0.112	22.822	<.0001	1.709	1.372 - 2.130
Age		0.023	0.003	52.617	<.0001	1.023	1.017 - 1.030
Gender [b]	Female	0.014	0.062	0.052	0.820	1.014	0.898 - 1.146
Race [c]	White	0.440	0.078	32.128	<.0001	1.553	1.334 - 1.808
	Other	0.414	0.185	5.016	0.025	1.512	1.053 - 2.172
Region of residence [d]	Northeast	0.056	0.088	0.407	0.524	1.058	0.890 - 1.256
	South	-0.149	0.085	3.090	0.079	0.862	0.730 - 1.017
	West	0.121	0.114	1.127	0.288	1.128	0.903 - 1.410
ESRD duration		0.009	0.010	0.847	0.358	1.009	0.990 - 1.028
Primary disease causing ESRD [e]	Hypertension	0.186	0.086	4.682	0.031	1.204	1.018 - 1.426
	Glomerulonephritis	0.273	0.132	4.302	0.038	1.314	1.015 - 1.700
	Cystic Kidney	-0.212	0.216	0.964	0.326	0.809	0.529 - 1.236
	Other	0.116	0.113	1.053	0.305	1.123	0.900 - 1.402
Charlson Comorbidity Index (CCI) score		-0.012	0.035	0.124	0.725	0.988	0.923 - 1.057
Presence of chronic disease	Diabetes mellitus	0.017	0.096	0.030	0.862	1.017	0.843 - 1.226
	Hypertension	0.127	0.066	3.699	0.054	1.135	0.998 - 1.291
	Dyslipidemia	-0.088	0.077	1.306	0.253	0.916	0.787 - 1.065
	Cancer	0.012	0.146	0.007	0.935	1.012	0.761 - 1.346
	Chronic lung disease	-0.077	0.088	0.761	0.383	0.926	0.780 - 1.100
	Cardiovascular disease	-0.182	0.086	4.553	0.033	0.833	0.705 - 0.985

Model parameters: Likelihood Ratio = 301.49; d.f.=22; p<0.0001; Score = 291.76; d.f.=22; p<0.0001; Wald = 273.98; d.f.=22; p< 0.0001.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Phosphate binders

Table 3.11 shows the results of the logistic regression model comparing the proportion of patients with MPR≥ 80% in patients receiving phosphate binders among cohorts, while controlling for covariates. The overall statistics for the model testing the null hypothesis that all parameter estimates are equal to zero indicated that the null hypothesis was rejected ($p<0.001$). In addition, the Hosmer-Lemeshow test indicated that the model was of good fit ($\chi^2=10.35$; d.f.=8; $p=0.2413$).

This model indicated that patients in cohort 1 and cohort 2 were 61.1 percent and 35.3 percent less likely to be adherent to phosphate binders compared to those in cohort 4, respectively (OR=0.389; 95% CI= 0.320 – 0.474; OR=0.647; 95% CI= 0.549 – 0.761). However, patients in cohort 3 were 67.6 percent more likely to be adherent to phosphate binders compared to those in cohort 4 after controlling for covariates (OR= 1.676; 95% CI= 1.399 – 2.008).

Significant predictors of adherence to phosphate binders were age, gender, race, and region of residence (south). Each year increase in age was associated with a 1.3 percent increase in the odds of being adherent to phosphate binders (OR=1.013; 95% CI= 1.008 – 1.018). Female gender was associated with a 12.7 percent decrease in the odds of being adherent to phosphate binders compared with male gender (OR = 0.873; 95% CI: 0.779 – 0.979). Being white and other were 98.4 percent and two times more likely to be adherent to phosphate binders compared to being black (OR=1.984; 95% CI=1.701 -

2.314; OR=3.008; 95% CI= 2.236 – 4.046). Patients who resided in the south region were 23.8 percent less likely to adhere to phosphate binders compared to those in the Midwest region (OR = 0.762; 95% CI: 0.653 – 0.889).

$H_{0\ (3i)}$: Rejected.

Table 3.11 Logistic Regression Model Comparing the Proportion of Patients with MPR ≥ 80% in Patients Receiving Phosphate Binders while Controlling for Covariates (N=7753)

Variable		Parameter Estimate	Standard Error	Wald Chi-Square	p-value	Odds Ratio	95% Confidence Interval
Intercept		-2.249	0.220	104.856	<.0001		
Cohort [a]	1	-0.944	0.100	88.538	<.0001	0.389	0.320 - 0.474
	2	-0.436	0.083	27.484	<.0001	0.647	0.549 - 0.761
	3	0.517	0.092	31.326	<.0001	1.676	1.399 - 2.008
Age		0.013	0.003	23.012	<.0001	1.013	1.008 - 1.018
Gender [b]	Female	-0.135	0.058	5.375	0.020	0.873	0.779 - 0.979
Race [c]	White	0.685	0.079	76.170	<.0001	1.984	1.701 - 2.314
	Other	1.101	0.151	52.989	<.0001	3.008	2.236 - 4.046
Region of residence [d]	Northeast	0.015	0.080	0.032	0.857	1.015	0.867 - 1.188
	South	-0.272	0.079	11.888	0.001	0.762	0.653 - 0.889
	West	0.101	0.101	1.002	0.317	1.106	0.908 - 1.348
ESRD duration		-0.009	0.008	1.336	0.248	0.991	0.975 - 1.007
Primary disease causing ESRD [e]	Hypertension	0.033	0.082	0.162	0.688	1.033	0.881 - 1.213
	Glomerulonephritis	0.013	0.111	0.013	0.910	1.013	0.815 - 1.259
	Cystic Kidney	0.035	0.178	0.038	0.845	1.035	0.731 - 1.467
	Other	-0.051	0.101	0.251	0.616	0.951	0.780 - 1.159
Charlson Comorbidity Index (CCI) score		-0.021	0.033	0.407	0.524	0.979	0.918 - 1.044
Presence of chronic disease	Diabetes mellitus	0.054	0.091	0.347	0.556	1.055	0.883 - 1.261
	Hypertension	0.041	0.062	0.437	0.509	1.042	0.922 - 1.177
	Dyslipidemia	-0.098	0.087	1.269	0.260	0.907	0.764 - 1.075
	Cancer	0.094	0.136	0.479	0.489	1.098	0.842 - 1.433
	Chronic lung disease	0.126	0.082	2.356	0.125	1.135	0.966 - 1.333
	Cardiovascular disease	-0.108	0.078	1.900	0.168	0.898	0.770 - 1.047

Model parameters: Likelihood Ratio = 502.69; d.f.=22; p<0.0001; Score = 497.12; d.f.=22; p<0.0001; Wald = 455.11; d.f.=22; p< 0.0001.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Cinacalcet

Table 3.12 shows the results of the logistic regression model comparing the proportion of patients with MPR≥ 80% in patients receiving cinacalcet among cohorts, while controlling for covariates. The overall statistics for the model testing the null hypothesis that all parameter estimates are equal to zero indicated that the null hypothesis was rejected ($p<0.001$). In addition, the Hosmer-Lemeshow test indicated that the model was of good fit ($\chi^2=8.92$; d.f.=8; $p=0.3493$).

This model indicated that patients in cohort 1 and cohort 2 were 73.1 percent and 61.5 percent less likely to be adherent to cinacalcet compared with patients in cohort 4, respectively (OR=0.269; 95% CI= 0.186 – 0.390; OR=0.385; 95% CI= 0.301 – 0.491). However, patients in cohort 3 were 44.6 percent more likely to be adherent to cinacalcet compared to those in cohort 4 after controlling for covariates (OR= 1.446; 95% CI= 1.127 – 1.854).

Significant predictors of adherence to cinacalcet were age, race, and the presence of dyslipidemia. Each year increase in age was associated with a 1.4 percent increase in the odds of adherence to cinacalcet (OR=1.014; 95% CI= 1.006 – 1.022). Being white were 50.9 percent more likely to be adherent to cinacalcet compared with being black (OR=1.509; 95% CI=1.228 - 1.854). The presence of dyslipidemia was associated with a 35.9 percent increase in the odds of adherence to cinacalcet (OR=1.359; 95% CI=1.033 - 1.788). **$H_{0\ (3j)}$: Rejected.**

Table 3.12 Logistic Regression Model Comparing the Proportion of Patients with MPR ≥ 80% in Patients Receiving Cinacalcet while Controlling for Covariates (N=2436)

Variable		Parameter Estimate	Standard Error	Wald Chi-Square	p-value	Odds Ratio	95% Confidence Interval
Intercept		-1.309	0.319	16.841	<.0001		
Cohort [a]	1	-1.313	0.190	47.981	<.0001	0.269	0.186 - 0.390
	2	-0.955	0.125	58.694	<.0001	0.385	0.301 - 0.491
	3	0.369	0.127	8.443	0.004	1.446	1.127 - 1.854
Age		0.014	0.004	11.752	0.001	1.014	1.006 - 1.022
Gender [b]	Female	-0.017	0.092	0.036	0.851	0.983	0.821 - 1.177
Race [c]	White	0.411	0.105	15.280	<.0001	1.509	1.228 - 1.854
	Other	0.145	0.276	0.275	0.600	1.156	0.673 - 1.985
Region of residence [d]	Northeast	0.101	0.138	0.542	0.462	1.107	0.845 - 1.450
	South	-0.095	0.133	0.510	0.475	0.909	0.700 - 1.180
	West	0.273	0.179	2.333	0.127	1.314	0.926 - 1.865
ESRD duration		-0.006	0.011	0.315	0.575	0.994	0.974 - 1.015
Primary disease causing ESRD [e]	Hypertension	-0.191	0.136	1.980	0.159	0.826	0.634 - 1.078
	Glomerulonephritis	0.200	0.166	1.448	0.229	1.221	0.882 - 1.690
	Cystic Kidney	-0.066	0.246	0.072	0.788	0.936	0.577 - 1.517
	Other	-0.047	0.164	0.084	0.772	0.954	0.692 - 1.314
Charlson Comorbidity Index (CCI) score		-0.003	0.056	0.003	0.960	0.997	0.893 - 1.113
Presence of chronic disease	Diabetes mellitus	-0.297	0.152	3.817	0.051	0.743	0.552 - 1.001
	Hypertension	0.147	0.099	2.187	0.139	1.158	0.953 - 1.407
	Dyslipidemia	0.307	0.140	4.811	0.028	1.359	1.033 - 1.788
	Cancer	0.273	0.221	1.518	0.218	1.314	0.851 - 2.027
	Chronic lung disease	0.101	0.136	0.548	0.459	1.106	0.847 - 1.444
	Cardiovascular disease	-0.116	0.126	0.858	0.354	0.890	0.696 - 1.138

Model parameters: *Likelihood Ratio* = 267.88; *d.f.*=22; $p<0.0001$; *Score* = 259.36; *d.f.*=22; $p<0.0001$; *Wald* = 236.04; *d.f.*=22; $p<0.0001$.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

3.3.2.3 Mean MPR Before and After Coverage Gap

To determine whether medication adherence differs before and after the coverage gap is exceeded among patients receiving drug therapy in the primary cohort (cohort 2) who reached coverage gap but not catastrophic coverage.

For this analysis, patients in cohort 2 who had at least two prescriptions and at least one prescription before the coverage gap was exceeded (each therapeutic classes separately analyzed).

$H_{0\ (3k\text{-}o)}$: Medication adherence with antihyperglycemics [$H_{0(3k)}$], antihypertensives [$H_{0(3l)}$], lipid-lowering drugs [$H_{0(3m)}$], phosphate binders [$H_{0(3n)}$], or cinacalcet [$H_{0(3o)}$]) will not differ significantly before and after the gap is exceeded.

Table 3.13 shows the mean MPR by five therapeutic classes of outpatient prescription drugs before and after reaching coverage gap among cohort 2. Paired t- tests revealed that the mean MPR differed significantly before and after reaching the coverage gap across all five therapeutic classes of outpatient prescription medications.

Among patients who received **antihyperglycemic drugs (n=1578)**, the mean MPR significantly declined after reaching the coverage gap (Mean= 57.88%; SD=34.28) compared to the mean before reaching the coverage gap (Mean=72.41%; SD=26.62) ($t=18.53$; d.f.=1577; $p<0.0001$).

$H_{0\ (3k)}$: Rejected.

Among patients who received **antihypertensive drugs (n=3815)**, mean MPR significantly declined after reaching the coverage gap (Mean= 75.37%; SD=28.45) compared to the mean before reaching the coverage gap (Mean=84.87%; SD=19.60) (t=21.07; d.f.=1577; p <0.0001).

$H_{0\ (3l)}$: Rejected.

Among patients who received **lipid-lowering drugs (n=2501)**, mean MPR significantly declined after reaching the coverage gap (Mean= 67.31%; SD=33.11) compared to the mean before reaching the coverage gap (Mean=81.13%; SD=22.43) (t=20.35; d.f.=1577; p <0.0001).

$H_{0\ (3m)}$: Rejected.

Among patients who received **phosphate binders (n=3101)**, mean MPR significantly declined after reaching the coverage gap (Mean= 48.94%; SD=32.99) compared to the mean before reaching the coverage gap (Mean=65.74%; SD=24.68) (t=27.94; d.f.=1577; p <0.0001).

$H_{0\ (3n)}$: Rejected.

Among patients who received **cinacalcet (n=779)**, mean MPR significantly declined after reaching the coverage gap (Mean= 47.81%; SD=34.36) compared to the mean before reaching the coverage gap (Mean=68.97%; SD=25.92) (t=16.03; d.f.=1577; p <0.0001).

$H_{0\ (3o)}$: Rejected.

Table 3.13 Mean MPR by Five Therapeutic Classes of Outpatient Prescription Drugs Before and After Reaching Part D Coverage Gap among Cohort 2

	Before		After		Test statistics	p-value
	Mean	**SD**	**Mean**	**SD**		
Antihyperglycemic drugs (n=1578)						
Study period (days)	176	77	158	73		
MPR (Mean, SD)	72.41	26.62	57.88	34.28	18.53	<.0001
Antihypertensive drugs (n=3815)						
Study period (days)	200	74	159	75		
MPR (Mean, SD)	84.87	19.60	75.37	28.45	21.07	<.0001
Lipid-lowering drugs (n=2501)						
Study period (days)	179	76	159	75		
MPR (Mean, SD)	81.13	22.43	67.31	33.11	20.35	<.0001
Phosphate binders (n=3101)						
Study period (days)	179	76	148	72		
MPR (Mean, SD)	65.74	24.68	48.94	32.99	27.94	<.0001
Cinacalcet (n=779)						
Study period (days)	142	78	166	74		
MPR (Mean, SD)	68.97	25.92	47.81	34.36	16.03	<.0001

Note: Degrees of freedom equal 1 for all paired t-tests

3.3.2.4 Proportion of Patients with MPR ≥ 80% Before and After Coverage Gap

$H_{0\ (3p\text{-}t)}$: The proportion of patients who were adherent (MPR ≥ 80%) to antihyperglycemics [$H_{0(3p)}$], antihypertensives [$H_{0(3q)}$], lipid-lowering drugs [$H_{0(3r)}$], phosphate binders [$H_{0(3s)}$], or cinacalcet [$H_{0(3t)}$]) will not differ significantly before and after reaching the gap.

Table 3.14 shows the McNemar test comparisons of MPR≥80% before and after reaching the Part D coverage gap by five therapeutic classes of outpatient prescription drugs. McNemar tests revealed that proportion of patients with MPR ≥ 80% differed significantly before and after reaching the Part D coverage gap across all five therapeutic classes of outpatient prescription medications.

Among patients on antihyperglycemic drugs (n=1578), the proportion of patients with MPR ≥ 80% for antihyperglycemic drugs was 34.66 percent after reaching the part D coverage gap, significantly lower than the proportion (48.16 %) before the coverage gap (χ^2=95.57; d.f.=3; p<.0001).

Among patients on drugs for hypertension (n=3518), 55.96 percent patients were adherent (MPR≥ 80%) to antihypertensive drugs after reaching the Part D coverage gap, significantly lower than that of 68.49 percent before the coverage gap (χ^2=173.62; d.f.=3; p<.0001).

Among patients on lipid-lowering drugs (n=2501), 48.37 percent patients were adherent (MPR≥ 80%) to lipid-lowering after reaching the Part D coverage gap, significantly lower than that of 65.72 percent before the coverage gap (χ^2=179.01; d.f.=3; p<.0001).

Among patients on phosphate binders (n=3101), 22.38 percent patients were adherent (MPR≥ 80%) to lipid-lowering after reaching the Part D coverage gap, significantly lower than that of 33.57 percent before the coverage gap (χ^2=126.61; d.f.=3; p<.0001).

Among patients who received cinacalcet (n=779), 24.13 percent patients were adherent (MPR≥ 80%) to cinacalcet after reaching the Part D coverage gap, significantly lower than that of 42.23 percent before the coverage gap (χ^2=67.85; d.f.=3; p<.0001).

Table 3.14 Proportion of Patients with MPR ≥ 80% by Five Therapeutic Classes of Outpatient Prescription Drugs Before and After Reaching Part D Coverage Gap

	Before		After		$\chi 2$	p-value
	N	%	N	%		
Antidiabetic drugs (n=1578)						
MPR ≥ 80%	760	48.16	547	34.66	95.57	<.0001
Antihypertensive drugs (n=3815)						
MPR ≥ 80%	2613	68.49	2135	55.96	173.62	<.0001
Lipid-lowering drugs (n=2501)						
MPR ≥ 80%	1348	65.72	992	48.37	179.01	<.0001
Phosphate binders (n=3101)						
MPR ≥ 80%	1041	33.57	694	22.38	126.61	<.0001
Cinacalcet (n=779)						
MPR ≥ 80%	329	42.23	188	24.13	67.85	<.0001

Note: Degrees of freedom equal 1 for all McNemar tests

Based on the results from descriptive statistics, **MPR<80%** was used as the dependent variable for generalized estimating regression models to assess the risk of drug nonadherence as patients reached the coverage gap.

Antihyperglycemics

Table 3.15 shows the results of a generalized estimating regression model comparing the proportion of patients with MPR< 80% in patients receiving antihyperglycemic drugs before and after reaching the Part D coverage gap among cohort 2, while controlling for covariates. This model indicated that patients were 71.7 percent more likely to be nonadherent to antihyperglycemic drugs after reaching the coverage gap while controlling for covariates. (Adjusted OR=1.717; 95% CI= 1.483 – 1.989). Significant predictors of nonadherence to antihyperglycemic drugs were race, region of residence, primary disease causing ESRD, and CCI score. Being white was associated with a 28.9 percent decrease in the odds of being nonadherent compared with being black (OR= exp (-0.3405) = 0.711; 95% CI=0.591 – 0.857). Patients who resided in the south regions were 21.0 percent more likely to be nonadherent to antihyperglycemic drugs compared to those in Midwest (OR= exp (0.190) = 1.210; 95% CI: 1.005 – 1.456). Cystic kidney as the primary disease causing ESRD was associated with a 64.2 percent decrease in the odds of being nonadherent to antihyperglycemic drugs compared with diabetes mellitus (OR= exp (-1.028) =0.358; 95% CI= 0.155 – 0.824). Each unit increase in CCI score was associated with a 13.0 percent decrease in the odds of being nonadherent to

antihyperglycemic drugs (OR= exp (0.123) =1.130; 95% CI = 1.045-1.224). [Odds ratios for predictors are not shown] **$H_{0\ (3p)}$: Rejected.**

Table 3.15 Generalized Estimating Equation Model Comparing the Proportion of Patients with MPR < 80% for Antihyperglycemics Before and After Reaching Part D Coverage Gap while Controlling for Covariates (N=1578)

Variable		Parameter Estimate	Standard Error	95% Confidence Limits		Pr > |Z|
Intercept		-0.294	0.316	-0.913	0.325	0.352
After [a]		0.541	0.075	0.394	0.688	<.0001
Adjusted odds ratio (after vs before)		**1.717**	**0.129**	**1.483**	**1.989**	
Age		0.007	0.004	-0.001	0.014	0.094
Gender [b]	Female	-0.013	0.073	-0.157	0.131	0.860
Race [c]	White	-0.341	0.095	-0.527	-0.154	0.000
	Other	-0.374	0.207	-0.780	0.032	0.071
Region of residence [d]	Northeast	-0.064	0.099	-0.258	0.130	0.516
	South	0.190	0.095	0.005	0.376	0.044
	West	0.114	0.129	-0.138	0.367	0.375
ESRD duration		0.018	0.015	-0.012	0.047	0.240
Primary disease causing ESRD [e]	Hypertension	-0.197	0.107	-0.407	0.014	0.067
	Glomerulonephritis	0.526	0.309	-0.079	1.132	0.088
	Cystic Kidney	-1.028	0.426	-1.862	-0.194	0.016
	Other	-0.128	0.191	-0.502	0.246	0.503
Charlson Comorbidity Index (CCI) score		0.123	0.041	0.044	0.202	0.002
Presence of chronic disease	Diabetes mellitus	-0.223	0.140	-0.498	0.052	0.112
	Hypertension	-0.019	0.078	-0.173	0.134	0.804
	Dyslipidemia	0.179	0.099	-0.016	0.373	0.072
	Cancer	-0.313	0.163	-0.633	0.006	0.055
	Chronic lung disease	-0.042	0.109	-0.256	0.171	0.697
	Cardiovascular disease	-0.132	0.104	-0.335	0.070	0.201

Model distribution= binomial; link=logit

Antihypertensives

Table 3.16 shows the results of a generalized estimating regression model comparing the proportion of patients with MPR< 80% in patients receiving antihypertensive drugs before and after reaching the Part D coverage gap among cohort 2, while controlling for covariates.

This model indicated that patients were 69.0 percent more likely to be nonadherent to antihypertensive drugs after reaching coverage gap after controlling for covariates. (Adjusted OR=1.690; 95% CI= 1.541 – 1.853). Significant predictors of nonadherence to antihypertensive drugs were age, region of residence, primary disease causing ESRD, and CCI score. Each year increase in age was associated with a 0.6 percent increase in the odds of being nonadherent to antihypertensive drugs (OR=0.994; 95% CI= 0.989 – 0.999). Patients who resided in the western region were 22.3 percent more likely to be nonadherent to antihypertensive drugs compared to those in the Midwest (OR = 1.223; 95% CI: 1.030 – 1.452). 'Other' as the primary disease category causing ESRD was associated with a 64.2 percent decrease in the odds of nonadherence to antihypertensive drugs compared with diabetes mellitus (OR=1.287; 95% CI= 1.086 – 1.526). Each unit increase in CCI score was associated with a 6.4 percent increase in the odds of being nonadherent to antihypertensive drugs (OR=1.064; 95% CI = 1.007-1.125).

$H_{0\ (3Q)}$: Rejected.

Table 3.16 Generalized Estimating Equation Model Comparing the Proportion of Patients with MPR < 80% for Antihypertensives Before and After Reaching Part D Coverage Gap while Controlling for Covariates (N=3815)

Variable		Parameter Estimate	Standard Error	95% Confidence Limits		Pr > |Z|
Intercept		-0.389	0.210	-0.800	0.023	0.064
After [a]		0.525	0.047	0.433	0.617	<.0001
Adjusted odds ratio (after vs before)		**1.690**	**0.080**	**1.541**	**1.853**	
Age		-0.006	0.003	-0.011	-0.001	0.021
Gender [b]	Female	-0.075	0.050	-0.173	0.022	0.131
Race [c]	White	-0.099	0.065	-0.226	0.029	0.131
	Other	-0.281	0.164	-0.602	0.041	0.087
Region of residence [d]	Northeast	0.094	0.067	-0.036	0.225	0.157
	South	-0.024	0.066	-0.153	0.105	0.712
	West	0.201	0.088	0.030	0.373	0.021
ESRD duration		0.010	0.007	-0.005	0.024	0.178
Primary disease causing ESRD [e]	Hypertension	0.022	0.070	-0.115	0.158	0.754
	Glomerulonephritis	-0.061	0.099	-0.254	0.132	0.536
	Cystic Kidney	0.173	0.158	-0.137	0.482	0.274
	Other	0.252	0.087	0.082	0.423	0.004
Charlson Comorbidity Index (CCI) score		0.062	0.028	0.007	0.118	0.027
Presence of chronic disease	Diabetes mellitus	0.018	0.077	-0.133	0.169	0.814
	Hypertension	-0.088	0.053	-0.191	0.016	0.097
	Dyslipidemia	0.094	0.072	-0.047	0.235	0.191
	Cancer	-0.007	0.114	-0.230	0.216	0.948
	Chronic lung disease	-0.129	0.070	-0.265	0.008	0.065
	Cardiovascular disease	-0.107	0.069	-0.243	0.028	0.121

Model distribution= binomial; link=logit.

[a] Reference : Before part D coverage gap

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Lipid-lowering drugs

Table 3.17 shows the results of a generalized estimating regression model comparing the proportion of patients with MPR< 80% in patients receiving lipid-lowering drugs before and after reaching the Part D coverage gap among cohort 2, while controlling for covariates.

This model indicated that patients were 2 times more likely to be nonadherent to lipid-lowering drugs after reaching the coverage gap after controlling for covariates. (Adjusted OR=2.006; 95% CI= 1.541 – 1.853). Significant predictors of nonadherence to lipid lowering drugs were age, race, and primary disease causing ESRD. Each year increase in age was associated with a 1.3 percent decrease in the odds of being nonadherent to antihypertensive drugs (OR=0.987; 95% CI= 0.980 – 0.994). Being white was associated with an 18.0 percent decrease in the odds of being nonadherent compared with being black (OR= 0.820; 95% CI=0.694 – 0.969). Being other was associated with a 40.3 percent decrease in the odds of being nonadherent compared with being black (OR= 0.597; 95% CI=0.405 – 0.880). Hypertension as the primary disease category causing ESRD was associated with an 18.3 percent decrease in the odds of nonadhernce to antihypertensive drugs compared with diabetes mellitus (OR=0.817; 95% CI= 0.686 – 0.972).

$H_{0\ (3r)}$: Rejected.

Table 3.17 Generalized Estimating Equation Model Comparing the Proportion of Patients with MPR < 80% For Lipid-lowering Drugs Before and After Reaching Part D Coverage Gap while Controlling for Covariates (N=2501)

Variable		Parameter Estimate	Standard Error	95% Confidence Limits		Pr > |Z|
Intercept		0.502	0.287	-0.059	1.064	0.080
After [a]		0.696	0.067	0.565	0.827	<.0001
Adjusted odds ratio (after vs before)		**2.006**	**0.134**	**1.760**	**2.287**	
Age		-0.013	0.003	-0.020	-0.006	0.000
Gender [b]	Female	0.075	0.063	-0.049	0.199	0.235
Race [c]	White	-0.198	0.085	-0.365	-0.032	0.020
	Other	-0.516	0.198	-0.904	-0.128	0.009
Region of residence [d]	Northeast	-0.116	0.087	-0.287	0.054	0.181
	South	0.086	0.084	-0.079	0.250	0.307
	West	-0.214	0.111	-0.431	0.003	0.053
ESRD duration		0.001	0.010	-0.020	0.021	0.947
Primary disease causing ESRD [e]	Hypertension	-0.203	0.089	-0.376	-0.029	0.022
	Glomerulonephritis	-0.203	0.127	-0.452	0.046	0.110
	Cystic Kidney	-0.221	0.202	-0.618	0.175	0.274
	Other	0.078	0.112	-0.141	0.297	0.487
Charlson Comorbidity Index (CCI) score		0.014	0.036	-0.056	0.083	0.703
Presence of chronic disease	Diabetes mellitus	-0.165	0.097	-0.355	0.026	0.091
	Hypertension	0.063	0.067	-0.069	0.194	0.353
	Dyslipidemia	0.145	0.078	-0.008	0.297	0.064
	Cancer	-0.045	0.146	-0.331	0.240	0.756
	Chronic lung disease	-0.118	0.091	-0.297	0.061	0.196
	Cardiovascular disease	0.101	0.089	-0.074	0.275	0.257

Model distribution= binomial; link=logit.

[a] Reference : Before part D coverage gap

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Phosphate binders

Table 3.18 shows the results of a generalized estimating regression model comparing the proportion of patients with MPR< 80% in patients receiving phosphate binders before and after reaching the Part D coverage gap among cohort 2, while controlling for covariates.

This model indicated that patients were 1.74 times more likely to be nonadherent to phosphate binders after reaching coverage gap after controlling for covariates. (Adjusted OR=1.735; 95% CI= 1.547 – 1.945). A significant predictor of nonadherence to phosphate binders was race. Being white were 23 percent times less likely to be nonadherent compared with being black (OR= 0.769; 95% CI=0.661 – 0.893).

$H_{0\ (3s)}$: Rejected.

Table 3.18 Generalized Estimating Equation Model Comparing the Proportion of Patients with MPR < 80% for Phosphate Binders Before and After Reaching Part D Coverage Gap while Controlling for Covariates (N=3101)

Variable		Parameter Estimate	Standard Error	95% Confidence Limits		Pr > |Z|
Intercept		1.042	0.243	0.566	1.518	<.0001
After [a]		0.551	0.058	0.436	0.665	<.0001
Adjusted odds ratio (after vs before)		**1.735**	**0.101**	**1.547**	**1.945**	
Age		-0.002	0.003	-0.008	0.004	0.546
Gender [b]	Female	0.071	0.058	-0.042	0.184	0.215
Race [c]	White	-0.263	0.077	-0.414	-0.113	0.001
	Other	-0.048	0.185	-0.411	0.316	0.797
Region of residence [d]	Northeast	0.061	0.077	-0.089	0.211	0.426
	South	0.140	0.075	-0.007	0.287	0.061
	West	0.108	0.100	-0.088	0.304	0.279
ESRD duration		-0.012	0.009	-0.029	0.005	0.175
Primary disease causing ESRD [e]	Hypertension	-0.055	0.080	-0.212	0.102	0.490
	Glomerulonephritis	0.000	0.108	-0.212	0.212	0.998
	Cystic Kidney	0.047	0.197	-0.339	0.432	0.812
	Other	-0.016	0.099	-0.210	0.177	0.870
Charlson Comorbidity Index (CCI) score		-0.017	0.031	-0.078	0.044	0.578
Presence of chronic disease	Diabetes mellitus	-0.100	0.089	-0.275	0.074	0.258
	Hypertension	-0.060	0.062	-0.181	0.062	0.338
	Dyslipidemia	-0.056	0.081	-0.215	0.102	0.486
	Cancer	-0.032	0.132	-0.291	0.226	0.806
	Chronic lung disease	0.029	0.082	-0.131	0.189	0.720
	Cardiovascular disease	0.104	0.077	-0.046	0.255	0.174

Model distribution= binomial; link=logit.

[a] Reference : Before part D coverage gap

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Cinacalcet

Table 3.19 shows the results of a generalized estimating regression model comparing the proportion of patients with MPR< 80% in patients receiving cinacalcet before and after reaching the Part D coverage gap among cohort 2, while controlling for covariates.

This model indicated that patients were two times more likely to be nonadherent to cinacalcet after reaching the coverage gap after controlling for covariates. (Adjusted OR=2.079; 95% CI= 1.664 – 2.598). Significant predictors of nonadherence to cinacalcet were age and race. Each year increase in age was associated with a 0.7 percent increase in the odds of being nonadherent to cinacalcet (OR=0.993; 95% CI= 0.799 – 0.994). Being white was associated with a 25 percent decrease in the odds of being nonadherent compared with being black (OR= 0.750; 95% CI=0.584 – 0.963).

$H_{0\ (3t)}$: Rejected.

Table 3.19 Generalized Estimating Equation Model Comparing the Proportion of Patients with MPR < 80% for Cinacalcet Before and After Reaching Part D Coverage Gap while Controlling for Covariates (N=779)

Variable		Parameter Estimate	Standard Error	95% Confidence Limits		Pr > |Z|
Intercept		1.694	0.437	0.837	2.551	0.000
After [a]		0.732	0.114	0.509	0.955	<.0001
Adjusted odds ratio (after vs before)		**2.079**	**0.236**	**1.664**	**2.598**	
Age		-0.016	0.005	-0.026	-0.006	0.002
Gender [b]	Female	-0.007	0.111	-0.225	0.210	0.949
Race [c]	White	-0.288	0.128	-0.538	-0.038	0.024
	Other	-0.031	0.379	-0.773	0.711	0.934
Region of residence [d]	Northeast	-0.142	0.151	-0.438	0.154	0.347
	South	0.022	0.150	-0.272	0.316	0.883
	West	-0.244	0.213	-0.661	0.173	0.251
ESRD duration		-0.016	0.015	-0.045	0.013	0.284
Primary disease causing ESRD[e]	Hypertension	0.237	0.152	-0.060	0.535	0.118
	Glomerulonephritis	-0.153	0.170	-0.487	0.180	0.368
	Cystic Kidney	0.019	0.238	-0.447	0.484	0.938
	Other	0.175	0.186	-0.189	0.539	0.347
Charlson Comorbidity Index (CCI) score		0.046	0.065	-0.082	0.174	0.481
Presence of chronic disease	Diabetes mellitus	-0.186	0.170	-0.520	0.148	0.275
	Hypertension	0.094	0.116	-0.132	0.321	0.414
	Dyslipidemia	0.126	0.171	-0.209	0.460	0.461
	Cancer	-0.487	0.268	-1.011	0.038	0.069
	Chronic lung disease	-0.076	0.162	-0.393	0.240	0.636
	Cardiovascular disease	-0.046	0.151	-0.342	0.250	0.760

Model distribution= binomial; link=logit.

[a] Reference : Before part D coverage gap

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

3.3.2.5 Mean Persistence

$H_{0\ (3u\text{-}y)}$: Medication persistence with antihyperglycemics [$H_{0(3u)}$], antihypertensives [$H_{0(3v)}$], lipid-lowering drugs [$H_{0(3w)}$], phosphate binders [$H_{0(3x)}$], or cinacalcet [$H_{0(3y)}$]) will not differ significantly when categorized by Part D coverage.

Table 3.20 shows mean persistence until the first 30-day treatment gap in taking medication for five therapeutic classes of outpatient prescription medications. One-way ANOVAs revealed that mean persistence differed significantly across all five therapeutic classes of outpatient prescription medications among cohorts. Mean persistence until the first 60-day treatment gap was also conducted as sensitivity analysis. Appendix C1 provides mean persistence until the first 60-day treatment gap for five therapeutic classes of outpatient prescription medications. Results using a 60-day gap trended in the same direction as the 30-day gap.

Antihyperglycemics

Regarding antihyperglycemic drug therapies, the mean persistence for patients in cohort 3 was 209 days (SD=135), higher than the means of 166 days (SD=131) for patients in cohort 2 and that of 168 days for patients in cohort 4 (SD=135). The mean persistence was lowest for patients in cohort 1 (Mean=139 days; SD=126) compared to the other 3 cohorts. A one-way ANOVA indicated that mean persistence for antihyperglycemic drugs differed significantly among the cohorts ($F=30.50$; d.f.=3; $p<.0001$). A Kruskal-

Wallis test also showed a statistically significant difference among the cohorts (χ^2=84.59; d.f.=3; p<.0001). **$H_{0\ (3u)}$: Rejected.**

Antihypertensives

Regarding antihypertensive drug therapies, the mean persistence for patients in cohort 3 was 291 days (SD=113), longer than that of 271 days for patients in cohort 2 (SD=121) and that of 252 days for patients in cohort 4 (SD=132). The mean persistence was lowest for patients in cohort 1 (Mean=211 days; SD=136) compared to the other 3 cohorts. A one-way ANOVA indicated that mean persistence for antihypertensive drugs differed significantly among the cohorts (F=165.01; d.f.=3; p<.0001). A Kruskal-Wallis test also showed a statistically significant difference among the cohorts (χ^2=484.68; d.f.=3; p<.0001).

$H_{0\ (3v)}$: Rejected.

Lipid-lowering drugs

Regarding lipid-lowering drug therapies, the mean persistence for patients in cohort 3 was 262 days (SD=119), longer than that of 222 days for those in cohort 2 (SD=126) and that of 212 days for those in cohort 4 (SD=132). The mean persistence was lowest for patients in cohort 1 (Mean=179 days; SD=128) compared to the other 3 cohorts. A one-way ANOVA indicated that that mean persistence for lipid-lowering drugs differed significantly among the cohorts (F=61.44; d.f.=3; p<.0001). A Kruskal-Wallis test also

showed a statistically significant difference among the cohorts (χ^2=188.40; d.f.=3; p<.0001).

$H_{0\ (3w)}$: Rejected.

Phosphate binders

Regarding phosphate binder therapies, the mean persistence for patients in cohort 3 was 195 days (SD=132), longer than that of 146 days for those in cohort 2 (SD=117) and that of 134 days for those in cohort 4 (SD=123). The mean persistence was lowest for patients in cohort 1 (Mean=103 days; SD=102) compared to the other 3 cohorts. A one-way ANOVA indicated that mean persistence for phosphate binders differed significantly among the cohorts (F=142.73; d.f.=3; p<.0001). A Kruskal-Wallis test also showed a statistically significant difference among the cohorts (χ^2=419.14; d.f.=3; p<.0001).

$H_{0\ (3x)}$: Rejected.

Cinacalcet

Regarding cinacalcet therapies, the mean persistence for patients in cohort 3 was 200 days (SD=128), longer than that of 132 days for those in cohort 2 (SD=103) and that of 161 days for those in cohort 4 (SD=124). The mean persistence was lowest for patients in cohort 1 compared to the other 3 cohorts (Mean=100 days; SD=89). A one-way ANOVA indicated that mean persistence for cinacalcet differed significantly among the

cohorts (F=62.56; d.f.=3; p<.0001). A Kruskal-Wallis test also showed a statistically significant difference among the cohorts (χ^2=151.55; d.f.=3; p<.0001).

$H_{0\ (3y)}$: Rejected.

Table 3.20 Medication Persistence (Mean Days Until First 30-day Treatment Gap) by Five Therapeutic Classes of Outpatient Prescription Drugs among Cohorts (N=11732)

	Cohort 1 (n=3678)		Cohort 2 (n=4349)		Cohort 3 (n=1310)		Cohort 4 (n=2395)		F-value	p-value
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Antihyperglycemic drugs (n=3819)	851		1630		523		815			
persistence (Mean, SD)	139	126	166	131	209	135	168	135	30.50	<.0001
Antihypertensive drugs (n=9863)	2975		3976		1189		2133			
persistence (Mean, SD)	211	136	271	121	291	113	252	132	165.01	<.0001
Lipid-lowering drugs (n=4607)	922		2119		746		820			
persistence (Mean, SD)	179	128	222	126	262	119	212	132	61.44	<.0001
Phosphate binders (n=7753)	1729		3185		1151		1688			
persistence (Mean, SD)	103	102	146	117	195	132	134	123	142.73	<.0001
Cinacalcet (n=2436)	261		854		606		718			
persistence (Mean, SD)	100	89	132	103	200	128	161	124	62.56	<.0001

Note: Degrees of freedom equal 3 for all one-way ANOVAs

3.3.2.6 Proportion of Patients with Therapy Discontinuation

$H_{0\ (3z\text{-}zd)}$: The proportion of patients who are persistent (until a 30-day treatment gap) to antihyperglycemics [$H_{0(3z)}$], antihypertensives [$H_{0(3za)}$], lipid-lowering drugs [$H_{0(3zb)}$], phosphate binders [$H_{0(3zc)}$], or cinacalcet [$H_{0(3zd)}$]) will not differ significantly when categorized by Part D coverage.

Table 3.21 shows the chi-square comparison of the proportion of patients with a 30-day treatment gap (discontinuation) by five therapeutic classes of outpatient prescription drugs among the cohorts.

For patients on **antihyperglycemic drugs**, about eighty percent of patients in cohort 1 discontinued therapy, higher than the proportions in cohort 2 (77.24%) and cohort 4 (72.52%), respectively. A lower proportion of patients in cohort 3 (62.72%) discontinued therapy than any other cohorts. A chi-square analysis showed a significant difference among the cohorts (χ^2=54.46; d.f.=3; p<.0001).

For patients on **antihypertensive drugs**, about sixty percent of patients in cohort 1 discontinued therapy, higher than the proportions in cohort 2 (43.49%) and cohort 4 (46.77%). A lower proportion of patients in cohort 3 (34.02%) discontinued therapy than any other cohorts. A chi-square analysis showed a significant difference among the cohorts (χ^2=293.54; d.f.=3; p<.0001).

For patients on **lipid-lowing drugs**, about seventy percent of patients in cohort 1 discontinued therapy, higher than the proportions in cohort 2 (61.68%) and cohort 4

(57.44%). A lower proportion of patients in cohort 3 (46.11%) discontinued therapy than any other cohorts. A chi-square analysis showed a significant difference among the cohorts (χ^2=96.30; d.f.=3; p<.0001).

For patients on **phosphate binders**, about ninety percent of patients in cohort 1 discontinued therapy, higher than the proportions in cohort 2 (84.46%) and cohort 4 (83.06%). A lower proportion of patients in cohort 3 (68.11%) discontinued therapy than any other cohorts. A chi-square analysis showed a significant difference among the cohorts (χ^2=237.24; d.f.=3; p<.0001).

For patients on **cinacalcet**, about eight-five percent of patients in cohort 1 discontinued therapy, higher than the proportions in cohort 2 (82.67%) and cohort 4 (69.92%). A lower proportion of patients in cohort 3 (55.78%) discontinued therapy than any other cohorts. A chi-square analysis showed a significant difference among the cohorts (χ^2=149.60; d.f.=3; p<.0001).

Table 3.21 Proportion of Patients with a 30-day Treatment Gap (Discontinuation) by Five Therapeutic Classes of Outpatient Prescription Drugs among Cohorts (N=11732)

	Cohort 1 (n=3678)		Cohort 2 (n=4349)		Cohort 3 (n=1310)		Cohort 4 (n=2395)		$\chi 2$	p-value
	N	%	N	%	N	%	N	%		
Antidiabet drugs (n=3819)	851		1630		523		815			
Discontinuation (N, %)	674	79.2	1259	77.24	328	62.72	591	72.52	54.46	<.0001
Antihypertensive drugs (n=9863)	2975		3976		1189		2133			
Discontinuation (N, %)	1673	60.35	1680	43.49	397	34.02	964	46.77	293.54	<.0001
Lipid-lowering drugs (n=4607)	922		2119		746		820			
Discontinuation (N, %)	637	69.09	1307	61.68	344	46.11	471	57.44	96.30	<.0001
Phosphate binders (n=7753)	1729		3185		1151		1688			
Discontinuation (N, %)	1549	89.59	2690	84.46	784	68.11	1402	83.06	237.24	<.0001
Cinacalcet (n=2436)	261		854		606		718			
Discontinuation (N, %)	220	84.29	706	82.67	338	55.78	502	69.92	149.60	<.0001

Antihyperglycemics

Figure 3.2 shows Kaplan-Meier curves comparing the percentage of patients who remain persistent on antihyperglycemic drugs among the cohorts. The Log-Rank test (χ^2= 75.17; d.f.=3; p<0.0001) showed a significant difference among cohorts. As shown in the figure, a higher percentage of patients in cohort 3 remained persistent to antihyperglycemic drugs compared with the other 3 cohorts.

Figure 3.2 Kaplan-Meier survival curves comparing percentage of patients who remain on antihyperglycemic drugs among cohorts

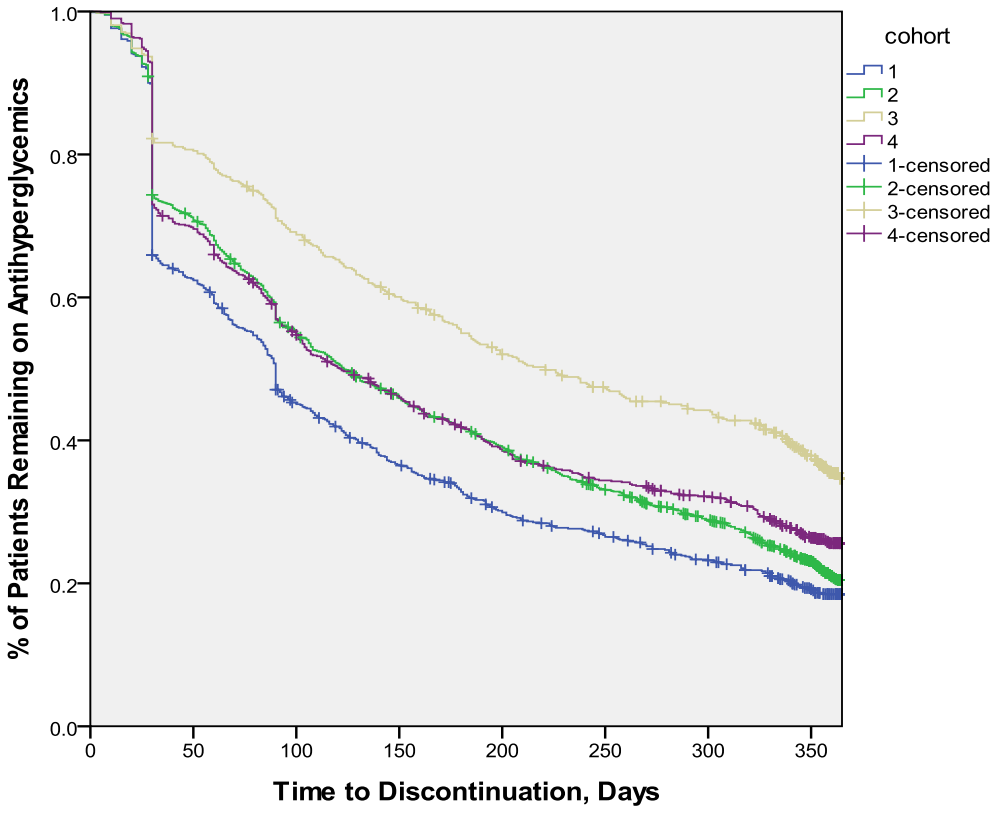


Table 3.22 shows the results of the Cox proportional hazards regression model comparing persistence for antihyperglycemic drugs among the cohorts, while controlling for covariates. The overall statistics for the model testing the null hypothesis that all parameter estimates are equal to zero indicated that the null hypothesis was rejected ($p<0.0001$). This model indicated that patients in cohort 1 and cohort 2 were 38.3 percent (hazard ratio (HR) = 1.383; 95% CI= 1.232 – 1.552) and 17.8 percent more likely to discontinue antihyperglycemic drug therapies (HR= 1.178; 95% CI= 1.061 – 1.309) compared to those in cohort 4, respectively. However, patients in cohort 3 had a 21.7 percent decrease in the risk for discontinuation (HR= 0.783; 95% CI= 0.681 – 0.902) compared to patients in cohort 4, after controlling for covariates.

Significant predictors for discontinuation of antihyperglycemic drugs were age, race, primary disease causing ESRD, ESRD duration, CCI score and presence of cancer. Each year increase in age was associated with a 0.5 percent decrease in the risk of discontinuation (HR=0.995; 95% CI= 0.991 – 0.998). Being white were 17.4 percent less likely to discontinue antihyperglycemic drugs compared to being black (HR=0.826; 95% CI=0.756 - 0.901). Each unit increase in the year of ESRD duration was associated with a 3.1 percent increase in the risk of discontinuation (HR=1.031; 95% CI=1.018-1.044). Hypertension as the primary disease causing ESRD was associated with a 3.1 percent decrease in the risk of discontinuation compared to diabetes mellitus (HR=0.818; 95% CI= 0.726 – 0.923). Each unit increase in CCI score was associated with an 11.0 percent increase in the risk of discontinuation (HR=1.110; 95% CI = 1.067-1.154). The

presence of cancer was associated with a 22.9 percent decrease in the risk of discontinuation (HR=0.771; 95% CI= 0.634 – 0.939).

$H_{0\ (3z)}$: Rejected.

Table 3.22 Cox Proportional Hazards Regression Model Comparing Therapy Discontinuation for Antihyperglycemic Drugs with a 30-day Treatment Gap among Cohorts while Controlling for Covariates (N=3819)

Variable		Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits
Cohort [a]	1	0.324	0.059	30.146	<.0001	1.383	1.232 - 1.552
	2	0.164	0.053	9.433	0.002	1.178	1.061 - 1.309
	3	-0.244	0.072	11.583	0.001	0.783	0.681 - 0.902
Age		-0.005	0.002	7.650	0.006	0.995	0.991 - 0.998
Gender [b]	Female	0.061	0.038	2.543	0.111	1.063	0.986 - 1.145
Race [c]	White	-0.192	0.045	18.256	<.0001	0.826	0.756 - 0.901
	Other	-0.155	0.106	2.138	0.144	0.856	0.695 - 1.054
Region of residence [d]	Northeast	-0.030	0.056	0.298	0.585	0.970	0.870 - 1.082
	South	0.015	0.051	0.086	0.769	1.015	0.918 - 1.122
	West	-0.060	0.071	0.734	0.392	0.941	0.820 - 1.081
ESRD duration		0.030	0.007	21.048	<.0001	1.031	1.018 - 1.044
Primary disease causing ESRD [e]	Hypertension	-0.200	0.061	10.650	0.001	0.818	0.726 - 0.923
	Glomerulonephritis	-0.184	0.149	1.521	0.217	0.832	0.621 - 1.115
	Cystic Kidney	-0.205	0.304	0.454	0.501	0.815	0.449 - 1.479
	Other	-0.123	0.095	1.650	0.199	0.885	0.734 - 1.067
Charlson Comorbidity Index (CCI) score		0.104	0.020	27.301	<.0001	1.110	1.067 - 1.154
Presence of chronic disease	Diabetes mellitus	-0.141	0.073	3.703	0.054	0.869	0.753 - 1.003
	Hypertension	0.010	0.041	0.062	0.803	1.010	0.933 - 1.094
	Dyslipidemia	0.091	0.052	3.030	0.082	1.095	0.989 - 1.213
	Cancer	-0.260	0.100	6.723	0.010	0.771	0.634 - 0.939
	Chronic lung disease	0.018	0.055	0.104	0.747	1.018	0.914 - 1.134
	Cardiovascular disease	-0.001	0.053	0.000	0.990	0.999	0.900 - 1.109

Model parameters: *Likelihood Ratio* = 221.94; *d.f.*=22; p<0.0001; *Score* = 223.65; *d.f.*=22; p<0.0001; *Wald* = 222.40; *d.f.*=22; p< 0.0001.

Antihypertensives

Figure 3.3 shows Kaplan-Meier curves comparing the percentage of patients who remain persistent on antihypertensive drugs among cohorts. The Log-Rank test (χ^2= 406.37; d.f.=3; p<0.0001) showed a significant difference among cohorts. As shown in the figure, a higher percentage of patients in cohort 3 remained persistent to antihypertensive drugs compared with the other 3 cohorts.

Figure 3.3 Kaplan-Meier survival curves comparing percentage of patients who remain on antihypertensive drugs among cohorts

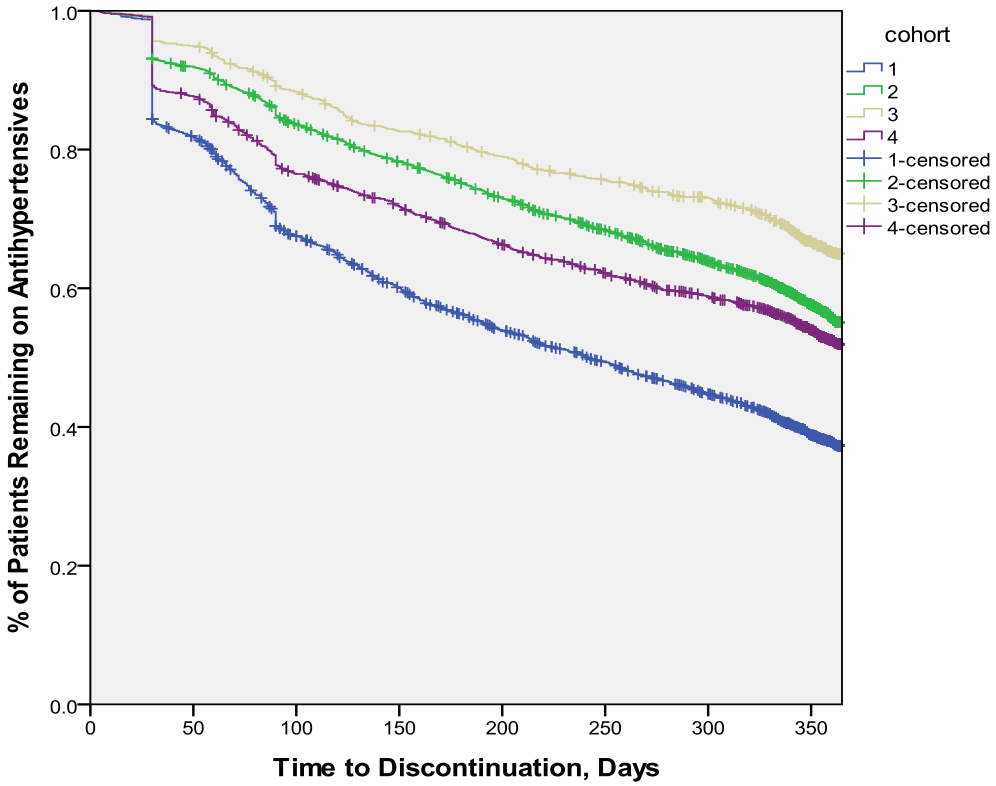


Table 3.23 shows the results of the Cox proportional hazards regression model comparing persistence for antihypertensive drugs among the cohorts, while controlling for covariates. The overall statistics for the model testing the null hypothesis that all parameter estimates are equal to zero indicated that the null hypothesis was rejected ($p<0.0001$). This model indicated that patients in cohort 1 were 69.2 percent more likely to discontinue (HR= 1.692; 95% CI= 1.558 – 1.838) but those in cohort 3 were 26.7 percent less likely to discontinue antihypertensive drug therapies (HR= 0.733; 95% CI= 0.649 – 0.827) compared to those in cohort 4, respectively. There was no significant difference between cohort 2 and cohort 4 (HR= 1.012; 95% CI= 0.930 – 1.102), after controlling for covariates.

Significant predictors for discontinuation of antihypertensive drug therapy were age, gender, race, region of residence, ESRD duration, CCI score and presence of cancer. Each year increase in age was associated with a 0.8 percent decrease in the risk of discontinuation (HR=0.992; 95% CI= 0.990 – 0.995). Female gender was associated with an 11.6 percent decrease in the risk of discontinuation compared with male gender (HR = 0.884; 95% CI: 0.833 - 0.937). Being white were 19.6 percent less likely to discontinue antihypertensive drugs compared with being black (HR=0.804; 95% CI=0.752 - 0.859). Patients who lived in the northeast and south regions were 9.3 percent and 11.6 percent more likely to discontinue compared with those in Midwest, respectively (HR = 1.093; 95% CI= 1.003 – 1.191; HR=1.116; 95% CI= 1.030 – 1.210). Each unit increase in the year of ESRD duration was associated with a 1.8 percent

increase in the risk of discontinuation (HR=1.018; 95% CI=1.011-1.026). Each unit increase in CCI score was associated with a 6.8 percent increase in the risk of discontinuation (HR=1.068; 95% CI = 1.034-1.102). The presence of cancer was associated with a 19.4 percent decrease in the risk of discontinuation (HR=0.806; 95% CI= 0.699 – 0.930).

$H_{0\ (3za)}$: Rejected.

Table 3.23 Cox Proportional Hazards Regression Model Comparing Therapy Discontinuation for Antihypertensive Drugs with a 30-day Treatment Gap among Cohorts while Controlling for Covariates (N=9863)

Variable		Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits
Cohort [a]	1	0.526	0.042	155.349	<.0001	1.692	1.558 - 1.838
	2	0.012	0.043	0.082	0.774	1.012	0.930 - 1.102
	3	-0.311	0.062	25.375	<.0001	0.733	0.649 - 0.827
Age		-0.008	0.001	33.820	<.0001	0.992	0.990 - 0.995
Gender [b]	Female	-0.124	0.030	16.873	<.0001	0.884	0.833 - 0.937
Race [c]	White	-0.219	0.034	41.472	<.0001	0.804	0.752 - 0.859
	Other	-0.216	0.086	6.240	0.013	0.806	0.680 - 0.955
Region of residence [d]	Northeast	0.089	0.044	4.114	0.043	1.093	1.003 - 1.191
	South	0.110	0.041	7.139	0.008	1.116	1.030 - 1.210
	West	0.110	0.056	3.800	0.051	1.116	0.999 - 1.247
ESRD duration		0.018	0.004	23.784	<.0001	1.018	1.011 - 1.026
Primary disease causing ESRD [e]	Hypertension	-0.070	0.041	2.888	0.089	0.932	0.860 - 1.011
	Glomerulonephritis	-0.049	0.058	0.723	0.395	0.952	0.850 - 1.066
	Cystic Kidney	0.106	0.094	1.279	0.258	1.112	0.925 - 1.337
	Other	0.007	0.054	0.016	0.900	1.007	0.906 - 1.119
Charlson Comorbidity Index (CCI) score		0.065	0.016	16.006	<.0001	1.068	1.034 - 1.102
Presence of chronic disease	Diabetes mellitus	-0.045	0.046	0.966	0.326	0.956	0.873 - 1.046
	Hypertension	-0.040	0.031	1.612	0.204	0.961	0.903 - 1.022
	Dyslipidemia	0.055	0.043	1.620	0.203	1.057	0.971 - 1.151
	Cancer	-0.216	0.073	8.735	0.003	0.806	0.699 - 0.930
	Chronic lung disease	-0.052	0.042	1.473	0.225	0.950	0.874 - 1.032
	Cardiovascular disease	0.019	0.040	0.215	0.643	1.019	0.942 - 1.102

Model parameters: *Likelihood Ratio* = 610.85; *d.f.*=22; $p<0.0001$; *Score* = 639.35; *d.f.*=22; $p<0.0001$; *Wald* = 625.35; *d.f.*=22; $p<0.0001$.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Lipid-lowering drugs

Figure 3.4 shows Kaplan-Meier curves comparing the percentage of patients who remain persistent on lipid lowering drugs among cohorts. The Log-Rank test (χ^2= 142.42; d.f.=3; p<0.0001) showed a significant difference among cohorts. As shown in the figure, a higher percentage of patients in cohort 3 who remained persistent to lipid-lowering drugs compared with the other 3 cohorts.

Figure 3.4 Kaplan-Meier survival curves comparing percentage of patients who remain on lipid-lowering drugs among cohorts

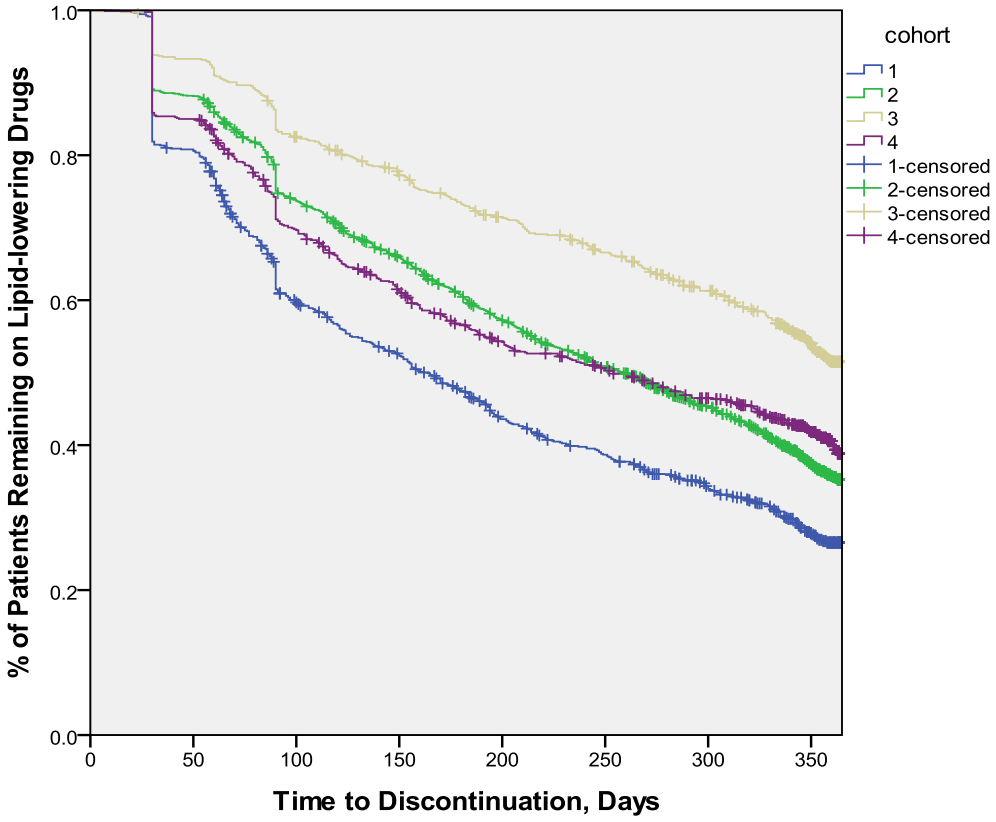


Table 3.24 shows the results of the Cox proportional hazards regression model comparing persistence for lipid-lowering drugs among cohorts, while controlling for covariates. The overall statistics for the model testing the null hypothesis that all parameter estimates are equal to zero indicated that the null hypothesis was rejected ($p<0.0001$). This model indicated that patients in cohort 1 and cohort 2 were 70.7 percent (HR= 1.707; 95% CI= 1.506 – 1.935) and 25.4 percent more likely to discontinue lipid-lowering drug therapies (HR= 1.254; 95% CI= 1.120 – 1.404) compared to those in cohort 4, respectively. However, patients in cohort 3 had a 21.9 percent decrease in the risk for discontinuation (HR= 0.781; 95% CI= 0.676 – 0.902) compared to patients in cohort 4 after controlling for covariates.

Significant predictors for discontinuation of lipid-lowering drug therapies were age, race, region of residence, and presence of hypertension. Each year increase in age was associated with a 1.2 percent decrease in the risk of discontinuation (HR=0.988; 95% CI= 0.984 – 0.992). Being white were 25.5 percent less likely to discontinue lipid-lowering drugs compared to being black (HR=0.745; 95% CI=0.680 - 0.817). Patients who lived in the south regions were 11.6 percent more likely to discontinue compared to those in the Midwest (HR = 1.116; 95% CI= 1.005 – 1.239). The presence of hypertension and CVD were associated with an 8.2 percent decrease (HR=0.918; 95% CI= 0.847 – 0.995) and a 12.5 percent increase in the risk of discontinuation (HR=1.125; 95% CI= 1.014 – 1.249), respectively.

$H_{0\ (3zb)}$: Rejected.

Table 3.24 Cox Proportional Hazards Regression Model Comparing Therapy Discontinuation for Lipid-lowering Drugs with a 30-day Treatment Gap among Cohorts while Controlling for Covariates (N=4607)

Variable		Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits
Cohort [a]	1	0.535	0.064	70.041	<.0001	1.707	1.506 - 1.935
	2	0.227	0.058	15.477	<.0001	1.254	1.120 - 1.404
	3	-0.247	0.074	11.291	0.001	0.781	0.676 - 0.902
Age		-0.012	0.002	37.718	<.0001	0.988	0.984 - 0.992
Gender [b]	Female	-0.014	0.039	0.136	0.712	0.986	0.913 - 1.064
Race [c]	White	-0.294	0.047	39.744	<.0001	0.745	0.680 - 0.817
	Other	-0.205	0.114	3.249	0.072	0.815	0.652 - 1.018
Region of residence [d]	Northeast	0.005	0.056	0.010	0.922	1.005	0.901 - 1.122
	South	0.109	0.053	4.206	0.040	1.116	1.005 - 1.239
	West	0.058	0.072	0.659	0.417	1.060	0.921 - 1.220
ESRD duration		-0.001	0.006	0.012	0.914	0.999	0.988 - 1.011
Primary disease causing ESRD [e]	Hypertension	-0.042	0.054	0.592	0.442	0.959	0.863 - 1.067
	Glomerulonephritis	-0.086	0.083	1.070	0.301	0.917	0.779 - 1.080
	Cystic Kidney	0.184	0.129	2.018	0.156	1.202	0.933 - 1.549
	Other	-0.024	0.072	0.114	0.736	0.976	0.848 - 1.124
Charlson Comorbidity Index (CCI) score		0.022	0.021	1.063	0.302	1.022	0.980 - 1.066
Presence of chronic disease	Diabetes mellitus	0.008	0.060	0.020	0.888	1.009	0.896 - 1.135
	Hypertension	-0.086	0.041	4.371	0.037	0.918	0.847 - 0.995
	Dyslipidemia	0.026	0.048	0.290	0.590	1.026	0.934 - 1.128
	Cancer	-0.062	0.092	0.451	0.502	0.940	0.786 - 1.125
	Chronic lung disease	0.009	0.055	0.025	0.875	1.009	0.906 - 1.123
	Cardiovascular disease	0.118	0.053	4.930	0.026	1.125	1.014 - 1.249

Model parameters: *Likelihood Ratio* = 279.46; *d.f.*=22; $p<0.0001$; *Score* = 283.11; *d.f.*=22; $p<0.0001$; *Wald* = 278.71; *d.f.*=22; $p<0.0001$.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Phosphate binders

Figure 3.5 shows Kaplan-Meier curves comparing the percentage of patients who remain persistent on phosphate binders among cohorts. The Log-Rank test (χ^2= 380.57; d.f.=3; p<0.0001) showed a significant difference among cohorts. As shown in the figure 3.5, a higher percentage of patients in cohort 3 remained persistent to phosphate binders compared with the other 3 cohorts.

Figure 3.5 Kaplan-Meier survival curves comparing percentage of patients who remain on phosphate binders among cohorts

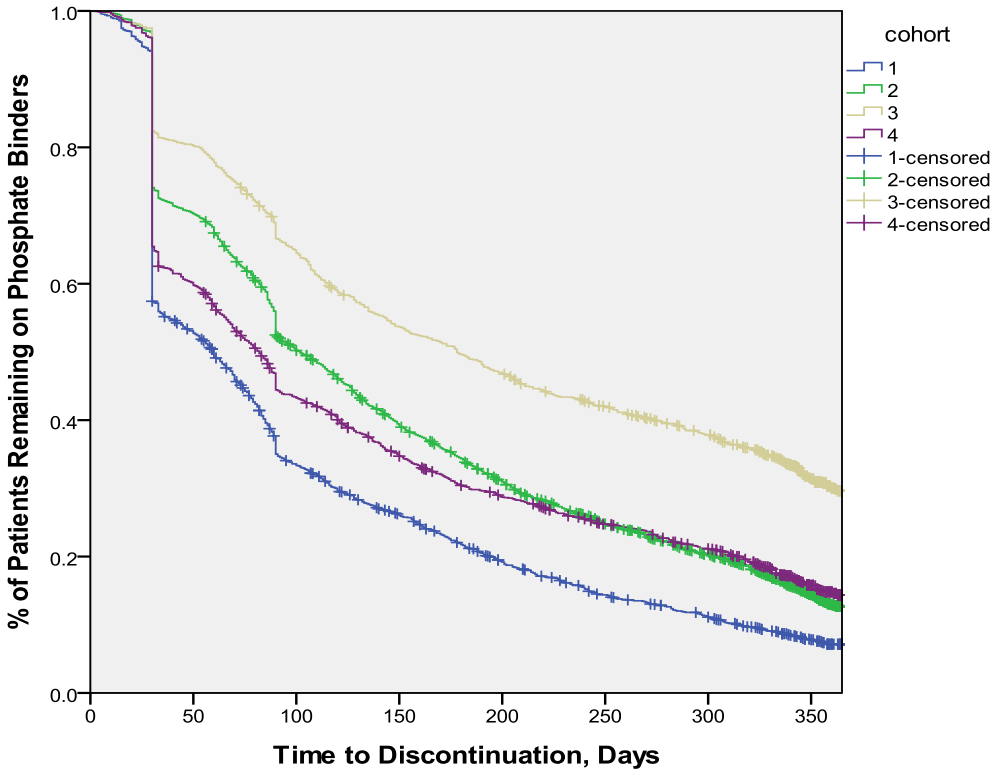


Table 3.25 shows the results of the Cox proportional hazards regression model comparing persistence for phosphate binders among cohorts, while controlling for covariates. The overall statistics for the model testing the null hypothesis that all parameter estimates are equal to zero indicated that the null hypothesis was rejected ($p<0.0001$). This model indicated that patients in cohort 1 and cohort 2 were 54.9 percent (HR= 1.549; 95% CI= 1.434 – 1.673) and 12.5 percent more likely to discontinue phosphate binder therapies (HR= 1.125; 95% CI= 1.047 – 1.208) compared to those in cohort 4, respectively. However, patients in cohort 3 had a 29.1 percent decrease in the risk for discontinuation (HR= 0.709; 95% CI= 0.646 – 0.778) compared to those in cohort 4 after controlling for covariates.

Significant predictors for discontinuation of phosphate binder therapies were age, gender, race, region of residence, ESRD duration, primary disease causing ESRD, and the presence of CVD. Each year increase in age was associated with a 0.6 percent decrease in the risk of discontinuation (HR=0.994; 95% CI= 0.992 – 0.996). Female gender was associated with a 6.4 percent increase in the risk of discontinuation compared to male gender (HR = 1.064; 95% CI: 1.012 - 1.119). Being white, and patients of 'Other' races were 23.8 percent and 31.9 percent less likely to discontinue phosphate binders compared with being black (HR=0.762; 95% CI=0.719 - 0.809; HR=0.681; 95% CI=0.590 - 0.785). Patients who lived in the South were 12.1 percent more likely to discontinue compared to those in the Midwest (HR = 1.121; 95% CI= 1.047 – 1.202). Each year increase in ESRD duration was associated with a 0.7 percent increase in the risk of discontinuation

(HR=1.007; 95% CI = 1.000 - 1.014). The presence of CVD was associated with a 7.9 percent increase in the risk of discontinuation (HR=1.079; 95% CI= 1.009 – 1.154).

$H_{0\ (3zc)}$: Rejected.

Table 3.25 Cox Proportional Hazards Regression Model Comparing Therapy Discontinuation for Phosphate Binders with a 30-day Treatment Gap among Cohorts while Controlling for Covariates (N=7753)

Variable		Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits
Cohort [a]	1	0.437	0.039	123.803	<.0001	1.549	1.434 - 1.673
	2	0.118	0.036	10.394	0.001	1.125	1.047 - 1.208
	3	-0.345	0.047	52.818	<.0001	0.709	0.646 - 0.778
Age		-0.006	0.001	26.234	<.0001	0.994	0.992 - 0.996
Gender [b]	Female	0.062	0.026	5.949	0.015	1.064	1.012 - 1.119
Race [c]	White	-0.271	0.030	81.358	<.0001	0.762	0.719 - 0.809
	Other	-0.384	0.073	27.895	<.0001	0.681	0.590 - 0.785
Region of residence [d]	Northeast	-0.025	0.037	0.452	0.501	0.975	0.907 - 1.049
	South	0.115	0.035	10.590	0.001	1.121	1.047 - 1.202
	West	0.047	0.049	0.926	0.336	1.048	0.953 - 1.153
ESRD duration		0.007	0.003	4.274	0.039	1.007	1.000 - 1.014
Primary disease causing ESRD [e]	Hypertension	-0.069	0.036	3.749	0.053	0.933	0.870 - 1.001
	Glomerulonephritis	-0.102	0.049	4.239	0.040	0.903	0.820 - 0.995
	Cystic Kidney	-0.131	0.082	2.588	0.108	0.877	0.747 - 1.029
	Other	-0.071	0.045	2.523	0.112	0.931	0.853 - 1.017
Charlson Comorbidity Index (CCI) score		0.005	0.014	0.112	0.738	1.005	0.977 - 1.033
Presence of chronic disease	Diabetes mellitus	-0.048	0.040	1.477	0.224	0.953	0.881 - 1.030
	Hypertension	0.000	0.027	0.000	0.993	1.000	0.948 - 1.055
	Dyslipidemia	-0.004	0.038	0.011	0.915	0.996	0.924 - 1.073
	Cancer	-0.007	0.060	0.015	0.903	0.993	0.882 - 1.117
	Chronic lung disease	0.029	0.037	0.647	0.421	1.030	0.959 - 1.106
	Cardiovascular disease	0.076	0.034	4.949	0.026	1.079	1.009 - 1.154

Model parameters: *Likelihood Ratio* = 562.47; *d.f.*=22; $p<0.0001$; *Score* = 567.70; *d.f.*=22; $p<0.0001$; *Wald* = 556.32; *d.f.*=22; $p< 0.0001$. [a] Reference: Cohort 4; [b] Reference: Male; [c] Reference: Black; [d] Reference: Midwest; [e] Reference: Diabetes

Cinacalcet

Figure 3.6 shows Kaplan-Meier curves comparing the percentage of patients who remain persistent on cinacalcet among cohorts. The Log-Rank test (χ^2= 199.74; d.f.=3; p<0.0001) showed a significant difference among cohorts. As shown in the figure, a higher percentage of patients in cohort 3 remained persistent to cinacalcet compared with the other 3 cohorts.

Figure 3.6 Kaplan-Meier survival curves comparing percentage of patients who remain on cinacalcet among cohorts

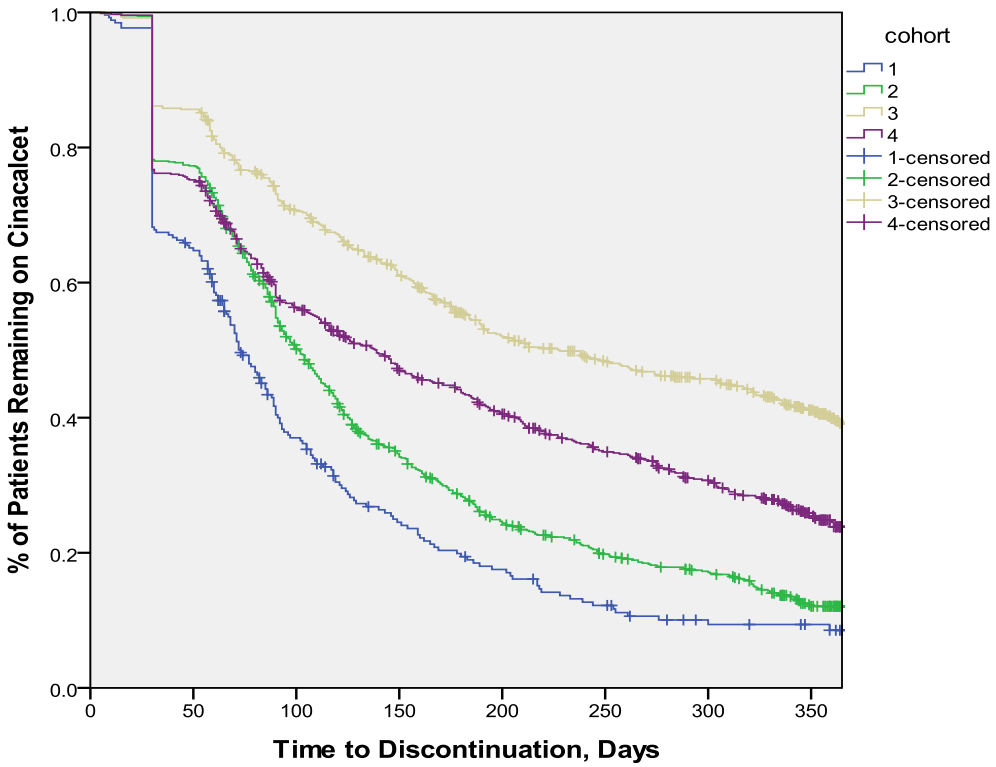


Table 3.26 shows the results of the Cox proportional hazards regression model comparing persistence for cinacalcet among cohorts, while controlling for covariates. The overall statistics for the model testing the null hypothesis that all parameter estimates are equal to zero indicated that the null hypothesis was rejected ($p<0.0001$). This model indicated that patients in cohort 1 and cohort 2 were about 100 percent (HR= 2.067; 95% CI= 1.751 – 2.439) and 60.8 percent more likely to discontinue cinacalcet therapies (HR= 1.608; 95% CI= 1.418 – 1.823) compared to those in cohort 4, respectively. However, patients in cohort 3 had a 22.7 percent decrease in the risk for discontinuation (HR= 0.773; 95% CI= 0.666 – 0.899) compared to those in cohort 4 after controlling for covariates.

Significant predictors for discontinuation of cinacalcet therapies were age, gender, race, and presence of diabetes mellitus. Each year increase in age was associated with a 0.7 percent decrease in the risk of discontinuation (HR=0.993; 95% CI= 0.989 – 0.997). Being white were 17.6 percent less likely to discontinue compared to being black (HR=0.824; 95% CI=0.740 - 0.918). The presence of diabetes mellitus was associated with a 18.6 percent increase in the risk of discontinuation (HR=1.186; 95% CI= 1.017 – 1.384).

$H_{0\ (3zd)}$: Rejected.

Table 3.26 Cox Proportional Hazards Regression Model Comparing Therapy Discontinuation for Cinacalcet with a 30-day Treatment Gap among Cohorts while Controlling for Covariates (N=2436)

Variable		Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits
Cohort [a]	1	0.726	0.085	73.733	<.0001	2.067	1.751 - 2.439
	2	0.475	0.064	55.053	<.0001	1.608	1.418 - 1.823
	3	-0.257	0.077	11.250	0.001	0.773	0.666 - 0.899
Age		-0.007	0.002	10.516	0.001	0.993	0.989 - 0.997
Gender [b]	Female	0.030	0.049	0.372	0.542	1.030	0.936 - 1.134
Race [c]	White	-0.194	0.055	12.408	0.000	0.824	0.740 - 0.918
	Other	0.032	0.144	0.051	0.822	1.033	0.779 - 1.370
Region of residence [d]	Northeast	-0.094	0.075	1.590	0.207	0.910	0.786 - 1.054
	South	0.041	0.072	0.329	0.566	1.042	0.905 - 1.199
	West	-0.058	0.099	0.347	0.556	0.943	0.778 - 1.145
ESRD duration		0.006	0.006	1.053	0.305	1.006	0.995 - 1.017
Primary disease causing ESRD [e]	Hypertension	0.091	0.070	1.676	0.196	1.095	0.954 - 1.257
	Glomerulonephritis	-0.135	0.092	2.183	0.140	0.873	0.730 - 1.045
	Cystic Kidney	0.029	0.135	0.045	0.831	1.029	0.790 - 1.340
	Other	-0.030	0.089	0.110	0.741	0.971	0.815 - 1.157
Charlson Comorbidity Index (CCI) score		-0.022	0.029	0.563	0.453	0.979	0.925 - 1.035
Presence of chronic disease	Diabetes mellitus	0.171	0.078	4.740	0.030	1.186	1.017 - 1.384
	Hypertension	-0.028	0.053	0.276	0.599	0.973	0.877 - 1.079
	Dyslipidemia	-0.101	0.078	1.662	0.197	0.904	0.776 - 1.054
	Cancer	-0.125	0.121	1.069	0.301	0.882	0.696 - 1.119
	Chronic lung disease	0.104	0.074	1.974	0.160	1.109	0.960 - 1.282
	Cardiovascular disease	0.068	0.066	1.078	0.299	1.070	0.941 - 1.217

Model parameters: *Likelihood Ratio* = 250.71; *d.f.*=22; $p<0.0001$; *Score* = 251.72; *d.f.*=22; $p<0.0001$; *Wald* = 243.90; *d.f.*=22; $p< 0.0001$.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

3.4 Phase III: Medical Services and Costs

3.4.1 Objective 4: Cardiovascular Disease Morbidity

To determine whether cardiovascular morbidity rates differ when categorized by Part D coverage.

3.4.1.1 Incidence of Cardiovascular Disease

Patients who did not have any CVD events in 2006 were included to compare incidence of CVD among cohorts in 2007. The incidence of CVD was measured using both descriptive analysis and multivariate regression. The descriptive analysis estimated the number of patients who were newly diagnosed with CVD, with statistical significance determined using chi-square test. A logistic regression model was constructed to determine if the incidence of CVD is associated with the Part D coverage gap while controlling for age, gender, race, region of residence, primary disease causing ESRD, ESRD duration, CCI score, presence of chronic disease including diabetes mellitus, hypertension, dyslipidemia, cancer and chronic lung disease.

$H_{0\ (4)}$: Incidence of cardiovascular disease will not differ significantly when categorized by Part D coverage

Of 5254 patients who had no CVD diagnosis during 2006, a total of 2151 (41%) patients newly developed CVD during 2007. Table 3.27 shows chi-square test comparison of

incidence of CVD among the cohorts. This test revealed that the incidence of CVD differed significantly among cohorts (χ^2=60.29; d.f.=3; p<.0001). Patients in cohort 2 (46.89%) and cohort 3 (45.42%) were more likely to develop CVD than those in cohort 1 (38.44%) and cohort 4 (33.78%), respectively.

Table 3.27 The Proportion of Patients who Newly Developed Cardiovascular Disease in 2007 among Cohorts (N= 5254)

Cohort 1 (n=1761)		Cohort 2 (n=1787)		Cohort 3 (n=513)		Cohort 4 (n=1193)		χ^2	p-value
N	%	N	%	N	%	N	%		
677	38.44	838	46.89	233	45.42	403	33.78	60.29	<.0001

Note: Degree of freedom equal 3 for chi-square test.

Table 3.28 shows the results of the logistic regression model comparing incidence of CVD among cohorts, while controlling for covariates. The overall statistics for the model testing the null hypothesis that all parameter estimates are equal to zero indicated that the null hypothesis was rejected (p<0.0001). In addition, the Hosmer-Lemeshow test indicated that the model was of decent fit (χ^2=15.83; d.f.=8; p=.05).

The incidence of CVD was significantly different among cohorts after controlling for covariates. Patients in cohort 2 and cohort 3 were 42.0 percent and 37.6 percent more likely to develop CVD compared to those in cohort 4, respectively (OR=1.420; 95% CI= 1.203 – 1.675; OR=1.376; 95% CI=1.100-1.720) However, there was no significant

difference in the incidence of CVD between patients in cohort 1and cohort 4 (OR=1.085; 95% CI=0.921 – 1.277).

Significant predictors of CVD in the model were age, race, primary disease causing ESRD, and the presence of chronic lung disease. Each year increase in age was associated with a 1.6 percent higher likelihood to develop CVD (OR=1.016; 95% CI= 1.011 – 1.021). Being white was associated with a 15.8 percent higher likelihood to develop CVD compared with being black (OR=1.158; 95% CI=1.011 - 1.326). Hypertension, glomerulonephritis, cystic kidney, and 'other' as the primary disease causing ESRD were associated with a 17.7 percent (OR=0.823; 95% CI= 0.704 – 0.961), a 33.9 percent (OR=0.661; 95% CI= 0.536 – 0.814), a 37.3 percent (OR=0.627; 95% CI= 0.443 – 0.887) and a 33.7 percent (OR=0.663; 95% CI= 0.546 – 0.804) lower likelihood to develop CVD when compared with the patients with a diabetes mellitus listed as the major disease causing ESRD. The presence of chronic lung disease was associated with a 61.7 percent higher likelihood to develop CVD (OR=1.617; 95% CI= 1.299 – 2.013).

$H_{0\ (4)}$: Rejected.

Table 3.28 Logistic Regression Model Comparing the Proportion of Patients who Newly Developed Cardiovascular Disease in 2007 among Cohorts while Controlling for Covariates (N= 5254)

Variable		Parameter Estimate	Standard Error	Wald Chi-Square	p-value	Odds Ratio	95% Confidence Interval
Intercept		-1.6518	0.205	65.260	<.0001		
Cohort [a]	1	0.0813	0.083	0.950	0.330	1.085	0.921 - 1.277
	2	0.3503	0.084	17.265	<.0001	1.420	1.203 - 1.675
	3	0.3190	0.114	7.838	0.005	1.376	1.100 - 1.720
Age		0.0157	0.002	40.197	<.0001	1.016	1.011 - 1.021
Gender [b]	Female	-0.0694	0.059	1.397	0.237	0.933	0.832 - 1.047
Race [c]	White	0.1466	0.069	4.489	0.034	1.158	1.011 - 1.326
	Other	0.0767	0.165	0.216	0.642	1.08	0.781 - 1.492
Region of residence [d]	Northeast	-0.0028	0.088	0.001	0.975	0.997	0.839 - 1.185
	South	0.0529	0.082	0.422	0.516	1.054	0.899 - 1.237
	West	-0.1871	0.106	3.103	0.078	0.829	0.674 - 1.021
ESRD duration		-0.0016	0.007	0.047	0.829	0.998	0.984 - 1.013
Primary disease causing ESRD [e]	Hypertension	-0.1950	0.079	6.036	0.014	0.823	0.704 - 0.961
	Glomerulonephritis	-0.4145	0.106	15.204	<.0001	0.661	0.536 - 0.814
	Cystic Kidney	-0.4667	0.177	6.958	0.008	0.627	0.443 - 0.887
	Other	-0.4112	0.099	17.359	<.0001	0.663	0.546 - 0.804
Charlson Comorbidity Index (CCI) score		0.0140	0.050	0.079	0.778	1.014	0.920 - 1.118
Presence of chronic disease	Diabetes mellitus	0.1587	0.104	2.342	0.126	1.172	0.956 - 1.436
	Hypertension	0.1037	0.068	2.348	0.126	1.109	0.971 - 1.267
	Dislipidemia	0.0525	0.105	0.248	0.619	1.054	0.857 - 1.296
	Cancer	-0.0429	0.172	0.062	0.804	0.958	0.683 - 1.343
	Chronic lung disease	0.4806	0.112	18.459	<.0001	1.617	1.299 - 2.013

Model parameters: *Likelihood Ratio* = 223.38; *d.f.*=21; $p<0.0001$; *Score* = 217.76; *d.f.*=21; $p<0.0001$; *Wald* = 208.71; *d.f.*=21; $p<0.0001$.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

3.4.2 Objective 5: Cardiovascular-related and All-cause Medical Service Utilization and Costs

To determine whether all-cause and cardiovascular-related medical service utilization and costs differ when categorized by Part D coverage.

3.4.2.1 Proportion of Patients with All-cause Medical Service Visits

$H_{0\,(5a\text{-}c)}$: The proportion of patients who used all-cause medical services including inpatient [$H_{0(5a)}$], outpatient [$H_{0(5b)}$], and other visits [$H_{0(5c)}$] will not differ significantly when categorized by Part D coverage.

Medical service utilization was measured by the percentage of patients who have medical services (i.e., inpatient, outpatient or other visits) for the 1-year follow-up period, with statistical significance determined using chi-square.

Table 3.29 shows the chi-square comparison of patients who utilized all-cause medical services including inpatient, outpatient, and other visits (i.e., home health agency, skilled nursing facility, or hospice). The chi-square tests of medical service utilization revealed that the proportion of patients with all-cause medical service visits including inpatient, outpatient and other visits differed significantly among cohorts.

The proportions of patients with ≥ 1 claims for all-cause **inpatient visits** were 65.39 percent in cohort 2 and 63.21 percent in cohort 3, higher than the proportions in cohort 1 (59.49%) and cohort 4 (58.37%) (χ^2=45.15; d.f.=3; p<.0001).

$H_{0\ (5a)}$: Rejected.

The proportion of patients with ≥ 1 claims for all-cause **outpatient visits** were 93.40 percent in cohort 2 and 92.37 percent in cohort 3, slightly higher than the proportions in cohort 1 (89.97%) and cohort 4 (90.73%) (χ^2=34.97; d.f.=3; p<.0001).

$H_{0\ (5b)}$: Rejected.

The proportion of patients with ≥ 1 claims for all-cause **other visits** were 37.80 percent in cohort 2 and 35.97 percent in cohort 3, higher than the proportions in cohort 1 (31.89%) and cohort 4 (65.20%) (χ^2=34.97; d.f.=3; p<.0001).

$H_{0\ (5c)}$: Rejected.

Table 3.29 Proportion of Patients with Any Medical Service Utilization during 2007 among Cohorts (N=11732)

Medical services	Cohort 1 (n=3678)		Cohort 2 (n=4349)		Cohort 3 (n=1310)		Cohort 4 (n=2395)			
No. of patients with at least 1 visit, N (%)	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	χ^2	**p-value**
Inpatient	2188	59.49	2844	65.39	828	63.21	1398	58.37	45.15	<.0001
Outpatient	3309	89.97	4062	93.40	1210	92.37	2173	90.73	34.97	<.0001
Other	1173	31.89	1651	37.96	469	35.80	697	29.10	65.20	<.0001

Note: Degrees of freedom equal 3 for all chi-square tests
Other included home health agency, skilled nursing facility, and hospice.

3.4.2.2 Mean Numbers of All-cause Medical Service Utilization

$H_{0\ (5d\text{-}f)}$: The mean number of medical service visits (i.e., inpatient [$H_{0(5d)}$], outpatient [$H_{0(5e)}$], and other visits [$H_{0(5f)}$]) will not differ significantly when categorized by Part D coverage.

Descriptive analysis estimated the unadjusted mean number of medical service visits among cohorts, with statistical significance determined by using one-way ANOVAs and Kruskal-Wallis tests. In addition, Poisson regressions or zero-inflated Poisson regressions were used to estimate the adjusted mean number of medical service visits and differences among costs after controlling for age, gender, race, region of residence, primary disease causing ESRD, ESRD duration, CCI score, and presence of chronic diseases (including diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease or CVD).

Table 3.30 shows the unadjusted mean numbers of all-cause medical service visits including inpatient, outpatient, other visits, and dialysis. One-way ANOVAs revealed that the unadjusted mean number of all-cause medical service visits (i.e., inpatient, outpatient, and other visits) differed significantly among the cohorts.

The unadjusted mean numbers of **all-cause inpatient visits** for patients in cohort 2 (Mean=1.76; SD=2.18) and cohort 3 (Mean= 1.64; SD=1.99) were higher than means for patients in cohort 1 (Mean= 1.50; SD=1.97) and cohort 4 (Mean=1.56; SD=2.11),

respectively. A one-way ANOVA indicated a significant difference among the cohorts (F=10.64; d.f.=3; p<.0001). A Kruskal-Wallis test showed a significant difference among the cohorts (χ^2=42.00; d.f.=3; p<.0001).

The unadjusted mean numbers of **all-cause outpatient visits** for patients in cohort 2 (Mean=8.31; SD=9.85) and cohort 3 (Mean=8.34; SD=8.84) were higher than the means for patients in cohort 1 (Mean=6.87; SD=8.27) and cohort 4 (Mean=6.43; SD=7.15), respectively. A one-way ANOVA indicated a significant difference among the cohorts (F=34.58; d.f.=3; p<.0001). A Kruskal-Wallis test also showed a significant difference among the cohorts (χ^2=128.40; d.f.=3; p<.0001).

The unadjusted mean numbers of **all-cause other visits** for patients in cohort 2 (Mean=1.29; SD=2.56) and cohort 3 (Mean=1.17; SD=2.34) were also higher than the means for those in cohort 1 (Mean=1.09; SD=2.33) and cohort 4 (Mean=0.94; SD=2.26), respectively. A one-way ANOVA indicated a significant difference among the cohorts (F=11.84; d.f.=3; p<.0001). A Kruskal-Wallis test showed a significant difference among the cohorts (χ^2=65.27; d.f.=3; p<.0001).

Table 3.30 Mean Numbers of All-cause Medical Service Visits during 2007 among Cohorts (N=11732)

Medical services	Cohort 1 (n=3678)		Cohort 2 (n=4349)		Cohort 3 (n=1310)		Cohort 4 (n=2395)			
No. of visits, Mean (SD)	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F-value	p-value
Inpatient	1.50	1.97	1.76	2.18	1.64	1.99	1.56	2.11	10.64	<.0001
Outpatient	6.87	8.27	8.31	9.85	8.34	8.84	6.43	7.15	34.58	<.0001
Other	1.09	2.33	1.29	2.56	1.17	2.34	0.94	2.26	11.84	<.0001

Note: Degrees of freedom equal 3 for all one-way ANOVAs

Table 3.31 shows the results of the zero-inflated Poisson regression model comparing adjusted mean numbers of all-cause inpatient visits (a) and differences (b), while controlling for covariates.

This model indicated that the adjusted mean number of inpatient visits for patients in cohort 2 was 1.732 (CI= 1.682 – 1.783), 0.16 higher than the mean of 1.572 for those in cohort 4 (p <0.001). Appendix D1 shows the results of the zero-inflated Poission regression model of each predictor variable included in the model.

$H_{0\ (5d)}$: Rejected.

Table 3.31 Zero-inflated Poisson Regression Adjusted All-cause Inpatient Visits (A) and Differences (B) during 2007 among Cohorts while Controlling for Covariates (N=11732)

(a) Zero-inflated Poisson regression adjusted all-cause inpatient visits

Cohort	Mean	Standard Error	z	95% Confidence Interval	
1	1.551	0.026	58.580	1.499	1.603
2	1.732	0.026	67.340	1.682	1.783
3	1.575	0.044	35.800	1.489	1.661
4	1.572	0.035	45.040	1.504	1.640

(b) Differences in zero-inflated Poisson regression adjusted all-cause inpatient visits compared with cohort 4

Contrast	Mean	Standard Error	z	95% Confidence Interval		p-value
1	-0.021	0.044	-0.480	-0.107	0.065	0.629
2	0.160	0.045	3.590	0.073	0.247	0.000
3	0.003	0.057	0.050	-0.109	0.115	0.960

Table 3.32 shows the results of the zero-inflated Poisson regression model comparing adjusted mean numbers of all-cause outpatient visits (a) and differences (b), while controlling for covariates. This model indicated that the adjusted mean number of outpatient visits for patients in cohort 1, cohort 2, and cohort 3 were 7.091 (95% CI= 6.982 – 7.200), 8.011 (95% CI= 7.908 – 8.114), and 7.821 (95% CI = 7.632 – 8.009), 0.257, 1.174, 0.987 higher than the mean of 6.834 for those in cohort 4, respectively (p <0.005). Appendix D2 shows the results of the zero-inflated Poission regression model of each predictor variable included in the model.

$H_{0\ (5e)}$: Rejected.

Table 3.32 Zero-inflated Poisson Regression Adjusted All-cause Outpatient Visits (A) and Differences (B) during 2007 among Cohorts while Controlling for Covariates (N=11732)

(a) Zero-inflated Poisson regression adjusted all-cause outpatient visits

Cohort	Mean	Standard Error	z	95% Confidence Interval	
1	7.091	0.055	127.880	6.982	7.200
2	8.011	0.053	152.260	7.908	8.114
3	7.821	0.096	81.420	7.632	8.009
4	6.834	0.069	98.900	6.698	6.969

(b) Differences in zero-inflated Poisson regression adjusted all-cause outpatient visits compared with cohort 4

Contrast	Mean	Standard Error	z	95% Confidence Interval		p-value
1	0.257	0.088	2.910	0.084	0.430	0.004
2	1.177	0.089	13.210	1.003	1.352	< 0.001
3	0.987	0.120	8.230	0.752	1.222	< 0.001

Table 3.33 shows the results of the zero-inflated Poisson regression model comparing adjusted mean numbers of all-cause other medical service visits (a) and differences (b), while controlling for covariates. This model indicated that the adjusted mean numbers of other visits for patients in cohort 1 and cohort 2 were 1.161 (95% CI= 1.101 – 1.222) and 1.204 (95% CI= 1.151 – 1.257), 0.119, 0.162 higher than the mean of 1.042 for patients in cohort 4, respectively ($p < 0.05$). Appendix D3 shows the results of the zero-inflated Poission regression model of each predictor variable included in the model.

$H_{0\ (5f)}$: Rejected.

Table 3.33 Zero-inflated Poisson Regression Adjusted All-cause Other Medical Service Utilization (A) and Differences (B) during 2007 among Cohorts while Controlling for Covariates (N=11732)

(a) Zero-inflated Poisson regression adjusted all-cause other medical service utilization

Cohort	Mean	Standard Error	z	95% Confidence Interval	
1	1.161	0.031	37.590	1.101	1.222
2	1.204	0.027	44.420	1.151	1.257
3	1.065	0.046	23.360	0.976	1.154
4	1.042	0.037	27.850	0.968	1.115

(b) Differences in zero-inflated Poisson regression adjusted all-cause other medical service utilization compared with cohort 4

Contrast	Mean	Standard Error	z	95% Confidence Interval		p-value
1	0.119	0.048	2.480	0.025	0.214	0.013
2	0.162	0.047	3.430	0.070	0.255	0.001
3	0.023	0.060	0.390	-0.094	0.140	0.696

3.4.2.3 Proportion of Patients with Cardiovascular-related Medical Services

$H_{0\ (5g\text{-}i)}$: The proportion of patients who used medical services related to cardiovascular disease including inpatient [$H_{0(5g)}$], outpatient [$H_{0(5h)}$], and other visits [$H_{0(5i)}$], will not differ significantly when categorized by Part D coverage.

Table 3.34 shows the chi-square comparison of patients who utilized cardiovascular-related medical services including inpatient, outpatient, and other visits (i.e., home health agency, skilled nursing facility, and hospice). Chi-square tests of medical service utilization revealed that the proportion of patients with cardiovascular-related medical service visits including inpatient, outpatient and other visits differed significantly among the cohorts.

The proportion of patients with ≥ 1 claims for **cardiovascular-related hospitalization** were 41.16 percent in cohort 2 and 39.47 percent in cohort 3, higher than those in cohort 1 (34.91%) and cohort 4 (34.82%). A chi-square test showed that the proportion of patients with ≥ 1 claims for cardiovascular-related hospitalization differed significantly among the cohorts (χ^2=44.51; d.f.=3; p<.0001).

$H_{0\ (5g)}$: Rejected.

The proportion of patients with ≥ 1 claims for **cardiovascular-related outpatient visits** were 38.79 percent in cohort 2 and 35.88 percent in cohort 3, higher than those in cohort

1 (31.21%) and cohort 4 (31.65%). A chi-square test showed that the proportion of patients with ≥ 1 claims for **cardiovascular-related outpatient visits** differed significantly among the cohorts (χ^2=62.53; d.f.=3; p<.0001).

$H_{0\ (5h)}$: Rejected.

The proportion of patients with ≥ 1 claims for **cardiovascular-related other visits** (i.e., home health agency, skilled nursing facility, or hospice) was 15.01 percent in cohort 2, higher than the proportions in cohort 1 (11.83%), cohort 3 (12.82%), and cohort 4 (10.56%). A chi-square test showed that the proportion of patients with ≥ 1 claims for cardiovascular-related other visits differed significantly among the cohorts (χ^2=32.79; d.f.=3; p<.0001).

$H_{0\ (5i)}$: Rejected.

Table 3.34 Proportion of Patients with Cardiovascular-related Medical Service Utilization during 2007 among Cohorts (N=11732)

Medical services	Cohort 1 (n=3678)		Cohort 2 (n=4349)		Cohort 3 (n=1310)		Cohort 4 (n=2395)			
No. of patients with at least 1 visit, n (%)	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**Test statistics**	**p-value**
Inpatient	1284	34.91	1790	41.16	517	39.47	834	34.82	44.51	<.0001
Outpatient	1148	31.21	1687	38.79	470	35.88	758	31.65	62.53	<.0001
Other	435	11.83	653	15.01	168	12.82	253	10.56	32.79	<.0001

Degrees of freedom equal 3 for all chi-square tests

3.4.2.4 Mean Numbers of Cardiovascular-related Medical Service Utilization

$H_{0\ (5j\text{-}l)}$: The mean number of medical service visits (i.e., inpatient [$H_{0(5j)}$], outpatient [$H_{0(5k)}$], and other visits [$H_{0(5l)}$]) will not differ significantly when categorized by Part D coverage.

Descriptive analysis estimated the unadjusted mean numbers of cardiovascular-related medical service visits among cohorts, with statistical significance determined by using the Kruskal-Wallis test. Poisson regressions or Zero-inflated Poisson regressions were used to estimate the adjusted mean number of medical service visits and differences among cohorts after controlling for age, gender, race, region of residence, primary disease causing ESRD, ESRD duration, CCI score, and presence of chronic diseases (including diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease and CVD.)

Table 3.35 shows the unadjusted mean number of cardiovascular-related medical service visits including inpatient, outpatient, and other visits. One-way ANOVAs revealed that the unadjusted mean numbers of cardiovascular-related medical service differed significantly among the cohorts.

The unadjusted mean number of **cardiovascular-related inpatient visits** for patients in cohort 2 (Mean=0.77; SD=2.17) was higher than the means for those in cohort 1 (Mean= 0.63; SD=1.14) and cohort 4 (Mean=0.65; SD=1.22), respectively. A one-way ANOVA

indicated a significant difference among the cohorts (F=10.82; d.f.=3; p<.0001). A kruskal-wallis test also showed a statistically significant difference among the cohorts (χ^2=46.14; d.f.=3; p<.0001).

The unadjusted mean numbers of **cardiovascular-related outpatient visits** for patients in cohort 2 (Mean=0.85; SD=2.16) and cohort 3 (Mean=0.79; SD=1.67) were higher than the means for patients in cohort 1 (Mean=0.65; SD=1.82) and cohort 4 (Mean=0.63; SD=1.37), respectively. A one-way ANOVA indicated a significant difference among the cohorts (F=10.82; d.f.=3; p<.0001). A Kruskal-Wallis test also showed a statistically significant difference among the cohorts (χ^2=65.72; d.f.=3; p<.0001).

The unadjusted mean number of **cardiovascular-related other visits** for patients in cohort 2 (Mean=0.35; SD=1.17) was higher than the means for patients in cohort 1 (Mean=0.26; SD=0.98) and cohort 4 (Mean=0.22; SD= 0.88), respectively. A one-way ANOVA indicated a significant difference among the cohorts (F=10.25; d.f.=3; p<.0001). A Kruskal-Wallis test also showed a statistically significant difference among the cohorts (χ^2=34.90; d.f.=3; p<.0001).

Table 3.35 Mean Numbers of Cardiovascular-related Medical Service Visits during 2007 among Cohorts (N=11732)

Medical services	Cohort 1 (n=3678)		Cohort 2 (n=4349)		Cohort 3 (n=1310)		Cohort 4 (n=2395)			
No. of visits, mean (SD)	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Test statistics	p-value
Inpatient	0.63	1.14	0.77	1.27	0.71	1.18	0.65	1.22	10.82	<.0001
Outpatient	0.65	1.82	0.85	2.16	0.79	1.67	0.63	1.37	10.82	<.0001
Other	0.26	0.98	0.35	1.17	0.27	0.90	0.22	0.88	10.25	<.0001

Note: Degrees of freedom equal 3 for all one-way ANOVAs

Table 3.36 shows the results of the zero-inflated Poisson regression model comparing adjusted mean numbers of cardiovascular-related inpatient visits (a) and differences (b), while controlling for covariates. This model indicated that the adjusted mean number of inpatient visits for patients in cohort 2 was 0.743 (95% CI= 0.711 – 0.775), 0.06 higher than the mean of 0.682 for patients in cohort 4 ($p < 0.05$). Appendix D4 shows the results of the zero-inflated Poission regression model of each predictor variable included in the model.

$H_{0\ (5j)}$: Rejected.

Table 3.36 Zero-inflated Poisson Regression Adjusted Cardiovascular-related Inpatient Visits (A) and Differences (B) during 2007 among Cohorts while Controlling for Covariates (N=11732)

(a) Zero-inflated Poisson regression adjusted cardiovascular-related inpatient visits

Cohort	Mean	Standard Error	z	95% Confidence Interval	
1	0.652	0.017	38.620	0.619	0.685
2	0.743	0.016	45.630	0.711	0.775
3	0.663	0.027	24.480	0.610	0.716
4	0.682	0.023	30.330	0.638	0.727

(b) Differences in zero-inflated Poisson regression adjusted cardiovascular-related inpatient visits compared with cohort 4

Contrast	Mean	Standard Error	z	95% Confidence Interval		p-value
1	-0.030	0.028	-1.070	-0.085	0.025	0.284
2	0.060	0.028	2.110	0.004	0.116	0.035
3	-0.019	0.036	-0.540	-0.089	0.051	0.589

Table 3.37 shows the results of the zero-inflated Poisson regression model comparing adjusted mean numbers of cardiovascular-related outpatient visits (a) and differences (b), while controlling for covariates. This model indicated that the adjusted mean number of outpatient visits for patients in cohort 2 was 0.795 (95% CI= 0.759 – 0.830), 0.087 higher than the mean of 0.708 for patients in cohort 4 ($p < 0.001$). Appendix D5 shows the results of the zero-inflated Poission regression model of each predictor variable included in the model.

$H_{0\ (5k)}$: Rejected.

Table 3.37 Zero-inflated Poisson Regression Adjusted Cardiovascular-related Outpatient Visits (A) and Differences (B) during 2007 among Cohorts while Controlling for Covariates (N=11732)

(a) Zero-inflated Poisson regression adjusted cardiovascular-related outpatient visits

Cohort	Mean	Standard Error	z	95% Confidence Interval	
1	0.679	0.019	35.810	0.642	0.716
2	0.795	0.018	43.920	0.759	0.830
3	0.726	0.031	23.110	0.665	0.788
4	0.708	0.025	28.150	0.659	0.757

(b) Differences in zero-inflated Poisson regression adjusted cardiovascular-related outpatient visits compared with cohort 4

Contrast	Mean	Standard Error	z	95% Confidence Interval		p-value
1	-0.029	0.031	-0.930	-0.090	0.032	0.353
2	0.087	0.032	2.740	0.025	0.149	0.006
3	0.019	0.041	0.460	-0.061	0.098	0.649

Table 3.38 shows the results of the zero-inflated Poisson regression model comparing adjusted mean numbers of cardiovascular-related other medical service visits (a) and differences (b), while controlling for covariates. This model indicated that there were no significant differences in adjusted mean number of cardiovascular-related other visits among the cohorts. Appendix D6 shows the results of the zero-inflated Poission regression model of each predictor variable included in the model.

$H_{0\ (5I)}$: Not rejected.

Table 3.38 Zero-Inflated Poisson Regression Adjusted Cardiovascular-related Other Medical Service Utilization (A) and Differences (B) during 2007 among Cohorts while Controlling for Covariates (N=11732)

(a) Zero-inflated Poisson regression adjusted cardiovascular-related other medical service utilization

Cohort	Mean	Standard Error	z	95% Confidence Interval	
1	0.283	0.014	19.760	0.255	0.311
2	0.315	0.013	24.160	0.290	0.341
3	0.234	0.019	12.140	0.196	0.272
4	0.271	0.019	14.580	0.235	0.308

(b) Differences in zero-inflated Poisson regression adjusted cardiovascular-related other medical service utilization compared with cohort 4

Contrast	Mean	Standard Error	z	95% Confidence Interval		p-value
1	0.012	0.023	0.520	-0.034	0.058	0.604
2	0.044	0.023	1.910	-0.001	0.090	0.056
3	-0.037	0.027	-1.360	-0.090	0.016	0.172

3.4.2.5 All-cause Medical Care Costs

$H_{0\ (5m\text{-}t)}$: All-cause medical care costs including inpatient [$H_{0(5m)}$], outpatient [$H_{0(5n)}$], other visits [$H_{0(5o)}$], physician/supplier [$H_{0(5p)}$], dialysis [$H_{0(5q)}$], total medical costs [$H_{0(5r)}$], pharmacy costs [$H_{0(5s)}$], and total health care costs [$H_{0(5t)}$] will not differ significantly when categorized by Part D coverage.

Descriptive analyses of unadjusted medical care costs among cohorts are presented, with statistical significance between cohorts determined by using one-way ANOVA and the Kruskal-Wallis tests. The regression model was based on a two-part model or generalized linear model to estimate the adjusted medical care costs and costs differences among cohorts after controlling for age, gender, race, region of residence, primary disease causing ESRD, ESRD duration, CCI score, presence of chronic disease including diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease and CVD. Health care costs were estimated from a Medicare perspective using both medical and pharmacy claims data during 2007.

Table 3.39 shows the unadjusted mean costs for all-cause medical care services including inpatient, outpatient, other visits, physician/supplier, dialysis, total medical service, pharmacy and total health care. One-way ANOVAs and Kruskal-Wallis tests revealed that unadjusted all-cause medical care costs differed significantly among cohorts.

The unadjusted mean cost for all-cause inpatient services for patients in cohort 2 was $17,447 (SD=26,163), higher than means for patients in cohort 3 (Mean= $16,405; SD=24,324) and cohort 4 (Mean=$16,038; SD=26,330), respectively. Patients in cohort 1 had relatively the lowest unadjusted mean cost for all-cause inpatient services among the cohorts (Mean= $15,631; SD=25,130). A one-way ANOVA indicated a statistically significant difference among the cohorts (F=3.64; d.f.=3; p <.05). A Kruskal-Wallis test also showed a statistically significant difference among the cohorts (χ^2=33.23; d.f.=3; p<.0001).

The unadjusted mean cost for all-cause outpatient services for patients in cohort 2 (Mean=$3,831; SD=5,294) and cohort 3 (Mean=$3,933; SD=5,486) were higher than the means for patients in cohort 1 (Mean=$3,307; SD=4,641) and cohort 4 (Mean=$3,362; SD=4,938), respectively. A one-way ANOVA indicated a statistically significant difference among the cohorts (F=10.80; d.f.=3; p<.0001). A Kruskal-Wallis test also showed a statistically significant difference among the cohorts (χ^2=57.89; d.f.=3; p<.0001).

The unadjusted mean cost for all-cause physician/supplier services for patients in cohort 4 was $3,255 (SD=6203), higher than the means for patients in cohort 1 (Mean=$2,897; SD= 5,708) and cohort 3 (Mean=$2,844; SD=6,702). Patients in cohort 2 had relatively the lowest unadjusted mean cost for all-cause physician/supplier services

among the cohorts (Mean= $2,607; SD=6,019). A one-way ANOVA indicated a statistically significant difference among the cohorts (F=6.00; d.f.=3; p=0.0004). A Kruskal-Wallis test also showed a statistically significant difference among the cohorts (χ^2=37.95; d.f.=3; p<.0001).

The unadjusted mean cost for all-cause other services for patients in cohort 2 was $4,172 (SD=8623), higher than the means for patients in cohort 1 (Mean=$3,634; SD= 8,470) and cohort 3 (Mean=$3,634; SD=7,570). Patients in cohort 4 had relatively the lowest unadjusted mean cost for all-cause other services among the cohorts (Mean= $2,704; SD=6,766). A one-way ANOVA indicated a statistically significant difference among the cohorts (F=16.86; d.f.=3; p<.0001). A Kruskal-Wallis test also showed a statistically significant difference among the cohorts (χ^2=71.47; d.f.=3; p<.0001).

The unadjusted mean cost for dialysis for patients in cohort 3 was $28,725 (SD=7307), higher than the means for patients in cohort 2 (Mean=$27,652; SD= 6,943) and cohort 4 (Mean=$27,758; SD=7,775). Patients in cohort 1 had relatively the lowest unadjusted mean cost (Mean= $26,982; SD=7,582) for dialysis compared to the means for the other 3 cohorts. A one-way ANOVA indicated a statistically significant difference among the cohorts (F=19.27; d.f.=3; p<.0001). A Kruskal-Wallis test also showed a statistically significant difference among the cohorts (χ^2=92.72; d.f.=3; p<.0001).

Total medical service costs included costs from medical services including inpatient, outpatient, physician/supplier, other, and dialysis costs. **The unadjusted mean cost for total medical services** for patients in cohort 2 and cohort 3 were $55,708 (SD=32,897) and $55,541 (SD=30,959), higher than the means for patients in cohort 1 (Mean=$52,451; SD= 32,060) and cohort 4 (Mean=$53,117; SD=31,951). A one-way ANOVA indicated a statistically significant difference among the cohorts (F=8.43; d.f.=3; p<.0001). A Kruskal-Wallis test also showed a statistically significant difference among the cohorts (χ^2=52.18; d.f.=3; p<.0001).

The unadjusted mean costs for pharmacy for patients in cohort 3 and cohort 4 were $6506 (SD=6,719) and $5120 (SD=4,866), higher than the mean of $ 2577 (SD=2,513) for patients cohort 2. Patients in cohort 1 had the lowest unadjusted mean cost for pharmacy among the cohorts (Mean=$1,397; SD=1,535). A one-way ANOVA indicated a statistically significant difference among the cohorts (F=946.74; d.f.=3; p<.0001). A Kruskal-Wallis test also showed a statistically significant difference among the cohorts (χ^2=4418.93; d.f.=3; p<.0001). These pharmacy costs were defined as payment made by Medicare, different from total drug (Medicare payment + out-of-pocket costs) and out-of-pocket drug costs in Table 3.5 ($H_{o(2p)}$) .

Total all-cause health care costs included costs from medical services and pharmacy claims for any reason. **The unadjusted mean cost for total health care services** for

patients in cohort 3 was $62,047 (SD=31,747), $3,762 and $3,810 higher than the means of $58,285 (SD=32,904) and $58,237 (SD=32,492) for patients in cohort 2 and cohort 4, respectively. Patients in cohort 1 had relatively the lowest unadjusted mean cost for total health care services among cohorts (Mean=$53,847; SD=32,182). A one-way ANOVA indicated a statistically significant difference among the cohorts (F=25.20; d.f.=3; p<.0001). A Kruskal-Wallis test also showed a statistically significant difference among the cohorts (χ^2=184.12; d.f.=3; p<.0001).

Table 3.39 All-cause Medical Service Costs during 2007 among Cohorts (N=11732)

Medical services	Cohort 1 (n=3678)		Cohort 2 (n=4349)		Cohort 3 (n=1310)		Cohort 4 (n=2395)		F-value	p-value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Inpatient	$15,631	25,130	$17,447	26,163	$16,405	24,324	$16,038	26,330	3.64	0.0123
Outpatient	$3,307	4,641	$3,831	5,294	$3,933	5,486	$3,362	4,938	10.80	<.0001
Physician/supplier	$2,897	5,708	$2,607	6,019	$2,844	6,702	$3,255	6,203	6.00	0.0004
Other	$3,634	8,470	$4,172	8,623	$3,634	7,570	$2,704	6,766	16.86	<.0001
Dialysis	$26,982	7,582	$27,652	6,943	$28,725	7,307	$27,758	7,775	19.27	<.0001
Total medical service	$52,451	32,060	$55,708	32,897	$55,541	30,959	$53,117	31,951	8.43	<.0001
Pharmacy	$1,397	1,535	$2,577	2,513	$6,506	6,719	$5,120	4,866	946.74	<.0001
Total health care cost	**$53,847**	**32,182**	**$58,285**	**32,904**	**$62,047**	**31,747**	**$58,237**	**32,492**	**25.20**	**<.0001**

Note: Degrees of freedom equal 3 for all one-way ANOVAs

Table 3.40 shows the results of the two-part model comparing adjusted mean costs for all-cause inpatient services (a) and differences (b) among cohorts, while controlling for covariates. This model indicated that the adjusted mean cost for inpatient services was $17,560 for patients in cohort 2, $1,949 higher than the mean for those in cohort 4 (Mean=$15,611) ($p<0.01$). However, the adjusted mean cost for all-cause inpatient services did not differ significantly for patients in cohort 1 (Mean=$15,948) and cohort 3 (Mean=$15,973) compared to the mean for those in cohort 4 ($p>0.05$). Appendix E1 shows the results of the two-part model of each predictor variable included in the models.

$H_{0\ (5m)}$: Rejected.

Table 3.40 A Two-part Model Adjusted All-cause Inpatient Costs (A) and Differences (B) during 2007 among Cohorts while Controlling for Covariates (N=11732)

(a) A two-part model adjusted all-cause inpatient costs

Cohort	Mean	Standard Error	z	95% Confidence Interval	
1	$15,948	418	38.12	$15,129	$16,768
2	$17,560	403	43.62	$16,744	$18,375
3	$15,973	626	25.51	$14,701	$17,245
4	$15,611	513	30.44	$14,639	$16,583

(b) Differences in a two-part model adjusted all-cause inpatient costs compared with cohort 4

Contrast	Mean	Standard Error	z	95% Confidence Interval		p-value
1 vs 4	$337	654	0.52	-$944	$1,619	0.606
2 vs 4	$1,949	644	3.03	$687	$3,211	0.002
3 vs 4	$362	806	0.45	-$1,218	$1,943	0.653

Table 3.41 shows the results of the two-part model comparing adjusted mean costs for all-cause outpatient services (a) and differences (b) among cohorts, while controlling for covariates. This model indicated that the adjusted mean cost for outpatient services were $3,829 for patients in cohort 2 and $3,859 for patients in cohort 3, $473 and $503 higher than the mean of $3,356 for patients in cohort 4, respectively ($p<0.01$). The adjusted mean costs for all-cause outpatient services did not differ significantly between patients in cohort 1 (Mean=$3,346) and cohort 4 (Mean=$3,356). Appendix E2 shows the results of the two-part model of each predictor variable included in the models.

$H_{0\ (5n)}$: Rejected.

Table 3.41 A Two-part Model Adjusted All-cause Outpatient Costs (A) and Differences (B) during 2007 among Cohorts while Controlling for Covariates (N=11732)

(a) A two-part model adjusted all-cause outpatient costs

Cohort	Mean	Standard Error	z	95% Confidence Interval	
1	$3,346	76	44.08	$3,197	$3,495
2	$3,829	83	46.41	$3,667	$3,991
3	$3,859	141	27.3	$3,582	$4,136
4	$3,356	105	31.88	$3,149	$3,562

(b) Differences in a two-part model adjusted all-cause outpatient costs compared with cohort 4

Contrast	Mean	Standard Error	z	95% Confidence Interval		p-value
1 vs 4	-$10	131	-0.07	-$265	$246	0.942
2 vs 4	$473	141	3.35	$197	$750	0.001
3 vs 4	$503	183	2.75	$144	$862	0.006

Table 3.42 shows the results of the two-part model comparing adjusted mean costs for all-cause physician/supplier services (a) and differences (b) among cohorts, while controlling for covariates. This model indicated that the adjusted mean costs for physician/supplier services among the 4 cohorts were not significantly different ($p>0.05$). Appendix E3 shows the results of the two-part model of each predictor variable included in the models.

$H_{0\ (5o)}$: Not rejected.

Table 3.42 A Two-part Model Adjusted All-cause Physician/Supplier Costs (A) and Differences (B) during 2007 among Cohorts while Controlling for Covariates (N=11732)

(a) A two-part model adjusted all-cause physician/supplier costs

Cohort	Mean	Standard Error	z	95% Confidence Interval	
1	$2,852	90	31.61	$2,675	$3,029
2	$2,783	98	28.3	$2,590	$2,975
3	$3,019	194	15.6	$2,640	$3,399
4	$2,884	123	23.44	$2,642	$3,125

(b) Differences in a two-part model adjusted all-cause physician/supplier costs compared with cohort 4

Contrast	Mean	Standard Error	z	95% Confidence Interval		p-value
1 vs 4	-$32	152	-0.21	-$330	$266	0.835
2 vs 4	-$101	165	-0.61	-$424	$222	0.541
3 vs 4	$136	232	0.59	-$319	$591	0.558

Table 3.43 shows the results of the two-part model comparing adjusted mean costs for all-cause other services (a) and differences (b) among cohorts, while controlling for covariates. This model indicated that the adjusted mean costs for all-cause other services were $3,890 and $3,801 for patients in cohort 1 and cohort 2, $724 and $635 higher than the mean of $3,166 for those in cohort 4, respectively ($p<0.01$). The adjusted mean costs for all-cause other services did not differ significantly between patients in cohort 3 (Mean=$3,270) and cohort 4 (Mean=$3,166) ($p>0.05$). Appendix E4 shows the results of the two-part model of each predictor variable included in the model.

$H_{0\ (5p)}$: Rejected.

Table 3.43 A Two-part Model Adjusted All-cause Other Costs (A) and Differences (B) during 2007 among Cohorts while Controlling for Covariates (N=11732)

(a) A two-part model adjusted all-cause other costs

Cohort	Mean	Standard Error	z	95% Confidence Interval	
1	$3,890	144	26.97	$3,607	$4,173
2	$3,801	121	31.5	$3,564	$4,037
3	$3,270	191	17.14	$2,896	$3,644
4	$3,166	163	19.47	$2,847	$3,485

(b) Differences in a two-part model adjusted all-cause other costs compared with cohort 4

Contrast	Mean	Standard Error	z	95% Confidence Interval		p-value
1 vs 4	$724	214	3.39	$305	$1,142	0.001
2 vs 4	$635	203	3.12	$236	$1,033	0.002
3 vs 4	$104	259	0.40	-$404	$611	0.689

Table 3.44 shows the results of the generalized linear model comparing adjusted mean costs for dialysis (a) and differences (b) among cohorts, while controlling for covariates. This model indicated that the adjusted mean costs for dialysis were $27,917 for patients in cohort 2 and $29,030 for patients in cohort 3, $644 and $1,757 higher than the mean of $27,274 for those in cohort 4, respectively ($p<0.005$). The adjusted mean cost for dialysis for patients in cohort 1 was $384 lower than the mean for those in cohort 4, but the difference was not statistically significant ($p>0.05$). Appendix E5 shows the results of the two-part model of each predictor variable included in the models.

$H_{0\ (5q)}$: Rejected.

Table 3.44 A Generalized Linear Model Adjusted Dialysis Costs (A) and Differences (B) during 2007 among Cohorts while Controlling for Covariates (N=11732)

(a) A generalized linear model adjusted dialysis costs

Cohort	Mean	Standard Error	z	95% Confidence Interval	
1	$26,890	120	224.62	$26,655	$27,125
2	$27,917	105	265.44	$27,711	$28,123
3	$29,030	206	141.12	$28,627	$29,433
4	$27,274	160	170.51	$26,960	$27,587

(b) Differences in a generalized linear model adjusted dialysis costs compared with cohort 4

Contrast	Mean	Standard Error	z	95% Confidence Interval		p-value
1 vs 4	-$384	200	-1.91	-$776	$9	0.056
2 vs 4	$644	197	3.27	$258	$1,029	0.001
3 vs 4	$1,757	268	6.56	$1,232	$2,282	<0.001

Table 3.45 shows the results of the generalized linear model comparing adjusted mean costs for all-cause medical services (a) and differences (b) among cohorts, while controlling for covariates. This model indicated that the adjusted mean costs for all-cause medical service were $55,819 for patients in cohort 2 and $55,187 for patients in cohort 3, $3,369 and $2,736 higher than the mean of $52,451 for those in cohort 4, respectively ($p<0.001$). The adjusted mean costs for all-cause medical service did not differ significantly between patients in cohort 1 (Mean=$52,879) and cohort 4 (Mean=$52,451). Appendix E6 shows the results of the generalized linear model of each predictor variable included in the model. **$H_{0\ (5r)}$: Rejected.**

Table 3.45 A Generalized Linear Model Adjusted All-cause Medical Service Costs (A) and Differences (B) during 2007 among Cohorts while Controlling for Covariates (N=11732)

(a) A generalized linear model adjusted all-cause medical service costs

Cohort	Mean	Standard Error	z	95% Confidence Interval	
1	$52,879	498	106.08	$51,902	$53,856
2	$55,819	494	112.89	$54,850	$56,789
3	$55,187	826	66.81	$53,568	$56,806
4	$52,451	662	79.27	$51,154	$53,748

(b) Differences in a generalized linear model adjusted all-cause medical service costs compared with cohort 4

Contrast	Mean	Standard Error	z	95% Confidence Interval		p-value
1 vs 4	$428	849	0.50	-$1,236	$2,091	0.614
2 vs 4	$3,369	833	4.04	$1,735	$5,002	<0.001
3 vs 4	$2,736	1111	2.46	$558	$4,914	0.014

Table 3.46 shows the results of the generalized linear model comparing adjusted mean costs for pharmacy (a) and differences (b) among cohorts, while controlling for covariates. This model indicated that the adjusted mean cost for all-cause pharmacy was $6,325 for patients in cohort 3, $1,299 higher than the mean of $5,026 for those in cohort 4 ($p<0.001$). However, the adjusted mean costs for all-cause pharmacy were $1,408 and $2,607 for patients in cohort 1 and cohort 2, $3618 and $2419 lower than the mean for patients in cohort 4. Appendix E7 shows the results of the generalized liner model of each predictor variable included in the model.

$H_{0\ (5s)}$: Rejected.

Table 3.46 A Generalized Linear Model Adjusted All-cause Pharmacy Costs (A) and Differences (B) during 2007 among Cohorts while Controlling for Covariates (N=11732)

(a) A generalized linear model adjusted all-cause pharmacy costs

Cohort	Mean	Standard Error	z	95% Confidence Interval	
1	$1,408	24	57.97	$1,360	$1,455
2	$2,607	38	68.70	$2,532	$2,681
3	$6,325	158	39.91	$6,015	$6,636
4	$5,026	101	49.64	$4,827	$5,224

(b) Differences in a generalized linear model adjusted all-cause pharmacy costs compared with cohort 4

Contrast	Mean	Standard Error	z	95% Confidence Interval		p-value
1 vs 4	-$3,618	103	-35.24	-$3,819	-$3,417	< 0.001
2 vs 4	-$2,419	111	-21.77	-$2,637	-$2,201	<0.001
3 vs 4	$1,299	189	6.87	$929	$1,670	< 0.001

Table 3.47 shows the results of the generalized linear model comparing adjusted mean costs for all-cause health care services (a) and differences (b) among cohorts, while controlling for covariates. This model indicated that the adjusted mean costs for all-cause health care services was $61,663 for patients in cohort 3, $4,211 higher than the mean of $57,453 for patients in cohort 4 ($p<0.001$). The adjusted mean cost for all-cause health care services for patients in cohort 1 was $54,265, $3,188 lower than the mean for patients in cohort 4. The adjusted mean costs for all-cause health care services for patients in cohort 2 and cohort 4 did not differ significantly ($p>0.05$). Appendix E8 shows the results of the two-part model of each predictor variable included in the model.

$H_{0\ (5t)}$: Rejected.

Table 3.47 A Generalized Linear Model Adjusted All-cause Health Care (Medical Service + Pharmacy) Costs (A) and Differences (B) during 2007 among Cohorts while Controlling for Covariates (N=11732)

Cohort	Mean	Standard Error	z	95% Confidence Interval	
1	$54,265	508	106.76	$53,269	$55,261
2	$58,451	502	116.45	$57,468	$59,435
3	$61,663	849	72.67	$60,000	$63,327
4	$57,453	637	90.12	$56,203	$58,702

(b) Differences in a generalized linear model adjusted all-cause health care costs compared with cohort 4

Contrast	Mean	Standard Error	z	95% Confidence Interval		p-value
1 vs 4	-$3,188	820	-3.89	-$4,794	-$1,581	< 0.001
2 vs 4	$999	834	1.2	-$636	$2,634	0.231
3 vs 4	$4,211	1067	3.95	$2,119	$6,303	< 0.001

3.4.2.6 Cardiovascular-related Medical Care Costs

$H_{0\ (5u\text{-}y)}$: Cardiovascular disease-related medical care costs including inpatient [$H_{0(5u)}$], outpatient [$H_{0(5v)}$], and other visits [$H_{0(5w)}$], and physician/supplier [$H_{0(5x)}$], and total costs [$H_{0(5y)}$], will not differ significantly when categorized by Part D coverage.

Descriptive analysis estimated unadjusted mean costs for cardiovascular-related medical care services among cohorts, with statistical significance determined by using one-way ANOVAs and the Kruskal-Wallis tests. The regression model was based on two-part model or generalized linear model to estimate the adjusted mean costs for cardiovascular-related medical care services and cost differences among cohorts after controlling for age, gender, race, region of residence, primary disease causing ESRD, ESRD duration, CCI score, presence of chronic disease including diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease and CVD.

Table 3.48 shows the unadjusted mean costs for cardiovascular-related medical care services including inpatient, outpatient, other visits, physician/supplier and total medical services. One-way ANOVAs and Kruskal-Wallis tests revealed that unadjusted mean costs for cardiovascular-related medical care services differed significantly among the cohorts.

The unadjusted mean cost for <u>cardiovascular-related inpatient services</u> for patients in cohort 2 was $7,422 (SD=14,608), higher than the means for those in cohort 3 (Mean= $6,957; SD=13,966) and cohort 4 (Mean=$6,824; SD=15,391), respectively. Patients in

cohort 1 had relatively the lowest unadjusted mean cost for cardiovascular-related inpatient services among cohorts (Mean= $6,403; SD=14,398). A one-way ANOVA indicated a statistically significant difference among the cohorts (F=3.27; d.f.=3; p=0.0203). A Kruskal-Wallis test showed a statistically significant difference among the cohorts (χ^2=57.69; d.f.=3; p<.0001).

The unadjusted mean cost for **cardiovascular-related outpatient services** for patients in cohort 2 (Mean=$586; SD=1,881) was higher than the means for patients in cohort 1 (Mean=$464; SD=1,740), cohort 3 (Mean = $518; SD= 2033) and cohort 4 (Mean=$486; SD=1,606), respectively. A one-way ANOVA indicated a statistically significant difference among the cohorts (F=3.41; d.f.=3; p=0.0167). A Kruskal-Wallis test also showed a statistically significant difference among the cohorts (χ^2=57.69; d.f.=3; p<.0001).

The unadjusted mean cost for **cardiovascular-related physician/supplier services** for patients in cohort 2 was $636 (SD=2,419), higher than patients in cohort 1 (Mean=$497; SD= 2,005), cohort 3 (Mean=$569; SD=1,614), and cohort 4 (Mean=$500; SD=3,121). A one-way ANOVA indicated a statistically significant difference among the cohorts (F=2.82; d.f.=3; p=0.0375). A kruskal-wallis test also showed a statistically significant difference among the cohorts (χ^2=125.59; d.f.=3; p<.0001).

The unadjusted mean cost for **cardiovascular-related other services** for patients in cohort 2 was $1,200 (SD=4,196), higher than the means for patients in cohort 1 (Mean=$905; SD= 3,676) and cohort 3 (Mean=$846; SD=3,281). Patients in cohort 4 had the lowest unadjusted mean cost for cardiovascular-related other services among the cohorts (Mean= $664; SD=3031). A one-way ANOVA indicated a statistically significant difference among the cohorts (F=11.77; d.f.=3; p<0.0001). A Kruskal-Wallis test also showed a statistically significant difference among the cohorts (χ^2=35.93; d.f.=3; p<.0001).

Cardiovascular-related total medical service costs included costs from cardiovascular-related medical services including inpatient, outpatient, physician/supplier, and other costs. The unadjusted mean cost for **cardiovascular-related total medical services** for patients in cohort 2 (Mean=$9,843; SD=16,961) was higher than the means for patients in cohort 3 (Mean=$8,890; SD= 15,886) and cohort 4 (Mean=$8,474; SD=17,309). Patients in cohort 1 had relatively the lowest unadjusted mean cost for cardiovascular-related medical service among the cohorts (Mean= $8,269; SD=16,453). A one-way ANOVA indicated a statistically significant difference among the cohorts (F=6.79; d.f.=3; p=0.0001). A Kruskal-Wallis test also showed a statistically significant difference among the cohorts (χ^2=107.41; d.f.=3; p=0.0001).

Table 3.48 Cardiovascular-Related Medical Service Costs during 2007 among Cohorts (N=11732)

Medical services	Cohort 1 (n=3678)		Cohort 2 (n=4349)		Cohort 3 (n=1310)		Cohort 4 (n=2395)		F-value	p-value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Inpatient	$6,403	14,398	$7,422	14,608	$6,957	13,966	$6,824	15,391	3.27	0.0203
Outpatient	$464	1,740	$586	1,881	$518	2,033	$486	1,606	3.41	0.0167
Physician/supplier	$497	2,005	$636	2,419	$569	1,614	$500	3,121	2.82	0.0375
Other	$905	3,676	$1,200	4,196	$846	3,281	$664	3,031	11.77	<0.0001
Total medical service	$8,269	16,453	$9,843	16,961	$8,890	15,886	$8,474	17,309	6.79	0.0001

Note: Degrees of freedom equal 3 for all one-way ANOVAs

$H_{0\ (5u-y)}$: Cardiovascular-related medical care costs including inpatient [$H_{0(5u)}$], outpatient [$H_{0(5v)}$], other visits [$H_{0(5w)}$], physician/supplier [$H_{0(5x)}$], and total medical costs [$H_{0(5y)}$], will not differ significantly when categorized by Part D coverage.

Table 3.49 shows the results of the two-part model comparing adjusted mean costs for cardiovascular-related inpatient services (a) and differences (b) among cohorts, while controlling for covariates. This model indicated that the adjusted mean costs for cardiovascular-related inpatient services were not significantly different among the 4 cohorts ($p>0.05$). Appendix E9 shows the results of the two-part model of each predictor variable included in the model. **$H_{0\ (5u)}$: Not rejected.**

Table 3.49 A Two-part Model Adjusted Cardiovascular-related Inpatient Costs (A) and Differences (B) during 2007 among Cohorts while Controlling for Covariates (N=11732)

(a) A two-part model adjusted cardiovascular-related inpatient costs

Cohort	Mean	Standard Error	z	95% Confidence Interval	
1	$6,584	235	28.02	$6,123	$7,045
2	$7,292	213	34.23	$6,874	$7,709
3	$6,553	348	18.83	$5,871	$7,235
4	$6,980	313	22.3	$6,367	$7,594

(b) Differences in a two-part model adjusted cardiovascular-related inpatient costs compared with cohort 4

Contrast	Mean	Standard Error	z	95% Confidence Interval		p-value
1 vs 4	-$396	388	-1.02	-$1,156	$364	0.307
2 vs 4	$312	399	0.78	-$470	$1,093	0.435
3 vs 4	-$428	482	-0.89	-$1,372	$517	0.375

Table 3.50 shows the results of the two-part model comparing adjusted mean costs for cardiovascular-related outpatient services (a) and differences (b) among cohorts, while controlling for covariates. This model indicated that the adjusted mean costs for cardiovascular-related outpatient services among the 4 cohorts were not significantly different ($p>0.05$). Appendix F10 shows the results of the two-part model of each predictor variable included in the model.

$H_{0\ (5v)}$: Not rejected.

Table 3.50 A Two-part Model Adjusted Cardiovascular-related Outpatient Costs (A) and Differences (B) during 2007 among Cohorts while Controlling for Covariates (N=11732)

(a) A two-part model adjusted cardiovascular-related outpatient costs

Cohort	Mean	Standard Error	z	95% Confidence Interval	
1	$475	28	16.85	$420	$530
2	$562	26	21.38	$510	$613
3	$499	51	9.81	$399	$599
4	$519	37	14.20	$448	$591

(b) Differences in a two-part model adjusted cardiovascular-related outpatient costs compared with cohort 4

Contrast	Mean	Standard Error	z	95% Confidence Interval		p-value
1 vs 4	-$45	46	-0.96	-$135	$46	0.336
2 vs 4	$42	45	0.94	-$46	$131	0.348
3 vs 4	-$20	62	-0.33	-$143	$102	0.743

Table 3.51 shows the results of the two-part model comparing adjusted mean costs for cardiovascular-related physician/supplier services (a) and differences (b) among cohorts, while controlling for covariates. This model indicated that adjusted mean costs for cardiovascular-related physician/supplier services among the 4 cohorts were not significantly different ($p>0.05$). Appendix E11 shows the results of the two-part model of each predictor variable included in the model.

$H_{0\ (5w)}$: Not rejected.

Table 3.51 A Two-part Model Adjusted Cardiovascular-related Physician/Supplier Costs (A) and Differences (B) during 2007 among Cohorts while Controlling for Covariates (N=11732)

(a) A two-part model adjusted cardiovascular-related physician/supplier costs

Cohort	Mean	Standard Error	z	95% Confidence Interval	
1	$518	29	17.85	$461	$575
2	$592	29	20.12	$535	$650
3	$533	38	14.15	$459	$607
4	$566	61	9.32	$447	$685

(b) Differences in a two-part model adjusted cardiovascular-related physician/supplier costs compared with cohort 4

Contrast	Mean	Standard Error	z	95% Confidence Interval		p-value
1 vs 4	-$48	63	-0.76	-$172	$76	0.448
2 vs 4	$26	67	0.39	-$106	$158	0.696
3 vs 4	-$33	70	-0.47	-$171	$105	0.641

Table 3.52 shows the results of the two-part model comparing adjusted mean costs for cardiovascular-related other services (a) and differences (b) among cohorts, while controlling for covariates. This model indicated that the adjusted mean cost for cardiovascular-related other services for patients in cohort 2 was $1,056, $201 higher than the mean for patients in cohort 4 (Mean=$854) ($p<0.05$). The adjusted mean costs for cardiovascular-related other services did not differ significantly for patients in cohort 1 (Mean=$985) and cohort 3 (Mean=$729) compared to those in cohort 4, respectively ($p>0.05$). Appendix E12 shows the results of two-part model of each predictor variable included in the models. **$H_{0\ (5x)}$: Rejected.**

Table 3.52 A Two-part Model Adjusted Cardiovascular-related Other Costs (A) and Differences (B) during 2007 among Cohorts while Controlling for Covariates (N=11732)

(a) A two-part model adjusted cardiovascular-related other costs

Cohort	Mean	Standard Error	z	95% Confidence Interval	
1	$985	65	15.06	$857	$1,114
2	$1,056	54	19.55	$950	$1,162
3	$729	80	9.14	$572	$885
4	$854	80	10.67	$697	$1,011

(b) Differences in a two-part model adjusted cardiovascular-related physician/supplier costs compared with cohort 4

Contrast	Mean	Standard Error	z	95% Confidence Interval		p-value
1 vs 4	$131	100	1.31	-$65	$327	0.190
2 vs 4	$201	99	2.03	$7	$396	0.042
3 vs 4	-$126	117	-1.07	-$354	$103	0.283

Table 3.53 shows the results of the two-part model comparing adjusted mean costs for cardiovascular-related total medical services (a) and differences (b) among cohorts, while controlling for covariates. This model indicated that the adjusted mean costs for cardiovascular-related total medical services were $9,530 and $8,275 for patients in cohort 2 and cohort 3, $502 higher and $753 lower than the mean for patients in cohort 4 (Mean=$9,028), but the differences were not statistically significant (p>0.05). Appendix E13 shows the results of the two-part model of each predictor variable included in the model.

$H_{0\ (5y)}$: Not rejected.

Table 3.53 A Two-part Model Adjusted Cardiovascular-related Total Medical Service Costs (A) and Differences (B) during 2007 among Cohorts while Controlling for Covariates (N=11732)

(a) A two-part model adjusted cardiovascular-related other costs

Cohort	Mean	Standard Error	z	95% Confidence Interval	
1	$8,501	261	32.51	$7,988	$9,013
2	$9,530	256	37.19	$9,028	$10,032
3	$8,275	407	20.31	$7,476	$9,073
4	$9,028	386	23.37	$8,271	$9,785

(b) Differences in a two-part model adjusted cardiovascular-related other costs compared with cohort 4

Contrast	Mean	Standard Error	z	95% Confidence Interval		p-value
1 vs 4	-$527	468	-1.13	-$1,444	$390	0.260
2 vs 4	$502	470	1.07	-$419	$1,423	0.286
3 vs 4	-$753	566	-1.33	-$1,863	$357	0.183

3.5 Phase IV: Mortality Rates

Phase IV of the study examined all-cause and cardiovascular-related mortality rates.

3.5.1 Objective 6: All-cause and Cardiovascular-related Mortality

To determine whether all-cause mortality rates differ when categorized by Part D coverage.

The associations between Part D coverage and a 3-year mortality rates were assessed using descriptive and survival analyses. The descriptive analysis estimated the numbers of patients who died from any or CVD-related reasons, with statistical significance determined using chi-square test. Survival curves were calculated using the Kaplan-Meier method. Cox proportional hazards regression models were constructed to determine if mortality rates are associated with the Part D coverage gap while controlling for age, gender, race, region of residence, primary disease causing ESRD, ESRD duration, CCI score, and presence of chronic diseases (including diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease and CVD). Sensitivity analyses were also performed to control for laboratory data including GFR, BMI, serum creatinine, serum hematocrit, hemoglobin value (g/dl), serum albumin (g/dl), BUN, ethnicity (Hispanic vs. Non-Hispanic), and the receipt of a transplant in addition to covariates included in base case analyses above. Note: These laboratory data were obtained from the CMS End-Stage Renal Disease Medical Evidence Report (CMS-2728), which is used to register patients at the onset of ESRD.

3.5.1.1 All-cause Mortality Rates

$H_{0\ (6a)}$: All-cause mortality rates will not differ when categorized by Part D coverage.

Of the 11732 patients included in this study, 9814 (83.65%) deaths were observed during a 3-year follow-up period. Table 3.54 shows the chi-square test comparison of mortality status among the cohorts. This test revealed that all-cause mortality differed significantly among the cohorts (χ^2=651.90; d.f.=3; p<.0001). Greater proportions of patients in cohort 1 (85.07%), cohort 2 (89.68%) and cohort 3 (90.23%) died compared to those in cohort 4 (66.93%).

Table 3.54 All-cause Mortality between January 2008 and December 2010 among Cohorts (N=11732)

Cohort 1 (n=3678)		Cohort 2 (n=4349)		Cohort 3 (n=1310)		Cohort 4 (n=2395)		Test statistics	p-value
N	%	N	%	N	%	N	%		
3129	85.07	3900	89.68	1182	90.23	1603	66.93	651.9	<.0001

Note: Degree of freedom equal 1 for all chi-square tests

Figure 3.7 shows Kaplan-Meier curves comparing the percentage of patients who survived during the 3-year follow-up period among cohorts. The Log-Rank test (χ^2= 492.72; d.f.=3; p<0.0001) showed a significant difference among cohorts. As shown in the figure, patients in cohort 4 had a higher survival rate compared with the other 3 cohorts.

Figure 3.7 Kaplan-Meier survival curves comparing survival rates among cohorts

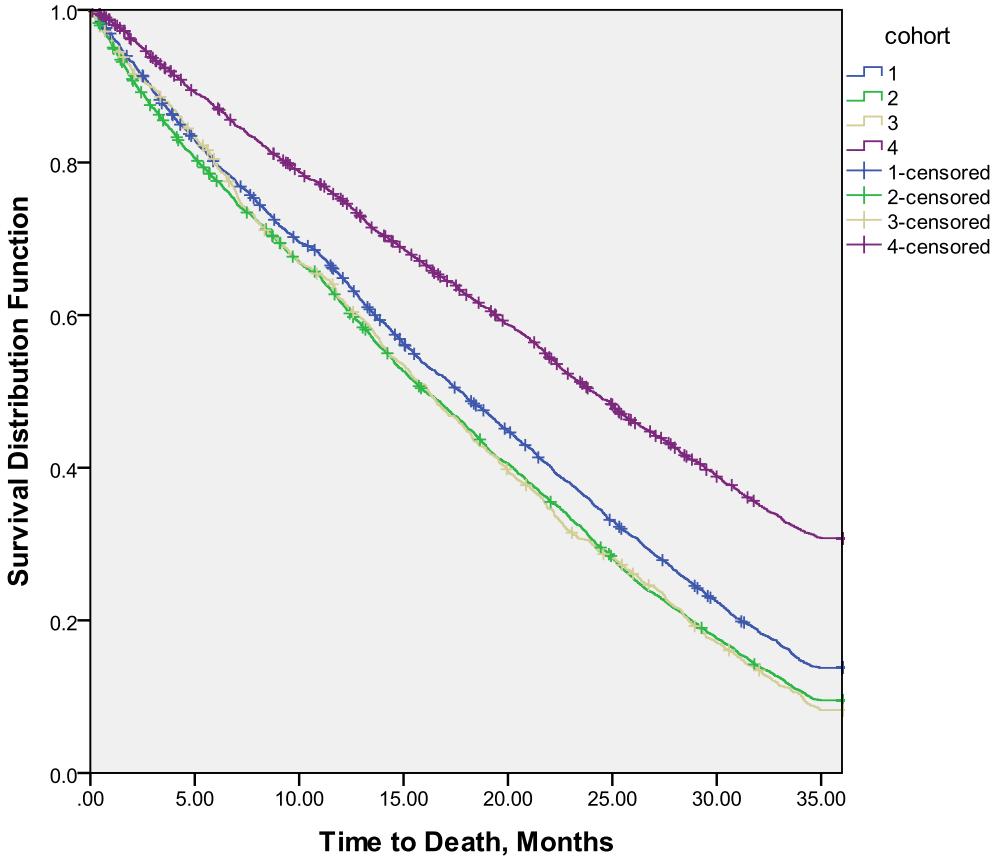


Table 3.55 shows the results of the Cox proportional hazards regression model comparing the mortality rates among cohorts, while controlling for covariates. The overall statistics for the model testing the null hypothesis that all parameter estimates are equal to zero indicated that the null hypothesis was rejected ($p<0.0001$). This model indicated that patients in cohort 1, cohort 2, and cohort 3 had a 30.4 percent (HR= 1.304; 95% CI= 1.225 – 1.388), a 35.5 percent (HR= 1.355; 95% CI= 1.273 – 1.441), and a 37.1 percent

increased risk of death (HR= 1.371; 95% CI= 1.268 – 1.482) compared to those in cohort 4, respectively.

Significant predictors for death were age, gender, race, ESRD duration, primary disease causing ESRD, CCI score, presence of CVD and newly developed CVD in 2007. Each year increase in age was associated with a 2.3 percent increase in the risk of death (HR=1.023; 95% CI= 1.021 – 1.025). Female gender was associated with an 8 percent decrease in the risk of death compared with male gender (HR = 0.920; 95% CI: 0.883 - 0.958). Being white and other were a 33.2 percent and a 16.6 percent increased risk of death compared with being black (HR=1.332; 95% CI=1.267 - 1.401; HR=1.166; 95% CI=1.033 - 1.316). Each year increase in ESRD duration was associated with a 0.9 percent increase in the risk of death (HR=1.009; 95% CI = 1.004 - 1.015). Hypertension, glomerulonephritis, cystic kidney, other as primary disease causing ESRD were associated with a 5.9 percent, a 10 percent, a 19.9 percent, and a 12.3 percent decreased risk of death compared to diabetes mellitus (HR=0.941; 95% CI= 0.889 – 0.995; HR=0.900; 95% CI=0.831-0.974; HR=0.801; 95% CI=0.702 – 0.913; HR=0.877; 95% CI=0.817-0.942). Each unit increase in CCI score was associated with an 8.3 percent increase in the risk of death (HR=1.083; 95% CI = 1.059-1.106). The presence of diabetes mellitus, hypertension, dyslipidemia, and cancer were associated with a 7.1 percent, a 5.5 percent, a 6.5 percent, and a 13.4 percent decreased risk of death (HR=0.929; 95% CI= 0.873 – 0.989; HR=0.945; 95% CI= 0.905 – 0.986; HR= 0.935; 95% CI=0.881- 0.992; HR=0.866; 95% CI=0.788-0.952). In contrast, the presence of

CVD and newly diagnosis of CVD were associated with a 25.3 percent and 33.5 percent increased risk of death (HR=1.253; 95% CI=1.179-1.332; HR=1.335; 95% CI=1.254-1.420).

Table 3.55 Cox Proportional Hazards Regression Model Comparing a 3-year All-cause Mortality Rates among Cohorts while Controlling for Covariates (N=11732)

Variable		Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits
cohort [a]	1	0.266	0.032	69.414	<.0001	1.304	1.225 - 1.388
	2	0.303	0.032	92.511	<.0001	1.355	1.273 - 1.441
	3	0.315	0.040	62.567	<.0001	1.371	1.268 - 1.482
Age		0.022	0.001	516.355	<.0001	1.023	1.021 - 1.025
Gender [b]	Female	-0.084	0.021	16.258	<.0001	0.920	0.883 - 0.958
Race [c]	White	0.287	0.026	124.571	<.0001	1.332	1.267 - 1.401
	Other	0.154	0.062	6.213	0.013	1.166	1.033 - 1.316
Region of residence [d]	Northeast	-0.013	0.029	0.216	0.642	0.987	0.932 - 1.044
	South	-0.005	0.028	0.037	0.847	0.995	0.942 - 1.050
	West	-0.024	0.037	0.424	0.515	0.976	0.907 - 1.050
ESRD duration		0.009	0.003	11.285	0.001	1.009	1.004 -1.015
Primary disease causing ESRD [e]	Hypertension	-0.061	0.029	4.520	0.034	0.941	0.889 - 0.995
	Glomerulonephritis	-0.106	0.041	6.735	0.010	0.900	0.831 - 0.974
	Cystic Kidney	-0.222	0.067	11.063	0.001	0.801	0.702 - 0.913
	Other	-0.131	0.036	12.970	0.000	0.877	0.817 - 0.942
Charlson Comorbidity Index (CCI) score		0.079	0.011	51.348	<.0001	1.083	1.059 - 1.106
Presence of chronic disease	Diabetes mellitus	-0.074	0.032	5.359	0.021	0.929	0.873 - 0.989
	Hypertension	-0.057	0.022	6.752	0.009	0.945	0.905 - 0.986
	Dyslipidemia	-0.068	0.030	4.970	0.026	0.935	0.881 - 0.992
	Cancer	-0.144	0.048	8.871	0.003	0.866	0.788 - 0.952
	Chronic lung disease	-0.001	0.029	0.001	0.972	0.999	0.944 - 1.057
	Cardiovascular disease	0.226	0.031	52.546	<.0001	1.253	1.179 - 1.332
Newly diagnosis of cardiovascular disease 2007		0.289	0.032	82.938	<.0001	1.335	1.254 - 1.420

Model parameters: Likelihood Ratio = 1820.96; d.f.=23; p<0.0001; Score = 1681.55; d.f.=23; p<0.0001; Wald = 1644.18; d.f.=23; p< 0.0001.

a Reference: Cohort 4; b Reference: Male; c Reference: Black; d Reference: Midwest; e Reference: Diabetes mellitus

Table 3.56 shows the sensitivity analysis results of the Cox proportional hazards regression model comparing the mortality rates among cohorts, while controlling for GFR, BMI, serum creatinine, serum hematocrit, hemoglobin value (g/dl), serum albumin (g/dl), BUN, ethnicity (Hispanic vs. Non-Hispanic), and the receipt of transplant in addition to covariates included in Table 3.55. A total of 5989 patients were used for this sensitivity analysis due to missing values. The overall statistics for the model testing the null hypothesis that all parameter estimates are equal to zero indicated that the null hypothesis was rejected ($p<0.0001$). This model indicated that patients in cohort 1, cohort 2, cohort 3 were associated with a 24.6 percent (HR= 1.246; 95% CI= 1.141 – 1.362), a 31.6 percent (HR= 1.355; 95% CI= 1.205 – 1.437), and a 34.5 percent increased risk of death (HR= 1.371; 95% CI= 1.206 – 1.500) compared to those in cohort 4, respectively.

Significant predictors for death were age, gender, race, CCI score, presence of cardiovascular disease, newly developed CVD in 2007, serum albumin and ethnicity (Hispanic vs non-Hispanic). Compared with Table 3.55, serum albumin and ethnicity became significant predictors while primary disease causing ESRD and presence of chronic diseases were not significant in this sensitivity analysis. Each year increase in age was associated with a 1.5 percent increase in the risk of death (HR=1.015; 95% CI= 1.012 – 1.018). Female gender was associated with a 14.7 percent decrease in the risk of death compared with male gender (HR = 0.853; 95% CI: 0.839 - 0.952). Being white was associated with a 40.8 percent increase in the risk of death compared with being

black (HR=1.408; 95% CI=1.303 - 1.521). Each year increase in ESRD duration was associated with a 1.1 percent increase in the risk of death (HR=1.011; 95% CI = 1.000 - 1.021). Each unit increase in CCI score was associated with an 8.4 percent increase in the risk of death (HR=1.084; 95% CI = 1.052 - 1.170). The presence of CVD and having a new diagnosis of CVD were associated with a 23.5 percent and a 42.2 percent increased risk of death (HR=1.235; 95% CI=1.134-1.344; HR=1.422; 95% CI=1.306-1.549). Each unit increase in serum albumin was associated with a 4.7 percent decrease in the risk of death (HR=0.953; 95% CI= 0.911 – 0.998). Lastly, being Hispanic was associated with a 23.3 percent decrease in the risk of death compared to non-Hispanic patients (HR=0.767; 95% CI = 0.686 – 0.858).

$H_{0\ (6a)}$: Rejected.

Table 3.56 Cox Proportional Hazards Regression Model Comparing a 3-year All-cause Mortality Rates among Cohorts while Controlling for Covariates (N=5989) : Sensitivity Analysis

Variable		Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits
cohort [a]	1	0.220	0.045	23.657	<.0001	1.246	1.141 - 1.362
	2	0.275	0.045	37.141	<.0001	1.316	1.205 - 1.437
	3	0.296	0.056	28.278	<.0001	1.345	1.206 - 1.500
Age		0.023	0.001	237.594	<.0001	1.023	1.020 - 1.026
Gender [b]	Female	-0.113	0.032	12.189	0.001	0.894	0.839 - 0.952
Race [c]	White	0.342	0.039	75.146	<.0001	1.408	1.303 - 1.521
	Other	0.266	0.084	10.126	0.002	1.304	1.107 - 1.536
Region of residence [d]	Northeast	0.041	0.041	1.003	0.317	1.042	0.962 - 1.128
	South	0.030	0.040	0.576	0.448	1.031	0.953 - 1.115
	West	0.031	0.054	0.319	0.572	1.031	0.927 - 1.146

Table 3.56 (continued)

ESRD duration		0.011	0.005	4.172	0.041	1.011	1.000 - 1.021
Primary disease causing ESRD [e]	Hypertension	-0.028	0.041	0.475	0.491	0.972	0.897 - 1.054
	Glomerulonephritis	-0.109	0.056	3.754	0.053	0.897	0.803 - 1.001
	Cystic Kidney	-0.140	0.096	2.123	0.145	0.869	0.720 - 1.050
	Other	-0.101	0.051	3.851	0.050	0.904	0.817 - 1.000
Charlson Comorbidity Index (CCI) score		0.081	0.015	27.475	<.0001	1.084	1.052 - 1.170
Presence of chronic disease	Diabetes mellitus	-0.015	0.045	0.111	0.739	0.985	0.902 - 1.076
	Hypertension	-0.043	0.031	1.922	0.166	0.958	0.902 - 1.018
	Dyslipidemia	-0.066	0.042	2.457	0.117	0.936	0.861 - 1.017
	Cancer	-0.172	0.068	6.347	0.012	0.842	0.737 - 0.963
	Chronic lung disease	-0.035	0.041	0.743	0.389	0.965	0.891 - 1.046
	Cardiovascular disease	0.211	0.043	23.631	<.0001	1.235	1.134 - 1.344
Newly diagnosis of cardiovascular disease 2007		0.352	0.043	65.669	<.0001	1.422	1.306 - 1.549
GFR		0.004	0.006	0.399	0.527	1.004	0.992 - 1.016
BMI		0.000	0.002	0.025	0.875	1.000	0.995 - 1.004
Serum creatinine		-0.001	0.008	0.005	0.943	0.999	0.983 - 1.016
Serum hematocrit		0.004	0.010	0.162	0.687	1.004	0.985 - 1.023
Hemoglobin		-0.006	0.030	0.037	0.848	0.994	0.938 - 1.054
Serum albumin		-0.048	0.023	4.245	0.039	0.953	0.911 - 0.998
Blood urea nitrogen (BUN)		0.000	0.001	0.127	0.721	1.000	0.999 - 1.001
Kidney transplant		-0.201	0.179	1.260	0.262	0.818	0.575 - 1.162
Hispanic		-0.265	0.057	21.616	<.0001	0.767	0.686 - 0.858

Model parameters: *Likelihood Ratio* = 1820.96; *d.f.*=23; $p<0.0001$; *Score* = 1681.55; *d.f.*=23; $p<0.0001$; *Wald* = 1644.18; *d.f.*=23; $p< 0.0001$. Number of observations used : 5989.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

3.5.1.2 Cardiovascular-related Mortality Rates

$H_{0\ (6b)}$: Cardiovascular-related mortality rates will not differ when categorized by Part D coverage.

Of the 11732 patients in this study, 4149 (35.4%) cardiovascular-related deaths were observed during a 3-year follow-up period. Table 3.57 shows a chi-square test comparison of cardiovascular-related mortality status among the cohorts. This test revealed that cardiovascular-related mortality differed significantly among cohorts (χ^2=56.63; d.f.=3; p<.0001). Greater proportions of patients in cohort 1 (35.18%), cohort 2 (38.49%) and cohort 3 (36.41%) had CVD-related deaths compared to those in cohort 4 (29.39%).

Table 3.57 Cardiovascular-related Mortality Rates between January 2008 and December 2010 among Cohorts (N=11732)

Cohort 1 (n=3678)		Cohort 2 (n=4349)		Cohort 3 (n=1310)		Cohort 4 (n=2395)		Test statistics	p-value
N	%	N	%	N	%	N	%		
1294	35.18	1674	38.49	477	36.41	704	29.39	56.63	<.0001

Note: Degree of freedom equal 1 for all chi-square tests

Figure 3.8 shows Kaplan-Meier curves comparing the percentage of patients who survive during a 3-year follow-up period among cohorts. The Log-Rank test (χ^2= 163.96; d.f.=3; p<0.0001) showed a significant difference among cohorts. As shown in the figure, patients in cohort 4 had a higher survival rates compared with other cohorts.

Figure 3.8 Kaplan-Meier survival curves comparing cardiovascular-related survival rates among cohorts

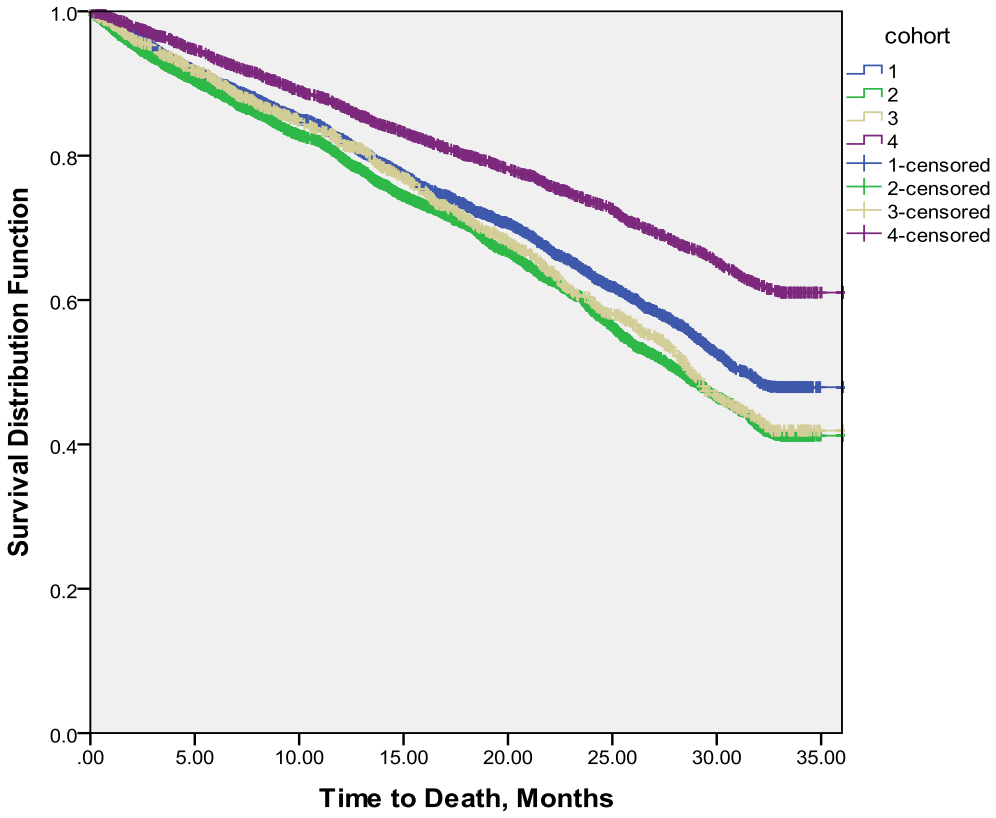


Table 3.58 shows the results of the Cox proportional hazards regression model comparing cardiovascular-related mortality rates among cohorts, while controlling for covariates. The overall statistics for the model testing the null hypothesis that all parameter estimates are equal to zero indicated that the null hypothesis was rejected ($p<0.0001$). This model indicated that patients in cohort 1, cohort 2, cohort 3 had a 26.5 percent (HR= 1.265; 95% CI= 1.151 – 1.392), a 37.8 percent (HR= 1.378; 95% CI= 1.255 – 1.514), and a 30.4 percent increased risk of cardiovascular-related death (HR= 1.304; 95% CI= 1.156 – 1.472) compared to those in cohort 4, respectively.

Significant predictors for death were age, gender, race, region of residence, ESRD duration, primary disease causing ESRD, CCI score, presence of CVD and newly developed CVD in 2007. Each year increase in age was associated with a 1.5 percent increase in the risk of cardiovascular-related death (HR=1.015; 95% CI= 1.012 – 1.018). Female gender was associated with a 14.7 percent decrease in the risk of cardiovascular-related death compared to male gender (HR = 0.853; 95% CI: 0.801 - 0.908). Being white was associated with a 31.1 percent increase in the risk of cardiovascular-related death compared to black (HR=1.311; 95% CI=1.215 - 1.415). Patient who lived in the Northeast and South were 17.6 percent and 16.2 percent more likely to die from cardiovascular-related reasons compared with those in Midwest, respectively (HR = 1.176; 95% CI= 1.075 – 1.287; HR=1.162; 95% CI= 1.067 – 1.267). Hypertension, glomerulonephritis, cystic kidney, and ‘other’ as the primary disease causing ESRD were associated with an 11.5 percent, a 14.8 percent, a 33.8 percent, and a 21.5 percent

decreased risk of cardiovascular-related death compared with diabetes mellitus (HR=0.885; 95% CI= 0.812 – 0.965; HR=0.852; 95% CI=0.753-0.964; HR=0.662; 95% CI=0.532 – 0.823; HR=0.785; 95% CI=0.702-0.879). Each unit increase in CCI score was associated with a 6.9 percent increase in the risk of cardiovascular-related death (HR=1.069; 95% CI = 1.034 - 1.106). The presence of CVD and having a new diagnosis of CVD were associated with a 37.5 percent and a 45.5 percent increased risk of cardiovascular-related death (HR=1.375; 95% CI=1.250-1.513; HR=1.455; 95% CI=1.321 - 1.602).

Table 3.58 Cox Proportional Hazards Regression Model Comparing 3-year Cardiovascular-Related Mortality Rates among Cohorts while Controlling for Covariates (N=11732)

Variable		Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits
cohort [a]	1	0.235	0.049	23.509	<.0001	1.265	1.151 - 1.392
	2	0.321	0.048	44.967	<.0001	1.378	1.255 - 1.514
	3	0.266	0.062	18.552	<.0001	1.304	1.156 - 1.472
Age		0.015	0.001	106.319	<.0001	1.015	1.012 - 1.018
Gender [b]	Female	-0.159	0.032	24.638	<.0001	0.853	0.801 - 0.908
Race [c]	White	0.271	0.039	48.365	<.0001	1.311	1.215 -1.415
	Other	0.175	0.092	3.608	0.058	1.192	0.994 - 1.428
Region of residence [d]	Northeast	0.163	0.046	12.596	0.000	1.176	1.075 - 1.287
	South	0.150	0.044	11.804	0.001	1.162	1.067 - 1.267
	West	0.090	0.059	2.351	0.125	1.094	0.975 - 1.228
ESRD duration		0.002	0.004	0.230	0.632	1.002	0.994 - 1.011

Table 3.58 (continued)

Primary disease causing ESRD [e]	Hypertension	-0.122	0.044	7.702	0.006	0.885	0.812 - 0.965
	Glomerulonephritis	-0.160	0.063	6.447	0.011	0.852	0.753 - 0.964
	Cystic Kidney	-0.413	0.111	13.823	0.000	0.662	0.532 - 0.823
	Other	-0.242	0.057	17.769	<.0001	0.785	0.702 - 0.879
Charlson Comorbidity Index (CCI) score		0.067	0.017	15.162	<.0001	1.069	1.034 - 1.106
Presence of chronic disease	Diabetes mellitus	-0.037	0.049	0.561	0.454	0.964	0.875 -1.061
	Hypertension	-0.059	0.034	3.109	0.078	0.942	0.882 - 1.007
	Dyslipidemia	-0.060	0.046	1.671	0.196	0.942	0.860 - 1.031
	Cancer	-0.200	0.076	6.880	0.009	0.818	0.705 - 0.951
	Chronic lung disease	-0.030	0.044	0.444	0.505	0.971	0.890 - 1.059
	Cardiovascular disease	0.318	0.049	42.692	<.0001	1.375	1.250 - 1.513
Newly diagnosis of cardiovascular disease 2007		0.375	0.049	58.064	<.0001	1.455	1.321 - 1.602

Model parameters: *Likelihood Ratio* = 1057.18; *d.f.*=32; $p<0.0001$; *Score* = 975.07; *d.f.*=32; $p<0.0001$; *Wald* = 949.12; *d.f.*=32; $p< 0.0001$.

Number of observations used : 5989 patients

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Table 3.59 shows the sensitivity analysis results of the Cox proportional hazards regression model comparing cardiovascular-related mortality rates among cohorts, while controlling for GFR, BMI, serum creatinine, serum hematocrit, hemoglobin value (g/dl), serum albumin (g/dl), BUN, ethnicity (Hispanic vs Non-Hispanic), and the receipt of transplant in addition to covariates included in Table 3.58. A total of 5989 patients were used for this sensitivity analysis due to missing values. The overall statistics for the

model testing the null hypothesis that all parameter estimates are equal to zero indicated that the null hypothesis was rejected ($p<0.0001$). This model indicated that patients in cohort 1, cohort 2, cohort 3 had a 20.9 percent (HR= 1.209; 95% CI= 1.056 – 1.385), a 34.9 percent (HR= 1.349; 95% CI= 1.180 – 1.542), and a 22.2 percent increased risk of cardiovascular-related death (HR= 1.222; 95% CI= 1.031 – 1.449) compared to those in cohort 4, respectively.

Significant predictors for death were age, gender, race, region of residence, primary disease causing ESRD, CCI score, presence of cancer and CVD, newly developed CVD in 2007, serum albumin and ethnicity (Hispanic vs non-Hispanic).

Compared with Table 3.58, serum albumin and ethnicity became significant predictors in addition to significant predictors in the previous model (Table 3.57). Each year increase in age was associated with a 1.5 percent increase in the risk of cardiovascular-related death (HR=1.015; 95% CI= 1.010 – 1.019). Female gender was associated with a 20.4 percent decrease in the risk of cardiovascular-related death compared with male gender (HR = 0.796; 95% CI: 0.721 - 0.879). Being white was associated with a 36.4 percent increase in the risk of cardiovascular-related death compared with being black (HR=1.364; 95% CI=1.212 - 1.534). Patients who lived in the Northeast and South were 22.4 percent and 17.4 percent more likely to die from cardiovascular-related reasons compared with those in Midwest, respectively (HR = 1.224; 95% CI= 1.080 – 1.388;

HR=1.174; 95% CI= 1.038 – 1.329). Glomerulonephritis, cystic kidney, and 'other' as the primary disease causing ESRD were associated with a 20.8 percent, a 30.6 percent, and a 25.3 percent decreased risk of cardiovascular-related death compared with patients who had diabetes mellitus as the primary disease causing ESRD (HR=0.792; 95% CI= 0.667 – 0.942; HR=0.694; 95% CI=0.507 - 0.948; HR=0.747; 95% CI=0.636 – 0.878). Each unit increase in CCI score was associated with a 7.7 percent increase in the risk of cardiovascular-related death (HR=1.077; 95% CI = 1.028 - 1.128). The presence of cancer was associated with a 20.6 percent decrease in the risk of cardiovascular-related death (HR=0.794; 95% CI = 0.643 – 0.980). The presence of CVD and having a new diagnosis of CVD were associated with a 44.0 percent and a 58.8 percent increased risk of cardiovascular-related death (HR=1.440; 95% CI=1.259 - 1.647; HR=1.588; 95% CI=1.388 - 1.816). Each unit increase in serum albumin was associated with a 7.9 percent decrease in the risk of death (HR=0.921; 95% CI= 0.858 – 0.988). Lastly, being Hispanic was associated with a 29 percent decrease in the risk of death compared to non-Hispanic patients (HR=0.710; 95% CI = 0.598 – 0.843).

$H_{0\ (6b)}$: Rejected.

Table 3.59 Cox Proportional Hazards Regression Model Comparing 3-year Cardiovascular-related Mortality Rates among Cohorts while Controlling for Covariates (N=5989) : Sensitivity Analysis

Variable		Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits
cohort [a]	1	0.190	0.069	7.553	0.006	1.209	1.056 - 1.385
	2	0.299	0.068	19.201	<.0001	1.349	1.180 - 1.542
	3	0.201	0.087	5.335	0.021	1.222	1.031 - 1.449
Age		0.014	0.002	40.883	<.0001	1.015	1.010 - 1.019
Gender [b]	Female	-0.228	0.051	20.407	<.0001	0.796	0.721 - 0.879
Race [c]	White	0.310	0.060	26.698	<.0001	1.364	1.212 - 1.534
	Other	0.211	0.127	2.751	0.097	1.235	0.962 - 1.583
Region of residence[d]	Northeast	0.202	0.064	9.957	0.002	1.224	1.080 - 1.388
	South	0.161	0.063	6.475	0.011	1.174	1.038 - 1.329
	West	0.083	0.086	0.915	0.339	1.086	0.917 - 1.286
ESRD duration		0.000	0.008	0.001	0.983	1.000	0.984 - 1.016
Primary disease causing ESRD [e]	Hypertension	-0.124	0.063	3.833	0.050	0.884	0.781 - 1.000
	Glomerulonephritis	-0.233	0.088	6.950	0.008	0.792	0.667 - 0.942
	Cystic Kidney	-0.366	0.159	5.272	0.022	0.694	0.507 - 0.948
	Other	-0.291	0.082	12.553	0.000	0.747	0.636 - 0.878
Charlson Comorbidity Index (CCI) score		0.074	0.024	9.615	0.002	1.077	1.028 - 1.128
Presence of chronic disease	Diabetes mellitus	-0.050	0.070	0.512	0.474	0.951	0.829 - 1.091
	Hypertension	-0.011	0.047	0.051	0.821	0.989	0.902 - 1.086
	Dyslipidemia	-0.060	0.065	0.869	0.351	0.941	0.829 - 1.069
	Cancer	-0.231	0.107	4.612	0.032	0.794	0.643 - 0.980
	Chronic lung disease	-0.096	0.063	2.324	0.127	0.908	0.802 - 1.028
	Cardiovascular disease	0.365	0.068	28.382	<.0001	1.440	1.259 - 1.647
Newly diagnosis of cardiovascular disease 2007		0.462	0.069	45.488	<.0001	1.588	1.388 - 1.816
GFR		-0.016	0.010	2.711	0.100	0.984	0.965 - 1.003
BMI		-0.004	0.003	1.273	0.259	0.996	0.989 - 1.003
Serum creatinine		-0.024	0.013	3.222	0.073	0.976	0.951 - 1.002
Serum hematocrit		-0.005	0.015	0.100	0.752	0.995	0.966 - 1.025

Table 3.59 (continued)

Hemoglobin	0.015	0.046	0.099	0.753	1.015	0.927 - 1.11
Serum albumin	-0.083	0.036	5.311	0.021	0.921	0.858 - 0.988
Blood urea nitrogen (BUN)	0.000	0.001	0.011	0.916	1.000	0.999 - 1.002
Kidney transplant	-0.621	0.320	3.776	0.052	0.537	0.287 - 1.005
Hispanic	-0.343	0.088	15.276	<.0001	0.710	0.598 - 0.843

Model parameters: *Likelihood Ratio* = 426.78; *d.f.*=32; $p<0.0001$; *Score* = 393.36; *d.f.*=32; $p<0.0001$; *Wald* = 381.97; *d.f.*=32; $p< 0.0001$. Number of observations used : 5989.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Table 3.60 shows a summary of hypothesis testing results for the present study

Table 3.60 Summary of Hypotheses Testing

Study phase/Objective/Hypothesis	Objective/Hypothesis	Result
PHASE I	**DEMOGRAPHIC AND CLINICAL CHARACTERISTICS**	
Objective 1	**To compare patient characteristics for Medicare beneficiaries with dialysis, categorized into four cohorts based on their Part D coverage.**	
$H_{0\ (1a)}$	Mean age will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (1b)}$	The proportion of patients in each gender category will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (1c)}$	The proportion of patients in each race category will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (1d)}$	The proportion of patients in each region category will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (1e)}$	The proportion of patients in primary disease causing ESRD will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (1f)}$	Mean ESRD duration will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (1g)}$	Mean comorbidity score will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (1h)}$	The proportion of patients in the presence of cardiovascular disease will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (1i)}$	The proportion of patients in the presence of diabetes will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (1j)}$	The proportion of patients in the presence of hypertension will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (1k)}$	The proportion of patients in the presence of chronic diseases dyslipidemia will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (1l)}$	The proportion of patients in the presence of cancer will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (1m)}$	The proportion of patients in the presence of chronic lung disease will not differ significantly when categorized by Part D coverage.	Rejected

Table 3.60 (continued)

PHASE II	**MEDICATION ADHERENCE AND COSTS**	
Objective 2	**To determine whether the proportion and number of oral prescription medications and pharmacy costs differ when categorized by Part D coverage.**	
$H_{0\ (2a)}$	The proportion of patients using will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (2b)}$	The proportion of patients using antihypertensives will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (2c)}$	The proportion of patients using lipid-lowering drugs will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (2d)}$	The proportion of patients using phosphate binders will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (2e)}$	The proportion of patients using cinacalcet will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (2f)}$	The mean number of antihyperglycemics will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (2g)}$	The mean number of antihypertensives will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (2h)}$	The mean number of lipid-lowering drugs will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (2i)}$	The mean number of phosphate binders will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (2j)}$	The mean number of cinacalcet will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (2k)}$	Pharmacy costs for antihyperglycemics will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (2l)}$	Pharmacy costs for antihypertensives will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (2m)}$	Pharmacy costs for lipid-lowering drugs will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (2n)}$	Pharmacy costs for phosphate binders will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (2o)}$	Pharmacy costs for cinacalcet will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (2p)}$	Pharmacy costs for all prescription medications will not differ significantly when categorized by Part D coverage.	Rejected

Table 3.60 (continued)

Objective 3	To determine whether medication adherence and persistence among patients receiving drug therapy for diabetes, hypertension, hyperlipidemia, hyperphosphatemia or secondary parathyroid differ when categorized by Part D coverage.	
$H_{0\ (3a)}$	Medication adherence for antihyperglycemics will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (3b)}$	Medication adherence for antihypertensives will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (3c)}$	Medication adherence for lipid-lowering drugs will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (3d)}$	Medication adherence for phosphate binders will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (3e)}$	Medication adherence for cinacalcet will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (3f)}$	The proportion of patients who are adherent (MPR $\geq$ 80%) to antihyperglycemics will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (3g)}$	The proportion of patients who are adherent (MPR $\geq$ 80%) to antihypertensives will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (3h)}$	The proportion of patients who are adherent (MPR $\geq$ 80%) to lipid-lowering drugs will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (3i)}$	The proportion of patients who are adherent (MPR $\geq$ 80%) to phosphate binders will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (3j)}$	The proportion of patients who are adherent (MPR $\geq$ 80%) to cinacalcet will not differ significantly when categorized by Part D coverage.	Rejected
	To determine whether medication adherence differs before and after the coverage gap is exceed among patients receiving drug therapy in our primary cohort (**cohort 2**) who reach coverage gap but not catastrophic coverage.	
$H_{0\ (3k)}$	Medication adherence with antihyperglycemics will not differ significantly before and after reaching the gap.	Rejected
$H_{0\ (3l)}$	Medication adherence with antihypertensives will not differ significantly before and after reaching the gap.	Rejected

Table 3.60 (continued)

$H_{0\ (3m)}$	Medication adherence with lipid-lowering drugs will not differ significantly before and after reaching the gap.	Rejected
$H_{0\ (3n)}$	Medication adherence with phosphate binders will not differ significantly before and after reaching the gap.	Rejected
$H_{0\ (3o)}$	Medication adherence with cinacalcet will not differ significantly before and after reaching the gap.	Rejected
$H_{0\ (3p)}$	The proportion of patients who are adherent (MPR ≥ 80%) to antihyperglycemics will not differ significantly before and after reaching the gap.	Rejected
$H_{0\ (3q)}$	The proportion of patients who are adherent (MPR ≥ 80%) to antihypertensives will not differ significantly before and after reaching the gap.	Rejected
$H_{0\ (3r)}$	The proportion of patients who are adherent (MPR ≥ 80%) to lipid-lowering drugs will not differ significantly before and after reaching the gap.	Rejected
$H_{0\ (3s)}$	The proportion of patients who are adherent (MPR ≥ 80%) to phosphate binders will not differ significantly before and after reaching the gap.	Rejected
$H_{0\ (3t)}$	The proportion of patients who are adherent (MPR ≥ 80%) to cinacalcet will not differ significantly before and after reaching the gap.	Rejected
$H_{0\ (3u)}$	Medication persistence with antihyperglycemics will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (3u)}$	Medication persistence with antihypertensives will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (3u)}$	Medication persistence with lipid-lowering drugs will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (3u)}$	Medication persistence with phosphate binders will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (3u)}$	Medication persistence with cinacalcet will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (3z)}$	The proportion of patients who are persistent (until 30days gap) to antihyperglycemics will not differ significantly when categorized by Part D coverage.	Rejected

Table 3.60 (continued)

$H_{0\ (3za)}$	The proportion of patients who are persistent (until 30days gap) to antihypertensives will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (3zb)}$	The proportion of patients who are persistent (until 30days gap) to lipid-lowering drugs will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (3zc)}$	The proportion of patients who are persistent (until 30days gap) to phosphate binders will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (3zd)}$	The proportion of patients who are persistent (until 30days gap) to cinacalcet will not differ significantly when categorized by Part D coverage.	Rejected
PHASE III	**MEDICAL SERVICES AND COSTS**	
Objective 4	To determine whether cardiovascular morbidity rates differ when categorized by Part D coverage.	
$H_{0\ (4)}$	Incidence of cardiovascular disease will not differ significantly when categorized by Part D coverage	Rejected
Objective 5	To determine whether all-cause and cardiovascular-related medical service utilization (i.e., inpatient, outpatient and other visits) and costs differ when categorized by Part D coverage.	
$H_{0\ (5a)}$	The proportion of patients used all-cause inpatient services will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (5b)}$	The proportion of patients used all-cause outpatient services will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (5c)}$	The proportion of patients used all-cause other services will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (5d)}$	Mean number of all-cause inpatient visits will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (5e)}$	Mean number of all-cause outpatient visits will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (5f)}$	Mean number of all-cause other visits will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (5g)}$	The proportion of patients used cardiovascular-related inpatient services will not differ significantly when categorized by Part D coverage.	Rejected

Table 3.60 (continued)

$H_{0\ (5h)}$	The proportion of patients used cardiovascular-related inpatient services will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (5i)}$	The proportion of patients used cardiovascular-related outpatient services will not differ significantly when categorized by Part D coverage.	Not rejected
$H_{0\ (5g)}$	The proportion of patients used cardiovascular-related other services will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (5j)}$	Mean numbers of cardiovascular-related inpatient visits will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (5k)}$	Mean numbers of cardiovascular-related outpatient visits will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (5l)}$	Mean numbers of cardiovascular-related other visits will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (5m)}$	All-cause inpatient service costs will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (5n)}$	All-cause medical inpatient costs will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (5o)}$	All-cause physician/supplier costs will not differ significantly when categorized by Part D coverage.	Not rejected
$H_{0\ (5p)}$	All-cause other service costs will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (5q)}$	All-cause dialysis costs will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (5r)}$	All-cause total medical care costs will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (5s)}$	All-cause total pharmacy costs will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (5t)}$	All-cause total health care costs will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (5u)}$	Cardiovascular-related inpatient service costs will not differ significantly when categorized by Part D coverage.	Not rejected
$H_{0\ (5v)}$	Cardiovascular-related outpatient service costs will not differ significantly when categorized by Part D coverage.	Not rejected
$H_{0\ (5w)}$	Cardiovascular-related physician/supplier costs will not differ significantly when categorized by Part D coverage.	Not rejected

Table 3.60 (continued)

$H_{0\ (5x)}$	Cardiovascular-related other service costs will not differ significantly when categorized by Part D coverage.	Rejected
$H_{0\ (5y)}$	Cardiovascular-related total medical service costs will not differ significantly when categorized by Part D coverage.	Not rejected
PHASE IV	**MORTALITY RATES**	
Objective 6	To determine whether cardiovascular-related and all-cause mortality rates differ when categorized by Part D coverage.	
$H_{0\ (6a)}$	All-cause mortality rates will not differ when categorized by Part D coverage.	Rejected
$H_{0\ (6b)}$	Cardiovascular-related mortality rates will not differ when categorized by Part D coverage.	Rejected

Chapter 4: Discussion and Conclusions

4.1 Chapter Overview

This chapter provides a detailed discussion of the results of the study. The chapter begins with a brief review of objectives and corresponding study results. Possible explanations for the study findings are proposed. This is followed by a discussion of the study strengths and limitations. The chapter concludes with a summary of the major findings and recommendations for future research.

Study purpose

The purpose of this study was to evaluate the impact of Medicare Part D coverage on health outcomes in dialysis patients. Health outcomes included medication adherence and costs, medical service utilization and costs, CVD morbidity, all-cause and CVD-related mortality among Medicare beneficiaries with dialysis, categorized into four cohorts based on their Part D coverage.

Six objectives were address in this study. The results of the study are discussed according to the study objectives in line with the four study phases, i.e.:

- Phase I: Demographic and Clinical Characteristics (Objective 1)
- Phase II: Medication Adherence and Costs (Objectives 2-3)
- Phase III: Medical Services and Costs (Objectives 4-5)
- Phase IV: Mortality Rates (Objective 6)

4.2 Phase I and Phase II

4.2.1 Objective 1: Demographic and Clinical Characteristics

The proportion of dialysis patients whose out-of-pocket spending reached the coverage gap threshold of $799 and the catastrophic coverage phase threshold of $3850 were calculated. A total of 11732 patients were identified as meeting inclusion criteria: 3678 patients (31.3%) had out-of-pocket costs <$799; 4349 patients (37.1%) had out-of-pocket costs between $799 and $3850; 1310 patients (11.2%) had out-of-pocket costs > $3850; and the remaining 2395 patients (20.4%) had out-of-pocket costs < $799 with a low income subsidy (LIS). Overall, in present study, 61 percent of Part D non-LIS enrollees (cohort 1, cohort 2 and cohort 3) reached the coverage gap. Of these patients who reached the coverage gap, 23 percent reached the catastrophic coverage level (cohort 3). According to the 2012 USRDS annual report, in 2010, 41 percent of hemodialysis patients reached the coverage gap, and 23 percent of patients reached catastrophic coverage. (US Renal Data System 2012) Possible explanations for the differences in the proportion of patients who reached the coverage gap (61 versus 41 percent) could be differences in study populations. In the present study, we used the inclusion criteria of patients who were continuously enrolled in Parts A, B and D plans in 2007 and alive at the end of 2007. In addition, the coverage cost sharing structure in 2007 was different from 2010, where patients fell into the coverage gap with out-of-pocket drug spending from $940 to $4550. For the entire study cohort, the mean age was 69.4 years (SD=12.7), 56.2 percent were male, and 66.2 percent were white. The primary disease

causing ESRD was diabetes (43.1%), followed by hypertension (30.8%), and glomerulonephritis (10.4%). The mean ESRD duration was 5.3 years (SD=4.1). The mean CCI was 2.1 (1.8) and 44.8 percent had a cardiovascular diagnosis during 2006.

4.2.2 Objective 2: Medication Utilization and Costs

Overall, antihypertensive drugs were the most commonly used (87.6%), followed by phosphate binders (75.5%), lipid-lowering drugs (44.3%), antihyperglycemic drugs (36.6%), and cinacalcet (25.7%). Regarding mean total and out-of-pocket drug costs per person per year, cinacalcet was the most costly drug ($2653 and $592), followed by phosphate binders ($1520 and $377), antihypertensive drugs ($696 and $247), antihyperglycemic drugs ($572 and $207), and lipid-lowering drugs ($504 and $183). Similar results were observed within cohorts. Among the 4 cohorts, patients who received LIS assistance (cohort 4) experienced much lower mean out-of-pocket costs (n=2395; $192 for out-of-pocket cost; $5312 for total drug cost; ratio of out-of-pocket cost to total cost= 3.6%) than patients not receiving the subsidy (cohorts 1, 2 and 3). Patients in cohort 3 experienced the highest mean out-of-pocket costs (n=1310; $4153 for out-of-pocket cost; $10659 for total drug cost; ratio of out-of-pocket costs to total costs= 39.0%) but those in cohort 2 had the highest ratio of out-of-pocket costs to total costs (n=4349; $4153 for out-of-pocket cost; $10659 for total drug cost; ratio of out-of-pocket costs to total costs= 41.8%). Patients in cohort 1 experienced the lowest mean out-of-pocket cost and the ratio of out-of-pocket costs to total costs among those not receiving

the LIS assistance (n=3678; $423 for out-of-pocket cost; $1820 for total drug cost; ratio of out-of-pocket cost to total cost= 23.2%)

4.2.3 Objective 3: Medication Adherence and Persistence

The effects of Part D coverage on medication adherence and persistence were examined. Poor medication adherence (MPR ≥ 80%) was common, and in the four cohorts ranged from: 29 to 53 percent for antihyperglycemic drugs; 47 to 73 percent for antihypertensive drug; 43 to 71 percent for lipid-lowering drugs; 13 to 40 percent for phosphate binders; and 17 to 55 percent for cinacalcet. These results were consistent with previous adherence studies in dialysis patients, which found that adherence to phosphate binder was 38 percent (Chiu, Teitelbaum et al. 2009), adherence to cinacalcet was 29 percent (Gincherman, Moloney et al. 2010), and adherence to antihypertensives was 58 percent. (Curtin, Svarstad et al. 1999)

High medication discontinuation (using a 30-day treatment gap) was also observed, ranging from 63 to 79 percent for antihyperglycemic drugs; 34 to 60 percent for antihypertensive drugs; 46 to 69 percent for lipid-lowering drugs; 68 to 89 percent for phosphate binders; and 56 to 84 percent for cinacalcet. These results were consistent with the previous study, which reported that the monthly refill rate for cinacalcet fell significantly over five quarterly periods from 53 percent in the first quarter to 37 percent in the 5^{th} quarter. (Gincherman, Moloney et al. 2010)

In general, adherence and persistence to dialysis-specific medications (i.e., phosphate binders and cinacalcet) were worse than those to non dialysis-specific medications (i.e., antihyperglycemics, antihypertensives, and lipid-lowering drugs). A possible explanation for these differences could be differences in drug costs by therapeutic classes. Based on the findings from pharmacy costs, total and out-of-pocket costs for phosphate binders and cinacalcet were significantly higher than drug costs for diabetes mellitus, hypertension, and dyslipidemia.

There were consistently significant differences in medication adherence and discontinuation among the 4 cohorts across all five therapeutic classes of outpatient prescription drugs. Patients in cohort 2 had significantly lower adherence and persistence levels compared to those in cohort 4. Interestingly, after adjustment for the covariates measured in our study, patients in cohort 1 had the lowest while those in cohort 3 had the highest adherence and persistence among the 4 cohorts. This may be explained by the operational definitions used to categorize patients into 4 cohorts. Patients may fall into the initial coverage phase (cohort 1), evidenced by out-of-pocket spending < $799, because they may not be adherent or persistent with filling prescriptions. In addition patients may fall into the catastrophic coverage phase (cohort 3), evidenced by out-of-pocket spending ≥ $3850, because they were adherent and persistent with filling prescriptions.

Further analysis of patients' adherence before and after reaching the coverage gap (cohort 2) provides information regarding the association between the coverage gap and adherence. After adjustment for the covariates, patients were significantly more likely to be nonadherent to prescription drugs; as indicated by a 72 percent, 70 percent, 101 percent, 74 percent, and 108 percent increased risk for nonadherence to antihyperglycemics, antihypertensives, lipid-lowering drugs, phosphate binders, and cinacalcet after reaching coverage gap. Our findings were consistent with previous studies. Several studies on the Part D coverage gap used the number of prescriptions filled as the outcome variable (Pedan, Lu et al. 2009; Zhang, Donohue et al. 2009; US Renal Data System 2011), while few studies compared the adherence or discontinuation before and after reaching the coverage gap. (Gu, Zeng et al. 2010; Polinski, Shrank et al. 2011) Gu et al. found that compared with Part D beneficiaries with full coverage of both generic and brand name drugs, beneficiaries with no coverage were 62 percent less likely to be adherent to diabetic medication after reaching the coverage gap. (Gu, Zeng et al. 2010) Polinski et al. also found that gap-exposed patients were twice as likely to discontinue their medications for cardiovascular conditions, diabetes, depression, dementia, or rheumatoid arthritis. (Polinski, Shrank et al. 2011)

4.3 Phase III: Medical Services and Costs

4.3.1 Objective 4: Cardiovascular Disease Morbidity

The effects of Part D coverage on incident CVD were examined. No previous study had evaluated the effects of Part D or cost sharing on incident CVD in dialysis patients, even though CVD is the leading cause of mortality in dialysis patients. This study found that patients with out-of-pocket spending ≥ $799 (cohort 2 and cohort 3) had a 42 percent and a 38 percent increased risk of CVD compared to those in cohort 4, but there was no significant difference between patients in cohort 1 and cohort 4, after controlling for covariates.

4.3.2 Objective 5: All-cause and Cardiovascular-related Medical Service Utilization and Costs

The effects of Part D coverage on all-cause and cardiovascular-related medical service utilization and costs were examined. This study found that patients in cohort 2 had increased all-cause inpatient and outpatient visits compared to those in cohort 4 (1.73 versus 1.58 for inpatient visits and 7.98 versus 6.95 for outpatient visits) after controlling for covariates. There were no significant differences between those in cohort 1 or cohort 3 and cohort 4 except for patients in cohort 3 had higher inpatient visits than those in cohort 4. Similar results were observed for cardiovascular-related medical service utilization, where patients in cohort 2 had increased medical service utilization compared to those in cohort 4 (0.75 versus 0.69 for inpatient visits and 0.75 versus 0.71 for

outpatient visits). There were no significant differences in cardiovascular-related medical service utilization between patients in cohort 1 or cohort 3 and cohort 4. Accordingly, patients in cohort 2 had $1949 higher inpatient and $473 higher outpatient costs, which contributed to $3368 higher medical service costs compared to those in cohort 4, after controlling for covariates ($p<0.0001$). Patients in cohort 3 also had $2736 higher medical service costs compared to those in cohort 4, after controlling for covariates. The adjusted mean pharmacy costs for patients in cohort 1 and cohort 2 were $3618 and $ 2419 lower but the mean was $1299 higher for patients in cohort 3 compared to those in cohort 4, respectively. Taken together, the lower pharmacy costs and the higher medical service costs led to an overall $2644 increase in total health care costs for patients in cohort 2 ($60304) compared to those in cohort 4 ($57660), after controlling for covariates ($p<0.0001$). Patients in cohort 1 and cohort 3 had $3188 lower and $4211 higher all-cause health care costs compared to those in cohort 4, after controlling for covariates ($p<0.0001$). These results were consistent with a previous study, which found that patients whose drug benefits were capped at $1000 had higher relative rates of visits to the emergency department and nonelective hospitalizations. (Hsu, Price et al. 2006)

4.4 Phase IV: Mortality Rates

4.4.1 Objective 6: All-cause and Cardiovascular-related Mortality

The effects of Part D coverage on all-cause and cardiovascular-related mortality were examined. Results indicated that patients in cohort 1, cohort 2, and cohort 3 had a 30.4 percent, a 35.5 percent and a 37.1 percent increased risk of all-cause death compared to those in cohort 4 for a 3-year follow-up period, respectively ($p<0.0001$). Similar results were observed for cardiovascular-related deaths, where patients in cohort 1, cohort 2, and cohort 3 had a 26.5 percent, a 37.8 percent, and a 30.4 percent increased risk of cardiovascular-related deaths, compared to those in cohort 4 for a 3-year follow-up period, respectively ($p<0.0001$). These relationships remained significant after controlling for additional potential confounders including GFR, BMI, serum creatinine, serum hematocrit, hemoglobin value (g/dl), serum albumin (g/dl), BUN, ethnicity (Hispanic vs. Non-Hispanic), and the receipt of transplant and were robust to sensitivity analyses. After controlling for 22 covariates, patients in cohort 2 had a 31.6 percent, increased risk of all-cause death and a 34.0 percent increased risk of cardiovascular death, compared to those in cohort 4 ($p<0.0001$). Despite controlling for additional important variables, the time periods observed to obtain laboratory values might have been different among patients because the evidence file contained data collected at ESRD onset. The mean ESRD duration ranged from 4.8 – 6.0 years among the 4 cohorts ($p<0.0001$). Several previous studies suggested that mild-to-moderate elevations in serum creatinine levels (Mann, Gerstein et al. 2001; Drey, Roderick et al. 2003), a

reduced GFR (Muntner, He et al. 2002; Go, Chertow et al. 2004), or high and low HgbA1c levels (Kalantar-Zadeh, Kopple et al. 2007; Shurraw, Majumdar et al. 2010) were independently associated with an increased risk of death in dialysis patients and the presence of malnutrition/inflammations including cholesterol levels, serum albumin, and BMI were also important predictors. (Liu, Coresh et al. 2004; Kalantar-Zadeh, Kopple et al. 2007; Baigent, Landray et al. 2011) Thus, it is important to control for these factors using sensitivity analyses despite some limited time period issues. Interestingly, sensitivity analyses found that increased serum albumin was associated with a decreased risk of all-cause and cardiovascular-related deaths, after controlling for all other covariates. A study of Japanese patients receiving hemodialysis reported that high cholesterol levels were associated with lower mortality in persons with low albumin levels but were associated with higher mortality in a subgroup with high serum albumin levels. (Iseki, Yamazato et al. 2002)

Results indicated that CVD accounted for 41 to 44 percent of all deaths. This result was consistent with a previous study, which reported that CVD is the leading cause of mortality in ESRD, accounting for about 45 percent of all deaths. (Wright and Hutchison 2009)

4.5 Comparison of Main Study Findings for Cohort 2 vs Cohort 4

Previous studies that evaluated the effect of drug cost sharing on health outcomes compared patients with a cap on drug benefits versus unlimited drug benefits. (Federman, Adams et al. 2001; Tamblyn, Laprise et al. 2001; Hsu, Price et al. 2006) For comparison with previous studies, this section summarized main study findings for patients in cohort 2 compared with those in cohort 4.

Overall, an important finding was that the Part D coverage gap was consistently associated with negative economic and clinical outcomes. Among dialysis patients who fell into the coverage gap phase in 2007, defined as out-of-pocket costs ≥ $799, the coverage gap was associated with decreased drug adherence, increased incident CVD, increased inpatient and outpatient visits, increased medical service costs, and increased mortality rates. Patients in cohort 2 were 70 to 108 percent more likely to be nonadherent to outpatient prescription drugs including antihyperglycemics, antihypertensives, lipid-lowering drugs, phosphate binders, and cinacalcet after reaching the coverage gap, while controlling for covariates ($p<0.0001$). After adjustment for the covariates measured in this study, patients in cohort 2 had higher mean total medical costs due to increased rates of hospitalizations and outpatient visits compared to those in cohort 4. When comparing cohort 2 to cohort 4, despite having lower pharmacy costs, the increase in higher medical service costs resulted in significantly higher mean total health care costs, after controlling for covariates ($p<0.0001$). The higher costs of

hospitalizations and outpatient visits did not offset much of the savings in pharmacy costs as the cost sharing burden was shifted from Medicare to patients. In addition, patients in cohort 2 had a 42% increased risk of CVD during a 1-year follow-up. These patients also had a 35.5 percent and a 37.8 percent increased risk of all-cause and cardiovascular-related deaths for a 3-year follow-up period compared to those in cohort 4, respectively. These relationships remained significant after controlling for additional potential confounders and were robust to sensitivity analyses. Our findings were consistent with previous retrospective and prospective studies that compared cost sharing in prescription drug coverage plans. (Tamblyn, Laprise et al. 2001; Hsu, Price et al. 2006) Tamblyn et al. conducted a retrospective time-series analysis of data before and after the introduction of a prescription coinsurance and deductible cost-sharing policy in Quebec. (Tamblyn, Laprise et al. 2001) Researchers found that increased cost-sharing for prescription drugs in elderly persons in Canada was followed by a 9 percent reduction in the use of essential drugs and a 7 percent higher rate of serious adverse events and a 14 percent increase in ED visits associated with these reductions. (Tamblyn, Laprise et al. 2001)

A prospective study compared health outcomes for beneficiaries whose annual drug benefits were capped at $1000 and those who had unlimited drug benefits. (Hsu, Price et al. 2006) The results indicated that individuals whose benefits were capped had a 13 percent increase in hospitalizations, a 9 percent increase in ER visits, and a 22 percent increase in deaths.

4.6 Study Strengths and Limitations

Study aims were to investigate the associations between Medicare Part D coverage and health outcomes including: mortality, incident CVD, medical service utilization and costs, and medication adherence and persistence in dialysis patients. To the best of our knowledge, this is the first study to examine the associations between the Medicare Part D coverage cost sharing structure and health outcomes in dialysis patients. This provided valuable information on association between Medicare Part D coverage and mortality, as well as on incident CVD; neither of which has been examined previously among dialysis patients. This is important because it was reported that morbidity and mortality of dialysis patients remains high due to high cardiovascular morbidity and mortality although survival rates have improved steadily in the US ESRD population since the late 1980s. (Foley and Collins 2007) All-cause mortality is clinically meaningful and provides a measure of net benefits versus harms. In addition, there is now increasing interest in the cardiovascular status of patients due to high CVD-related morbidity and mortality. (Go, Chertow et al. 2004)

Using national USRDS data, the study provides national estimates on medication adherence, health care utilization, health care costs, CVD morbidity and mortality for dialysis patients who were enrolled in Medicare's Part D program in 2007. The USRDS database includes almost 95 percent of ESRD patients in the U.S. The generalizability is a clear advantage over studies that were based on specific or regional health plans.

Furthermore, availability of data on laboratory values including GFR, BMI, serum creatinine, serum hematocrit, hemoglobin value (g/dl), serum albumin (g/dl), and BUN allowed for sensitivity analyses.

Relatively few studies have evaluated the impact of Part D coverage in the Medicare population. This is one of few studies that focused on the impact of Part D coverage on direct health outcomes. Although several studies reported that the lack of drug coverage has been associated with poor outcomes (Soumerai, Ross-Degnan et al. 1991; Federman, Adams et al. 2001; Tamblyn, Laprise et al. 2001; Hsu, Price et al. 2006), this is the only study that compared patients based on the Part D coverage phases including initial, coverage gap, and catastrophic coverage phases. In addition, this study directly investigated the associations between the coverage gap and patient outcomes compared to previous studies that mainly focused on drug utilization and adherence during the coverage gap. (Schmittdiel, Ettner et al. 2009; Zhang, Donohue et al. 2009; Fung, Mangione et al. 2010; Polinski, Shrank et al. 2011) Therefore, findings from this study provide valuable information to existing literature on the Medicare Part D.

This study also has several limitations that deserve mention. Although patients were categorized into 4 cohorts based on the Part D coverage, it is possible that patients' coverage within cohorts might have been different. Prescription drug plans (PDPs) have the latitude to structure their plans differently from standard Part D plans; nonstandard plans are available when their coverage is at least actuarially equivalent to the standard

plan. (US Renal Data System 2012) Many PDPs have developed plans with no deductibles or with drug copayments instead of the 25 percent co-insurance, and some include drug coverage during the coverage gap. According to the 2012 USRDS annual report, in 2010, 60 percent and 15 percent hemodialysis patients had no deductible and some type of gap coverage. (US Renal Data System 2012) The structure of standard Part D plans used for this study may be different from some patients' nonstandard plans. However, actual out-of-pocket drug spending was used to categorize patients into 4 cohorts that apply to all Part D beneficiaries as thresholds for coverage gap and catastrophic coverage phases regardless the presence of deductibles.

According to 2013 Medicare Part D Plan Facts, in 2012, during the coverage gap, only7 percent of Part D plans had some brand coverage while a 26 percent of Part D plans had some generic coverage. (Medicare 2013) Fung et al. observed that generic gap coverage did not contribute to patients' annual out-of-pocket spending compared to those without gap coverage because there were no available generics within some therapeutic classes and the optimal drug regimen might not have a generic equivalent for some patients. (Fung, Mangione et al. 2010) In the present study, most out-of-pocket drug spending was observed for phosphate binders and cinacalcet where generics or equivalent generics are not available. Thus, we assumed that generic gap coverage would have a limited impact on patients' out-of-pocket spending in dialysis patients; and only few patients might have brand coverage during coverage gap.

Second, because this was an observational retrospective study, we could not conclude that there was a causal relationship between the Part D coverage gap and poor adherence, poor clinical outcomes, high medical service costs, and high mortality, only associations. This relationship warrants further consideration.

Third, although many important demographic and clinical factors were controlled for in this study, there may be residual confounding, such as kidney functioning, inflammatory factors (Shlipak, Fried et al. 2003; Go, Chertow et al. 2004), hemoglobin A1c levels (Kalantar-Zadeh, Kopple et al. 2007; Shurraw, Majumdar et al. 2010; Williams, Lacson et al. 2010), blood pressure readings (Zager, Nikolic et al. 1998; Foley, Herzog et al. 2002) and cholesterol levels, which all affect patient' health outcomes. However, sensitivity analyses for all-cause and cardiovascular-related mortality that adjusted for additional laboratory values yielded similar findings.

Fourth, as a general limitation with the use of a claims database, MPR was used as a proxy measure of adherence, which could not ascertain that the patients used the medications as prescribed, but merely that they had picked up their medication fills or refills. In addition, there is the possibility that MPR calculations might have under- or over-estimated adherence. Patients were classified as using polytherapy (i.e., dual, triple, or quad therapy) only during the period when the medications overlapped but received monotherapy for the remaining part of the study period. This might have underestimated adherence measures. Patients classified as using monotherapy may have

received two different drugs in the same class of medication (e.g., 2 beta-blockers), which might have overestimated adherence measures.

Fifth, patients may have filled prescriptions outside the Part D benefit. To what extent dialysis patients fill prescriptions outside of their Part D plans is unknown, (Frankenfield, Howell et al. 2011) but inclusion/exclusion criteria in this study probably were conservative. Patients were excluded if they were dual-eligible, received a retiree drug subsidy, or were on an employer-sponsored health benefit plans.

Lastly, patients' out-of-pocket drug spending in 2007 was used to categorize patients into the 4 cohorts. Our findings were from the 2007 of Part D, and extrapolation to another year or generalization to dialysis patients not enrolled in Part D may not be appropriate.

4.7 Study Implications and Future Research

To control prescription drug costs, health plans and employers have increased prescription drug cost sharing amounts for patients. For Medicare as well as other payers, determining ways to control and pay drug costs is an ongoing concern. (Hsu, Fung et al. 2008) In comparison with commercial insurance, Part D benefits use complex and high levels of cost sharing due to budget constraints, including monthly premiums, a deductible, and a coverage gap. A controversial and unique aspect of the Part D benefit design was the donut hole, a gap in coverage of out-of-pocket spending

between $799 and $3850, meaning that beneficiaries were responsible for all of their drug costs during this gap. (Zhang, Donohue et al. 2009) To date, the lack of drug coverage has been associated with poor outcomes in non-Medicare populations (Tamblyn, Laprise et al. 2001; Hsu, Price et al. 2006). In Medicare populations, the coverage gap has been associated with reduced drug adherence. (Raebel, Delate et al. 2008; Schmittdiel, Ettner et al. 2009; Zhang, Donohue et al. 2009; Fung, Mangione et al. 2010; Polinski, Shrank et al. 2011) However, there is little information available regarding how and to what extent the Part D coverage impacts health outcomes in dialysis patients, although a majority of dialysis patients are enrolled in Part D. We have shown that 60 percent of dialysis patients reached the coverage gap after enrollment. Dialysis patients appear to be more vulnerable than the general Medicare population, especially regarding their experiences under Medicare Part D. The findings for this study suggest that the coverage gap may adversely affect health outcomes through its effects on drug utilization. Considering the substantial impact that drug policy can have on patient's health, there is a need for more studies on the outcomes associated with the coverage gap and, possibly, to modify cost sharing policies for drugs used by dialysis patients.

4.8 Conclusions and Future Research

In conclusion, reaching the Part D coverage gap was associated with decreased medication adherence and unfavorable clinical and economic outcomes in dialysis patients. The coverage gap was associated with increased out-of-pocket spending,

decreased drug adherence, decreased pharmacy costs, increased medical service utilization and costs, increased total health care costs, increased incident CVD, increased all-cause and CVD-related mortality among dialysis patients with Part A, B and D benefits.

Several areas deserve attention in future research. Since the associations between Part D coverage and medication adherence for patients in cohort 2 was measured in this study, future studies can focus on medication adherence for patients in cohort 3 who went through the coverage gap and reached the catastrophic coverage phase. Further study is warranted to delineate patients' medication taking behaviors by the Part D coverage phases (i.e., initial coverage, coverage gap, and catastrophic coverage gap phases). In addition, we only examined the 1- year follow-up period for medication adherence, medical service utilization and costs, and incident CVD. Because the Part D coverage resets on January 1 each year, it is not feasible to measure medication adherence longer than 1-year for patients with Part D benefits. However, repeated exposure to Part D coverage for multiple years may confirm our findings. Additional research is needed to shed light on how repeated exposure to the Part D coverage gap impacts health outcomes in dialysis patients.

Appendices

Appendix A List of Acronyms

BUN – Blood Urea Nitrogen

CCI - Charlson Comorbidity Index

CKD-MBD – Chronic Kidney Disease –Mineral and Bone Disorder

CMS – Centers for Medicare & Medicaid

DOPPS - Dialysis Outcomes and Practice Patterns Study

HDL – High Density Lipoprotein

HIE – Health Insurance Experiment

IRB – Institutional Review Board

KDIGO – Kidney Disease Improving Global Outcomes

KDOQI - Kidney Disease Outcomes Quality Initiative

LDL - Low Density Lipoprotein

LIS – Low Income Subsidy

MPR – Medication Possession Ratio

MAPDs- Medicare Advantage prescription drug plans

MCBS – Medicare Current beneficiary Survey

MSP – Medicare as Secondary Payer

NIDDK – National Institute of Diabetes and Digestive and Kidney Diseases

NKF - National Kidney Foundation

PDPs – stand-alone prescription drug plans

PMMIS – Program Management and Medical Information System

PTH – Parathyroid hormone

REBUS – Renal Beneficiary and Utilization System

SAFs – Standard Analytical Files

USRDS – United States Renal Data System

UNOS – United Network for Organ Sharing

Appendix B ICD-9 Codes for Cardiovascular Disease

Cardiovascular disease	ICD-9-CM	CPT
Atrial fibrillation (AF)	427.3	
Acute myocardial infarction (AMI)	410, 410.x0, and 410.x1	
Congestive heart failure (CHF)	398.91, 425.x, 428.xx, 402.x1, 404.x1, and 404.x3	
Cerebrovascular accident/transient ischemic attack (CVA/TIA)	430–437	
Peripheral arterial disease (PAD)	440–444, 447, and 557 (ICD-9-CM diagnosis codes); 84.0, 84.1, 84.91, 39.25, 39.26, and 39.29 (ICD-9-CM procedure codes)	24900, 24920, 25900, 25905, 25920, 25927, 27295, 27590, 27591, 27592, 27598, 27880, 27881, 27882, 27888, 27889, 28800, 28805, 34900, 35131, 35132, 35141, 35142, 35151, 35152, 34051, 34151, 34201, 34203, 34800–34834, 35081–35103, 35331, 35341, 35351, 35355, 35361, 35363, 35371, 35372, 35381, 35450, 35452, 35454, 35456, 35459, 35470, 35471, 35472, 35473, 35474, 35480, 35481, 35482, 35483, 35485, 35490, 35491, 35492, 35493, 35495, 35521, 35531, 35533, 35541, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35571, 35583, 35585, 35587, 35621, 35623, 35646, 35647, 35651, 35654, 35656, 35661, 35663, 35665, 35666, and 35671
Coronary artery bypass graft surgery (CABG)	36.1x (ICD-9-CM procedure codes)	33510–33523 and 33533–33536
Use of an implantable cardioverter defibrillator (ICD)	37.94 (ICD-9-CM procedure code)	
Use of cardiac resynchronization therapy with defibrillator (CRT-D)	00.51 (ICD-9-CM procedure code)	

Appendix C1 Medication Persistence (Mean Days Until First a 60-day Treatment Gap) by Five Therapeutic Classes of Outpatient Prescription Drugs among Cohorts (N=11732)

Medication persistence (60 days)	Cohort 1 (n=3678)		Cohort 2 (n=4349)		Cohort 3 (n=1310)		Cohort 4 (n=2395)		F-value	p-value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Antidiabetic drugs (n=3819)										
persistence (Mean, SD)	191.40	130.67	220.16	128.51	259.06	121.28	223.20	132.96	30.09	<.0001
Antihypertensive drugs (n=9863)	2975		3976		1189		2133			
persistence (Mean, SD)	254.12	124.61	304.54	99.16	320.34	87.16	290.65	111.29	155.44	<.0001
Lipid-lowering drugs (n=4607)	922		2119		746		820			
persistence (Mean, SD)	222.70	123.68	258.71	114.69	297.45	98.35	254.31	120.14	58.33	<.0001
Phosphate binders (n=7753)	1729		3185		1151		1688			
persistence (Mean, SD)	158.70	119.40	204.74	120.97	258.02	118.52	203.09	131.30	152.57	<.0001
Cinacalcet (n=2436)	261		854		606		718			
persistence (Mean, SD)	136.62	105.98	171.47	111.07	244.68	119.36	202.88	125.91	70.48	<.0001

Appendix C2 Number of Patients with a 60-day Treatment Gap (Discontinuation) by Five Therapeutic Classes of Outpatient Prescription Drugs among Cohorts (N=11732)

Medication persistence (60 days)	Cohort 1 (n=3678)		Cohort 2 (n=4349)		Cohort 3 (n=1310)		Cohort 4 (n=2395)		Test statistics	p-value
	N	%	N	%	N	%	N	%		
Antidiabetic drugs (n=3819)	851		1630		523		815			
Discontinuation (N, %)	583	68.51	1089	66.81	259	49.52	481	59.02	17.37	0.0006
Antihypertensive drugs (n=9863)	2975		3976		1189		2133			
Discontinuation (N, %)	1346	48.56	1264	32.72	272	23.31	728	35.32	286.15	<.0001
Lipid-lowering drugs (n=4607)	922		2119		746		820			
Discontinuation (N, %)	524	56.83	1066	50.31	246	32.98	372	45.37	103.08	<.0001
Phosphate binders (n=7753)	1729		3185		1151		1688			
Discontinuation (N, %)	1401	81.03	2365	74.25	590	51.26	1149	68.07	325.76	<.0001
Cinacalcet (n=2436)	261		854		606		718			
Discontinuation (N, %)	198	75.86	643	75.29	257	42.41	413	57.52	190.07	<.0001

Appendix C3 Cox Proportional Hazards Regression Model Comparing Therapy Discontinuation for Antihyperglycemic Drugs with a 60-day Treatment Gap among Cohorts while Controlling for Covariates (N=3819)

Variable		Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits
Cohort [a]	1	0.379	0.065	34.380	<.0001	1.461	1.287 - 1.658
	2	0.234	0.059	15.822	<.0001	1.263	1.126 - 1.418
	3	-0.249	0.080	9.711	0.002	0.779	0.666 - 0.912
Age		-0.004	0.002	3.612	0.057	0.996	0.992 - 1.000
Gender [b]	Female	0.073	0.042	3.128	0.077	1.076	0.992 - 1.167
Race [c]	White	-0.222	0.048	21.357	<.0001	0.801	0.728 - 0.880
	Other	-0.256	0.118	4.681	0.031	0.774	0.614 - 0.976
Region of residence [d]	Northeast	0.012	0.060	0.039	0.844	1.012	0.899 - 1.139
	South	0.038	0.056	0.470	0.493	1.039	0.932 - 1.159
	West	-0.079	0.078	1.020	0.313	0.924	0.793 - 1.077
ESRD duration		0.021	0.007	8.787	0.003	1.022	1.007 - 1.036
Primary disease causing ESRD [e]	Hypertension	-0.080	0.066	1.504	0.220	0.923	0.811 - 1.049
	Glomerulonephritis	0.059	0.156	0.141	0.707	1.060	0.781 - 1.439
	Cystic Kidney	-0.253	0.356	0.506	0.477	0.776	0.386 - 1.560
	Other	-0.059	0.102	0.333	0.564	0.943	0.771 - 1.152
Charlson Comorbidity Index (CCI) score		0.102	0.022	22.011	<.0001	1.107	1.061 - 1.155
Presence of chronic disease	Diabetes mellitus	-0.146	0.079	3.404	0.065	0.864	0.740 - 1.009
	Hypertension	-0.023	0.044	0.273	0.602	0.977	0.896 - 1.065
	Dyslipidemia	0.061	0.057	1.153	0.283	1.063	0.951 - 1.188
	Cancer	-0.280	0.111	6.410	0.011	0.756	0.609 - 0.939
	Chronic lung disease	-0.046	0.060	0.582	0.446	0.955	0.849 - 1.075
	Cardiovascular disease	0.028	0.058	0.239	0.625	1.029	0.919 - 1.152

Model parameters: *Likelihood Ratio* = 187.32; *d.f.*=22; $p<0.0001$; *Score* = 187.27; *d.f.*=22; $p<0.0001$; *Wald* = 185.66; *d.f.*=22; $p< 0.0001$.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Appendix C4 Cox Proportional Hazards Regression Model Comparing Therapy Discontinuation for Antihypertensive Drugs with a 60-day Treatment Gap among Cohorts while Controlling for Covariates (N=9863)

Variable		Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits
Cohort [a]	1	0.599	0.048	155.944	<.0001	1.821	1.658 - 2.001
	2	0.045	0.050	0.821	0.365	1.046	0.949 - 1.154
	3	-0.364	0.073	24.598	<.0001	0.695	0.602 - 0.802
Age		-0.010	0.001	45.244	<.0001	0.990	0.987 - 0.993
Gender [b]	Female	-0.112	0.034	10.631	0.001	0.894	0.836 - 0.956
Race [c]	White	-0.184	0.039	22.596	<.0001	0.832	0.771 - 0.898
	Other	-0.224	0.101	4.944	0.026	0.799	0.656 - 0.974
Region of residence [d]	Northeast	0.057	0.050	1.309	0.253	1.059	0.960 - 1.168
	South	0.083	0.047	3.163	0.075	1.086	0.992 - 1.190
	West	0.010	0.066	0.021	0.885	1.010	0.888 - 1.148
ESRD duration		0.022	0.004	25.973	<.0001	1.022	1.013 - 1.030
Primary disease causing ESRD [e]	Hypertension	-0.083	0.047	3.080	0.079	0.920	0.839 - 1.010
	Glomerulonephritis	-0.065	0.066	0.963	0.326	0.937	0.823 - 1.067
	Cystic Kidney	0.064	0.108	0.354	0.552	1.066	0.863 - 1.318
	Other	0.009	0.061	0.023	0.880	1.009	0.895 - 1.138
Charlson Comorbidity Index (CCI) score		0.061	0.019	10.900	0.001	1.063	1.025 - 1.103
Presence of chronic disease	Diabetes mellitus	0.001	0.053	0.001	0.978	1.001	0.903 - 1.110
	Hypertension	-0.097	0.036	7.267	0.007	0.907	0.845 - 0.974
	Dyslipidemia	0.061	0.050	1.484	0.223	1.062	0.964 - 1.171
	Cancer	-0.206	0.084	6.000	0.014	0.814	0.690 - 0.960
	Chronic lung disease	-0.003	0.048	0.005	0.945	0.997	0.907 - 1.096
	Cardiovascular disease	0.031	0.046	0.461	0.497	1.032	0.943 - 1.128

Model parameters: *Likelihood Ratio* = 579.49; *d.f.*=22; $p<0.0001$; *Score* = 606.39; *d.f.*=22; $p<0.0001$; *Wald* = 589.80; *d.f.*=22; $p< 0.0001$.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Appendix C5 Cox Proportional Hazards Regression Model Comparing Therapy Discontinuation for Lipid-lowering Drugs with a 60-day Treatment Gap among Cohorts while Controlling for Covariates (N=4607)

Variable		Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits
Cohort [a]	1	0.607	0.072	72.091	<.0001	1.835	1.595 - 2.111
	2	0.323	0.065	24.925	<.0001	1.381	1.216 - 1.567
	3	-0.297	0.085	12.217	0.001	0.743	0.629 - 0.878
Age		-0.015	0.002	48.243	<.0001	0.985	0.981 - 0.989
Gender [b]	Female	0.010	0.044	0.052	0.821	1.010	0.927 - 1.100
Race [c]	White	-0.287	0.052	30.747	<.0001	0.751	0.678 - 0.831
	Other	-0.147	0.127	1.346	0.246	0.863	0.673 - 1.107
Region of residence [d]	Northeast	0.012	0.062	0.039	0.843	1.012	0.896 - 1.144
	South	0.132	0.059	4.979	0.026	1.142	1.016 - 1.282
	West	-0.054	0.082	0.436	0.509	0.947	0.806 - 1.113
ESRD duration		-0.007	0.007	1.127	0.288	0.993	0.980 - 1.006
Primary disease causing ESRD [e]	Hypertension	-0.024	0.060	0.164	0.686	0.976	0.868 - 1.098
	Glomerulonephritis	-0.029	0.093	0.100	0.752	0.971	0.809 - 1.165
	Cystic Kidney	0.226	0.145	2.427	0.119	1.254	0.943 - 1.667
	Other	0.038	0.080	0.230	0.631	1.039	0.889 - 1.215
Charlson Comorbidity Index (CCI) score		0.019	0.024	0.649	0.421	1.020	0.973 - 1.069
Presence of chronic disease	Diabetes mellitus	0.031	0.067	0.213	0.645	1.032	0.904 - 1.177
	Hypertension	-0.083	0.046	3.285	0.070	0.921	0.842 - 1.007
	Dyslipidemia	0.037	0.053	0.495	0.482	1.038	0.935 - 1.152
	Cancer	-0.138	0.104	1.746	0.186	0.871	0.710 - 1.069
	Chronic lung disease	0.031	0.061	0.250	0.617	1.031	0.915 - 1.162
	Cardiovascular disease	0.170	0.060	8.077	0.005	1.185	1.054 - 1.332

Model parameters: *Likelihood Ratio* = 294.35; *d.f.*=22; $p<0.0001$; *Score* = 292.26; *d.f.*=22; $p<0.0001$; *Wald* = 286.55; *d.f.*=22; $p<0.0001$.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Appendix C6 Cox Proportional Hazards Regression Model Comparing Therapy Discontinuation for Phosphate Binders with a 60-day Treatment Gap among Cohorts while Controlling for Covariates (N=7753)

Variable		Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits
Cohort [a]	1	0.605	0.042	203.673	<.0001	1.832	1.686 - 1.990
	2	0.290	0.040	52.918	<.0001	1.337	1.236 -1.446
	3	-0.357	0.053	44.457	<.0001	0.700	0.630 - 0.777
Age		-0.007	0.001	30.903	<.0001	0.993	0.991 - 0.996
Gender [b]	Female	0.062	0.028	5.045	0.025	1.064	1.008 - 1.123
Race [c]	White	-0.303	0.032	87.938	<.0001	0.738	0.693 - 0.787
	Other	-0.441	0.080	30.157	<.0001	0.643	0.549 - 0.753
Region of residence [d]	Northeast	-0.081	0.040	4.122	0.042	0.922	0.852 - 0.997
	South	0.071	0.038	3.544	0.060	1.074	0.997 - 1.157
	West	-0.011	0.053	0.042	0.837	0.989	0.892 - 1.097
ESRD duration		0.004	0.004	1.439	0.230	1.004	0.997 - 1.011
Primary disease causing ESRD [e]	Hypertension	-0.020	0.038	0.276	0.599	0.980	0.909 - 1.057
	Glomerulonephritis	-0.014	0.053	0.066	0.797	0.986	0.888 - 1.095
	Cystic Kidney	-0.010	0.088	0.013	0.908	0.990	0.833 - 1.176
	Other	0.013	0.048	0.073	0.788	1.013	0.922 - 1.114
Charlson Comorbidity Index (CCI) score		0.018	0.015	1.430	0.232	1.018	0.988 - 1.049
Presence of chronic disease	Diabetes mellitus	0.003	0.043	0.006	0.939	1.003	0.923 - 1.091
	Hypertension	-0.021	0.030	0.524	0.469	0.979	0.924 - 1.037
	Dyslipidemia	0.009	0.041	0.051	0.821	1.009	0.931 - 1.094
	Cancer	-0.024	0.065	0.131	0.718	0.977	0.859 - 1.110
	Chronic lung disease	0.042	0.039	1.114	0.291	1.042	0.965 - 1.126
	Cardiovascular disease	0.081	0.037	4.890	0.027	1.085	1.009 - 1.166

Model parameters: *Likelihood Ratio* = 663.76; *d.f.*=22; $p<0.0001$; *Score* = 663.62; *d.f.*=22; $p<0.0001$; *Wald* = 644.35; *d.f.*=22; $p< 0.0001$.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Appendix C7 Cox Proportional Hazards Regression Model Comparing Therapy Discontinuation for Cinacalcet with a 60-day Treatment Gap among Cohorts while Controlling for Covariates (N=2436)

Variable		Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits
Cohort [a]	1	0.835	0.091	84.677	<.0001	2.305	1.929 - 2.754
	2	0.603	0.069	76.266	<.0001	1.827	1.596 - 2.092
	3	-0.317	0.086	13.528	0.000	0.729	0.615 - 0.863
Age		-0.007	0.002	9.344	0.002	0.993	0.989 - 0.997
Gender [b]	Female	0.062	0.053	1.367	0.242	1.064	0.959 - 1.180
Race [c]	White	-0.182	0.059	9.503	0.002	0.834	0.743 - 0.936
	Other	0.042	0.156	0.072	0.789	1.043	0.767 - 1.417
Region of residence [d]	Northeast	-0.077	0.081	0.900	0.343	0.926	0.789 - 1.086
	South	0.110	0.078	2.018	0.155	1.117	0.959 - 1.300
	West	-0.122	0.109	1.254	0.263	0.885	0.714 - 1.096
ESRD duration		0.002	0.006	0.059	0.808	1.001	0.990 - 1.014
Primary disease causing ESRD [e]	Hypertension	0.095	0.075	1.589	0.208	1.100	0.949 - 1.275
	Glomerulonephritis	-0.204	0.100	4.158	0.041	0.815	0.670 - 0.992
	Cystic Kidney	0.191	0.140	1.881	0.170	1.211	0.921 - 1.592
	Other	-0.028	0.096	0.082	0.774	0.973	0.805 - 1.175
Charlson Comorbidity Index (CCI) score		-0.015	0.031	0.223	0.637	0.985	0.927 - 1.047
Presence of chronic disease	Diabetes mellitus	0.119	0.085	1.928	0.165	1.126	0.952 - 1.331
	Hypertension	-0.045	0.057	0.607	0.436	0.956	0.855 - 1.070
	Dyslipidemia	-0.021	0.084	0.062	0.803	0.979	0.830 - 1.155
	Cancer	-0.112	0.132	0.723	0.395	0.894	0.689 - 1.158
	Chronic lung disease	0.004	0.081	0.002	0.962	1.004	0.856 - 1.177
	Cardiovascular disease	0.098	0.070	1.964	0.161	1.103	0.961 - 1.266

Model parameters: *Likelihood Ratio* = 300.10; *d.f.*=22; $p<0.0001$; *Score* = 299.50; *d.f.*=22; $p<0.0001$; *Wald* = 285.20; *d.f.*=22; $p<0.0001$.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Appendix D1 Zero-Inflated Poission Regression Model Comparing Total Inpatient Visits during 2007 among Cohorts

Variable		Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Intercept		1.101	0.066	16.570	0.000	0.971	1.231
Cohort [a]	1	-0.042	0.025	-1.670	0.095	-0.091	0.007
	2	0.028	0.024	1.170	0.242	-0.019	0.076
	3	-0.037	0.032	-1.140	0.256	-0.100	0.026
Age		-0.006	0.001	-7.460	0.000	-0.007	-0.004
Gender [b]	Female	-0.021	0.017	-1.210	0.227	-0.054	0.013
Race [c]	White	-0.038	0.020	-1.890	0.058	-0.077	0.001
	Other	-0.138	0.052	-2.650	0.008	-0.241	-0.036
Region of residence [d]	Northeast	0.051	0.024	2.150	0.032	0.004	0.098
	South	-0.022	0.023	-0.980	0.327	-0.067	0.022
	West	0.003	0.033	0.080	0.937	-0.061	0.067
ESRD duration		-0.004	0.002	-1.650	0.099	-0.009	0.001
Primary disease causing ESRD [e]	Hypertension	0.031	0.024	1.320	0.185	-0.015	0.078
	Glomerulonephritis	0.045	0.034	1.310	0.190	-0.022	0.112
	Cystic Kidney	0.081	0.057	1.420	0.156	-0.031	0.193
	Other	0.015	0.030	0.490	0.626	-0.045	0.075
Charlson Comorbidity Index (CCI) score		0.090	0.008	11.220	0.000	0.074	0.105
Presence of chronic disease	Diabetes mellitus	-0.012	0.026	-0.480	0.630	-0.063	0.038
	Hypertension	-0.002	0.018	-0.130	0.898	-0.037	0.032
	Dyslipidemia	0.058	0.023	2.520	0.012	0.013	0.103
	Cancer	-0.196	0.037	-5.250	0.000	-0.269	-0.122
	Chronic lung disease	0.066	0.021	3.170	0.002	0.025	0.107
	Cardiovascular disease	-0.126	0.023	-5.410	0.000	-0.172	-0.080
Inflate							
Intercept		-0.225	0.197	-1.140	0.254	-0.610	0.161
Cohort [a]	1	-0.096	0.072	-1.330	0.182	-0.238	0.045
	2	-0.248	0.073	-3.390	0.001	-0.391	-0.105
	3	-0.133	0.099	-1.350	0.177	-0.327	0.060
Age		-0.006	0.002	-2.630	0.009	-0.010	-0.001
Gender [b]	Female	0.147	0.053	2.790	0.005	0.044	0.250
Race [c]	White	0.004	0.061	0.060	0.950	-0.115	0.123
	Other	-0.169	0.162	-1.040	0.297	-0.485	0.148
Region of	Northeast	-0.122	0.076	-1.600	0.110	-0.272	0.027

residence [d]	South	-0.021	0.071	-0.300	0.762	-0.160	0.117
	West	-0.021	0.098	-0.210	0.831	-0.213	0.171
ESRD duration		-0.009	0.007	-1.230	0.220	-0.022	0.005
Primary disease causing ESRD [e]	Hypertension	0.078	0.072	1.080	0.279	-0.063	0.220
	Glomerulonephritis	0.084	0.100	0.850	0.397	-0.111	0.279
	Cystic Kidney	0.280	0.154	1.820	0.068	-0.021	0.582
	Other	0.107	0.091	1.180	0.238	-0.071	0.286
Charlson Comorbidity Index (CCI) score		-0.131	0.031	-4.170	0.000	-0.192	-0.069
Presence of chronic disease	Diabetes mellitus	0.055	0.082	0.660	0.507	-0.107	0.216
	Hypertension	-0.116	0.057	-2.040	0.041	-0.226	-0.005
	Dyslipidemia	-0.035	0.079	-0.440	0.661	-0.190	0.121
	Cancer	0.005	0.133	0.040	0.970	-0.256	0.266
	Chronic lung disease	-0.215	0.078	-2.770	0.006	-0.367	-0.063
	Cardiovascular disease	0.411	0.071	5.780	0.000	0.272	0.551

Model parameters: *Inflation model=logit; Log Likelihood* = -20905.28; LR chi^2 725.45; p<0.0001.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Vuong test of zip vs. standard Poisson: z = 22.20 Pr>z = 0.0000

Appendix D2 Zero-Inflated Poission Regression Model Comparing Total Outpatient Visits during 2007 among Cohorts

Variable		Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Intercept		2.183	0.027	80.100	0.000	2.130	2.237
Cohort [a]	1	0.048	0.011	4.540	0.000	0.028	0.069
	2	0.147	0.010	14.200	0.000	0.127	0.168
	3	0.136	0.013	10.390	0.000	0.110	0.162
Age		-0.005	0.000	-15.080	0.000	-0.005	-0.004
Gender [b]	Female	-0.014	0.007	-2.060	0.039	-0.028	-0.001
Race [c]	White	0.121	0.009	14.090	0.000	0.104	0.138
	Other	-0.018	0.021	-0.840	0.399	-0.060	0.024
Region of residence [d]	Northeast	-0.127	0.009	-13.670	0.000	-0.145	-0.109
	South	-0.308	0.009	-34.030	0.000	-0.326	-0.290
	West	-0.177	0.012	-14.330	0.000	-0.202	-0.153
ESRD duration		-0.001	0.001	-1.430	0.153	-0.003	0.000
Primary disease causing ESRD [e]	Hypertension	-0.018	0.010	-1.820	0.069	-0.037	0.001
	Glomerulonephritis	0.047	0.013	3.460	0.001	0.020	0.073
	Cystic Kidney	0.112	0.021	5.240	0.000	0.070	0.153
	Other	0.117	0.012	9.950	0.000	0.094	0.140
Charlson Comorbidity Index (CCI) score		0.053	0.003	15.570	0.000	0.046	0.060
Presence of chronic disease	Diabetes mellitus	0.052	0.010	4.960	0.000	0.031	0.072
	Hypertension	0.201	0.007	28.130	0.000	0.187	0.215
	Dyslipidemia	0.111	0.009	11.820	0.000	0.092	0.129
	Cancer	0.129	0.015	8.900	0.000	0.101	0.158
	Chronic lung disease	-0.002	0.009	-0.270	0.786	-0.020	0.016
	Cardiovascular disease	-0.091	0.009	-9.910	0.000	-0.109	-0.073
Inflate							
Intercept		-1.769	0.272	-6.510	0.000	-2.301	-1.236
Cohort [a]	1	0.154	0.098	1.580	0.115	-0.037	0.346
	2	-0.181	0.104	-1.750	0.081	-0.385	0.022
	3	0.017	0.135	0.130	0.897	-0.248	0.283
Age		-0.006	0.003	-2.200	0.028	-0.012	-0.001
Gender [b]	Female	0.233	0.072	3.220	0.001	0.091	0.375
Race [c]	White	0.078	0.083	0.940	0.349	-0.085	0.241
	Other	0.259	0.184	1.410	0.159	-0.102	0.621
Region of	Northeast	0.607	0.111	5.450	0.000	0.388	0.825

residence [d]	South	0.426	0.108	3.950	0.000	0.214	0.637
	West	0.446	0.136	3.270	0.001	0.179	0.712
ESRD duration		-0.007	0.009	-0.800	0.424	-0.024	0.010
Primary disease causing ESRD [e]	Hypertension	-0.176	0.098	-1.800	0.072	-0.369	0.016
	Glomerulonephritis	-0.501	0.138	-3.630	0.000	-0.771	-0.231
	Cystic Kidney	-0.677	0.244	-2.770	0.006	-1.155	-0.198
	Other	-0.210	0.121	-1.730	0.083	-0.447	0.028
Charlson Comorbidity Index (CCI) score		-0.139	0.051	-2.740	0.006	-0.238	-0.040
Presence of chronic disease	Diabetes mellitus	-0.383	0.120	-3.180	0.001	-0.618	-0.147
	Hypertension	-0.560	0.086	-6.500	0.000	-0.729	-0.391
	Dyslipidemia	-0.432	0.136	-3.170	0.002	-0.699	-0.165
	Cancer	-0.478	0.222	-2.150	0.031	-0.914	-0.043
	Chronic lung disease	-0.244	0.123	-1.980	0.048	-0.486	-0.002
	Cardiovascular disease	0.157	0.102	1.540	0.124	-0.043	0.357

Model parameters: *Inflation model=logit; Log Likelihood* = -54619.76; LR chi^2 7073.80; p<0.0001.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Vuong test of zip vs. standard Poisson: z = 22.21 Pr>z = 0.0000

Appendix D3 Zero-Inflated Poission Regression Model Comparing Total Other Medical Service Utilization during 2007 among Cohorts

Variable		Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Intercept		0.575	0.084	6.810	0.000	0.410	0.741
Cohort [a]	1	0.096	0.029	3.300	0.001	0.039	0.154
	2	0.057	0.028	2.010	0.044	0.001	0.113
	3	-0.004	0.037	-0.110	0.913	-0.077	0.069
Age		0.004	0.001	4.670	0.000	0.003	0.006
Gender [b]	Female	-0.102	0.019	-5.380	0.000	-0.139	-0.065
Race [c]	White	0.060	0.023	2.650	0.008	0.015	0.104
	Other	-0.097	0.072	-1.350	0.177	-0.239	0.044
Region of residence [d]	Northeast	-0.039	0.028	-1.420	0.156	-0.093	0.015
	South	0.166	0.025	6.640	0.000	0.117	0.215
	West	-0.084	0.039	-2.150	0.031	-0.161	-0.008
ESRD duration		0.003	0.003	0.990	0.322	-0.003	0.008
Primary disease causing ESRD [e]	Hypertension	-0.066	0.026	-2.490	0.013	-0.117	-0.014
	Glomerulonephritis	-0.147	0.044	-3.350	0.001	-0.233	-0.061
	Cystic Kidney	0.011	0.064	0.160	0.870	-0.115	0.136
	Other	-0.074	0.036	-2.080	0.037	-0.144	-0.004
Charlson Comorbidity Index (CCI) score		0.059	0.009	6.620	0.000	0.041	0.076
Presence of chronic disease	Diabetes mellitus	0.022	0.030	0.710	0.476	-0.038	0.081
	Hypertension	0.136	0.020	6.940	0.000	0.097	0.174
	Dyslipidemia	0.011	0.025	0.440	0.658	-0.038	0.061
	Cancer	-0.198	0.043	-4.620	0.000	-0.281	-0.114
	Chronic lung disease	-0.011	0.024	-0.480	0.635	-0.058	0.036
	Cardiovascular disease	-0.096	0.027	-3.610	0.000	-0.148	-0.044
Inflate							
Intercept		3.074	0.181	16.970	0.000	2.718	3.429
Cohort [a]	1	-0.021	0.064	-0.330	0.741	-0.147	0.105
	2	-0.156	0.064	-2.450	0.014	-0.280	-0.031
	3	-0.046	0.083	-0.550	0.581	-0.208	0.117
Age		-0.029	0.002	-13.960	0.000	-0.033	-0.025
Gender [b]	Female	0.228	0.043	5.280	0.000	0.143	0.312
Race [c]	White	0.048	0.052	0.920	0.357	-0.054	0.150
	Other	0.474	0.140	3.390	0.001	0.200	0.748
Region of	Northeast	-0.168	0.062	-2.700	0.007	-0.290	-0.046

residence [d]	South	-0.257	0.058	-4.410	0.000	-0.371	-0.143
	West	-0.008	0.082	-0.100	0.920	-0.169	0.152
ESRD duration		-0.014	0.006	-2.350	0.019	-0.025	-0.002
Primary disease causing ESRD [e]	Hypertension	0.186	0.060	3.100	0.002	0.069	0.304
	Glomerulonephritis	0.196	0.088	2.230	0.026	0.023	0.369
	Cystic Kidney	0.064	0.138	0.460	0.644	-0.207	0.335
	Other	0.123	0.077	1.610	0.108	-0.027	0.274
Charlson Comorbidity Index (CCI) score		-0.215	0.023	-9.180	0.000	-0.261	-0.169
Presence of chronic disease	Diabetes mellitus	-0.035	0.067	-0.530	0.599	-0.166	0.096
	Hypertension	-0.281	0.045	-6.270	0.000	-0.369	-0.193
	Dyslipidemia	-0.078	0.062	-1.260	0.208	-0.199	0.043
	Cancer	0.455	0.102	4.480	0.000	0.256	0.654
	Chronic lung disease	0.140	0.060	2.340	0.019	0.023	0.256
	Cardiovascular disease	0.227	0.058	3.920	0.000	0.114	0.341

Model parameters: *Inflation model=logit; Log Likelihood* = -16515.78; LR chi^2 525.79; p<0.0001.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Vuong test of zip vs. standard Poisson: z = 31.24 Pr>z = 0.0000

Appendix D4 Zero-Inflated Poission Regression Model Comparing Cardiovascular-related Inpatient Visits during 2007 among Cohorts

Variable		Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Intercept		0.579	0.126	4.610	0.000	0.333	0.826
Cohort [a]	1	-0.030	0.046	-0.660	0.508	-0.119	0.059
	2	0.033	0.044	0.750	0.455	-0.053	0.118
	3	-0.067	0.058	-1.150	0.249	-0.182	0.047
Age		-0.005	0.001	-3.460	0.001	-0.008	-0.002
Gender [b]	Female	-0.042	0.031	-1.360	0.173	-0.103	0.019
Race [c]	White	-0.057	0.036	-1.590	0.112	-0.128	0.013
	Other	-0.183	0.098	-1.880	0.061	-0.375	0.008
Region of residence [d]	Northeast	0.054	0.043	1.250	0.210	-0.030	0.138
	South	-0.062	0.042	-1.500	0.134	-0.144	0.019
	West	-0.028	0.060	-0.470	0.638	-0.145	0.089
ESRD duration		-0.006	0.005	-1.170	0.243	-0.015	0.004
Primary disease causing ESRD [e]	Hypertension	0.053	0.042	1.260	0.209	-0.030	0.136
	Glomerulonephritis	0.090	0.062	1.440	0.150	-0.032	0.213
	Cystic Kidney	0.069	0.108	0.640	0.523	-0.143	0.281
	Other	-0.031	0.058	-0.540	0.591	-0.144	0.082
Charlson Comorbidity Index (CCI) score		0.088	0.014	6.170	0.000	0.060	0.115
Presence of chronic disease	Diabetes mellitus	-0.066	0.047	-1.410	0.160	-0.157	0.026
	Hypertension	-0.030	0.032	-0.940	0.347	-0.092	0.032
	Dyslipidemia	0.114	0.040	2.870	0.004	0.036	0.192
	Cancer	-0.146	0.065	-2.230	0.025	-0.274	-0.018
	Chronic lung disease	0.092	0.036	2.560	0.011	0.021	0.162
	Cardiovascular disease	-0.265	0.047	-5.620	0.000	-0.357	-0.173
Inflate							
Intercept		0.833	0.247	3.380	0.001	0.350	1.317
Cohort [a]	1	0.035	0.091	0.390	0.700	-0.143	0.213
	2	-0.127	0.090	-1.410	0.159	-0.305	0.050
	3	-0.094	0.124	-0.760	0.449	-0.338	0.149
Age		-0.013	0.003	-4.550	0.000	-0.018	-0.007
Gender [b]	Female	-0.051	0.065	-0.790	0.432	-0.179	0.076
Race [c]	White	-0.094	0.074	-1.260	0.208	-0.239	0.052
	Other	-0.164	0.203	-0.810	0.418	-0.562	0.234
Region of	Northeast	-0.173	0.091	-1.890	0.058	-0.352	0.006

residence [d]	South	-0.178	0.087	-2.050	0.040	-0.348	-0.008
	West	-0.141	0.123	-1.140	0.253	-0.383	0.101
ESRD duration		0.000	0.009	-0.030	0.976	-0.017	0.017
Primary disease causing ESRD [e]	Hypertension	0.123	0.089	1.380	0.168	-0.052	0.297
	Glomerulonephritis	0.378	0.120	3.170	0.002	0.144	0.613
	Cystic Kidney	0.430	0.196	2.190	0.028	0.046	0.814
	Other	0.262	0.115	2.280	0.022	0.037	0.486
Charlson Comorbidity Index (CCI) score		-0.095	0.034	-2.760	0.006	-0.162	-0.028
Presence of chronic disease	Diabetes mellitus	0.078	0.098	0.800	0.424	-0.114	0.271
	Hypertension	-0.044	0.068	-0.650	0.519	-0.178	0.090
	Dyslipidemia	0.076	0.089	0.850	0.394	-0.099	0.251
	Cancer	0.309	0.143	2.160	0.031	0.028	0.589
	Chronic lung disease	-0.294	0.087	-3.370	0.001	-0.464	-0.123
	Cardiovascular disease	0.670	0.089	7.500	0.000	0.495	0.846

Model parameters: *Inflation model=logit; Log Likelihood* = -13046.50; LR chi^2 300.23; $p<0.0001$.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Vuong test of zip vs. standard Poisson: z = 15.47 Pr>z = 0.0000

Appendix D5 Zero-Inflated Poission Regression Model Comparing Cardiovascular-related Outpatient Visits during 2007 among Cohorts

Variable		Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Intercept		0.377	0.118	3.200	0.001	0.146	0.608
Cohort [a]	1	0.043	0.044	0.990	0.322	-0.042	0.128
	2	0.091	0.042	2.180	0.029	0.009	0.173
	3	0.070	0.053	1.330	0.185	-0.034	0.174
Age		0.001	0.001	0.470	0.640	-0.002	0.003
Gender [b]	Female	0.101	0.028	3.590	0.000	0.046	0.157
Race [c]	White	0.015	0.035	0.410	0.681	-0.055	0.084
	Other	-0.086	0.092	-0.930	0.354	-0.267	0.096
Region of residence [d]	Northeast	-0.012	0.036	-0.350	0.726	-0.082	0.057
	South	-0.234	0.036	-6.500	0.000	-0.304	-0.163
	West	-0.012	0.051	-0.240	0.811	-0.112	0.088
ESRD duration		-0.010	0.004	-2.190	0.029	-0.019	-0.001
Primary disease causing ESRD [e]	Hypertension	-0.004	0.038	-0.090	0.926	-0.078	0.071
	Glomerulonephritis	-0.117	0.061	-1.930	0.054	-0.236	0.002
	Cystic Kidney	-0.167	0.102	-1.630	0.103	-0.367	0.033
	Other	-0.161	0.053	-3.040	0.002	-0.265	-0.057
Charlson Comorbidity Index (CCI) score		0.042	0.013	3.220	0.001	0.016	0.067
Presence of chronic disease	Diabetes mellitus	0.026	0.042	0.620	0.535	-0.056	0.109
	Hypertension	0.154	0.028	5.450	0.000	0.098	0.209
	Dyslipidemia	0.010	0.036	0.280	0.777	-0.060	0.080
	Cancer	-0.140	0.058	-2.420	0.016	-0.254	-0.026
	Chronic lung disease	0.155	0.034	4.600	0.000	0.089	0.220
	Cardiovascular disease	-0.343	0.044	-7.830	0.000	-0.429	-0.257
Inflate							
Intercept		0.549	0.214	2.570	0.010	0.131	0.968
Cohort [a]	1	0.168	0.080	2.100	0.036	0.011	0.324
	2	-0.051	0.079	-0.650	0.519	-0.206	0.104
	3	0.089	0.101	0.880	0.377	-0.109	0.288
Age		-0.005	0.002	-2.240	0.025	-0.010	-0.001
Gender [b]	Female	-0.090	0.053	-1.680	0.093	-0.195	0.015
Race [c]	White	-0.158	0.065	-2.440	0.015	-0.285	-0.031
	Other	0.021	0.159	0.130	0.894	-0.291	0.333
Region of	Northeast	0.247	0.072	3.450	0.001	0.107	0.387

residence [d]	South	0.029	0.071	0.410	0.683	-0.111	0.169
	West	0.424	0.094	4.530	0.000	0.240	0.607
ESRD duration		0.002	0.008	0.300	0.762	-0.013	0.017
Primary disease causing ESRD [e]	Hypertension	0.078	0.072	1.080	0.282	-0.064	0.220
	Glomerulonephritis	0.151	0.108	1.400	0.161	-0.060	0.362
	Cystic Kidney	-0.163	0.189	-0.860	0.388	-0.533	0.207
	Other	0.124	0.097	1.280	0.200	-0.066	0.313
Charlson Comorbidity Index (CCI) score		-0.136	0.029	-4.740	0.000	-0.193	-0.080
Presence of chronic disease	Diabetes mellitus	0.099	0.082	1.210	0.226	-0.061	0.259
	Hypertension	-0.057	0.055	-1.040	0.300	-0.164	0.051
	Dyslipidemia	-0.085	0.074	-1.140	0.255	-0.231	0.061
	Cancer	0.182	0.121	1.510	0.132	-0.055	0.418
	Chronic lung disease	0.064	0.070	0.910	0.364	-0.074	0.202
	Cardiovascular disease	0.545	0.075	7.290	0.000	0.399	0.692

Model parameters: *Inflation model=logit; Log Likelihood* = -14192.85; LR chi^2 514.57; $p<0.0001$.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Vuong test of zip vs. standard Poisson: z = 12.65 Pr>z = 0.0000

Appendix D6 Zero-Inflated Poission Regression Model Comparing Cardiovascular-related Other Medical Care Utilization during 2007 among Cohorts

Variable		Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Intercept		-0.280	0.211	-1.330	0.185	-0.693	0.133
Cohort [a]	1	0.078	0.069	1.130	0.259	-0.058	0.214
	2	0.130	0.066	1.950	0.051	0.000	0.260
	3	-0.060	0.091	-0.660	0.511	-0.239	0.119
Age		0.011	0.002	4.730	0.000	0.007	0.016
Gender [b]	Female	-0.183	0.044	-4.180	0.000	-0.269	-0.097
Race [c]	White	-0.039	0.052	-0.750	0.455	-0.141	0.063
	Other	-0.645	0.266	-2.420	0.015	-1.167	-0.123
Region of residence [d]	Northeast	-0.175	0.060	-2.920	0.003	-0.292	-0.058
	South	0.043	0.053	0.800	0.425	-0.062	0.147
	West	-0.341	0.099	-3.460	0.001	-0.534	-0.148
ESRD duration		0.010	0.007	1.340	0.180	-0.004	0.024
Primary disease causing ESRD [e]	Hypertension	0.036	0.059	0.600	0.546	-0.080	0.152
	Glomerulonephritis	-0.054	0.100	-0.540	0.590	-0.251	0.142
	Cystic Kidney	-0.006	0.147	-0.040	0.966	-0.294	0.281
	Other	-0.055	0.088	-0.620	0.532	-0.229	0.118
Charlson Comorbidity Index (CCI) score		0.083	0.020	4.050	0.000	0.043	0.123
Presence of chronic disease	Diabetes mellitus	-0.085	0.073	-1.170	0.244	-0.227	0.058
	Hypertension	-0.003	0.044	-0.080	0.938	-0.090	0.083
	Dyslipidemia	0.094	0.056	1.690	0.091	-0.015	0.203
	Cancer	-0.391	0.101	-3.880	0.000	-0.589	-0.193
	Chronic lung disease	-0.101	0.053	-1.910	0.056	-0.205	0.002
	Cardiovascular disease	-0.137	0.069	-1.970	0.048	-0.273	-0.001
Inflate							
Intercept		3.708	0.286	12.990	0.000	3.149	4.268
Cohort [a]	1	0.044	0.098	0.450	0.651	-0.148	0.237
	2	-0.028	0.095	-0.290	0.769	-0.214	0.158
	3	0.111	0.127	0.880	0.381	-0.137	0.360
Age		-0.027	0.003	-8.190	0.000	-0.033	-0.020
Gender [b]	Female	0.082	0.064	1.290	0.196	-0.042	0.207

Race [c]	White	-0.011	0.077	-0.140	0.888	-0.161	0.140
	Other	0.255	0.306	0.830	0.405	-0.345	0.855
Region of residence [d]	Northeast	-0.108	0.089	-1.220	0.224	-0.281	0.066
	South	-0.096	0.082	-1.160	0.246	-0.257	0.066
	West	-0.063	0.131	-0.480	0.630	-0.320	0.194
ESRD duration		0.005	0.010	0.490	0.623	-0.014	0.023
Primary disease causing ESRD [e]	Hypertension	0.166	0.088	1.890	0.059	-0.006	0.338
	Glomerulonephritis	0.204	0.138	1.480	0.139	-0.066	0.474
	Cystic Kidney	0.040	0.213	0.190	0.852	-0.378	0.458
	Other	0.338	0.122	2.760	0.006	0.098	0.577
Charlson Comorbidity Index (CCI) score		-0.170	0.031	-5.510	0.000	-0.230	-0.109
Presence of chronic disease	Diabetes mellitus	0.007	0.099	0.070	0.946	-0.188	0.202
	Hypertension	-0.227	0.065	-3.490	0.000	-0.355	-0.100
	Dyslipidemia	-0.002	0.085	-0.030	0.978	-0.170	0.165
	Cancer	0.327	0.149	2.200	0.028	0.035	0.619
	Chronic lung disease	-0.036	0.081	-0.450	0.652	-0.195	0.122
	Cardiovascular disease	0.686	0.091	7.520	0.000	0.508	0.865

Model parameters: *Inflation model=logit; Log Likelihood* = -6675.37; LR chi^2 145.78; p<0.0001.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Vuong test of zip vs. standard Poisson: z = 17.47 Pr>z = 0.0000

Appendix E1 A Two-part Model Comparing All-cause Inpatient Costs during 2007 among Cohorts

Variable		Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
probit							
Intercept		-0.137	0.088	-1.560	0.118	-0.309	0.035
Cohort [a]	1	0.029	0.035	0.830	0.405	-0.039	0.098
	2	0.135	0.034	3.980	0.000	0.068	0.201
	3	0.050	0.045	1.120	0.261	-0.037	0.138
Age		0.001	0.001	0.640	0.523	-0.001	0.003
Gender [b]	Female	-0.081	0.025	-3.270	0.001	-0.130	-0.033
Race [c]	White	-0.023	0.029	-0.790	0.431	-0.079	0.034
	Other	0.014	0.073	0.190	0.852	-0.129	0.156
Region of residence [d]	Northeast	0.077	0.035	2.170	0.030	0.008	0.146
	South	0.002	0.032	0.070	0.945	-0.061	0.065
	West	0.003	0.046	0.070	0.948	-0.087	0.093
ESRD duration		0.002	0.003	0.770	0.443	-0.004	0.008
Primary disease causing ESRD [e]	Hypertension	-0.030	0.033	-0.900	0.368	-0.096	0.035
	Glomerulonephritis	-0.020	0.049	-0.420	0.678	-0.116	0.075
	Cystic Kidney	-0.097	0.080	-1.220	0.222	-0.253	0.059
	Other	-0.052	0.043	-1.210	0.224	-0.137	0.032
Charlson Comorbidity Index (CCI) score		0.099	0.015	6.610	0.000	0.070	0.128
Presence of chronic disease	Diabetes mellitus	-0.027	0.038	-0.710	0.476	-0.102	0.048
	Hypertension	0.055	0.027	2.010	0.045	0.001	0.109
	Dyslipidemia	0.040	0.038	1.060	0.289	-0.034	0.114
	Cancer	-0.081	0.060	-1.360	0.174	-0.199	0.036
	Chronic lung disease	0.135	0.036	3.760	0.000	0.065	0.206
	Cardiovascular disease	0.263	0.034	7.670	0.000	0.196	0.330
glm							
Intercept		10.497	0.091	115.730	0.000	10.319	10.674
Cohort [a]	1	0.004	0.036	0.110	0.910	-0.066	0.074
	2	0.041	0.034	1.200	0.231	-0.026	0.109
	3	-0.007	0.044	-0.150	0.878	-0.092	0.079
Age		-0.008	0.001	-7.270	0.000	-0.010	-0.006
Gender [b]	Female	0.058	0.024	2.410	0.016	0.011	0.106
Race [c]	White	-0.085	0.029	-2.880	0.004	-0.143	-0.027
	Other	-0.166	0.070	-2.360	0.019	-0.304	-0.028
Region of residence [d]	Northeast	0.153	0.034	4.550	0.000	0.087	0.219
	South	0.007	0.032	0.230	0.820	-0.055	0.070

	West	0.160	0.043	3.690	0.000	0.075	0.246
ESRD duration		-0.002	0.003	-0.510	0.613	-0.008	0.005
Primary disease causing ESRD [e]	Hypertension	-0.028	0.034	-0.840	0.399	-0.094	0.038
	Glomerulonephritis	0.016	0.050	0.310	0.756	-0.083	0.115
	Cystic Kidney	0.102	0.078	1.310	0.191	-0.051	0.256
	Other	-0.002	0.043	-0.040	0.972	-0.085	0.082
Charlson Comorbidity Index (CCI) score		0.066	0.012	5.400	0.000	0.042	0.090
Presence of chronic disease	Diabetes mellitus	-0.003	0.037	-0.080	0.937	-0.075	0.069
	Hypertension	-0.027	0.026	-1.030	0.301	-0.078	0.024
	Dyslipidemia	0.063	0.035	1.770	0.076	-0.007	0.132
	Cancer	-0.163	0.057	-2.840	0.004	-0.275	-0.051
	Chronic lung disease	0.015	0.032	0.450	0.649	-0.049	0.078
	Cardiovascular disease	0.077	0.034	2.280	0.022	0.011	0.142

Model parameters: *Wald* chi^2 =741.58 ; df= 22; p<0.0001.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Appendix E2 A Two-part Model Comparing All-cause Outpatient Costs during 2007 among Cohorts

Variable		Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
probit							
Intercept		0.926	0.130	7.110	0.000	0.671	1.181
Cohort [a]	1	-0.068	0.048	-1.420	0.155	-0.163	0.026
	2	0.102	0.050	2.060	0.039	0.005	0.200
	3	0.007	0.068	0.110	0.913	-0.127	0.142
Age		0.003	0.002	2.060	0.039	0.000	0.006
Gender [b]	Female	-0.106	0.035	-3.000	0.003	-0.175	-0.037
Race [c]	White	-0.023	0.043	-0.530	0.597	-0.108	0.062
	Other	-0.095	0.096	-0.990	0.321	-0.284	0.093
Region of residence [d]	Northeast	-0.302	0.053	-5.710	0.000	-0.406	-0.198
	South	-0.212	0.051	-4.180	0.000	-0.311	-0.113
	West	-0.229	0.066	-3.490	0.000	-0.358	-0.101
ESRD duration		0.005	0.004	1.120	0.265	-0.004	0.013
Primary disease causing ESRD [e]	Hypertension	0.093	0.051	1.840	0.065	-0.006	0.192
	Glomerulonephritis	0.238	0.067	3.560	0.000	0.107	0.369
	Cystic Kidney	0.351	0.126	2.790	0.005	0.104	0.597
	Other	0.118	0.061	1.940	0.053	-0.001	0.237
Charlson Comorbidity Index (CCI) score		0.057	0.025	2.250	0.025	0.007	0.107
Presence of chronic disease	Diabetes mellitus	0.212	0.060	3.540	0.000	0.095	0.330
	Hypertension	0.274	0.042	6.560	0.000	0.192	0.355
	Dyslipidemia	0.198	0.063	3.150	0.002	0.075	0.322
	Cancer	0.217	0.099	2.190	0.029	0.023	0.411
	Chronic lung disease	0.123	0.058	2.100	0.035	0.008	0.237
	Cardiovascular disease	0.101	0.050	2.030	0.042	0.004	0.199
glm							
Intercept		8.422	0.098	86.170	0.000	8.230	8.613
Cohort [a]	1	0.008	0.039	0.210	0.834	-0.069	0.085
	2	0.117	0.039	3.030	0.002	0.041	0.193
	3	0.139	0.049	2.800	0.005	0.042	0.235
Age		-0.003	0.001	-2.750	0.006	-0.005	-0.001
Gender [b]	Female	0.012	0.025	0.480	0.632	-0.037	0.061
Race [c]	White	-0.101	0.032	-3.120	0.002	-0.164	-0.037
	Other	-0.118	0.071	-1.670	0.096	-0.256	0.021
Region of	Northeast	-0.073	0.037	-1.970	0.048	-0.145	-0.001

residence [d]	South	-0.136	0.032	-4.220	0.000	-0.200	-0.073
	West	-0.164	0.046	-3.610	0.000	-0.254	-0.075
ESRD duration		-0.003	0.003	-1.000	0.319	-0.010	0.003
Primary disease causing ESRD [e]	Hypertension	-0.110	0.035	-3.170	0.001	-0.177	-0.042
	Glomerulonephritis	-0.027	0.051	-0.530	0.593	-0.127	0.073
	Cystic Kidney	-0.024	0.082	-0.290	0.773	-0.184	0.137
	Other	0.047	0.045	1.050	0.295	-0.041	0.135
Charlson Comorbidity Index (CCI) score		0.047	0.014	3.290	0.001	0.019	0.075
Presence of chronic disease	Diabetes mellitus	0.041	0.040	1.010	0.312	-0.038	0.120
	Hypertension	0.097	0.027	3.640	0.000	0.045	0.149
	Dyslipidemia	0.061	0.036	1.690	0.092	-0.010	0.133
	Cancer	0.050	0.058	0.870	0.385	-0.063	0.163
	Chronic lung disease	-0.032	0.036	-0.890	0.373	-0.103	0.039
	Cardiovascular disease	0.051	0.036	1.400	0.161	-0.020	0.122

Model parameters: *Wald* chi^2 =354.08 ; df= 22; p<0.0001.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Appendix E3 A Two-part Model Comparing All-cause Physician/Supplier Costs during 2007 among Cohorts

Variable		Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
probit							
Intercept		1.542	0.115	13.430	0.000	1.317	1.767
Cohort [a]	1	0.016	0.045	0.360	0.719	-0.072	0.105
	2	-0.001	0.045	-0.010	0.991	-0.089	0.087
	3	0.012	0.059	0.200	0.843	-0.105	0.128
Age		-0.003	0.001	-2.420	0.016	-0.006	-0.001
Gender [b]	Female	-0.026	0.031	-0.850	0.397	-0.087	0.034
Race [c]	White	0.036	0.038	0.960	0.338	-0.038	0.110
	Other	0.012	0.091	0.140	0.892	-0.165	0.190
Region of residence [d]	Northeast	-0.010	0.046	-0.210	0.837	-0.100	0.081
	South	-0.105	0.044	-2.370	0.018	-0.191	-0.018
	West	-0.127	0.058	-2.190	0.029	-0.241	-0.013
ESRD duration		-0.007	0.004	-1.770	0.077	-0.014	0.001
Primary disease causing ESRD [e]	Hypertension	0.032	0.046	0.680	0.497	-0.060	0.123
	Glomerulonephritis	-0.010	0.063	-0.170	0.868	-0.133	0.112
	Cystic Kidney	0.051	0.103	0.500	0.618	-0.150	0.253
	Other	-0.027	0.053	-0.510	0.611	-0.131	0.077
Charlson Comorbidity Index (CCI) score		0.059	0.019	3.160	0.002	0.022	0.095
Presence of chronic disease	Diabetes mellitus	-0.134	0.051	-2.630	0.008	-0.234	-0.034
	Hypertension	-0.034	0.032	-1.050	0.296	-0.098	0.030
	Dyslipidemia	0.050	0.045	1.110	0.267	-0.039	0.139
	Cancer	-0.075	0.077	-0.980	0.326	-0.225	0.075
	Chronic lung disease	-0.040	0.046	-0.870	0.384	-0.131	0.050
	Cardiovascular disease	-0.123	0.041	-3.000	0.003	-0.204	-0.043
glm							
Intercept		8.786	0.133	66.120	0.000	8.526	9.046
Cohort [a]	1	-0.015	0.054	-0.270	0.786	-0.120	0.090
	2	-0.035	0.055	-0.640	0.521	-0.144	0.073
	3	0.044	0.076	0.570	0.567	-0.106	0.193
Age		-0.007	0.002	-4.070	0.000	-0.010	-0.003
Gender [b]	Female	-0.096	0.040	-2.420	0.015	-0.174	-0.018
Race [c]	White	-0.094	0.046	-2.030	0.043	-0.184	-0.003
	Other	-0.076	0.099	-0.770	0.440	-0.271	0.118
Region of	Northeast	0.127	0.056	2.250	0.024	0.017	0.238

residence [d]	South	0.090	0.051	1.770	0.076	-0.010	0.189
	West	0.013	0.063	0.200	0.842	-0.111	0.136
ESRD duration		0.002	0.005	0.400	0.692	-0.007	0.011
Primary disease causing ESRD [e]	Hypertension	-0.028	0.056	-0.490	0.622	-0.138	0.083
	Glomerulonephritis	0.022	0.066	0.330	0.740	-0.108	0.152
	Cystic Kidney	-0.043	0.082	-0.520	0.604	-0.204	0.119
	Other	0.142	0.066	2.140	0.032	0.012	0.272
Charlson Comorbidity Index (CCI) score		-0.062	0.027	-2.300	0.022	-0.114	-0.009
Presence of chronic disease	Diabetes mellitus	0.089	0.061	1.460	0.145	-0.031	0.208
	Hypertension	0.109	0.045	2.400	0.016	0.020	0.197
	Dyslipidemia	-0.067	0.064	-1.060	0.291	-0.193	0.058
	Cancer	0.250	0.099	2.520	0.012	0.056	0.444
	Chronic lung disease	-0.058	0.058	-0.990	0.321	-0.173	0.057
	Cardiovascular disease	-0.375	0.053	-7.120	0.000	-0.478	-0.271

Model parameters: *Wald* chi^2 =41.15 ; df= 22; p<0.0001.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Appendix E4 A Generalized Linear Model Comparing Dialysis Costs during 2007 among Cohorts

Variable		Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Intercept		10.333	0.019	535.890	0.000	10.295	10.371
Cohort [a]	1	-0.014	0.007	-1.920	0.055	-0.029	0.000
	2	0.023	0.007	3.260	0.001	0.009	0.037
	3	0.062	0.009	6.600	0.000	0.044	0.081
Age		-0.002	0.000	-9.720	0.000	-0.003	-0.002
Gender [b]	Female	0.059	0.005	11.670	0.000	0.049	0.069
Race [c]	White	-0.066	0.006	-11.180	0.000	-0.077	-0.054
	Other	-0.092	0.016	-5.920	0.000	-0.123	-0.062
Region of residence [d]	Northeast	0.027	0.007	3.820	0.000	0.013	0.041
	South	-0.023	0.007	-3.520	0.000	-0.036	-0.010
	West	0.012	0.009	1.270	0.206	-0.006	0.030
ESRD duration		0.000	0.001	0.450	0.655	-0.001	0.002
Primary disease causing ESRD [e]	Hypertension	0.002	0.007	0.290	0.769	-0.011	0.015
	Glomerulonephritis	0.028	0.010	2.840	0.004	0.009	0.047
	Cystic Kidney	-0.030	0.016	-1.910	0.057	-0.061	0.001
	Other	0.017	0.009	1.800	0.072	-0.001	0.035
Charlson Comorbidity Index (CCI) score		0.009	0.003	2.960	0.003	0.003	0.014
Presence of chronic disease	Diabetes mellitus	0.013	0.008	1.640	0.101	-0.002	0.028
	Hypertension	-0.001	0.005	-0.150	0.880	-0.011	0.010
	Dyslipidemia	0.002	0.007	0.300	0.762	-0.012	0.016
	Cancer	0.024	0.012	1.920	0.055	0.000	0.048
	Chronic lung disease	0.007	0.007	0.950	0.341	-0.007	0.021
	Cardiovascular disease	0.010	0.007	1.440	0.149	-0.004	0.023

Appendix E5 A Generalized Linear Model Comparing All-cause Other Costs during 2007 among Cohorts

Variable		Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
probit							
Intercept		-1.955	0.103	-18.970	0.000	-2.157	-1.753
Cohort [a]	1	0.029	0.039	0.760	0.448	-0.046	0.105
	2	0.103	0.038	2.720	0.007	0.029	0.177
	3	0.020	0.048	0.420	0.673	-0.073	0.114
Age		0.018	0.001	15.510	0.000	0.015	0.020
Gender [b]	Female	-0.149	0.025	-5.980	0.000	-0.198	-0.100
Race [c]	White	-0.019	0.029	-0.670	0.505	-0.077	0.038
	Other	-0.306	0.081	-3.780	0.000	-0.465	-0.148
Region of residence [d]	Northeast	0.092	0.037	2.470	0.013	0.019	0.165
	South	0.178	0.034	5.180	0.000	0.110	0.245
	West	-0.008	0.047	-0.160	0.869	-0.100	0.084
ESRD duration		0.008	0.003	2.550	0.011	0.002	0.015
Primary disease causing ESRD [e]	Hypertension	-0.122	0.034	-3.600	0.000	-0.188	-0.055
	Glomerulonephritis	-0.141	0.049	-2.890	0.004	-0.237	-0.045
	Cystic Kidney	-0.045	0.081	-0.560	0.575	-0.203	0.113
	Other	-0.082	0.043	-1.910	0.056	-0.167	0.002
Charlson Comorbidity Index (CCI) score		0.135	0.014	9.610	0.000	0.107	0.162
Presence of chronic disease	Diabetes mellitus	0.028	0.039	0.730	0.464	-0.047	0.104
	Hypertension	0.184	0.026	7.050	0.000	0.133	0.235
	Dyslipidemia	0.048	0.037	1.320	0.188	-0.024	0.121
	Cancer	-0.297	0.062	-4.780	0.000	-0.418	-0.175
	Chronic lung disease	-0.084	0.035	-2.410	0.016	-0.152	-0.016
	Cardiovascular disease	-0.152	0.035	-4.400	0.000	-0.220	-0.084
glm							
Intercept		8.374	0.146	57.400	0.000	8.088	8.660
Cohort [a]	1	0.177	0.052	3.420	0.001	0.076	0.279
	2	0.085	0.051	1.660	0.096	-0.015	0.185
	3	0.012	0.066	0.190	0.849	-0.116	0.141
Age		0.010	0.002	5.550	0.000	0.006	0.013
Gender [b]	Female	-0.116	0.032	-3.590	0.000	-0.179	-0.053
Race [c]	White	0.085	0.038	2.230	0.026	0.010	0.159
	Other	-0.002	0.116	-0.020	0.987	-0.230	0.226

Region of residence [d]	Northeast	0.033	0.046	0.730	0.468	-0.057	0.123
	South	-0.005	0.039	-0.130	0.896	-0.082	0.072
	West	-0.022	0.062	-0.350	0.726	-0.143	0.100
ESRD duration		0.006	0.005	1.270	0.204	-0.003	0.016
Primary disease causing ESRD [e]	Hypertension	-0.116	0.044	-2.640	0.008	-0.202	-0.030
	Glomerulonephritis	-0.176	0.075	-2.340	0.019	-0.323	-0.029
	Cystic Kidney	-0.098	0.100	-0.980	0.328	-0.294	0.098
	Other	-0.095	0.059	-1.610	0.108	-0.212	0.021
Charlson Comorbidity Index (CCI) score		0.041	0.016	2.610	0.009	0.010	0.071
Presence of chronic disease	Diabetes mellitus	0.011	0.050	0.220	0.823	-0.087	0.110
	Hypertension	0.104	0.033	3.180	0.001	0.040	0.168
	Dyslipidemia	0.020	0.044	0.460	0.647	-0.067	0.107
	Cancer	-0.163	0.071	-2.310	0.021	-0.301	-0.024
	Chronic lung disease	-0.014	0.042	-0.350	0.728	-0.096	0.067
	Cardiovascular disease	-0.056	0.046	-1.230	0.220	-0.146	0.034

Model parameters: *Wald chi*^{2} *= 1125.77* ; df =22 ; p<0.0001.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Appendix E6 A Generalized Linear Model Comparing All-cause Medical Service Costs during 2007 among Cohorts

Variable		Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Intercept		10.872	0.037	295.270	0.000	10.800	10.945
Cohort [a]	1	0.008	0.016	0.500	0.615	-0.024	0.040
	2	0.062	0.016	4.000	0.000	0.032	0.093
	3	0.051	0.021	2.470	0.013	0.011	0.091
Age		-0.002	0.000	-5.410	0.000	-0.003	-0.002
Gender [b]	Female	0.009	0.011	0.870	0.385	-0.011	0.030
Race [c]	White	-0.070	0.013	-5.520	0.000	-0.095	-0.045
	Other	-0.130	0.029	-4.520	0.000	-0.187	-0.074
Region of residence [d]	Northeast	0.080	0.016	5.000	0.000	0.049	0.112
	South	-0.011	0.013	-0.800	0.422	-0.037	0.015
	West	0.036	0.020	1.800	0.071	-0.003	0.075
ESRD duration		0.001	0.001	0.690	0.489	-0.002	0.004
Primary disease causing ESRD [e]	Hypertension	-0.029	0.015	-1.980	0.048	-0.058	0.000
	Glomerulonephritis	0.005	0.021	0.250	0.805	-0.036	0.046
	Cystic Kidney	-0.008	0.035	-0.230	0.814	-0.078	0.061
	Other	0.005	0.019	0.280	0.782	-0.032	0.043
Charlson Comorbidity Index (CCI) score		0.057	0.006	9.440	0.000	0.045	0.069
Presence of chronic disease	Diabetes mellitus	0.006	0.016	0.400	0.688	-0.025	0.038
	Hypertension	0.035	0.011	3.210	0.001	0.014	0.056
	Dyslipidemia	0.036	0.016	2.300	0.021	0.005	0.067
	Cancer	-0.068	0.026	-2.650	0.008	-0.119	-0.018
	Chronic lung disease	0.018	0.015	1.160	0.246	-0.012	0.047
	Cardiovascular disease	0.069	0.015	4.690	0.000	0.040	0.098

Model parameters: *Log likelihood= -139468; AIC = 23.78* ; BIC = -106811.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Appendix E7 A Generalized Linear Model Comparing All-cause Pharmacy Costs during 2007 among Cohorts

Variable		Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Intercept		8.777	0.050	174.330	0.000	8.678	8.876
Cohort [a]	1	-1.053	0.024	-44.040	0.000	-1.100	-1.006
	2	-0.163	0.022	-7.520	0.000	-0.206	-0.121
	3	0.687	0.025	27.720	0.000	0.639	0.736
Age		-0.005	0.001	-7.350	0.000	-0.006	-0.003
Gender [b]	Female	-0.070	0.014	-5.160	0.000	-0.096	-0.043
Race [c]	White	0.083	0.017	4.910	0.000	0.050	0.116
	Other	0.211	0.050	4.200	0.000	0.112	0.309
Region of residence [d]	Northeast	0.144	0.018	7.970	0.000	0.109	0.180
	South	0.013	0.016	0.820	0.414	-0.019	0.046
	West	0.088	0.025	3.590	0.000	0.040	0.137
ESRD duration		0.002	0.002	1.040	0.300	-0.002	0.006
Primary disease causing ESRD [e]	Hypertension	-0.057	0.018	-3.160	0.002	-0.092	-0.022
	Glomerulonephritis	-0.005	0.026	-0.190	0.849	-0.055	0.045
	Cystic Kidney	-0.030	0.040	-0.760	0.446	-0.108	0.048
	Other	0.028	0.026	1.060	0.287	-0.024	0.080
Charlson Comorbidity Index (CCI) score		-0.002	0.008	-0.210	0.837	-0.018	0.014
Presence of chronic disease	Diabetes mellitus	0.010	0.021	0.490	0.623	-0.031	0.052
	Hypertension	-0.003	0.014	-0.170	0.861	-0.031	0.026
	Dyslipidemia	0.030	0.019	1.620	0.106	-0.006	0.067
	Cancer	0.186	0.038	4.900	0.000	0.112	0.261
	Chronic lung disease	0.025	0.019	1.320	0.186	-0.012	0.062
	Cardiovascular disease	0.020	0.020	0.980	0.328	-0.020	0.059

Model parameters: *Log likelihood= -18.49; AIC = 23.78* ; BIC = -104177.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Appendix E8 A Generalized Linear Model Comparing All-cause Health Care Costs during 2007 among Cohorts

Variable		Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
Intercept		10.992	0.036	308.370	0.000	10.923	11.062
Cohort [a]	1	-0.053	0.015	-3.600	0.000	-0.082	-0.024
	2	0.045	0.014	3.170	0.002	0.017	0.073
	3	0.132	0.018	7.500	0.000	0.098	0.167
Age		-0.003	0.000	-6.050	0.000	-0.004	-0.002
Gender [b]	Female	0.004	0.010	0.390	0.693	-0.016	0.023
Race [c]	White	-0.061	0.012	-5.150	0.000	-0.084	-0.038
	Other	-0.109	0.027	-3.980	0.000	-0.162	-0.055
Region of residence [d]	Northeast	0.081	0.015	5.460	0.000	0.052	0.110
	South	-0.009	0.013	-0.740	0.458	-0.034	0.016
	West	0.038	0.018	2.120	0.034	0.003	0.074
ESRD duration		0.001	0.001	0.850	0.396	-0.001	0.004
Primary disease causing ESRD [e]	Hypertension	-0.031	0.013	-2.400	0.016	-0.057	-0.006
	Glomerulonephritis	0.007	0.019	0.360	0.718	-0.031	0.045
	Cystic Kidney	-0.008	0.032	-0.240	0.807	-0.070	0.054
	Other	0.011	0.018	0.640	0.524	-0.023	0.046
Charlson Comorbidity Index (CCI) score		0.053	0.006	9.560	0.000	0.042	0.064
Presence of chronic disease	Diabetes mellitus	0.005	0.016	0.310	0.753	-0.026	0.036
	Hypertension	0.033	0.010	3.140	0.002	0.012	0.053
	Dyslipidemia	0.037	0.015	2.430	0.015	0.007	0.066
	Cancer	-0.042	0.023	-1.820	0.068	-0.087	0.003
	Chronic lung disease	0.018	0.014	1.300	0.195	-0.009	0.045
	Cardiovascular disease	0.064	0.013	4.740	0.000	0.037	0.090

Model parameters: *Log likelihood= -140398; AIC = 23.94* ; BIC = -107150.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Appendix E9 A Two-part Model Comparing Cardiovascular-related Inpatient Costs during 2007 among Cohorts

Variable		Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
probit							
Intercept		-1.015	0.091	-11.200	0.000	-1.192	-0.837
Cohort [a]	1	-0.028	0.037	-0.770	0.442	-0.100	0.044
	2	0.072	0.037	1.950	0.051	0.000	0.144
	3	0.011	0.048	0.240	0.812	-0.083	0.106
Age		0.004	0.001	3.400	0.001	0.001	0.006
Gender [b]	Female	-0.004	0.025	-0.150	0.883	-0.052	0.045
Race [c]	White	0.015	0.031	0.470	0.636	-0.046	0.075
	Other	-0.019	0.075	-0.260	0.794	-0.166	0.127
Region of residence [d]	Northeast	0.101	0.035	2.890	0.004	0.032	0.169
	South	0.048	0.032	1.500	0.134	-0.015	0.111
	West	0.047	0.046	1.030	0.302	-0.042	0.136
ESRD duration		-0.003	0.003	-0.800	0.424	-0.009	0.004
Primary disease causing ESRD [e]	Hypertension	-0.030	0.035	-0.850	0.393	-0.099	0.039
	Glomerulonephritis	-0.127	0.048	-2.620	0.009	-0.222	-0.032
	Cystic Kidney	-0.157	0.079	-1.990	0.046	-0.312	-0.003
	Other	-0.140	0.046	-3.060	0.002	-0.229	-0.050
Charlson Comorbidity Index (CCI) score		0.089	0.014	6.250	0.000	0.061	0.117
Presence of chronic disease	Diabetes mellitus	-0.071	0.040	-1.800	0.072	-0.149	0.006
	Hypertension	0.005	0.026	0.180	0.855	-0.046	0.056
	Dyslipidemia	0.023	0.038	0.620	0.538	-0.051	0.098
	Cancer	-0.216	0.061	-3.560	0.000	-0.334	-0.097
	Chronic lung disease	0.179	0.036	4.910	0.000	0.107	0.250
	Cardiovascular disease	0.428	0.033	12.860	0.000	0.363	0.493
glm							
Intercept		10.244	0.121	84.760	0.000	10.007	10.480
Cohort [a]	1	-0.032	0.046	-0.690	0.492	-0.122	0.059
	2	-0.022	0.044	-0.500	0.618	-0.109	0.065
	3	-0.074	0.057	-1.290	0.195	-0.186	0.038
Age		-0.007	0.001	-5.230	0.000	-0.010	-0.005
Gender [b]	Female	0.042	0.030	1.410	0.159	-0.016	0.101
Race [c]	White	-0.068	0.038	-1.780	0.076	-0.143	0.007
	Other	-0.238	0.091	-2.630	0.009	-0.415	-0.060
Region of	Northeast	0.131	0.042	3.120	0.002	0.049	0.213

residence [d]	South	-0.005	0.039	-0.130	0.895	-0.082	0.072
	West	0.176	0.053	3.310	0.001	0.072	0.281
ESRD duration		-0.006	0.004	-1.510	0.132	-0.014	0.002
Primary disease causing ESRD [e]	Hypertension	-0.013	0.042	-0.310	0.754	-0.096	0.070
	Glomerulonephritis	-0.024	0.062	-0.390	0.698	-0.145	0.097
	Cystic Kidney	0.090	0.094	0.950	0.342	-0.095	0.275
	Other	-0.027	0.063	-0.430	0.669	-0.150	0.096
Charlson Comorbidity Index (CCI) score		0.050	0.014	3.440	0.001	0.021	0.078
Presence of chronic disease	Diabetes mellitus	-0.038	0.046	-0.820	0.413	-0.128	0.052
	Hypertension	-0.009	0.031	-0.300	0.766	-0.069	0.051
	Dyslipidemia	0.068	0.042	1.620	0.106	-0.014	0.151
	Cancer	-0.102	0.071	-1.440	0.149	-0.241	0.037
	Chronic lung disease	-0.028	0.038	-0.750	0.455	-0.102	0.046
	Cardiovascular disease	0.050	0.042	1.200	0.230	-0.032	0.132

Model parameters: *Wald chi*^{2} *= 939.94* ; df =22 ; p<0.0001.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Appendix E10 A Two-part Model Comparing Cardiovascular-related Outpatient Costs during 2007 among Cohorts

Variable		Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
probit							
Intercept		-1.006	0.093	-10.810	0.000	-1.188	-0.824
Cohort [a]	1	-0.063	0.038	-1.690	0.092	-0.137	0.010
	2	0.074	0.036	2.040	0.042	0.003	0.145
	3	-0.008	0.047	-0.170	0.866	-0.101	0.085
Age		0.003	0.001	2.770	0.006	0.001	0.005
Gender [b]	Female	0.084	0.026	3.270	0.001	0.034	0.135
Race [c]	White	0.083	0.031	2.710	0.007	0.023	0.144
	Other	-0.041	0.075	-0.550	0.581	-0.188	0.105
Region of residence [d]	Northeast	-0.136	0.037	-3.730	0.000	-0.208	-0.065
	South	-0.106	0.033	-3.180	0.001	-0.172	-0.041
	West	-0.234	0.047	-4.940	0.000	-0.326	-0.141
ESRD duration		-0.005	0.003	-1.550	0.122	-0.011	0.001
Primary disease causing ESRD [e]	Hypertension	-0.043	0.036	-1.190	0.236	-0.113	0.028
	Glomerulonephritis	-0.131	0.049	-2.700	0.007	-0.226	-0.036
	Cystic Kidney	0.004	0.082	0.050	0.962	-0.157	0.165
	Other	-0.134	0.044	-3.030	0.002	-0.220	-0.047
Charlson Comorbidity Index (CCI) score		0.086	0.014	6.180	0.000	0.059	0.113
Presence of chronic disease	Diabetes mellitus	-0.043	0.038	-1.110	0.266	-0.118	0.032
	Hypertension	0.091	0.027	3.400	0.001	0.039	0.144
	Dyslipidemia	0.051	0.037	1.370	0.169	-0.022	0.123
	Cancer	-0.150	0.060	-2.490	0.013	-0.269	-0.032
	Chronic lung disease	0.028	0.035	0.800	0.421	-0.041	0.097
	Cardiovascular disease	0.419	0.033	12.690	0.000	0.354	0.484
glm							
Intercept		7.140	0.225	31.800	0.000	6.700	7.580
Cohort [a]	1	-0.027	0.083	-0.330	0.745	-0.189	0.135
	2	0.008	0.078	0.110	0.916	-0.145	0.161
	3	-0.032	0.113	-0.290	0.775	-0.254	0.189
Age		-0.001	0.002	-0.370	0.708	-0.006	0.004
Gender [b]	Female	0.166	0.057	2.900	0.004	0.054	0.277
Race [c]	White	-0.059	0.072	-0.820	0.414	-0.199	0.082
	Other	-0.171	0.158	-1.080	0.278	-0.480	0.138
Region of	Northeast	0.022	0.082	0.270	0.789	-0.139	0.183

residence [d]	South	0.049	0.071	0.700	0.486	-0.090	0.188
	West	-0.037	0.100	-0.370	0.708	-0.233	0.158
ESRD duration		-0.001	0.008	-0.160	0.871	-0.016	0.014
Primary disease causing ESRD [e]	Hypertension	-0.096	0.078	-1.230	0.217	-0.248	0.056
	Glomerulonephritis	-0.068	0.142	-0.480	0.634	-0.346	0.211
	Cystic Kidney	0.055	0.284	0.200	0.845	-0.501	0.612
	Other	-0.270	0.100	-2.710	0.007	-0.466	-0.075
Charlson Comorbidity Index (CCI) score		0.023	0.031	0.760	0.447	-0.037	0.084
Presence of chronic disease	Diabetes mellitus	0.027	0.085	0.320	0.752	-0.140	0.193
	Hypertension	-0.041	0.060	-0.690	0.491	-0.159	0.076
	Dyslipidemia	-0.015	0.074	-0.200	0.842	-0.159	0.130
	Cancer	0.010	0.136	0.070	0.941	-0.256	0.276
	Chronic lung disease	-0.001	0.082	-0.010	0.991	-0.162	0.160
	Cardiovascular disease	0.245	0.081	3.010	0.003	0.085	0.404

Model parameters: *Wald chi*^{2} *= 966.10* ; df =22 ; p<0.0001.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Appendix E11 A Two-part Model Comparing Cardiovascular-related Physician/Supplier Costs during 2007 among Cohorts

Variable		Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
probit							
Intercept		-0.859	0.088	-9.800	0.000	-1.031	-0.687
Cohort [a]	1	0.038	0.035	1.070	0.287	-0.032	0.107
	2	0.161	0.036	4.440	0.000	0.090	0.231
	3	0.153	0.046	3.310	0.001	0.063	0.244
Age		0.008	0.001	7.750	0.000	0.006	0.010
Gender [b]	Female	0.056	0.025	2.280	0.023	0.008	0.104
Race [c]	White	0.064	0.029	2.250	0.025	0.008	0.120
	Other	-0.066	0.069	-0.950	0.344	-0.201	0.070
Region of residence [d]	Northeast	0.171	0.035	4.820	0.000	0.101	0.240
	South	0.043	0.033	1.300	0.194	-0.022	0.109
	West	0.070	0.046	1.520	0.129	-0.020	0.161
ESRD duration		-0.005	0.003	-1.720	0.085	-0.011	0.001
Primary disease causing ESRD [e]	Hypertension	-0.033	0.034	-0.970	0.331	-0.101	0.034
	Glomerulonephritis	-0.162	0.048	-3.380	0.001	-0.256	-0.068
	Cystic Kidney	-0.157	0.073	-2.140	0.032	-0.300	-0.013
	Other	-0.177	0.042	-4.160	0.000	-0.260	-0.093
Charlson Comorbidity Index (CCI) score		0.127	0.015	8.390	0.000	0.097	0.157
Presence of chronic disease	Diabetes mellitus	-0.085	0.039	-2.180	0.029	-0.161	-0.009
	Hypertension	-0.017	0.027	-0.610	0.539	-0.070	0.037
	Dyslipidemia	0.122	0.038	3.180	0.001	0.047	0.198
	Cancer	-0.262	0.060	-4.370	0.000	-0.379	-0.144
	Chronic lung disease	0.073	0.038	1.930	0.053	-0.001	0.147
	Cardiovascular disease	0.354	0.033	10.610	0.000	0.288	0.419
glm							
Intercept		6.145	0.229	26.880	0.000	5.697	6.593
Cohort [a]	1	-0.110	0.113	-0.970	0.332	-0.333	0.112
	2	-0.042	0.115	-0.370	0.711	-0.267	0.182
	3	-0.144	0.123	-1.170	0.240	-0.385	0.096
Age		0.005	0.003	1.350	0.178	-0.002	0.011
Gender [b]	Female	0.219	0.059	3.690	0.000	0.103	0.336
Race [c]	White	0.031	0.069	0.450	0.653	-0.104	0.166
	Other	0.130	0.227	0.570	0.567	-0.315	0.575
Region of	Northeast	0.378	0.094	4.000	0.000	0.193	0.562

residence [d]	South	0.125	0.062	2.000	0.045	0.003	0.247
	West	0.132	0.088	1.500	0.134	-0.041	0.305
ESRD duration		-0.023	0.007	-3.510	0.000	-0.036	-0.010
Primary disease causing ESRD [e]	Hypertension	-0.131	0.074	-1.760	0.078	-0.276	0.015
	Glomerulonephritis	-0.056	0.168	-0.340	0.737	-0.385	0.272
	Cystic Kidney	0.049	0.144	0.340	0.732	-0.233	0.332
	Other	-0.236	0.100	-2.360	0.018	-0.432	-0.040
Charlson Comorbidity Index (CCI) score		0.083	0.034	2.430	0.015	0.016	0.150
Presence of chronic disease	Diabetes mellitus	-0.090	0.093	-0.960	0.335	-0.273	0.093
	Hypertension	0.091	0.070	1.310	0.191	-0.046	0.228
	Dyslipidemia	-0.003	0.077	-0.040	0.971	-0.154	0.148
	Cancer	-0.459	0.106	-4.350	0.000	-0.666	-0.252
	Chronic lung disease	0.063	0.073	0.860	0.389	-0.081	0.207
	Cardiovascular disease	0.136	0.082	1.670	0.095	-0.024	0.296

Model parameters: *Wald chi*^{2} *= 1134.32* ; df =22 ; p<0.0001.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Appendix E12 A Two-part Model Comparing Cardiovascular-related Other Costs during 2007 among Cohorts

Variable		Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
probit							
Intercept		-2.741	0.123	-22.290	0.000	-2.982	-2.500
Cohort [a]	1	-0.002	0.049	-0.040	0.965	-0.098	0.094
	2	0.047	0.047	1.010	0.314	-0.044	0.138
	3	-0.072	0.062	-1.160	0.245	-0.194	0.050
Age		0.017	0.001	11.150	0.000	0.014	0.019
Gender [b]	Female	-0.083	0.032	-2.620	0.009	-0.145	-0.021
Race [c]	White	-0.007	0.038	-0.170	0.862	-0.081	0.068
	Other	-0.326	0.116	-2.820	0.005	-0.553	-0.100
Region of residence [d]	Northeast	0.007	0.046	0.160	0.871	-0.082	0.097
	South	0.055	0.044	1.260	0.207	-0.030	0.140
	West	-0.050	0.062	-0.800	0.421	-0.171	0.071
ESRD duration		0.001	0.004	0.150	0.878	-0.008	0.009
Primary disease causing ESRD [e]	Hypertension	-0.084	0.044	-1.900	0.057	-0.170	0.002
	Glomerulonephritis	-0.134	0.064	-2.100	0.036	-0.259	-0.009
	Cystic Kidney	-0.040	0.105	-0.390	0.700	-0.245	0.165
	Other	-0.196	0.058	-3.380	0.001	-0.310	-0.083
Charlson Comorbidity Index (CCI) score		0.113	0.016	7.180	0.000	0.082	0.144
Presence of chronic disease	Diabetes mellitus	-0.032	0.046	-0.700	0.486	-0.122	0.058
	Hypertension	0.115	0.032	3.610	0.000	0.053	0.177
	Dyslipidemia	0.023	0.045	0.510	0.609	-0.064	0.110
	Cancer	-0.278	0.072	-3.870	0.000	-0.420	-0.137
	Chronic lung disease	-0.007	0.040	-0.180	0.859	-0.086	0.072
	Cardiovascular disease	0.365	0.043	8.580	0.000	0.282	0.448
glm							
Intercept		7.855	0.242	32.420	0.000	7.380	8.330
Cohort [a]	1	0.146	0.086	1.700	0.090	-0.023	0.315
	2	0.143	0.088	1.620	0.105	-0.030	0.316
	3	-0.051	0.118	-0.430	0.669	-0.282	0.181
Age		0.013	0.003	4.540	0.000	0.007	0.019
Gender [b]	Female	-0.096	0.053	-1.810	0.070	-0.200	0.008
Race [c]	White	0.038	0.064	0.590	0.554	-0.087	0.163
	Other	-0.165	0.230	-0.720	0.473	-0.616	0.286
Region of	Northeast	-0.093	0.076	-1.230	0.218	-0.241	0.055

residence [d]	South	-0.067	0.065	-1.020	0.308	-0.195	0.061
	West	-0.143	0.103	-1.400	0.163	-0.345	0.058
ESRD duration		0.013	0.007	1.790	0.074	-0.001	0.028
Primary disease causing ESRD [e]	Hypertension	-0.079	0.084	-0.940	0.349	-0.243	0.086
	Glomerulonephritis	-0.243	0.124	-1.960	0.050	-0.486	0.000
	Cystic Kidney	-0.177	0.177	-1.000	0.316	-0.524	0.169
	Other	-0.082	0.111	-0.740	0.462	-0.299	0.136
Charlson Comorbidity Index (CCI) score		0.050	0.026	1.890	0.059	-0.002	0.102
Presence of chronic disease	Diabetes mellitus	-0.081	0.092	-0.880	0.378	-0.261	0.099
	Hypertension	-0.012	0.055	-0.220	0.827	-0.121	0.096
	Dyslipidemia	0.098	0.074	1.330	0.184	-0.047	0.242
	Cancer	-0.266	0.115	-2.310	0.021	-0.491	-0.041
	Chronic lung disease	-0.122	0.063	-1.940	0.052	-0.246	0.001
	Cardiovascular disease	0.036	0.075	0.480	0.630	-0.111	0.182

Model parameters: *Wald chi*^{2} *= 694.00* ; df =22 ; p<0.0001.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

Appendix E13 A Two-part Model Comparing Cardiovascular-related Other Costs during 2007 among Cohorts

Variable		Parameter Estimate	Standard Error	z	p-value	95% Confidence Interval	
probit							
Intercept		-0.699	0.090	-7.770	0.000	-0.876	-0.523
Cohort [a]	1	0.016	0.037	0.430	0.665	-0.056	0.088
	2	0.171	0.037	4.580	0.000	0.098	0.244
	3	0.152	0.052	2.930	0.003	0.050	0.253
Age		0.009	0.001	7.810	0.000	0.006	0.011
Gender [b]	Female	0.071	0.026	2.720	0.007	0.020	0.122
Race [c]	White	0.068	0.030	2.260	0.024	0.009	0.127
	Other	-0.105	0.075	-1.400	0.163	-0.253	0.042
Region of residence [d]	Northeast	0.123	0.038	3.230	0.001	0.048	0.198
	South	0.066	0.035	1.920	0.054	-0.001	0.134
	West	0.015	0.049	0.320	0.753	-0.081	0.111
ESRD duration		-0.006	0.003	-1.740	0.081	-0.012	0.001
Primary disease causing ESRD [e]	Hypertension	-0.045	0.037	-1.240	0.216	-0.117	0.026
	Glomerulonephritis	-0.198	0.050	-3.980	0.000	-0.296	-0.101
	Cystic Kidney	-0.111	0.077	-1.440	0.150	-0.262	0.040
	Other	-0.199	0.044	-4.530	0.000	-0.285	-0.113
Charlson Comorbidity Index (CCI) score		0.129	0.017	7.790	0.000	0.096	0.161
Presence of chronic disease	Diabetes mellitus	-0.058	0.043	-1.350	0.177	-0.141	0.026
	Hypertension	0.040	0.028	1.390	0.163	-0.016	0.095
	Dyslipidemia	0.090	0.042	2.150	0.031	0.008	0.173
	Cancer	-0.290	0.065	-4.430	0.000	-0.418	-0.162
	Chronic lung disease	0.156	0.041	3.810	0.000	0.076	0.236
	Cardiovascular disease	0.498	0.035	14.080	0.000	0.428	0.567
glm							
Intercept		9.326	0.132	70.850	0.000	9.068	9.584
Cohort [a]	1	-0.067	0.051	-1.300	0.193	-0.168	0.034
	2	-0.013	0.052	-0.250	0.803	-0.116	0.090
	3	-0.147	0.065	-2.270	0.023	-0.275	-0.020
Age		-0.002	0.002	-1.470	0.140	-0.005	0.001
Gender [b]	Female	0.021	0.034	0.610	0.543	-0.046	0.087
Race [c]	White	-0.061	0.040	-1.520	0.128	-0.139	0.018
	Other	-0.208	0.098	-2.130	0.033	-0.400	-0.016
Region of	Northeast	0.150	0.047	3.200	0.001	0.058	0.242

residence [d]	South	0.014	0.041	0.350	0.726	-0.066	0.094
	West	0.149	0.062	2.420	0.015	0.028	0.270
ESRD duration		-0.005	0.004	-1.160	0.247	-0.014	0.004
Primary disease causing ESRD [e]	Hypertension	-0.047	0.045	-1.040	0.297	-0.136	0.041
	Glomerulonephritis	-0.079	0.069	-1.140	0.253	-0.214	0.056
	Cystic Kidney	-0.036	0.110	-0.330	0.742	-0.251	0.179
	Other	-0.113	0.063	-1.770	0.076	-0.237	0.012
Charlson Comorbidity Index (CCI) score		0.093	0.015	6.000	0.000	0.062	0.123
Presence of chronic disease	Diabetes mellitus	-0.100	0.050	-2.000	0.046	-0.198	-0.002
	Hypertension	0.008	0.035	0.220	0.823	-0.061	0.077
	Dyslipidemia	0.043	0.043	0.980	0.327	-0.043	0.128
	Cancer	-0.228	0.076	-3.000	0.003	-0.376	-0.079
	Chronic lung disease	0.030	0.040	0.750	0.454	-0.048	0.108
	Cardiovascular disease	0.266	0.046	5.840	0.000	0.177	0.356

Model parameters: *Wald chi*^{2} *= 1319.33* ; df =22 ;
p<0.0001.

[a] Reference: Cohort 4

[b] Reference : Male

[c] Reference: Black

[d] Reference : Midwest

[e] Reference : Diabetes mellitus

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